博士論文

Development of catalyzed reaction for the synthesis of tetrasubstituted carbon compounds "cyclization, C-C bond cleavage reaction, stereospecific reaction"

(四置換炭素化合物合成用触媒反応開発 "環化反応, C-C 結合開裂反応, 立体特異的反応")

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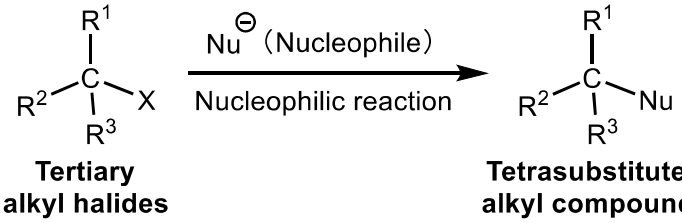
General introduction

The tetrasubstituted alkyl compounds are carbon compounds with four bulky substituents except for hydrogen atom. The tetrasubstituted carbon moieties are common structures of various bioactive molecules, and the development of efficient tetrasubstituted carbon moiety construction methods is a very important issue.

One of the methods for synthesizing new tetrasubstituted alkyl compounds is a substitution reaction using tertiary alkyl halides. There are two types of nucleophilic substitution reaction (S_N2 reaction, S_N1 reaction).



In the S_N2 reaction, the nucleophile attacks from the opposite side of the carbon-leaving group (X) bond of the haloalkane, so that this reaction is strongly affected by steric hinderance of the haloalkane. Therefore, the reactivity of haloalkanes decreases in the order of primary > secondary > tertiary, and it is almost impossible for tertiary haloalkane to proceed with the reaction.

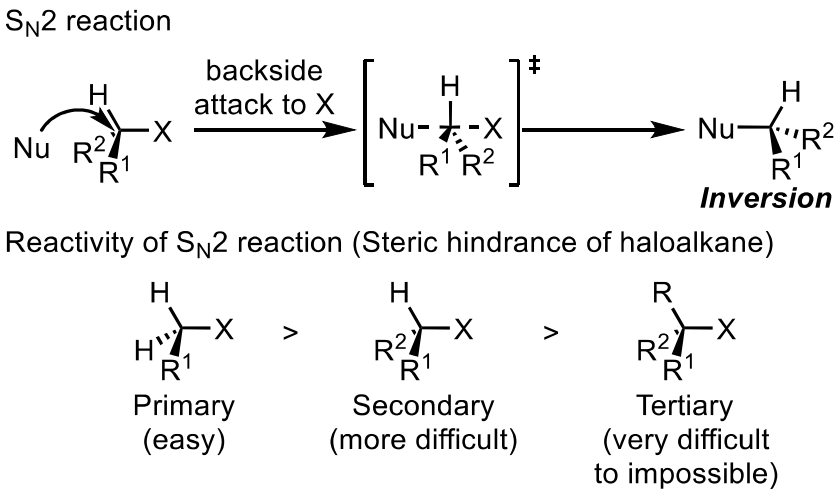


Figure 1 S_N2 reaction

The S_N1 reaction proceeds in two steps via carbocation intermediate, so the reaction rate of the S_N1 reaction is greater as the carbocation of the intermediate through is stable. Therefore, the reactivity of haloalkanes decreases in the order of tertiary > secondary > primary, and it is easy for tertiary alkyl halides to proceed with the reaction.

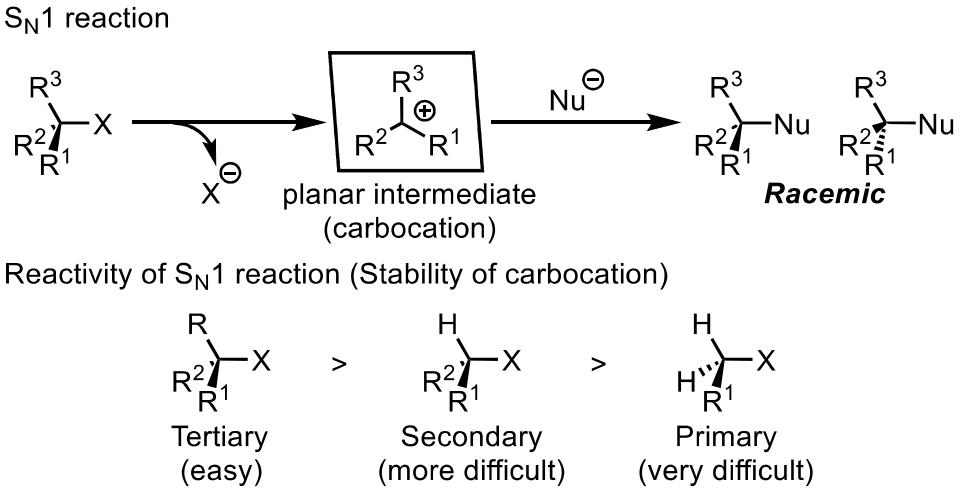


Figure 2 S_N1 reaction

Haloalkanes undergo a substitution reaction in which the nucleophile attacks the carbon atom, and an elimination reaction in which the nucleophile acts as a base. Nucleophilic substitution reaction is unlikely to occur due to steric hindrance between alkyl halide and nucleophile, and elimination reaction that are not much affected by the steric hindrance are preferred. Therefore, it is very difficult to synthesize tetrasubstituted alkyl compounds by nucleophilic substitution reaction (S_N1 reaction) between a tertiary alkyl halide and a nucleophile.

Radical chemistry[1] has experienced a renaissance in the past 10-15 years owing, in part, to developments in photoredox catalysis[2], electrochemistry[3]. In the radical reaction, haloalkanes are activated by the action of transition metals, photosensitizers and radical initiators, then radical intermediates are generated. Radical species are highly active, so it has become possible to overcome the effects of steric hindrance between haloalkanes and substrates. The reaction rate of radical reaction is greater as the radical intermediate is stable. Therefore, the reactivity of haloalkanes via radical intermediate decreases in the order of tertiary > secondary > primary.

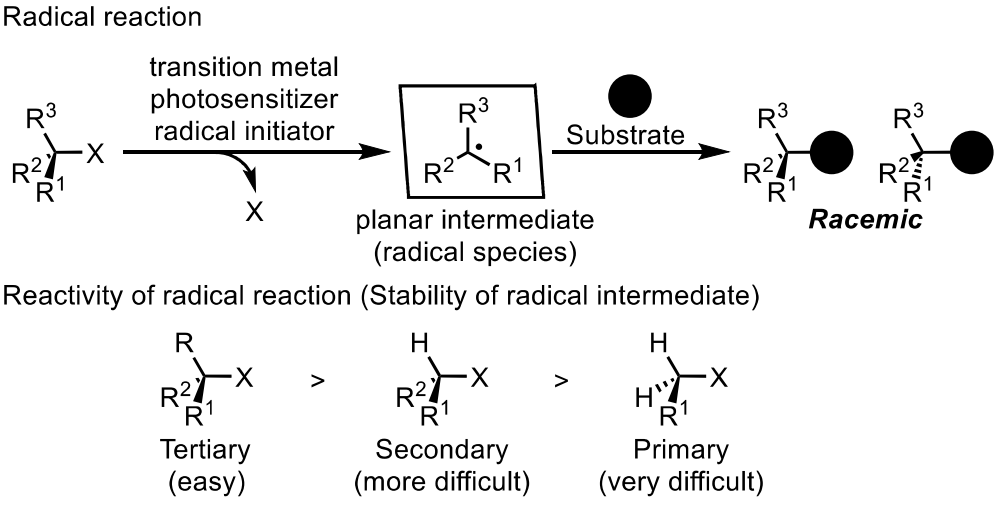
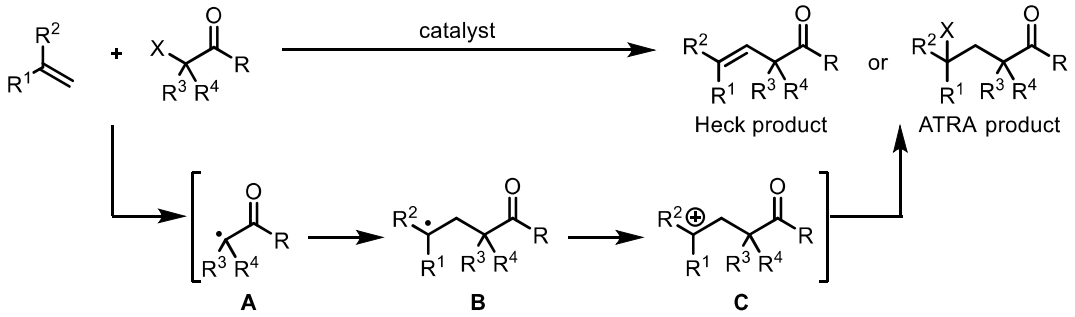


Figure 3 Radical reaction

Tertiary alkylation via catalytic activation of α-halocarbonyl compounds.

α-Halocarbonyl compounds are powerful reactive species, so they are one of the most useful tertiary alkyl sources in organic synthesis.[4] In recent years, a number of tetrasubstituted carbon compound synthesis methods of α-halocarbonyl compounds via catalytic activation have been developed. Here, I introduce examples of methods, ATRA, ATRC, Heck type reaction and dearomatized addition) for synthesizing tetrasubstituted carbon compounds using α-halocarbonyl compounds via catalytic activation. In particular, examples of ATRA, ATRC, Heck type reaction and dearomatized addition are introduced.

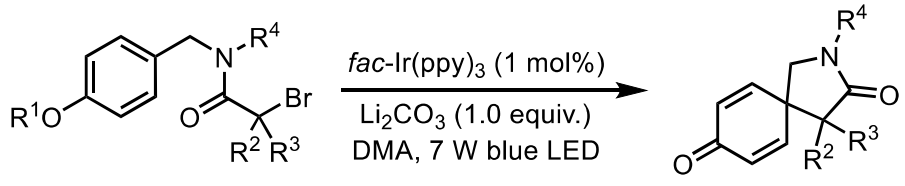
Tertiary alkylation using α-halocarbonyl compounds to alkene (Heck type reaction or ATRA, ATRC reaction)



Scheme 1 Tertiary alkylation to alkene

At first, tertiary alkylation using α-halocarbonyl compounds to alkene are summarized (Scheme 1).[5] Tertiary alkyl radical **A** is produced from α-halocarbonyl compound. Then, tertiary alkyl radicals **A** are added to alkenes resulting in the alkyl radical intermediate **B**. Next, cation intermediates **C** are generated by single-electron oxidation. If deprotonation proceeds from the intermediate **C**, a Heck product is obtained. On the other hand, if a halide departed from the α-halocarbonyl compound is added, an ATRA product can be obtained. The atom transfer radical cyclization (ATRC) reaction is a reaction in which a halide is introduced after the radical intermediate **B** undergoes a cyclization reaction.

Tertiary alkyl dearomatization using α-halocarbonyl compound



Scheme 2 Intramolecular dearomative *tert*-alkylation reported by Zhang

Intramolecular dearomative tertiary-alkylation to construct vicinal quaternary carbon centers was reported by Zhang in 2016 (Scheme 2).[6a] This reaction, shown in Scheme 2, was conducted using α-bromo-N-benzyl-alkylamide in the presence of iridium photoredox catalyst.

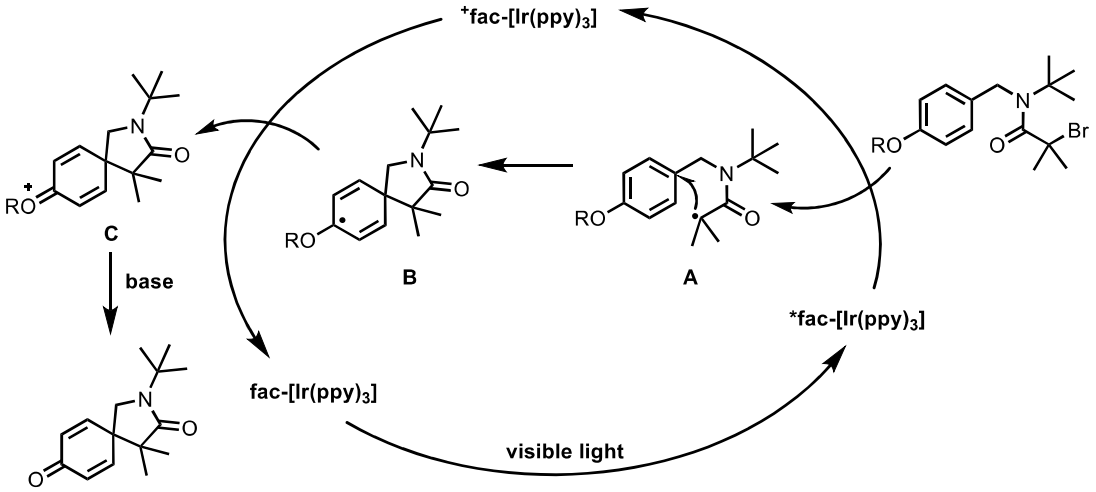
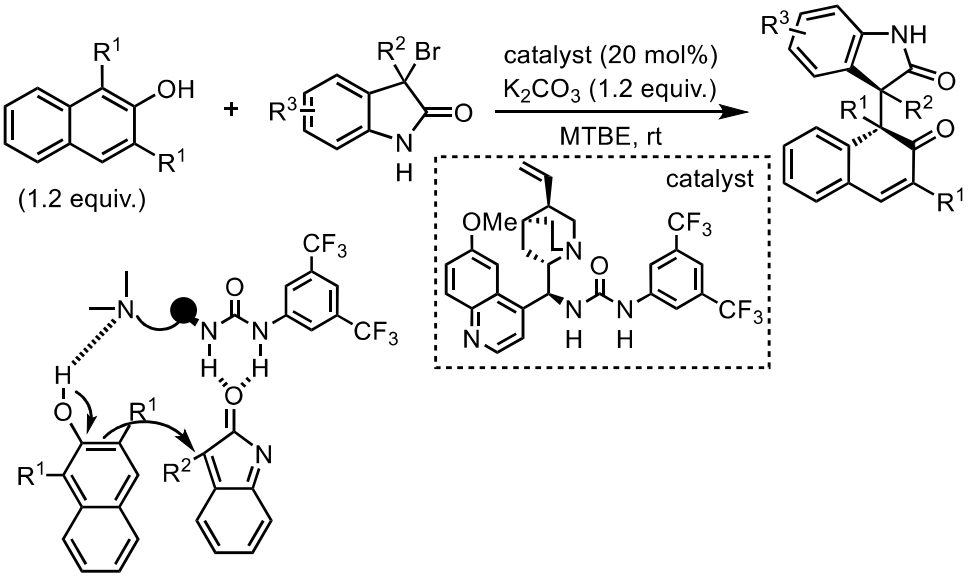


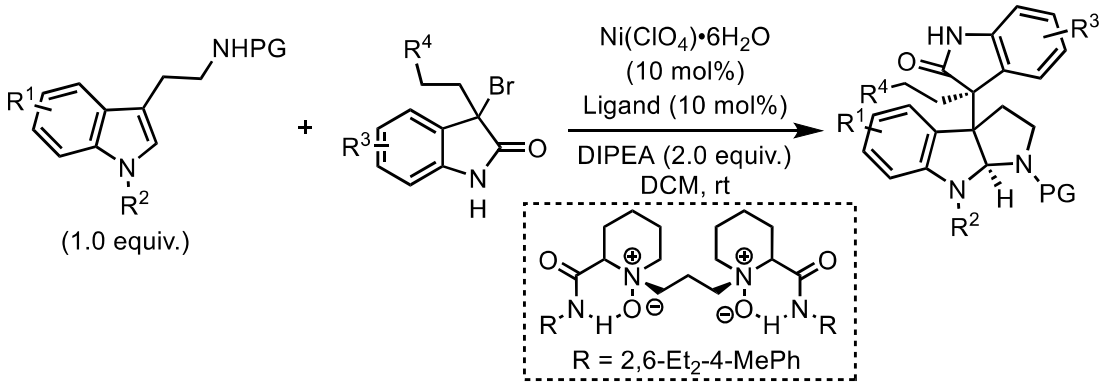
Figure 4 Proposed reaction mechanism

The estimated reaction mechanism of the reaction shown in Scheme 2 is shown (Figure 4). First, the iridium catalyst is excited by light irradiation, and single-electron reduction of α-bromo-N-benzyl-alkylamide occurs. Then, generated tertiary alkyl radical species **A** and $Ir^{(IV)}$ complex are generated. Next, site-selective dearomative addition via C-C bond formation occurs, and radical species **B** is produced. Subsequently, single-electron oxidation of radical species **B** by $Ir^{(IV)}$ complex occurs, resulting in cationic intermediate **C**. Finally, the spirocyclohexadienone is produced by the action of base.



Scheme 3 Enantioselective tertiary alkyl dearomatization catalyzed by urea catalyst

Enantioselective intermolecular tertiary-alkyl dearomatization to construct vicinal quaternary carbon centers was reported in 2018 (Scheme 3).[6b] This reaction was conducted using cyclic α-bromoamide and 2-naphthol derivative in the presence of urea catalyst. As shown in the figure on the lower left, it is proposed that the urea catalyst activates the substrates and expresses asymmetry.



Scheme 4 Enantioselective tertiary alkyl dearomatization catalyzed by Ni catalyst

Enantioselective intermolecular tertiary-alkyl dearomatization to construct vicinal quaternary carbon centers was reported by Xie in 2021 (Scheme 4).[6c] This reaction was conducted using cyclic α-bromoamide and N-protected indole derivative in the presence of Ni catalyst.

Since N-unprotected α-bromoamide can be activated only by the action of the base, the reaction can proceed without the involvement of radical intermediates (Scheme 3,4).

Challenges in the construction of tetrasubstituted carbon compounds

With the development of radical chemistry, the problem of steric hindrance in the synthesis of nucleophilic substitution reactions has been alleviated, but there are still problems.

Problem 1

When aiming for the synthesis of complex compounds, there may be situations where compounds having multiple leaving groups are used to react, but if there are leaving groups with similar reactivity, it is difficult to selectively activate only one of them, and both leaving groups are likely to react.

Problem 2

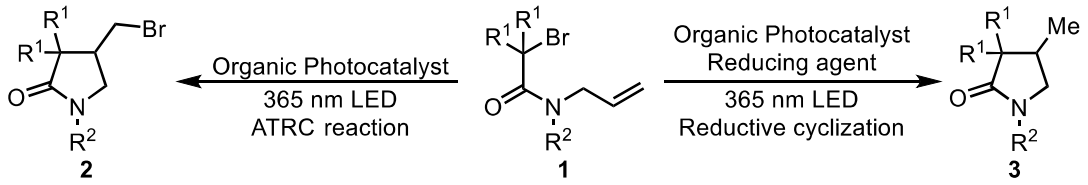
It is difficult to reflect the stereochemistry of chiral starting material in the product when free radical species are generated. Due to the planar free radical species, racemization proceeds when the substrate is introduced.

To solve these challenges, I conducted the following research.

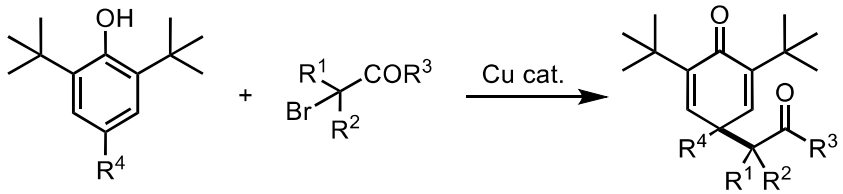
Outline of the present thesis

In Chapter 1, organic photoredox-catalyzed ATRC reaction with N-allyl-α-bromocarbonyl compound

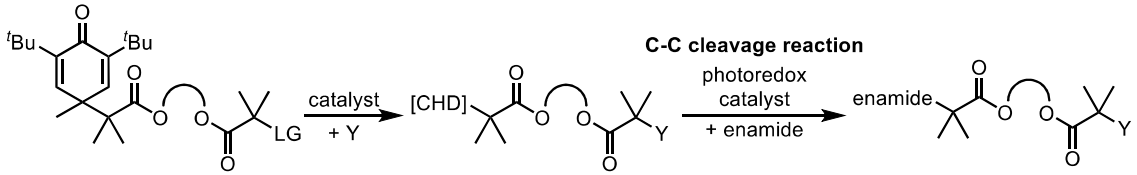
1 are described. It was also found that the reductive cyclization proceeds by addition of a reductant.



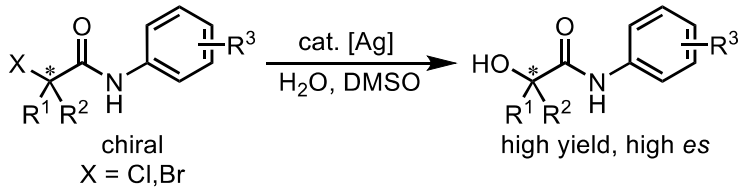
In Chapter 2, copper-catalyzed dearomative addition reaction using tertiary α-bromocarbonyl compound and BHT derivatives are described. In this reaction, dearomatized cyclohexadienone derivatives can be synthesized.



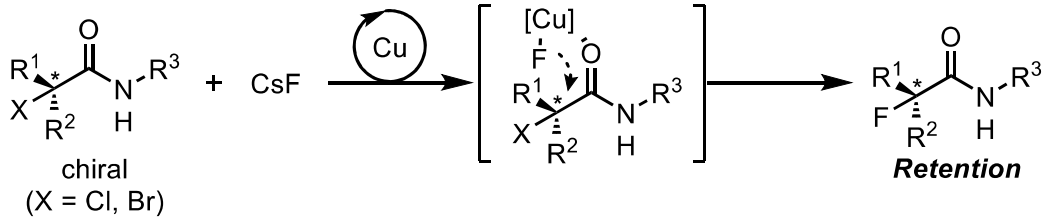
In Chapter 3, the photoredox-catalyzed enamide Heck-type tertiary alkylation via carbon-carbon bond cleavage of cyclohexadienone derivatives was developed. In this study, C-C bond cleavage of cyclohexadienone could be applied to chemoselective coupling.



In Chapter 4, silver-catalyzed stereospecific hydroxylation of chiral tertiary α-haloamides.

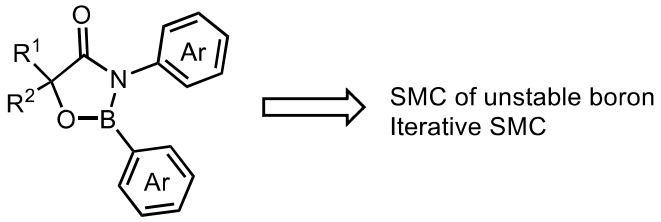


Chapter 5 are described stereospecific fluorination of chiral tertiary alkyl halides in the presence of Cu catalyst. The stereoretentive fluorinated product can be obtained in this reaction. It is suggested that CuF_2 is a reactive species and it is important that the presence of CsF and ligand for this reaction.



In chapter 6, development of masked organoboronic acid, OxB, are described. A back born (α-

hydroxycarboxamide) of OxB has bulky α-alkyl groups and a carboxamide group possessing both electronic and steric effect. OxB stabilizes unstable boron and undergoes Suzuki-Miyaura coupling efficiently and can be applied iterative Suzuki-Miyaura coupling.



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Chapter 1 Development of atom-transfer-radical-cyclization (ATRC) and reductive cyclization in the presence of photoredox catalyst

1.1 Introduction

γ-lactam is an important skeleton found in many biologically active substances and natural products. Examples include the respiratory stimulant Doxapram, the antiepileptic drug levetiracetam, and the imidazole alkaloid synometrine (Figure 1).[1] Since γ-lactams are contained in molecules such as bioactive substances, the development of efficient construction methods is an important issue.

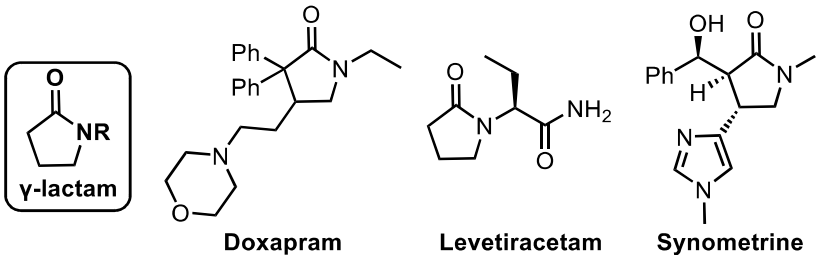
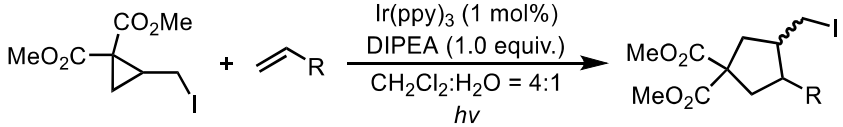


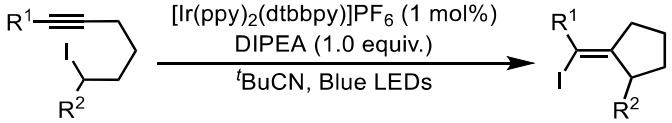
Figure 1 Biologically active substances and natural products including γ-lactam skeleton.

Atom-transfer-radical-cyclization (ATRC) reaction is an effective method to construct the γ-lactam compounds. ATRC reactions using organotin[2], Lewis acid[3] and transition metal catalysts[4] have been developed, but in recent years, photoredox-catalyzed ATRC reactions have been developed. Photoredox-catalyzed ATRC reactions have attracted much attention because they can efficiently form C-C bonds and C-X bonds simultaneously under mild reaction conditions. However, in the presence of a photoredox catalyst, the use of a reducing agent is necessary, and the possibility of reduction increase, so ATRC reaction is difficult. In this section, the authors will introduce the ATRC reaction using a photoredox catalyst.



Scheme 1 Gu's work.

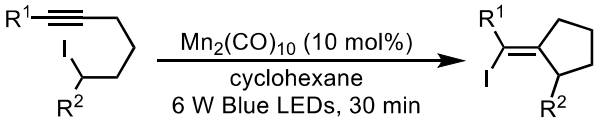
First, the reaction reported by Gu and coworkers in 2013 (Scheme 1).[5] This is a photoredox-catalyzed intermolecular ATRC reaction in which inert alkyl iodide and alkene are irradiated with a blue LED in the presence of an iridium photoredox catalyst.



Scheme 2 Shen's work

Shen and coworkers reported the photoredox-catalyzed intramolecular ATRC reaction in the

presence of iridium photoredox catalyst and DIPEA as reductant (Scheme 2).[6]



Scheme 3 Weng's work

Next, Weng and coworkers reported Mn-catalyzed intramolecular ATRC reaction in 2019 (Scheme 3).[7] The substrate is similar to the reaction shown in Scheme 2, but uses manganese, which is abundant on Earth, as a catalyst.

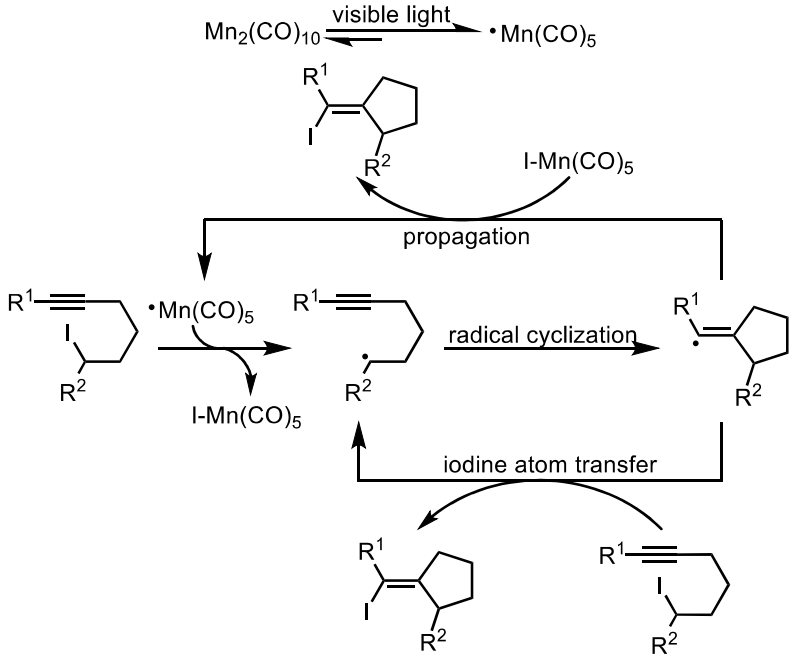
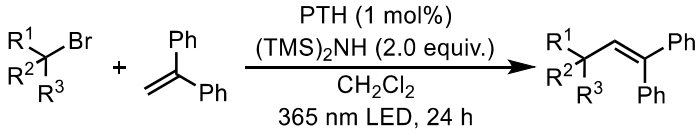


Figure 2 Proposed reaction mechanism

The proposed reaction mechanism is shown in Figure 2. First, manganese radical species are produced by cleaving manganese complexes with visible light. Then, manganese radical species abstract iodine from alkyl iodide, resulting in alkyl radical species and manganese iodide. After that, two types of processes have been estimated for the cyclization of alkyl radical species: the process of receiving iodine from manganese iodide, and the process of receiving iodine from the substrate alkyl iodide. By going through this process, the target ATRC product is generated and manganese radical species or alkyl radical species are generated.

1.2 Previous work and this work



Scheme 4 Previous work

The authors previously reported organic photocatalyzed Atom-Transfer-Radical-Substitution (ATRS) reaction using tertiary α-halocarbonyl compound and alkene (Scheme 4).[8] The reaction is carried out using N-Phenylphenothiazine (PTH) as an organic photoredox catalyst.

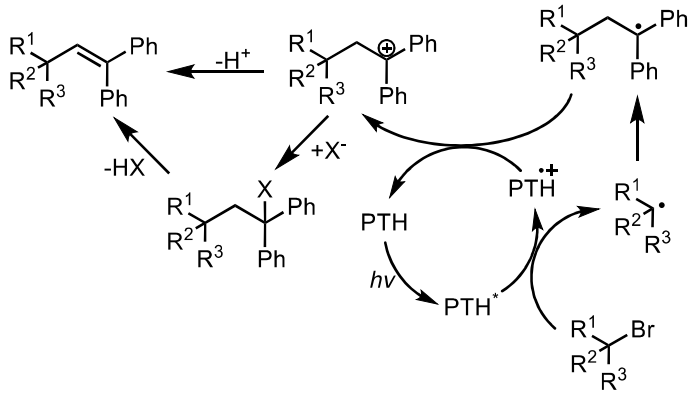
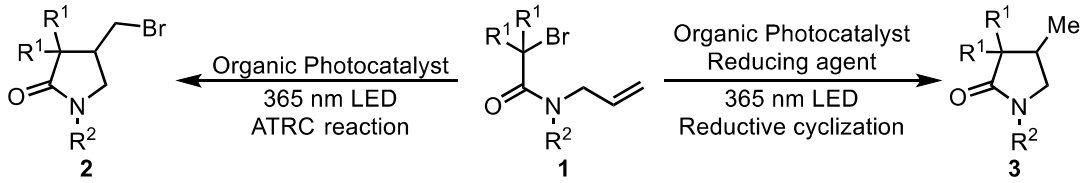


Figure 3 Proposed reaction mechanism

First, PTH is excited by visible light and then single-electron transfer occurs to the α-bromocarbonyl compound to produce alkyl radical species. Then, an alkyl radical species added to an alkene, and subsequent single-electron transfer results in the formation of cationic intermediates and the regeneration of PTH. After that, two processes have been considered: the first is the process in which the proton of the cationic intermediate is abstracted by the base, and the second is the process in which halogen atoms are trapped in the cationic intermediate subsequently elimination of HX occurs.



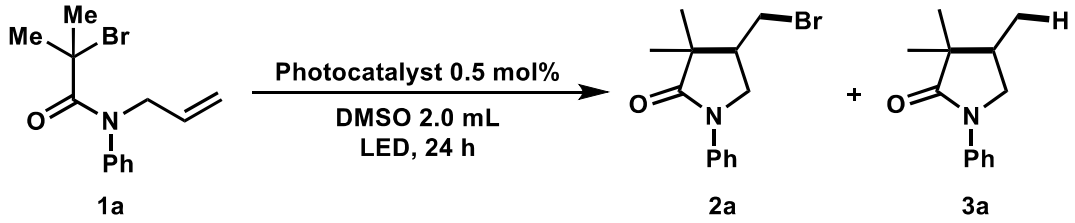
Scheme 5 This work

Herein, I developed an organic photoredox-catalyzed ATRC reaction with N-allyl-α-bromocarbonyl compound **1**. It was also found that the reductive cyclization proceeds by addition of a reductant (Scheme 5).

1.3 Results and discussion

1.3.1 Optimization of reaction conditions

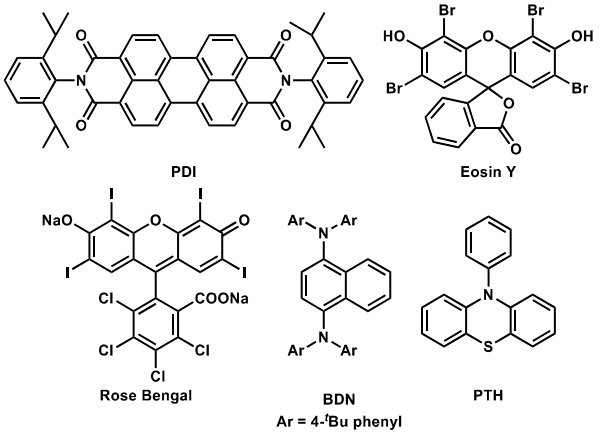
Table 1 Optimization of photocatalysts



1a 2a 3a

Entry	Photocatalyst	NMR Yield			ratio
		2a	3a	S.M.	2a:3a
1[a]	PDI	n.r.	n.r.	-	-
2[a]	Eosin Y	25%	-	62%	100:0
3[b]	Eosin Y	5%	-	95%	100:0
4[b]	Rose Bengal	6%	-	94%	100:0
5[c]	PTH	71% (60%)[d]	6% (3%)[d]	8%	92:8
6[c]	BDN	64%	8%	5%	89:11

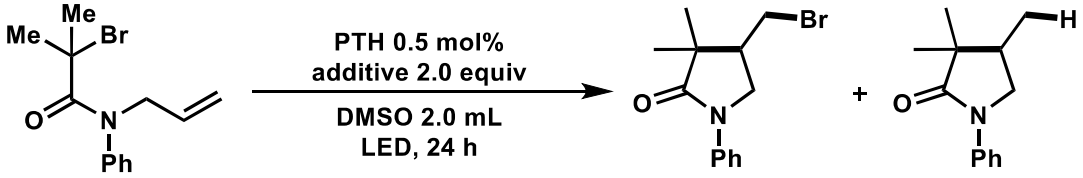
Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield. [a]455 nm LED was irradiated. [b]525 nm LED was irradiated. [c]365 nm LED was irradiated.



I initiated carried out the optimization of photocatalyst and wavelength of LED for photoredox-catalyzed ATRC reaction using N-allyl-2-bromo-2-methyl-N-phenylpropanamide (**1a**) as model substrate. When PDI was used as a photoredox catalyst and the reaction was performed under 455 nm LED irradiation, the reaction did not proceed at all. Next, when Eosin Y or rose Bengal under 525 nm LED irradiation was used, the reduction product **3a** was not detected, and only the ATRC product could be obtained. Subsequently, when PTH or BDN was used irradiated by 365 nm LED, **1a** was almost consumed, and ATRC product **2a** was obtained in 71% NMR yield (entry 5) and 64% NMR yield (entry 6). At this time, a small amount of the reductive product **3a** was also obtained. When the reaction using PTH was conducted, the ATRC product **2a** was obtained in 60% isolated

yield. From the results of optimization of photocatalysts, I determined PTH as the optimal photocatalyst.

Table 2 Optimization of additives



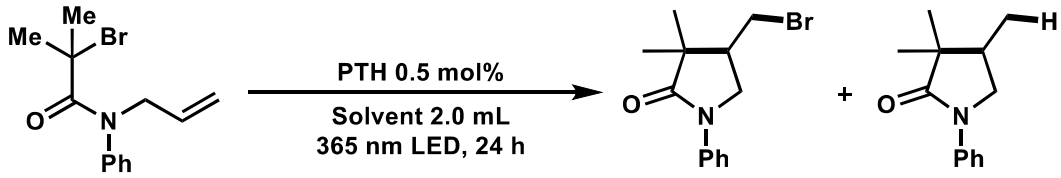
1a 2a 3a

Entry	additive	NMR Yield		ratio
		2a	3a	2a:3a
1	LiBr	70%	8%	94:6
2	KBr	76%	5%	90:10
3	$ZnBr_2$	65%	9%	88:12
4	$MgBr_2$	82% (72%)	6% (2%)	93:7

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

Next, I conducted the optimization of additives due to improving the yield of the ATRC product **2a**. As a result, when LiBr, KBr, and $ZnBr_2$ were used, there was no change in yield from the conditions without additives. When $MgBr_2$ was used as an additive, the yield of ATRC product **2a** improved in 82% NMR yield and 72% isolated yield. Therefore, I determined $MgBr_2$ as the optimal additive for the ATRC reaction.

Table 3 Optimization of solvents



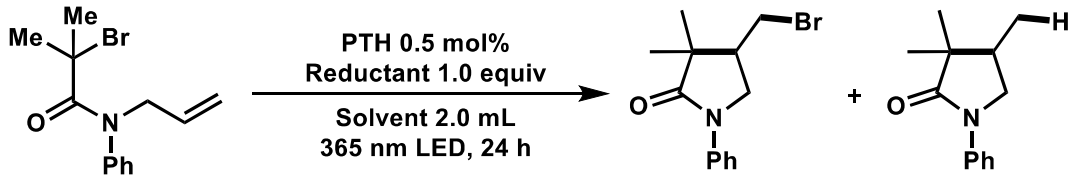
1a 2a 3a

Entry	Solvent	NMR Yield		ratio
		2a	3a	2a:3a
1	MeOH	63%	18%	78:22
2	H_2O	47%	-	100:0
3	IPA:H_2O=1:9	61%	8%	88:12
4	DMSO:H_2O=1:9	39%	9%	81:19
5[a]	DMSO:H_2O=1:9	41%	9%	82:18
6	EtOH:H_2O=1:9	46%	9%	84:16
7[a]	EtOH:H_2O=1:9	43%	8%	84:16
8	NMP	16%	49%	25:75
9[a]	MeCN	37%	27%	58:42
10	MeCN	78%	8%	91:9

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. [a]2.0 equiv. of $MgBr_2$ was used.

I carried out the optimization of solvents (Table 3). When I conducted the reaction using MeOH or H_2O, the ATRC product **2a** was obtained as the main product. When a mixed solvent with water was used, the yield and product ratio deteriorated (entry 3-7). Next, I carried out the reaction using N-methyl-2-pyrrolidone (NMP), the reductive product **3a** was obtained in 49% NMR yield (entry 8, **2a**:**3a** = 25:75). Finally, the reaction in MeCN did not show an improvement in product yield and product ratio (entry 9,10). From the results of optimization of solvents, I thought that the use of NMP might lead to selective synthesis of reductive product **3a**.

Table 4 Optimization of reductants and solvents for reductive cyclization reaction



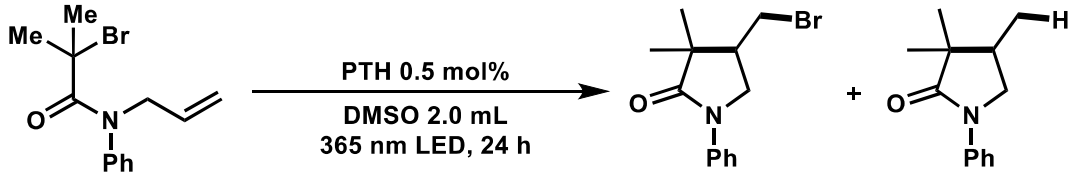
1a 2a 3a

Entry	Reductant	Solvent	NMR Yield		ratio
			2a	3a	2a:3a
1	-	DMF	57%	21%	73:27
2	-	DMA	45%	16%	74:26
3	-	NMP	16%	49%	25:75
4	Et_3N	NMP	14%	60%	19:81
5	$^nHex_3N$	NMP	25%	67%	27:73
6[a]	Hantzsch ester	NMP	8% (n.d.)	80% (72%)	9:91

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield. [a]1.5 equiv. of Hantzsch ester was used. n.d. = not detected.

Next, I optimized reductants and solvents for the reductive cyclization reaction. When the reaction in DMF or DMA carried out, the ATRC product **2a** was obtained as main product. Subsequently, I conducted the optimization of reductant in NMP. When $^nHex_3N$ was used, the yield of the reductive product **3a** was increased and the ratio of **2a**:**3a** was improved. Hantzsch ester shown in Entry 6 is used in many reduction reactions,[9] and I examined whether it could be applied to this reaction as well. As a result, the reductive product **3a** was obtained in 80% NMR yield and 72% isolated yield (entry 6, **2a**:**3a** = 9:91). The conditions shown in entry 6 were optimal conditions for reductive cyclization reaction.

Table 5 Control experiments



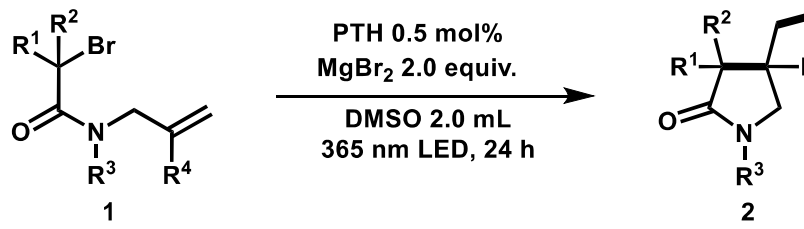
1a 2a 3a

Entry	Conditions	NMR Yield			ratio
		2a	3a	S.M.	2a:3a
1	Without PTH	-	-	>99%	-
2	In the dark	n.r.	n.r.	>99%	-

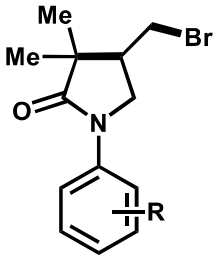
Finally, I conducted the control experiments. The reaction did not proceed in the absence of PTH or in the dark (entry 1,2). These results suggested that photocatalyst and visible light irradiation were necessary in this reaction.

1.3.2 Substrate scope

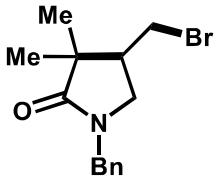
Table 6 Substrate scope for the ATRC reaction



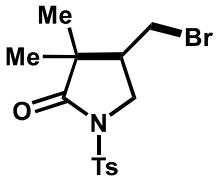
1 2



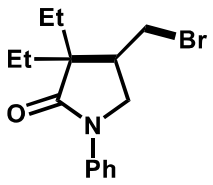
1b,2b: 2-F, 75%
1c,2c: 4-F, 80%
1d,2d: 4-I, 57%
1e,2e: 2-Me, 76%
1f,2f: 3-Me, 67%
1g,2g: 4-Me, 77%
1h,2h: 2-OMe, 72%
1i,2i: 3-OMe, 68%
1j,2j: 4-OMe, 76%



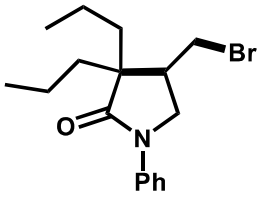
1k,2k: 79%



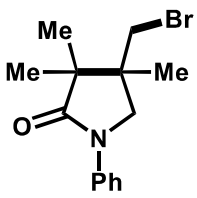
1l,2l: 80%



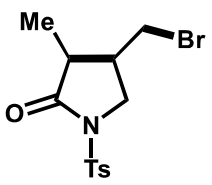
1m,2m: 39%



1n,2n: 52%



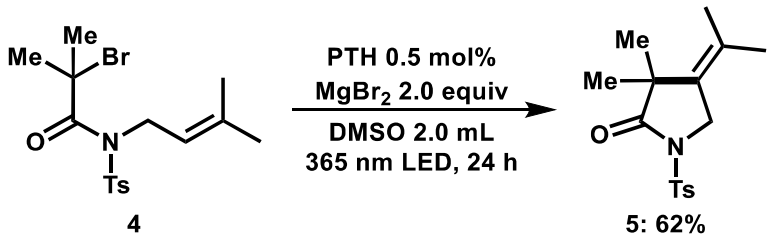
1o,2o: 82%



1p,2p: 52%
cis:*trans* = 2:98

With the optimal conditions, I investigated the substrate scope for the ATRC reaction (Table 6). First, α-bromoamide with aryl group substituted halogen or electron donating group (**2b-2j**), benzyl group (**2k**), tosyl group (**2l**) were tolerated, the desired ATRC product could be obtained in 57%-80% yield.

Subsequently, steric effect of alkyl group at carbonyl α-position was examined. As a result, when ^{n}ethyl substituted substrate (**1m**) or ^{n}propyl substituted substrate (**1n**) were used, the target products could be obtained in moderate yield. Surprisingly, it was possible to obtain ATRC product with vicinal quaternary carbon centers in 82% yield (**2o**). Further, when asymmetric α-bromocarbonyl compound (**1p**) was used, the desired product **2p** was obtained in 52% yield, and with excellent stereoselectivity.

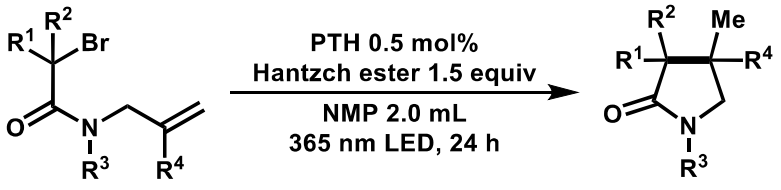


4 5: 62%

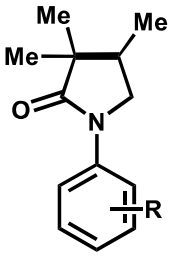
Scheme 6 The reaction of α-bromo carbonyl compound **4**

When the reaction using substrate **4** was carried out, the ATRC product could not be obtained, and Heck-type product **5** could be obtained in 62% yield (Scheme 6).

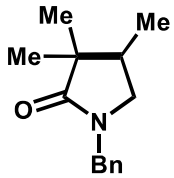
Table 7 Substrate Scope for reductive cyclization



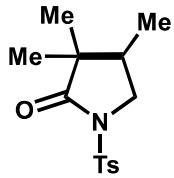
1 3



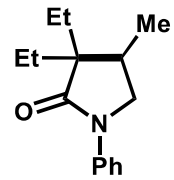
3b: 4-F, 71%
3c: 4-Cl, 59%
3d: 4-Br, 73%
3e: 4-I, 74%
3f: 2-Me, 34%
3g: 3-Me, 54%
3h: 4-Me, 78%
3i: 3-OMe, 70%
3j: 4-OMe, 73%



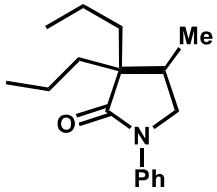
3k: 79%



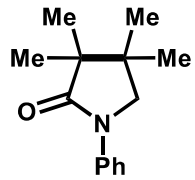
3l: 77%



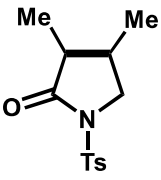
3m: 34%



3n: 86%



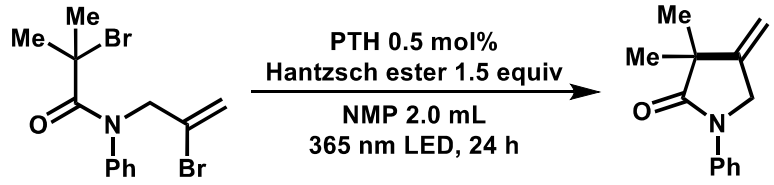
3o: 46%



3p: 66%
cis:*trans* = 8:92

With the optimal conditions, I investigated the substrate scope for reductive cyclization (Table 7). First, α-bromoamide with aryl group substituted halogen or electron donating group (**3b-3j**), benzyl

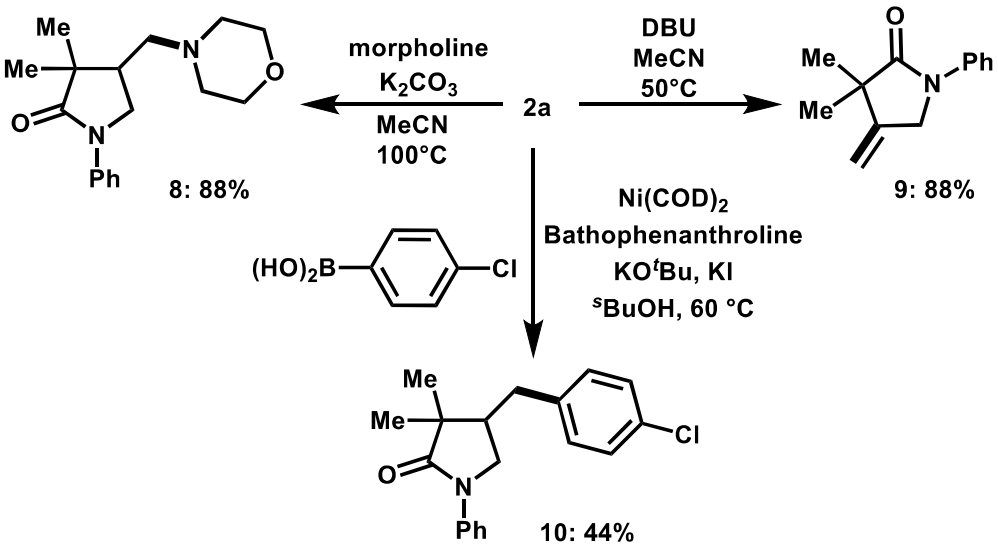
group (**3k**), tosyl group (**3l**) were tolerated,. Subsequently, steric effect of alkyl group at carbonyl α-position was examined. As a result, when ^{n}ethyl substituted substrate (**1m**) or ^{n}propyl substituted substrate (**1n**) were used, the target products could be obtained, but **3n** was obtained low yield. Next, it was possible to obtain reductive cyclization product with vicinal quaternary carbon centers in 46% yield (**3o**). Further, when asymmetric α-bromocarbonyl compound (**1p**) was used, the desired product **3p** was obtained in moderate yield, and with excellent stereoselectivity.



Scheme 7 The reaction of α-bromo carbonyl compound **6**

Also, when the reaction with substrate **6** was conducted, the product **7** eliminated HBr could be obtained in 77% isolated yield.

1.3.3 Application

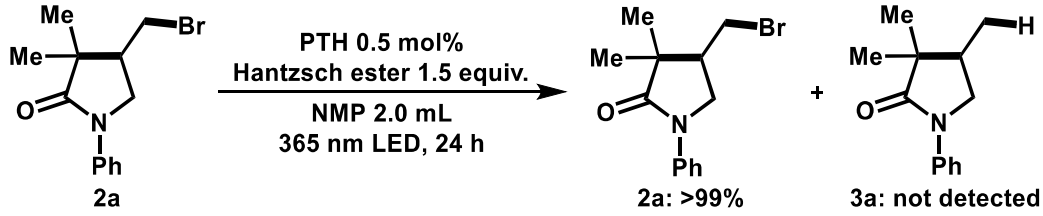


Scheme 8 Application of ATRC product **2a**

Various conversion reactions of ATRC product **2a** were performed. First, I conducted amination of ATRC product **2a**, the amination product **8** was obtained in 88% yield. Subsequently, when I used DBU (1,8-Diazabicyclo[5.4.0]-7-undecene) as a base, the elimination of HBr proceeded in 88% yield. Finally, I carried out Ni-catalyzed cross coupling with 4-chloro-phenyl boronic acid,[10] the coupling product **10** could be obtained with moderate yield.

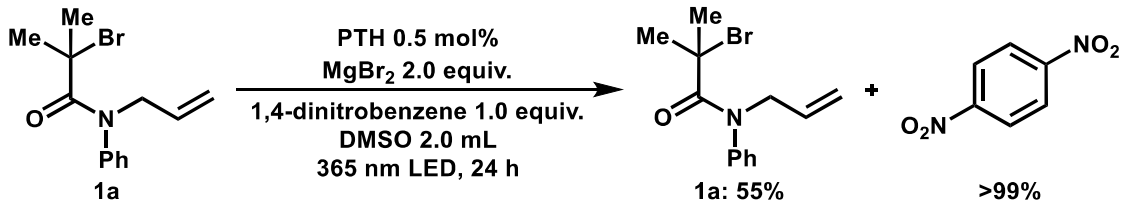
1.3.4 Mechanistic studies

Here, I conducted several mechanistic studies to propose mechanism of ATRC reaction and reductive cyclization.



Scheme 9 The reduction from ATRC product **2a**

In order to investigate whether the reductive cyclization product **3a** is formed from ATRC product **2a**, the reaction of ATRC product **2a** under visible light irradiation was performed (Scheme 9). As a result, reduction of **2a** did not proceed, ATRC compound **2a** fully recovered. This result suggested that the reductive cyclization product **3a** could not be formed from ATRC product **2a**.



Scheme 10 Single-electron transfer inhibition experiment

Subsequently, to investigate the involvement of the single-electron transfer process in this reaction, the reaction with 1,4-dinitrobenzene as a single-electron transfer inhibitor was attempted (Scheme 10). As a result, 1,4-dinitrobenzene and the substrate **1a** were recovered in 99% yield and 55% yield respectively, and ATRC product **2a** was not detected at all. This result suggested that the single-electron transfer reduction of the substrate **1a** proceeds in the presence of photoredox catalyst.

1.3.5 Proposed reaction mechanism

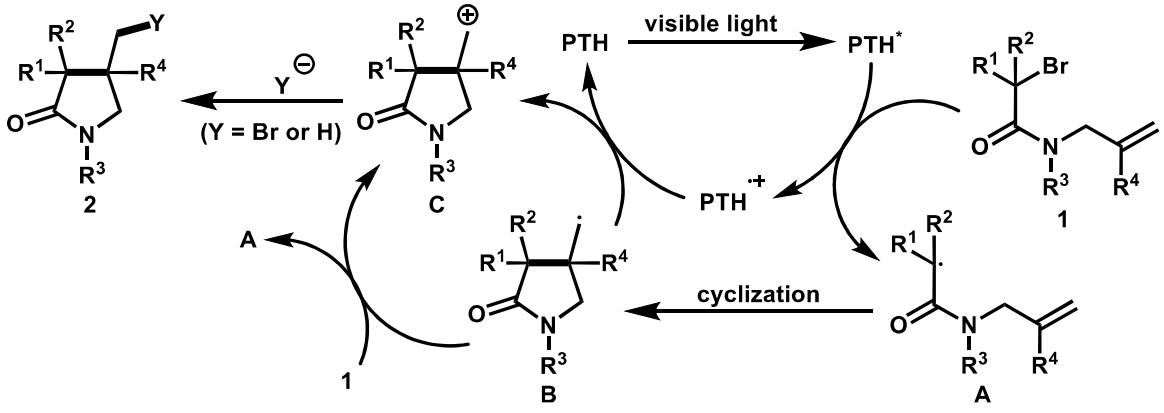


Figure 4 Proposed reaction mechanism

As a consequence of the control experiments and previous report,[11] a plausible catalytic cycle is proposed in Figure 4. First, PTH is excited by visible light and then single-electron reduction occurs to the α-bromocarbonyl compound **1** to produce alkyl radical species **A**. Then, intramolecular cyclization of **A** occurs, and subsequent single-electron transfer results in the formation of cationic intermediate **C** and the regeneration of PTH. Another path from intermediate **B** to intermediate **C** is a radical chain mechanism that reduces substrate **1** by single-electron transfer. Finally, intermediate **C** traps bromide ion (ATRC reaction) or hydride (reductive cyclization) to produce the product **2** or **3**.

1.4 Conclusion

In this study, I developed photoredox-catalyzed atom transfer radical cyclization of tertiary α-bromoamide. Also, I found that the reductive cyclization proceeds instead of ATRC reaction in the presence of Hantzsch ester as a reductant. These reactions have a wide range of α-bromoamides, and the synthesized ATRC product **2** is characterized by further conversion reactions.

1.5 Reference

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2011, *133*, 4160-4163.

1.6 Experimental section

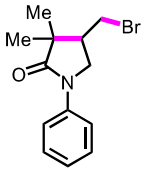
General procedure for ATRC reaction of alkyl halides.

PTH (0.70 mg, 2.5×10^{-3} mmol, 0.50 mol%) and 1 (0.50 mmol, 1.0 equiv) were added into a 5 mL screw-vial under air. Then, $MgBr_2$ (1.0 mmol, 2.0 equiv) and DMSO (2.0 mL) were added in glovebox. The reaction mixture was stirred upon 365 nm LED light irradiation in the photoreactor. After 24 hours, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **2**.

Characterization data of ATRC products

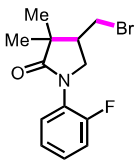
The compounds **2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2m, 2n, 2o, 5** are new compounds, whereas **2a**[1], **2k**[1], **2l**[1], **2p**[2] were reported elsewhere.

4-(bromomethyl)-3,3-dimethyl-1-phenylpyrrolidin-2-one (**2a**)



Following the general procedure above, using amide **1a** (84.2 mg, 0.30 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), $MgBr_2$ (110.1 mg, 0.60 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2a** (72%, 60.6 mg, 0.21 mmol) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66–7.64 (m, 2H), 7.40–7.36 (m, 2H), 7.16 (tt, J = 1.1, 5.2 Hz, 1H), 4.01 (dd, J = 7.5, 2.5 Hz, 1H), 3.60 (dd, J = 4.6, 5.5 Hz, 1H), 3.57 (dd, J = 8.6, 1.2 Hz, 1H), 3.40 (dd, J = 10.2, 0.7 Hz, 1H), 2.63–2.56 (m, 1H), 1.32 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.7, 139.3, 128.9, 124.7, 119.8, 50.6, 45.5, 45.3, 31.3, 24.4, 18.6.

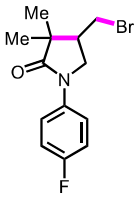
4-(bromomethyl)-1-(2-fluorophenyl)-3,3-dimethylpyrrolidin-2-one (**2b**)



Following the general procedure above, using amide **1b** (149.9 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), $MgBr_2$ (184.6 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2b** (75%, 111.9 mg, 0.37 mmol) as yellow oil; IR (cm^{-1}): 2965, 2870, 1698, 1610, 1588, 1501, 1458, 1400, 1306, 1267, 1233, 1099, 753; ^{1}H NMR (500 MHz,

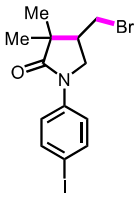
$CDCl_3$) δ: 7.40 (t, *J* = 7.8 Hz, 1H), 7.29–7.22 (m, 1H), 7.17–7.11 (m, 2H), 3.92 (dd, *J* = 7.4, 2.6 Hz, 1H), 3.60–3.55 (m, 2H), 3.40 (t, *J* = 10.3 Hz, 1H), 2.67-2.61 (m, 1H), 1.33 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.3, 157.0 (d, *J* = 250 Hz), 128.5 (d, *J* = 7.9 Hz), 128.0 (d, *J* = 1.0 Hz), 126.1 (d, *J* = 11.7 Hz), 124.5 (d, *J* = 3.6 Hz), 116.6 (d, *J* = 10.3 Hz), 52.0 (d, *J* = 4.1 Hz), 46.5, 44.1, 31.2, 24.7, 18.5; HRMS (ESI-MS) calcd. for C13H16OBrFN (M+H+): 300.0399; found 300.0399.

4-(bromomethyl)-1-(4-fluorophenyl)-3,3-dimethylpyrrolidin-2-one (**2c**)



Following the general procedure above, using amide **1c** (149.8 mg, 0.50 mmol), PTH (0.8 mg, 2.9×10^{-3} mmol), $MgBr_2$ (184.9 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2c** (80%, 119.2 mg, 0.40 mmol) as yellow solid; IR (cm^{-1}): 3026, 2961, 2898, 1685, 1506, 1395, 1357, 1298, 1247, 1218, 1093, 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63-7.58 (m, 2H), 7.09-7.04 (m, 2H), 3.97 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.60 (dd, *J* = 4.6, 5.6 Hz, 1H), 3.54 (dd, *J* = 8.8, 1.1 Hz, 1H), 3.40 (t, *J* = 10.4 Hz, 1H), 2.63-2.56 (m, 1H), 1.32 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.6, 159.0 (d, *J* = 245 Hz), 135.4 (d, *J* = 2.8 Hz), 121.5 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 2.3 Hz), 50.9, 45.5, 45.2, 31.2, 24.4, 18.6; HRMS (ESI-MS) calcd. for C13H16OBrFN (M+H+): 300.0399; found 300.0398.

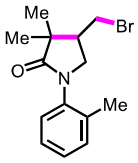
4-(bromomethyl)-1-(4-iodophenyl)-3,3-dimethylpyrrolidin-2-one (**2d**)



Following the general procedure above, using amide **1d** (203.9 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), MgBr2 (184.0 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2d** (57%, 115.5 mg, 0.28 mmol) as white solid; IR (cm^{-1}): 2965, 2867, 1683, 1582, 1476, 1388, 1360, 1294, 1171, 1000, 832, 811; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 9.0 Hz, 2H), 3.96 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.59 (dd, *J* = 4.7, 5.7 Hz, 1H), 3.52 (dd, *J* = 8.7, 0.9 Hz, 1H), 3.38 (t, *J* = 10.5 Hz, 1H), 2.61–2.55 (m, 1H), 1.31 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.8, 139.1, 137.8, 121.4, 88.2, 50.3, 45.39,

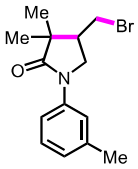
45.36, 31.0, 24.3, 18.6; HRMS (ESI-MS) calcd. for C13H19OBrIN (M+H+): 407.9460; found 407.9461.

4-(bromomethyl)-3,3-dimethyl-1-(o-tolyl)pyrrolidin-2-one (**2e**)



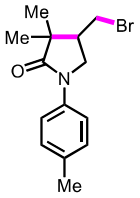
Following the general procedure above, using amide **1e** (148.7 mg, 0.50 mmol), PTH (1.2 mg, 4.4×10^{-3} mmol), $MgBr_2$ (183.6 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2e** (76%, 113.1 mg, 0.38 mmol) as yellow solid; IR (cm^{-1}): 2970, 2869, 1686, 1455, 1395, 1362, 1238, 1132, 1033, 945, 878, 763; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.25 (m, 1H), 7.22 (dd, *J* = 3.5, 2.1 Hz, 2H), 7.13-7.11 (m, 1H), 3.82 (dd, *J* = 7.4, 2.7 Hz, 1H), 3.61 (dd, *J* = 4.7, 5.3 Hz, 1H), 3.47 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.41 (dd, *J* = 10.3, 0.6 Hz, 1H), 2.70–2.64 (m, 1H), 2.20 (s, 3H), 1.33 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.6, 137.1, 135.6, 131.2, 128.0, 126.9, 126.7, 52.7, 46.8, 44.3, 31.4, 24.4, 18.6, 18.0; HRMS (ESI-MS) calcd. for C14H19OBrN (M+H+): 296.0650; found 296.0651.

4-(bromomethyl)-3,3-dimethyl-1-(m-tolyl)pyrrolidin-2-one (**2f**)



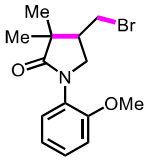
Following the general procedure above, using amide **1f** (148.3 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), $MgBr_2$ (184.2 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2f** (67%, 99.4 mg, 0.34 mmol) as white solid; IR(cm^{-1}): 2967, 2868, 1685, 1484, 1395, 1363, 1289, 1238, 1104, 887, 833, 771; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.51 (brs, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 3.99 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.60 (dd, *J* = 4.7, 5.5 Hz, 1H), 3.56 (dd, *J* = 9.0, 0.8 Hz, 1H), 3.40 (t, *J* = 10.3 Hz, 1H), 2.61–2.55 (m, 1H), 2.37 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.7, 139.2, 138.8, 128.7, 125.5, 120.6, 116.9, 50.7, 45.5, 45.3, 31.3, 24.4, 21.6, 18.6; HRMS (ESI-MS) calcd. for C14H19OBrN (M+H+): 296.0650; found 296.0651.

4-(bromomethyl)-3,3-dimethyl-1-(p-tolyl)pyrrolidin-2-one (**2g**)



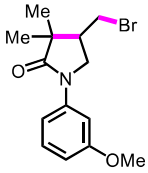
Following the general procedure above, using amide **1g** (148.6 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), $MgBr_2$ (184.7 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2g** (77%, 113.9 mg, 0.38 mmol) as brown solid; IR (cm^{-1}): 3025, 2968, 2870, 1686, 1508, 1391, 1295, 1246, 1098, 826, 805; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 3.97 (dd, J = 7.5, 2.5 Hz, 1H), 3.59 (dd, J = 4.6, 5.4 Hz, 1H), 3.54 (t, J = 9.0 Hz, 1H), 3.39 (t, J = 10.3 Hz, 1H), 2.61–2.55 (m, 1H), 2.32 (s, 3H), 1.31 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.5, 136.8, 134.4, 129.4, 119.8, 50.7, 45.5, 45.2, 31.3, 24.4, 20.9, 18.6; HRMS (ESI-MS) calcd. for C14H19OBrN ($M+H^+$): 296.0650; found 296.0651.

4-(bromomethyl)-1-(2-methoxyphenyl)-3,3-dimethylpyrrolidin-2-one (**2h**)



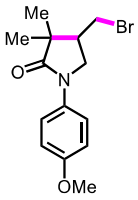
Following the general procedure above, using amide **1h** (156.4 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), $MgBr_2$ (183.7 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2h** (72%, 112.7 mg, 0.36 mmol) as yellow solid; IR (cm^{-1}): 3069, 2960, 2906, 1686, 1503, 1458, 1410, 1279, 1237, 1125, 1095, 1025, 878, 747; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.28 (dd, J = 1.6 Hz, 1H), 7.23 (dd, J = 1.6, 6.0 Hz, 1H), 6.98 (dd, J = 1.2, 6.4 Hz, 1H), 6.95 (dd, J = 1.2, 7.2 Hz, 1H), 3.83 (s, 3H), 3.82 (dd, J = 7.3, 2.6 Hz, 1H), 3.60 (dd, J = 4.7, 5.4 Hz, 1H), 3.53 (dd, J = 8.2, 1.7 Hz, 1H), 3.43 (dd, J = 10.1, 0.7 Hz, 1H), 2.65–2.58 (m, 1H), 1.32 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5, 154.9, 128.85, 128.80, 127.0, 120.9, 112.0, 55.7, 51.8, 46.7, 44.1, 31.8, 24.3, 18.6; HRMS (ESI-MS) calcd. for C14H19O2BrN ($M+H^+$): 312.0599; found 312.0599.

4-(bromomethyl)-1-(3-methoxyphenyl)-3,3-dimethylpyrrolidin-2-one (**2i**)



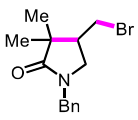
Following the general procedure above, using amide **1i** (156.7 mg, 0.50 mmol), PTH (0.7 mg, 2.5×10^{-3} mmol), $MgBr_2$ (184.5 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2i** (68%, 105.8 mg, 0.34 mmol) as yellow oil; IR (cm^{-1}): 2963, 2869, 1694, 1599, 1493, 1393, 1209, 1165, 1039, 850, 770; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.45 (brs, 1H), 7.26 (t, J = 8.1 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 3.99 (dd, J = 7.8, 2.0 Hz, 1H), 3.81 (s, 3H), 3.59–3.56 (m, 1H), 3.53 (d, J = 9.2 Hz, 1H), 3.39 (t, J = 10.4 Hz, 1H), 2.60 2.54 (m, 1H), 1.31 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.9, 160.1, 140.5, 129.6, 111.6, 110.6, 105.6, 55.4, 50.7, 45.5, 45.4, 31.2, 24.4, 18.6; HRMS (ESI-MS) calcd. for C14H19O2BrN ($M+H^+$): 312.0599; found 312.0599.

4-(bromomethyl)-1-(4-methoxyphenyl)-3,3-dimethylpyrrolidin-2-one (**2j**)



Following the general procedure above, using amide **1j** (156.7 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), $MgBr_2$ (184.3 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2j** (76%, 119.0 mg, 0.38 mmol) as brown solid; IR (cm^{-1}): 2963, 2860, 1685, 1508, 1393, 1364, 1278, 1244, 1099, 1025, 875, 816; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.54-7.51 (m, 2H), 6.91-6.88 (m, 2H), 3.95 (dd, J = 7.5, 2.4 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, J = 4.5, 5.6 Hz, 1H), 3.52 (dd, J = 8.8, 1.1 Hz, 1H), 3.39 (dd, J = 10.1, 0.7 Hz, 1H), 2.61–2.55 (m, 1H), 1.31 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.3, 156.6, 132.5, 121.5, 114.1, 55.5, 51.0, 45.6, 45.1, 31.4, 24.4, 18.6; HRMS (ESI-MS) calcd. for C14H19O2BrN ($M+H^+$): 312.0599; found 312.0599.

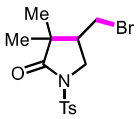
1-benzyl-4-(bromomethyl)-3,3-dimethylpyrrolidin-2-one (**2k**)



Following the general procedure above, using amide **1k** (148.3 mg, 0.50 mmol), PTH (0.8 mg,

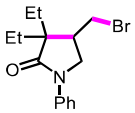
2.9×10^{-3} mmol), $MgBr_2$ (184.3 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2k** (79%, 117.0 mg, 0.39 mmol) as brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.27 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 2H), 4.54 (d, *J* = 14.6 Hz, 1H), 4.38 (d, *J* = 14.6 Hz, 1H) 3.49 (dd, *J* = 4.8, 5.2 Hz, 1H), 3.38 (dd, *J* = 7.6, 2.4 Hz, 1H), 3.25 (t, *J* = 10.4 Hz, 1H), 2.90 (t, *J* = 9.4 Hz, 1H), 2.47–2.40 (m, 1H), 1.26 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5, 136.4, 128.8, 128.1, 127.7, 48.9, 46.1, 44.1, 31.5, 24.3, 18.4.

4-(bromomethyl)-3,3-dimethyl-1-tosylpyrrolidin-2-one (**2l**)



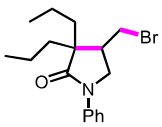
Following the general procedure above, using amide **1l** (179.7 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), $MgBr_2$ (184.0 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2l** (80%, 144.6 mg, 0.40 mmol) as brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.15 (dd, *J* = 7.5, 2.8 Hz, 1H), 3.47 (dd, *J* = 8.7, 1.7 Hz, 1H), 3.44 (dd, *J* = 4.7, 5.6 Hz, 1H), 3.20 (t, *J* = 10.4 Hz, 1H), 2.44 (s, 3H), 1.17 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.9, 145.4, 134.8, 129.8, 128.0, 48.8, 45.5, 45.1, 29.8, 23.5, 21.8, 17.9.

4-(bromomethyl)-3,3-diethyl-1-phenylpyrrolidin-2-one (**2m**)



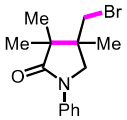
Following the general procedure above, using amide **1m** (155.4 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), $MgBr_2$ (184.7 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2m** (39%, 60.3 mg, 0.19 mmol) as yellow solid; IR (cm^{-1}): 2963, 2931, 2876, 1682, 1595, 1490, 1391, 1295, 1228, 1113, 942, 826, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 1.2, 7.6 Hz, 2H), 7.39–7.36 (m, 2H), 7.16 (tt, *J* = 1.3, 1.0, 5.1 Hz, 1H), 4.01 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.63 (dd, *J* = 4.4, 5.7 Hz, 1H), 3.58 (dd, *J* = 8.9, 0.7 Hz, 1H), 3.49 (dd, *J* = 10.1, 1.2 Hz, 1H), 2.85–2.79 (m, 1H), 1.88–1.80 (m, 1H), 1.70–1.58 (m, 2H), 1.53–1.47 (m, 1H), 1.00–0.91 (m, 6H); ^{13}C NMR (125 MHz, CDCl3) δ: 176.0, 139.3, 128.9, 124.7, 119.9, 52.4, 51.2, 41.3, 31.9, 27.4, 24.8, 9.1, 8.9; HRMS (ESI-MS) calcd. for C15H21OBrN (M+H$^+$): 310.0807; found 310.0807.

4-(bromomethyl)-1-phenyl-3,3-dipropylpyrrolidin-2-one (**2n**)



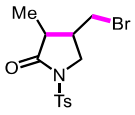
Following the general procedure above, using amide **1n** (169.5 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), $MgBr_2$ (184.1 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2n** (52%, 88.1 mg, 0.26 mmol) as brown oil; IR (cm^{-1}): 2957, 2871, 1690, 1597, 1496, 1391, 1295, 1221, 1112, 898, 755; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.65 (dd, J = 0.9, 7.0 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.15 (td, J = 1.1, 6.3, Hz, 1H), 3.99 (dd, J = 8.2, 1.3 Hz, 1H), 3.63 (dd, J = 4.3, 5.7 Hz, 1H), 3.57 (t, J = 9.4 Hz, 1H), 3.47 (t, J = 10.7 Hz, 1H), 2.83 2.77 (m, 1H), 1.75–1.69 (m, 1H), 1.60–1.51 (m, 2H), 1.42–1.27 (m, 5H), 0.98–0.92 (m, 3H), 0.90–0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3, 139.3, 128.9, 124.6, 119.9, 52.1, 51.2, 42.0, 37.8, 34.8, 32.0, 17.86, 17.83, 14.7, 14.6; HRMS (ESI-MS) calcd. for C17H25OBrN ($M+H^+$): 338.1120; found 338.1120.

4-(bromomethyl)-3,3,4-trimethyl-1-phenylpyrrolidin-2-one (**2o**)



Following the general procedure above, using amide **1o** (147.8 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), $MgBr_2$ (183.8 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2o** (82%, 121.0 mg, 0.41 mmol) as yellow oil; IR (cm^{-1}): 2972, 2934, 1682, 1595, 1482, 1399, 1375, 1312, 1245, 1100, 899, 859, 754; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.58 (d, J = 10.3 Hz, 1H), 3.48 (d, J = 10.0 Hz, 1H), 3.45 (d, J = 10.3 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.7, 139.5, 129.0, 124.6, 119.8, 55.9, 48.3, 42.3, 40.2, 20.5, 19.9, 19.4; HRMS (ESI-MS) calcd. for C14H19OBrN ($M+H^+$): 296.0650; found 296.0650.

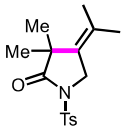
4-(bromomethyl)-3-methyl-1-tosylpyrrolidin-2-one (**2p**)



Following the general procedure above, using amide **1p** (174.2 mg, 0.50 mmol), PTH (0.7 mg, 2.5×10^{-3} mmol), $MgBr_2$ (184.0 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **2p** (52%, 90.5 mg, 0.26 mmol, cis:trans = 2:98) as white

solid; ^{1}H NMR (500 MHz, benzene-d_6) δ: 8.02 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.2 Hz, 2H), 3.76 (dd, J = 7.6, 2.3 Hz, 1H), 3.02 (dd, J = 9.3, 0.5 Hz, 1H), 2.46 (dd, J = 4.3, 6.1 Hz, 1H), 2.22 (dd, J = 8.2, 2.3 Hz, 1H), 1.72 (s, 3H), 1.30 (dq, J = 7.0, 3.5, 3.6, 3.4 Hz, 1H), 1.24–1.16 (m, 1H), 0.53 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1, 145.4, 135.0, 129.8, 128.2, 49.6, 42.8, 41.9, 32.8, 21.8, 13.6.

3,3-dimethyl-4-(propan-2-ylidene)-1-tosylpyrrolidin-2-one (**5**)



Following the general procedure above, using amide **4** (194.8 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), $MgBr_2$ (183.9 mg, 1.0 mmol), and dried DMSO (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **5** (62%, 94.9 mg, 0.31 mmol) as yellow solid; IR (cm^{-1}): 2965, 2926, 1722, 1595, 1457, 1355, 1240, 1163, 1128, 1089, 870, 815, 759, 704; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.35 (brs, 2H), 2.44 (s, 3H), 1.76 (s, 3H), 1.62 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.4, 145.2, 135.1, 129.7, 128.1, 127.3, 49.1, 45.7, 24.4, 21.8, 21.4, 20.3; HRMS (ESI-MS) calcd. for C15H20ON ($M+H^+$): 230.1545; found 230.1545.

Procedures and Characterization data of reduction products

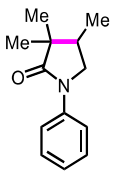
General procedure for reductive reaction of **1**.

PTH (0.70 mg, 2.5×10^{-3} mmol, 0.50 mol%), **1** (0.50 mmol, 1.0 equiv), Hantzsch ester (0.75 mmol, 1.5 equiv), and NMP (2.0 mL) were added into a 5 mL screw-vial in glovebox. The mixture was stirred upon 365 nm LED light irradiation in the photoreactor. After 24 hours, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **3**.

Characterization data of reductive cyclization products

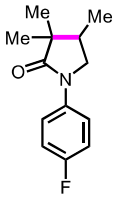
The compounds **3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3m, 3n, 3o, 7** are new compounds, whereas **3a**[3], **3l**[4], **3p**[5] were reported elsewhere.

3,3,4-trimethyl-1-phenylpyrrolidin-2-one (**3a**)



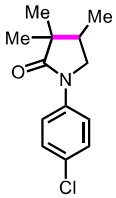
Following the general procedure above, using amide **1a** (84.3 mg, 0.30 mmol), PTH (0.7 mg, 2.5×10^{-3} mmol), Hantzsch ester (114.5 mg, 0.45 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3a** (72%, 43.7 mg, 0.21 mmol) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66–7.63 (m, 2H), 7.38–7.34 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 3.78 (dd, *J* = 7.5, 1.9 Hz, 1H), 3.38 (t, *J* = 9.3 Hz, 1H), 2.23–2.18 (m, 1H), 1.22 (s, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.3, 128.8, 124.2, 119.6, 52.3, 44.7, 37.7, 23.7, 18.4, 12.4.

1-(4-fluorophenyl)-3,3,4-trimethylpyrrolidin-2-one (**3b**)



Following the general procedure above, using amide **1c** (150.4 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), Hantzsch ester (190.9 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3b** (71%, 78.7 mg, 0.36 mmol) as white solid; IR (cm^{-1}): 2962, 2852, 1678, 1505, 1395, 1353, 1297, 1278, 1213, 1160, 1109, 1008, 830, 721; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (dd, *J* = 4.8, 4.4 Hz, 2H), 7.05 (dd, *J* = 8.4, 0.7 Hz, 2H), 3.74 (dd, *J* = 7.6, 1.8 Hz, 1H), 3.35 (t, *J* = 9.3 Hz, 1H), 2.23–2.18 (m, 1H), 1.22 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.2, 159.3 (d, *J* = 244 Hz), 135.9 (d, *J* = 2.9 Hz), 121.3 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 2.3 Hz), 52.5, 44.5, 37.7, 23.7, 18.4, 12.4; HRMS (ESI-MS) calcd. for C13H17OFN ($M+H^+$): 222.1294; found 222.1294.

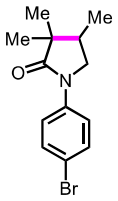
1-(4-chlorophenyl)-3,3,4-trimethylpyrrolidin-2-one (**3c**)



Following the general procedure above, using amide **1q** (157.7 mg, 0.50 mmol), PTH (0.8 mg, 2.9×10^{-3} mmol), Hantzsch ester (190.1 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3c** (59%, 69.9 mg, 0.29 mmol) as white solid; IR (cm^{-1}): 2963, 2861, 1685, 1592, 1491, 1418, 1391, 1348, 1293, 1213, 1082, 1006, 868, 823; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (dt, *J* = 3.2, 2.2, 4.6 Hz, 2H), 7.32 (dt, *J* = 3.2, 2.2, 4.6 Hz, 2H), 3.75 (dd, *J* = 7.6, 1.8 Hz, 1H), 3.35 (t, *J* = 9.3 Hz, 1H), 2.23–2.18 (m, 1H), 1.21 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.4, 138.4, 129.2, 128.8, 120.7, 52.2, 44.7, 37.6, 23.6, 18.4, 12.3; HRMS

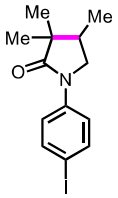
(ESI-MS) calcd. for C13H17OClN ($M+H^+$): 238.0999; found 238.0999.

1-(4-bromophenyl)-3,3,4-trimethylpyrrolidin-2-one (**3d**)



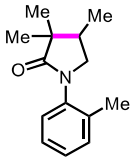
Following the general procedure above, using amide **1r** (181.1 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), Hantzsch ester (189.5 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3d** (73%, 103.3 mg, 0.37 mmol) as yellow oil; IR (cm^{-1}): 2963, 2869, 1691, 1588, 1482, 1391, 1348, 1291, 1213, 1073, 1004, 869, 823, 722; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.55 (dd, J = 2.2, 4.7 Hz, 2H), 7.45 (dd, J = 2.2, 4.7 Hz, 2H), 3.74 (dd, J = 7.6, 1.9 Hz, 1H), 3.33 (t, J = 9.4 Hz, 1H), 2.24–2.16 (m, 1H), 1.21 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.4, 138.9, 131.7, 121.0, 116.8, 52.1, 44.7, 37.5, 23.6, 18.4, 12.3; HRMS (ESI-MS) calcd. for C13H17OBrN ($M+H^+$): 282.0494; found 282.0495.

1-(4-iodophenyl)-3,3,4-trimethylpyrrolidine-2-one (**3e**)



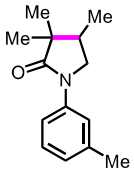
Following the general procedure above, using amide **1d** (204.7 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3} mmol), Hantzsch ester (190.4 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3e** (74%, 122.2 mg, 0.37 mmol) as yellow solid; IR (cm^{-1}): 3102, 2963, 1685, 1583, 1479, 1389, 1346, 1290, 1213, 1159, 999, 870, 820, 721; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.66–7.63 (m, 2H), 7.45–7.42 (m, 2H), 3.73 (dd, J = 7.6, 1.9 Hz, 1H), 3.33 (t, J = 9.3 Hz, 1H), 2.23–2.16 (m, 1H), 1.21 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.4, 139.6, 137.7, 121.3, 87.6, 52.0, 44.7, 37.5, 23.6, 18.4, 12.4; HRMS (ESI-MS) calcd. for C13H17OIN ($M+H^+$): 330.0355; found 330.0355.

3,3,4-trimethyl-1-(o-tolyl)pyrrolidin-2-one (**3f**)



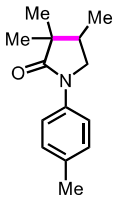
Following the general procedure above, using amide **1e** (148.7 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), Hantzsch ester (190.0 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3f** (34%, 37.6 mg, 0.17 mmol) as yellow oil; IR (cm^{-1}): 2960, 2870, 1689, 1492, 1402, 1349, 1276, 1212, 1131, 762, 726; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.24 (d, J = 4.5 Hz, 1H), 7.21-7.19 (m, 2H), 7.10–7.08 (m, 1H), 3.61 (dd, J = 7.5, 2.2 Hz, 1H), 3.28 (dd, J = 8.9, 0.7 Hz, 1H), 2.32–2.25 (m, 1H), 2.20 (s, 3H), 1.22 (s, 3H), 1.08 (d, J = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.0, 137.7, 135.6, 131.1, 127.7, 126.8, 126.7, 54.6, 43.5, 39.1, 23.7, 18.4, 18.0, 12.6; HRMS (ESI MS) calcd. for C14H20ON ($M+H^+$): 218.1545; found 218.1545.

3,3,4-trimethyl-1-(m-tolyl)pyrrolidin-2-one (**3g**)



Following the general procedure above, using amide **1f** (147.9 mg, 0.50 mmol), PTH (1.2 mg, 4.4×10^{-3} mmol), Hantzsch ester (189.6 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3g** (54%, 58.6 mg, 0.27 mmol) as white solid; IR (cm^{-1}): 2957, 2857, 1683, 1604, 1478, 1389, 1347, 1301, 1261, 1174, 1132, 1104, 858, 797, 694; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (brs, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.24–7.22 (m, 1H), 6.95 (d, J = 8.2 Hz, 1H), 3.77 (dd, J = 7.5, 2.0 Hz, 1H), 3.37 (t, J = 9.3 Hz, 1H), 2.36 (s, 3H), 2.23–2.15 (m, 1H), 1.21 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.3, 139.7, 138.7, 128.6, 125.0, 120.4, 116.6, 52.4, 44.7, 37.7, 23.7, 21.7, 18.3, 12.4; HRMS (ESI-MS) calcd. for C14H20ON ($M+H^+$): 218.1545; found 218.1545.

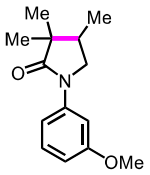
3,3,4-trimethyl-1-(p-tolyl)pyrrolidin-2-one (**3h**)



Following the general procedure above, using amide **1g** (148.4 mg, 0.50 mmol), PTH (1.1 mg, 4.0×10^{-3}

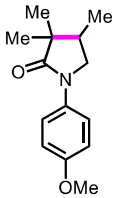
mmol), Hantzsch ester (190.2 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3h** (78%, 84.9 mg, 0.39 mmol) as white solid; IR (cm^{-1}): 2961, 2856, 1692, 1511, 1477, 1391, 1350, 1295, 1177, 1089, 957, 814, 721; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53–7.50 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 3.75 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.35 (t, *J* = 9.3 Hz, 1H), 2.31 (s, 3H), 2.23–2.15 (m, 1H), 1.21 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.1, 137.3, 133.8, 129.3, 119.6, 52.4, 44.6, 37.7, 23.7, 20.9, 18.4, 12.4; HRMS (ESI-MS) calcd. for C14H20ON ($M+H^+$): 218.1545; found 218.1545.

1-(3-methoxyphenyl)-3,3,4-trimethylpyrrolidin-2-one (**3i**)



Following the general procedure above, using amide **1i** (156.1 mg, 0.50 mmol), PTH (1.2 mg, 4.4×10^{-3} mmol), Hantzsch ester (189.9 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3i** (70%, 81.7 mg, 0.35 mmol) as brown oil; IR (cm^{-1}): 2961, 2871, 1691, 1599, 1482, 1394, 1351, 1228, 1206, 1171, 1102, 1040, 768, 686; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (brs, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 7.7, 1.7 Hz, 1H), 3.35 (t, *J* = 9.5 Hz, 1H), 2.22–2.17 (m, 1H), 1.22 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.5, 160.0, 141.1, 129.4, 111.3, 110.3, 105.3, 55.4, 52.4, 44.9, 37.5, 23.7, 18.4, 12.4; HRMS (ESI-MS) calcd. for C14H20O2N ($M+H^+$): 234.1494; found 234.1495.

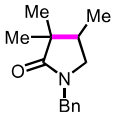
1-(4-methoxyphenyl)-3,3,4-trimethylpyrrolidin-2-one (**3j**)



Following the general procedure above, using amide **1j** (155.8 mg, 0.50 mmol), PTH (0.8 mg, 2.9×10^{-3} mmol), Hantzsch ester (189.3 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3j** (73%, 85.1 mg, 0.36 mmol) as white solid; IR (cm^{-1}): 2963, 2867, 1684, 1508, 1398, 1351, 1241, 1097, 1029, 833; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54 (dd, *J* = 3.4, 5.8 Hz, 2H), 6.89 (dd, *J* = 3.3, 5.9 Hz, 2H), 3.79 (s, 3H), 3.75–3.71 (m, 1H), 3.36–3.32 (m, 1H), 2.22–2.17 (m, 1H), 1.21 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.9, 156.3, 133.1, 121.3, 114.0, 55.5, 52.7, 44.5, 37.8, 23.7, 18.4, 12.4; HRMS (ESI-MS) calcd. for

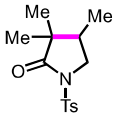
C14H20O2N ($M+H^+$): 234.1494; found 234.1496.

1-benzyl-3,3,4-trimethylpyrrolidin-2-one (**3k**)



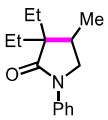
Following the general procedure above, using amide **1k** (148.5 mg, 0.50 mmol), PTH (0.6 mg, 2.2×10^{-3} mmol), Hantzsch ester (189.6 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3k** (79%, 86.0 mg, 0.40 mmol) as yellow oil; IR (cm^{-1}): 2961, 2869, 1680, 1425, 1265, 1079, 942, 750, 699; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.25 (d, J = 2.7 Hz, 1H), 7.18 (dd, J = 1.7, 5.0 Hz, 2H), 4.47 (dd, J = 3.0, 11.7 Hz, 1H), 4.37 (dd, J = 3.2, 11.4 Hz, 1H), 3.15 (dd, J = 7.6, 2.0 Hz, 1H), 2.73–2.68 (m, 1H), 2.04–1.98 (m, 1H), 1.14 (d, J = 3.0 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 180.0, 136.9, 128.7, 128.1, 127.5, 50.6, 46.6, 43.3, 38.3, 23.6, 18.2, 12.4; HRMS (ESI-MS) calcd. for C14H20ON ($M+H^+$): 218.1545; found 218.1545.

3,3,4-trimethyl-1-tosylpyrrolidin-2-one (**3l**)



Following the general procedure above, using amide **1l** (179.9 mg, 0.50 mmol), PTH (0.9 mg, 3.3×10^{-3} mmol), Hantzsch ester (190.2 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3l** (77%, 107.7 mg, 0.38 mmol) as white solid; IR (cm^{-1}): 2970, 1721, 1685, 1485, 1349, 1323, 1226, 1159, 1107, 875, 815, 778, 748; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.96 (dd, J = 7.4, 2.8 Hz 1H), 3.26 (t, J = 9.2 Hz, 1H), 2.43 (s, 3H), 2.11–2.06 (m, 1H), 1.06 (s, 3H), 0.97 (d, J = 6.4 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.5, 145.1, 135.1, 129.7, 127.9, 50.6, 44.9, 37.6, 22.5, 21.7, 17.5, 12.0.

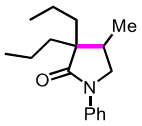
3,3-diethyl-4-methyl-1-phenylpyrrolidin-2-one (**3m**)



Following the general procedure above, using amide **1m** (155.1 mg, 0.50 mmol), PTH (0.7 mg, 2.5×10^{-3} mmol), Hantzsch ester (190.3 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3m** (34%, 39.3 mg, 0.17 mmol) as brown oil; IR (cm^{-1}): 2964, 2878, 1688, 1596, 1489, 1458, 1392, 1356, 1293, 1229, 1102, 757, 689; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.66 (dd, J = 1.1, 7.6 Hz, 2H), 7.38–7.34 (m, 2H), 7.14–7.10 (m, 1H), 3.79 (dd, J = 8.0, 1.4 Hz, 1H), 3.39

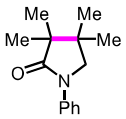
(t, J = 9.2 Hz, 1H), 2.49–2.41 (m, 1H), 1.81–1.74 (m, 1H), 1.67-1.46 (m, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.94–0.90 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.6, 139.8, 128.8, 124.2, 119.7, 52.8, 51.2, 33.3, 27.0, 24.4, 12.9, 8.9, 8.8; HRMS (ESI-MS) calcd. for C15H22ON ($M+H^+$): 232.1701; found 232.1701.

4-methyl-1-phenyl-3,3-dipropylpyrrolidin-2-one (**3n**)



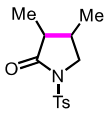
Following the general procedure above, using amide **1n** (168.7 mg, 0.50 mmol), PTH (0.6 mg, 2.2×10^{-3} mmol), Hantzsch ester (190.4 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3n** (86%, 111.2 mg, 0.43 mmol) as yellow oil; IR (cm^{-1}): 2956, 2871, 1687, 1597, 1492, 1392, 1294, 1220, 1111, 756, 689; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (dd, J = 1.0, 7.7 Hz, 2H), 7.37–7.34 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 3.77 (dd, J = 8.1, 1.3 Hz, 1H), 3.38 (t, J = 9.2 Hz, 1H), 2.46–2.41 (m, 1H), 1.69-1.63 (m, 1H), 1.54–1.48 (m, 2H), 1.40–1.29 (m, 5H), 1.11 (d, J = 7.1 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.8, 139.8, 128.8, 124.1, 119.6, 52.8, 50.9, 37.6, 34.5, 34.0, 17.7, 17.6, 14.9, 14.8, 12.9; HRMS (ESI-MS) calcd. for C17H26ON ($M+H^+$): 260.2014; found 260.2014.

3,3,4,4-tetramethyl-1-phenylpyrrolidin-2-one (**3o**)



Following the general procedure above, using amide **1o** (147.8 mg, 0.50 mmol), PTH (0.6 mg, 2.2×10^{-3} mmol), Hantzsch ester (189.6 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **3o** (46%, 49.9 mg, 0.23 mmol) as white solid; IR (cm^{-1}): 3064, 2967, 2870, 1682, 1595, 1484, 1403, 1376, 1313, 1189, 1098, 754, 688; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (dd, J = 1.1, 7.6 Hz, 2H), 7.36 (dd, J = 7.4, 1.3 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 3.49 (s, 2H), 1.09 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.2, 140.0, 128.9, 124.2, 119.6, 58.9, 47.9, 38.1, 22.9, 19.7; HRMS (ESI-MS) calcd. for C14H20ON ($M+H^+$): 218.1545; found 218.1545.

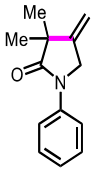
3,4-dimethyl-1-tosylpyrrolidin-2-one (**3p**)



Following the general procedure above, using amide **1p** (173.7 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), Hantzsch ester (190.0 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light

irradiation for 24 h, yielded the product **3p** (66%, 88.7 mg, 0.33 mmol, cis:trans = 8:92) as white solid; IR (cm^{-1}): 2967, 1726, 1351, 1326, 1156, 1115, 901, 814, 757, 713; ^1H NMR (500 MHz, benzene-d_6) δ: 8.07 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 3.61 (dd, *J* = 7.4, 2.3 Hz, 1H), 2.70 (t, *J* = 9.7 Hz, 1H), 1.74 (s, 3H), 1.13–1.07 (m, 1H), 1.03-0.96 (m, 1H), 0.65 (d, *J* = 6.9 Hz, 3H), 0.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.5, 145.1, 135.3, 129.7, 128.1, 52.2, 45.8, 35.7, 21.7, 16.5, 12.9.

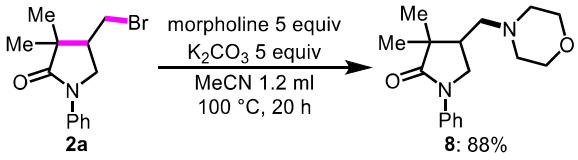
3,3-dimethyl-4-methylene-1-phenylpyrrolidin-2-one (**7**)



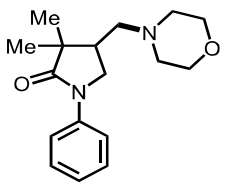
Following the general procedure above, using amide **6** (181.0 mg, 0.50 mmol), PTH (1.0 mg, 3.6×10^{-3} mmol), Hantzsch ester (189.6 mg, 0.75 mmol), and dried NMP (2.0 mL) upon 365 nm LED light irradiation for 24 h, yielded the product **7** (77%, 77.7 mg, 0.39 mmol) as yellow oil; IR (cm^{-1}): 2968, 2929, 2867, 1697, 1664, 1596, 1492, 1469, 1379, 1296, 1274, 1099, 896, 758, 689; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.72-7.70 (m, 2H), 7.39 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.17-7.14 (m, 1H), 5.15 (t, *J* = 2.0 Hz, 1H), 5.13 (t, *J* = 2.3 Hz, 1H), 4.45 (t, *J* = 2.2 Hz, 2H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.8, 147.7, 139.2, 129.0, 124.6, 119.8, 107.1, 51.4, 45.9, 25.2; HRMS (ESI-MS) calcd. for C13H16ON ($M+H^+$): 202.1232; found 202.1232.

Applications

3,3-dimethyl-4-(morpholinomethyl)-1-phenylpyrrolidin-2-one (**8**)

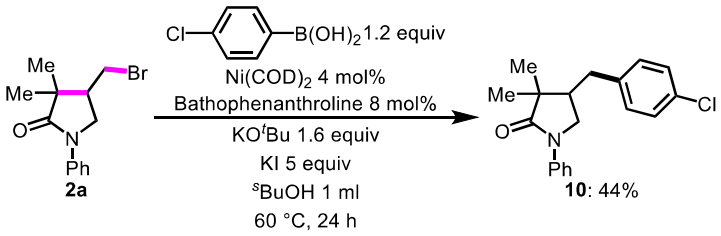


2a (0.30 mmol, 1.0 equiv), K_2CO_3 (1.5 mmol, 5.0 equiv) were sequentially added under air to a drum vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), morpholine (1.5 mmol, 5.0 equiv), and dried MeCN (1.2 mL) were added by syringe and the resulting mixture was vigorously stirred under nitrogen atmosphere at 100 °C for 20 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **8**.

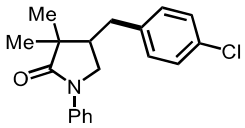


The product **8** was obtained in 88% yield (76.2 mg, 0.26 mmol) as white solid; IR (cm^{-1}): 2947, 2850, 1677, 1597, 1487, 1450, 1396, 1329, 1296, 1277, 1139, 1113, 1068, 1006, 911, 868, 764, 693; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.68-7.65 (m, 2H), 7.37 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.15-7.11 (m, 1H), 3.80 (dd, *J* = 7.3, 2.6 Hz, 1H), 3.72 (dd, *J* = 3.4, 5.9 Hz, 4H), 3.54 (dd, *J* = 8.6, 1.3 Hz, 1H), 2.52 (brs, 2H), 2.47-2.45 (m, 2H), 2.42-2.37 (m, 2H), 1.30 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.0, 139.7, 128.9, 124.3, 119.7, 67.0, 58.0, 54.2, 50.0, 44.1, 39.3, 24.6; HRMS (ESI-MS) calcd. for C17H25O2N2 ($M+H^+$): 289.1916; found 289.1917.

4-(4-chlorobenzyl)-3,3-dimethyl-1-phenylpyrrolidin-2-one (**10**)



2a (0.30 mmol, 1.0 equiv), (4-chlorophenyl)boronic acid (0.36 mmol, 1.2 equiv) and KI (1.5 mmol, 5.0 equiv) were sequentially added under air to a drum vial equipped with a stir bar and a screw cap. Then, $Ni(COD)_2$ (1.2×10^{-2} mmol, 4.0 mol%), Bathophenanthroline (2.4×10^{-2} mmol, 8.0 mol%), KOtBu (0.48 mmol, 1.6 equiv) and dried sBuOH (1.0 mL) were added in glovebox. The mixture was stirred at 60 °C for 24 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **10**.



The product **10** was obtained in 44% yield (41.4 mg, 0.13 mmol) as white solid; IR (cm^{-1}): 3044, 2963, 1682, 1594, 1488, 1395, 1297, 1100, 1014, 790, 762, 735; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.58 (dd, *J* = 1.2, 7.6 Hz, 2H), 7.33 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.31 (dd, *J* = 2.1, 4.3 Hz, 2H), 3.54 (dd, *J* = 7.5, 2.1 Hz, 1H), 3.44 (t, *J* = 9.6 Hz, 1H), 2.91 (dd, *J* = 4.6, 9.0 Hz, 1H), 2.58 (dd, *J* = 11.0, 2.6 Hz, 1H), 2.41-2.35 (m, 1H), 1.27 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.8, 139.6, 137.8, 132.4, 130.0, 128.9, 128.8, 124.4, 119.7, 50.4, 45.0, 44.7, 33.8, 24.0, 18.9; HRMS (ESI-MS) calcd. for C19H21OClN ($M+H^+$): 314.1312; found 314.1312.

References

[1] Clark, A. J.; Collis, A. E. C.; Fox, D. J.; Halliwell, L. L.; James, N.; O'Reilly, R. K.; Parekh, H.; Ross, A.; Sellars, A. B.; Willcock, H.; Wilson, P. *J. Org. Chem. 77* (**2012**) 6778–6788.

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8957.

[3] Chen, J.-Q.; Chang, R.; Lin, J.-B.; Luo, Y.-C.; Xu, P.-F. *Org. Lett. 20* (**2018**) 2395-2398.

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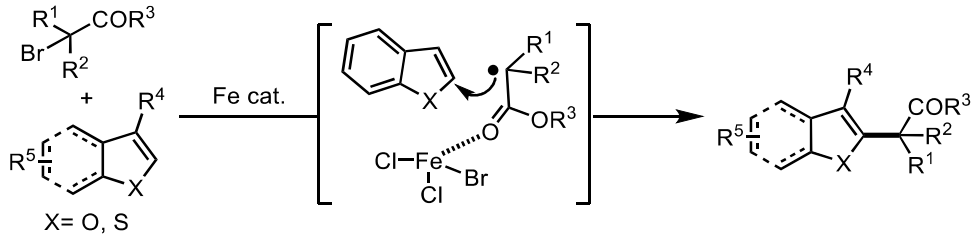
[5] Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Biomol. Chem.*, *9* (**2011**) 3415–3420.

Chapter 2 Development of Cu-catalyzed dearomative addition to BHT derivatives for the synthesis of cyclohexadienones

2.1 Introduction

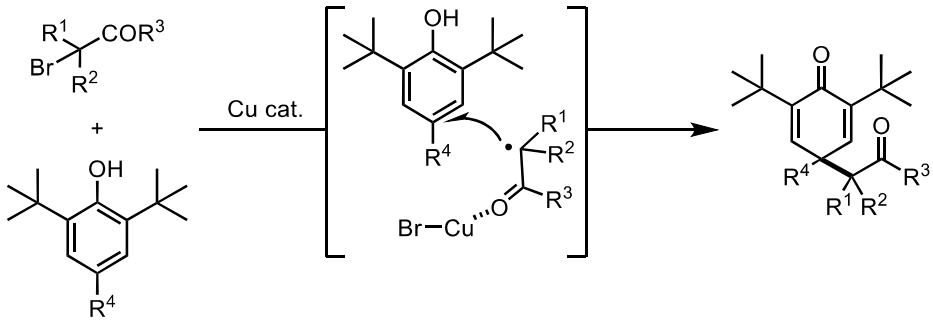
Dearomatization reactions, although one of the most difficult reactions in organic synthesis due to breaking aromaticity,[1] can efficiently convert aromatic compounds into aliphatic compounds. There are very few reports of dearomative tertiary alkylation to produce vicinal quaternary carbons. One of the difficulties is the stability of the dearomatized product. Most of the resulting products have a 1,4-cyclohexadiene structure that is easily oxidized to reproduce the starting aromatic ring. Therefore, the resulting product must be stabilized by bulky substituents in the successful dearomative addition to aromatic rings. In this study, BHT is a very attractive reaction partner for radical species, because the resulting dearomatized compound has sterically bulky tert-butyl groups to stabilize the structure.

2.2 Previous work and this work



Scheme 2 Previous work

The authors previously reported iron-catalyzed C-H alkylation reaction using tertiary α-bromocarbonyl compound and aromatic compound including benzofuran and benzothiophene (Scheme 2).[3] In this reaction, the iron catalyst interacts with the tertiary alkyl species, resulting in highly active radical species in the vicinity of benzofuran and benzothiophene derivatives, so that tertiary alkylation proceeds efficiently.



Scheme 3 This work

Herein, I developed a Cu-catalyzed dearomative addition reaction using tertiary α-bromocarbonyl

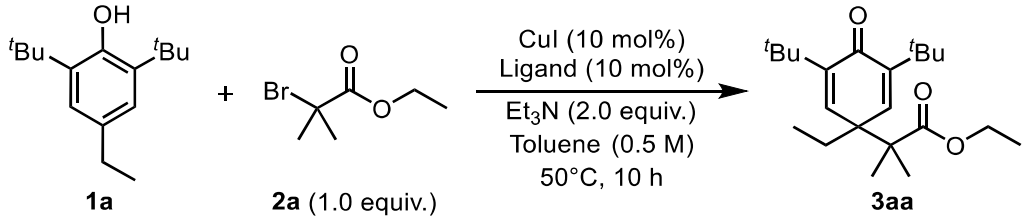
compound and BHT derivatives (Scheme 3). I hypothesized that the tertiary alkyl radical species generated by the one-electron reduction of the copper catalyst and BHT could approach each other using the coordination effect of the copper catalyst and efficiently proceed with the reaction.

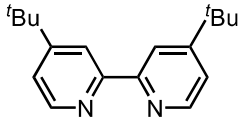
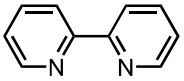
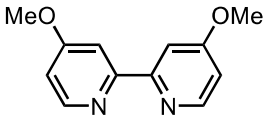
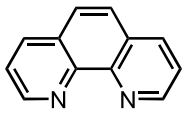
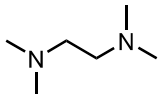
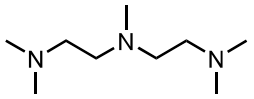
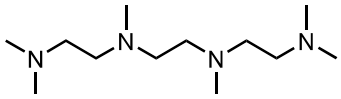
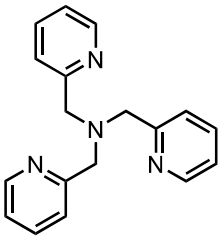
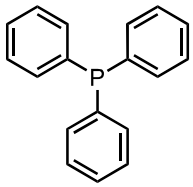
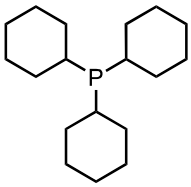
2.3 Results and discussion

2.3.1 Optimization of reaction conditions

I initiated carried out the optimization of ligand for copper-catalyzed dearomative radical addition reaction using 4-ethyl-2,6-di-tert-butylphenol (**1a**) and ethyl 2-bromo-2-methylpropanoate (**2a**) as model substrates. When I used dtbbpy (**L1**), dearomative product **3aa** was obtained in 76% NMR yield (81% isolated yield). However, the reaction did not proceed with **L2**, **L3** or **L4**. Next, I investigated about the effect of chain nitrogen ligand (**L5-L7**). As the electron density of the ligand increased, the yield of the product **3aa** increased. I conducted the reaction using TPMA (**L8**), **3aa** was obtained in 55% NMR yield. Finally, the use of phosphine type ligands (**L9**, **L10**) did not lead to any progress of the reaction. From the results of optimization of ligands, I determined dtbbpy (**L1**) as the optimal ligand.

Table 1 Optimization of ligand

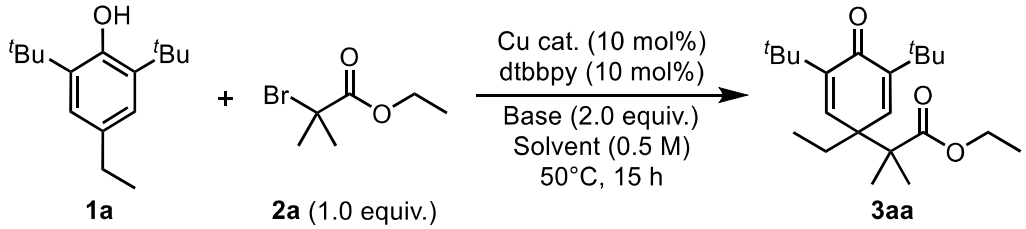


NMR yield of **3aa** (Isolated yield)			
 **L1** 76% (81%)	 **L2** n.r.	 **L3** n.r.	 **L4** n.r.
 **L5** trace	 **L6** 43%	 **L7** 62% (55%)	
 **L8** 55%	 **L9** n.r.	 **L10** n.r.	

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

Next, I conducted the optimization of the reaction conditions (Table 2). First, I investigated about the effect of solvent. The product **3aa** was obtained in 93% NMR yield (86% isolated yield), when I carried out the reaction in toluene at 50°C for 15 h (entry 1). The yield of the product was not improved using DCE, MeCN, 1,4-dioxane or DMF (entry 2-5). Next, to obtain the information about the effect of bases, I conducted the reaction using various organic or inorganic bases (entry 6-11). When DIPEA or ^{n}Hex$_3$N, bulky tertiary amine, was used, the product **3aa** was obtained in moderate yield (entry 6,7). The reaction proceeded to give the product in 80% NMR yield using ^{i}Pr$_2$NH (entry 8). Trace amount of **3aa** was detected when the reaction was conducted using DABCO. However, the yield of the product **3aa** was improved with DBU in 88% isolated yield (entry 10). Cs_2CO_3 as an inorganic base did not work well in this reaction. The reaction with $CuBr_2$ was also found to take place smoothly. However, since $CuBr_2$ is difficult to use, it was not adopted as the optimal copper catalyst. Finally, the product was obtained in excellent yield even at room temperature for 1 h (entry 15).

Table 2 Optimization of reaction conditions



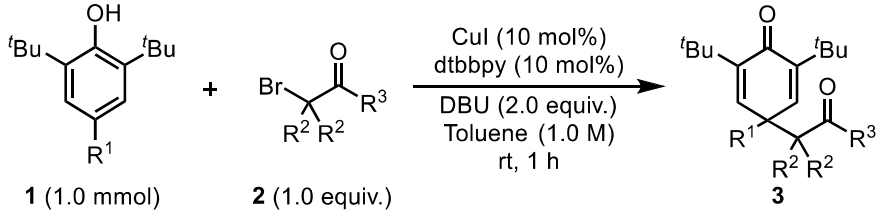
1a **2a** (1.0 equiv.) **3aa**

Entry	Cu cat.	Base	Solvent	NMR yield of **3aa**
1	CuI	Et_3N	Toluene	93% (86%)
2	CuI	Et_3N	DCE	85% (83%)
3	CuI	Et_3N	MeCN	84% (85%)
4	CuI	Et_3N	1,4-dioxane	75%
5	CuI	Et_3N	DMF	46%
6	CuI	DIPEA	Toluene	45%
7	CuI	^{n}Hex$_3$N	Toluene	19%
8	CuI	^{i}Pr$_2$NH	Toluene	80% (78%)
9	CuI	DABCO	Toluene	trace
10	CuI	DBU	Toluene	>99% (88%)
11	CuI	Cs_2CO_3	Toluene	17%
12	CuBr	DBU	Toluene	53%
13	CuCl	DBU	Toluene	63%
14	$CuBr_2$	DBU	Toluene	>99% (89%)
15[a]	CuI	DBU	Toluene	95% (85%)

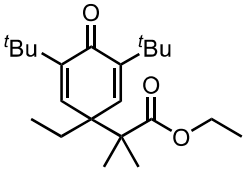
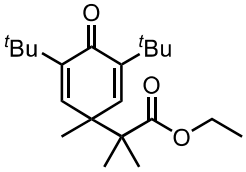
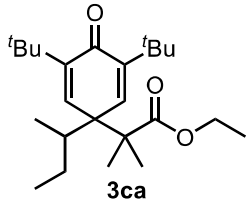
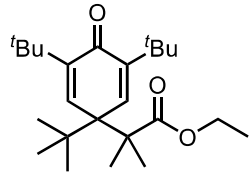
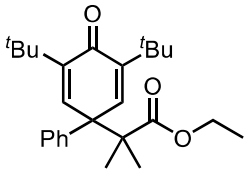
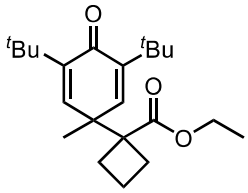
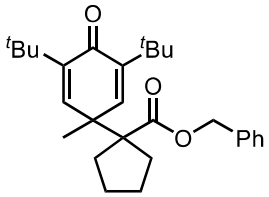
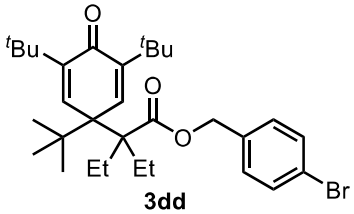
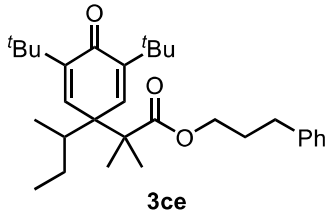
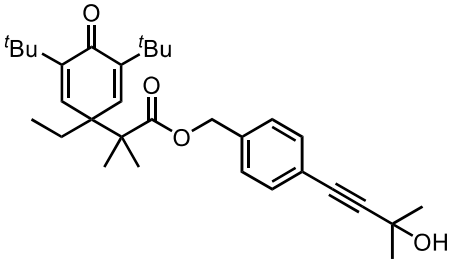
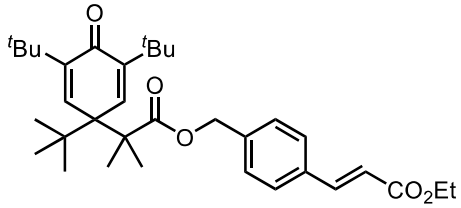
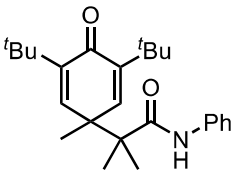
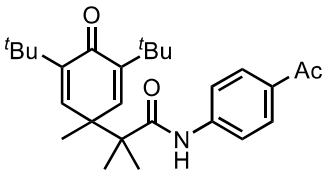
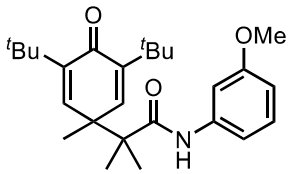
Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield. [a]The reaction was conducted at room temperature for 1 h.

2.3.2 Substrate scope

Table 3 Substrate scope for Cu-catalyzed dearomative addition.

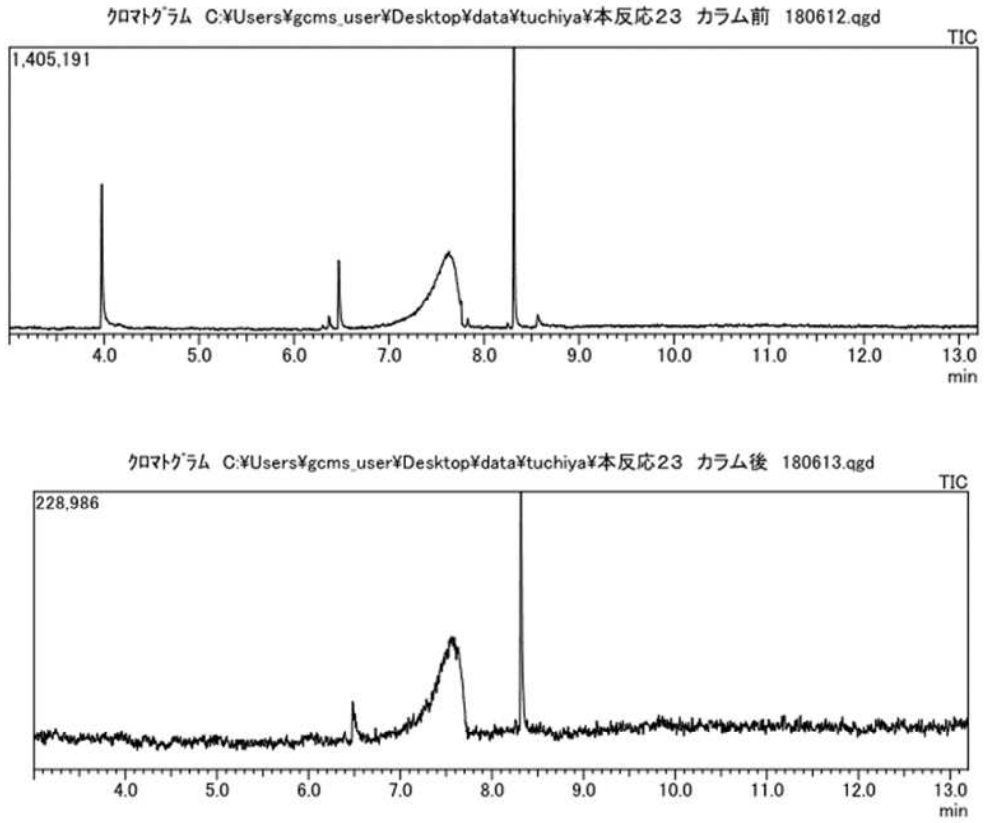


1 (1.0 mmol) **2** (1.0 equiv.) **3**

Isolated yield of **3**			
 **3aa** 96%	 **3ba** 90%	 **3ca** 98% (20 h)	 **3da** 98% (20 h)
 **3ea** 95% (5 h)	 **3bb** 64% (20 h)	 **3bc** >99%	
 **3dd** 88% (20 h)	 **3ce** 99% (20 h)		
 **3af** 91%	 **3dg** 81%		
 **3bh** 61% (20 h)	 **3bi** 69% (20 h)	 **3bj** 53% (20 h)	

With the optimal reaction conditions confirmed, the generality of the dearomative addition was examined (Table 3). First, the 1.0 mmol scale reaction was conducted at high concentration (1.0 M) for the mass synthesis of the product **3**. As a result, the **3aa** was obtained in 96% isolated yield. Next, to examine the steric effect at 4-position of BHT derivatives, the dearomative addition reaction was carried out using various BHT derivatives. When 4-methyl-2,6-di-tert-butylphenol **1b** was used, the product **3ba** was obtained in 90% yield for 1 h. As the substituent became bulkier, the reactivity of BHT derivative decreased, but by extending the reaction time to 20 h, a high yield of the product was produced (**3ca**: 98% and **3da**: 98%). Surprisingly, the reaction proceeded to give **3ea** in 95% yield using 4-phenyl-2,6-di-tert-butylphenol as substrate. Next, for the synthesis of dearomative addition product **3**, this protocol was applicable to a large variety of α-bromoester **2** to afford **3bb-3dh** in 64-99% yields. To examine the steric effect at α-position of carbonyl group, the reaction was conducted using α-bromoester bearing cyclic (**2b-2d**) or acyclic (**2e**) substituents. The product **3bd** was obtained quantitatively for 1 h, but the reaction using **2b**, **2c**, or **2e** proceeded to give the product in high yield for 20 h. Also, various substituents of ester site were allowed in this reaction (**3cf-3dh**). In addition, α-bromoamide (**2i-2k**) was also applicable, albeit in moderate yield (53-69%).

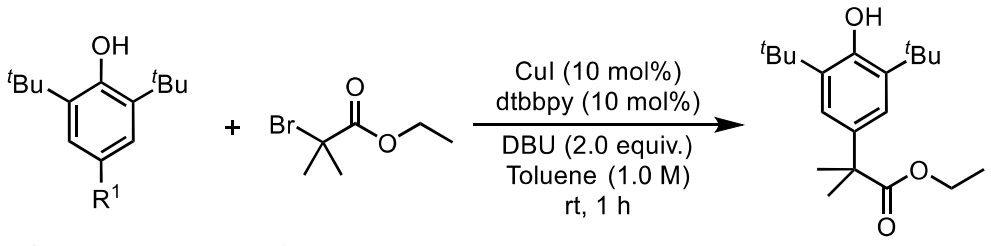
Figure 2 Charts of dearomative addition product **3ba**.



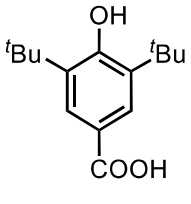
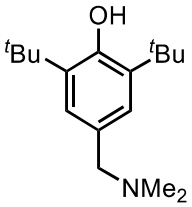
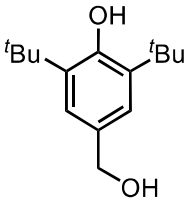
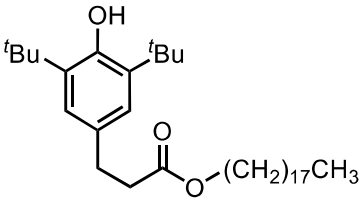
The GC-MS chart shows the chart when the dearomative addition reaction was performed (Figure

2). The upper row is the chart before the column chromatography was performed, and the lower row is the chart after the column chromatography was performed. The peak of 4.0 min is the peak indicating α-bromoester **2a**, the peak of 6.5 min is the peak of **1a**, and the peak of 8.3 min is the peak indicating the product **3ba**. The broad peak at 7.2-7.8 min is the peak indicating that the product **3ba** is broken in GC-MS. This phenomenon suggested that the dearomative addition product **3ba** is sensitive to heat.

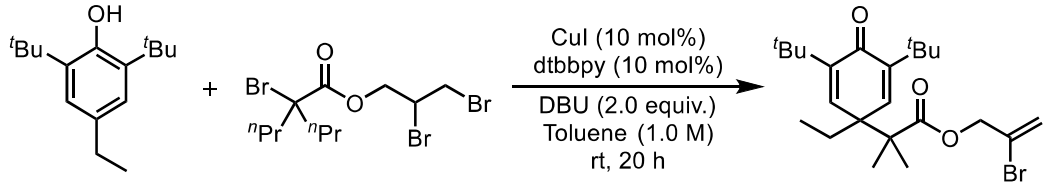
Table 4 C-C bond cleavage reaction



4 (1.0 mmol) **2a** (1.0 equiv.) **5**

Substrate **4** / Yield of **5**			
			
4a / 5	**4b / 5**	**4c / 5**	**4d / 5**
45%	52%	48%	trace (20 h)

Interestingly, when the reaction was carried out using phenol derivative **4a-4c**, the aromatization product **5** was obtained in moderate yield without detecting dearomative addition product (Table 4). Also, trace amount of aromatization product **5** was detected using phenol derivative **4d**. However, the reaction mechanism for this aromatization reaction is not clearly understood.



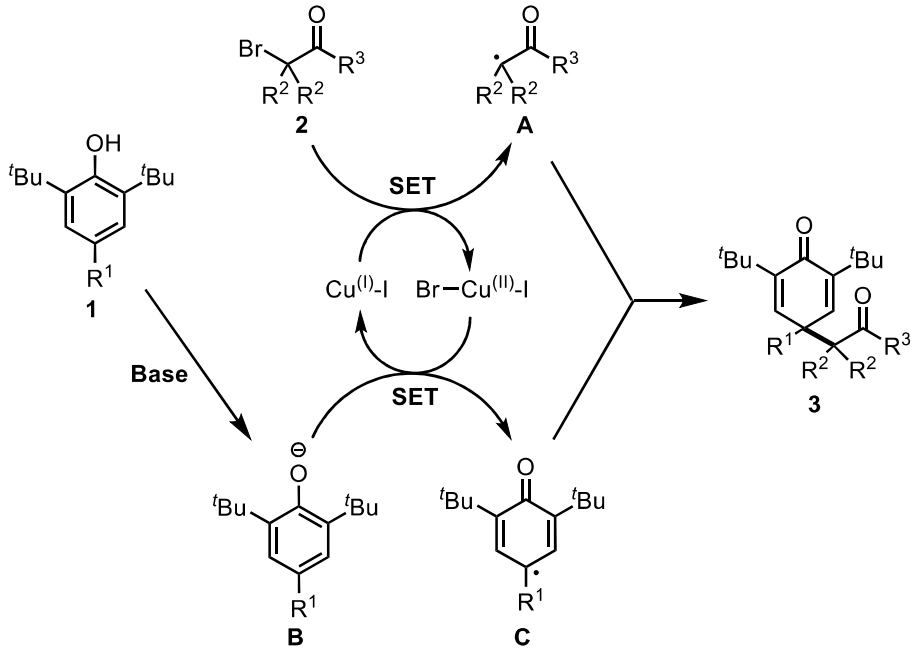
1a **2k** (1.0 equiv.) **3ak**: 80%

Scheme 4 The reaction between BHT derivative **1a** and α-bromoester **2l**

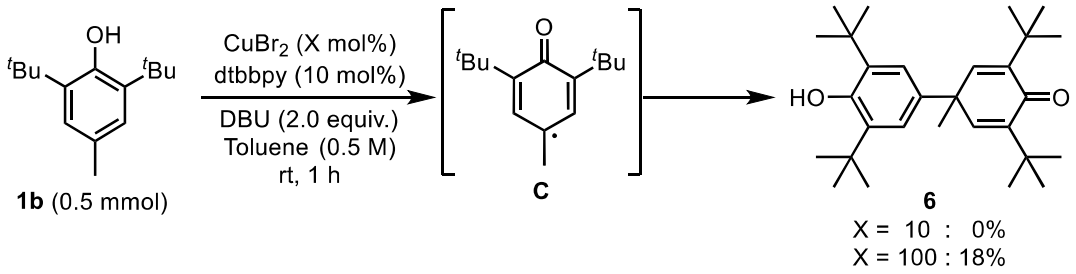
When the reaction was conducted using phenol derivative **1a** and α-bromoester **2l**, the dearomative addition product **3al** eliminated HBr was obtained in 80% yield unlike the target product (Scheme 4).

2.3.3 Proposed reaction mechanism

Figure 3 Proposed reaction mechanism.



First, the α-bromocarbonyl compound **2** reacts with CuI, and single-electron transfer occurs to produce alkyl radical species **A** and CuIBr. Next, the proton of the phenol derivative **1** is abstracted by the base, resulting in the formation of intermediate **B**. Then, Single-electron transfer between CuIBr and intermediate **B** occur, resulting in the formation of intermediate **C** and the regeneration of copper catalyst. Finally, the target product **3** can be obtained by radical-radical coupling of intermediate **A** and intermediate **C**.



Scheme 5 Mechanistic experiment.

To confirm the production of intermediate **C**, indirect mechanistic experiment was conducted. The phenol derivative **1b** and $CuBr_2$ were reacted by changing the equivalent of copper salt. As a result, when a study was performed using one equivalent of $CuBr_2$, a dimer product **6** of the phenol derivative **1b** was obtained in 18% yield. The formation of a dimer product **6** suggests that it is likely that the involvement of intermediate **C**.

2.4 Conclusion

In this reaction, a dearomative addition reaction between a BHT derivative **1** and α-bromocarbonyl compound **2** occurs at room temperature in the presence of a copper catalyst and a base, resulting in the dearomative product with vicinal quaternary carbon center in high yield. Also, when the reaction was conducted using several phenol derivatives, the aromative product was obtained in moderate yield. The result of mechanistic experiment suggested that the involvement of radical-radical coupling path in this dearomative addition reaction.

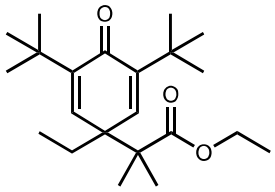
2.5 Reference

[1] Reviews: (a) Pape, A. R.; Kaliappan, K. P.; Kundig, E. P. *Chem. Rev.* **2000**, *100*, 2917-2940. (b) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett.* **2008**, 467-495. (c) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron*, **2010**, *66*, 2235-2261. (d) Roche, S. P.; Porco Jr., J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093. (e) Zhou, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12662-12686. (f) Ding, Q.; Ye, Y.; Fan, R. *Synthesis*, **2013**, *45*, 1-16. (g) Sun, W.; Li, G.; Hong, L.; Wang, R. *Org. Biomol. Chem.* **2016**, *14*, 2164-2176. (h) Wu, W.-T.; Zhang, L.; You, S.-L. *Chem. Soc. Rev.* **2016**, *45*, 1570-1580. (i) Reddy, C. R.; Prajapti, S. K.; Warudikar, K.; Ranjan, R.; Rao, B. B. *Org. Biomol. Chem.* **2017**, *15*, 3130-3151. (j) Park, S.; Chang, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 7720-7738.

[2] Yamane, Y.; Yoshinaga, K.; Sumimoto, M. *ACS Catal.* **2019**, *9*, 1757-1762.

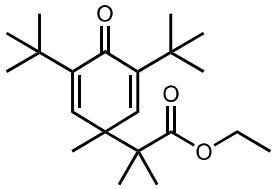
2.6 Experimental section

ethyl 2-(3,5-di-tert-butyl-1-ethyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**3aa**)



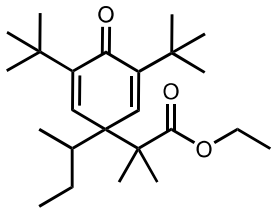
1a (234.5 mg, 1.0 mmol), CuI (18.9 mg, 0.10 mmol), L1 (27.0 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (195.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3aa** (333.6 mg, 96%); IR(cm^{-1}): 2959, 1724, 1660, 1638, 1462, 1366, 1254, 882; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.46 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 1.73 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.24 (s, 18H), 1.14 (s, 6H), 0.57 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.70, 175.72, 149.44, 142.67, 60.86, 49.52, 47.86, 35.31, 26.84, 22.28, 14.37, 8.97.

ethyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**3ba**)



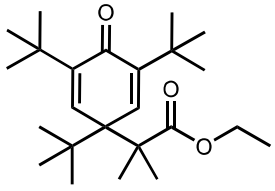
1b (220.4 mg, 1.0 mmol), CuI (19.2 mg, 0.10 mmol), L1 (27.0 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (195.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3ba** (301.4 mg, 90%); IR(cm^{-1}): 2959, 1716, 1656, 1637, 1458, 1365, 1254, 905; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.55 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 18H), 1.20 (s, 3H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.32, 175.62, 147.15, 143.83, 60.88, 49.10, 43.04, 35.06, 29.60, 21.73, 14.39.

ethyl 2-(1-(sec-butyl)-3,5-di-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**3ca**)



1c (262.0 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), L1 (27.0 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (195.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the brown oil product **3ca** (368.8 mg, 98%); IR(cm^{-1}): 2957, 1721, 1656, 1635, 1458, 1365, 1251, 881; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.71 (d, *J* = 3.3 Hz, 1H), 6.65 (d, *J* = 3.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.80 – 1.75 (m, 1H), 1.48 – 1.40 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 18H), 1.24 – 1.23 (m, 1H), 1.16 (d, J = 3.7 Hz, 6H), 0.85 – 0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.79, 176.54, 148.44, 147.80, 143.04, 142.50, 60.94, 49.96, 49.05, 40.30, 35.27, 29.62, 23.80, 14.94, 14.19, 12.87.

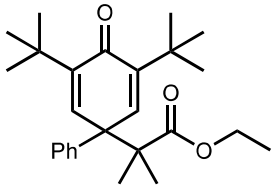
ethyl 2-methyl-2-(1,3,5-tri-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)propanoate (**3da**)



1d (262.6 mg, 1.0 mmol), CuI (19.2 mg, 0.10 mmol), L1 (26.9 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (195.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at

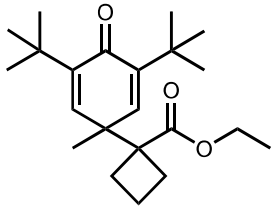
room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3da** (370.7 mg, 98%); IR(cm^{-1}): 2958, 1717, 1631, 1465, 1365, 1252, 907; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.99 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 18H), 1.19 (s, 6H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.72, 176.97, 147.52, 143.01, 61.03, 51.50, 48.30, 39.23, 35.46, 29.60, 28.65, 25.99, 14.04.

ethyl 2-(3,5-di-tert-butyl-4-oxo-[1,1'-biphenyl]-1(4H)-yl)-2-methylpropanoate (**3ea**)



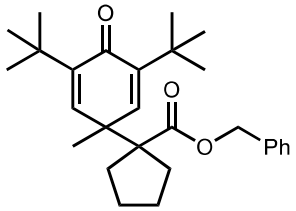
1e (115.0 mg, 0.40 mmol), CuI (7.8 mg, 0.04 mmol), L1 (11.2 mg, 0.04 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (80.0 mg, 0.40 mmol), DBU (125.0 mg, 0.80 mmol), dried Toluene (0.40 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 5 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3ea** (154.6 mg, 95%); IR(cm^{-1}): 2953, 2867, 1718, 1659, 1466, 1366, 1255, 1173, 1025; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (s, 2H), 7.33-7.28 (m, 4H), 7.26-7.22 (m, 1H), 3.97 (q, J = 7.1 Hz, 2H), 1.28 (s, 18H), 1.21 (s, 6H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.5, 175.4, 146.8, 141.9, 140.7, 128.2, 127.8, 127.1, 60.9, 50.9, 48.7, 35.4, 29.6, 22.7, 14.0.

ethyl 1-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)cyclobutane-1-carboxylate (**3bb**)



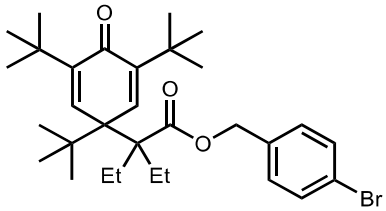
1b (220.4 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), L1 (26.8 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2b** (207.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3bb** (223.0 mg, 64%); IR(cm^{-1}): 2956, 1714, 1656, 1636, 1457, 1364, 1250, 1201, 905, 729; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.55 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.39-2.33 (m, 2H), 2.07-2.01 (m, 2H), 1.78-1.72 (m, 1H), 1.65-1.61 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.24 (s, 18H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.07, 175.88, 147.17, 143.06, 60.73, 54.51, 41.41, 34.94, 29.48, 26.88, 21.17, 15.25, 14.34.

benzyl 1-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)cyclopentane-1-carboxylate (**3bc**)



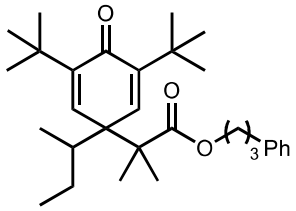
1b (220.4 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), L1 (26.8 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2c** (283.2 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3bc** (415.6 mg, >99%); IR(cm^{-1}): 2959, 1714, 1655, 1636, 1456, 1375, 1251, 1163, 904, 727; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36-7.34 (m, 5H), 5.11 (s, 2H), 2.20-2.18 (m, 2H), 1.52-1.47 (m, 6H), 1.19 (s, 3H), 1.18 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.29, 175.39, 146.80, 144.23, 135.89, 128.67, 128.37, 128.36, 66.79, 62.06, 42.56, 31.93, 29.48, 24.93, 22.60.

4-bromobenzyl-2-ethyl-2-(1,3,5-tri-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)butanoate (**3dd**)



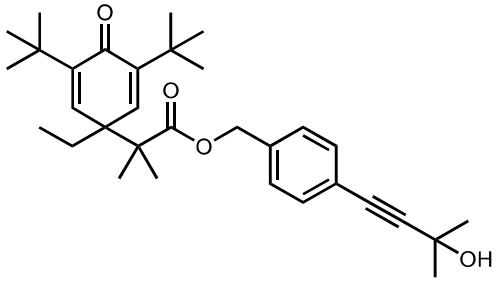
1d (117.1 mg, 0.5 mmol), CuI (9.5 mg, 0.05 mmol), L1 (13.3 mg, 0.05 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2d** (182.4 mg, 0.5 mmol), DBU (152.2 mg, 1.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the brown oil product **3dd** (227.3 mg, 88%); IR(cm^{-1}): 2956, 1719, 1656, 1635, 1487, 1456, 1367, 1210, 1124, 1071, 1013, 973, 880, 807, 740; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (s, 1H), 7.49 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 6.43 (s, 2H), 5.09 (s, 2H), 1.84-1.80 (m, 2H), 1.70-1.66 (m, 4H), 1.20 (s, 18H), 0.80 (t, J = 7.4 Hz, 6H), 0.48 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.8, 174.5, 148.3, 143.0, 134.7, 131.8, 130.3, 122.5, 65.7, 57.3, 48.6, 35.2, 29.4, 27.5, 23.8, 10.0, 8.4.

3-phenylpropyl 2-(1-(sec-butyl)-3,5-di-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**3ce**)



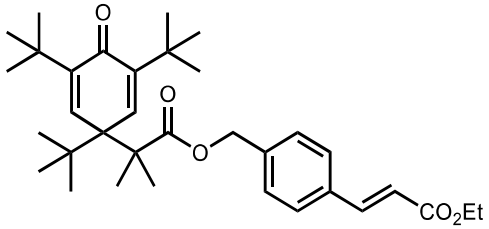
1c (262.1 mg, 1.0 mmol), CuI (19.1 mg, 0.10 mmol), L1 (26.7 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2e** (285.2 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3ce** (486.1 mg, >99%); IR(cm^{-1}): 2955, 1720, 1656, 1635, 1454, 1365, 1251, 1159, 1130, 881, 742, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 – 7.27 (m, 2H), 7.21 – 7.16 (m, 3H), 6.71 (ds, *J* = 2.8 Hz, 1H), 6.65 (ds, *J* = 2.8 Hz, 1H), 4.09 – 4.06 (m, 2H), 2.70 – 2.67 (m, 2H), 2.01 – 1.94 (m, 2H), 1.80 – 1.78 (m, 1H), 1.48 – 1.39 (m, 2H), 1.25 (s, 18H), 1.17 (ds, J = 2.1 Hz, 6H), 0.85 – 0.83 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.77, 176.51, 148.52, 147.90, 142.39, 141.03, 128.59, 128.43, 126.20, 64.38, 49.99, 49.23, 40.33, 32.37, 29.62, 23.91, 14.97, 12.88.

4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzyl 2-(3,5-di-tert-butyl-1-ethyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**3af**)



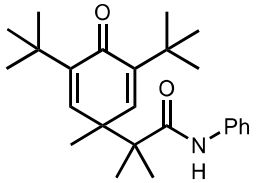
1a (234.4 mg, 1.0 mmol), CuI (19.2 mg, 0.10 mmol), L1 (27.0 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2f** (339.2 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the brown oil product **3af** (448.6 mg, 91%); IR(cm^{-1}): 3506, 2964, 2869, 1700, 1659, 1639, 1463, 1367, 1251, 1164, 1134, 961, 939, 904, 883, 825, 788, 742; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.40 (s, 2H), 5.09 (s, 2H), 2.03 (s, 1H), 1.70 (q, J = 7.4 Hz, 2H), 1.62 (s, 6H) 1.19 (s, 18H), 1.16 (s, 6H), 0.54 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.62, 175.39, 149.57, 142.34, 135.89, 131.93, 128.12, 122.84, 94.36, 81.75, 66.17, 65.72, 49.70, 47.86, 35.24, 31.55, 29.62, 26.85, 22.27, 8.90.

Ethyl-(E)-3-(4-(((2-methyl-2-(1,3,5-tri-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)propanoyl)oxy)methyl)phenyl)acrylate (**3dg**)



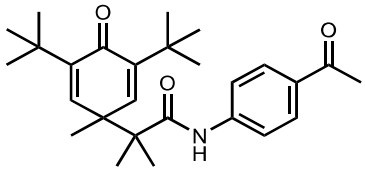
1d (262.4 mg, 1.0 mmol), CuI (19.5 mg, 0.10 mmol), L1 (26.9 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2g** (355.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow oil product **3dg** (435.9 mg, 81%); IR(cm^{-1}): 2956, 2255, 1713, 1635, 1464, 1389, 1365, 1310, 1251, 1203, 1174, 1115, 981, 909, 881, 819, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.93 (s, 2H), 6.45 (d, J = 16.1 Hz, 1H), 5.12 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.22 (s, 6H), 1.21 (s, 18H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.68, 176.67, 166.97, 147.70, 143.91, 142.67, 137.48, 134.67, 128.99, 128.37, 118.90, 66.67, 60.70, 51.53, 48.54, 39.27, 35.43, 29.54, 28.69, 26.03, 14.42.

2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methyl-N-phenylpropanamide (**3bh**)



1b (220.7 mg, 1.0 mmol), CuI (19.4 mg, 0.10 mmol), L1 (27.0 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2h** (242.0 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the white solid product **3bh** (231.9 mg, 61%); IR(cm^{-1}): 3351, 2959, 1640, 1596, 1518, 1436, 1364, 1242, 881, 756, 691; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.19 (brs, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.60 (s, 2H), 1.33 (s, 3H), 1.27 (s, 6H), 1.23 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.28, 173.09, 147.80, 143.50, 142.61, 129.19, 124.72, 120.18, 49.22, 43.58, 35.09, 29.62, 22.07, 21.64.

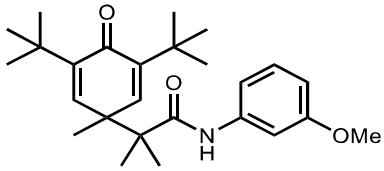
N-(4-acetylphenyl)-2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanamide (**3bi**)



1b (220.4 mg, 1.0 mmol), CuI (19.3 mg, 0.10 mmol), L1 (26.9 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas

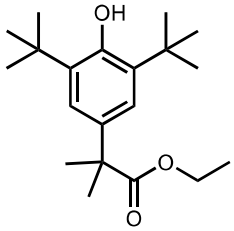
(purity 99.95%), **2i** (284.4 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the yellow solid product **3bi** (293.5 mg, 69%); IR(cm^{-1}): 3374, 2954, 1657, 1586, 1514, 1475, 1402, 1362, 1307, 1268, 1247, 1177, 1132, 958, 880, 836; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.32 (brs, 1H), 6.57 (s, 2H), 2.58 (s, 3H), 1.32 (s, 3H), 1.29 (s, 6H), 1.21 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.97, 186.12, 173.38, 148.06, 143.10, 141.62, 133.25, 129.89, 119.15, 49.59, 43.49, 35.11, 29.60, 26.57, 22.00, 21.61.

2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-N-(3-methoxyphenyl)-2-methylpropanamide (**3bj**)



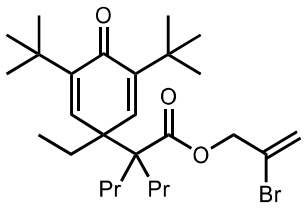
1b (220.7 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), L1 (26.7 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2j** (272.3 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the viscous oil product **3bj** (217.9 mg, 53%); IR(cm^{-1}): 2956, 2252, 1656, 1606, 1523, 1489, 1450, 1425, 1364, 1287, 1248, 1201, 1158, 1049, 906, 729, 686; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21 (t, J = 8.2 Hz, 2H), 7.16 (brs, 1H), 6.88 (d, J = 9.4 Hz, 1H), 6.67 (d, J = 10.7 Hz, 1H), 6.58 (s, 2H), 3.80 (s, 3H), 1.32 (s, 3H), 1.26 (s, 6H), 1.22 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.27, 173.09, 160.29, 147.83, 143.47, 138.57, 129.81, 112.14, 110.70, 105.68, 55.41, 49.30, 43.57, 35.10, 29.62, 22.04, 21.62.

ethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-methylpropanoate (**5**)



4b (236.4 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), L1 (26.8 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2a** (195.1 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **5** (168.7 mg, 52%); IR(cm^{-1}): 3567, 2955, 1706, 1464, 1433, 1388, 1362, 1295, 1258, 1229, 1175, 1147, 1115, 1016, 880, 857, 770, 663; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (s, 2H), 5.11 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.54 (s, 6H), 1.43 (s, 18H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.2, 152.4, 135.3, 126.6, 122.3, 60.7, 46.3, 34.6, 30.4, 26.9, 14.2 .

2-bromoallyl 2-(3,5-di-tert-butyl-1-ethyl-4-oxocyclohexa-2,5-dien-1-yl)-2-propylpentanoate (**3ak**)



1a (234.6 mg, 1.0 mmol), CuI (19.5 mg, 0.10 mmol), L1 (26.7 mg, 0.10 mmol) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), **2k** (422.3 mg, 1.0 mmol), DBU (304.5 mg, 2.0 mmol), dried Toluene (1.0 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 20 h at room temperature. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting hexane/EtOAc to afford the brown oil product **3ak** (393.7 mg, 80%); IR(cm^{-1}): 2963, 1719, 1633, 1456, 1368, 1252, 1204, 1125, 904, 727; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.49 (s, 2H), 5.96 (m, 1H), 5.70 (m, 1H), 4.73 (brs, 2H), 1.77-1.69 (m, 4H), 1.57 (t, J = 0.7 Hz, 2H), 1.31-1.25 (m, 2H), 1.24 (s, 18H), 1.17-1.11 (m, 2H), 0.86 (t, J = 7.3 Hz, 6H), 0.52 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.66, 174.05, 148.40, 143.04, 126.28, 120.67, 68.31, 57.09, 48.61, 35.25, 34.40, 27.45, 18.62, 14.98, 8.51.

Chapter 3 Development of new activation method for cyclohexadienone and application to chemoselective coupling

3.1 Introduction

Alkyl halides have weak carbon-halogen bonds, so they are easy to generate active species. However, they are likely to proceed side reaction such as HX elimination reaction. On the other hand, alkyl compounds have strong carbon-carbon bonds, so they are difficult to generate active species. However, if the active species can be released slowly, it is easy to control the reactivity. (Figure 1). Because of these advantages, it is useful to develop a C-C bond cleavage reaction of alkyl compounds.

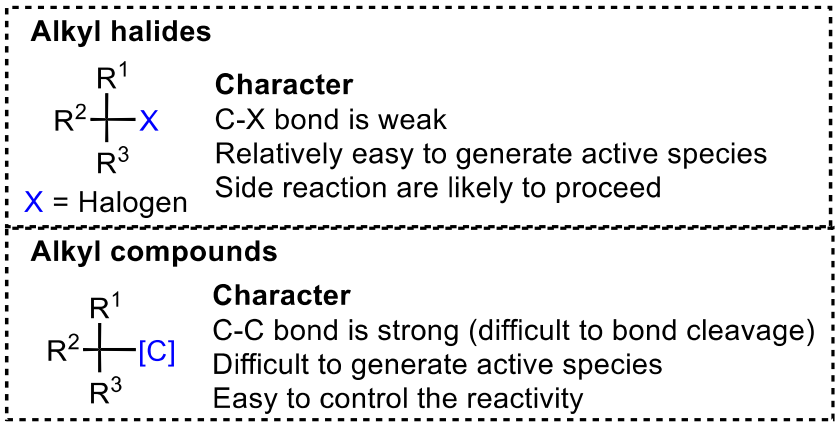


Figure 1 Alkyl halides and alkyl compounds

Recently, tertiary alkylation with carbon-carbon bonds cleavage has been developed using carboxylic acids,[1] acyloxyphthalimides[2], Hantzsch esters[3] and others[4] (Figure 2). However, there are limitations of the types of alkylating agents that can be used, and the development of new alkylating agents has been desired.

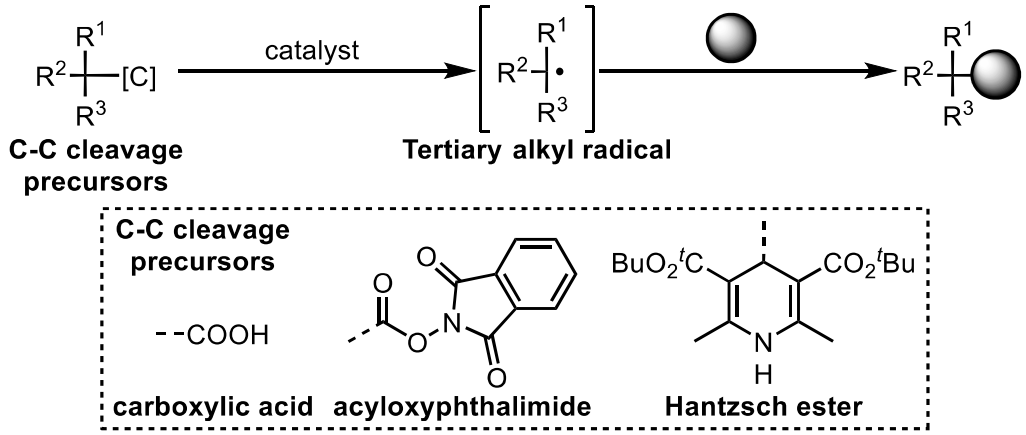
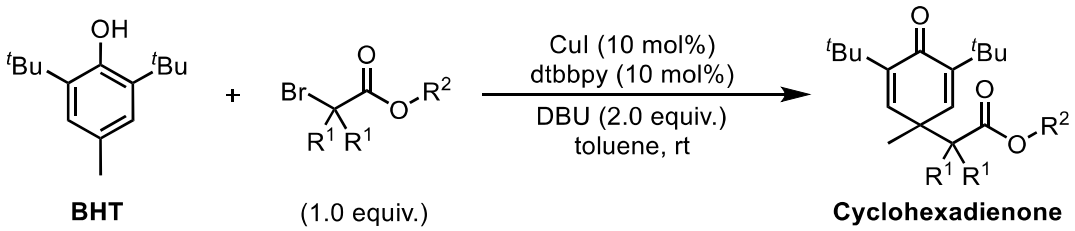


Figure 2 Examples of tertiary alkylation via C-C bond cleavage

3.2 Previous work and this work

As shown in Chapter 2, I previously developed the dearomative addition reaction with butylhydroxytoluene (BHT) and tertiary α-bromocarbonyl compound in the presence of Cu catalyst.[5] When GC-MS was measured in this synthesis, the result was that the peak of the cyclohexadienone derivative was broad (Figure 3). This result suggested that cyclohexadienone derivatives were homolysis at high temperature (235-255℃). However, C-C bond cleavage of cyclohexadienone did not proceed at room temperature. Therefore, in a photoredox catalyzed reaction in which the reaction can be performed under mild conditions, I thought that the C-C bond cleavage of cyclohexadienone derivatives could be made possible by heterolysis driven by aromatization.



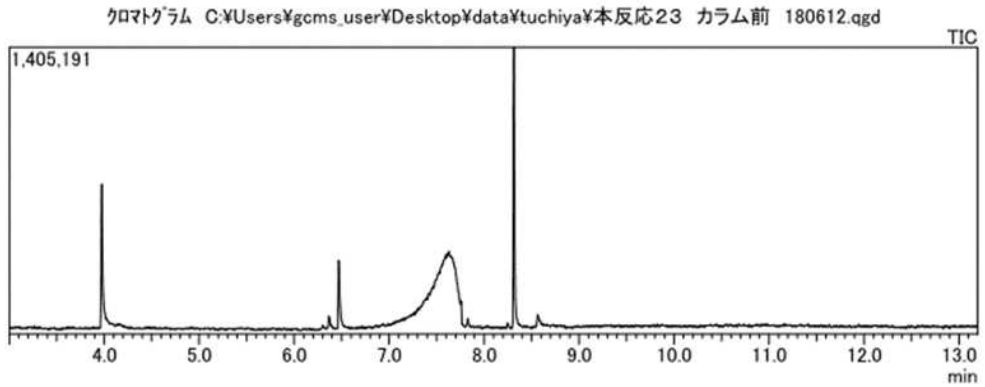
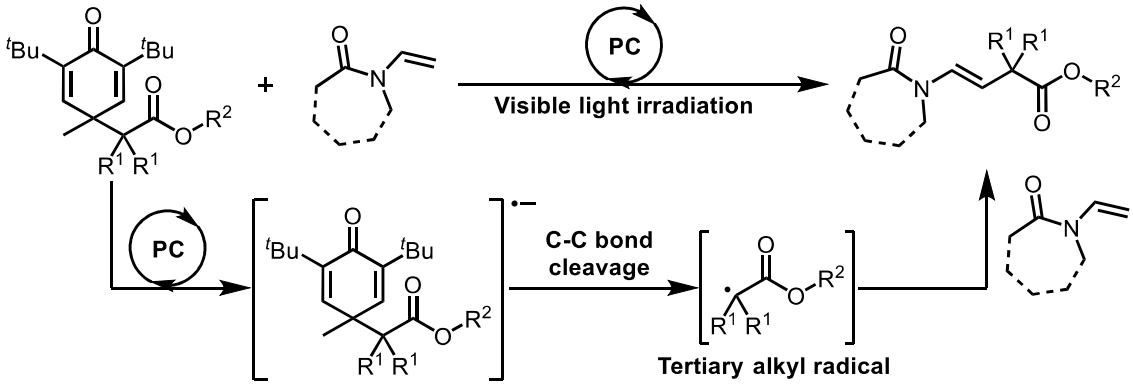


Figure 3 Synthesis of cyclohexadienone and GC-MS chart of cyclohexadienone

Here, I developed the photoredox-catalyzed enamide Heck-type tertiary alkylation via carbon-carbon bond cleavage of cyclohexadienone derivative (Scheme 1).

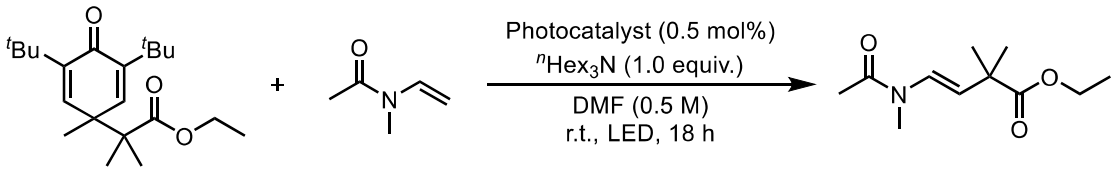


Scheme 1 This work (The photoredox-catalyzed tertiary alkylation via C-C bond cleavage)

3.3 Results and discussion

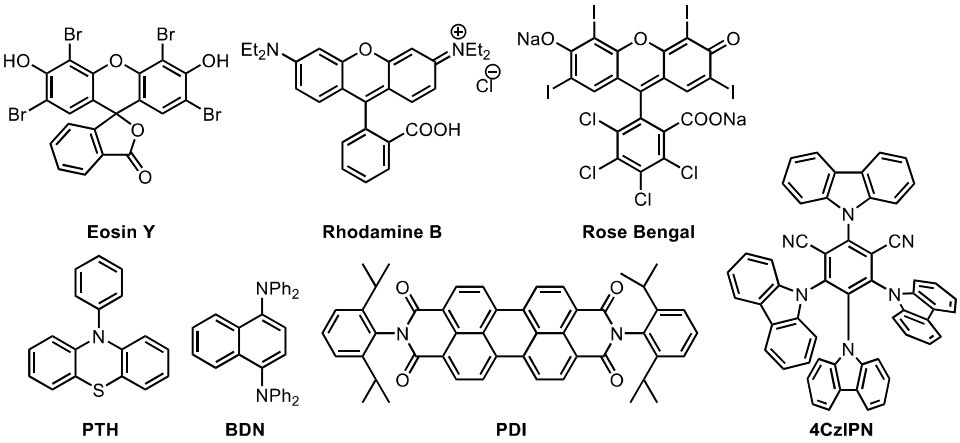
3.3.1 Optimization of reaction conditions

Table 1 Optimization of photocatalysts



1a **2a** (3.0 equiv.) **3aa**

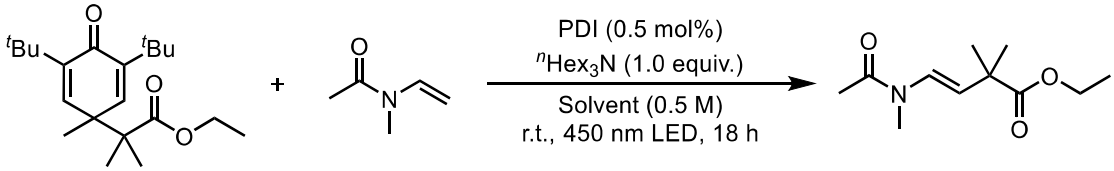
Entry	Photocatalyst (wavelength)	NMR yield of **3aa**
1	Eosin Y (540 nm)	n.r.
2	Rhodamine B (540 nm)	n.r.
3	Rose Bengal (540 nm)	n.r.
4	PTH (365 nm)	6%
5	BDN (365 nm)	trace
6	PDI (450 nm)	33%
7[a]	4CzIPN (450 nm)	n.r.



Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield. [a]^{n}Bu$_3$N and NMP were used instead of ^{n}Hex$_3$N and DMF.

I started the screening of photocatalysts in the reaction of cyclohexadienone **1a** and enamide **2a** (Table 1). The reaction using Eosin Y, Rhodamine B and Rose Bengal upon 540 nm LED irradiation were not proceeded (entry 1-3). When the reaction using PTH and BDN respectively was conducted, trace product was obtained (entry 4,5). However, PDI produced the product **3aa** in 33% NMR yield (entry 6). When 4CzIPN was used upon 455 nm LED irradiation, the reaction was not proceeded (entry 7).

Table 2 Optimization of solvents



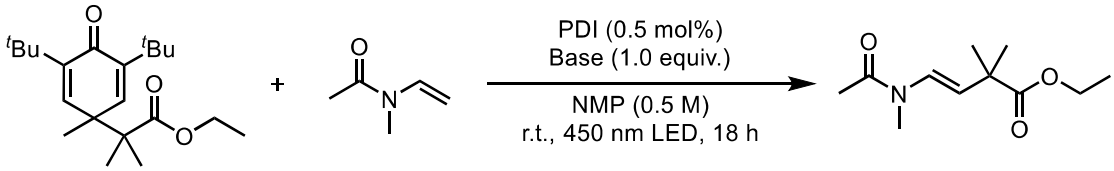
1a **2a** (3.0 equiv.) **3aa**

Entry	Solvent	NMR yield of **3aa**
1	Toluene	n.r.
2	MeCN	n.r.
3	1,4-dioxane	n.r.
4	DCM	n.r.
5	DMSO	n.r.
6	DMF	33%
7	NMP	68% (58%)

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

To obtain information about optimal solvents in the reaction of cyclohexadienone **1a** and enamide **2a** (Table 2). Several solvents did not afford the product **3aa** (entry 1-5). However, the product **3aa** was obtained in 33% NMR yield using DMF. Finally, the reaction proceeded to give the product **3aa** in 68% NMR yield (isolated yield 58%) when NMP was used.

Table 3 Optimization of bases



1a **2a** (3.0 equiv.) **3aa**

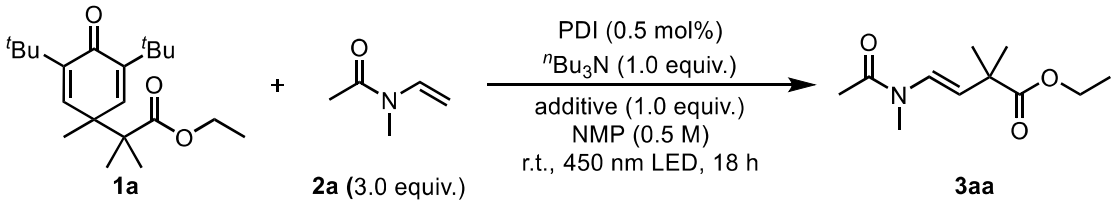
Entry	Base	NMR yield of **3aa**
1	Et_3N	72% (60%)
2	^{n}Bu$_3$N	78% (61%)
3	^{n}Hex$_3$N	68% (58%)
4	DIPEA	32% (21%)
5	^{i}Pr$_2$NH	n.r.
6	pyrrolidine	n.r.
7	DABCO	n.r.
8	DBU	n.r.
9	aniline	n.r.

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

I investigated the effects of bases (Table 3). Addition of Et_3N or ^{n}Bu$_3$N was increased the yield of **3aa** (entry 1,2). On the other hand, the product yield was decreased when DIPEA was used (entry 4).

Several bases, such as $^{i}Pr_2NH$ and aniline, did not afford the product **3aa** (entry 5-9). From these results, I determined that $^{n}Bu_3N$ was optimal base.

Table 4 Optimization of additives



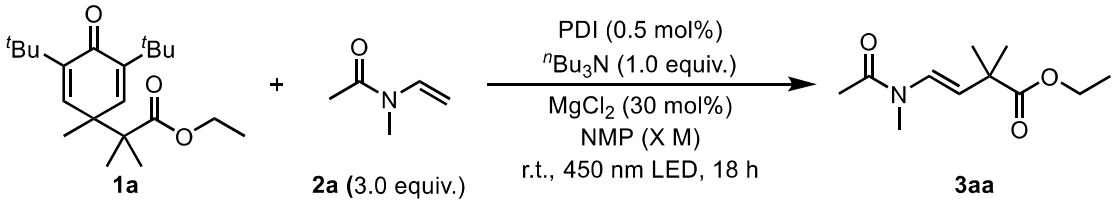
1a **2a** (3.0 equiv.) **3aa**

Entry	additive	NMR yield of **3aa**
1	Cs_2CO_3	n.r.
2	$NaO^{t}Bu$	n.r.
3	$MgBr_2$	55%
4	$MgCl_2$	83%
5[a]	$MgCl_2$	81% (68%)
6	$AlCl_3$	24%
7	Mg	65%
8	Al	63%

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield. [a]30 mol% of $MgCl_2$ was used.

To obtain information about effects of additive in the reaction of cyclohexadienone **1a** and enamide **2a** (Table 4). When the reaction using inorganic base such as Cs_2CO_3 and $NaO^{t}Bu$ was conducted, the product **3aa** was not obtained (entry 1,2). Next, I investigated about the effects of Lewis acid. Although addition of $MgBr_2$ was decreased the product yield, the yield of **3aa** was improved when $MgCl_2$ was added (entry 3,4). When 30 mol% of $MgCl_2$ was added, the reaction proceeded to give the product **3aa** in 81% NMR yield (isolated yield: 68%) (entry 5). However, addition of $AlCl_3$ was decreased the yield of **3aa** (entry 6). Finally, I did not get a good effect when metal such as Mg and Al was added in the reaction mixture (entry 7,8). Therefore, 30 mol% of $MgCl_2$ was optimal additive.

Table 5 Screening of reaction concentration



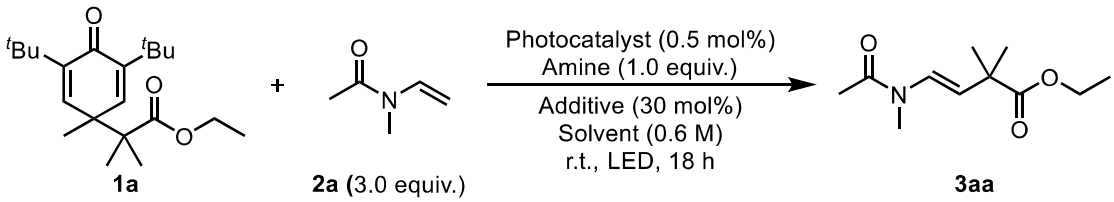
1a **2a** (3.0 equiv.) **3aa**

Entry	X	NMR yield of **3aa**
1	0.5	81% (68%)
2	0.4	77%
3	0.6	>99% (80%)

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

Subsequently, I investigated the effects of reaction concentration (Table 5). When the reaction was performed at a low concentration, the desired product **3aa** was obtained in 77% NMR yield (entry 2). On the other hand, the reaction at 0.6 M proceeded to give the product **3aa** in >99% NMR yield (isolated yield: 80%) (entry 3). Therefore, I determined that 0.6 M of NMP was optimal reaction concentration.

Table 6 Reproduction of reaction conditions



1a **2a** (3.0 equiv.) **3aa**

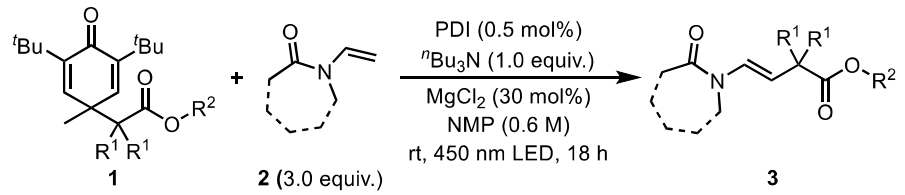
Entry	Photocatalyst (wavelength)	Amine	Additive	Solvent	NMR yield of **3aa**
1	Eosin Y (540 nm)	^{n}Hex$_3$N	-	DMF	n.r.
2	PDI (450 nm)	^{n}Hex$_3$N	-	DMF	65%
3	PTH (365 nm)	^{n}Hex$_3$N	-	DMF	trace
4	PDI (450 nm)	^{n}Hex$_3$N	-	MeCN	44%
5	PDI (450 nm)	^{n}Hex$_3$N	-	Toluene	n.r.
6	PDI (450 nm)	^{n}Hex$_3$N	-	NMP	81% (75%)
7	PDI (450 nm)	^{n}Bu$_3$N	-	NMP	80% (71%)
8	PDI (450 nm)	^{n}Bu$_3$N	$MgCl_2$	NMP	88% (76%)
9	PDI (540 nm)	^{n}Bu$_3$N	$MgCl_2$	NMP	57%
10	PDI (365 nm)	^{n}Bu$_3$N	$MgCl_2$	NMP	76%

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the isolated yield.

Finally, I reproduced the reaction conditions (Table 6). When I used Eosin Y or PTH, the reaction made little progress (entry 1,3). However, the product **3aa** was obtained in 65% NMR yield using PDI as photoredox catalyst (entry 2). Next, I conducted the screening of solvents. From these results, I determined that NMP was optimal solvent (entry 6). Next, the amine and additive were examined, and the conditions under which $MgCl_2$ was added were determined to be the optimal conditions for this reaction using ^{n}Bu$_3$N. Finally, when the wavelength of visible light was changed, no improvement in yield of **3aa** was observed.

3.3.2 Substrate scope for enamide Heck-type tertiary alkylation

Table 7 Substrate scope

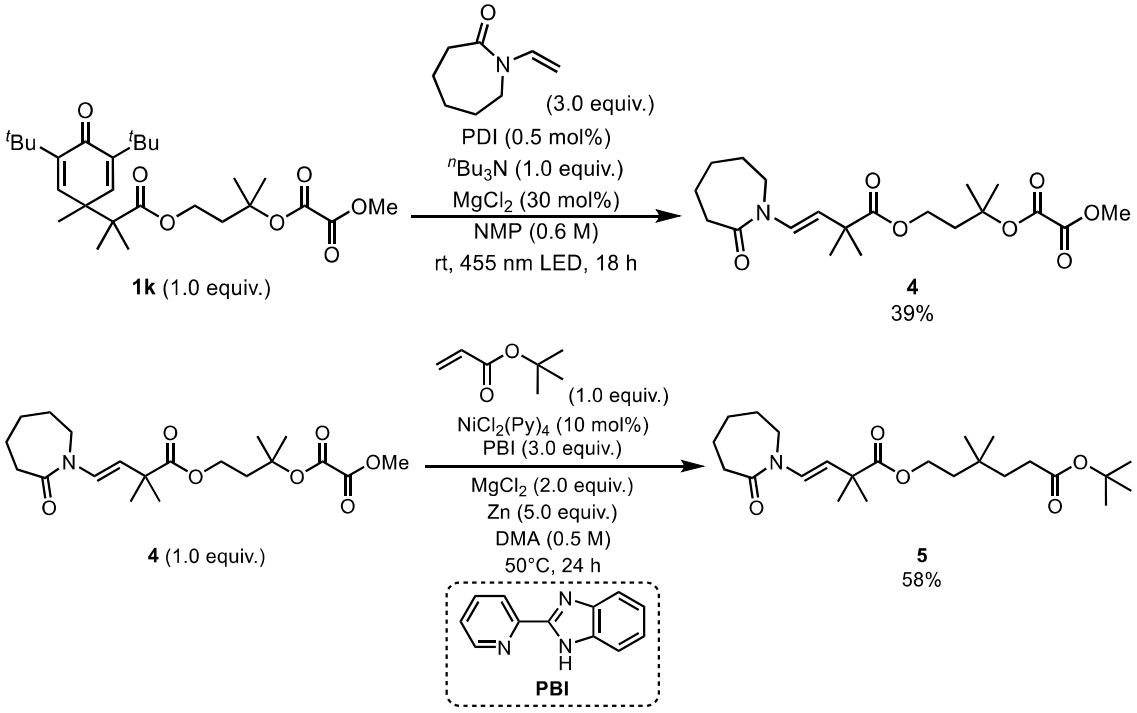


1 **2** (3.0 equiv.) **3**

Isolated yield of **3**		
3aa 76%	(Ar = Ph) **3ba**: 70% (Ar = 2,4,6-Me$_3$C$_6$H$_2$) **3ca**: 66%	(Ar = 4-OMeC$_6$H$_4$) **3da**: 71% (Ar = 4-BrC$_6$H$_4$) **3ea**: 60% (Ar = 3-BrC$_6$H$_4$) **3fa**: 56% (Ar = 2-BrC$_6$H$_4$) **3ga**: 60% (Ar = 2-furyl) **3ha**: 64%
3ia 74%	**3ja** 68%	**3ka** 87%
3la 37%	**3ab** 75%	**3ac** 95%

With the optimal reaction conditions, I examined the substrate scope for photoredox-catalyzed enamide Heck-type tertiary alkylation. First, the substituent effect of R^2 of cyclohexadienone **1** was examined. When the substrates with aryl substituent ester were used, the product **3ba** and **3ca** were obtained in 70% and 66% isolated yield. Products with benzyl substituent **3da-3ha** were produced with moderate yield. When I conducted the reaction using **1i**, the product **3ia** could be obtained in 74% yield. Next, substrates having a free alcohol skeleton and an oxalate skeleton were also adaptable to this reaction. Products **3ja** and **3ka** were obtained with moderate to good yield. Subsequently, the steric effect of carbonyl α-position of cyclohexadienone **1** was examined. As a result, the product **3la** was obtained in 37% isolated yield. Finally, I examined enamide **2**, five-membered cyclic enamide **2b** and six-membered cyclic enamide **2c** were adaptable to this reaction. The products **3ab** and **3ac** were obtained in 75% and 95% yield.

3.3.3 Application



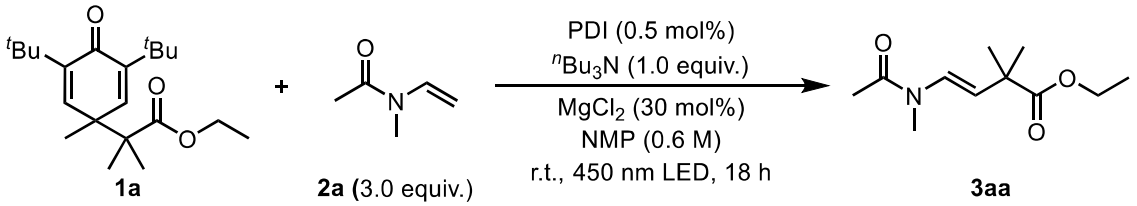
Scheme 2 Application (two-step coupling)

Subsequently, a two-step coupling was performed using a compound **1k** having a cyclohexadienone moiety and an oxalate moiety. At first, the photoredox-catalyzed enamide Heck-type tertiary alkylation was performed, the product **4** was obtained in 39% isolated yield. At second step, Ni-catalyzed coupling[6] between **4** and tert-butyl acrylate was conducted. As a result, the coupling product **5** was produced with moderate yield.

3.3.4 Mechanistic studies

3.3.4.1 Blank experiments

Table 8 Blank experiments



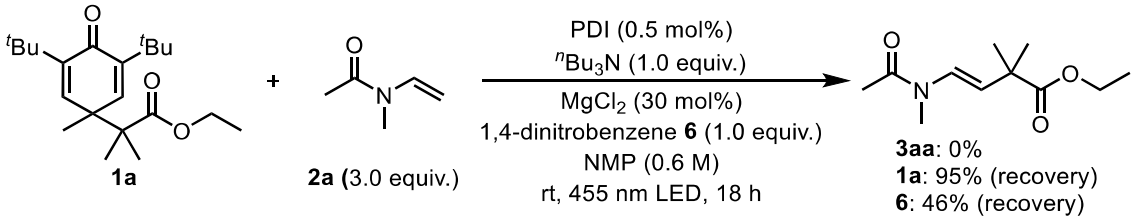
Entry	Deviation from standard conditions	NMR yield of **3aa**
1	none	88% (76%)
2	Without PDI	0%
3	Without ^{n}Bu$_3$N	0%
4	In the dark	0%

Determined by ^{1}H NMR with 1,1',2,2'-tetrachloroethane as an internal standard. The yield in parentheses was the

isolated yield.

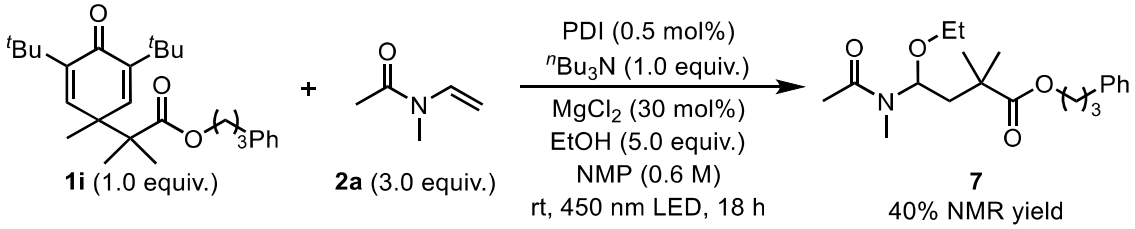
In the reaction of cyclohexadienone **1a** and enamide **2a**, the blank experiments were carried out (Table 8). In the absence of PDI or $^{n}Bu_3N$, the reaction did not proceed (entry 1,2). Next, the product was not afforded when the reaction was performed without LED light irradiation (entry 3). These results indicate that photocatalyst, amine reductant and visible light were all required for this transformation.

3.3.4.2 Single-electron transfer inhibition experiment



I conducted the single-electron transfer inhibition experiment. A single-electron transfer inhibitor, 1,4-dinitrobenzene **6**, was added to confirm whether the single-electron transfer process was involved. As a result, the enamide Heck-type product **3aa** could not be obtained at all, and cyclohexadienone **1a** was recovered in 95% yield and 1,4-dinitrobenzene **6** was recovered in 46% yield. This result suggested that 1,4-dinitrobenzene **6** inhibited the single-electron reduction from PDI to cyclohexadienone **1a**.

3.3.4.3 Study for trapping of cation intermediate



I conducted the study for trapping of cation intermediate. A nucleophile, EtOH, was added to trap the cation intermediate. As a result, the product **7** was obtained in 40% NMR yield.[7] This result suggested that enamide-Heck type reaction proceeded via cation intermediate.

3.3.4.4 Absorbance measurement

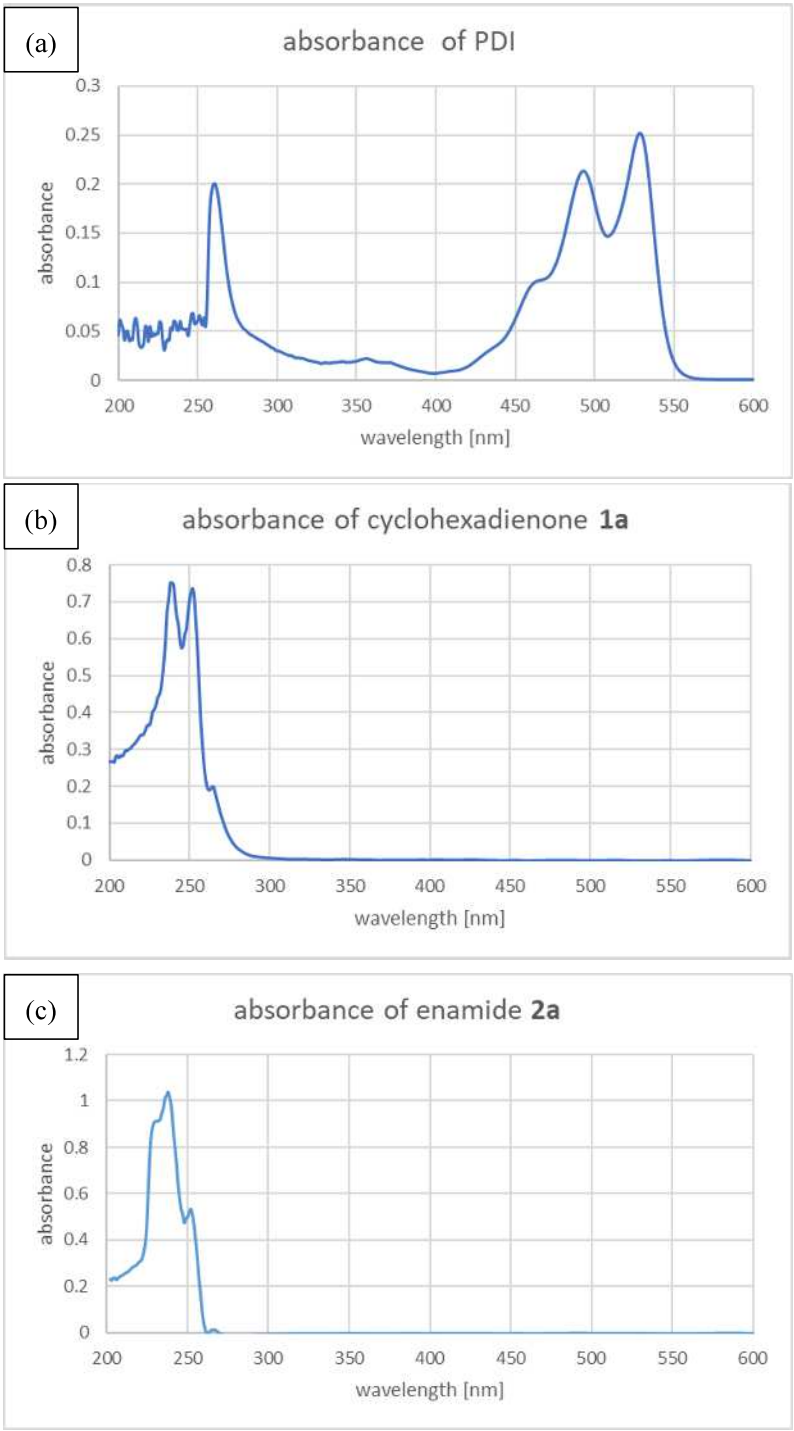
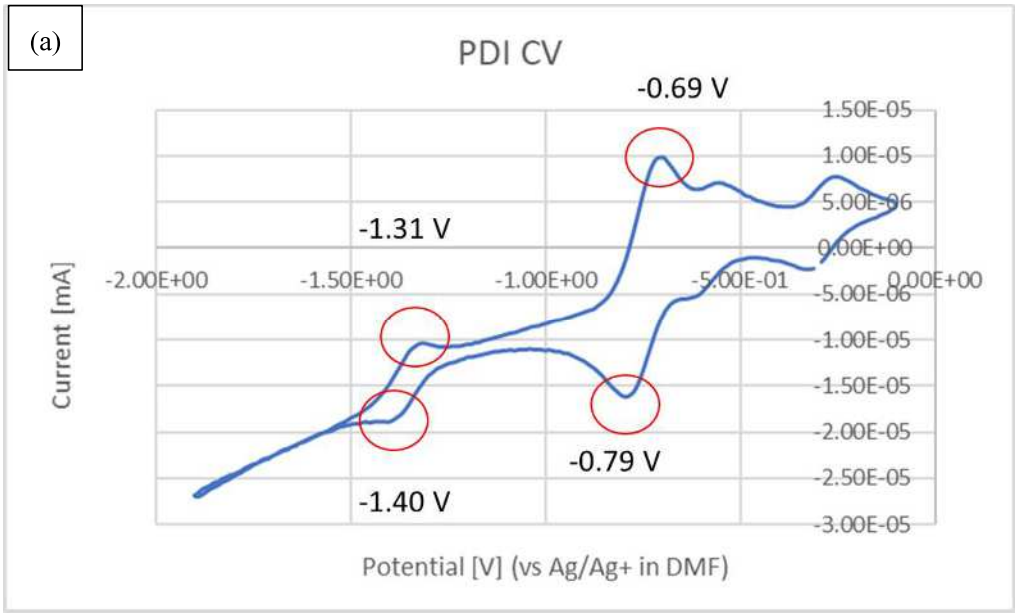


Figure 4 Absorbance of (a) PDI, (b) cyclohexadienone **1a**, (c) enamide **2a**.

I performed absorbance measurement to obtain absorbance information about PDI as a photoredox catalyst, cyclohexadienone **1a** and enamide **2a** (Figure 4). As a result, PDI has absorption between 420 nm and 550 nm, but cyclohexadienone **1a** and enamide **2a** have no absorption around 450 nm. These results suggested that even when irradiated with 450 nm LED, cyclohexadienone **1** was not excited, and the reaction proceeded with PDI assistance.

3.3.4.5 Cyclic voltammetry



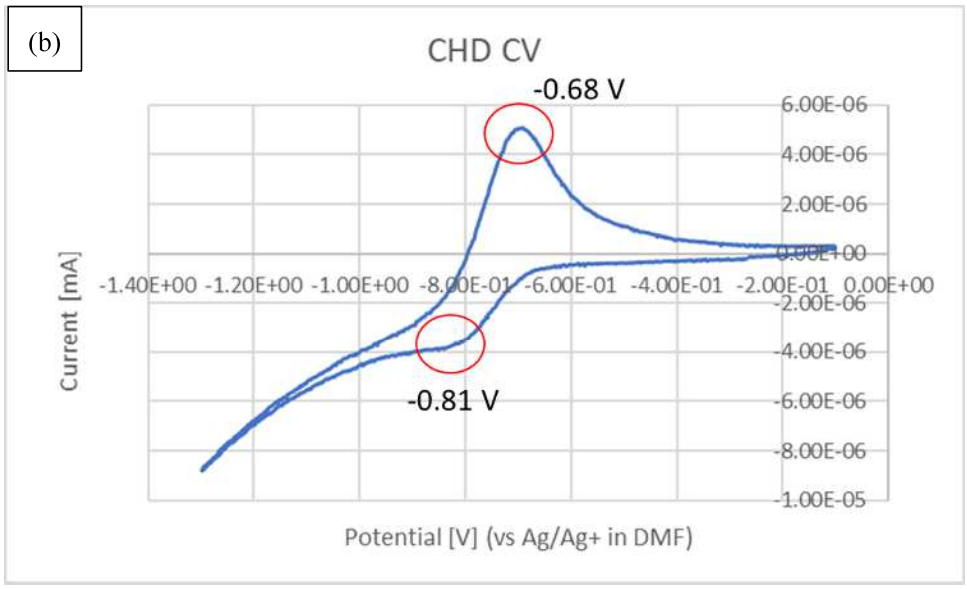


Figure 5 Cyclic voltammetry of (a) PDI, (b) cyclohexadienone **1a**.

Cyclic voltammetry of PDI was measured (Figure 5, a). As a result, the redox potential of PDI was $E_{1/2}[PDI^{-\cdot}/PDI^{*}]$ = -0.80 V and $E_{1/2}[PDI^{2-}/PDI^{-\cdot}]$ = -1.42 V (vs Fc in DMF). Previously, König group reported the redox potential of PDI was $E_{1/2}[PDI^{-\cdot}/PDI^{*}]$ = -0.88 V and $E_{1/2}[PDI^{2-}/PDI^{-\cdot}]$ = -1.18 V (vs Fc in DMF)[8]. Next, cyclic voltammetry of cyclohexadienone **1a** was measured (Figure 5, b). The redox potential of cyclohexadienone **1a** was $E_{1/2}[1a/1a^{-\cdot}]$ = -0.80 V (vs Fc in DMF). From these results, I proposed the catalytic cycle of PDI. Excited PDI^{*} is reductively quenched by $^{n}Bu_3N$ to give $PDI^{-\cdot}$ and the radical cation of *n*-butylamine ($^{n}Bu_3N^{\bullet+}$). Upon the second excitation, $PDI^{-\cdot *}$ reduces the cyclohexadienone **1** yielding the anion radical of cyclohexadienone **1** ($\mathbf{1}^{-\cdot}$) and

regenerating the neutral PDI.

3.3.4.6 Stern-Volmer quenching studies

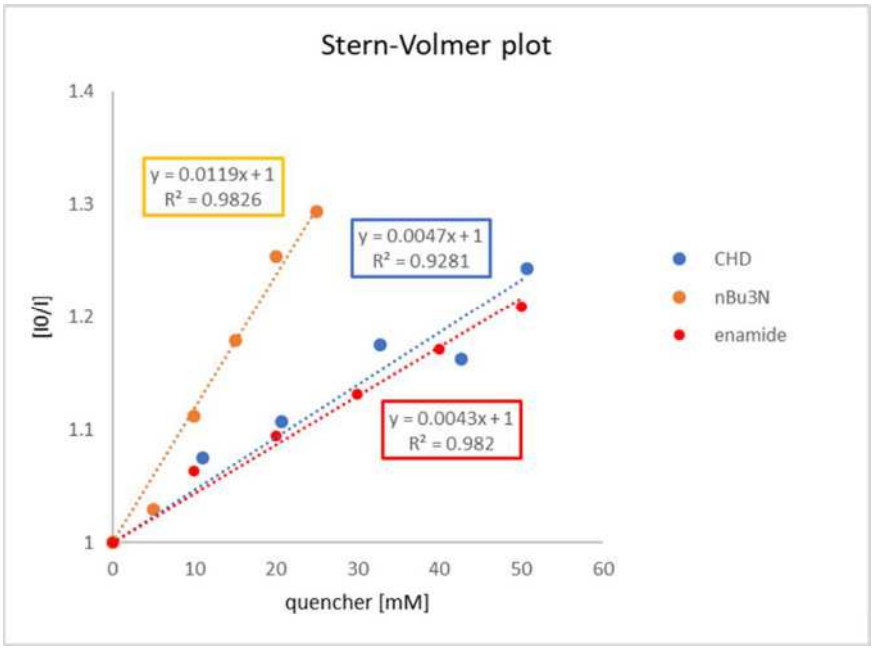


Figure 6 Stern-Volmer plot.

I carried out the Stern-Volmer studies of cyclohexadienone **1a**, enamide **2a** and tributylamine (Figure 6). The Stern-Volmer studies suggested that tributylamine rather than cyclohexadienone **1a** or enamide **2a** quenches the luminescence of the excited state of the photocatalyst.

3.3.4.7 Light ON/OFF experiment

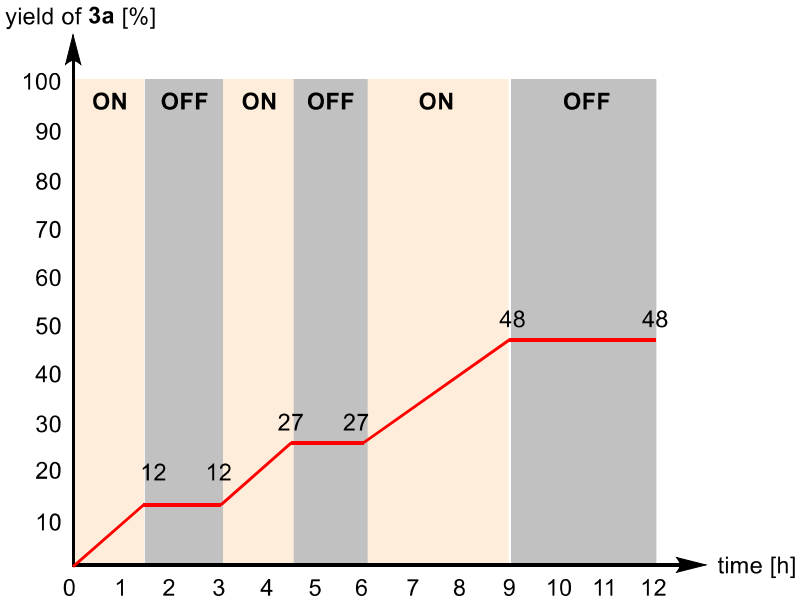


Figure 7 Light ON/OFF experiment.

I conducted the light ON/OFF experiment to make sure that it is progressing by the radical chain mechanism. The grey boxes represent the periods in which the reaction vessels were covered (dark period). The results shown that when the light was switched off, the reaction hardly carried out. These results demonstrated that the reaction might not undergo a radical-chain process.

3.4 Proposed reaction mechanism

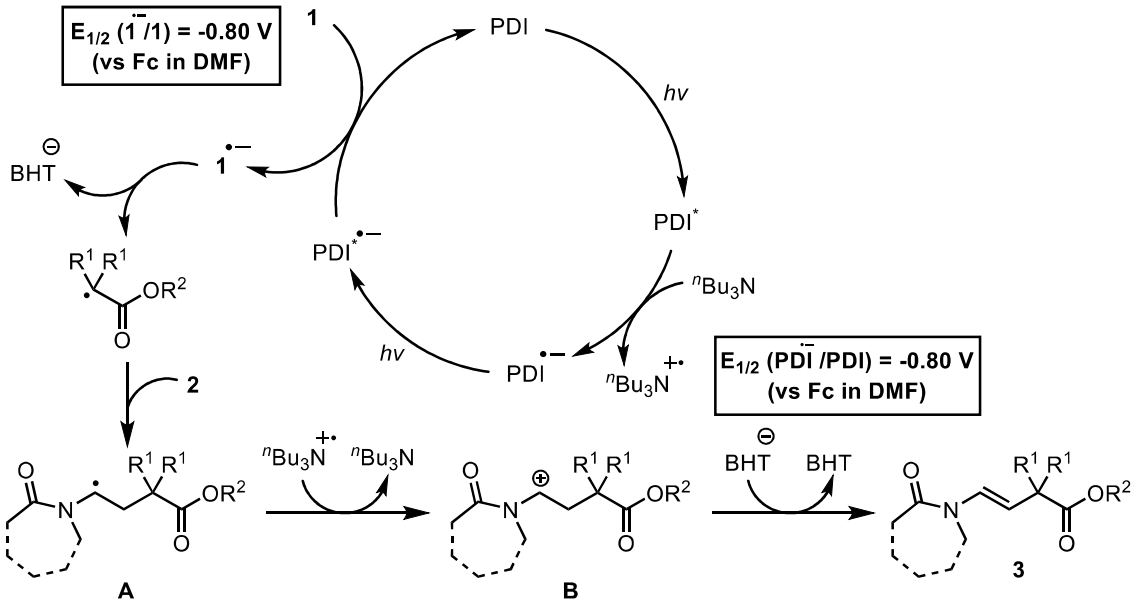


Figure 8 Proposed reaction mechanism

I proposed the reaction mechanism of photoredox-catalyzed enamide Heck-type tertiary alkylation with reference to the results of mechanistic experiments and the previous report by König group.[8] After PDI is excited by irradiation of LED to become an excited species, anionic radical species of PDI are generated by single-electron reduction by tributylamine. Upon the second excitation, $PDI^{-\cdot *}$ reduces the cyclohexadienone **1** yielding the anion radical of cyclohexadienone **1** ($\mathbf{1}^{-\cdot}$) and regenerating the neutral PDI. As for the catalytic cycle of PDI, it is not clear whether it proceeds with first excitation or second excitation. Next, the carbon-carbon bond cleavage of the anionic radical species of **1** proceeds. Then, radical addition of alkyl radical species proceeds to the enamide **2** resulting in radical intermediate **A**. Subsequently, the target product **3** is obtained by deprotonation.

3.5 Conclusion

In conclusion, I have developed the photoredox-catalyzed enamide-Heck type tertiary alkylation via carbon-carbon bond cleavage. This method gives moderate to good yields of enamide-Heck type products. Also, two-step coupling could be performed using a compound having cyclohexadienone moiety and oxalate moiety.

3.6 Reference

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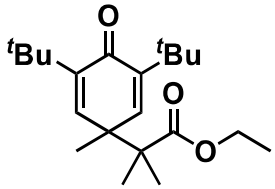
3.7 Experimental section

General procedure for synthesis of cyclohexadienone

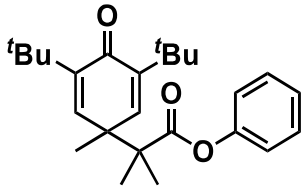
CuI (10 mol%), dtbbpy (10 mol%), and BHT (1.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar. The corresponding α-bromo carbonyl compound (1.0 equiv.) and DBU (2.0 equiv.), and dried toluene (1.0 M) were added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for overnight at room temperature. After this time, the contents of the flask were filtered through a plug of silica gel and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **1**.

ethyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1a**)



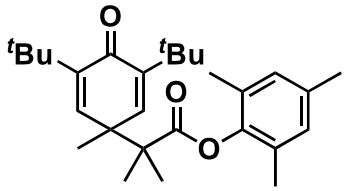
Following the general procedure above, using BHT (605.0 mg, 3.0 mmol), ethyl 2-bromo-2-methylpropanoate (585.2 mg, 3.0 mmol), CuI (57.2 mg, 0.30 mmol), dtbbpy (81.6 mg, 0.30 mmol), DBU (913.4 mg, 6.0 mmol) and dried toluene (3.0 mL) at room temperature for overnight, yielded the product **1a** (948.1 mg, 94%) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.55 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.23 (s, 18H), 1.21 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.4, 147.0, 143.7, 60.7, 49.0, 42.9, 34.9, 29.5, 21.9, 21.6, 14.3.

phenyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1b**)



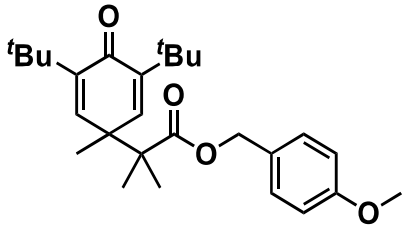
Following the general procedure above, using BHT (220.6 mg, 1.0 mmol), phenyl 2-bromo-2-methylpropanoate (247.5 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol), dtbbpy (26.4 mg, 0.10 mmol), DBU (304.5 mg, 2.0 mmol) and dried toluene (1.0 mL) at room temperature for overnight, yielded the product **1b** (641.9 mg, 85%) as yellow oil; IR (cm^{-1}): 2951, 2867, 1744, 1656, 1628, 1591, 1482, 1454, 1363, 1249, 1185, 1160, 1100, 930, 879, 744, 689; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.05-7.02 (m, 2H), 6.68 (s, 2H), 1.34 (s, 3H), 1.31 (s, 6H), 1.23 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 174.2, 150.7, 147.4, 143.3, 129.5, 125.9, 121.4, 49.4, 43.1, 35.1, 29.5, 22.1, 21.8.

mesityl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1c**)



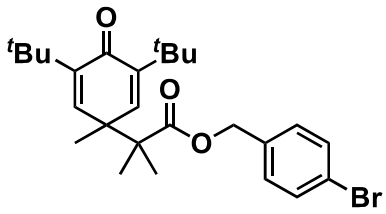
Following the general procedure above, using BHT (220.4 mg, 1.0 mmol), mesityl 2-bromo-2-methylpropanoate (301.4 mg, 1.1 mmol), CuI (19.5 mg, 0.10 mmol), dtbbpy (26.8 mg, 0.10 mmol), DBU (456.7 mg, 3.0 mmol) and dried toluene (1.0 mL) at room temperature for overnight, yielded the product **1c** (879.0 mg, 99%) as yellow oil; IR (cm^{-1}): 2952, 2868, 1734, 1639, 1464, 1248, 1192, 1125, 1101, 877, 853; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.88 (s, 2H), 6.77 (s, 2H), 2.27 (s, 3H), 2.13 (s, 3H), 1.42 (s, 3H), 1.34 (s, 6H), 1.24 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.3, 173.9, 147.6, 146.2, 143.6, 135.5, 129.5, 129.4, 49.7, 43.4, 35.1, 29.6, 22.8, 22.1, 20.8, 17.1.

4-methoxybenzyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1d**)



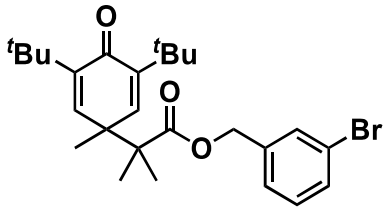
Following the general procedure above, using BHT (221.5 mg, 1.0 mmol), 4-methoxybenzyl 2-bromo-2-methylpropanoate (284.2 mg, 0.99 mmol), CuI (19.3 mg, 0.10 mmol), dtbbpy (26.8 mg, 0.10 mmol), DBU (456.7 mg, 3.0 mmol) and dried toluene (1.0 mL) at room temperature for overnight, yielded the product **1d** (846.0 mg, 99%) as yellow oil; IR (cm^{-1}): 2953, 2867, 1720, 1657, 1637, 1514, 1457, 1364, 1245, 1132, 1035, 879, 821; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.48 (s, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 1.18 (s, 18H), 1.16 (s, 3H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.4, 159.7, 147.2, 143.6, 130.2, 128.0, 114.0, 66.4, 55.3, 49.1, 43.0, 34.9, 29.5, 22.0, 21.6.

4-bromobenzyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1e**)



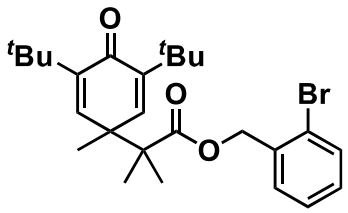
Following the general procedure above, using BHT (440.8 mg, 2.0 mmol), 4-bromobenzyl 2-bromo-2-methylpropanoate (672.0 mg, 2.0 mmol), CuI (38.0 mg, 0.20 mmol), dtbbpy (53.6 mg, 0.20 mmol), DBU (608.9 mg, 4.0 mmol) and dried toluene (2.0 mL) at room temperature for overnight, yielded the product **1e** (760.8 mg, 80%) as yellow oil; IR (cm^{-1}): 2954, 2866, 1724, 1657, 1638, 1487, 1458, 1364, 1250, 1133, 1107, 1070, 1012, 879, 798; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.48 (s, 2H), 5.05 (s, 2H), 1.18 (s, 21H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.2, 147.3, 143.3, 134.8, 131.8, 130.1, 122.4, 65.8, 49.2, 43.0, 34.9, 29.4, 22.0, 21.6.

3-bromobenzyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1f**)



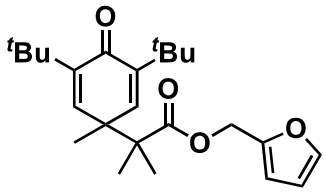
Following the general procedure above, using BHT (440.8 mg, 2.0 mmol), 3-bromobenzyl 2-bromo-2-methylpropanoate (672.0 mg, 2.0 mmol), CuI (38.0 mg, 0.20 mmol), dtbbpy (53.6 mg, 0.20 mmol), DBU (608.9 mg, 4.0 mmol) and dried toluene (2.0 mL) at room temperature for overnight, yielded the product **1f** (779.8 mg, 82%) as yellow oil; IR (cm^{-1}): 2953, 2866, 1723, 1657, 1637, 1487, 1457, 1364, 1249, 1131, 1070, 1012, 879, 799; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.49 (s, 2H), 5.07 (s, 2H), 1.19 (s, 3H), 1.19 (s, 18H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.2, 147.3, 143.3, 138.0, 131.5, 131.3, 130.3, 126.8, 122.7, 65.7, 49.3, 43.0, 35.0, 29.5, 22.0, 21.6.

2-bromobenzyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1g**)



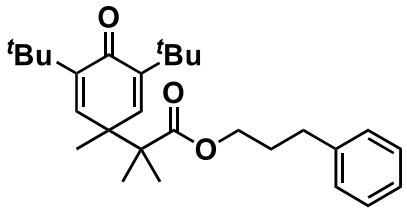
Following the general procedure above, using BHT (440.8 mg, 2.0 mmol), 2-bromobenzyl 2-bromo-2-methylpropanoate (672.0 mg, 2.0 mmol), CuI (38.0 mg, 0.20 mmol), dtbbpy (53.6 mg, 0.20 mmol), DBU (608.9 mg, 4.0 mmol) and dried toluene (2.0 mL) at room temperature for overnight, yielded the product **1g** (770.2 mg, 81%) as yellow oil; IR (cm^{-1}): 2954, 2866, 1726, 1658, 1638, 1458, 1364, 1241, 1133, 1046, 879, 750; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.52 (s, 2H), 5.19 (s, 2H), 1.23 (s, 3H), 1.18 (s, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.3, 175.2, 147.3, 143.5, 135.1, 133.0, 130.4, 130.0, 127.6, 123.8, 66.3, 49.4, 43.0, 34.9, 29.5, 22.1, 21.7.

furan-2-ylmethyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1h**)



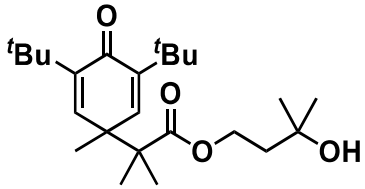
Following the general procedure above, using BHT (220.0 mg, 1.0 mmol), furan-2-ylmethyl 2-bromo-2-methylpropanoate (245.9 mg, 1.0 mmol), CuI (19.5 mg, 0.10 mmol), dtbbpy (26.6 mg, 0.10 mmol), DBU (456.7 mg, 3.0 mmol) and dried toluene (1.0 mL) at room temperature for overnight, yielded the product **1h** (637.1 mg, 82%) as yellow oil; IR (cm^{-1}): 2953, 2867, 1724, 1658, 1638, 1457, 1364, 1250, 1126, 1079, 1016, 918, 880, 814, 740; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41 (dd, J = 0.8, 1.9 Hz, 1H), 6.49 (s, 2H), 6.42 (dd, J = 0.4, 3.5 Hz, 1H), 6.36 (dd, J = 1.8, 3.3 Hz, 1H), 5.08 (s, 2H), 1.20 (s, 18H), 1.15 (s, 3H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.1, 149.4, 147.2, 143.5, 143.3, 110.9, 110.6, 58.2, 49.1, 43.0, 34.9, 29.5, 21.9, 21.5.

3-phenylpropyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1i**)



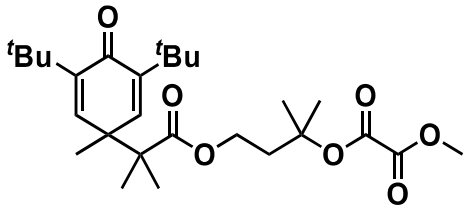
Following the general procedure above, using BHT (220.1 mg, 1.0 mmol), 3-phenylpropyl 2-bromo-2-methylpropanoate (282.9 mg, 1.0 mmol), CuI (19.6 mg, 0.10 mmol), dtbbpy (26.7 mg, 0.10 mmol), DBU (456.7 mg, 3.0 mmol) and dried toluene (1.0 mL) at room temperature for overnight, yielded the product **1i** (424.0 mg, 99%) as yellow oil; IR (cm^{-1}): 2952, 2865, 1721, 1658, 1637, 1454, 1364, 1251, 1164, 1136, 1020, 879, 741, 698; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 2H), 7.22-7.16 (m, 3H), 6.55 (s, 2H), 4.11 (t, J = 6.6 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 2.00-1.97 (m, 2H), 1.23 (s, 18H), 1.22 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.5, 147.2, 143.6, 141.0, 128.5, 128.4, 126.2, 64.2, 49.2, 43.0, 35.0, 32.3, 30.3, 29.5, 22.0, 21.7.

3-hydroxy-3-methylbutyl-2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoate (**1j**)



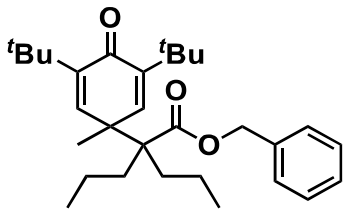
Following the general procedure above, using BHT (4406.8 mg, 20 mmol), 3-hydroxy-3-methylbutyl 2-bromo-2-methylpropanoate (5062.8 mg, 20 mmol), CuI (380.9 mg, 2.0 mmol), dtbbpy (536.8 mg, 2.0 mmol), DBU (6089.6 mg, 40 mmol) and dried toluene (40 mL) at room temperature for overnight, yielded the product **1j** (3376.2 mg, 43%) as a yellow oil; IR (cm^{-1}): 3515, 2958, 2868, 1719, 1657, 1637, 1458, 1364, 1251, 1165, 1137, 1079, 931, 879, 739; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.54 (s, 2H), 4.25 (t, J = 7.1 Hz, 2H), 1.85 (t, J = 7.1 Hz, 2H), 1.27 (s, 6H), 1.23 (s, 18H), 1.21 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.2, 175.5, 147.2, 143.5, 69.9, 61.8, 49.0, 43.0, 41.7, 35.0, 29.7, 29.5, 21.9, 21.7.

4-((2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-methylpropanoyl)oxy)-2-methylbutan-2-yl methyl oxalate (**1k**)



Cyclohexadienone **1j** (7066.4 mg, 18 mmol) and DMAP (219.9 mg, 1.8 mmol) were added under air to a flask equipped with a stir bar and Et_3N (4.99 mL, 36 mmol) and dried DCM (55 mL) were added by syringe. Then, methyl 2-chloro-2-oxoacetate (1.82 mL, 19.8 mmol) was dropped into the mixture at 0°C. After stirring overnight at room temperature, the contents were washed with saturated aqueous $NaHCO_3$ and brine (20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the product **1k** (4135.4 mg, 48%) as yellow oil; IR (cm^{-1}): 2954, 1723, 1658, 1637, 1457, 1364, 1324, 1251, 1201, 1167, 1128, 880, 790, 739; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.53 (s, 2H), 4.20 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 2.21 (t, J = 7.2 Hz, 2H), 1.59 (s, 6H), 1.23 (s, 18H), 1.21 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.1, 175.3, 158.6, 156.6, 147.1, 143.4, 85.2, 60.6, 53.4, 49.1, 42.9, 39.1, 34.9, 29.5, 25.9, 21.9, 21.6.

benzyl 2-(3,5-di-tert-butyl-1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-2-propylpentanoate (**1l**)

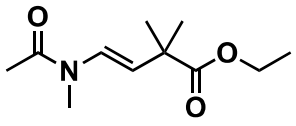


Following the general procedure above, using BHT (305.5 mg, 1.4 mmol), benzyl 2-bromo-2-propylpentanoate (438.5 mg, 1.4 mmol), CuI (27.3 mg, 0.14 mmol), dtbbpy (37.5 mg, 0.14 mmol), DBU (426.3 mg, 2.8 mmol) and dried toluene (1.4 mL) at room temperature for overnight, yielded the product **1l** (92.9 mg, 89%) as yellow oil; IR (cm^{-1}): 2958, 2871, 1720, 1656, 1637, 1455, 1363, 1211, 1140, 1044, 903, 880, 739, 696; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38-7.33 (m, 5H), 6.56 (s, 2H), 5.15 (s, 2H), 1.73-1.66 (m, 2H), 1.54-1.49 (m, 2H), 1.23-1.21 (m, 4H), 1.18 (s, 18H), 1.14 (s, 3H), 0.83 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 186.1, 174.5, 145.8, 144.6, 135.7, 128.6, 128.4, 128.1, 66.5, 56.1, 43.9, 42.1, 34.9, 34.2, 29.3, 23.2, 21.0, 18.5, 14.9, 14.2.

General procedure for alkyl transfer reaction

1 (0.50 mmol, 1.0 equiv), PDI (1.8 mg, 2.5×10^{-3} mmol, 0.50 mol%) were added into a 5 mL screw-vial under air. Then, $MgCl_2$ (14.2 mg, 0.15 mmol, 30 mol%), **2** (1.5 mmol, 3.0 equiv), $^nBu_3N$ (0.50 mmol, 1.0 equiv) and dried NMP (0.8 mL) were added in glovebox and sealed the vial. The reaction mixture was stirred upon 450 nm LED light irradiation in the photoreactor. After 18 hours, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **3**.

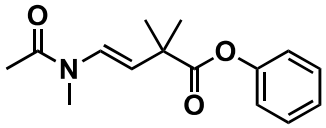
ethyl (E)-2,2-dimethyl-4-(N-methylacetamido)but-3-enoate (**3aa**)



Following the general procedure above, using **1a** (100.3 mg, 0.30 mmol), **2a** (89.2 mg, 0.90 mmol), PDI (1.1 mg, 1.5×10^{-3} mmol), $^nBu_3N$ (55.6 mg, 0.30 mmol), $MgCl_2$ (8.3 mg, 0.09 mmol) and dried

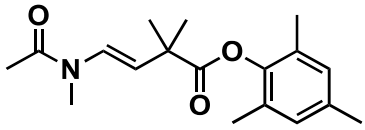
NMP (0.5 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3aa** (51.2 mg, 80%) as red oil; IR (cm^{-1}): 2976, 1723, 1675, 1642, 1380, 1245, 1140, 1018, 936; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 and 6.68 (both d, J = 14.8 and 14.0 Hz, 1H, rotamers), 5.20 and 5.19 (both d, J = 14.8 and 14.1 Hz, 1H, rotamers), 4.14 and 4.12 (both q, J = 7.0 and 7.2 Hz, 2H, rotamers), 3.10 and 3.06 (both s, 3H, rotamers), 2.21 and 2.20 (both s, 3H, rotamers), 1.35 (s, 6H), 1.27-1.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.8 and 176.4 (rotamers), 169.3 and 169.1 (rotamers), 128.2 and 126.2 (rotamers), 116.2 and 115.9 (rotamers), 60.9 and 60.8 (rotamers), 43.0 and 42.8 (rotamers), 33.1 and 29.5 (rotamers), 25.69 and 25.66 (rotamers), 22.8 and 22.0 (rotamers), 14.24 and 14.22 (rotamers).

phenyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3ba**)



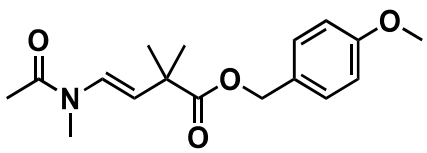
Following the general procedure above, using **1b** (191.3 mg, 0.50 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (14.2 mg, 0.15 mmol) and dried NMP (0.8 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ba** (91.5 mg, 70%) as red oil; IR (cm^{-1}): 2974, 1745, 1675, 1642, 1472, 1380, 1191, 1101, 1018; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.57 and 6.82 (both d, J = 14.9 and 14.1 Hz, 1H, rotamers), 7.40-7.35 (m, 2H), 7.25-7.22 (m, 1H), 7.06-7.04 (m, 2H), 5.33 and 5.30 (both s, 1H, rotamers), 3.14 and 3.11 (both s, 3H, rotamers), 2.25 and 2.23 (both s, 3H, rotamers), 1.51 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.3 and 175.0 (rotamers), 169.4 and 169.3 (rotamers), 151.1 and 151.0 (rotamers), 129.5 and 129.4 (rotamers), 128.9 and 126.9 (rotamers), 125.9 and 125.8 (rotamers), 121.5 and 121.4 (rotamers), 115.2 and 115.0 (rotamers), 43.4 and 43.1 (rotamers), 33.1 and 29.5 (rotamers), 25.7, 22.8 and 22.0 (rotamers).

mesityl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3ca**)



Following the general procedure above, using **1c** (212.1 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (16.5 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ca** (100.0 mg, 66%) as red oil; IR (cm^{-1}): 2922, 1738, 1640, 1473, 1378, 1353, 1306, 1244, 1193, 1118, 1022, 960, 868; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.57 and 6.84 (both d, J = 14.8 and 14.2 Hz, 1H, rotamers), 6.85 and 6.84 (both s, 2H, rotamers), 5.40 and 5.39 (both d, J = 14.9 and 14.1 Hz, 1H, rotamers), 3.14 and 3.11 (both s, 3H, rotamers), 2.26 and 2.25 (both s, 3H, rotamers), 2.23 (s, 3H), 2.06 (s, 6H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.4 and 174.1 (rotamers), 169.3 and 169.2 (rotamers), 145.99 and 145.91 (rotamers), 135.3 and 135.1 (rotamers), 129.68 and 129.60 (rotamers), 129.38 and 129.31 (rotamers), 128.9 and 126.8 (rotamers), 115.4 and 115.2 (rotamers), 43.5 and 43.2 (rotamers), 33.1 and 29.4 (rotamers), 25.7, 22.8 and 22.0 (rotamers), 20.8, 16.3.

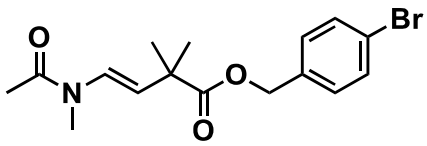
4-methoxybenzyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3da**)



Following the general procedure above, using **1d** (213.5 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.7 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (16.9 mg, 0.15 mmol) and dried NMP (0.8 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3da** (109.7 mg, 71%) as red oil; IR (cm^{-1}): 2969, 1722, 1674, 1641, 1513, 1465, 1381, 1302, 1241, 1120, 1018, 932, 821;

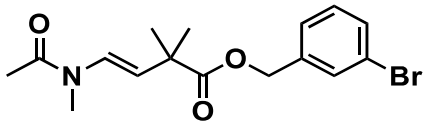
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 and 6.63 (both d, J = 15.1 and 14.1 Hz, 1H, rotamers), 7.27 (dd, J = 8.6, 5.2 Hz, 2H), 6.89-6.86 (m, 2H), 5.19 and 5.16 (both d, J = 14.9 and 14.1 Hz, 1H, rotamers), 5.06 and 5.04 (both s, 2H, rotamers), 3.80 (s, 3H), 3.06 and 3.02 (both s, 3H, rotamers), 2.20 and 2.13 (both s, 3H, rotamers), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.6 and 176.2 (rotamers), 169.3 and 169.1 (rotamers), 159.6 and 159.5 (rotamers), 129.8 and 129.7 (rotamers), 128.4 and 128.3 (rotamers), 128.2 and 126.3 (rotamers), 116.0 and 115.6 (rotamers), 113.98 and 113.93 (rotamers), 66.4 and 66.3 (rotamers), 55.3, 43.1 and 42.9 (rotamers), 33.1 and 29.4 (rotamers), 25.7 and 25.5 (rotamers), 22.7 and 21.9 (rotamers).

4-bromophenyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3ea**)



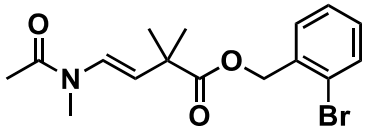
Following the general procedure above, using **1e** (237.8 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), ^{n}Bu$_3$N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.9 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ea** (106.4 mg, 60%) as red oil; IR (cm^{-1}): 2971, 1725, 1675, 1642, 1380, 1242, 1121, 1012, 936, 799; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 (dd, J = 8.3, 3.2 Hz, 2H), 7.45 and 6.66 (both d, J = 14.6 and 14.1 Hz, 1H, rotamers), 7.21 (dd, J = 8.2, 4.7 Hz, 2H), 5.17 (d, J = 13.9 Hz, 1H), 5.07 and 5.05 (both s, 2H, rotamers), 3.07 and 3.04 (both s, 3H, rotamers), 2.21 and 2.16 (both s, 3H, rotamers), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.4 and 176.1 (rotamers), 169.3 and 169.2 (rotamers), 135.2 and 135.1 (rotamers), 131.8 and 131.7 (rotamers), 129.7 and 129.6 (rotamers), 128.5 and 126.6 (rotamers), 122.3 and 122.1 (rotamers), 115.6 and 115.3 (rotamers), 65.8 and 65.7 (rotamers), 43.1 and 42.9 (rotamers), 33.1 and 29.4 (rotamers), 25.69 and 25.61 (rotamers), 22.8 and 21.9 (rotamers).

3-bromobenzyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3fa**)



Following the general procedure above, using **1f** (237.8 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.6 mg, 2.5×10^{-3} mmol), ^{n}Bu$_3$N (92.7 mg, 0.5 mmol), $MgCl_2$ (17.6 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3fa** (99.2 mg, 56%) as red oil; IR (cm^{-1}): 2975, 1725, 1673, 1640, 1570, 1473, 1380, 1242, 1120, 1017, 780; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48-7.42 (m, 2H), 7.24-7.20 (m, 2H), 6.68 (d, J = 14.0 Hz, 1H), 5.19 and 5.18 (both d, J = 14.9 and 14.1 Hz, 1H, rotamers), 5.09 and 5.07 (both s, 2H, rotamers), 3.09 and 3.05 (both s, 3H, rotamers), 2.21 and 2.17 (both s, 3H, rotamers), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3 and 175.9 (rotamers), 169.3 and 169.2 (rotamers), 138.6 and 138.4 (rotamers), 131.3 and 131.1 (rotamers), 130.7 and 130.6 (rotamers), 130.24 and 130.20 (rotamers), 128.7 and 126.6 (rotamers), 126.3 and 126.2 (rotamers), 122.6 and 122.5 (rotamers), 115.5 and 115.2 (rotamers), 65.5 and 65.4 (rotamers), 43.1 and 42.9 (rotamers), 33.1 and 29.4 (rotamers), 25.6 and 25.5 (rotamers), 22.8 and 21.9 (rotamers).

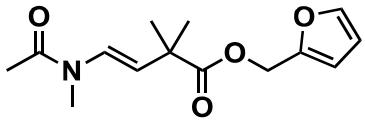
2-bromobenzyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3ga**)



Following the general procedure above, using **1g** (237.8 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.6 mg, 2.5×10^{-3} mmol), ^{n}Bu$_3$N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.6 mg, 0.15 mmol) and dried

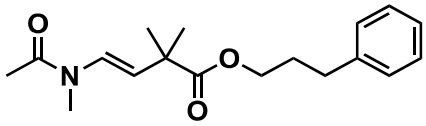
NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ga** (106.4 mg, 60%) as red oil; IR (cm^{-1}): 2972, 1726, 1675, 1642, 1471, 1381, 1241, 1119, 1017, 936, 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59-7.56 (m, 2H), 7.46 and 6.68 (both d, J = 14.7 and 14.1 Hz, 1H, rotamers), 7.37 (dd, J = 1.9, 7.6 Hz, 1H), 7.31 (ddd, J = 1.3, 7.6, 7.6 Hz, 1H), 7.22-7.17 (m, 1H), 5.24 and 5.21 (both d, J = 14.9 and 14.1 Hz, 1H), 5.19 and 5.17 (both s, 2H, rotamers), 3.09 and 3.05 (both s, 3H, rotamers), 2.20 and 2.17 (both s, 3H, rotamers), 1.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3 and 175.9 (rotamers), 169.3 and 169.2 (rotamers), 135.5 and 135.3 (rotamers), 133.0 and 132.9 (rotamers), 130.0 and 129.9 (rotamers), 129.78 and 129.72 (rotamers), 128.6 and 126.4 (rotamers), 127.5, 123.6 and 123.4 (rotamers), 115.7 and 115.5 (rotamers), 66.4 and 66.2 (rotamers), 43.3 and 43.0 (rotamers), 33.1 and 29.4 (rotamers), 25.7 and 25.6 (rotamers), 22.8 and 22.0 (rotamers).

furan-2-ylmethyl (E)-2,2-dimethyl-4-(N-methylacetamido)-but-3-enoate (**3ha**)



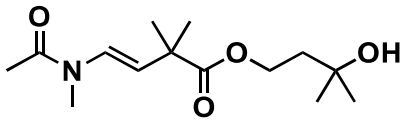
Following the general procedure above, using **1h** (193.6 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.7 mg, 2.5×10^{-3} mmol), ^{n}Bu_3N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.4 mg, 0.15 mmol) and dried NMP (0.8 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ha** (85.2 mg, 64%) as red oil; IR (cm^{-1}): 2972, 1726, 1675, 1642, 1471, 1380, 1241, 1118, 1015, 920, 884, 815, 745; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 and 6.65 (both d, J = 15.1 and 14.1 Hz, 1H, rotamers), 7.41 (dd, J = 0.8, 1.0 Hz, 1H), 6.40-6.35 (m, 2H), 5.19 and 5.15 (both d, J = 14.8 and 14.2 Hz, 1H, rotamers), 5.08 and 5.05 (both s, 2H, rotamers), 3.07 and 3.03 (both s, 3H, rotamers), 2.20 and 2.17 (both s, 3H, rotamers), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.4 and 176.0 (rotamers), 169.4 and 169.2 (rotamers), 149.7 and 149.5 (rotamers), 143.3 and 143.2 (rotamers), 128.5 and 126.4 (rotamers), 115.8 and 115.5 (rotamers), 110.6, 110.5 and 110.4 (rotamers), 58.58 and 58.54 (rotamers), 43.2 and 43.0 (rotamers), 33.1 and 29.4 (rotamers), 25.7 and 25.5 (rotamers), 22.8 and 21.9 (rotamers).

3-phenylpropyl (E)-2,2-dimethyl-4-(N-methylacetamido)but-3-enoate (**3ia**)



Following the general procedure above, using **1i** (211.8 mg, 0.50 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.9 mg, 2.6×10^{-3} mmol), ^{n}Bu_3N (92.7 mg, 0.50 mmol), $MgCl_2$ (14.0 mg, 0.15 mmol) and dried NMP (0.8 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ia** (112.4 mg, 74%) as red oil; IR (cm^{-1}): 2966, 1722, 1675, 1642, 1380, 1245, 1140, 1017, 935, 745, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 and 6.69 (both d, J = 14.9 and 14.3 Hz, 1H, rotamers), 7.29 (t, J = 7.3 Hz, 2H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 5.22 and 5.21 (both d, J = 14.9 and 14.1 Hz, 1H, rotamers), 4.12-4.07 (m, 2H), 3.10 and 3.07 (both s, 3H, rotamers), 2.70-2.66 (m, 2H), 2.21 and 2.20 (both s, 3H, rotamers), 2.00-1.93 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.7 and 176.3 (rotamers), 169.3 and 169.1 (rotamers), 141.2 and 141.1 (rotamers), 128.56 and 128.52 (rotamers), 128.48 and 126.3 (rotamers), 128.44 and 128.3 (rotamers), 126.1 and 126.0 (rotamers), 116.1 and 115.7 (rotamers), 64.2 and 64.0 (rotamers), 43.1 and 42.9 (rotamers), 33.0 and 32.1 (rotamers), 30.28, 30.27 and 29.4 (rotamers), 25.7, 22.7 and 21.9 (rotamers).

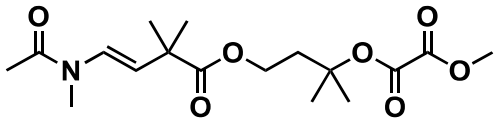
3-hydroxy-3-methylbutyl (E)-2,2-dimethyl-4-(N-methylacetamido)but-3-enoate (**3ja**)



Following the general procedure above, using **1j** (196.0 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.7 mg, 2.5×10^{-3} mmol), ^{n}Bu_3N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.7 mg, 0.15 mmol) and dried NMP

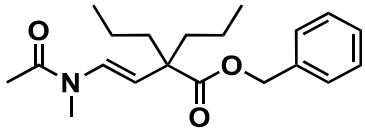
(0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ja** (92.6 mg, 68%) as red oil; IR (cm^{-1}): 3434, 2969, 1724, 1673, 1637, 1471, 1380, 1311, 1247, 1140, 1019, 937; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 and 6.68 (both d, J = 14.8 and 14.2 Hz, 1H, rotamers), 5.17 (d, J = 14.3 Hz, 1H), 4.28-4.23 (m, 2H), 3.09 and 3.06 (both s, 3H, rotamers), 2.21 and 2.20 (both s, 3H, rotamers), 1.85-1.82 (m, 2H), 1.35 (s, 6H), 1.26 and 1.26 (both s, 6H, rotamers); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.8 and 176.4 (rotamers), 169.4 and 169.3 (rotamers), 128.4 and 126.4 (rotamers), 115.8 and 115.6 (rotamers), 70.07 and 70.05 (rotamers), 62.1 and 62.0 (rotamers), 43.0 and 42.8 (rotamers), 41.5, 33.1 and 29.71 (rotamers), 29.75 and 29.4 (rotamers), 25.69 and 25.63 (rotamers), 22.8 and 22.0 (rotamers).

(E)-4-((2,2-dimethyl-4-(N-methylacetamido)but-3-enoyl)oxy)-2-methylbutan-2-yl methyl oxalate (**3ka**)



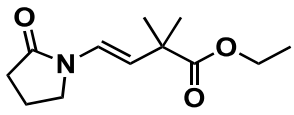
Following the general procedure above, using **1k** (239.5 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.7 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (16.9 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ka** (155.5 mg, 87%) as orange oil; IR (cm^{-1}): 2976, 2342, 2103, 1900, 1725, 1643, 1472, 1381, 1322, 1245, 1203, 1122, 1019, 962, 790; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43 and 6.68 (both d, J = 14.9 and 14.0 Hz, 1H, rotamers), 5.17 (d, J = 14.7 Hz, 1H), 4.22-4.18 (m, 2H), 3.87 (s, 3H), 3.09 and 3.06 (both s, 3H, rotamers), 2.23-2.19 (m, 2H), 2.21 (both s, 3H, rotamers), 1.59 and 1.58 (both s, 6H, rotamers), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.7 and 176.3 (rotamers), 169.3 and 169.2 (rotamers), 158.77 and 158.73 (rotamers), 156.6, 128.4 and 126.4 (rotamers), 115.7 and 115.4 (rotamers), 85.5 and 85.4 (rotamers), 60.9 and 60.7 (rotamers), 53.4, 43.0 and 42.8 (rotamers), 39.0 and 38.9 (rotamers), 33.0 and 29.4 (rotamers), 26.08 and 26.06 (rotamers), 25.6, 22.7 and 21.9 (rotamers).

benzyl (E)-2-(2-(N-methylacetamido)-vinyl)-2-propylpentanoate (**3la**)



Following the general procedure above, using **1l** (226.3 mg, 0.5 mmol), **2a** (148.7 mg, 1.5 mmol), PDI (1.6 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (16.5 mg, 0.15 mmol) and dried NMP (0.8 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3la** (61.3 mg, 37%) as red oil; IR (cm^{-1}): 2956, 2871, 1724, 1674, 1640, 1387, 1296, 1206, 1126, 1010; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39 and 6.66 (both d, J = 14.7 and 14.4 Hz, 1H, rotamers), 7.36-7.30 (m, 5H), 5.22 and 5.07 (both d, J = 15.3 and 14.3 Hz, 1H, rotamers), 5.13 and 5.12 (both s, 2H, rotamers), 3.09 and 3.05 (both s, 3H, rotamers), 2.20 and 2.11 (both s, 3H, rotamers), 1.75-1.62 (m, 4H), 1.25-1.09 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.9 and 175.4 (rotamers), 169.3 and 169.0 (rotamers), 136.3 and 136.1 (rotamers), 129.5 and 128.3 (rotamers), 128.6 and 128.5 (rotamers), 128.2 and 128.16 (rotamers), 128.10 and 127.1 (rotamers), 113.7 and 112.9 (rotamers), 66.5 and 66.4 (rotamers), 50.9 and 50.6 (rotamers), 39.7 and 39.5 (rotamers), 33.1 and 29.5 (rotamers), 22.8 and 22.0 (rotamers), 17.86 and 17.83 (rotamers), 14.6 and 14.5 (rotamers).

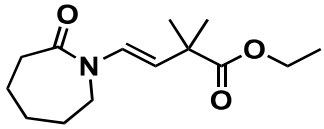
ethyl (E)-2,2-dimethyl-4-(2-oxopyrrolidin-1-yl)-but-3-enoate (**3ab**)



Following the general procedure above, using **1a** (167.3 mg, 0.5 mmol), **2b** (166.7 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), $^nBu_3N$ (92.7 mg, 0.5 mmol), $MgCl_2$ (16.7 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ab** (169.0 mg, 75%)

as red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.98 (d, J = 14.8 Hz, 1H), 5.17 (d, J = 14.7 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.52 (t, J = 7.3 Hz, 2H), 2.51-2.48 (m, 2H), 2.13-2.07 (m, 2H), 1.35 (s, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.5, 173.3, 122.9, 116.8, 60.8, 45.2, 42.9, 31.3, 25.5, 17.4, 14.1.

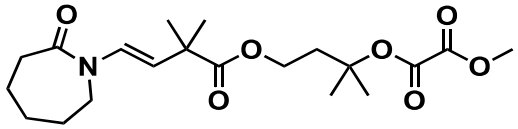
ethyl (E)-2,2-dimethyl-4-(2-oxoazepan-1-yl)-but-3-enoate (**3ac**)



Following the general procedure above, using **1a** (167.6 mg, 0.5 mmol), **2c** (208.6 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), ^{n}Bu$_3$N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.5 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **3ac** (120.3 mg, 95%) as red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (d, J = 14.8 Hz, 1H), 5.25 (d, J = 15.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.58 (t, J = 4.9 Hz, 2H), 2.63-2.61 (m, 2H), 1.76-1.63 (m, 6H), 1.35 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.9, 174.4, 125.9, 115.4, 60.8, 45.3, 43.0, 37.3, 29.5, 27.3, 25.6, 23.5, 14.2.

Application

(E)-4-((2,2-dimethyl-4-(2-oxoazepan-1-yl)but-3-enoyl)oxy)-2-methylbutan-2-yl methyl oxalate (**4**)

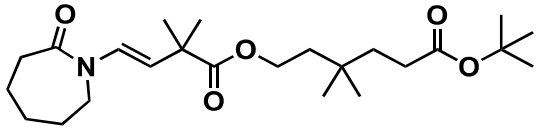


Following the general procedure above, using **1k** (256.7 mg, 0.54 mmol), **2c** (208.7 mg, 1.5 mmol), PDI (1.8 mg, 2.5×10^{-3} mmol), ^{n}Bu$_3$N (92.7 mg, 0.5 mmol), $MgCl_2$ (16.7 mg, 0.15 mmol) and dried NMP (0.83 mL) upon 450 nm LED light irradiation for 18 h, yielded the product **4** (83.4 mg, 39%) as red solid; IR (cm^{-1}): 2974, 2927, 2858, 1753, 1726, 1638, 1439, 1319, 1206, 1120, 1077, 991, 967, 817; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (d, J = 15.0 Hz, 1H), 5.21 (d, J = 15.0 Hz, 1H), 4.20 (t, J = 6.7 Hz, 2H), 3.87 (s, 3H), 3.58-3.56 (m, 2H), 2.63-2.61 (m, 2H), 2.20 (t, J = 6.7 Hz, 2H), 1.77-1.63 (m, 6H), 1.58 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.7, 174.3, 158.7, 156.6, 126.2, 114.8, 85.5, 60.7, 53.4, 45.3, 43.0, 39.0, 37.2, 29.5, 27.3, 26.0, 25.5, 23.4.

General procedure for synthesis of **5**

4 (0.50 mmol, 1.0 equiv.), $NiCl_2(Py)_2$ (5.0×10^{-2} mmol, 10 mol%), PBI (1.5 mmol, 3.0 equiv.), $MgCl_2$ (1.0 mmol, 2.0 equiv.) and Zn (2.5 mmol, 5.0 equiv.) were added into a 5 mL screw-vial under air. Then, *tert*-butyl acrylate (0.50 mmol, 1.0 equiv.) and dried DMA (0.5 M) were added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for 24 h at 50°C. After 24 hours, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **5**.

tert-butyl (E)-6-((2,2-dimethyl-4-(2-oxoazepan-1-yl)but-3-enoyl)oxy)-4,4-dimethylhexanoate (**5**)



Following the general procedure above, using **4** (203.8 mg, 0.51 mmol), *tert*-butyl acrylate (65.4 mg, 0.51 mmol), $NiCl_2(Py)_2$ (22.3 mg, 5.0×10^{-2} mmol), PBI (292.8 mg, 1.5 mmol), $MgCl_2$ (95.2 mg, 1.0 mmol), Zn (163.5 mg, 2.5 mmol) and dried DMA (1.0 mL) at 50°C for 24 h, yielded the product **5** (125.4 mg, 58%) as a red oil; IR (cm^{-1}): 3072, 2974, 2875, 1737, 1696, 1651, 1458, 1399, 1295, 1203, 1125, 965, 808; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (d, J = 15.8 Hz, 1H), 5.24 (d, J = 15.0 Hz, 1H), 4.11 (t, J = 7.3 Hz, 2H), 3.59-3.57 (m, 2H), 2.63-2.61 (m, 2H), 2.21-2.18 (m, 2H), 1.75-1.65 (m, 6H),

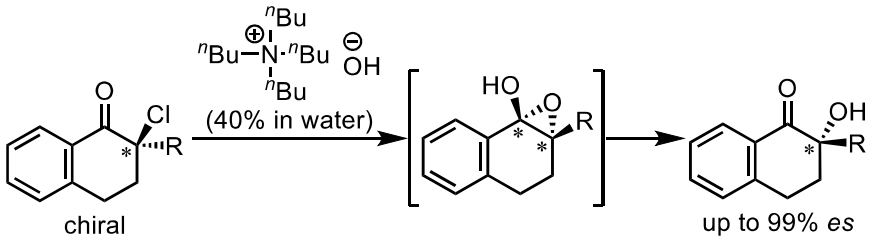
1.54 (t, J = 7.3 Hz, 4H), 1.44 (s, 9H), 1.34 (s, 6H), 0.91 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.9, 174.3, 173.5, 126.0, 115.2, 80.2, 62.1, 45.3, 43.0, 39.5, 37.3, 37.0, 32.0, 30.8, 29.5, 28.1, 27.3, 27.0, 25.6, 23.5.

Chapter 4 Lewis acid-catalyzed stereospecific hydroxylation of chiral tertiary alkyl halides

4.1 Introduction

Tertiary α-hydroxycarbonyl compounds bearing chiral center are important structural motifs that are present in many biologically active and pharmaceutically relevant compounds[1]. Furthermore, they are valuable synthetic intermediates in some important organic syntheses.[2] Therefore, the development of methods for synthesizing chiral tertiary α-hydroxycarbonyl compounds has received considerable attention.

Many methods of α-hydroxylation of carbonyl compounds have been developed with oxygen or peroxide as oxidant.[3] Also, synthesis of chiral tertiary α-hydroxycarbonyl compounds have been reported recently. There are two methods (enantioselective and enantiospecific method) as synthesis of chiral compounds. Because enantioselective hydroxylation with chiral catalyst is very difficult, many of the reports are cyclic compounds in which intermediates tend to have a planar structure.[4,5] On the other hand, Liu group reported enantioselective hydroxylation to 1,3-dicarbonyl compound.[6] This reaction achieved a high enantioselectivity by using a chiral catalyst derived from amino acids. Another synthesis of chiral alcohols is a stereospecific reaction that is excellent as a method of reflecting the chirality of the raw material in the product without impairing it. S_N2 reactions are generally known as stereospecific reactions, but these reactions to tertiary alkyl halides are difficult due to steric hindrance, and reported examples are limited. For example, Shibatomi group achieved enantiospecific hydroxylation of chiral cyclic tertiary alkyl chloride to obtain the steric inversion hydroxy products (Scheme 1).[7]

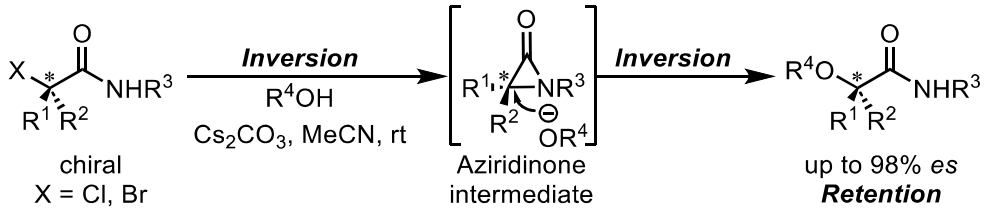


Scheme 1 Enantiospecific hydroxylation reported by Shibatomi group

Since there are few synthetic methods for chiral tertiary α-hydroxycarbonyl compounds, development of efficient methods is highly desired.

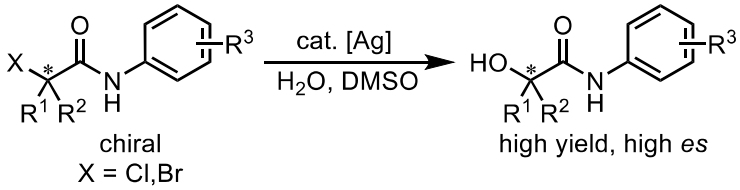
4.2 Previous work and this work

The authors have previously reported stereospecific etherification of α-halocarboxamide as chiral tertiary alkyl halides.[8] The authors proposed that stereospecific etherification proceed via formation of aziridinone intermediate promoted by base, S_N2 reaction of alcohol to aziridinone intermediate (Scheme 2).



Scheme 2 Previous work (stereospecific etherification)

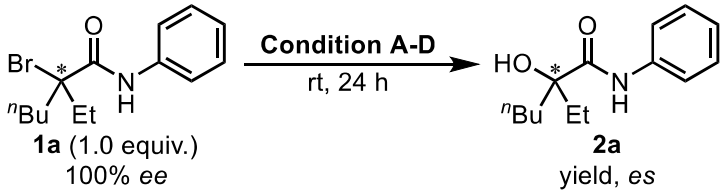
Here, I reported that Ag-catalyzed stereospecific hydroxylation of chiral tertiary α-haloamides (Scheme 3).



Scheme 3 This work

4.3 Results and discussion

4.3.1 Optimization of reaction conditions



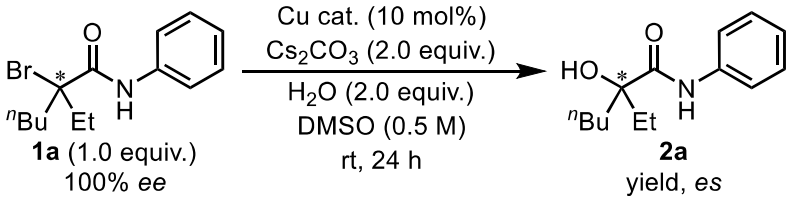
Condition A	Condition B	Condition C	Condition D
CuCN (without)	CuCN (without)	CuCN (without)	CuCN (10 mol%)
Cs_2CO_3 (2.0 equiv.)	Cs_2CO_3 (2.0 equiv.)	Cs_2CO_3 (2.0 equiv.)	Cs_2CO_3 (2.0 equiv.)
MeCN (0.5 M)	DMSO (0.5 M)	DMSO (0.5 M)	DMSO (0.5 M)
H_2O (without)	H_2O (without)	H_2O (2.0 equiv.)	H_2O (2.0 equiv.)
2a: 60%, 36% *es*	**2a**: 62%, 90% *es*	**2a**: 64%, 90% *es*	**2a**: 76%, 95% *es*

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Figure 1 Preliminary results for optimization of reaction conditions

Based on previous reported stereospecific etherification,[8] the reaction of chiral α-halocarboxamide **1a** (100% ee) and Cs_2CO_3 (2.0 equiv.) in MeCN (0.5 M) was initially carried out (Figure 1, Condition A). But **2a** was low enantiospecificity (36% es). I next examined that the reactions in dimethylsulfoxide (DMSO) were carried out (Figure 1, Condition B-D). Enantiospecificity of **2a** was extremely improved, **2a** was obtained in 76% yield, 95% es by adding 10 mol% of CuCN and 2.0 equivalents of water (Figure 1, Condition D).

Table 1 Optimization of Cu catalysts

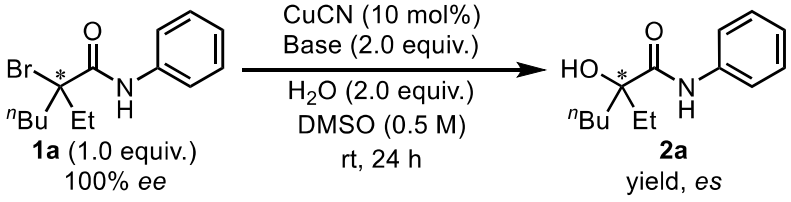


Entry	Cu cat.	Yield of **2a** (%)	*es* of **2a** (%)
1	CuCN	76	95
2	CuI	73	94
3	$CuBr(SMe_2)$	70	95
4	$CuCl_2$	80	92
5	$CuBr_2$	>99	92
6	$Cu(OAc)_2$	85	91
7	CuO	88	92

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

I conducted optimization of Cu catalyst for enantiospecific hydroxylation (Table 1). As a result of studying monovalent copper catalysts (entry 1-3), the yield was 70-76%, and the enantiospecificity was high. On the other hand, when a divalent copper catalyst was used (entry 4-7), the yield of the product **2a** was excellent, but a slight decrease in es was observed. From these results, I determined that optimal Cu catalyst was CuCN.

Table 2 Optimization of bases



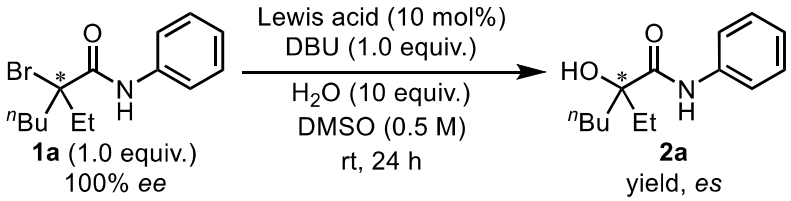
Entry	Base	Yield of **2a** (%)	*es* of **2a** (%)
1	Cs_2CO_3	76	95
2	K_2CO_3	58	98
3	Na_2CO_3	14	98
4	^{t}BuOK	13	78
5	$CsOH/H_2O$	35	72
6	DABCO	trace	-
7	DBU	44	99
8	DBU + Cs_2CO_3	63	97
9[a]	DBU	54	99
10[a,b]	DBU	54	99

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**. [a]10

equiv. of H_2O was used. [b]1.0 equiv. of DBU was used.

Subsequently, I examined the effects of bases. When K_2CO_3 and Na_2CO_3 were used, the product yield was low but excellent enantiospecificity (entry 2,3). Also, when I used ^{t}BuOK or CsOH, the product was produced with very low yield. Then, I examined the effect of organic base. When using DABCO (entry 6), only trace amount of product was detected, but when DBU was used (entry 7), the product **2a** was obtained in 44% yield and 99% es. Next, when the reaction was performed by combining DBU, which obtained good results in enantiospecificity, and Cs_2CO_3, which obtained a high yield, very good results were not obtained. Finally, the product **2a** was obtained in 54% yield and 99% es with 10 equivalents of H_2O and 1 equivalent of DBU (entry 10).

Table 3 Optimization of Lewis acids



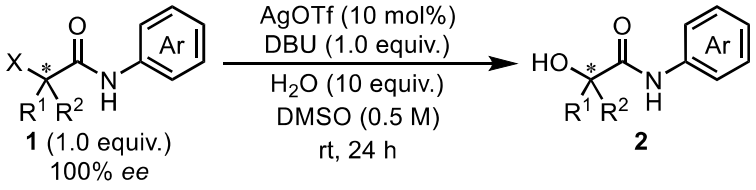
Entry	Lewis acid	Yield of **2a** (%)	*es* of **2a** (%)
1	CuCN	54	99
2	AgOTf	79	99
3	$AgSbF_6$	80	97
4	$Ag(CF_3SO_2)_2N$	70	98
5	AgBr	81	98
6	Ag_3PO_4	70	97
7	$Cu(OTf)_2$	62	98
8	$Zn(OTf)_2$	49	98
9	$Yt(OTf)_3$	49	97

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Next, I conducted the optimization of Lewis acids (Table 3). First, silver salts were examined (entry 2-6). As a result, product **2a** could be obtained with yields of 70-81%, and the enantiospecificity was also excellent. When I used AgOTf as a Lewis acid, the product **2a** was obtained in 79% yield and 99% es (entry 2). Other triflate salts were considered, but the yield could not be improved (entry 7-9). From these optimization results, I determined that AgOTf was optimal Lewis acid.

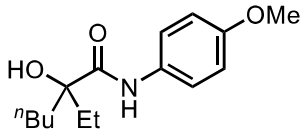
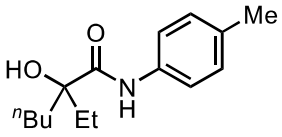
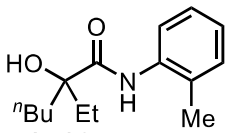
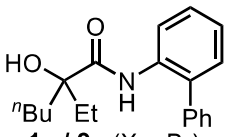
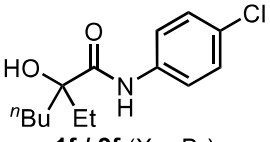
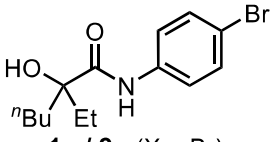
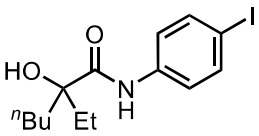
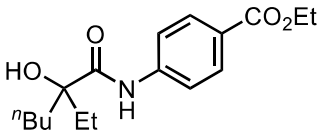
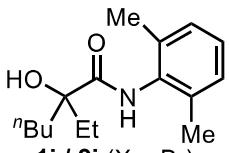
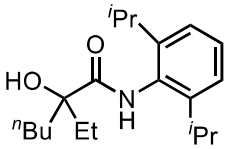
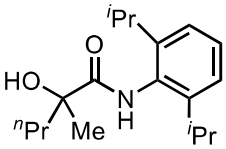
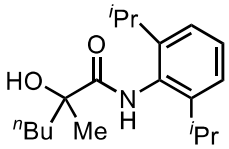
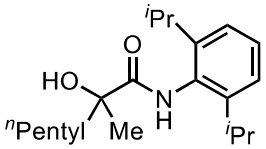
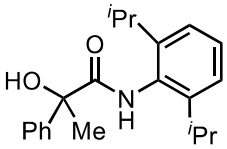
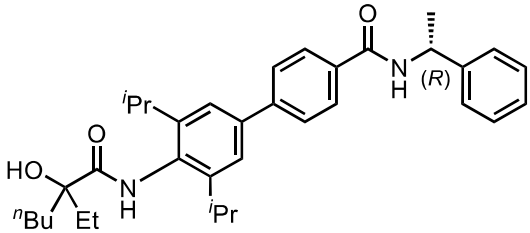
4.3.2 Substrate scope for enantiospecific hydroxylation

Table 4 Substrate scope



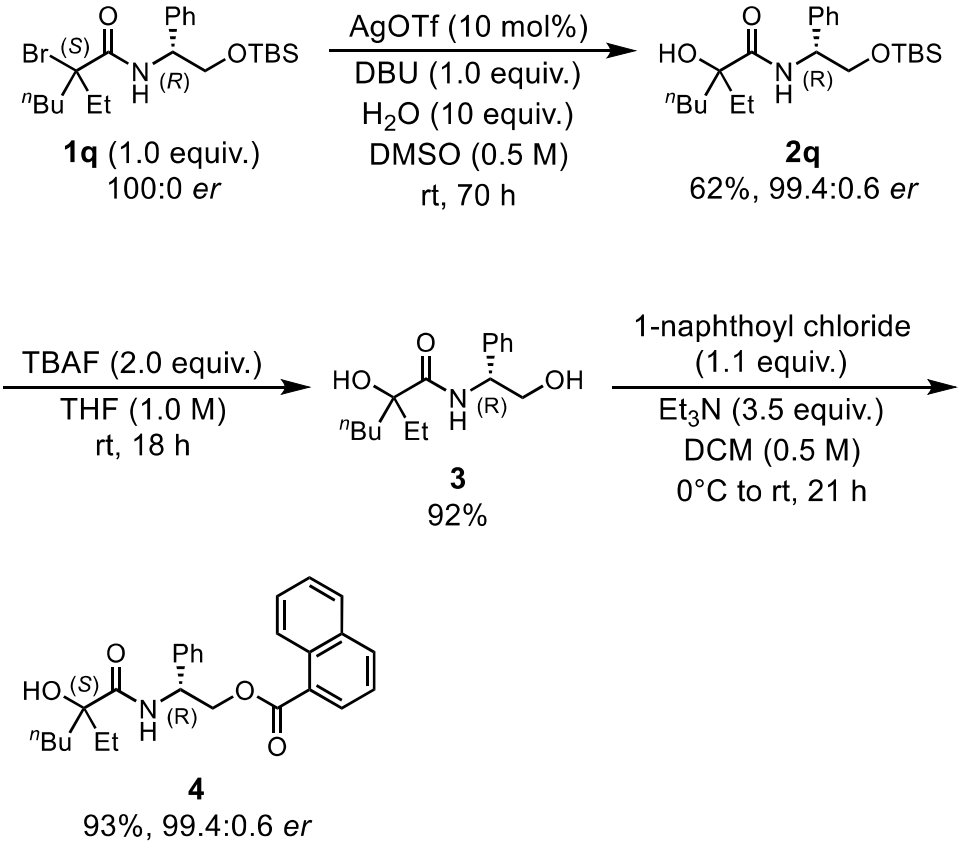
1 (1.0 equiv.)
100% *ee*

2

Substrate **1** / Product **2** (Yield and Enantiospecificity)
 **1b / 2b** (X = Br) 81%, 97% *es*
 **1c / 2c** (X = Br) 81%, 99% *es*
 **1d / 2d** (X = Br) 86%, 99% *es*
 **1e / 2e** (X = Br) 84%, 95% *es*
 **1f / 2f** (X = Br) 90%, 99% *es*
 **1g / 2g** (X = Br) 84%, 99% *es*
 **1h / 2h** (X = Br) 84%, 99% *es*
 **1i / 2i** (X = Br) 91%, 99% *es*
 **1j / 2j** (X = Br) 85%, >99% *es*
 **1k / 2k** (X = Br) 87%, >99% *es*
 **1l / 2l** (X = Br) 84%, >99% *es*
 **1m / 2m** (X = Br) 76%, >99% *es*
 **1n / 2n** (X = Br) 80%, 99% *es*
 **1o / 2o** (X = Cl) 83%, 92% *es*
 **1p / 2p** (X = Br) 41%, 92% *ds*

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2**/ee of substrate **1**.

With optimal reaction conditions, I next examined the substrate scope of enantiospecific hydroxylation (Table 4). A wide variety of structurally diverse can be hydroxylated in good yields and with excellent enantiospecificity. For example, *N*-aryl moiety tolerated electron-rich (**2b-2d**) and electron-deficient (**2e-2i**) substituents and sterically bulky (**2j**,**2k**) substituents. Also, I investigated about steric effect of carbonyl α-position. ^{n}Propyl, ^{n}butyl and ^{n}pentyl substituents were tolerated (**2l-2n**, 76-84% yield, up to >99% es). Surprisingly, hydroxylated product **2o** was obtained in 82% yield with 92% es when phenyl methyl substrate **1o** was used. The reaction with large α-bromocarboxamide (**1p**) possessing (*R*)-phenethylamine moiety gave the corresponding product (**2p**) in 41% yield and with 92% diastereospecificity (ds).



Scheme 4 Absolute configuration

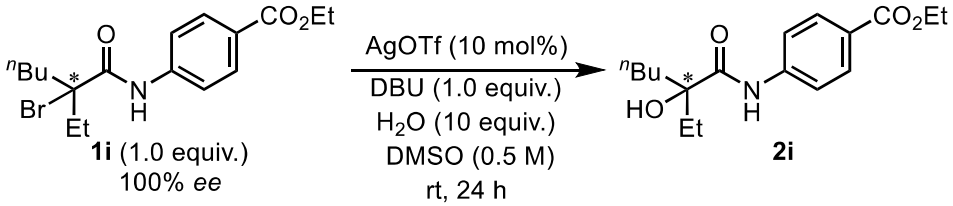
I next investigated whether the reaction proceeds via retention or inversion of configuration by examining enantiomerically pure α-bromocarboxamide **1q** possessing both (*S*)-*tert*-alkyl and (*R*)-phenethylalcohol moieties. Consequently, the enantiospecific hydroxylation of (*S*,*R*)-**1q** produced hydroxylated product (**2q**) in 62% yield and with 99% diastereospecificity (ds) (Scheme 4). But **2q** was not solid. Therefore, **2q** was further chemically converted to solid **4**. Product **4** was purified by HPLC using a chiral stationary phase and subsequently crystallized. X-ray crystallography revealed that **4** has the (S,R)-configuration, thereby confirming that the reaction proceeded with retention of

stereochemistry.

4.3.3 Mechanistic studies

To gain more insight into the mechanism of enantiospecific hydroxylation, several control experiments were conducted.

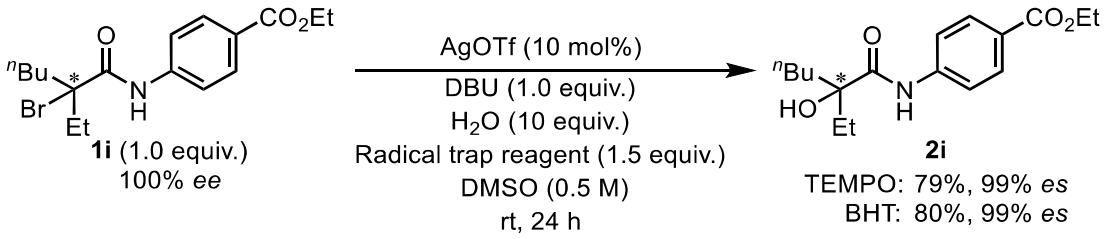
Table 5 Blank experiments



Entry	Deviation from the conditions	Isolated yield of **2i**	*es* of **2i**
1	none	91%	99%
2	without AgOTf	69%	99%
3	without DBU	0%	-
4	without DMSO	42%	99%

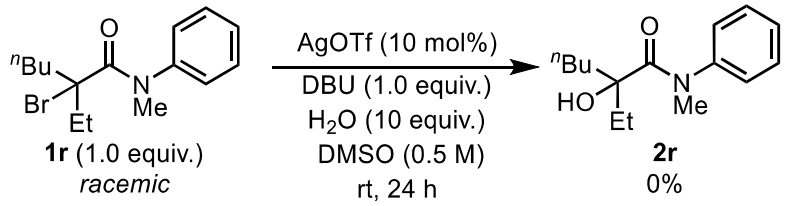
The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2i**/ee of substrate **1i**.

Initially, blank experiments were performed to confirm the effect of the additive. In the absence of AgOTf as a catalyst and DMSO as a solvent, the yield was lower than under standard conditions, but hydroxylation proceeded without loss of ee. In the absence of DBU, the reaction did not proceed at all. These blank experiments revealed that DBU is critical for this reaction and AgOTf, DMSO were also found to be necessary for increased product yield.



Scheme 5 Radical trap experiments

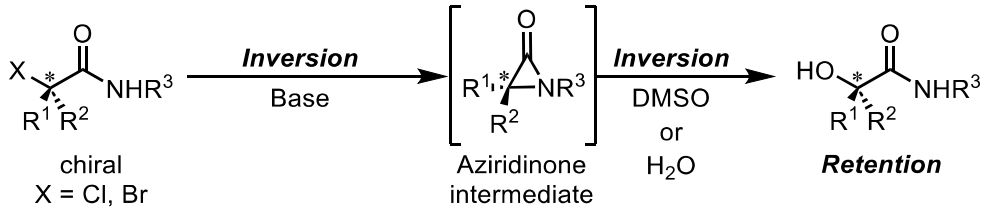
Radical trapping experiments with 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) or 2,6-di-tert-butyl-p-cresol (BHT) as a radical trap reagent, and substrate **1i** were carried out under the standard conditions (Scheme 5). **2i** was obtained in high yield and without loss of enantioselectivity even in the presence of radical trap reagent. These results suggested that the reaction does not proceed via radical intermediates.



Scheme 6 Confirmation of the need for amide NH

Next, I investigated the necessity of amide NH. **2r** was not observed as a product when I performed the reaction using racemic substrate **1r**. This result demonstrated the amide NH need for this reaction.

4.4 Reaction mechanism



Scheme 7 Proposed reaction mechanism

I proposed that stereospecific hydroxylation proceed via formation of aziridinone intermediate promoted by base, S_N2 reaction of DMSO or water to aziridinone intermediate (Scheme 7).

4.5 Conclusion

In conclusion, I have developed stereopecific hydroxylations of chiral α-bromocarboxamides. The reaction to produce α-hydroxycarboxamides was promoted by Ag salt and occurred in a retentive manner via an aziridinone intermediate.

4.6 Reference

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4.7 Experimental Section

Procedures and Characterizations

General procedure for synthesis of α-bromo(or Chloro)carboxamides

Method A

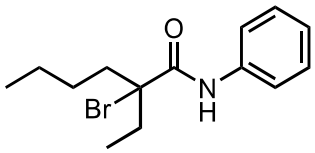
Carboxylic acid (10 mmol, 1.0 equiv.), and PBr_3 (0.33 mL, 3.3 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90°C. After this time, Br_2 (0.82 mL, 16 mmol) was added to the reaction mixture and the temperature was raised up 110°C. When the temperature was reached at 110°C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110°C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110°C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step.

α-bromo acid bromide synthesized above, Et_3N (4.2 mL, 30 mmol) were sequentially added to CH_2Cl_2 (20 mL, 0.5 M), then desired amine (10 mmol, 1.0 equiv.) was dropped into the mixture at 0°C. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were washed with saturated aqueous $NaHCO_3$ (20 mL), EtOAc (20 mL) and brine (20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic α-bromocarboxamide. Chiral α-bromocarboxamide was obtained after chiral separation with chiral column.

Method B

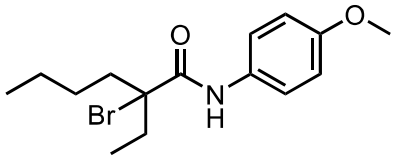
Carboxylic acid (12 mmol, 1.2 equiv.) and Thionyl chloride (2.88 mL, 40 mmol) were sequentially added under air to a reaction vessel equipped with stir bar. The resulting mixture stirred 30 minutes at 85°C. After this time, NCS (3.34 g, 25 mmol), Thionyl chloride (0.25 mL) and conc. HCl (4 drops) was added to the reaction mixture was stirred for 2.5 hours at 95°C. Then, the mixture was filtrated and concentrated in vacuo. Amine (10 mmol, 1.0 equiv.) and Et_3N (4.2 mL, 30 mmol) were sequentially added in CH_2Cl_2 (20 mL, 0.5 M), then the resulting crude including 2-chloro acid was dropped into the mixture at 0°C. After stirring overnight at room temperature, the contents of the reaction vessel dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting Hexane-EtOAc to afford the product.

2-bromo-2-ethyl-*N*-phenylhexanamide (**1a**)



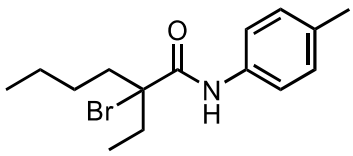
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), Aniline (0.90 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.52 g, 7.7 mmol, 77%) as yellow oil; IR (cm^{-1}): 3386, 2958, 2932, 2872, 1813, 1736, 1671, 1597, 1524, 1440, 1380, 1309, 1238, 1044, 931, 900, 829, 753, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.67 (brs, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.37-7.34 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 2.35-2.22 (m, 2H), 2.07-1.96 (m, 2H), 1.60-1.58 (m, 1H), 1.40-1.32 (m, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 137.3, 129.1, 125.0, 120.1, 79.4, 43.0, 36.6, 28.2, 22.5, 14.0, 10.6.
1a was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = -3.62 (c 0.152, CH_2Cl_2).

2-bromo-2-ethyl-*N*-(4-methoxyphenyl) hexanamide (**1b**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), p-anisidine (1232 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.78 g, 8.5 mmol, 85%) as yellow oil; IR (cm^{-1}): 3385, 2955, 2932, 2872, 2115, 1810, 1742, 1663, 1596, 1509, 1458, 1412, 1380, 1299, 1245, 1178, 1150, 1110, 1034, 932, 827, 756; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.57 (brs, 1H), 7.44 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 2.34-2.22 (m, 2H), 2.06-1.95 (m, 2H), 1.62-1.58 (m, 1H), 1.41-1.30 (m, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 157.0, 130.4, 122.0, 114.2, 79.5, 55.6, 43.0, 36.6, 28.2, 22.5, 13.9, 10.6.
1b was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-IA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +1.46 (c 0.235, CH_2Cl_2).

2-bromo-2-ethyl-N-(p-tolyl) hexanamide (**1c**)



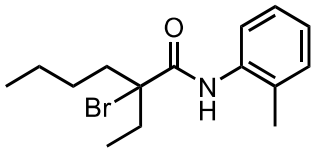
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), p-toluidine (1074 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.53 g, 8.2 mmol, 82%) as yellow solid; IR (cm^{-1}): 3292, 3193, 3124, 3034, 2953, 2930, 2870,

1890, 1812, 1749, 1654, 1599, 1508, 1449, 1402, 1378, 1310, 1243, 1125, 1069, 990, 934, 910, 858, 810, 751, 728, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.61 (brs, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 2.33 (s, 3H), 2.31-2.22 (m, 2H), 2.06-1.95 (m, 2H), 1.63-1.57 (m, 1H), 1.41-1.30 (m, 3H), 1.07 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 134.8, 134.7, 129.6, 120.2, 79.5, 43.0, 36.6, 28.2, 22.5, 20.9, 13.9, 10.6.

1c was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)

$[\alpha]^{25}_{D}$ = -6.65 (c 0.283, CH_2Cl_2).

2-bromo-2-ethyl-N-(o-tolyl) hexanamide (**1d**)

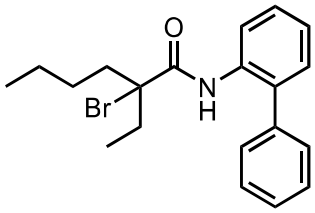


Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), o-toluidine (1.06 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.57 g, 8.2 mmol, 82%) as yellow oil; IR (cm^{-1}): 3398, 3338, 2957, 2931, 2872, 1811, 1675, 1589, 1523, 1454, 1379, 1302, 1251, 1207, 1151, 1113, 1046, 932, 821, 751, 712; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.63 (brs, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.25-7.20 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.36-2.24 (m, 5H), 2.09-1.98 (m, 2H), 1.67-1.59 (m, 1H), 1.43-1.31 (m, 3H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 168.5, 135.6, 130.5, 128.9, 126.9, 125.5, 122.1, 80.2, 43.1, 36.7, 28.3, 22.5, 17.9, 14.0, 10.6.

1d was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)

$[\alpha]^{25}_{D}$ = -1.10 (c 0.235, CH_2Cl_2).

2-bromo-N-(5-bromo-[1,1'-biphenyl]-2-yl)-2-ethylhexanamide (**1e**)

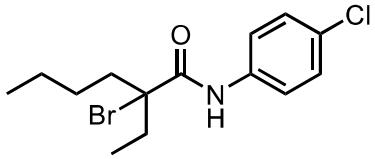


Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), [1,1'-biphenyl]-2-amine (1.692 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.74 g, 8.5 mmol, 85%) as yellow oil; IR(cm^{-1}): 3362, 3059, 2956, 2931, 2862, 2098, 1811, 1743, 1674, 1583, 1519, 1493, 1447, 1380, 1300, 1269, 1215, 1160, 1112, 1046, 946, 820, 755, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.70 (brs, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.50-7.47 (m, 2H), 7.44-7.36 (m, 4H), 7.29 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 2.26-2.13 (m, 2H), 1.95-1.83 (m, 2H), 1.47-1.40 (m, 1H), 1.34-1.25 (m, 3H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 137.8, 134.7, 133.2, 130.0, 129.5, 129.1, 128.4, 128.1, 124.8, 120.8, 78.7, 43.0, 36.5, 28.2, 22.5, 14.0, 10.5.

1e was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)

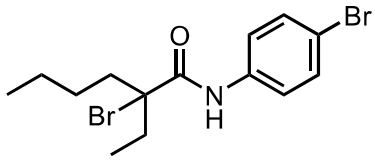
$[\alpha]^{25}_D$ = -20.1 (c 0.196, CH_2Cl_2).

2-bromo-N-(4-chlorophenyl)-2-ethylhexanamide (**1f**)



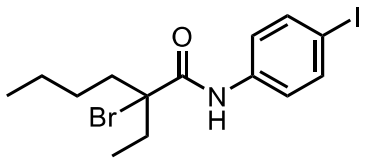
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), p-chloroaniline (1281 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.63 g, 7.9 mmol, 79%) as yellow solid; IR (cm^{-1}): 3294, 3191, 3117, 3058, 2952, 2871, 1891, 1672, 1652, 1595, 1524, 1489, 1452, 1396, 1302, 1235, 1177, 1150, 1092, 1012, 934, 880, 823, 730, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.66 (brs, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 2.33-2.21 (m, 2H), 2.07-1.96 (m, 2H), 1.61-1.56 (m, 1H), 1.39-1.32 (m, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 135.8, 130.1, 129.1, 121.3, 79.2, 42.9, 36.6, 28.2, 22.5, 14.0, 10.6.
1f was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/Acetone = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +2.44 (c 0.130, CH_2Cl_2).

2-bromo-*N*-(4-bromophenyl)-2-ethylhexanamide (**1g**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), p-bromoaniline (1281 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.83 g, 7.5 mmol, 75%) as white solid; IR (cm^{-1}): 3305, 2952, 2927, 2868, 1656, 1596, 1523, 1485, 1391, 1305, 1234, 1073, 1007, 919, 820; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.64 (brs, 1H), 7.45 (s, 4H), 2.31-2.19 (m, 2H), 2.06-1.95 (m, 2H), 1.60-1.52 (m, 1H), 1.37-1.29 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* =7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 136.3, 132.1, 121.6, 117.7, 79.2, 42.9, 36.6, 28.2, 22.5, 14.0, 10.6.
1g was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +2.22 (c 0.495, CH_2Cl_2).

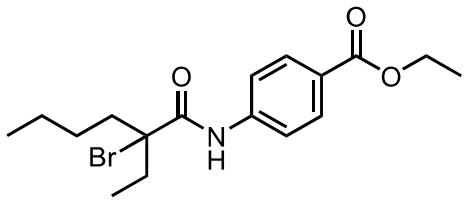
2-bromo-2-ethyl-N-(4-iodophenyl) hexanamide (**1h**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), p-

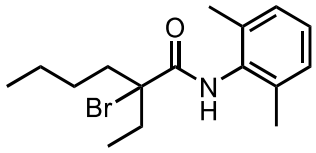
iodoaniline (2195 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (3.97 g, 9.4 mmol, 94%) as white solid; IR (cm^{-1}): 3320, 2949, 2924, 2866, 1655, 1593, 1518, 1481, 1387, 1306, 1233, 1180, 1002, 817; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.64 (brs, 1H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 2.32-2.20 (m, 2H), 2.07-1.96 (m, 2H), 1.61-1.51 (m, 1H), 1.40-1.27 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 138.0, 137.0, 121.8, 88.4, 79.2, 43.0, 36.6, 28.2, 22.5, 14.0, 10.6.
1h was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +1.93 (c 0.120, CH_2Cl_2).

ethyl 4-(2-bromo-2-ethylhexanamido) benzoate (**1i**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), ethyl 4-aminobenzoate (1659 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.25 g, 6.1 mmol, 61%) as yellow oil; IR (cm^{-1}): 3310, 3094, 2965, 2935, 2862, 2656, 2120, 1925, 1708, 1656, 1590, 1506, 1458, 1405, 1364, 1309, 1269, 1230, 1177, 1104, 1018, 935, 917, 877, 858, 826, 807, 769, 693, 675; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.81 (brs, 1H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.34-2.22 (m, 2H), 2.09-1.97 (m, 2H), 1.61-1.52 (m, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.36-1.30 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 166.1, 141.2, 130.8, 126.7, 119.1, 79.0, 61.0, 42.9, 36.5, 28.2, 22.5, 14.4, 14.0, 10.6.
1i was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +1.86 (c 0.250, CH_2Cl_2).

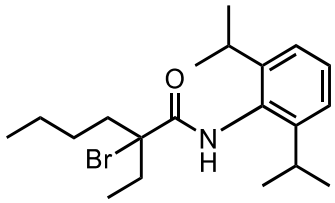
2-bromo-*N*-(2,6-dimethylphenyl)-2-ethylhexanamide (**1j**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), 2,6-dimethylaniline (1.24 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.15 g, 6.6 mmol, 66%) as white solid; IR (cm^{-1}): 3248, 3025, 2961, 2857, 2735, 2669, 2292, 1938, 1859, 1734, 1654, 1594, 1519, 1458, 1377, 1340, 1300, 1269, 1226, 1168, 1142, 1106, 1050, 1003, 966, 930, 915, 891, 835, 809, 769, 732; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.24 (brs, 1H), 7.13-7.07 (m, 3H), 2.38-2.23 (m, 2H), 2.26 (s, 6H), 2.13-2.00 (m, 2H), 1.70-1.61 (m, 1H), 1.51-1.45 (m, 1H), 1.41-1.34 (m, 2H), 1.16 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 135.1, 134.0, 128.4, 127.5, 79.7, 42.8, 36.4, 28.4, 22.6, 18.9, 14.0, 10.8.
1j was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)

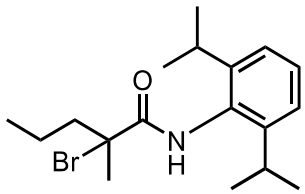
$[\alpha]^{25}_D$ = +4.26 (c 0.300, CH_2Cl_2).

2-bromo-*N*-(2,6-diisopropylphenyl)-2-ethylhexanamide (**1k**)



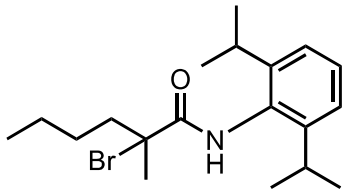
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), 2,6-diisopropylaniline (1.86 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (3.21 g, 8.4 mmol, 84%) as white solid; IR (cm^{-1}): 3349, 3309, 3067, 3025, 2958, 2867, 2101, 1927, 1857, 1653, 1590, 1490, 1458, 1379, 1255, 1219, 1180, 1140, 1115, 1058, 1038, 958, 935, 891, 839, 794, 741, 696, 659; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (brs, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 308 (sept, *J* = 6.8 Hz, 2H), 2.36-2.24 (m, 2H), 2.13-2.02 (m, 2H), 1.67-1.60 (m, 1H), 1.54-1.46 (m, 1H), 1.41-1.34 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 12H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 145.9, 131.2, 128.5, 123.5, 79.7, 42.7, 36.1, 28.7, 28.5, 23.7, 22.7, 14.1, 10.7.
1k was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = +2.23 (c 0.250, CH_2Cl_2).

2-bromo-N-(2,6-diisopropylphenyl)-2-methylpentanamide (**1l**)



Following the general procedure above (Method A), using 2-methylpentanoic acid (1.21 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), 2,6-diisopropylaniline (1.89 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.23 g, 6.3 mmol, 63%) as white solid; IR (cm^{-1}): 3298, 3069, 2958, 2929, 2868, 1588, 1498, 1464, 1379, 1330, 1243, 1179, 1155, 1141, 1100, 1053, 1018, 955, 935, 890, 832, 794, 739; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (brs, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.09 (sept, *J* = 6.9 Hz, 2H), 2.32-2.25 (m, 1H), 2.07 (s, 3H), 2.04-1.97 (m, 1H), 1.68-1.56 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 146.1, 131.1, 128.5, 123.5, 70.9, 46.1, 31.5, 28.8, 23.7, 19.8, 14.0.
1l was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)
$[\alpha]^{25}_D$ = -10.86 (c 0.228, CH_2Cl_2).

2-bromo-*N*-(2,6-diisopropylphenyl)-2-methylhexanamide (**1m**)

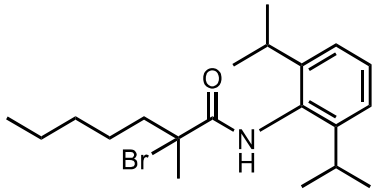


Following the general procedure above (Method A), using 2-methylhexanoic acid (1.35 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), 2,6-diisopropylaniline (1.86 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (2.62 g, 7.2 mmol, 72%) as white solid; IR (cm^{-1}): 3342, 3312, 2958, 1644, 1488, 1465, 1273, 1127, 942, 796; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.07 (brs, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 2H), 3.09-3.03 (m, 2H), 2.34-2.27 (m, 1H), 2.07 (s, 3H), 2.06-2.00 (m, 1H), 1.62-1.56 (m, 1H), 1.52-1.46 (m, 1H), 1.43-1.35 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 7.0 Hz, 6H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 146.1, 131.1, 128.5, 123.5, 71.1, 43.9, 31.5, 28.8, 28.7, 23.7, 22.6, 14.0.

1m was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)

$[\alpha]^{25}_D$ = -2.09 (c 0.744, CH_2Cl_2).

2-bromo-*N*-(2,6-diisopropylphenyl)-2-methylheptanamide (**1n**)

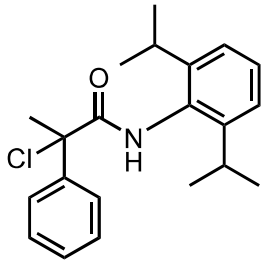


Following the general procedure above (Method A), using 2-methylheptanoic acid (1.58 mL, 10 mmol), Phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), 2,6-diisopropylaniline (1.86 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (3.23 g, 8.5 mmol, 85%) as white solid; IR (cm^{-1}): 3330, 3068, 2959, 2929, 2865, 2166, 2107, 1852, 1792, 1650, 1497, 1459, 1383, 1361, 1255, 1237, 1198, 1181, 1124, 1089, 1057, 1023, 936, 909; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.08 (brs, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.06 (sept, *J* = 6.9 Hz, 2H), 2.33-2.27 (m, 1H), 2.07 (s, 3H), 2.04-1.98 (m, 1H), 1.67-1.59 (m, 1H), 1.55-1.48 (m, 1H), 1.37-1.32 (m, 4H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 170.6, 146.1, 131.1, 128.5, 123.5, 71.2, 44.1, 31.65, 31.61, 28.8, 26.2, 23.7, 22.6, 14.0.

1n was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)

$[\alpha]^{25}_D$ = +1.94 (c 0.768, CH_2Cl_2).

2-chloro-N-(2,6-diisopropylphenyl)-2-phenylpropanamide (**1o**)

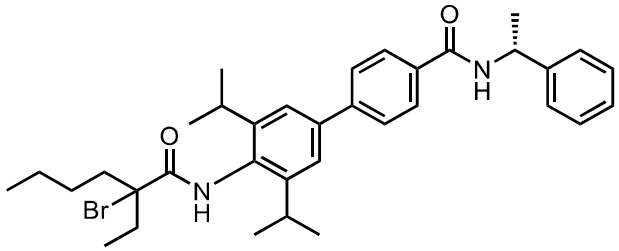


Following the general procedure above (Method B), using hydratropic acid (1.64 mL, 12 mmol), Thionyl chloride (2.88 mL, 40 mmol), NCS (3.34 mL, 25 mmol), Thionyl chloride (0.25 mL), conc. HCl (4 drops), 2,6 -diisopropylaniline (1.86 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (3.12 g, 9.1 mmol, 91%) as white solid; IR (cm^{-1}): 3307, 3065, 2962, 2931, 2867, 2100, 1655, 1590, 1490, 1439, 1280, 1240, 1179, 1123, 1053, 929, 831, 795, 772, 756, 732, 698; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 7.5 Hz, 2H), 7.65 (brs, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* =7.7 Hz, 2H), 2.89 (brs, 2H), 2.25 (s, 3H), 1.14 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.7, 146.3, 141.2, 130.6, 128.69, 128.64, 128.60, 126.0, 123.5, 73.4, 30.3, 28.6, 23.5.

1o was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)

$[\alpha]^{25}_D$ = +36.78 (c 0.499, CH_2Cl_2).

4'-(2-bromo-2-ethylhexanamido)-3',5'-diisopropyl-N-((R)-1-phenylethyl)-[1,1'-biphenyl]-4-carboxamide (**1p**)



Following the general procedure above (Method A), using 2-hexanoic acid (0.48 mL, 3.0 mmol), Phosphorus tribromide (0.15 mL, 1.1 mmol), Bromine (0.30 mL, 2.9 mmol), cyclohexene (0.70 mL), (R)-4`-amino-3`,5`-diisopropyl-N-(1-phenylethyl)-[1,1`-biphenyl]-4-carboxamide (1.02 g, 2.50 mmol), Triethylamine (1.3 mL, 3.0 equiv.) and CH_2Cl_2 (6.0 mL, 0.4 M), yielded the product (0.97 g, 1.6 mmol, 64%) as white solid; IR (cm^{-1}): 3293, 2959, 2868, 1636, 1534, 1490, 1457, 1302, 1266, 1210, 1108, 849, 768, 697; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.21 (brs, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.43-7.36 (m, 6H), 7.31-7.28 (m, 1H), 6.34 (d, *J* = 8.1 Hz, 1H), 5.37 (quint, *J* = 7.2 Hz, 1H), 3.13 (quint, *J* = 6.9 Hz, 2H), 2.37-2.25 (m, 2H), 2.14-2.03 (m, 2H), 1.68-1.59 (m, 1H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.52-1.48 (m, 1H), 1.42-1.34 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 12H), 1.17 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 166.3, 153.9, 146.5, 144.6, 143.2, 140.2, 133.3, 131.3, 128.8, 127.5, 127.4, 126.3, 122.6, 79.6, 49.3, 42.7, 36.1, 28.9, 28.5, 23.8, 22.7, 21.8, 14.0, 10.7.

1q was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent)

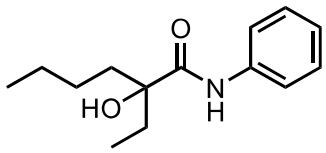
$[\alpha]^{25}_D$ = -34.98 (c 0.250, CH_2Cl_2).

Procedures and Characterization data for stereospecific hydroxylation

General procedure for hydroxylation

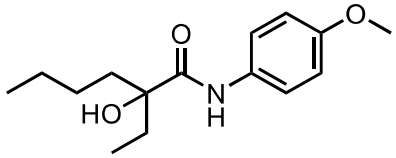
Alkyl bromide (0.25 mmol, 1.0 equiv.) or Alkyl chloride (0.25 mmol, 1.0 equiv.), was added under air to a dram vial equipped with a stir bar and a screw cap. Next, AgOTf (6.4 mg, 0.025 mmol, 10 mol%) was added to screw vial under glove box. After flashing nitrogen gas (purity 99.95%), dried DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL), H_2O (0.045 mL, 10 equiv.) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 24 h at 20 °C. After this time, the contents of the flask were washed with water and EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the hydroxylated product **2**.

2-ethyl-2-hydroxy-*N*-phenylhexanamide (**2a**)



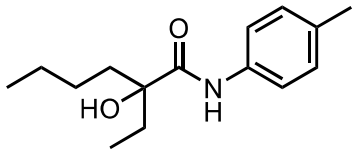
Following the general procedure above, using **1a** (74.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2a** (46.5 mg, 79%, 99% *ee*) as yellow oil; IR (cm^{-1}): 3361, 2956, 2928, 2860, 2108, 1661, 1596, 1521, 1440, 1378, 1309, 1241, 1169, 1076, 1029, 980, 901, 864, 752, 691; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.57 (brs, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 2.05-1.94 (m, 3H), 1.69-1.58 (m, 2H), 1.53-1.41 (m, 1H), 1.35-1.25 (m, 3H), 0.95 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.3, 137.5, 129.0, 124.4, 119.8, 79.4, 39.6, 32.8, 25.7, 23.0, 14.1, 7.8; $[\alpha]^{25}_D$ = +0.715 (c 0.365, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{22}NO_2$ ($M+H^+$): 236.1651; found 236.1652.

2-ethyl-2-hydroxy-*N*-(4-methoxyphenyl)hexanamide (**2b**)



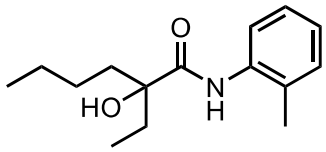
Following the general procedure above, using **1b** (82.2 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2b** (53.8 mg, 81%, 97% *ee*) as white solid; IR (cm^{-1}): 3310, 3085, 2955, 2931, 2872, 2858, 2834, 2729, 2678, 1978, 1958, 1875, 1648, 1595, 1508, 1464, 1438, 1411, 1377, 1296, 1261, 1231, 1171, 1150, 1112, 1072, 1031, 995, 919, 896, 872, 823, 800, 756, 730, 707; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.44 (brs, 1H), 7.50 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.1 Hz, 2H), 3.80 (s, 3H), 2.03-1.93 (m, 3H), 1.69-1.57 (m, 2H), 1.47-1.39 (m, 1H), 1.36-1.23 (m, 3H), 0.95 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 172.7, 156.4, 130.7, 121.4, 114.2, 79.4, 55.6, 39.6, 32.9, 25.7, 23.0, 14.1, 7.8; $[\alpha]^{25}_D$ = +2.20 (c 0.169, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{24}NO_3$ ($M+H^+$): 266.1756; found 266.1759.

2-ethyl-2-hydroxy-*N*-(p-tolyl)hexanamide (**2c**)



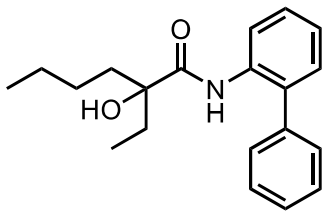
Following the general procedure above, using **1c** (78.1 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2c** (50.6 mg, 81%, 99% *ee*) as white solid; IR (cm^{-1}): 3391, 3347, 3032, 2955, 2925, 2861, 1651, 1588, 1522, 1457, 1401, 1375, 1311, 1273, 1232, 1160, 1109, 1017, 992, 924, 874, 815, 714; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.48 (brs, 1H), 7.47 (d, *J* = 8.6 Hz, 2H) 7.14 (d, *J* = 8.1 Hz, 2H), 2.32 (s, 3H), 2.05-1.93 (m, 3H), 1.67-1.57 (m, 2H), 1.45-1.39 (m, 1H), 1.36-1.23 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 172.8, 135.0, 134.0, 129.5, 119.7, 79.5, 39.6, 32.9, 25.6, 23.0, 20.9, 14.1, 7.8; $[\alpha]^{25}_D$ = +4.18 (c 0.152, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{24}NO_2$ ($M+H^+$): 250.1807; found 250.1809.

2-ethyl-2-hydroxy-*N*-(o-tolyl)hexanamide (**2d**)



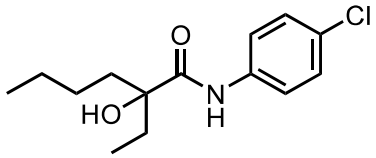
Following the general procedure above, using **1d** (78.1 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2d** (54.2 mg, 86%, 99% *ee*) as yellow oil; IR (cm^{-1}): 3361, 2956, 2929, 2872, 2323, 1660, 1587, 1520, 1455, 1377, 1290, 1251, 1216, 1169, 1113, 1045, 989, 838, 746, 710; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.52 (brs, 1H), 7.99 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.24-7.18 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 2.28 (s, 3H), 2.17-1.95 (m, 3H), 1.70-1.59 (m, 2H), 1.51-1.43 (m, 1H), 1.38-1.24 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 172.8, 135.6, 130.4, 128.2, 126.9, 124.8, 122.0, 79.7, 39.7, 33.0, 25.7, 23.0, 17.7, 14.1, 7.8; $[\alpha]^{25}_D$ = +1.19 (c 0.123, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{24}NO_2$ ($M+H^+$): 250.1807; found 250.1808.

N-([1,1'-biphenyl]-2-yl)-2-ethyl-2-hydroxyhexanamide (**2e**)



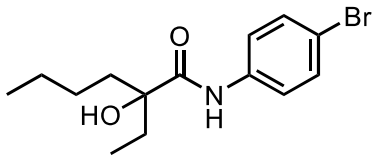
Following the general procedure above, using **1e** (93.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2e** (65.7 mg, 84%, 95% *ee*) as white solid; IR (cm^{-1}): 3265, 2955, 2928, 2857, 1655, 1583, 1522, 1447, 1301, 1268, 1215, 1170, 1112, 1072, 992, 919, 870, 750, 696; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.52 (brs, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.49-7.46 (m, 2H), 7.42-7.37 (m, 4H), 7.27 (dd, *J* = 1.8, 7.7 Hz, 1H), 7.19 (ddd, *J* = 1.1, 7.5 Hz, 1H), 1.94 (s, 1H), 1.87-1.76 (m, 2H), 1.59-1.47 (m, 2H), 1.35-1.23 (m, 3H), 1.20-1.12 (m, 1H), 0.88-0.84 (m, 6H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.0, 138.1, 134.5, 132.6, 130.1, 129.4, 128.9, 128.5, 128.0, 124.3, 121.0, 79.2, 39.6, 32.9, 25.6, 22.9, 14.1, 7.7; $[\alpha]^{25}_D$ = -18.2 (c 0.177, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{26}NO_2$ ($M+H^+$): 312.1964; found 312.1965.

N-(4-chlorophenyl)-2-ethyl-2-hydroxyhexanamide (**2f**)



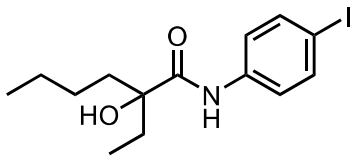
Following the general procedure above, using **1f** (83.2 mg, 0.25 mmol, 99.5% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2f** (61.4 mg, 90%, 99% *ee*) as white solid; IR (cm^{-1}): 3357, 2956, 2929, 2872, 2111, 1886, 1662, 1589, 1514, 1491, 1458, 1397, 1301, 1239, 1216, 1169, 1089, 1012, 981, 919, 870, 825, 679; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.61 (brs, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 2.05-1.90 (m, 3H), 1.67-1.57 (m, 2H), 1.44-1.40 (m, 1H), 1.34-1.21 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.1, 135.9, 129.2, 128.9, 120.8, 79.5, 39.4, 32.7, 25.5, 22.8, 13.9, 7.7; $[\alpha]^{25}_D$ = +3.76 (c 0.188, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{21}ClNO_2$ ($M+H^+$): 270.1261; found 270.1263.

N-(4-bromophenyl)-2-ethyl-2-hydroxyhexanamide (**2g**)



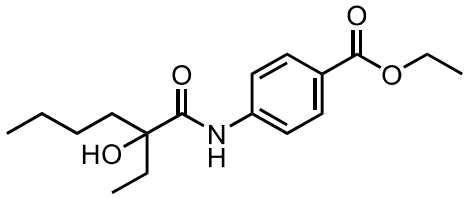
Following the general procedure above, using **1g** (94.3 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2g** (66.3 mg, 84%, 99% *ee*) as white solid; IR (cm^{-1}): 3331, 2957, 2931, 2860, 2110, 1888, 1654, 1587, 1515, 1438, 1394, 1300, 1218, 1170, 1137, 1125, 1071, 1007, 985, 949, 826, 713, 671; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.61 (brs, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 2H), 2.05-1.93 (m, 3H), 1.69-1.57 (m, 2H), 1.47-1.38 (m, 1H), 1.35-1.21 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.1, 136.5, 132.0, 121.2, 116.9, 79.6, 39.5, 32.8, 25.6, 22.9, 14.0, 7.8; $[\alpha]^{25}_D$ = +4.88 (c 0.177, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{21}BrNO_2$ ($M+H^+$): 314.0756; found 314.0756.

2-ethyl-2-hydroxy-*N*-(4-iodophenyl)hexanamide (**2h**)



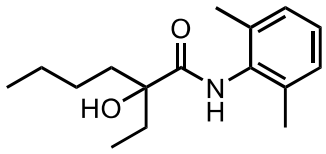
Following the general procedure above, using **1h** (106.0 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2h** (76.3 mg, 84%, 99% *ee*) as white solid; IR (cm^{-1}): 3394, 3333, 3110, 2956, 2919, 2857, 2819, 1661, 1580, 1511, 1457, 1388, 1303, 1274, 1231, 1160, 1114, 1059, 1026, 993, 923, 877, 814, 712; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.60 (brs, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 2.05-1.93 (m, 2H), 1.91 (s, 1H), 1.68-1.59 (m, 2H), 1.44-1.38 (m, 1H), 1.34-1.20 (m, 3H), 0.93 (t, *J* = 7.8 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.1, 138.0, 137.2, 121.6, 87.5, 79.6, 39.5, 32.8, 25.6, 22.9, 14.0, 7.8; $[\alpha]^{25}_D$ = +2.88 (c 0.165, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{21}INO_2$ ($M+H^+$): 362.0617; found 362.0620.

ethyl 4-(2-ethyl-2-hydroxyhexanamido)benzoate (**2i**)



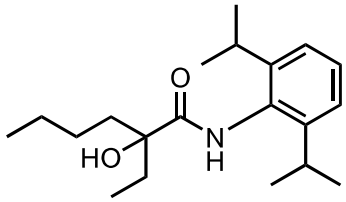
Following the general procedure above, using **1i** (92.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2i** (66.4 mg, 91%, 99% *ee*) as white solid; IR (cm^{-1}): 3459, 3316, 2960, 2933, 2873, 2414, 1688, 1589, 1518, 1458, 1401, 1367, 1289, 1172, 1132, 1109, 1023, 981, 918, 862, 814, 768, 727, 697; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.79 (brs, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.05-1.97 (m, 2H), 1.94 (s, 1H), 1.70-1.59 (m, 2H), 1.44-1.42 (m, 1H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.35-1.22 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.5, 166.3, 141.5, 130.8, 126.0, 118.8, 79.7, 60.9, 39.5, 32.8, 25.6, 22.9, 14.4, 14.0, 7.8; $[\alpha]^{25}_D$ = +6.38 (c 0.151, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{17}H_{26}NO_4$ ($M+H^+$): 308.1862; found 308.1864.

N-(2,6-dimethylphenyl)-2-ethyl-2-hydroxyhexanamide (**2j**)



Following the general procedure above, using **1j** (81.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2j** (57.3 mg, 85%, >99% *ee*) as white solid; IR (cm^{-1}): 3388, 3325, 2928, 2871, 1663, 1591, 1498, 1464, 1377, 1264, 1217, 1165, 1111, 1070, 1034, 978, 909, 826, 773, 723, 681; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.04 (brs, 1H), 7.11-7.06 (m, 3H), 2.25 (s, 6H), 2.16 (s, 1H), 2.05-1.93 (m, 2H), 1.74-1.63 (m, 2H) 1.54-1.50 (m, 1H), 1.42-1.31 (m, 3H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.0, 135.0, 133.8, 128.3, 127.1, 79.6, 39.6, 32.8, 25.9, 23.0, 18.9, 14.1, 8.0; $[\alpha]^{25}_D$ = +6.89 (c 0.181, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{16}H_{26}NO_2$ ($M+H^+$): 264.1964; found 264.1965.

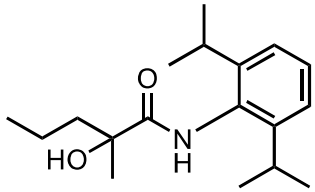
N-(2,6-diisopropylphenyl)-2-ethyl-2-hydroxyhexanamide (**2k**)



Following the general procedure above, using **1k** (95.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2k** (69.4 mg, 91%, 99% *ee*) as white solid; IR (cm^{-1}): 3321, 2959, 2932, 2867, 1652, 1587, 1497, 1459, 1379, 1330, 1296, 1255, 1202, 1170, 1140, 1058, 991, 935, 894, 803, 741; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.96 (brs, 1H), 7.30-7.28 (m, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.13-3.07 (m, 2H), 2.17 (brs, 1H), 2.05-1.93 (m, 2H), 1.77-1.69 (m, 2H), 1.58-1.52 (m, 1H), 1.38-1.34 (m, 3H), 1,21 (d, *J* = 6.9 Hz, 12H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.0, 146.0, 131.0, 128.1, 123.4, 79.6, 39.4, 32.7, 28.6, 25.9, 23.8, 23.1, 14.1, 7.8; $[\alpha]^{25}_D$ = +3.62 (c 0.164,

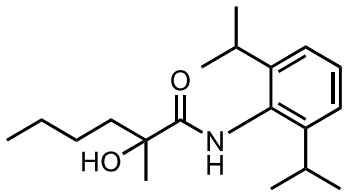
CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{34}NO_2$ ($M+H^+$): 320.2590; found 320.2593.

N-(2,6-diisopropylphenyl)-2-hydroxy-2-methylpentanamide (**2l**)



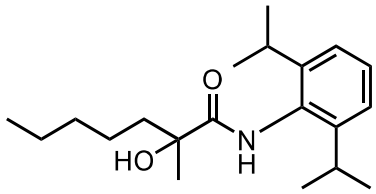
Following the general procedure above, using **1l** (88.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2l** (61.5 mg, 84%, >99% *ee*) as white solid; IR (cm^{-1}): 3325, 2960, 2930, 2868, 1655, 1587, 1499, 1463, 1379, 1361, 1245, 1205, 1177, 1151, 1055, 949, 858, 804, 746; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (brs, 1H), 7.30-7.27 (m, 1H), 7.18 (d, J = 7.7 Hz, 2H), 3.08-3.02 (m, 2H), 2.30 (s, 1H), 2.05-1.97 (m, 1H), 1.72-1.65 (m, 1H), 1.56 (s, 3H), 1.45-1.41 (m, 1H), 1.27-1.22 (m, 1H), 1.21 (d, J = 2.1, 6.9 Hz, 6H), 1.20 (d, J = 2.1, 6.9 Hz, 6H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.7, 146.0, 130.9, 128.2, 123.4, 76.8, 42.7, 28.7, 27.3, 23.6, 17.0, 14.4; $[\alpha]^{25}_D$ = +3.55 (c 0.139, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{30}NO_2$ ($M+H^+$): 292.2277; found 292.2279.

N-(2,6-diisopropylphenyl)-2-hydroxy-2-methylhexanamide (**2m**)



Following the general procedure above, using **1m** (92.1 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2m** (58.2 mg, 76%, >99% *ee*) as white solid; IR (cm^{-1}): 3326, 2960, 2927, 2866, 1654, 1588, 1499, 1458, 1361, 1331, 1291, 1255, 1202, 1173, 1149, 1058, 938, 874, 804, 745; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.94 (brs, 1H), 7.30-7.27 (m, 1H), 7.18 (d, J = 7.8 Hz, 2H), 3.09-3.04 (m, 2H), 2.31 (s, 1H), 2.05-1.99 (m, 1H), 1.72-1.66 (m, 1H), 1.59-1.50 (m, 1H), 1.56 (s, 3H), 1.40-1.36 (m, 3H), 1.21 (d, J = 6.9 Hz, 6H), 1.20 (d, J = 1.8, 6.9 Hz, 6H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.7, 146.1, 130.9, 128.2, 123.4, 76.8, 40.3, 28.7, 27.4, 26.0, 23.7, 23.0, 14.1; $[\alpha]^{25}_D$ = +13.2 (c 0.125, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{19}H_{32}NO_2$ ($M+H^+$): 306.2433; found 306.2433.

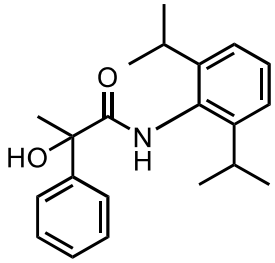
N-(2,6-diisopropylphenyl)-2-hydroxy-2-methylheptanamide (**2n**)



Following the general procedure above, using **1n** (95.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2n** (63.6 mg, 80%, 99% *ee*) as white solid; IR (cm^{-1}): 3327, 2960, 2924, 2865, 1655, 1588, 1498, 1458, 1362, 1332, 1205, 1172, 1060, 935, 803, 745; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95

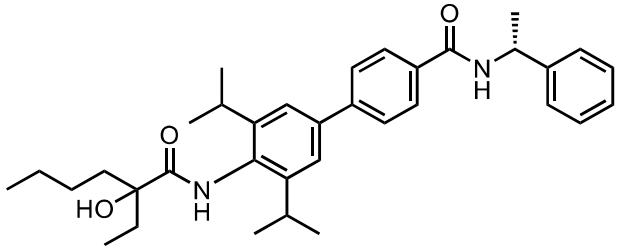
(brs, 1H), 7.30-7.27 (m, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 3.09-3.03 (m, 2H), 2.30 (s, 1H), 2.05-1.99 (m, 1H), 1.71-1.65 (m, 1H), 1.58-1.52 (m, 1H), 1.56 (s, 3H), 1.43-1.30 (m, 5H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 174.7, 146.0, 130.9, 128.2, 123.4, 76.8, 40.6, 32.0, 28.7, 27.4, 23.6, 23.4, 22.7, 14.0; $[\alpha]^{25}_D$ = +12.5 (c 0.138, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{34}NO_2$ ($M+H^+$): 320.2590; found 320.2591.

N-(2,6-diisopropylphenyl)-2-hydroxy-2-phenylpropanamide (**2o**)



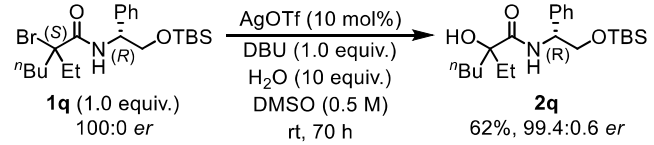
Following the general procedure above, using **1o** (85.6 mg, 0.25 mmol, >99% *ee*), AgOTf (6.4 mg, 0.025 mmol), DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL) and H_2O (0.045 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2o** (68.2 mg, 83%, 92% *ee*) as white solid; IR (cm^{-1}): 3325, 2960, 2930, 2868, 1655, 1587, 1499, 1463, 1379, 1361, 1245, 1205, 1177, 1151, 1055, 949, 858, 804, 746; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 7.2 Hz, 2H), 7.45-7.41 (m, 2H), 7.37-7.34 (m, 1H), 7.29 (brs, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.69 (s, 1H), 2.76-2.71 (m, 2H), 1.98 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 6H), 1.02 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 174.1, 146.1, 143.0, 130.5, 128.7, 128.4, 128.2, 125.5, 123.4, 76.4, 28.6, 26.8, 23.5, 23.3; $[\alpha]^{25}_D$ = +34.4 (c 0.159, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{21}H_{28}NO_2$ ($M+H^+$): 326.2120; found 326.2118.

4'-(2-ethyl-2-hydroxyhexanamido)-3',5'-diisopropyl-N-((R)-1-phenylethyl)-[1,1'-biphenyl]-4-carboxamide (**2p**)



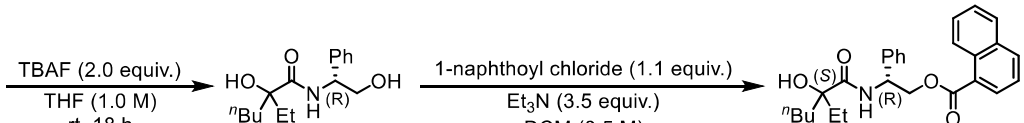
Following the general procedure above, using **1p** (121.4 mg, 0.20 mmol, >99% *ee*), AgOTf (5.3 mg, 0.02 mmol), DBU (0.030 mL, 1.0 equiv.), DMSO (0.4 mL) and H_2O (0.036 mL, 10 equiv.) at room temperature for 24 h, yielded the product **2p** (44.5 mg, 41%, 92% *ee*) as white solid; IR (cm^{-1}): 3312, 2959, 2931, 2868, 1634, 1538, 1490, 1303, 1267, 1209, 1110, 983, 886, 849, 750, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.37-7.34 (m, 4H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.36 (quint, *J* = 7.2 Hz, 1H), 3.21-3.14 (m, 2H), 3.02 (brs, 1H), 2.03-1.92 (m, 2H), 1.74-1.66 (m, 2H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.57-1.51 (m, 1H), 1.39-1.28 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 12H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.7, 166.5, 146.6, 144.7, 143.3, 139.8, 132.9, 131.3, 128.8, 127.5, 127.4, 127.3, 126.3, 122.5, 79.5, 49.3, 39.5, 32.6, 28.8, 25.9, 23.9, 23.7, 23.1, 21.8, 14.2, 7.9; $[\alpha]^{25}_D$ = -17.0 (c 0.310, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{35}H_{47}N_2O_3$ ($M+H^+$): 543.3587; found 543.3585.

3. Determination of the absolute configuration



1q (1.0 equiv.)
100:0 *er*

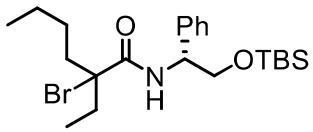
2q
62%, 99.4:0.6 *er*



3
92%

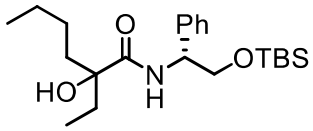
4
93%, 100:0 *er*

2-bromo-N-((R)-2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-2-ethylhexanamide (**1q**)



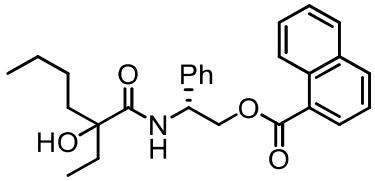
Carboxylic acid (20 mmol, 1.0 equiv.), and PBr_3 (0.67 mL, 6.6 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90°C. After this time, Br_2 (1.6 mL, 32 mmol) was added to the reaction mixture and the temperature was raised up 110°C. When the temperature was reached at 110°C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110°C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110°C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step. Then, desired amine (20 mmol, 1.0 equiv.), Et_3N (5.5 mL, 40 mmol) were sequentially added to CH_2Cl_2 (20 mL, 1.0 M), then synthesized α-bromo acid bromide was dropped into the mixture at 0°C. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were washed with saturated aqueous $NaHCO_3$ (20 mL), EtOAc (20 mL) and brine (20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic α-bromocarboxamide. Next, synthesized α-bromocarboxamide (3.0 mmol, 1.0 equiv.), imidazole (9.0 mmol, 3.0 equiv.) and DCM (0.5 M) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. Next, TBSCl (9.0 mmol, 3.0 equiv.) was added to screw vial under air at 0°C. Then, the resulting mixture vigorously stirred for overnight at room temperature. After this time, the contents of the flask were quenched with saturated $NaHCO_3$ and extracted with EtOAc and washed with brine. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the product **1q** (2.93 mmol, 98%) as viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83 (d, J = 7.2 Hz, 1H), 7.31-7.30 (m, 4H), 7.25-7.24 (m, 1H), 4.96-4.93 (m, 1H), 3.89 (dd, J = 4.2, 10.2 Hz, 1H), 3.78 (dd, J = 4.5, 10.2 Hz, 1H), 2.25-2.09 (m, 2H), 2.00-1.86 (m, 2H), 1.52-1.44 (m, 1H), 1.27-1.13 (m, 3H), 1.06 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.82 (t, J = 7.3 Hz, 3H), 0.00 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.9, 140.0, 128.3, 127.4, 126.9, 79.5, 66.2, 55.7, 43.2, 36.4, 28.2, 25.8, 22.5, 18.2, 13.9, 10.6, -5.5, -5.6.
Enantiomers were separated by Daicel CHIRALPAK IA-3 (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 95/5 as an eluent)
$[\alpha]^{25}_D$ = +2.17 (c 0.117, $CHCl_3$).

N-((R)-2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)-2-ethyl-2-hydroxyhexanamide (**2q**)



Following the general procedure for enantiospecific hydroxylation, using **1q** (227.8 mg, 0.50 mmol, >99% *ee*), AgOTf (12.4 mg, 0.05 mmol), DBU (0.07 mL, 1.0 equiv.), DMSO (1.0 mL) and H_2O (0.09 mL, 10 equiv.) at room temperature for 70 h, yielded the product **2q** (121.8 mg, 62%, 99% *ee*) as white solid; IR (cm^{-1}): 3351, 2952, 2927, 2856, 1645, 1514, 1458, 1379, 1251, 1103, 963, 831, 780, 697; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.31-7.29 (m, 5H), 7.25-7.23 (m, 1H), 5.03-4.99 (m, 1H), 3.88 (dd, *J* = 4.3, 10.1 Hz, 1H), 3.81 (dd, *J* = 4.7, 10.4 Hz, 1H), 2.33 (s, 1H), 1.89-1.75 (m, 2H), 1.64-1.53 (m, 2H), 1.40-1.22 (m, 3H), 1.16-1.08 (m, 1H), 0.90-0.83 (m, 15H), -0.02 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 174.5, 140.3, 128.3, 127.4, 126.9, 78.6, 66.3, 54.6, 39.8, 33.0, 25.8, 25.6, 23.0, 18.2, 14.0, 7.8, -5.55, -5.57; $[\alpha]^{25}_D$ = -22.96 (c 0.09, $CHCl_3$). HRMS (ESI-MS) calcd. for $C_{22}H_{40}NO_3Si$ ($M+H^+$): 394.2777; found 394.2775.

(2R)-2-(2-ethyl-2-hydroxyhexanamido)-2-phenylethyl 1-naphthoate (**4**)



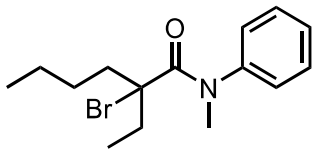
2q (0.31 mmol, 1.0 equiv., >99% ee) and 1 M TBAF in THF solution (2.0 equiv.) were added under air to a dram vial equipped with a stir bar and a screw cap. Next, the resulting mixture vigorously stirred under air for 18 h at room temperature. After this time, the contents of the flask were washed with water and EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the **3** (79.9 mg, 0.29 mmol, 92%). Next, synthesized **3** (0.29 mmol, 1.0 equiv.), Et_3N (1.0 mmol, 3.5 equiv.) and DCM (0.33 M) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. Next, 1-naphtoyl chloride (0.31 mmol, 1.1 equiv.) was added to screw vial under air at 0°C. Then, the resulting mixture vigorously stirred for 21 h at room temperature. After this time, the contents of the flask were quenched with saturated $NaHCO_3$ and extracted with EtOAc and washed with brine. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the product **4** (115.8 mg, 0.27 mmol, 93%, >99% ee) as white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 8.6 Hz, 1H), 8.13 (dd, *J* = 1.3, 7.4 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.60-7.57 (m, 1H), 7.55-7.52 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.43-7.38 (m, 5H), 7.34-7.31 (m, 1H), 5.52-5.48 (m, 1H), 4.80 (dd, *J* = 7.8, 11.5 Hz, 1H), 4.59 (dd, *J* = 4.7, 11.5 Hz, 1H), 2.14 (s, 1H), 1.86-1.75 (m, 1H), 1.57-1.48 (m, 2H), 1.36-1.26 (m, 2H), 1.16-0.99 (m, 3H), 0.77 (t, *J* = 7.5 Hz, 3H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 174.7, 167.6, 138.5, 133.9, 133.8, 131.4, 130.6, 128.9, 128.6, 128.1, 128.0, 126.9, 126.39, 126.38, 125.7, 124.5, 78.9, 66.7, 52.8, 39.6, 32.8, 25.6, 23.8, 13.9, 7.6; $[\alpha]^{25}_D$ = -18.82 (c 0.096, $CHCl_3$). HRMS (ESI-MS) calcd. for $C_{27}H_{32}NO_4$ ($M+H^+$): 434.2331; found 434.2332.

4. Control Experiments

General procedure for radical trapping experiments

Alkyl bromide **1i** (0.10 mmol, 1.0 equiv.), 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO, 0.15 mmol, 1.5 equiv.) or 2,6-di-tert-butyl-p-cresol (BHT, 0.15 mmol, 1.5 equiv.) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. Next, AgOTf (6.4 mg, 0.025 mmol, 10 mol%) was added to screw vial under glove box. After flashing nitrogen gas (purity 99.95%), dried DBU (0.038 mL, 1.0 equiv.), DMSO (0.5 mL), H_2O (0.045 mL, 10 equiv.) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 24 h at 20 °C. After this time, the contents of the flask were washed with water and EtOAc. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography eluting with hexane/EtOAc to afford the hydroxylated product **2i**.

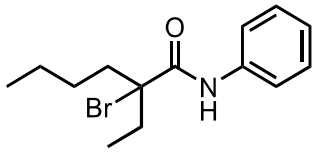
2-bromo-2-ethyl-N-methyl-N-phenylhexanamide (**1r**)



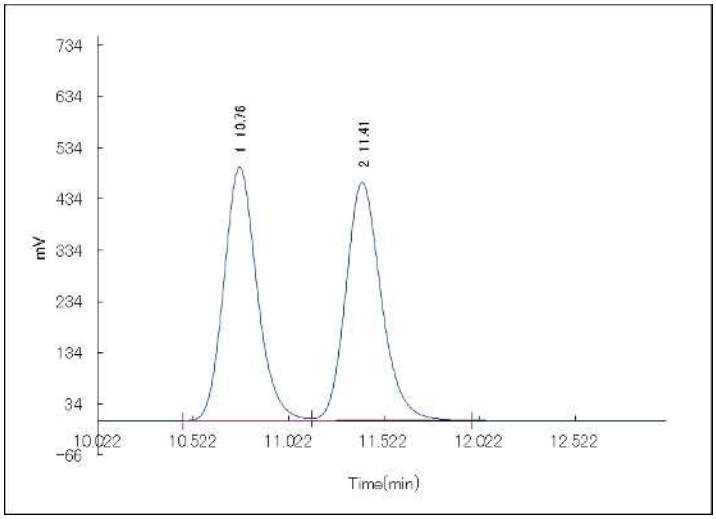
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.60 mL, 10 mmol), Phosphorus tribromide (0.31 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2.0 mL), N-methyl aniline (1.20 mL, 11 mmol), Triethylamine (4.2 mL, 3.0 equiv.), DMAP (121.7 mg, 10 mol%) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product **1s** (1.59 g, 5.1 mmol, 51%) as yellow oil; IR (cm^{-1}): 2956, 2930, 2871, 1638, 1592, 1493, 1359, 1255, 1118, 773, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.32 (m, 5H), 3.35 (s, 3H), 2.07-1.85 (m, 4H), 1.38-1.20 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.5, 144.5, 129.2, 128.2, 128.0, 70.6, 42.3, 39.7, 33.4, 27.7, 22.7, 14.0, 10.2. HRMS (ESI-MS) calcd. for $C_{15}H_{23}BrNO$ ($M+H^+$): 312.0963; found 312.0965.

5. HPLC profiles

(**1a**)

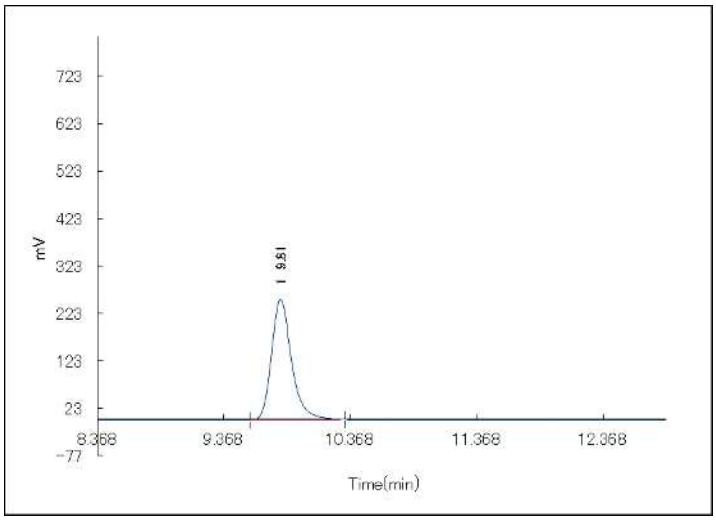


(a)



retention time (min)	Area (%)
10.76	49.9583
11.41	50.0417

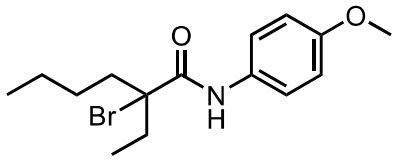
(b)



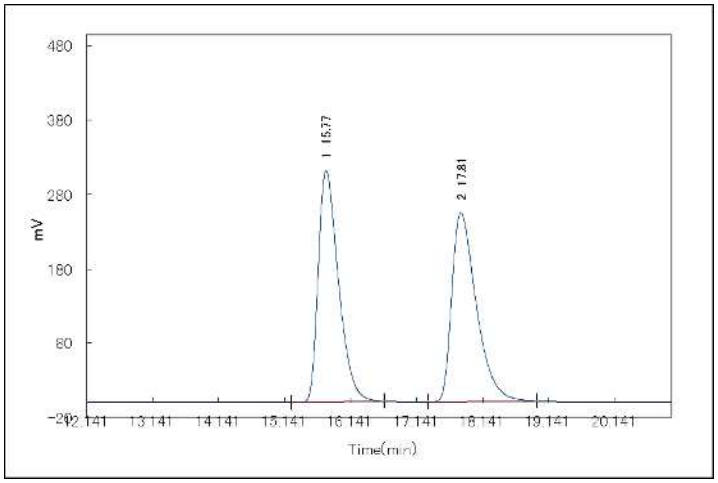
retention time (min)	Area (%)
9.81	100

Supporting Figure 1a Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1a** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1b**)

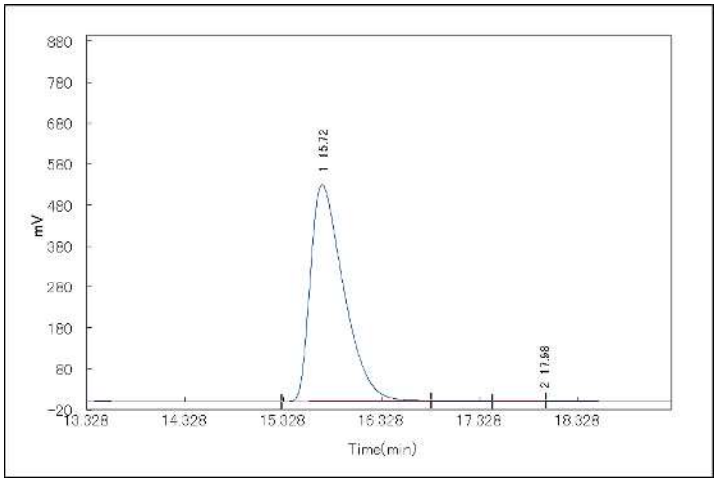


(a)



retention time (min)	Area (%)
15.77	50.30
17.81	49.70

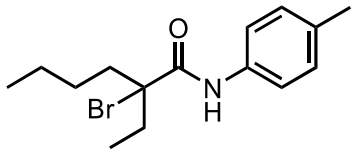
(b)



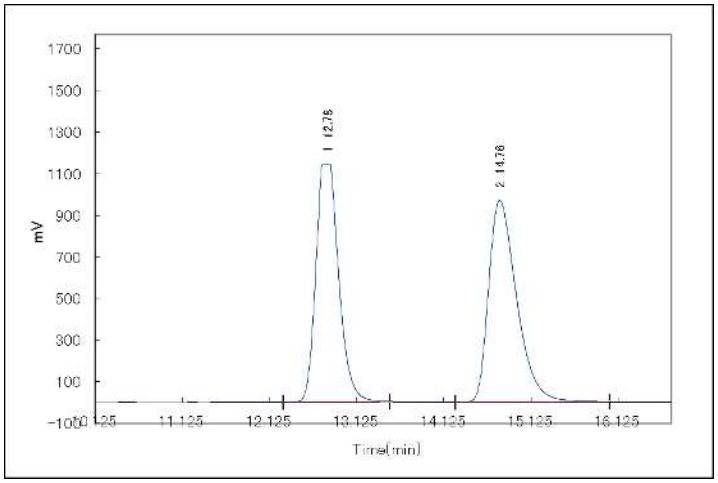
retention time (min)	Area (%)
15.72	100.0

Supporting Figure 1b Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1b** using YMC CHIRAL ART Amylose-IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1c**)

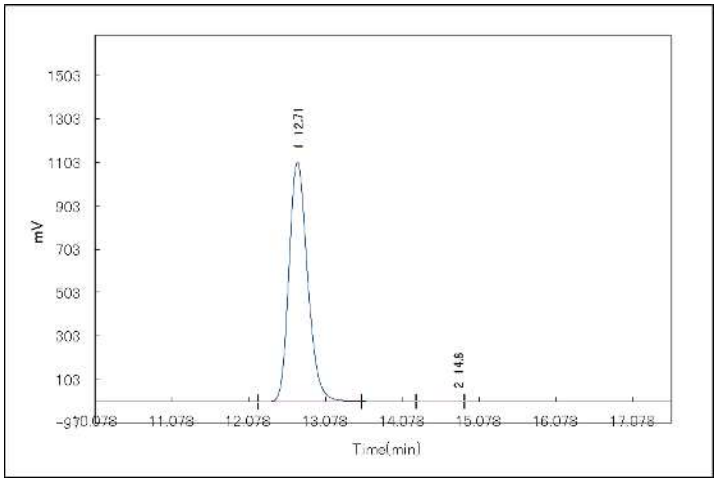


(a)



retention time (min)	Area (%)
12.78	49.07
14.76	50.93

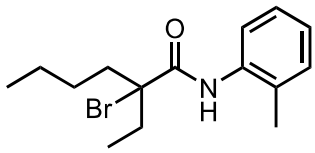
(b)



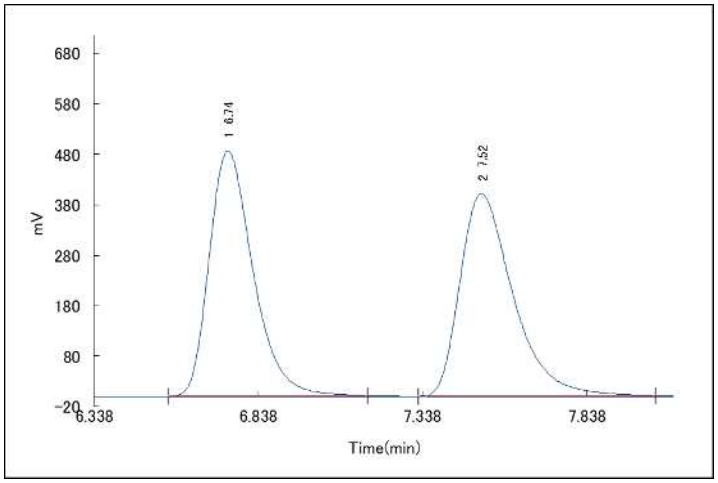
retention time (min)	Area (%)
12.71	100.0

Supporting Figure 1c Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1c** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1d**)

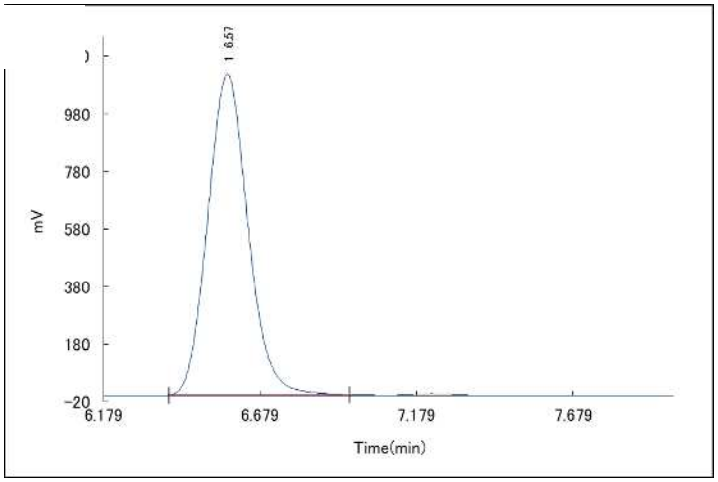


(a)



retention time (min)	Area (%)
6.74	50.0396
7.52	49.9604

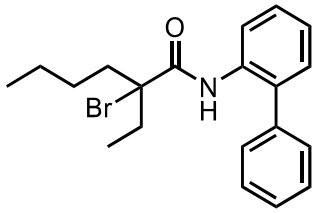
(b)



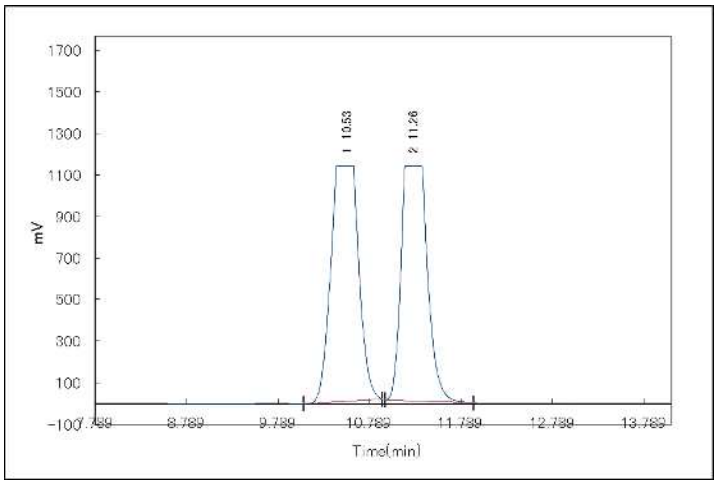
retention time (min)	Area (%)
6.57	100

Supporting Figure 1d Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1d** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1e**)

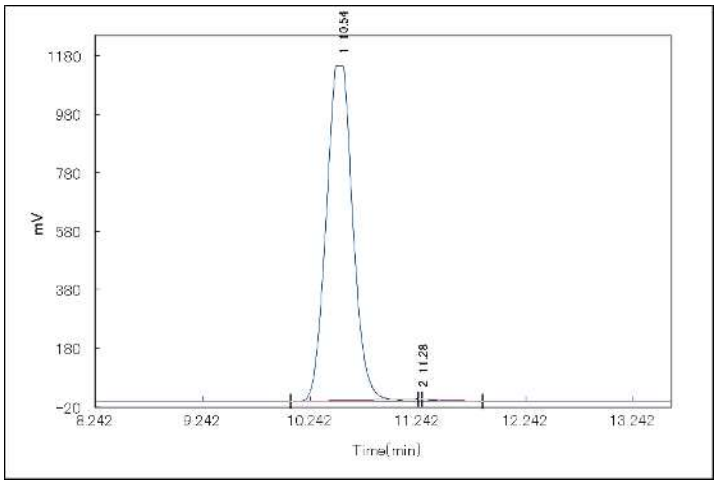


(a)



retention time (min)	Area (%)
10.53	51.52
11.26	48.48

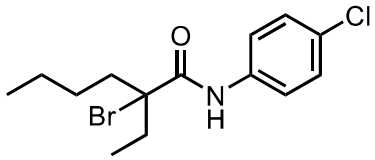
(b)



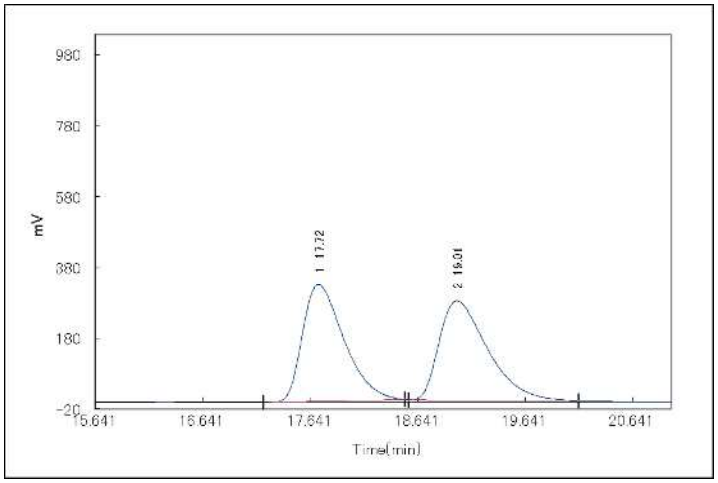
retention time (min)	Area (%)
10.54	100.0

Supporting Figure 1e Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1e** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1f**)

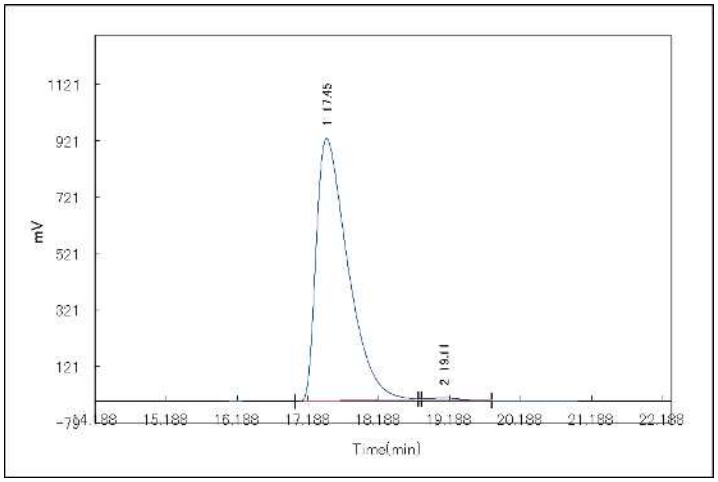


(a)



retention time (min)	Area (%)
17.72	50.18
19.01	49.82

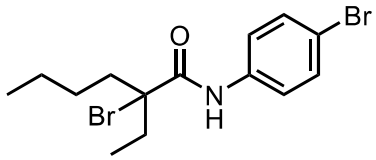
(b)



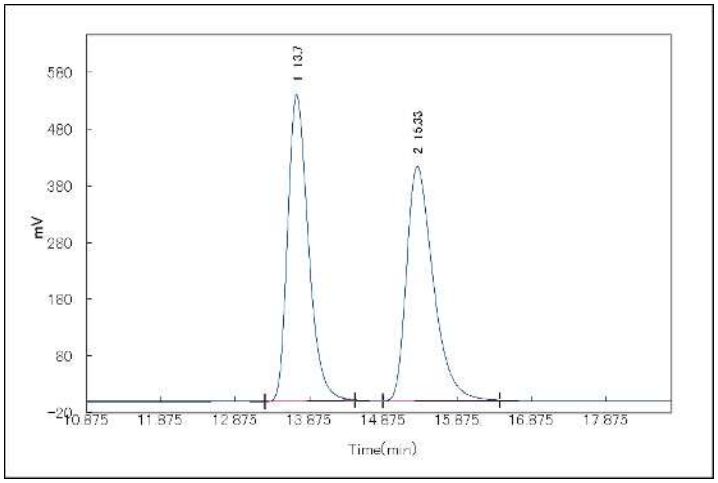
retention time (min)	Area (%)
17.45	99.54
19.11	0.46

Supporting Figure 1f Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1f** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/Acetone = 99/1 as an eluent monitored at 254 nm).

(**1g**)

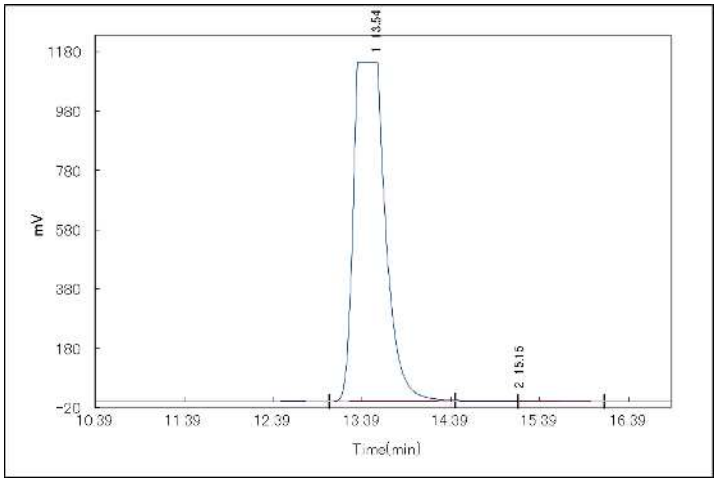


(a)



retention time (min)	Area (%)
13.7	50.26
15.33	49.74

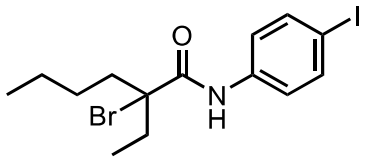
(b)



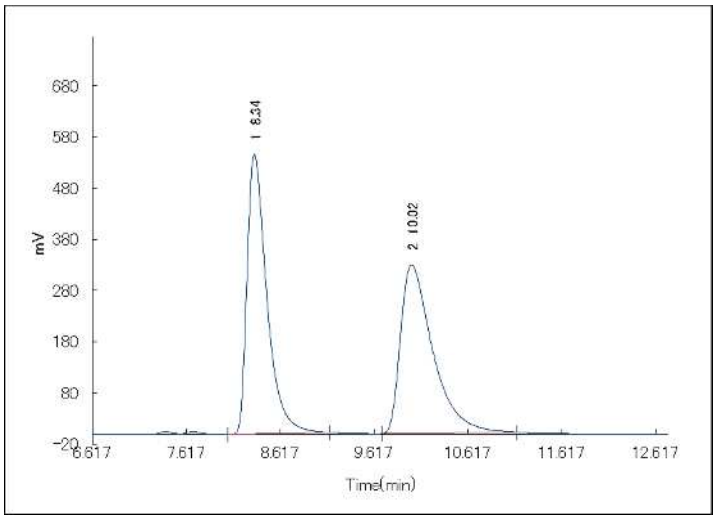
retention time (min)	Area (%)
13.54	100.0

Supporting Figure 1g Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1g** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1h**)

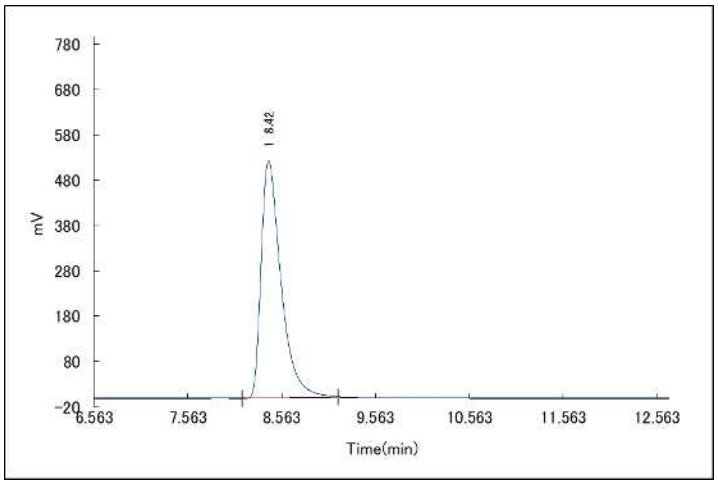


(a)



retention time (min)	Area (%)
8.34	50.3486
10.02	49.6514

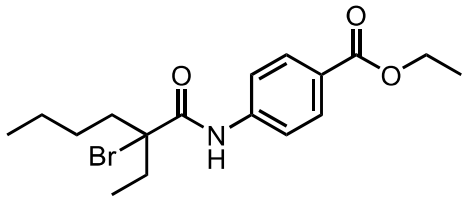
(b)



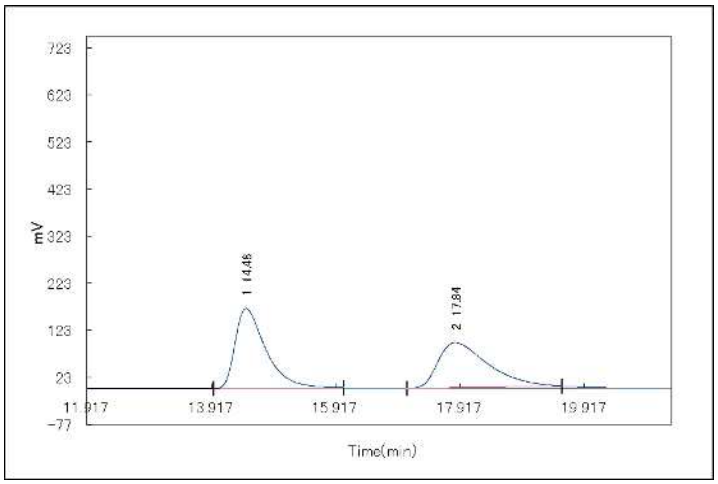
retention time (min)	Area (%)
8.42	100

Supporting Figure 1h Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1h** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1i**)

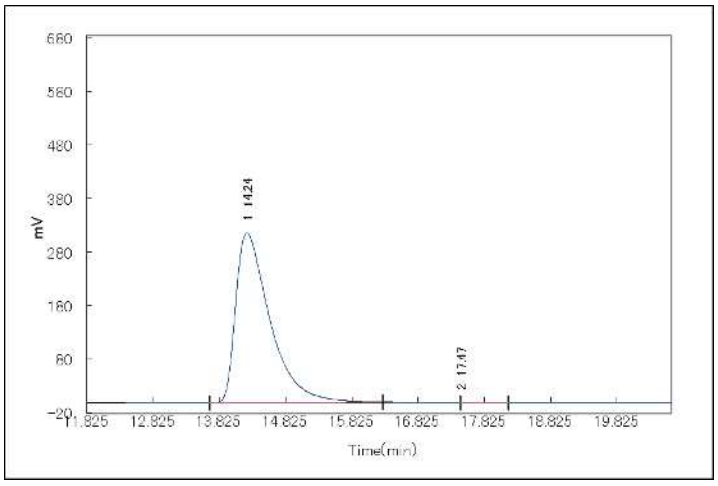


(a)



retention time (min)	Area (%)
14.48	52.05
17.84	47.95

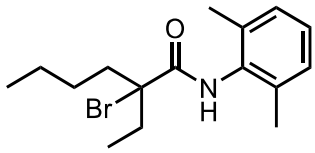
(b)



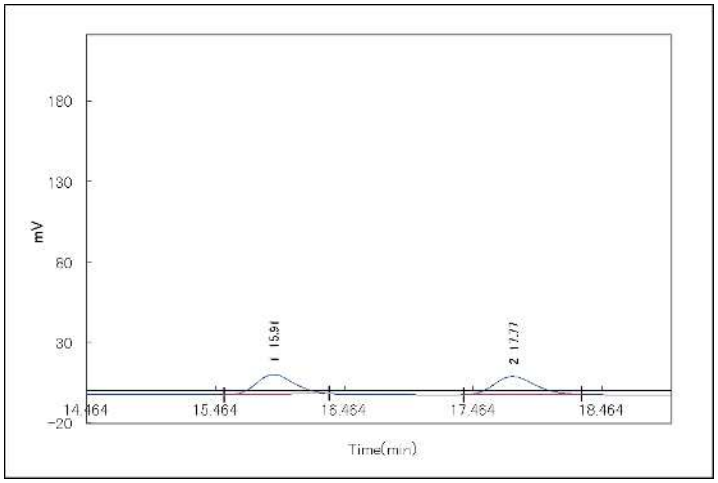
retention time (min)	Area (%)
14.24	100.0

Supporting Figure 1i Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1i** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1j**)

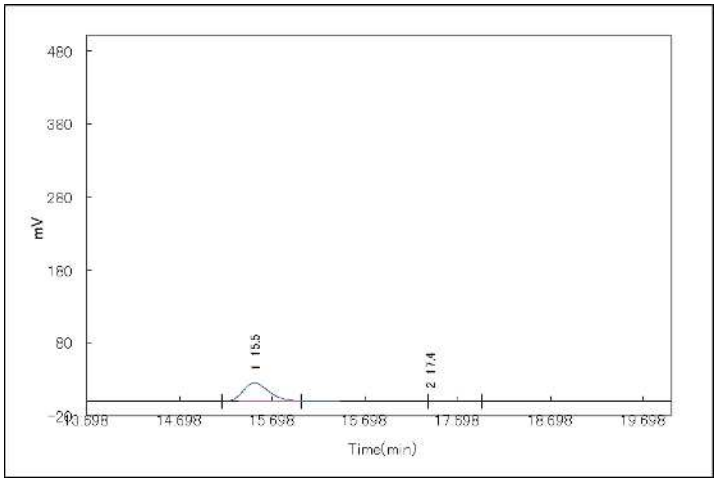


(a)



retention time (min)	Area (%)
15.91	49.88
17.77	50.12

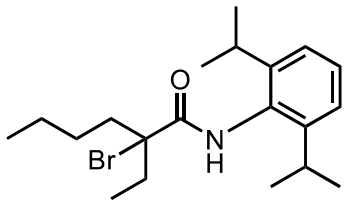
(b)



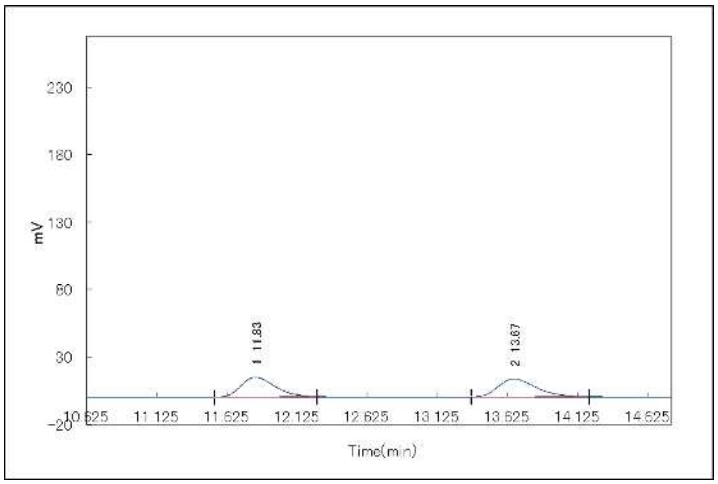
retention time (min)	Area (%)
15.5	100.0

Supporting Figure 1j Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1j** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1k**)

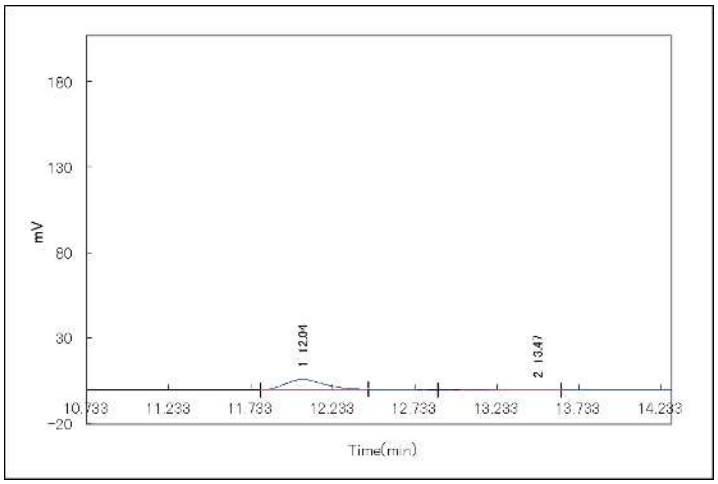


(a)



retention time (min)	Area (%)
11.83	49.55
13.67	50.45

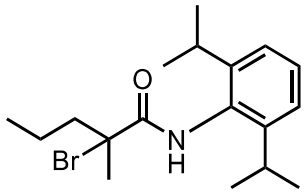
(b)



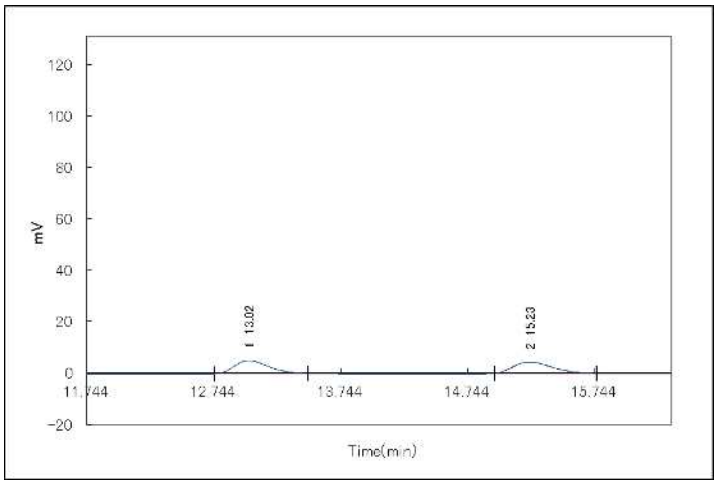
retention time (min)	Area (%)
12,04	100.0

Supporting Figure 1k Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1k** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1l**)

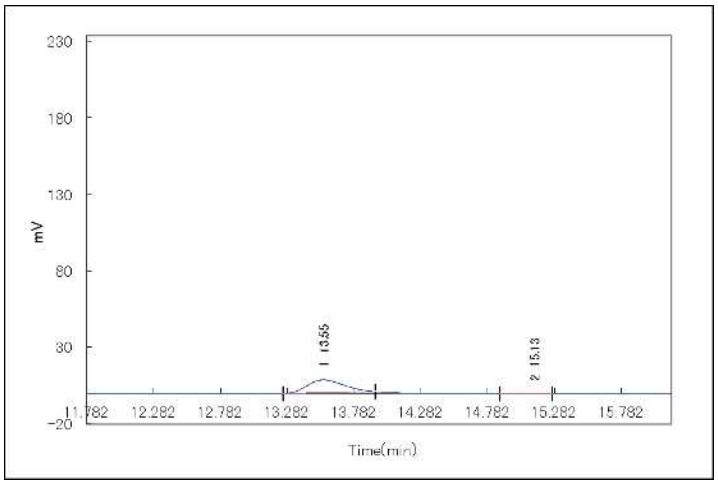


(a)



retention time (min)	Area (%)
13.02	50.89
15.23	49.11

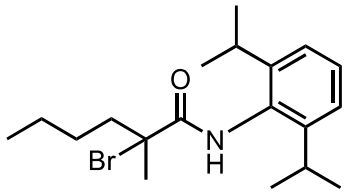
(b)



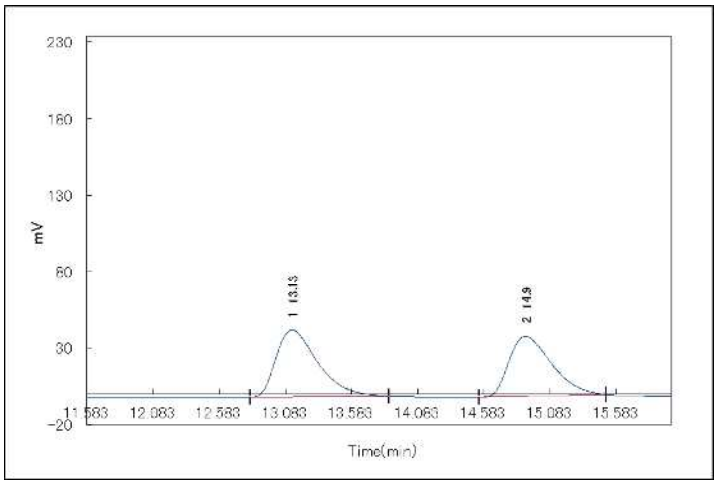
retention time (min)	Area (%)
13.55	100.0

Supporting Figure 1l Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1l** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1m**)

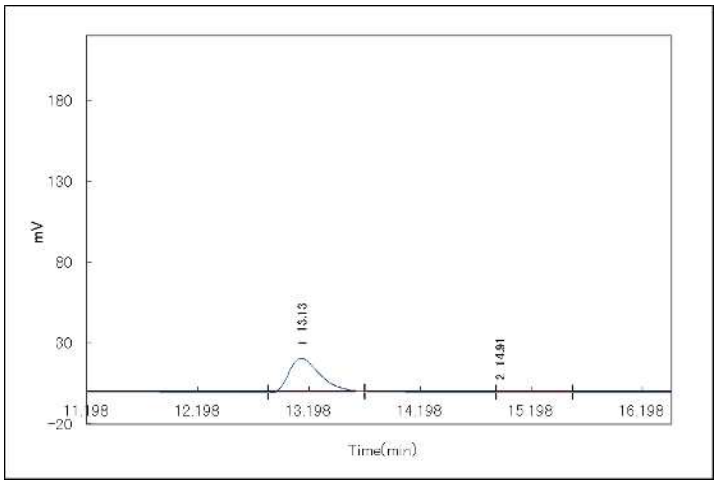


(a)



retention time (min)	Area (%)
13.13	52.29
14.9	47.71

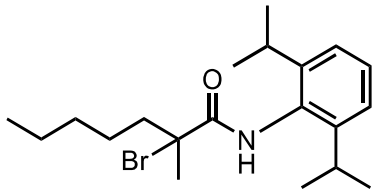
(b)



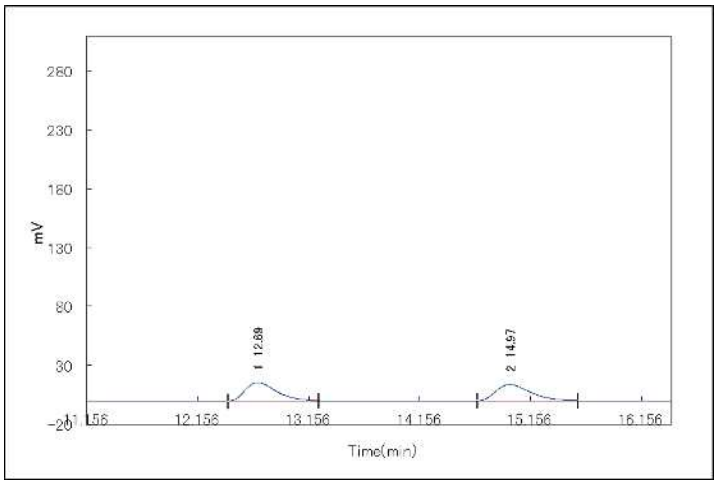
retention time (min)	Area (%)
13.13	100.0

Supporting Figure 1m Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1m** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1n**)

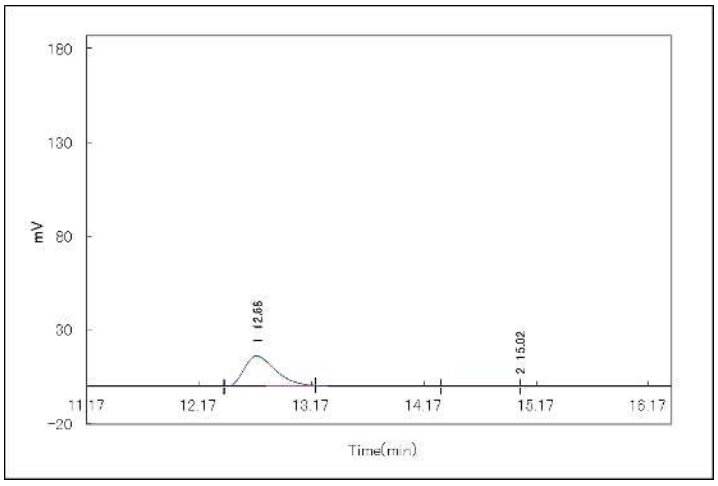


(a)



retention time (min)	Area (%)
12.69	50.25
14.97	49.75

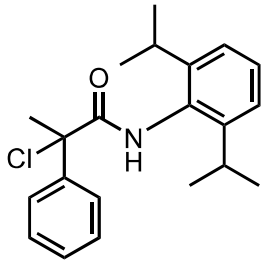
(b)



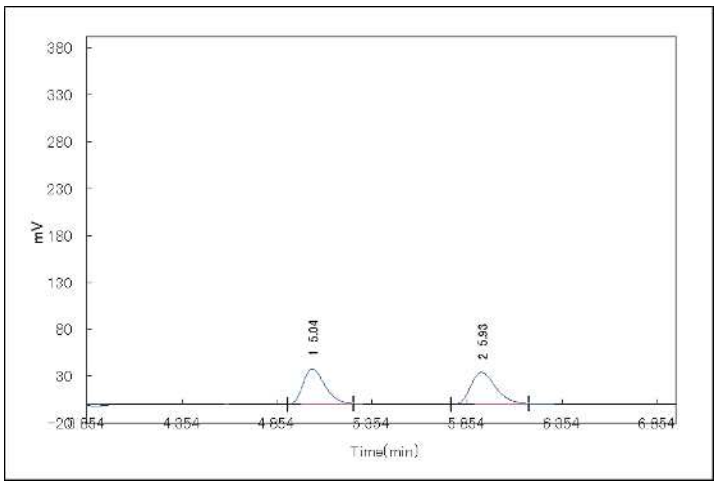
retention time (min)	Area (%)
12.68	100.0

Supporting Figure 1n Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1n** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1o**)

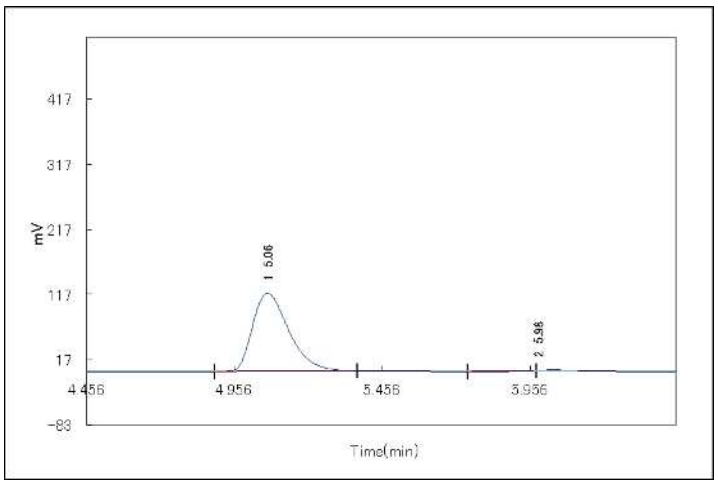


(a)



retention time (min)	Area (%)
5.04	49.25
5.93	50.75

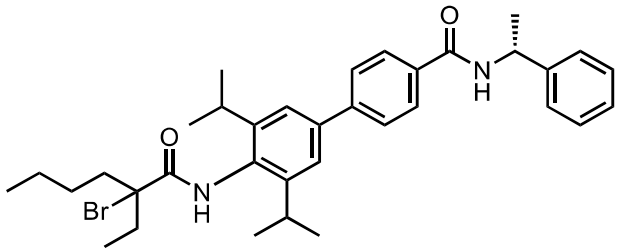
(b)



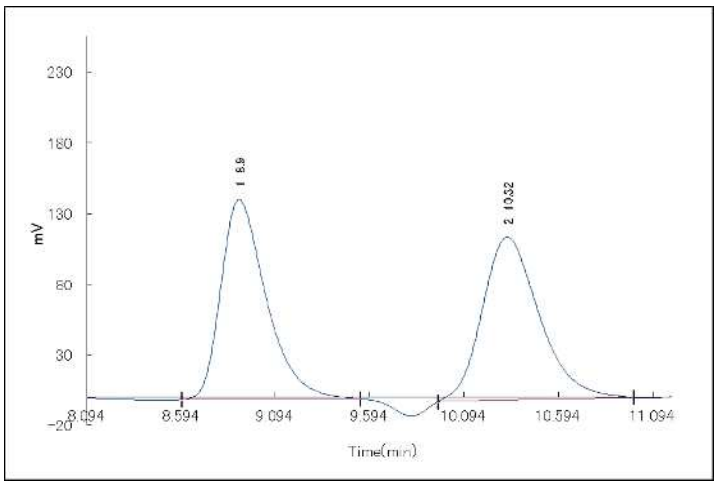
retention time (min)	Area (%)
5.06	100.0

Supporting Figure 1o Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1o** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 95/5 as an eluent monitored at 254 nm).

(**1p**)

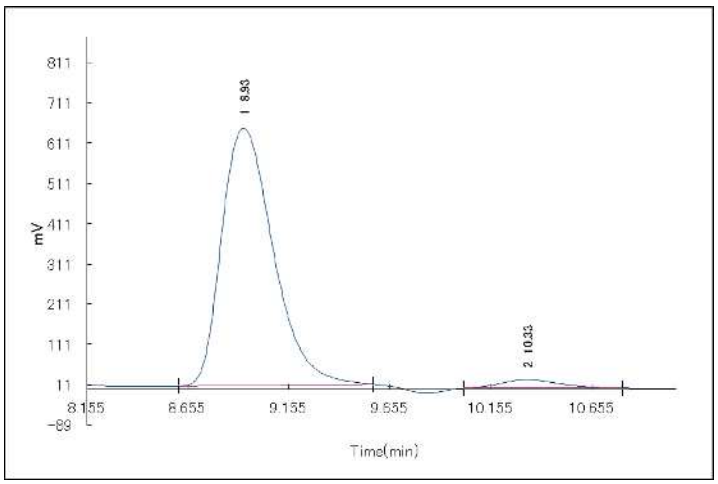


(a)



retention time (min)	Area (%)
8.9	49.439
10.32	50.561

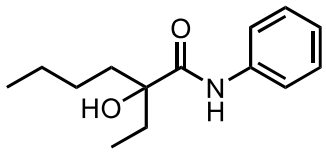
(b)



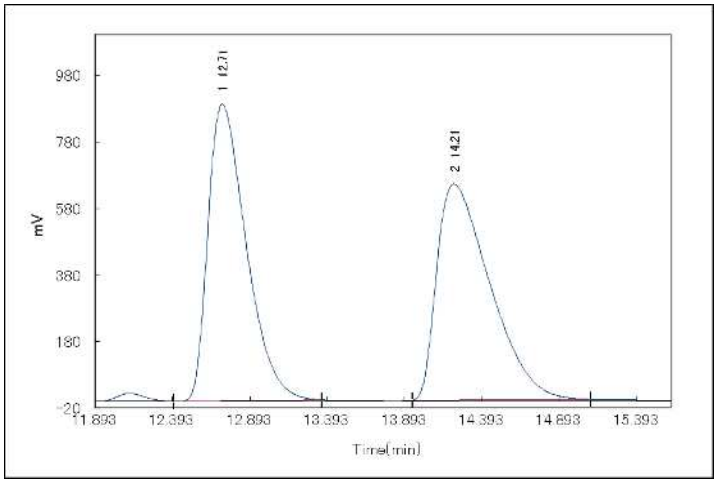
retention time (min)	Area (%)
8.93	96.444
10.33	3.556

Supporting Figure 1p Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1p** using Daicel CHIRALPAK IC-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 70/30 as an eluent monitored at 254 nm).

(**2a**)

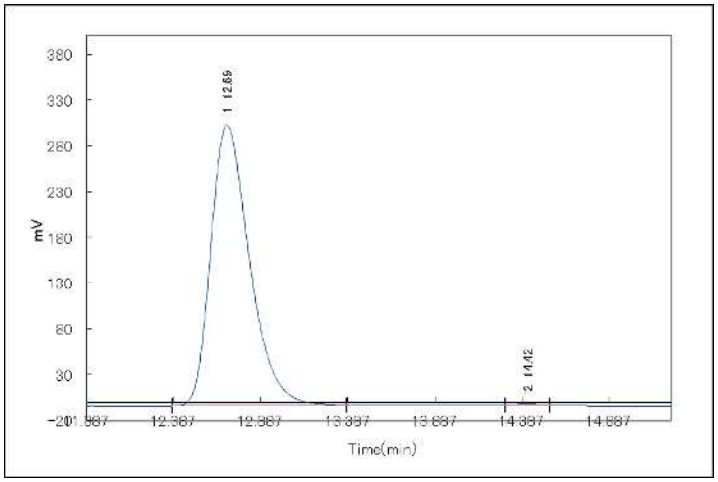


(a)



retention time (min)	Area (%)
12.71	49.66
14.21	50.34

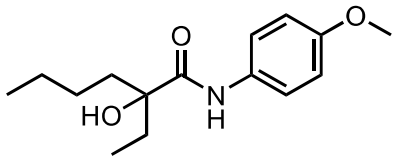
(b)



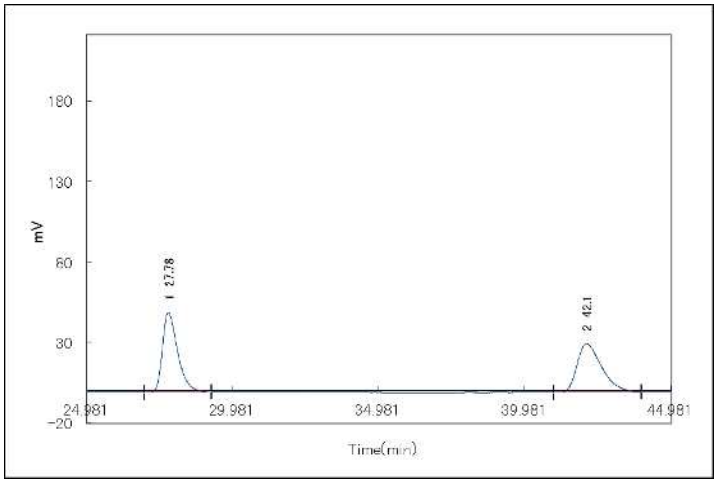
retention time (min)	Area (%)
12.69	99.81
14.42	0.19

Supporting Figure 2a Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2a** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2b**)

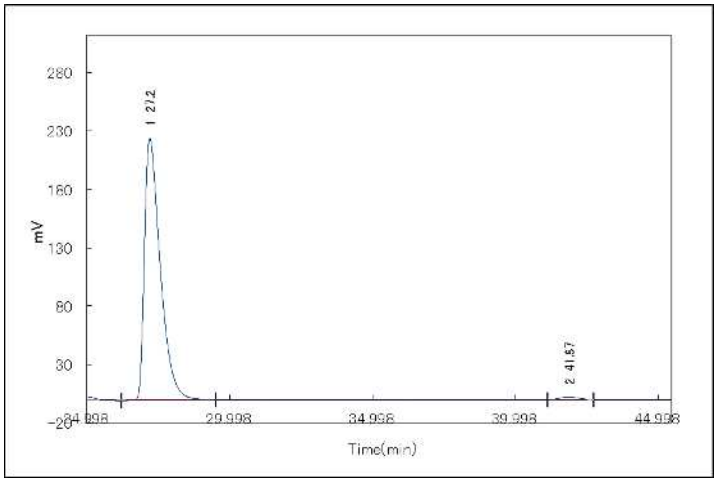


(a)



retention time (min)	Area (%)
27.78	50.34
42.1	49.66

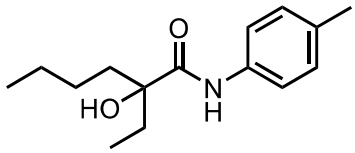
(b)



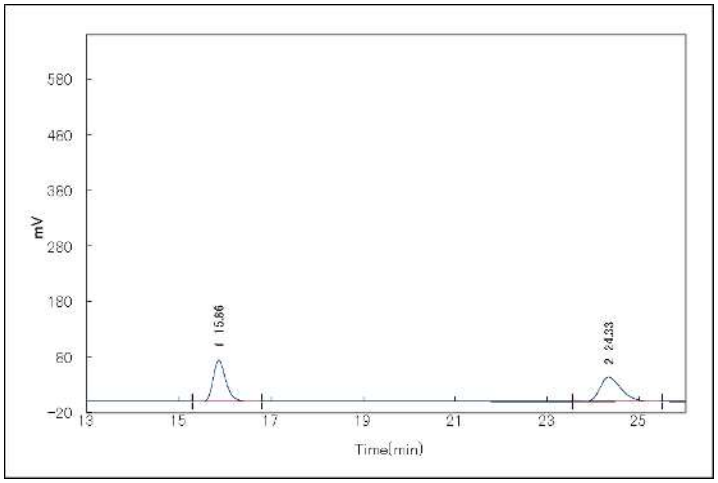
retention time (min)	Area (%)
27.2	98.68
41.87	1.32

Supporting Figure 2b Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2b** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2c**)

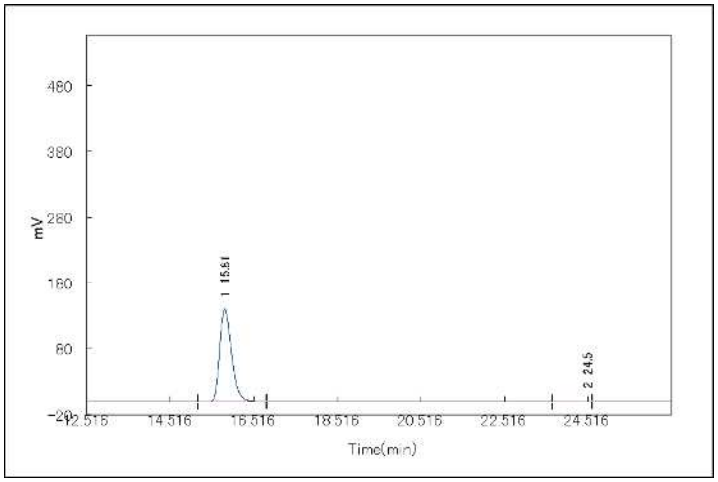


(a)



retention time (min)	Area (%)
15.81	50.09
24.33	49.91

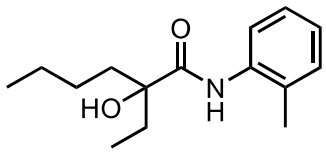
(b)



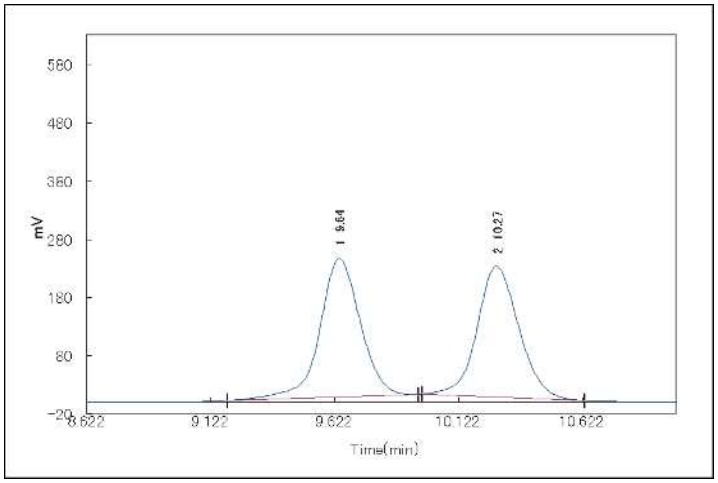
retention time (min)	Area (%)
15.81	100.00

Supporting Figure 2c Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2c** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2d**)

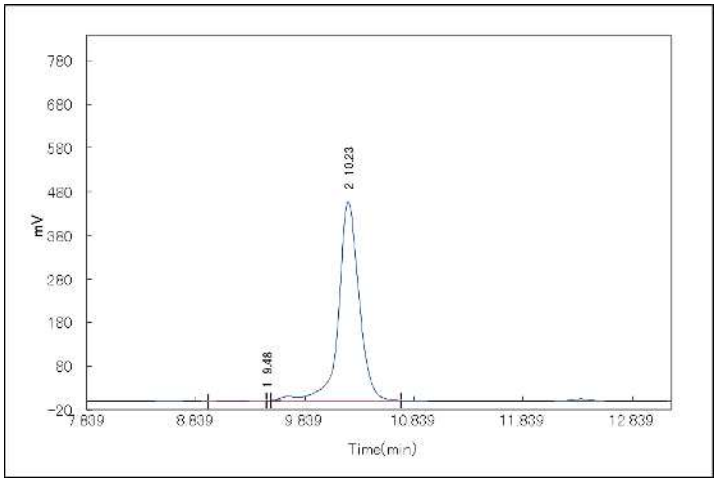


(a)



retention time (min)	Area (%)
9.64	50.62
10.27	49.38

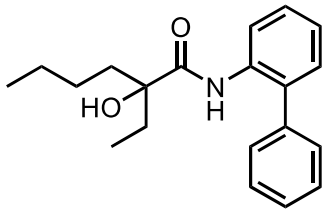
(b)



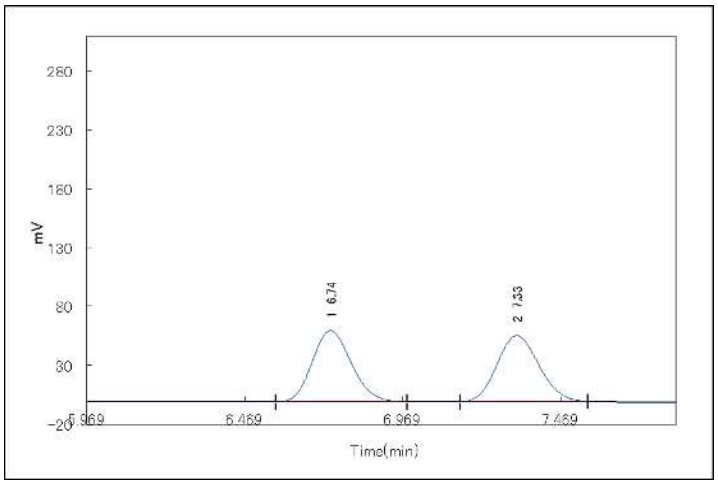
retention time (min)	Area (%)
10.23	100.0

Supporting Figure 2d Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2d** using Daicel CHIRALPAK IB-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2e**)

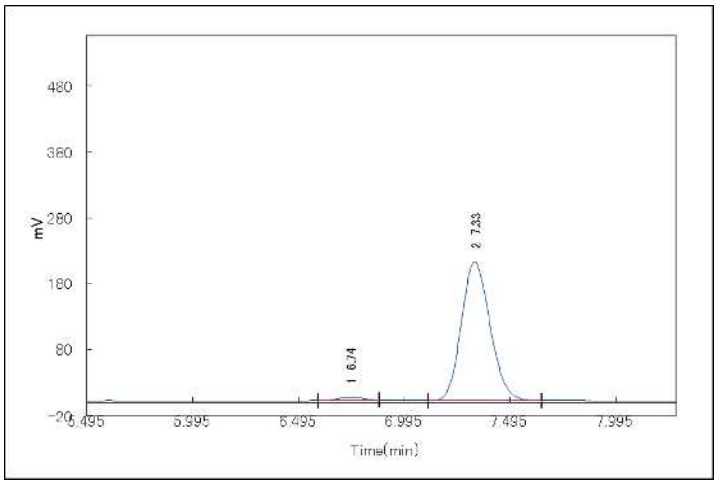


(a)



retention time (min)	Area (%)
6.74	50.12
7.33	49.88

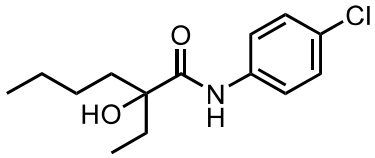
(b)



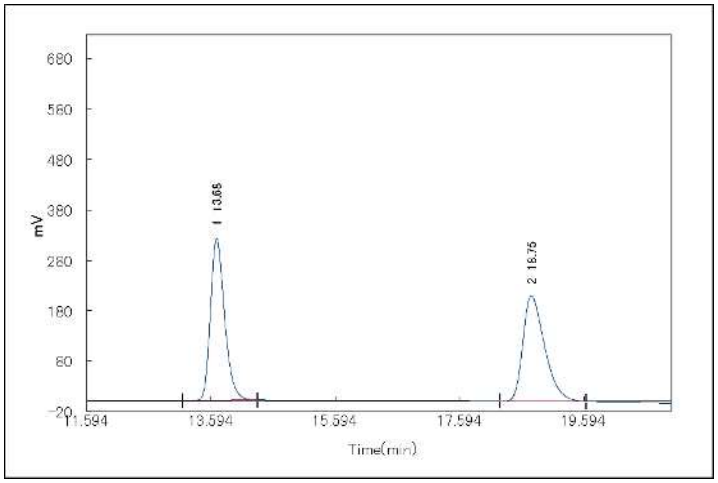
retention time (min)	Area (%)
6.74	1.96
7.33	98.04

Supporting Figure 2e Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2e** using Daicel CHIRALPAK IC-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2f**)

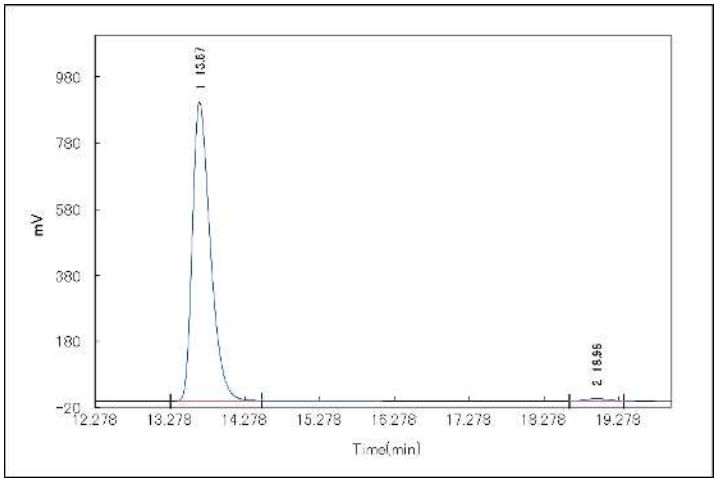


(a)



retention time (min)	Area (%)
13.68	50.13
18.75	49.87

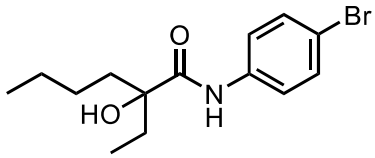
(b)



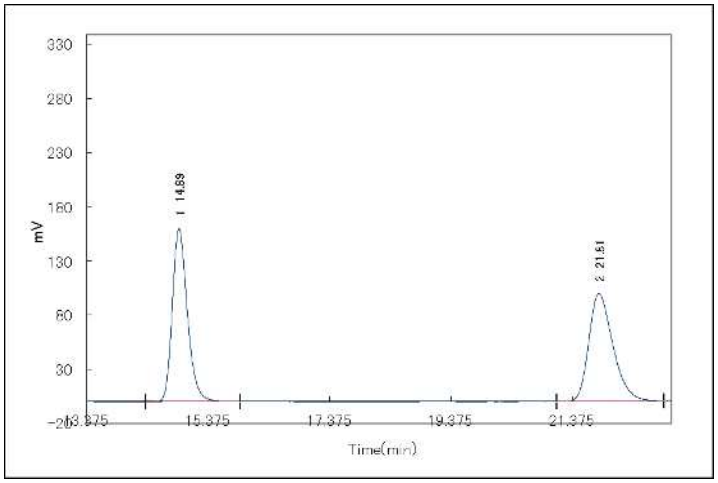
retention time (min)	Area (%)
13.67	98.98
18.98	1.02

Supporting Figure 2f Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2f** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2g**)

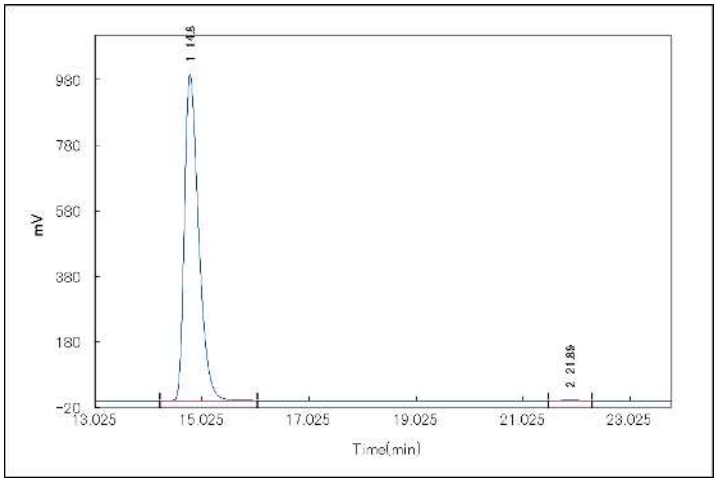


(a)



retention time (min)	Area (%)
14.89	50.12
21.81	49.88

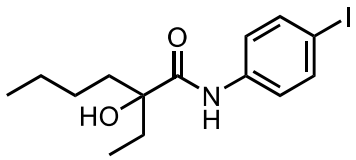
(b)



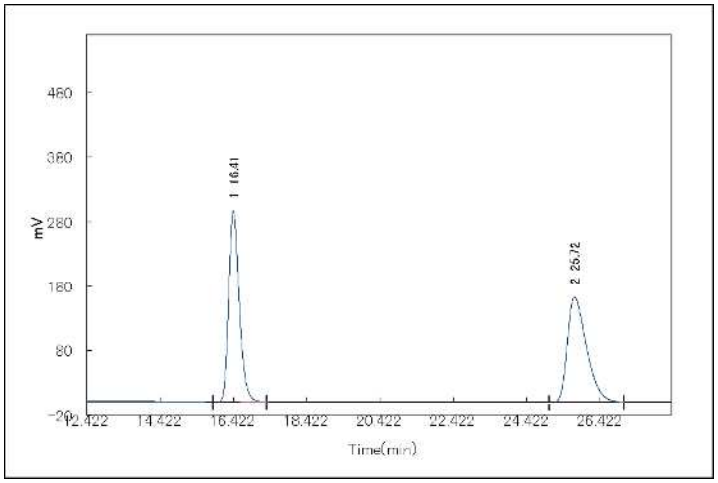
retention time (min)	Area (%)
14.8	99.80
21.89	0.20

Supporting Figure 2g Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2g** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2h**)

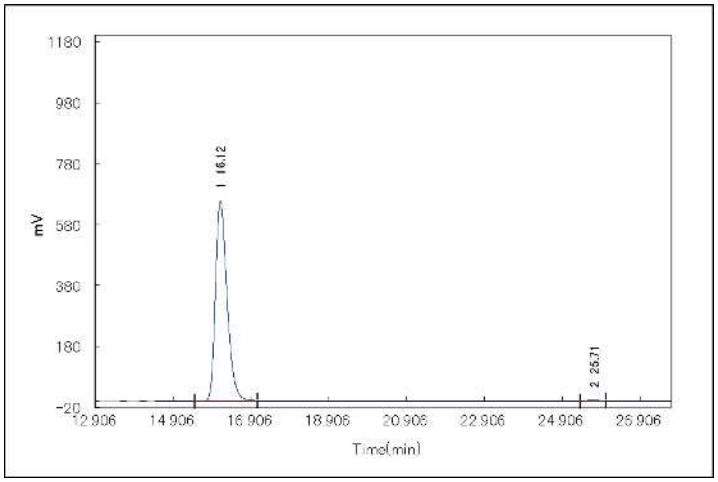


(a)



retention time (min)	Area (%)
16.41	50.03
25.72	49.97

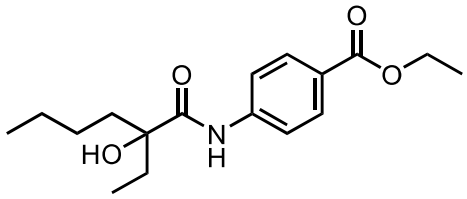
(b)



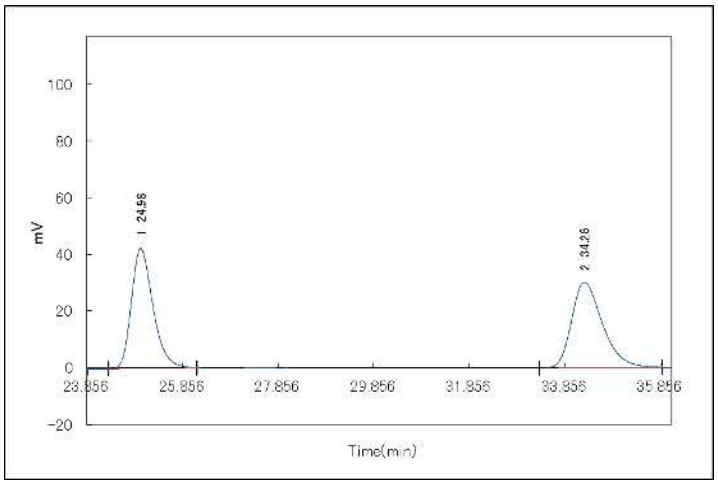
retention time (min)	Area (%)
16.12	99.67
25.71	0.33

Supporting Figure 2h Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2h** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2i**)

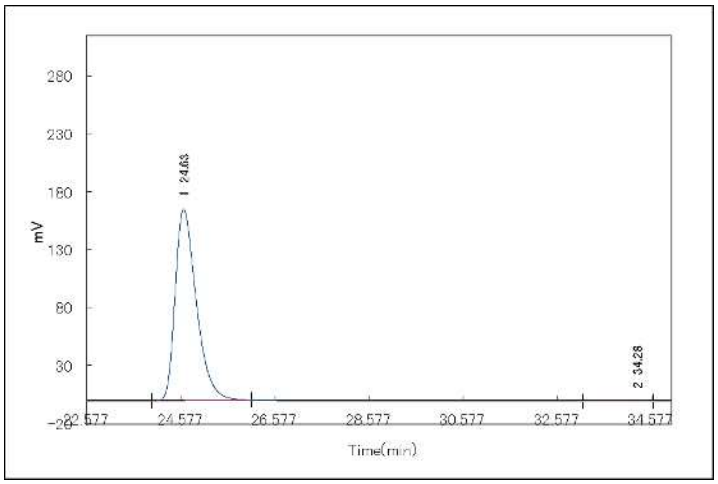


(a)



retention time (min)	Area (%)
24.98	49.66
34.26	50.34

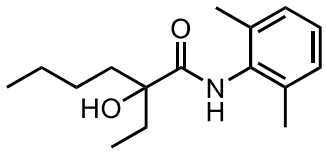
(b)



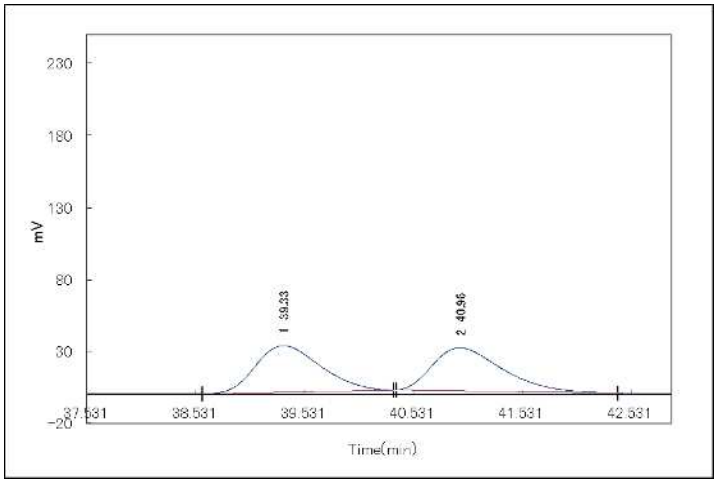
retention time (min)	Area (%)
24.63	99.92
34.28	0.08

Supporting Figure 2i Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2i** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 254 nm).

(**2j**)

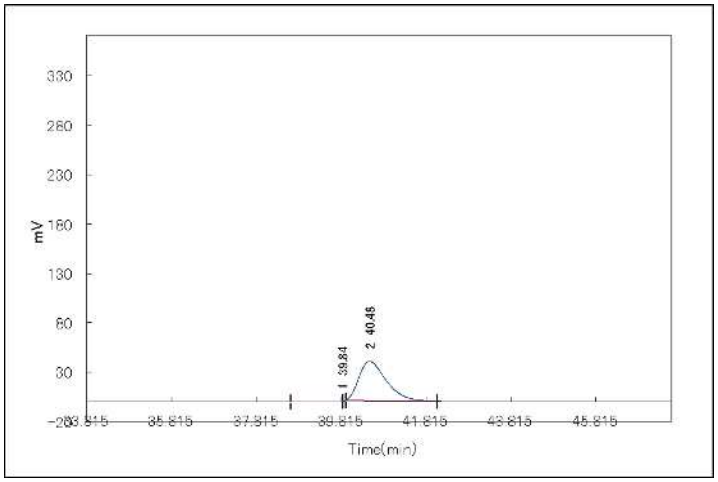


(a)



retention time (min)	Area (%)
39.33	50.28
40.96	49.72

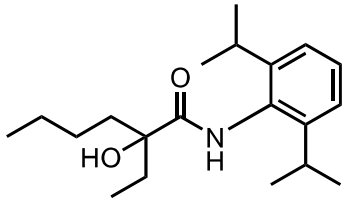
(b)



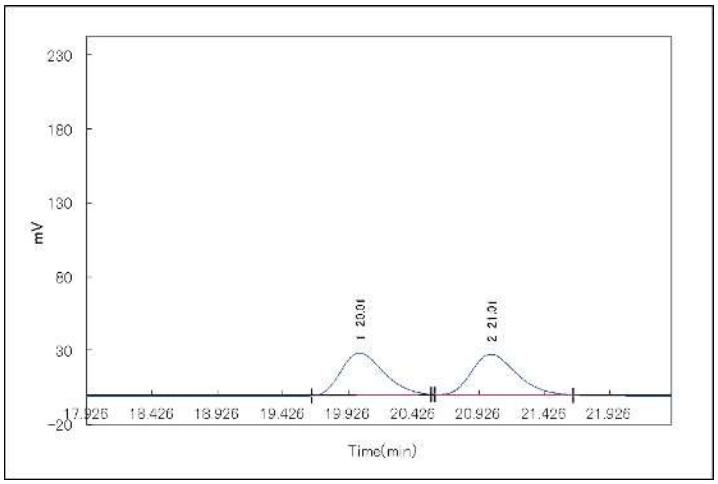
retention time (min)	Area (%)
40.48	100.00

Supporting Figure 2j Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2j** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 214 nm).

(**2k**)

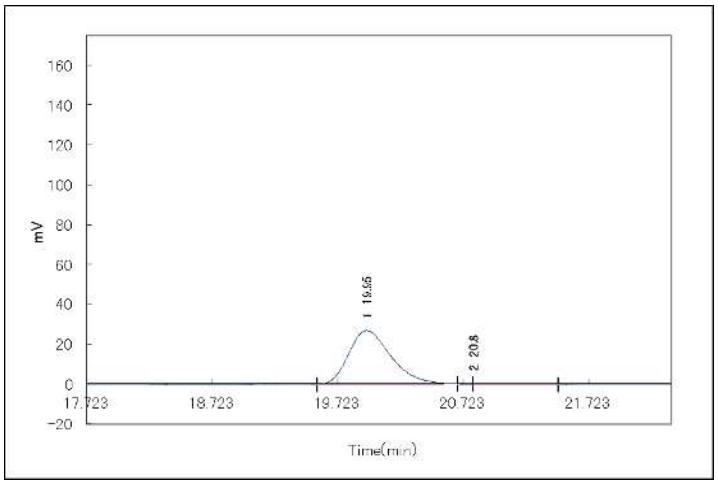


(a)



retention time (min)	Area (%)
20.01	49.99
21.01	50.01

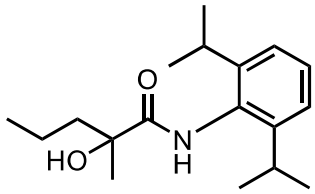
(b)



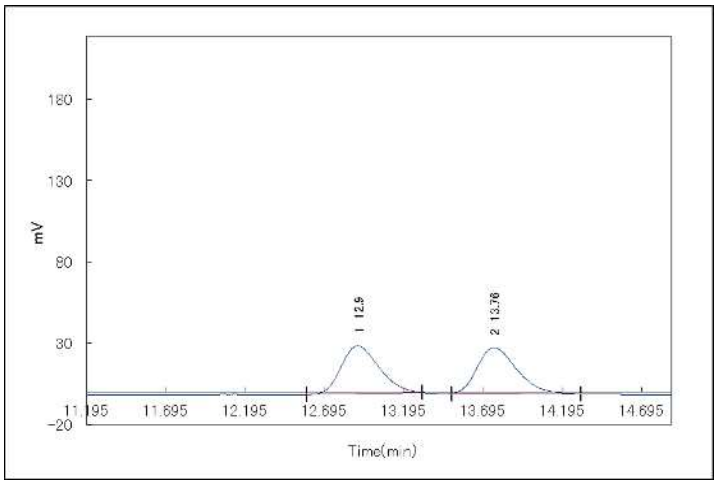
retention time (min)	Area (%)
19.95	100.0

Supporting Figure 2k Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2k** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 97/3 as an eluent monitored at 214 nm).

(**2l**)

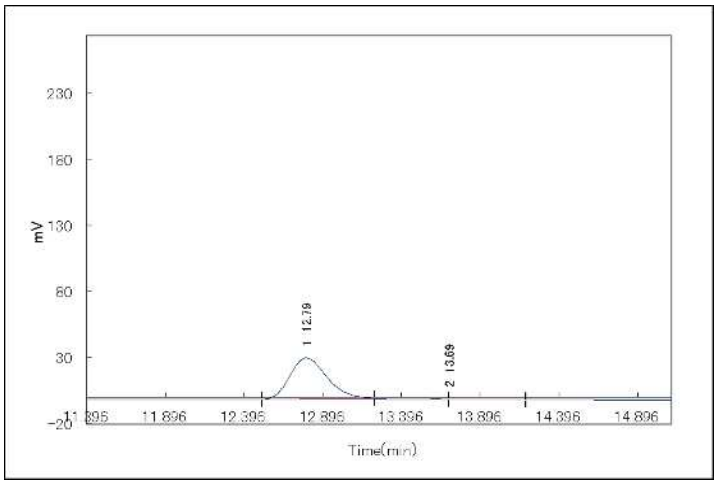


(a)



retention time (min)	Area (%)
12.9	50.08
13.76	49.92

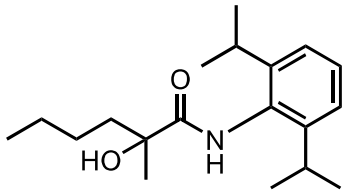
(b)



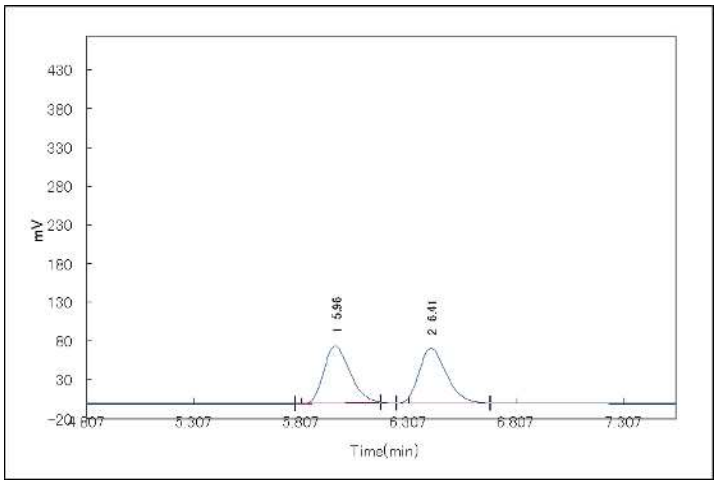
retention time (min)	Area (%)
12.79	100.0

Supporting Figure 2l Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2l** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 214 nm).

(**2m**)

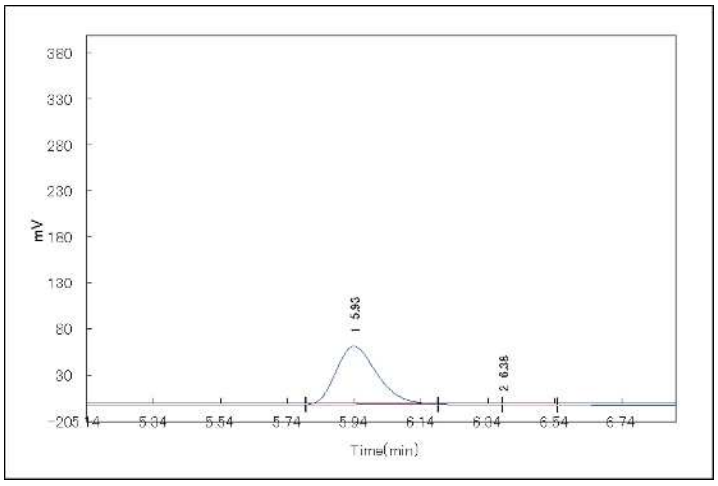


(a)



retention time (min)	Area (%)
5.96	49.67
6.41	50.33

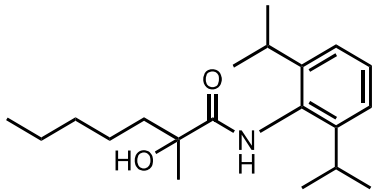
(b)



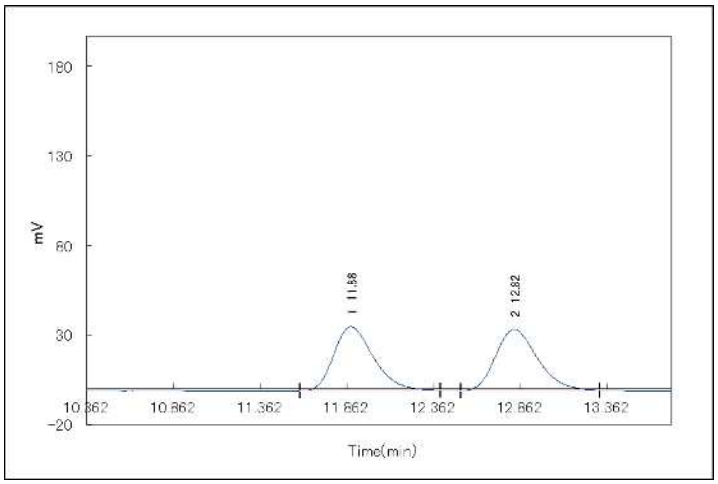
retention time (min)	Area (%)
5.93	100.0

Supporting Figure 2m Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2m** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 214 nm).

(**2n**)

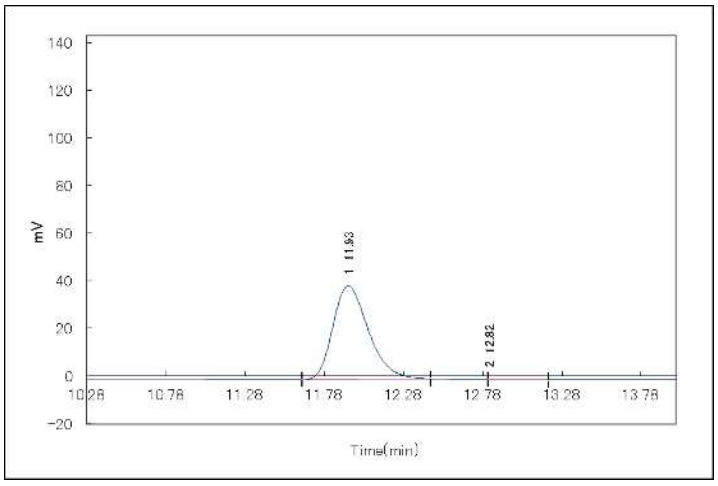


(a)



retention time (min)	Area (%)
11.88	49.85
12.82	50.15

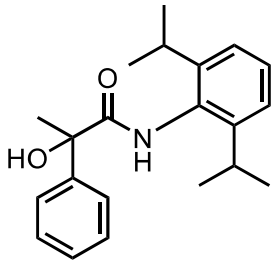
(b)



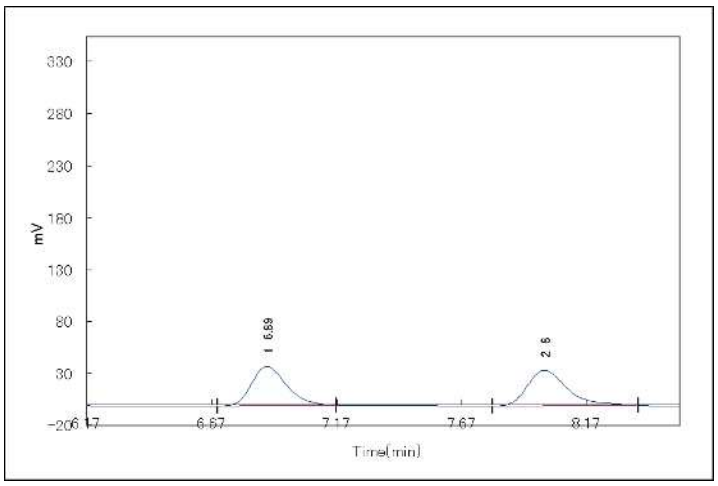
retention time (min)	Area (%)
11.93	100.0

Supporting Figure 2n Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2n** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 214 nm).

(**2o**)

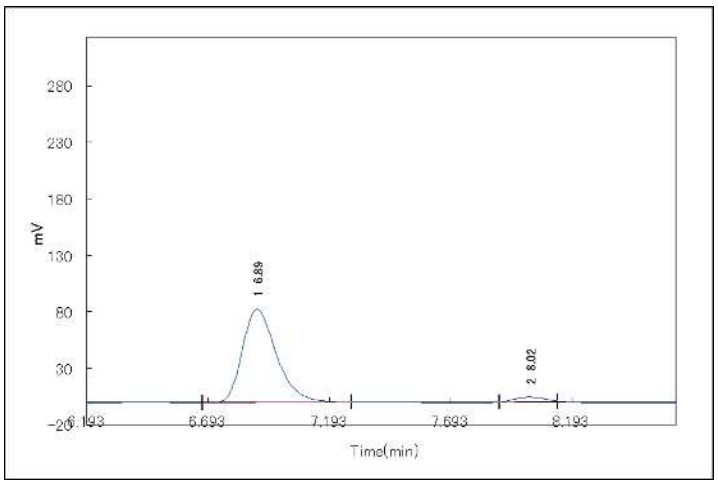


(a)



retention time (min)	Area (%)
6.89	49.16
8.00	50.84

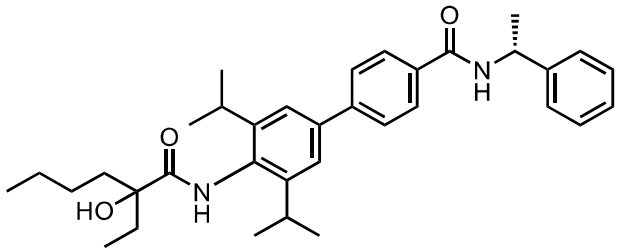
(b)



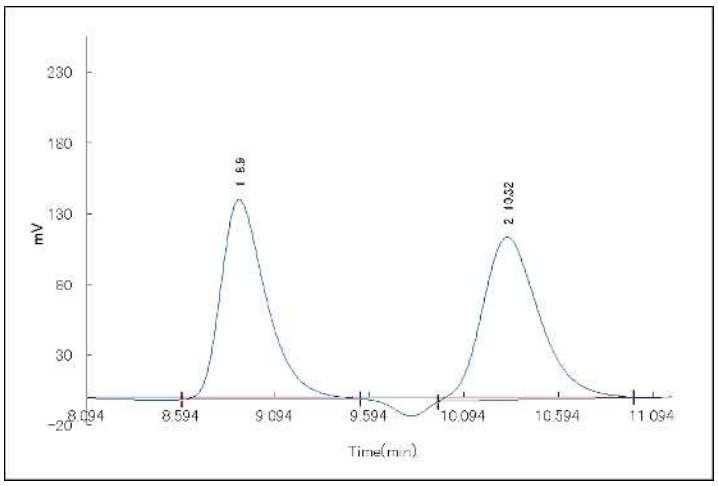
retention time (min)	Area (%)
6.89	96.3
8.02	3.71

Supporting Figure 2o Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2o** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 214 nm).

(**2p**)

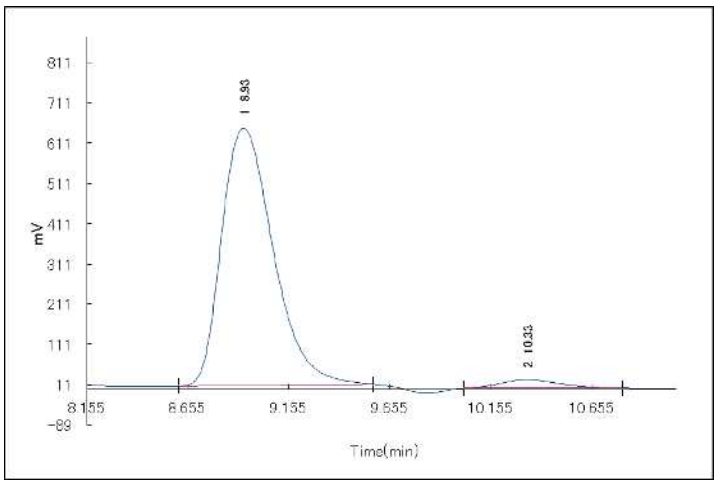


(a)



retention time (min)	Area (%)
8.9	49.439
10.32	50.561

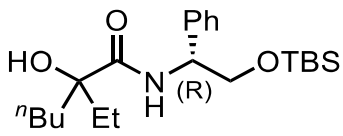
(b)



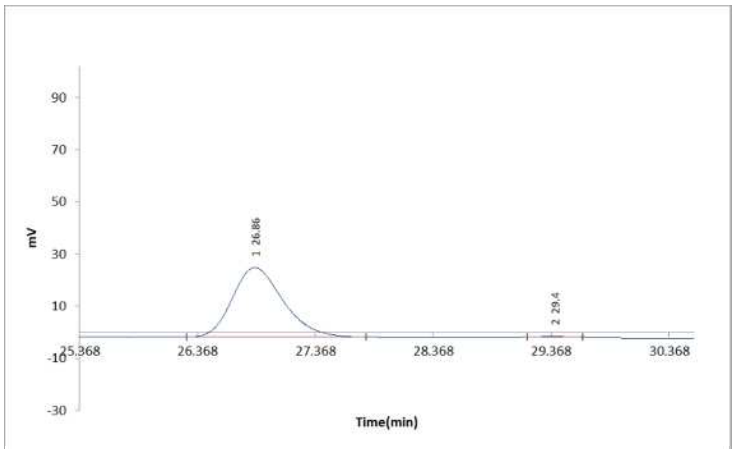
retention time (min)	Area (%)
8.93	96.444
10.33	3.556

Supporting Figure 2p Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2p** using Daicel CHIRALPAK IC-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 70/30 as an eluent monitored at 254 nm).

(**2q**)

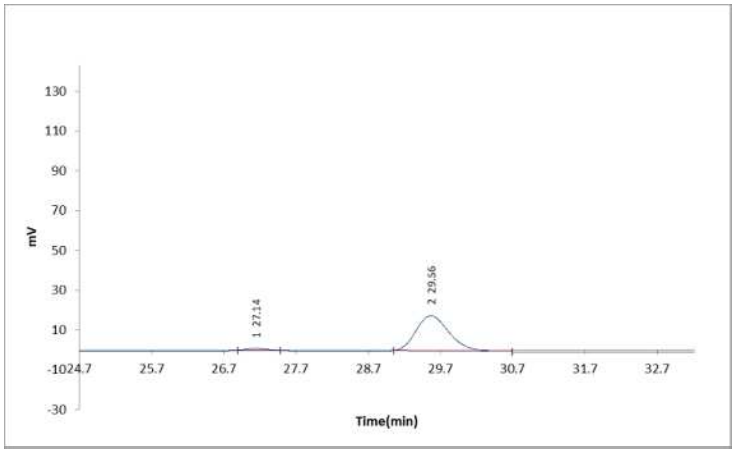


(a)



retention time (min)	Area (%)
26.86	99.3753
29.4	0.6247

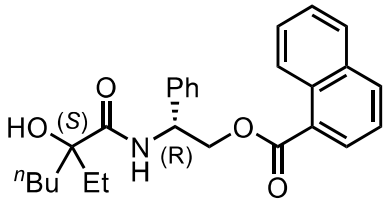
(b)



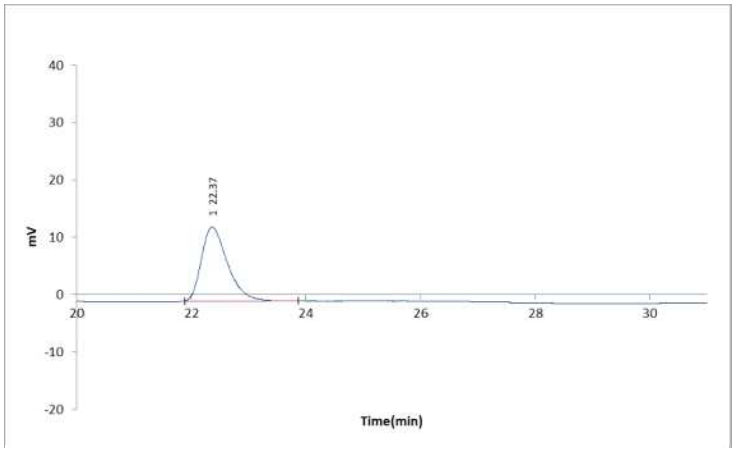
retention time (min)	Area (%)
27.14	2.9125
29.56	97.0875

Supporting Figure 2q Chiral HPLC profiles of (a) 1st eluent and (b) 2nd eluent **2q** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 95/5 as an eluent monitored at 220 nm).

(**4**)

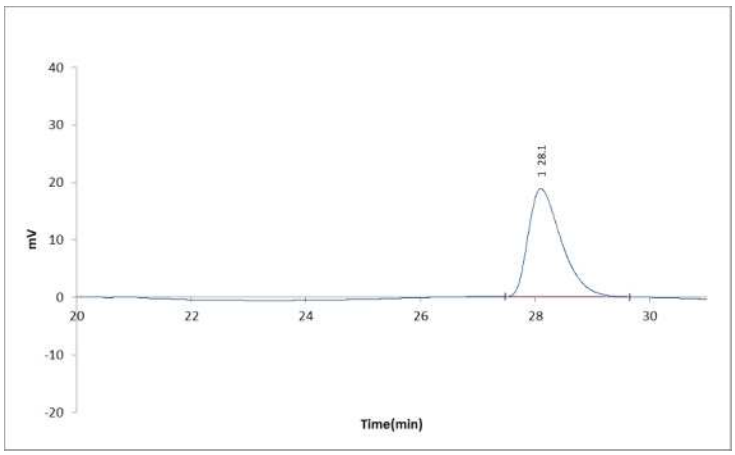


(a)



retention time (min)	Area (%)
22.37	100

(b)



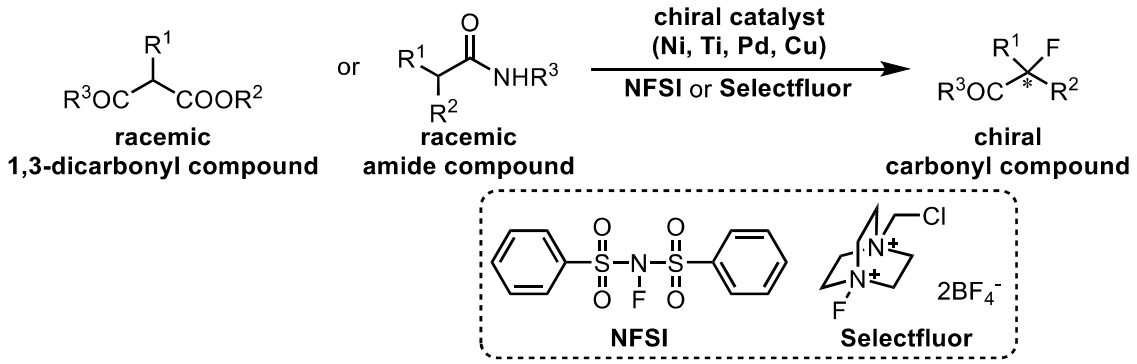
retention time (min)	Area (%)
28.1	100

Supporting Figure 4 Chiral HPLC profiles of (a) 1st eluent and (b) 2nd eluent **4** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 70/30 as an eluent monitored at 254 nm).

Chapter 5 Development of stereospecific fluorination of chiral tertiary alkyl halides in the presence of copper catalyst

5.1 Introduction

Among stereospecific transformations, the fluorination of a tertiary (3°) alkyl group using fluoride is a hot research topic; such transformations provide useful organofluorine compounds that are often found in pharmaceuticals, agrochemicals, and functional materials.[1] Moreover, organofluorine compounds are becoming increasingly important in the pharmaceuticals market.[2]

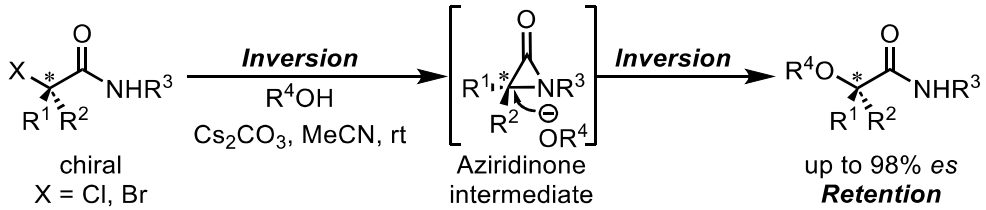


Scheme 1 Enantioselective fluorination to tertiary alkyl compounds

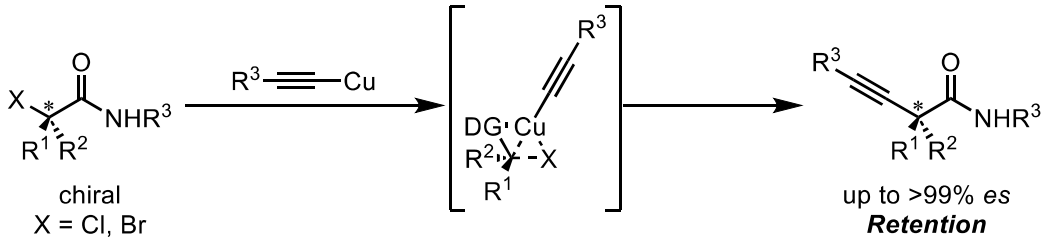
Since 2004, many reports have been reported of enantioselective fluorination reactions that can synthesize chiral tertiary alkyl fluorides with high enantioselectivity by using racemic 1,3-dicarbonyl compounds[3] and amide compounds[4] as substrates and acting with various chiral metal catalysts (Scheme 1). Another synthesis of chiral organofluorine is a stereospecific reaction that is excellent as a method of reflecting the chirality of the raw material in the product without impairing it. Enantiospecific fluorination reactions of tertiary alkyl compounds were reported[5], but other methods for stereospecifically transforming the stereocenters in organic substrates have not been well explored. So, developing such methods for preparing a range of compounds bearing chiral tertiary alkyl groups is highly desirable.

5.2 Previous works and this work

The authors reported the stereospecific etherifications (via ionic processes)[6] and alkynylations (via Cu^{I}-catalyzed radical processes)[7] of α-bromocarboxamides as chiral *tert*-alkyl sources (Scheme 2,3).

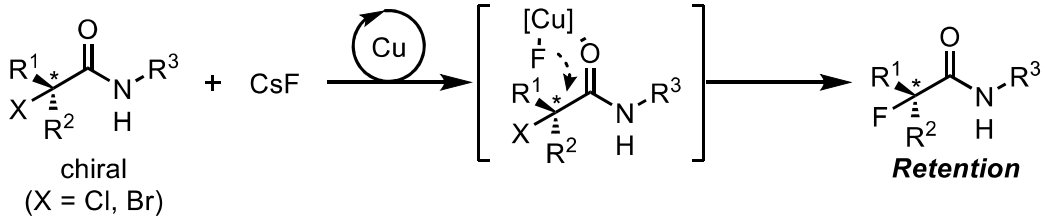


Scheme 2 Previous work (stereospecific etherification)



Scheme 3 Previous work (stereospecific alkynylation)

Herein, I reported stereoretentive fluorination chemistry for tertiary stereogenic centers using CsF in combination with a Cu^{II} catalyst (Scheme 4).

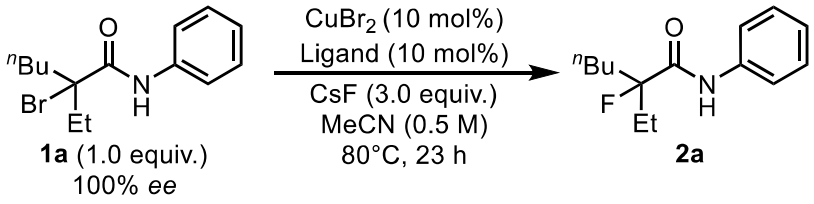


Scheme 4 This work

5.3 Results and discussion

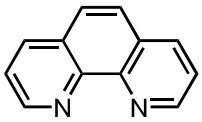
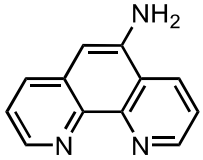
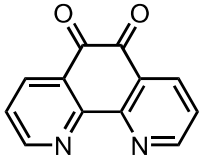
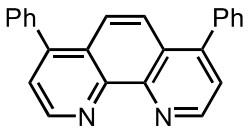
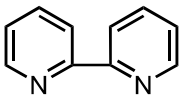
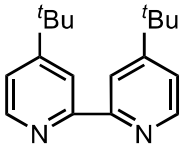
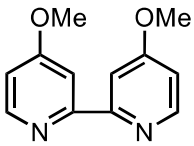
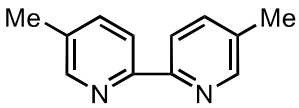
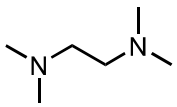
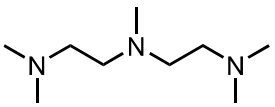
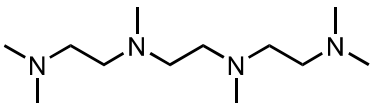
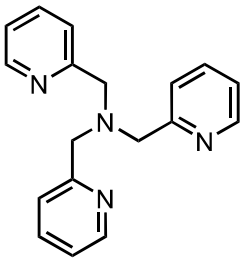
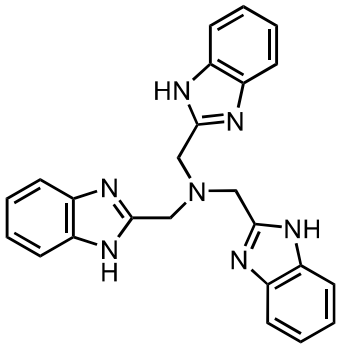
5.3.1 Optimization of reaction conditions

Table 1 Optimization of ligands



1a (1.0 equiv.)
100% *ee*

2a

Isolated yield of **2a**, *es* of **2a**			
 **L1**: 82%, 79% *es*	 **L2**: 60%, 44% *es*	 **L3**: 74%, 74% *es*	 **L4**: 87%, 93% *es*
 **L5**: 88%, 98% *es*	 **L6**: 88%, 99% *es* 86%, >99% *es*[a] 89%, 98% *es*[a,b]	 **L7**: 85%, 17% *es*	 **L8**: 95%, 97% *es*
 **L9**: 33%, 55% *es*	 **L10**: 57%, 34% *es*	 **L11**: 20%, 17% *es*	
 **L12**: 53%, 1% *es*	 **L13**: 22%, 10% *es*		PPh_3: 16%, 84% *es* PCy_3: 20%, 84% *es*

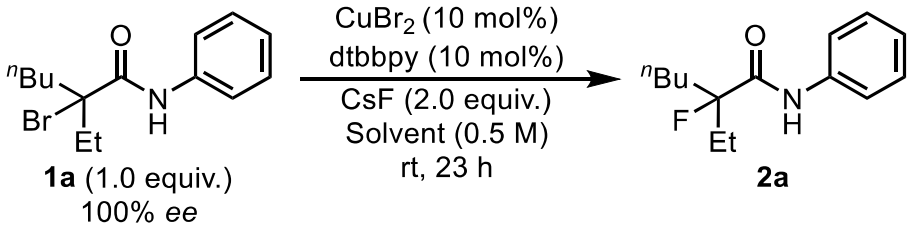
The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

[a]room temperature. [b]2.0 equiv. of CsF was used.

I conducted optimization of ligands using **1a** (100% ee), $CuBr_2$ and CsF in MeCN at 80°C for 23 hours. When 1,10-phenanthroline (**L1**) was used, **2a** was obtained in 82% isolated yield with 79% es. Next, I examined the effect of 1,10-phenanthroline derivatives (**L2-L4**) and 2,2-bipyridyl derivatives (**L5-L8**). When **L4** was used, isolated yield and es of product **2a** improved (87% yield

and 93% es). While es of product **2a** decreased significantly when I used **L7**, the results of both isolated yield and es were excellent when **L5**, **L6** and **L8**. The use of **L6** resulted in completely retention of stereo information of substrate **1a**. Subsequently, I examined the effect of alkyl nitrogen-type ligands (**L9-L11**) and other nitrogen ligands (**L12**, **L13**). These ligands gave worse results. When tris(2-pyridylmethyl)amine (TPMA, **L12**) was used, racemic product **2a** was obtained. Finally, when phosphine-type ligand (PPh_3, PCy_3) was used, the fluorination product **2a** was obtained with low isolated yield.

Table 2 Optimization of solvents

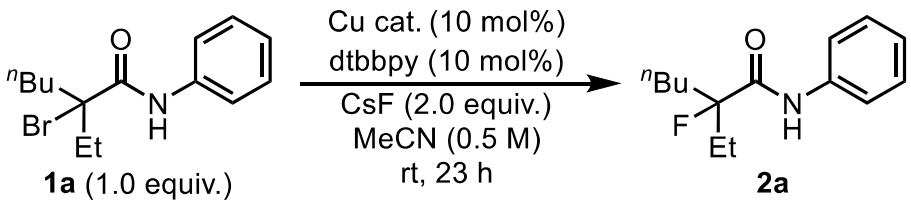


Entry	Solvent	Isolated yield of **2a**	*es*
1	MeCN	89%	98%
2	THF	41%	>99%
3	DCM	22%	>99%
4	Toluene	trace	-
5	DMF	trace	-
6	DMSO	trace	-

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Subsequently, I examined the effects of solvents (Table 2). When THF and dichloromethane (DCM) were used, the fluorination product **2a** was obtained with low yield (entry 2,3). When toluene was used, the reaction almost did not progress (entry 4). Enantiospecific fluorination hardly progressed, and side reactions progressed in DMF or DMSO (entry 5,6). From the results of these solvent studies, acetonitrile was determined to be the optimal solvent.

Table 3 Optimization of Cu catalysts



1a (1.0 equiv.)
100% *ee*

Entry	Cu cat.	Isolated yield of **2a**	*es*
1	$CuBr_2$	89%	98%
2	$CuCl_2$	36%	>99%
3	CuF_2	12%	19%
4	$Cu(OAc)_2$	35%	>99%
5	CuI	71%	4%
6	CuBr	58%	2%
7	CuCN	77%	10%

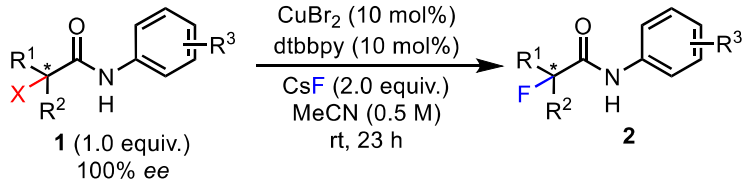
The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Table 3 shows the results of the studies of copper catalysts. When using $CuCl_2$ or $Cu(OAc)_2$, the result was that the steric information was completely retention, albeit with a low yield, but when using CuF_2, the yield was surprisingly low in both es. When a monovalent copper catalyst was used, the result was that racemization proceeded, probably because the single-electron reduction to the substrate of the copper catalyst proceeded.

From these results, I determined $CuBr_2$ as an optimal copper catalyst.

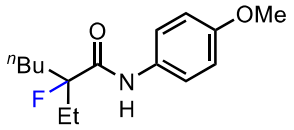
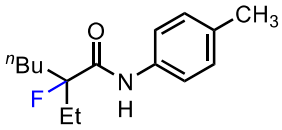
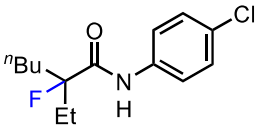
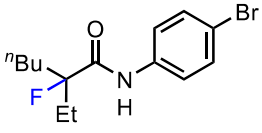
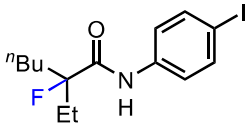
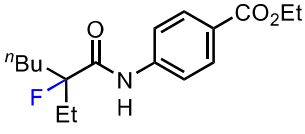
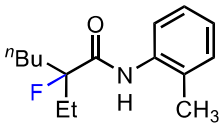
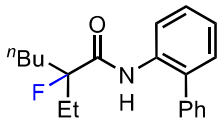
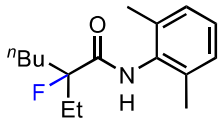
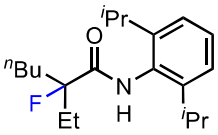
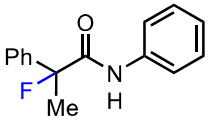
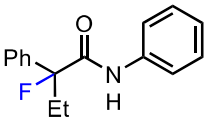
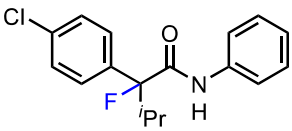
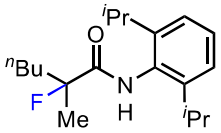
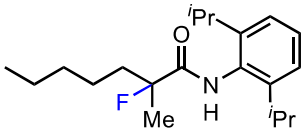
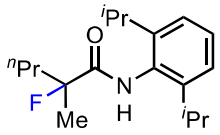
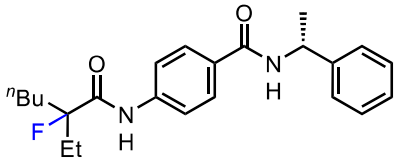
5.3.2 Substrate Scopes for enantiospecific fluorination

Table 4 Substrate scopes for enantiospecific fluorination



1 (1.0 equiv.)
100% *ee*

2

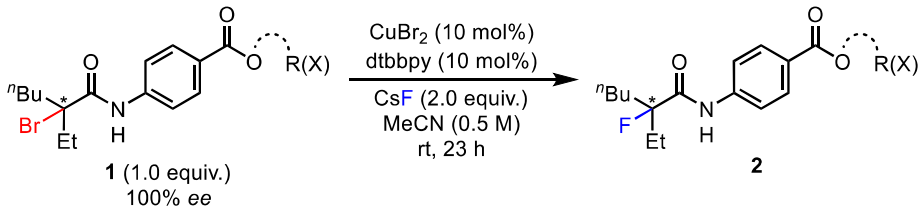
Isolated yield of **2**, *es*			
 **2b** 92%, >99% *es*[a]	 **2c** 83%, 90% *es*	 **2d** 82%, 95% *es*	 **2e** 89%, 97% *es*[b] 83%, 74% *es* (standard)
 **2f** 91%, >99% *es*	 **2g** 87%, 91% *es*[a]	 **2h** 81%, >99% *es*[c] 77%, 86% *es* (standard)	 **2i** 87%, 96% *es*[c] 87%, 83% *es* (standard)
 **2j** 88%, >99% *es*	 **2k** 87%, 91% *es*[a]	 **2l** (X = Cl) 61%, 83% *es*	 **2m** (X = Cl) 77%, 94% *es*
 **2n** (X = Cl) 89%[e], 98% *es*	 **2o** 92%, 98% *es*[a,d] 87%, 77% *es* (standard)	 **2p** 90%, 94% *es*[a,d] 86%, 72% *es* (standard)	
 **2q** 96%, 96% *es*[a,d] 93%, 73% *es* (standard)	 **2r** 44%, 87% *es*[a,b,c]		

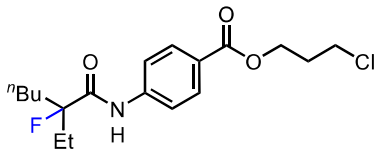
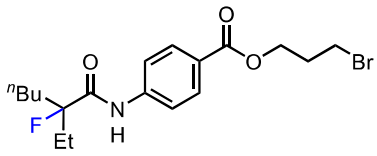
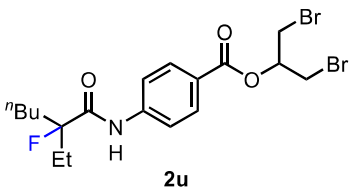
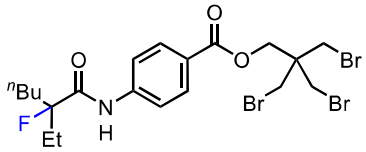
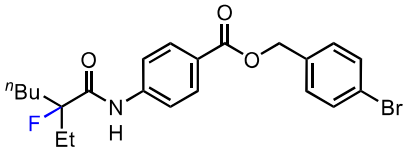
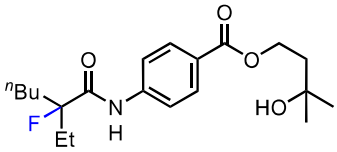
The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2**/ee of substrate **1**. [a]80°C. [b]3.0 equiv. of CsF was used. [c]2,2'-bipyridyl was used instead of dtbbpy. [d]1.5 equiv. of TEMPO was added. [e]GPC yield.

With the optimal conditions, I investigated the substrate scope for enantiospecific fluorination (Table

4). First, the range of substituents on amide aryl groups was examined. When α-bromoamides having electron donating groups (**2b**, **2c**) and having electoron deficient groups (**2d-2g**) at para position were used, some substrates had slightly changed conditions, but high yield and high enantiospecificity were given. Further, even when α-bromoamide having methyl group and phenyl group at ortho position (**2h**, **2i**) were used, the target product could be obtained with excellent enantiospecificity. Next, when **1j** and **1k** were used, the fluorinated product was obtained with high yield and good enantiospecificity. Subsequently, steric effects of carbonyl α-position was examined. Stereospecific fluorination proceeded without any problems with α-chloroamide, and **2l-2n** were obtained with good results. The target fluorinated products (**2o-2q**) could be obtained with an excellent yield and enantiospecificity by raising the temperature to 80°C and adding TEMPO. Finally, when α-bromoamide **1r** was used, the product **2r** could be obtained in 44% isolated yield and 87% es.

Table 5 Substrate scope (continued)

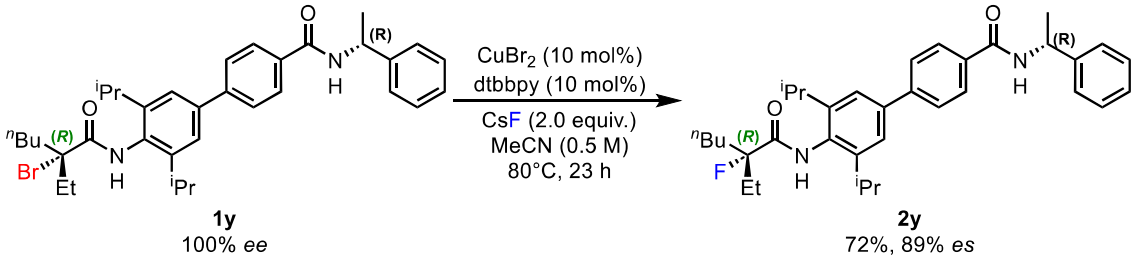


Isolated yield of **2**, *es*		
 **2s** 91%, >99% $es^{a,b}$ 89%, 93% *es* (standard)	 **2t** 85%, 99% $es^{a,b}$ 73%, 92% *es* (standard)	 **2u** 84%, >99% es^{a} 78%, >99% *es* (standard)
 **2v** 94%, 98% $es^{a,b}$ 72%, 91% *es* (standard)	 **2w** 50%, 93% es^{c} 81%, 78% *es* (standard)	 **2x** 77%, 90% *es*

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2**/ee of substrate **1**. [a]2,2'-bipyridyl was used instead of dtbbpy. [b]3.0 equiv. of CsF was used. [c]CuI was used instead of $CuBr_2$ and 1.5 equiv. of TEMPO was added.

Next, in the reaction using the substrate **1s-1v** having several primary halogen substituents in the molecule, the tertiary C-Br bond was selectively fluorinated rather than the primary C-halogen bond, and the target product was obtained with a high yield and excellent enantiospecificity.

In addition, in this stereospecific fluorination reaction, a substrate having a phenyl bromide and a tertiary hydroxy group was also applied, the fluorinated product could be obtained with moderate yield and a good enantiospecificity.



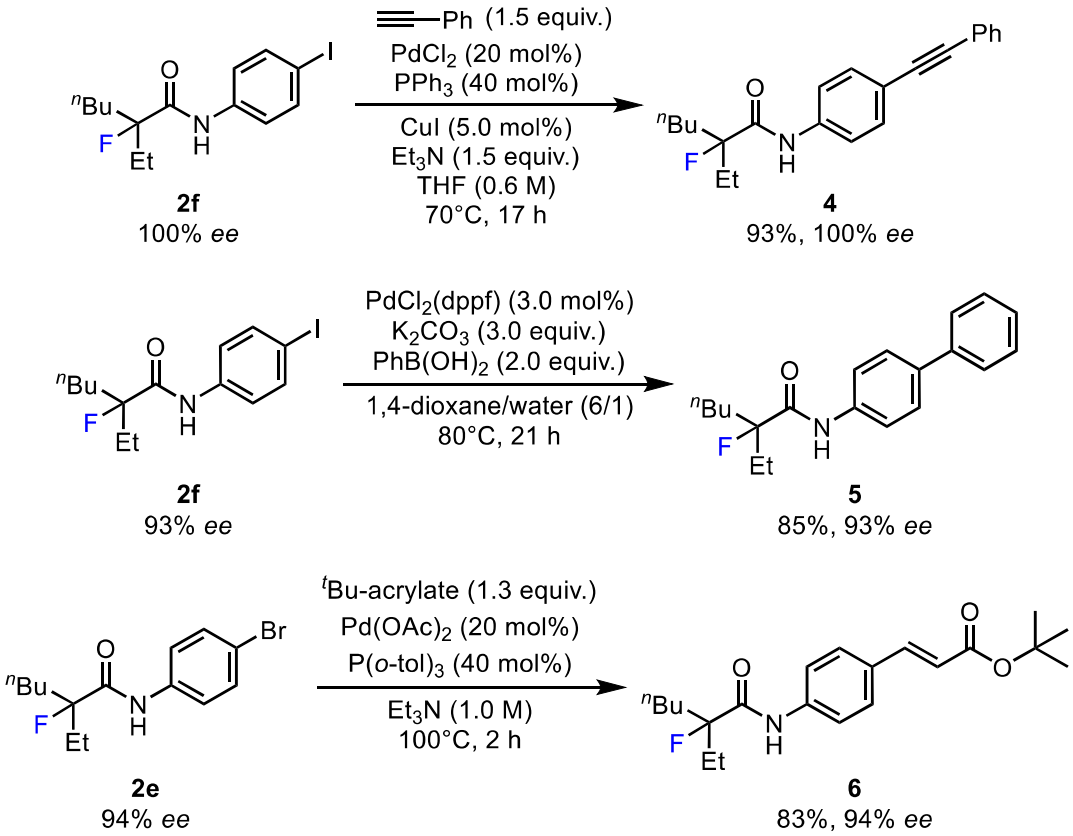
1y
100% *ee*

2y
72%, 89% *es*

Scheme 5 The reaction with α-bromoamide **1y**

Stereospecific fluorination using substrate **1y** was performed (Scheme 5). As a result, fluorinated product **2y** could be obtained in 82% isolated yield and 89% es. This product **2y** was purified with HPLC to create a single crystal with a single stereoisomer. As a result of single crystal X-ray structural analysis, when *R*-**1y** was used in this reaction, *R*-**2y** was obtained. From this result, it was found that this reaction proceeded with steric retention.

5.3.3 Application



2f
100% *ee*

4
93%, 100% *ee*

2f
93% *ee*

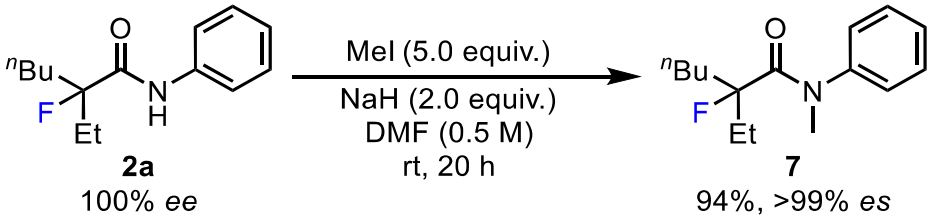
5
85%, 93% *ee*

2e
94% *ee*

6
83%, 94% *ee*

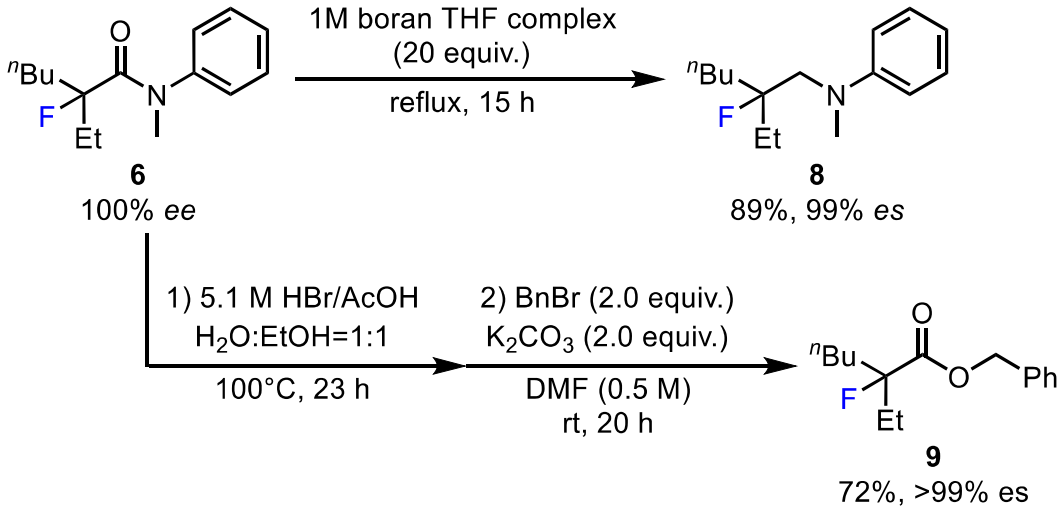
Scheme 6 Application with fluorinated product **2**

Various conversion reactions of enantiospecific fluorinated product **2** were performed (Scheme 6). First, I conducted Sonogashira coupling and Suzuki-Miyaura coupling of fluorinated products **2f**, the product **4** and **5** were obtained with high yield and without compromising ee. Subsequently, I carried out Pd-catalyzed Heck reaction with tert-butyl acrylate, the coupling product **6** could be obtained in 83% yield and without compromising ee.



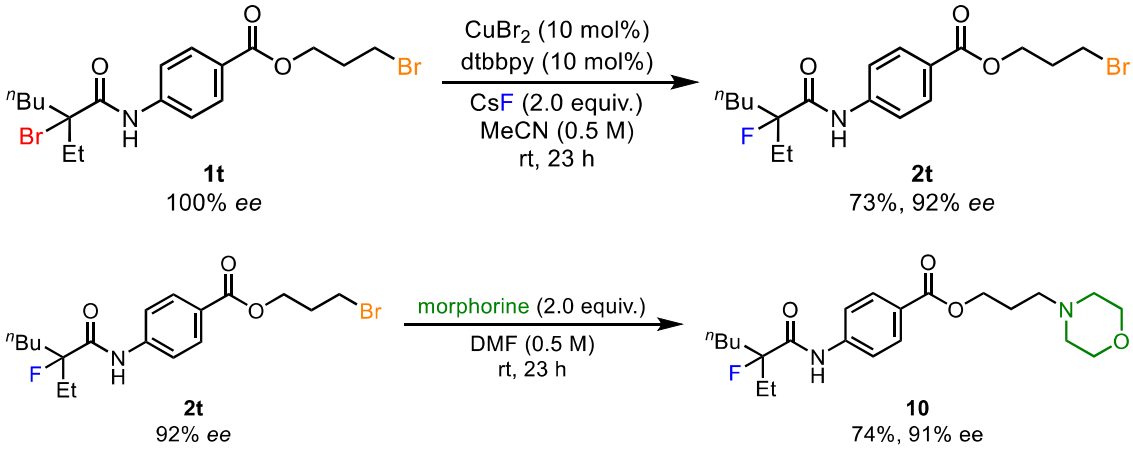
Scheme 7 N-methylation of **2a**

Subsequently, N-methylation product **7** could be obtained in 94% yield without any impairment of ee by reacting fluorinated product **2a** with MeI and NaH at room temperature (Scheme 7). N-methylation reactions are useful because it is known that fluorination reactions using N-methyl α-bromoamide do not proceed at all.



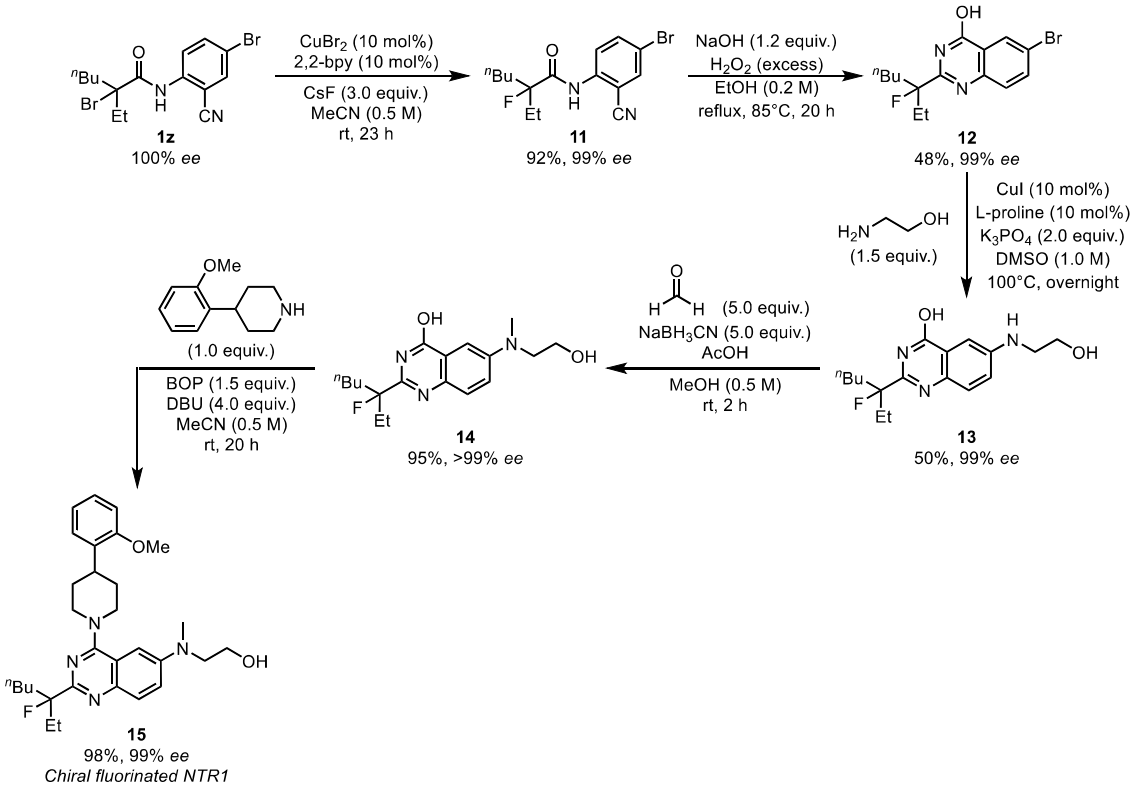
Scheme 8 Transformation of **6**

Using the obtained **6**, a carbonyl reduction and an elimination of the amide site were attempted (Scheme 8). The carbonyl reduction proceeded by acting 20 equivalents of 1M borane THF complex, and the reduction product **8** could be obtained with a high yield and an excellent enantiospecificity. Then, the transformation from amide **6** to ester **9** was conducted. As a result, the ester product **9** could be obtained in 72% yield without impairing ee at all.



Scheme 9 Chemoselective reaction (Enantiospecific fluorination and amination)

Subsequently, I conducted chemoselective reaction (Scheme 9). At first, tertiary C-Br bond selective enantiospecific fluorination proceeded, the fluorinated product **2t** could be obtained in 73% yield and 92% ee. Next, S_N2 amination to primary C-Br bond gave the product **10** with high yield and excellent enantiospecificity.



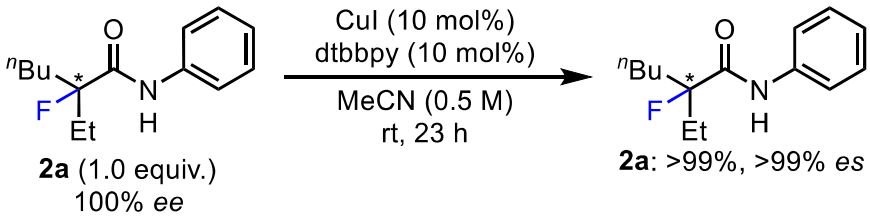
Scheme 10 Synthesis of chiral fluorinated NTR1

A highlight of our current work is the synthesis of a chiral analog of SBI-553, a potent, brain-penetrating NTR1 allosteric modulator that facilitates biased β-arrestin interactions and acts as a Ca^{2+}-pathway antagonist for Gq-mediated activation. While the reported modulator[8] contains a

fluorinated tert-alkyl moiety, an enantio-enriched fluorinated modulator is unknown. In this context, I synthesized **15**, which is an analog of SBI-553 (Scheme 10). The stereospecific fluorination of enantiopure **1z** afforded **11** in 92% yield and 99% ee. H_2O_2-promoted cyclization of the nitrile and carboxamide groups resulted in quinazoline **12**. The alcohol side-chain was introduced via Cu-catalyzed amination, after which methylation through the reductive amination of **13** yielded **14**. Finally, substitution of the OH group in **14** with the piperidine moiety provided **15** in 98% yield without any loss of chirality.

5.3.4 Mechanistic studies

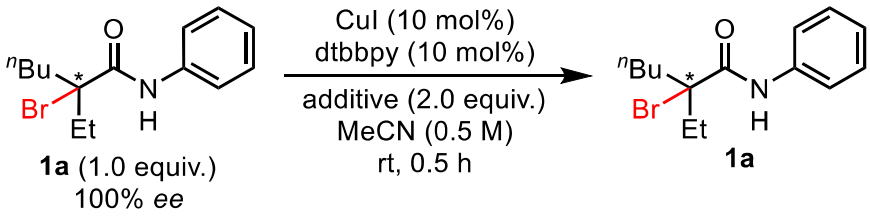
I conducted several mechanistic studies to propose this reaction mechanism.



Scheme 11 The stability of fluorinated product **2a**

In the optimization of the reaction conditions of this study, when CuI was used as a copper catalyst, the result was that racemization of **1a** progressed. Therefore, in order to deny the racemization of the generated fluorinated product **2a**, **2a** was stirred at room temperature for 23 hours in the presence of CuI (Scheme 11). As a result, since **2a** could be recovered quantitatively and without any loss of ee, the progress of racemization of fluorination products by monovalent copper catalyst could be ruled out.

Table 6 The stability of α-bromoamide **1a**



Entry	additive	Isolated yield of **1a**	*es* of **1a**
1	none	99%	73%
2	none (9 h)	99%	41%
3	none (23 h)	78%	4%
4[a]	none (23 h)	90%	>99%
5	CsF	79%	19%
6	CsBr	99%	82%
7	Cs_2CO_3	99%	90%
8	CsOAc	99%	98%

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **1a**/ee of substrate **1a**.

[a]$CuBr_2$ was used instead of CuI.

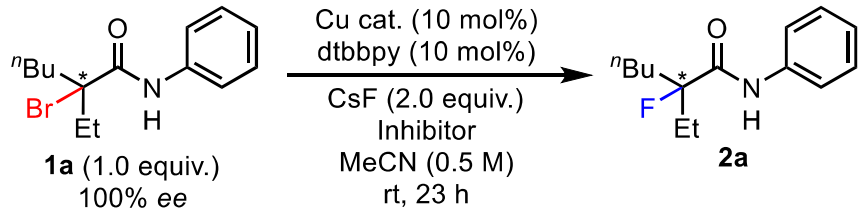
Subsequently, the stability of α-bromoamide **1a** against CuI was investigated. The stability of the raw material **1a** was examined in the presence of CuI catalyst in the absence of additives (entry 1-3). As a result, when the reaction time was extended to 9 hours, and 23 hours, racemization of **1a** was remarkably observed. However, when $CuBr_2$ was used instead of CuI, racemization of **1a** was not observed at all (entry 4). In entry 5-8, cesium salts (CsF, CsBr, Cs_2CO_3, CsOAc) were added as additives, and the raw material **1a** was reacted for 30 minutes in the presence of CuI. As a result, when CsF was added and reacted for 30 minutes, a significant decrease in ee of **1a** was observed and recovered. However, when CsBr, Cs_2CO_3, and CsOAc were added, no effect was observed on the racemization of the raw material **1a**. These results suggested that

The presence of $CuBr_2$ suppresses the progress of racemization.

The reaction proceeds via free-radical intermediate produced by the single-electron reduction of **1a** by CuI.

CsF promotes racemization of **1a** by monovalent copper catalyst.

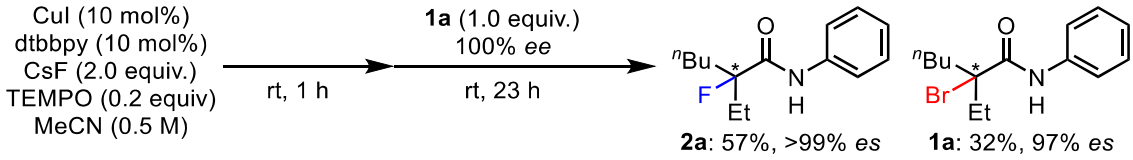
Table 7 Radical inhibition experiments



Entry	Cu cat.	Inhibitor	Isolated yield of **2a**	*es* of **2a**
1	CuI	none	71%	4%
2	CuBr	none	58%	2%
3	$CuBr_2$	none	89%	98%
4	CuI	TEMPO (0.2 equiv.)	95%	41%
5	CuI	TEMPO (1.5 equiv.)	77%	>99%

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Next, I carried out radical inhibition experiments added TEMPO as radical inhibitor in order to confirm involvement of radical intermediate (Table 7). Entry 1-3 show the results of the study in the absence of TEMPO. In the presence of monovalent copper catalysts (CuI, CuBr), fluorination product **2a** was obtained in moderate yield, and racemization proceeded. However, when $CuBr_2$ was used, **2a** was obtained in 89% yield and 98% es. Therefore, CuI was used and TEMPO was added. When 0.2 equivalents of TEMPO were added, **2a** was obtained in 95% yield and 41% es. Subsequently, when TEMPO was increased to 1.5 equivalents, **2a** was obtained in 77% yield, resulting in complete retention.



Scheme 12

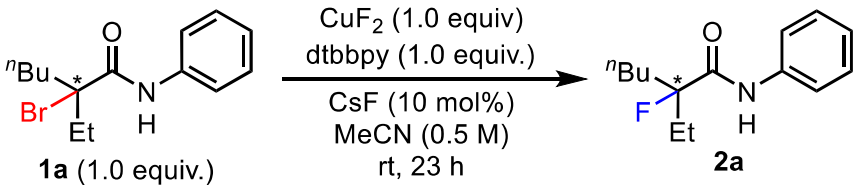
Further, CuI, CsF, and 0.2 equivalents of TEMPO were added and stirred for 1 hour in advance, and after stirring, chiral raw material **1a** was added and further stirred for 23 hours (Scheme 12). As a result, fluorinated product **2a** was obtained in 57% yield, >99% es, and raw material **1a** was obtained in 32% yield and 97% es.

These results suggested that

Enantiospecific fluorination did not proceed via free radical intermediate.

TEMPO (E^0 = +0.492 V, vs. SCE)[9] functioned as an oxidant for monovalent copper catalyst (E^0 = +0.159 V, vs. SCE)[10] rather than as a radical inhibitor.

Table 8 Equivalent reaction experiments of CuF_2



1a (1.0 equiv.)
100% *ee*

Entry	Variation from standard conditions	Isolated yield of **2a**	*es* of **2a**
1	without CsF	0%	-
2	none	62%	>99%
3	bpy instead of dtbbpy	62%	>99%
4	without dtbbpy	0%	-
5	TEMPO (1.0 equiv.) was added	68%	>99%
6	Cs_2CO_3 instead of CsF	54%	>99%
7	CsOAc instead of CsF	51%	>99%
8	AgF instead of CsF	2%	-
9	$CuBr_2$ instead of CsF	6%	-
10	K_3PO_4 instead of CsF	17%	-
11	DABCO instead of CsF	3%	-

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

Subsequently, I investigated whether CuF_2 was a reactive species. Initially, the reaction did not proceed at all in the absence of a catalytic amount of CsF. When 2,2-bipyridyl was used, the same results were obtained when dtbbpy was used. Next, it was found that the reaction did not proceed at all in the absence of ligand (entry 4). Even when the reaction was performed with the addition of TEMPO, the same result as the conditions without TEMPO was obtained, suggesting that it did not proceed via a free radical intermediate in this study as well (entry 5). Then, when other cesium salts (Cs_2CO_3, CsOAc) were added instead of CsF, a slight decrease in yield was observed compared to CsF, but **2a** was obtained with a moderate yield, and without any loss of ee. In addition, various additives were added instead of CsF, but the product **2a** was obtained in low yields.

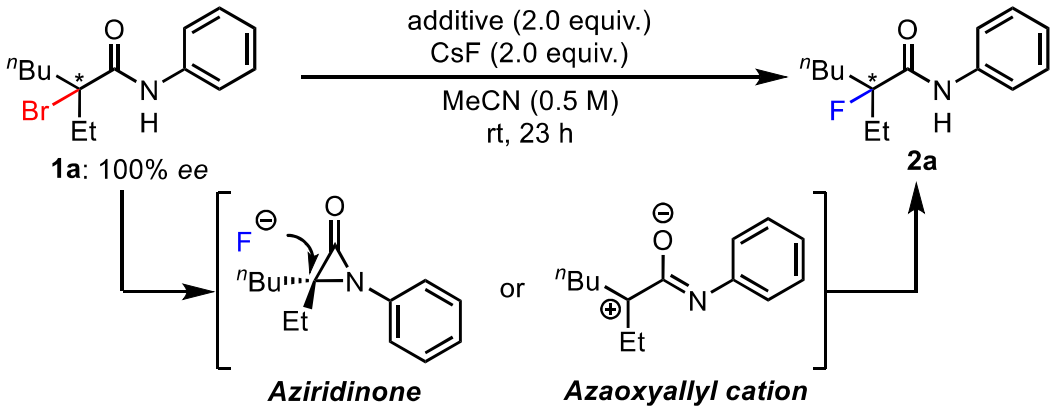
These results suggested that

CuF_2 was a reactive species.

In this reaction, catalytic amounts of CsF and ligand needed.

Cesium cation accelerated the reaction.

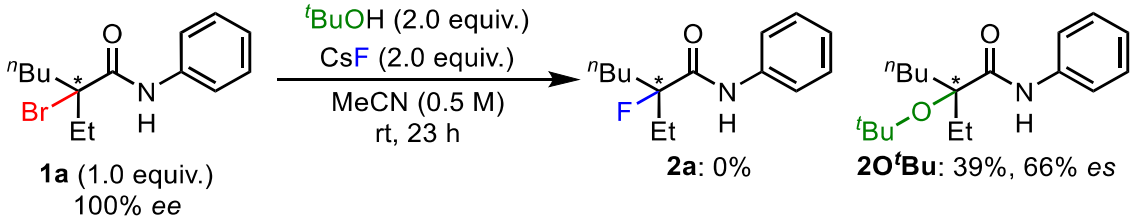
Table 9 Checking aziridinone or azaoxyallyl cation intermediates



Entry	additive	Isolated yield of **2a**	*es* of **2a**	Memo
1	-	37%	26%	**1a**: 28%, 96% *es*
2	Cs_2CO_3	52%	35%	**Elimination:** 11%

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2a**/ee of substrate **1a**.

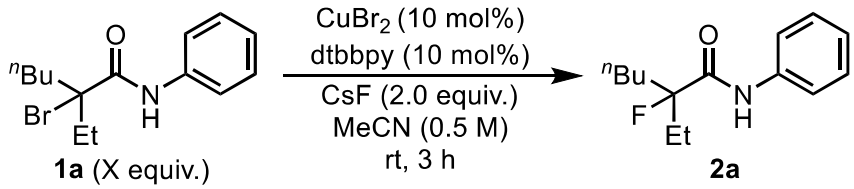
In the stereospecific etherification previously reported,[6] it is proposed that the reaction proceeds via aziridinone intermediate. Based on this stereospecific etherification, I investigated whether this reaction proceeded via aziridinone or azaoxyallyl cation[11] (Table 9). In the absence of additives or when Cs_2CO_3 was added as a base, **2a** was obtained with a moderate yield and low es. In these cases, it was presumed that it proceeded via azaoxyallyl cation, and that cationic species were generated and racemization of **1a** proceeded.

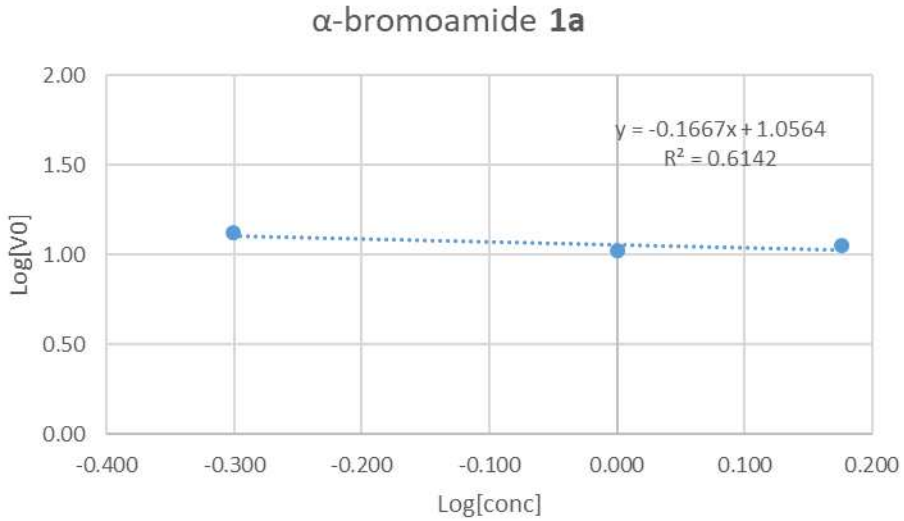


Scheme 13 The reaction with tert-butanol

When tert-butanol and CsF were added, **2a** was not produced at all, and **2O^{t}Bu** was obtained in 39% yield and 66% es (Scheme 13). In the absence of a copper catalyst, CsF acts as a base, and it is highly likely that the ee of **2O^{t}Bu** was lowered via aziridinone or azaoxyallyl cation. From these results, it is considered that the stereospecific fluorination reaction does not pass through aziridinone or azaoxyallyl cation intermediates.

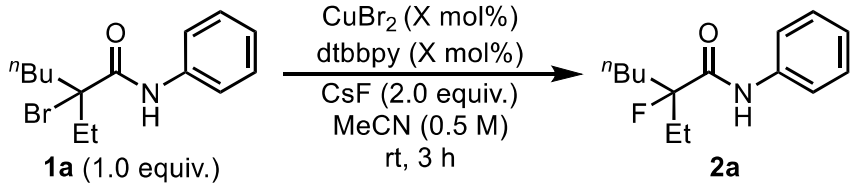
5.3.5 Kinetics studies

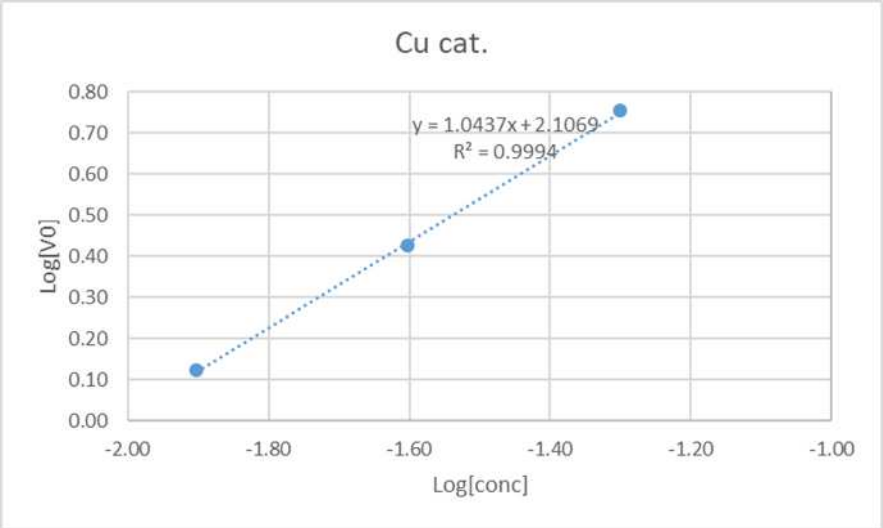




x	1.0	2.0	3.0
concentration	0.5	1.00	1.50
yield/2a	39.8	31.6	33.6
log[conc]	-0.301	0.00	0.18
log[V_0]	1.12	1.02	1.05

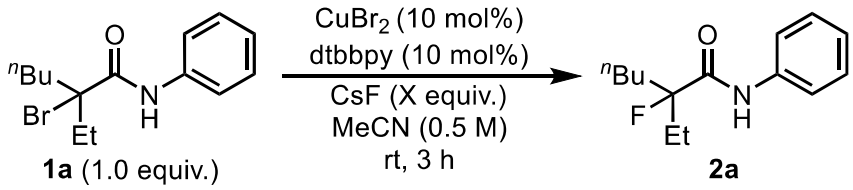
Figure 1 Kinetics studies of α-bromoamide **1a** in the enantiospecific fluorination

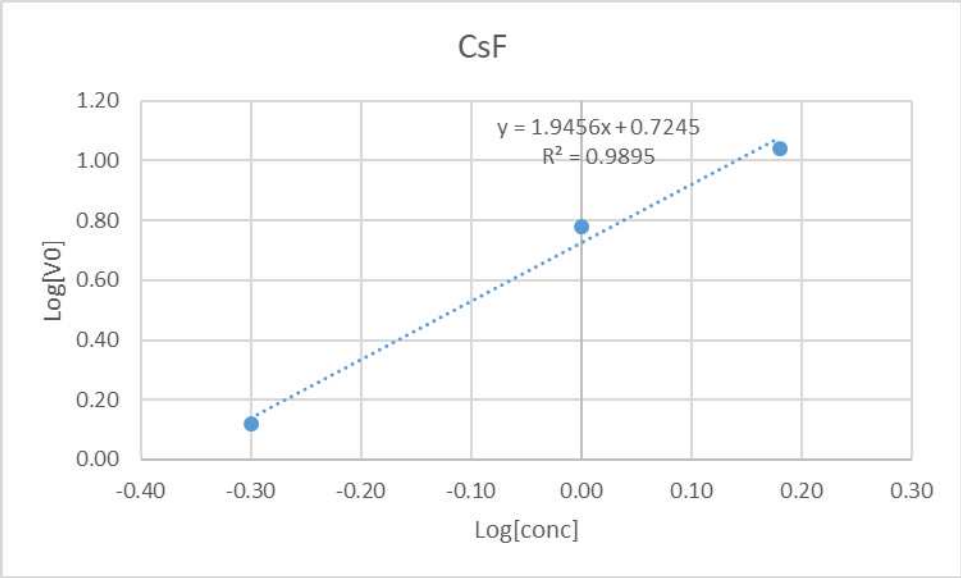




x	2.5	5.0	10.0
concentration	0.0125	0.025	0.05
yield/2a	4	8	17
log[conc]	-1.90	-1.60	-1.30
log[Vo]	0.12	0.43	0.75

Figure 2 Kinetics studies of Cu catalyst and ligand in the enantiospecific fluorination



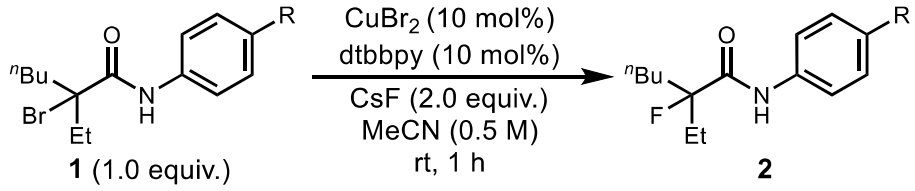


x	1.0	2.0	3.0
concentration	0.5	1	1.5
yield/2a	4	18	33
log[conc]	-0.30	0.00	0.18
log[Vo]	0.12	0.78	1.04

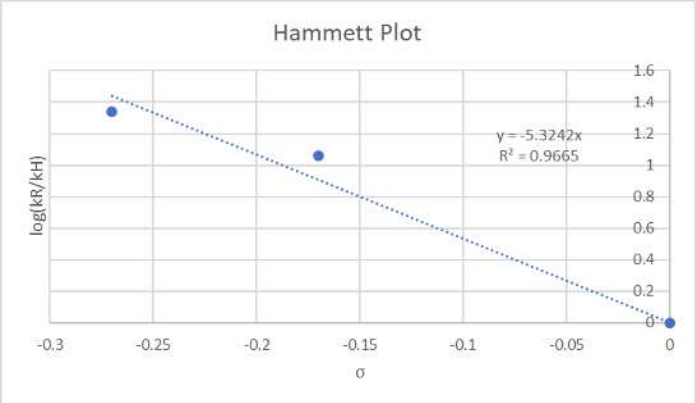
Figure 3 Kinetics studies of CsF in the enantiospecific fluorination

Here, the reaction order of the reaction substrate **1a** (Figure 1), copper catalyst (Figure 2), and CsF (Figure 3) was determined. From these results of kinetics studies, I determined that the reaction substrate **1a** is zero-order, Cu catalyst is first-order, and CsF is second-order.

5.3.6 Hammet plot studies



substituent	p-OMe	p-Me	H	p-Cl	p-COOEt
σ	-0.27	-0.17	0	0.23	0.45
log(kR/kH)	1.34	1.06	0	0.85	1.41



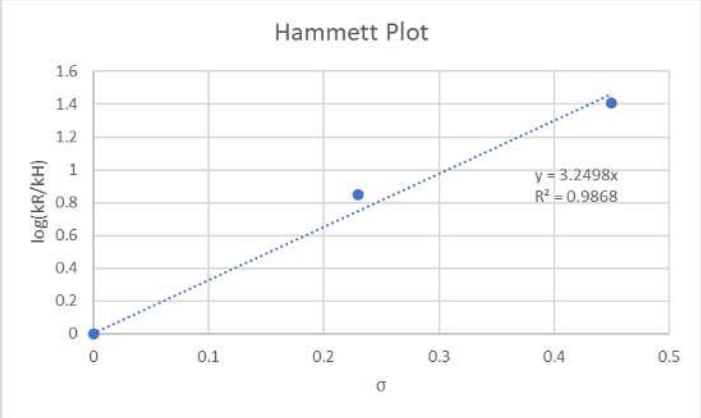
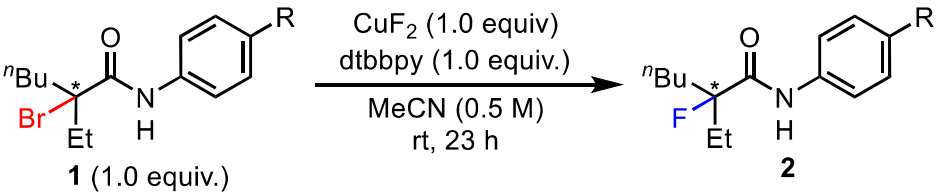


Figure 4 Hammet plot studies in the enantiospecific fluorination

Subsequently, a Hammett plot experiments using **1a-1d** and **1g** was performed (Scheme 4). As a result, it was found that both the electron-donating substituent and the electron-deficient substituent affect the reaction rate of the reaction.

Table 10 Confirmation of substituent effect of α-bromoamide in the equivalent of CuF_2



Entry	R	Yield of **2**	*es* of **2**
1	H (**1a**)	0%	-
2[a]	H (**1a**)	62%	>99%
3	OMe (**1b**)	22%	-
4	CO_2Et (**1g**)	20%	-

The *ee* values were determined by HPLC analysis. Enantiospecificity (es) = ee of product **2**/ee of substrate **1**. [a]CsF (10 mol%) was added.

Then, in the equivalent reaction of CuF_2, when the reaction was performed using the substrate **1a**, the reaction did not proceed at all when CsF was not added (entry 1), but when a catalytic amounts of CsF was added, the product **2a** was obtained in 62% yield and 99% es (entry 2). Therefore, as a result of performing the reaction in the absence of a catalytic amounts of CsF using **1b** having an electron-donating substituent on the amide aryl group and **1g** of an electron-deficient substituent, about 20% of the product was obtained in either case (entry 3,4).

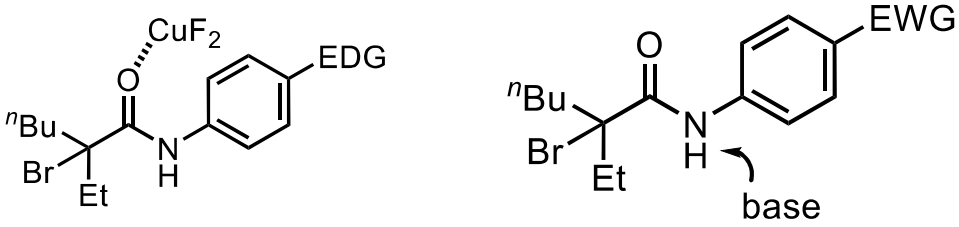
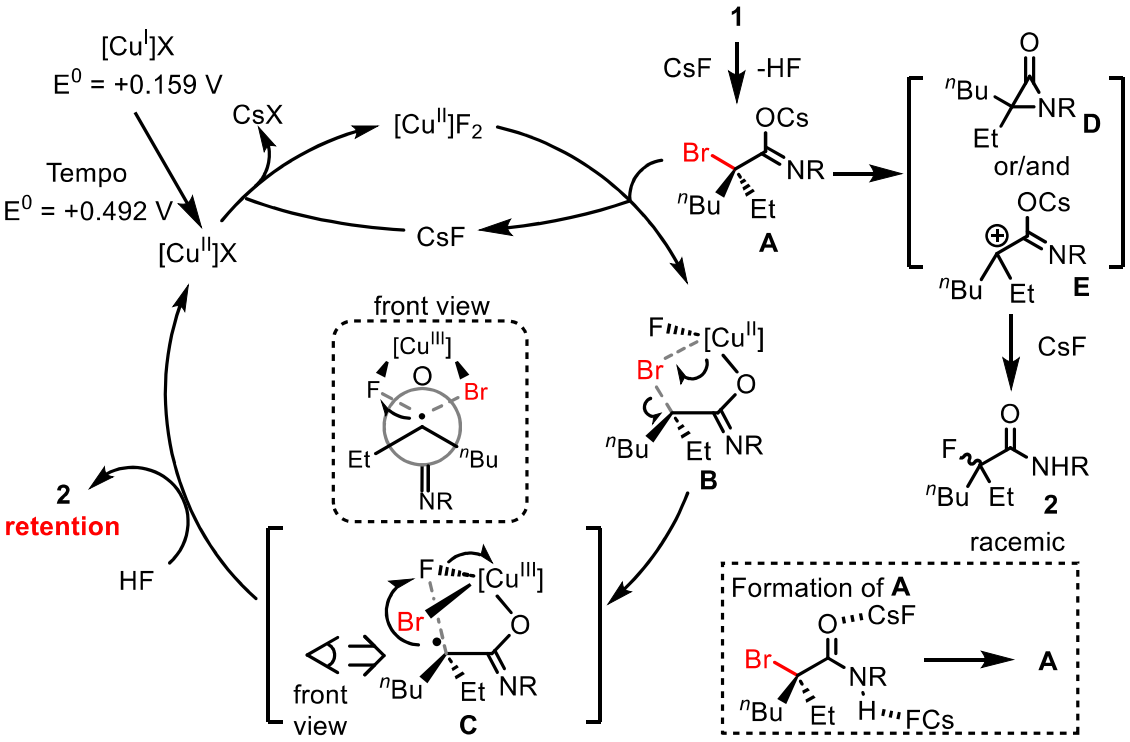


Figure 5 Consideration of results showed in Table 10

These results suggested that in a substrate having an electron-donating substituent on an amide aryl group, the coordination of CuF_2 to carbonyl oxygen promotes the fluorination reaction (Figure 5, left), while in a substrate having an electron-deficient substituent on the amide aryl group, the deprotonation of amide NH tends to proceed and the reaction rate is improved (Figure 5, right).

5.3.7 Proposed reaction mechanism



The reaction mechanism of this enantiospecific fluorination reaction was estimated from the mechanism studies.

Divalent copper catalyst and CsF occurs ligand exchange to produce CuF_2. Next, deprotonation of NH of substrate **1** results in intermediate **A**. Therefore, the reaction of intermediate **A** and CuF_2 gives the copper complex **B** and regeneration of CsF. After C-Br bond cleavage proceeds and radical intermediate **C** is generated, a C-F bond is immediately formed to form a stereoretentive fluorination product **2**. When a monovalent copper catalyst is used, it was considered that in the presence of TEMPO, the product can be obtained stereospecifically because it becomes a divalent copper catalyst by single-electron oxidation of the copper catalyst. Then, in the absence of a copper catalyst, it was estimated that the loss of ee was observed because it was via aziridinone intermediate **D** or azaoxyallyl cation intermediate **E** from intermediate **A**.

Alternatively, oxidative addition of the C-Br bond to Cu^{II} followed by reductive elimination, while possible, is unlikely to proceed because the oxidative addition of a C-Br bond to Cu^{I} has a high energy barrier even when Cu^{I} is used as the catalyst[12]. Therefore, Cu^{II} is unlikely to oxidatively add to generate C-[Cu^{IV}]-Br based on its redox potential. I described my proposed reaction mechanism, but I cannot exclude other reaction mechanism involving radical species, ionic species, or organometallic species.

5.4 Conclusion

In this study, I developed stereospecific fluorination of chiral tertiary alkyl halides in the presence of Cu catalyst. This enantiospecific fluorination has a wide range of substrate scope, and the fluorinated product was obtained with good yield and enantiospecificity. Also, the stereoretentive product could be obtained in this reaction. The synthesis of chiral NTR1 was also achieved. From the results of mechanistic studies, it is suggested that CuF_2 is a reactive species and it is important that the presence of CsF and ligand for this reaction.

5.5 Reference

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5.6 Experimental Section

General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick) were used; for column chromatography Silica *Flash*® P60 (SiliCycle, 40-63 μm) was used. Visualization was accomplished by UV light (254 nm), ^{1}H and ^{13}C NMR spectra were obtained using a JEOL 400 MHz NMR spectrometer. Chemical shifts for 1H NMR were described in parts per million (chloroform as an internal standard δ = 7.26) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard (δ = 77.16), unless otherwise noted. High resolution mass analyses were obtained using an ACQUITY UPLC/ TOF-MS for EI. Specific rotation was recorded by JASCO P-2100. Chiral compounds were separated by YMC CHIRALART column (amylose-SA) and DAICEL chiral column series. Anhydrous MeCN was purchased from Kanto Chemical Co., Ltd. Other chemicals were purchased from TCI, Aldrich and Wako and directly used from the bottles.

General procedure for synthesis of α-bromocarboxamides

Method A

Carboxylic acid (10 mmol, 1.0 equiv.), and PBr_3 (0.33 mL, 3.3 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90˚C. After this time, Br_2 (0.82mL, 16 mmol) was added to the reaction mixture and the temperature was raised up 110 °C. When the temperature was reached at 110 °C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110 °C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110 °C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40.0 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step.

α-bromo acid bromide synthesized above, Et_3N (4.2 mL, 30 mmol) were sequentially added to CH_2Cl_2 (10 mL, 1.0 M), then desired amine (10 mmol, 1.0 equiv.) was dropped into the mixture at 0 ºC. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were washed with saturated aqueous $Na_2S_2O_3$ (20 mL × 3), saturated aqueous $NaHCO_3$ (20 mL × 3) and brine (20 mL × 1). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic α-bromocarboxamide. Chiral α-bromocarboxamide was obtained after chiral separation with chiral column.

Method B

Carboxylic acid (10 mmol, 1.0 equiv.), and PBr_3 (0.33 mL, 3.3 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90˚C. After this time, Br_2 (0.82mL, 16 mmol) was added to the reaction mixture and the temperature was raised up 110 °C. When the temperature was reached at 110 °C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110 °C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110 °C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40.0 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step.

4-aminobenzoic acid (10 mmol, 1.0 equiv.) was sequentially added to THF (30 mL, 0.33 M), then α-bromo acid bromide synthesized above, was dropped into the mixture at 0 ºC. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were filtered by vacuum

filtration. The combined organic layer was evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the alkyl bromide. Then, obtained alkyl bromide (5.0 mmol, 1.0 equiv.), carbodiimide (CDI, 5.5 mmol, 1.1 equiv.) and DMAP (0.50 mmol, 0.10 equiv.) were sequentially added under air to a reaction tube equipped with a stir bar and septum. Et_3N (1.2 mL, 7.5 mmol, 1.5 equiv.) and CH_2Cl_2 (10 mL) were added by syringe and the resulting mixture vigorously stirred for 3 h at ambient temperature. After this time, corresponding alcohol (10 mmol, 2.0 equiv.) was sequentially added to this solution and the resulting mixture again stirred for 14 h at ambient temperature. After this time, the resulting solution was quenched with Sat. NH_4Cl aq. and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic α-bromocarboxamides. Chiral α-bromocarboxamide was obtained after chiral separation with chiral column.

Method C

Carboxylic acid (10 mmol, 1.0 equiv.), and PBr_3 (0.33 mL, 3.3 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90˚C. After this time, Br_2 (0.82mL, 16 mmol) was added to the reaction mixture and the temperature was raised up 110 °C. When the temperature was reached at 110 °C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110 °C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110 °C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40.0 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step.

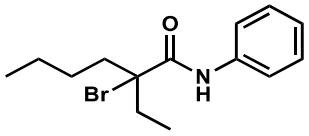
4-aminobenzoic acid (10 mmol, 1.0 equiv.) was sequentially added to THF (30 mL, 0.33 M), then α-bromo acid bromide synthesized above, was dropped into the mixture at 0 ºC. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were filtered by vacuum filtration. The combined organic layer was evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the alkyl bromide. Then, obtained alkyl bromide (5.0 mmol, 1.0 equiv.), N-ethyl-N'-methylaminopropylcarbodiimide (EDC, 5.0 mmol, 1.0 equiv.), and DMAP (5.0 mmol, 1.0 equiv.), CH_2Cl_2 (0.5 M) were sequentially added under air to a reaction tube equipped with a stir bar and septum. After this time, corresponding alcohol (7.5 mmol, 1.5 equiv.) was dropped into the mixture at 0°C, and the resulting mixture stirred overnight at room temperature. After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic α-bromocarboxamides. Chiral α-bromocarboxamides was obtained after chiral separation with chiral column.

Method D

Carboxylic acid (10 mmol, 1.0 equiv) and Thionyl chloride (2.88 mL, 40 mmol) were sequentially added under air to a reaction vessel equipped with stir bar. The resulting mixture stirred 30 minutes at 80˚C. After this time, NCS (3.34g, 25 mmol), Thionyl chloride (0.25 mL) and conc. HCl (4 drop) was added to the reaction mixture, and the reaction mixture was stirred for 2.5 hours at 95˚C. Then, the mixture was filtrated and concentrated in vacuo. Amine (10 mmol, 1.0 equiv.) and Et_3N (4.2 mL, 30 mmol) were sequentially added in CH_2Cl_2 (20 mL, 0.5 M), then the resulting crude including 2-chloro acid chloride was dropped into the mixture at 0˚C. After stirring overnight at room temperature, the contents of the reaction vessel were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the product.

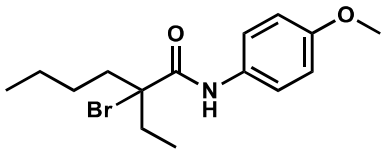
1a, 1b, 1c, 1d, 1g, 1i, 1j, 1k, 1o, 1p, 1q (H. Akagawa, N. Tsuchiya, A. Morinaga, Y. Katayama, M. Sumimoto, T. Nishikata, *ACS Catal.* **2022**, *12*, 9831–9838.) and **1s, 2s** (S. Ishida, R. Fujimoto, T. Nishikata, *Angew. Chem. Int. Ed.* **2016**, *55*, 10008–10012.) were repoted.

2-bromo-2-ethyl-*N*-phenylhexanamide (**1a**)



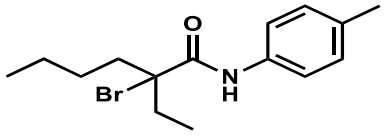
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), Aniline (0.91 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.74 g, 9.2 mmol, 92%) as yellow oil; IR (cm^{-1}): 3386, 2958, 2932, 2872, 1813, 1736, 1671, 1597, 1524, 1440, 1380, 1309, 1238, 1044, 931, 900, 829, 753, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.67 (brs, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 2.05-2.22 (m, 2H), 2.07-1.96 (m, 2H), 1.64-1.58 (m, 1H), 1.41-1.30 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 137.3, 129.1, 125.1, 120.1, 79.4, 43.1, 36.7, 28.3, 22.6, 14.0, 10.6.
1a was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = -3.62 (c 0.152, CH_2Cl_2).

2-bromo-2-ethyl-*N*-(4-methoxyphenyl)hexanamide (**1b**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), p-Anisidine (1232 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.89 g, 8.8 mmol, 88%) as yellow oil; IR (cm^{-1}): 3385, 2955, 2932, 2872, 2115, 1810, 1742, 1663, 1596, 1509, 1458, 1412, 1380, 1299, 1245, 1178, 1150, 1110, 1034, 932, 827, 756; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.56 (brs, 1H), 7.44 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 9.1 Hz, 2H), 3.79 (s, 3H), 2.33-2.21 (m, 2H), 2.06-1.95 (m, 2H), 1.62-1.55 (m, 1H), 1.39-1.29 (m, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 157.0, 130.4, 122.0, 114.3, 79.5, 55.6, 43.1, 36.7, 28.3, 22.6, 14.0, 10.6.
1b was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).
$[\alpha]^{25}_D$ = +1.46 (c 0.235, CH_2Cl_2).

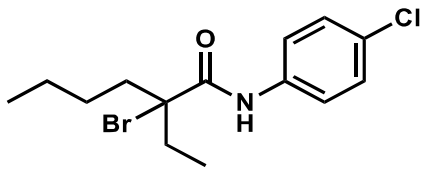
2-bromo-2-ethyl-*N*-(p-tolyl)hexanamide (**1c**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), p-Toluidine (1072 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.72 g, 8.7 mmol, 87%) as yellow solid; IR (cm^{-1}): 3292, 3193, 3124, 3034, 2953, 2930, 2870, 1890, 1812, 1749, 1654, 1599, 1508, 1449, 1402, 1378, 1310, 1243, 1125, 1069, 990, 934, 910, 858, 810, 751, 728, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.60 (brs, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 2.35-2.21 (m, 2H), 2.32 (s, 3H), 2.06-1.95 (m, 2H), 1.61-1.56 (m, 1H), 1.40-1.29 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 134.8, 134.7, 129.6, 120.2,

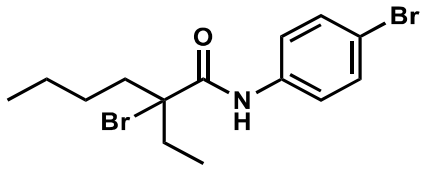
79.5, 43.1, 36.7, 28.3, 22.6, 21.0, 14.0, 10.6.
1c was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent)
$[\alpha]^{25}_{D}$ = -6.65 (c 0.283, CH_2Cl_2).

2-bromo-*N*-(4-bromophenyl)-2-ethylhexanamide (**1d**)



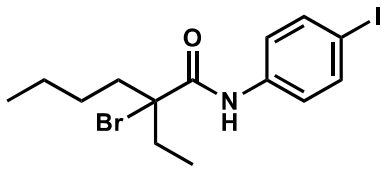
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-chloroaniline (1275.7 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.66 g, 8.0 mmol, 80%) as yellow solid; IR (cm^{-1}): 3294, 3191, 3117, 3058, 2952, 2871, 1891, 1672, 1652, 1595, 1524, 1489, 1452, 1396, 1302, 1235, 1177, 1150, 1092, 1012, 934, 880, 823, 730, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.66 (brs, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 9.8 Hz, 2H), 2.33-2.20 (m, 2H), 2.07-1.96 (m, 2H), 1.62-1.54 (m, 1H), 1.39-1.29 (m, 3H), 1.06 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 135.8, 130.1, 129.1, 121.4, 79.2, 43.0, 36.6, 28.3, 22.6, 14.0, 10.6.
1d was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/Acetone = 99/1 as an eluent).
$[\alpha]^{25}_{D}$ = +2.44 (c 0.130, CH_2Cl_2).

2-bromo-*N*-(4-bromophenyl)-2-ethylhexanamide (**1e**)



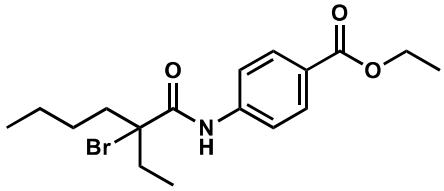
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-bromoaniline (1721 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.83 g, 7.5 mmol, 75%) as white solid; IR (cm^{-1}): 3305, 2952, 2927, 2868, 1656, 1596, 1523, 1485, 1391, 1305, 1234, 1073, 1007, 919, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.66 (brs, 1H), 7.46 (s, 4H), 2.32-2.20 (m, 2H), 2.07-1.96 (m, 2H), 1.63-1.52 (m, 1H), 1.38-1.29 (m, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 136.3, 132.1, 121.7, 117.7, 79.0, 42.9, 36.5, 28.2, 22.5, 14.0, 10.6. HRMS (ESI-MS) calcd. for $C_{14}H_{20}Br_2NO$ [M+H$^+$]: 375.9912, found 375.9912.
1e was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).
$[\alpha]^{25}_{D}$ = +2.22 (c 0.495, CH_2Cl_2).

2-bromo-2-ethyl-*N*-(4-iodophenyl)hexanamide (**1f**)



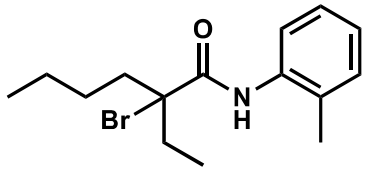
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-iodoaniline (2190 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.25 g, 7.7 mmol, 77%) as white solid; IR (cm^{-1}): 3320, 2949, 2924, 2866, 1655, 1593, 1518, 1481, 1387, 1306, 1233, 1180, 1002, 817; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.64 (brs, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 2.32-2.20 (m, 2H), 2.07-1.95 (m, 2H), 1.60-1.53 (m, 1H), 1.38-1.29 (m, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 138.0, 137.0, 121.8, 88.4, 79.1, 42.9, 36.6, 28.2, 22.5, 14.0, 10.6.
HRMS (ESI-MS) calcd. for $C_{14}H_{20}BrINO$ $[M+H^+]$: 423.9773, found 423.9774.
1f was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).
$[\alpha]^{25}_D$ = +1.93 (c 0.120, CH_2Cl_2).

ethyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1g**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), Ethyl 4-aminobenzoate (1652.2 mg, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.37 g, 9.1 mmol, 91%) as yellow oil; IR (cm^{-1}): 3310, 3094, 2965, 2935, 2862, 2656, 2120, 1925, 1708, 1656, 1590, 1506, 1458, 1405, 1364, 1309, 1269, 1230, 1177, 1104, 1018, 935, 917, 877, 858, 826, 807, 769, 693, 675; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.80 (brs, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.33-2.21 (m, 2H), 2.08-1.97 (m, 2H), 1.62-1.54 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.37-1.36 (m, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 166.1, 141.2, 130.9, 126.8, 119.1, 79.0, 61.0, 42.9, 36.6, 28.3, 22.6, 14.4, 14.0, 10.6.
1g was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).
$[\alpha]^{25}_D$ = +1.86 (c 0.250, CH_2Cl_2).

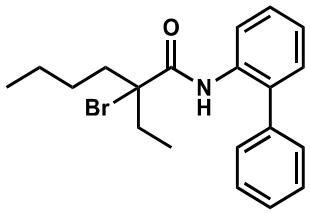
2-bromo-2-ethyl-*N*-(o-tolyl)hexanamide (**1h**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), o-Toluidine (1.07 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.65 g, 8.5 mmol, 85%) as yellow oil; IR (cm^{-1}): 3398, 3338, 2957, 2931, 2872, 1811, 1675, 1589,

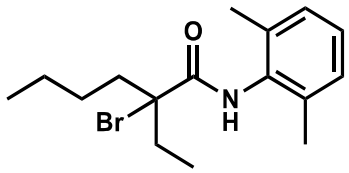
1523, 1454, 1379, 1302, 1251, 1207, 1151, 1113, 1046, 932, 821, 751, 712; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.63 (brs, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.25-7.20 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.36-2.24 (m, 5H), 2.09-1.98 (m, 2H), 1.67-1.59 (m, 1H), 1.43-1.31 (m, 3H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.5, 135.6, 130.6, 129.0, 126.9, 125.5, 122.1, 80.3, 43.2, 36.8, 28.3, 22.6, 18.0, 14.0, 10.7.
HRMS (ESI-MS) calcd. for $C_{15}H_{23}BrNO$ [M+H$^+$]: 312.0963, found 312.0964.
1h was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).
$[\alpha]^{25}_D$ = -1.10 (c 0.235, CH_2Cl_2).

N-([1,1'-biphenyl]-2-yl)-2-bromo-2-ethylhexanamide (**1i**)



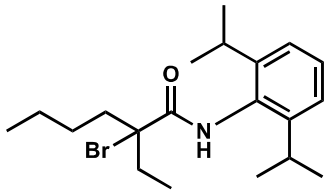
Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2-aminobiphenyl (1.69 g, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.07 g, 8.2 mmol, 82%) as yellow oil; IR(cm^{-1}): 3362, 3059, 2956, 2931, 2862, 2098, 1811, 1743, 1674, 1583, 1519, 1493, 1447, 1380, 1300, 1269, 1215, 1160, 1112, 1046, 946, 820, 755, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.71 (brs, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.44-7.36, (m, 4H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 2.26-2.13 (m, 2H), 1.95-1.83 (m, 2H), 1.48-1.40 (m, 1H), 1.34-1.22 (m, 3H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.6, 137.8, 134.7, 133.2, 130.1, 129.6, 129.2, 128.5, 128.2, 120.9, 78.8, 43.1, 36.6, 28.3, 22.6, 14.1, 10.6.
1i was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).
$[\alpha]^{25}_D$ = -20.1 (c 0.196, CH_2Cl_2).

2-bromo-*N*-(2,6-dimethylphenyl)-2-ethylhexanamide (**1j**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2,6-dimethylaniline (1.24 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.71 g, 8.3 mmol, 83%) as white solid; IR (cm^{-1}): 3248, 3025, 2961, 2857, 2735, 2669, 2292, 1938, 1859, 1734, 1654, 1594, 1519, 1458, 1377, 1340, 1300, 1269, 1226, 1168, 1142, 1106, 1050, 1003, 966, 930, 915, 891, 835, 809, 769, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.25 (brs, 1H), 7.13-7.07 (m, 3H), 2.38-2.23 (m, 2H), 2.26 (s, 6H), 2.13-2.00 (m, 2H), 1.70-1.61 (m, 1H), 1.54-1.45 (m, 1H), 1.41-1.34 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8, 135.2, 134.0, 128.4, 127.5, 79.8, 42.9, 36.4, 28.5, 22.7, 18.9, 14.1, 10.8.
1j was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).
$[\alpha]^{25}_D$ = +4.26 (c 0.300, CH_2Cl_2).

2-bromo-*N*-(2,6-diisopropylphenyl)-2-ethylhexanamide (**1k**)

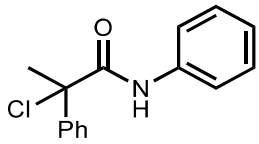


Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2,6-diisopropylaniline (1.89 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.35 g, 8.3 mmol, 83%) as white solid; IR (cm^{-1}): 3349, 3309, 3067, 3025, 2958, 2867, 2101, 1927, 1857, 1653, 1590, 1490, 1458, 1379, 1255, 1219, 1180, 1140, 1115, 1058, 1038, 958, 935, 891, 839, 794, 741, 696, 659; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.16 (brs, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 3.08 (sept, *J* = 6.9 Hz, 2H), 2.36-2.24 (m, 2H), 2.13-2.02(m, 2H), 1.68-1.60 (m, 1H), 1.54-1.45 (m, 1H), 1.41-1.34 (m, 2H), 1.22 (d, *J* = 7.6 Hz, 12H), 1.15 (t, *J* = 6.7 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 145.9, 131.2, 128.5, 123.5, 79.6, 42.7, 36.1, 28.7, 28.4, 23.7, 22.7, 14.0, 10.6.

1k was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).

$[\alpha]^{25}_D$ = +2.23 (c 0.250, CH_2Cl_2).

2-chloro-*N*,2-diphenylpropanamide (**1l**)



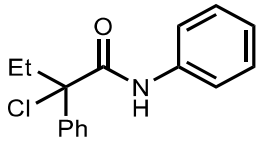
Following the general procedure above (Method D), using carboxylic acid (1.58 mL, 10 mmol), , Thionyl chloride (2.88 mL, 40 mmol), NCS (3.34g, 25 mmol), Thionyl chloride (0.25 mL), conc.HCl (4 drop), 2, 6-Diisopropylaniline (1.51 mL, 8 mmol), Triethylamine (4.2 mL, 30 mmol), CH_2Cl_2 (20 mL, 0.5 M), yielded the product (8.6 mmol, 86 %) as yellow oil; IR (cm^{-1}): 3301, 3060, 2987, 1672, 1595, 1529, 1489, 1314, 1247, 1074, 1053, 930, 745; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.39 (brs, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.36-7.33 (m, 3H), 2.07-1.96 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 141.4, 137.3, 129.2, 128.8, 128.7, 126.1, 125.0, 119.9, 73.7, 30.4.

HRMS (ESI-MS) calcd. for $C_{15}H_{15}ClNO$ $[M+H^+]$: 260.0842, found 260.0842.

1l was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)

$[\alpha]^{25}_D$ = +3.79 (c 0.345, CH_2Cl_2).

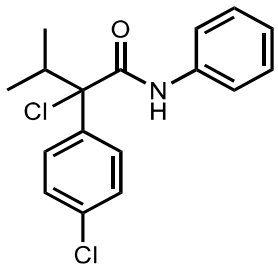
2-chloro-*N*,2-diphenylbutanamide (**1m**)



Following the general procedure above (Method D), using carboxylic acid (1.58 mL, 10 mmol), , Thionyl chloride (2.88 mL, 40 mmol), NCS (3.34g, 25 mmol), Thionyl chloride (0.25 mL), conc.HCl (4 drop), 2, 6-Diisopropylaniline (1.51 mL, 8 mmol), Triethylamine (4.2 mL, 30 mmol), CH_2Cl_2 (20 mL, 0.5 M), yielded the product (8.0 mmol, 80%) as yellow oil; IR (cm^{-1}): 3309, 2968, 2935, 1658, 1595, 1521, 1499, 1437, 1234, 878, 752; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (brs, 1H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* =

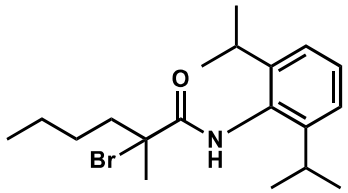
7.5 Hz, 2H), 7.39-7.31 (m, 5H), 7.14 (t, *J* = 7.4 Hz, 1H), 2.67 (dq, *J* = 7.2 and 14.3 Hz, 1H), 2.42 (dq, *J* = 7.2 and 14.4 Hz, 1H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.0, 140.5, 137.3, 129.1, 128.7, 128.6, 126.4, 125.0, 120.0, 79.5, 35.0, 9.6.
HRMS (ESI-MS) calcd. for $C_{16}H_{17}ClNO$ [M+H$^+$]: 274.0999, found 274.0998.
1m was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = -15.6 (c 0.26, CH_2Cl_2).

2-chloro-2-(4-chlorophenyl)-3-methyl-*N*-phenylbutanamide (**1n**)



Following the general procedure above (Method D), using carboxylic acid (1.58 mL, 10 mmol), , Thionyl chloride (2.88 mL, 40 mmol), NCS (3.34g, 25 mmol), Thionyl chloride (0.25 mL), conc.HCl (4 drop), 2, 6-Diisopropylaniline (1.51 mL, 8 mmol), Triethylamine (4.2 mL, 30 mmol), CH_2Cl_2 (20 mL, 0.5 M), yielded the product (6.8 mmol, 68%) as yellow oil; IR (cm^{-1}): 3303, 2969, 1738, 1659, 1593, 1503, 1438, 1388, 1233, 1091, 1011, 776, 747; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.56 (brs, 1H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.49 (dd, *J* = 0.9 and 8.5 Hz, 2H), 7.34-7.29 (m, 4H), 7.12 (t, *J* = 7.4 Hz, 1H), 3.14 (sept, *J* = 6.6 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 137.7, 137.1, 134.4, 129.1, 128.5, 128.2, 125.1, 120.1, 85.0, 37.8, 19.0, 17.0.
HRMS (ESI-MS) calcd. for $C_{17}H_{18}Cl_2NO$ [M+H$^+$]: 322.0765, found 322.0766.
1n was prepared from the corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent)
$[\alpha]^{25}_D$ = -82.43 (c 0.4, CH_2Cl_2).

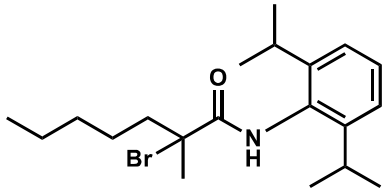
2-bromo-*N*-(2,6-diisopropylphenyl)-2-methylhexanamide (**1o**)



Following the general procedure above (Method A), using 2-Methyl hexanoic acid (1.41 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2,6-diisopropylaniline (1.89 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.12 g, 8.5 mmol, 83%) as white solid; IR (cm^{-1}): 3342, 3312, 2958, 1644, 1488, 1465, 1273, 1127, 942, 796; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (brs, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.05 (sept, *J* = 6.8 Hz, 2H), 2.33-2.27 (m, 2H), 2.06 (s, 3H), 2.05-1.99 (m, 2H), 1.64-1.58 (m, 1H), 1.53-1.45 (m, 1H), 1.42-1.36 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 146.1, 131.1, 128.5, 123.5, 71.1, 43.9, 31.5, 28.8, 28.7, 23.7, 22.6, 14.0.
1o was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).

$[\alpha]^{25}_D$ = -2.09 (c 0.744, CH_2Cl_2).

2-bromo-*N*-(2,6-diisopropylphenyl)-2-methylheptanamide (**1p**)

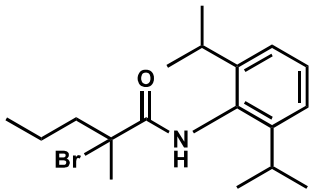


Following the general procedure above (Method A), using 2-Methyl heptanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2,6-diisopropylaniline (1.89 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (3.23 g, 8.5 mmol, 85%) as white solid; IR (cm^{-1}): 3330, 2958, 1649, 1496, 1382, 1253, 1124, 936, 796; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (brs, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 3.06 (sept, *J* = 6.9 Hz, 2H), 2.33-2.27 (m, 1H), 2.07 (s, 3H), 2.04-1.98 (m,1H), 1.67-1.59 (m, 1H), 1.55-1.48 (m, 1H), 1.37-1.32 (m, 4H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 146.1, 131.1, 128.5, 123.5, 71.2, 44.1, 31.65, 31.61, 28.8, 26.2, 23.7, 22.6, 14.0.

1p was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).

$[\alpha]^{25}_D$ = +1.94 (c 0.768, CH_2Cl_2).

2-bromo-N-(2,6-diisopropylphenyl)-2-methylpentanamide (**1q**)

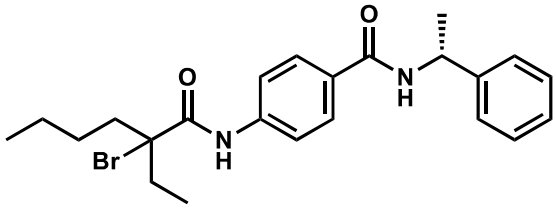


Following the general procedure above (Method A), using 2-Methyl pentanoic acid (1.26 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 2,6-diisopropylaniline (1.89 mL, 10 mmol), Triethylamine (4.2 mL, 3.0 equiv.) and CH_2Cl_2 (10 mL, 1.0 M), yielded the product (2.23 g, 6.3 mmol, 63%) as white solid; IR (cm^{-1}): 3298, 3069, 2958, 2929, 2868, 1588, 1498, 1464, 1379, 1330, 1243, 1179, 1155, 1141, 1100, 1053, 1018, 955, 935, 890, 832, 794, 739; ^{1}H NMR (500 MHz, CDCl3) δ: 8.06 (brs, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 2H), 3.04 (sept, *J* = 6.9 Hz, 2H), 2.28 (ddd, *J* = 4.5, 11.7, and 14.3 Hz, 1H), 2.06 (s, 3H), 2.00 (ddd, *J* = 4.4, 12.0 and 14.3 Hz, 1H), 1.69-1.51 (m, 2H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ: 170.7, 146.1, 131.1, 128.6, 123.6, 71.0, 46.2, 31.5, 28.8, 23.7, 19.9, 14.0; HRMS (ESI-MS) m/z [M+H+] calcd. for $C_{19}H_{31}NOBr$ 368.1589, found 368.1590.

1q was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent).

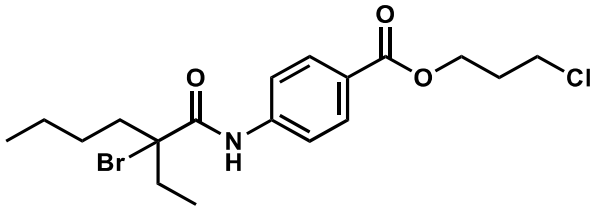
$[\alpha]^{25}_D$ = -10.86 (c 0.228, CH_2Cl_2)

4-(2-bromo-2-ethylhexanamido)-*N*-((*R*)-1-phenylethyl)benzamide (**1r**)



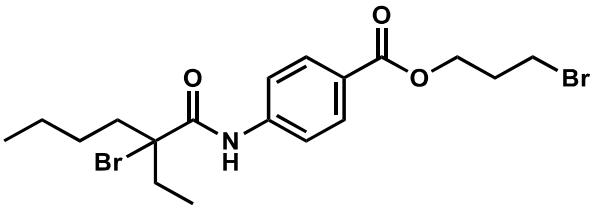
Following the general procedure above (Method C), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372mg, 10 mmol), THF (30 mL, 0.33 M), CDI (892.0 mg, 5.0 mmol), DMAP (61.1 mg, 0.50 mmol), Et_3N (1.2 mL, 7.5 mmol), CH_2Cl_2 (10 mL), alcohol (1.3 mL, 10 mmol) yielded the product (957.6 g, 2.1 mmol, 43%) as white solid; IR (cm^{-1}): 3298, 2967, 2930, 2872, 1662, 1627, 1500, 1403, 1320, 1244, 1186, 851, 760; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.78 (brs, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.40-7.35 (m, 4H), 7.29 (t, *J* = 7.0 Hz, 1H), 6.32 (d, *J* = 7.9 Hz, 1H), 5.33 (quint, *J* = 7.1 Hz, 1H), 2.33-2.21 (m, 2H), 2.08-1.97 (m, 2H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.59-1.53 (m, 1H), 1.39-1.31 (m, 3H), 1.07 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 165.7, 143.1, 140.1, 130.7, 128.8, 128.1, 127.6, 126.3, 119.4, 79.0, 49.3, 42.9, 36.5, 28.2, 22.5, 21.8, 14.0, 10.6.
HRMS (ESI-MS) calcd. for $C_{23}H_{30}BrN_2O_2$ [M+H$^+$]: 445.1491, found 445.1491.
1r was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).
$[\alpha]^{25}_D$ = -37.97 (c 0.198, CH_2Cl_2).

3-chloropropyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1s**)



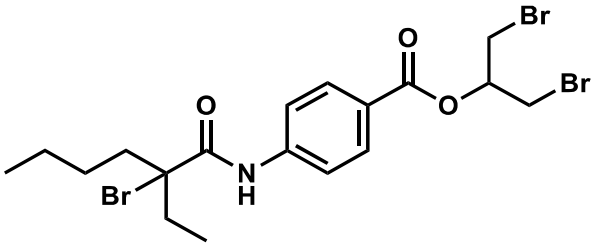
Following the general procedure above (Method B), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372 mg, 10 mmol), THF (30 mL, 0.33 M), CDI (892.0 mg, 5.5 mmol), DMAP (61.0 mg, 0.5 mmol), Et_3N (1.2 mL, 7.5 mmol), CH_2Cl_2 (10 mL), alcohol (0.83 mL, 10 mmol) yielded the product (1.57 g, 7.5 mmol, 75%) as yellow oil; IR (cm^{-1}): 3371, 2957, 2871, 1714, 1678, 1591, 1515, 1406, 1267, 1174, 1108, 1016, 853, 767; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.82 (brs, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 4.47 (t, *J* = 6.0 Hz, 2H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.33-2.21 (m, 4H), 2.09-1.98 (m, 2H), 1.63-1.53 (m, 1H), 1.40-1.30 (m, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 165.7, 141.5, 130.8, 126.1, 119.2, 78.5, 61.7, 42.7, 41.3, 36.3, 31.8, 28.2, 22.5, 13.9, 10.5.
HRMS (ESI-MS) calcd. for $C_{18}H_{26}BrClNO_3$ [M+H$^+$]: 418.0785, found 418.0785.
1s was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 80/20 as an eluent).
$[\alpha]^{25}_D$ = +3.09 (c 0.320, CH_2Cl_2).

3-bromopropyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1t**)



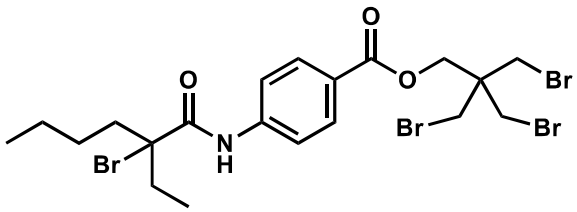
Following the general procedure above (Method B), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372 mg, 10 mmol), THF (30 mL, 0.33 M), CDI (891.8 mg, 5.5 mmol), DMAP (61.1 mg, 0.5 mmol), Et_3N (1.2 mL, 7.5 mmol), CH_2Cl_2 (10 mL), alcohol (0.89 mL, 10 mmol) yielded the product (0.90 g, 1.9 mmol, 39%) as white solid; IR (cm^{-1}): 3371, 2956, 2871, 1714, 1679, 1591, 1515, 1406, 1269, 1174, 1105, 1015, 853, 767; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.82 (brs, 1H), 8.03-8.01 (m, 2H), 7.66-7.63 (m, 2H), 4.45 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 6.5 Hz, 2H), 2.34-2.21 (m, 4H), 2.08-1.97 (m, 2H), 1.62-1.54 (m, 1H), 1.39-1.30 (m, 3H), 1.07 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 165.8, 141.5, 130.9, 126.2, 119.1, 78.9, 62.7, 42.9, 36.5, 31.9, 29.5, 28.2, 22.5, 14.0, 10.6.
HRMS (ESI-MS) calcd. for $C_{18}H_{26}Br_2NO_3$ $[M+H^+]$: 462.0279, found 462.0280.
1t was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent).
$[\alpha]^{25}_D$ = +4.06 (c 0.112, CH_2Cl_2).

1,3-dibromopropan-2-yl-4-(2-bromo-2-ethylhexanamido)benzoate (**1u**)



Following the general procedure above (Method B), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372 mg, 10 mmol), THF (30 mL, 0.33 M), CDI (891.3 mg, 5.5 mmol), DMAP (61.6 mg, 0.5 mmol), Et_3N (1.2 mL, 7.5 mmol), CH_2Cl_2 (10 mL), alcohol (1.0 mL, 10 mmol) yielded the product (2.03 g, 3.7 mmol, 75%) as yellow oil; IR (cm^{-1}): 3371, 2956, 2871, 1714, 1679, 1591, 1515, 1406, 1269, 1174, 1105, 1015, 853, 767; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.84 (brs, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 5.35 (quint, J = 5.3 Hz, 1H), 3.77-3.70 (m, 4H), 2.32-2.20 (m, 2H), 2.08-1.97 (m, 2H), 1.61-1.53 (m, 1H), 1.39-1.29 (m, 3H), 1.06 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.1, 164.6, 141.9, 131.3, 125.2, 119.2, 78.8, 71.3, 42.8, 36.5, 31.6, 28.2, 22.5, 14.0, 10.6.
HRMS (ESI-MS) calcd. for $C_{18}H_{25}Br_3NO_3$ $[M+H^+]$: 539.9385, found 539.9385.
1u was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).
$[\alpha]^{25}_D$ = -1.92 (c 0.201, CH_2Cl_2).

3-bromo-2,2-bis(bromomethyl)propyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1v**)



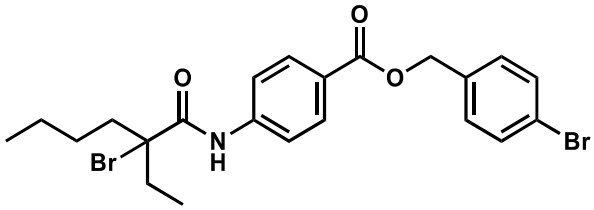
Following the general procedure above (Method B), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372 mg, 10 mmol), THF (30 mL, 0.33 M), CDI (891.9 mg, 5.5 mmol), DMAP (61.1 mg, 0.5 mmol), Et_3N (1.2 mL, 7.5 mmol), CH_2Cl_2 (10 mL), alcohol (3249.0 mg, 10 mmol) yielded the product (2.64 g, 4.0 mmol, 82%) as white solid; IR (cm^{-1}): 3395, 3380, 2956, 2871, 1715, 1687, 1591, 1515, 1460, 1407, 1260, 1173, 1108, 854, 813, 765; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.84 (brs, 1H), 7.99 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.62 (s, 6H), 2.33-2.21 (m, 2H), 2.08-1.97 (m, 2H), 1.62-1.53 (m, 1H), 1.38-1.29 (m, 3H), 1.07 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.1, 164.9, 141.8, 130.9, 125.4, 119.3, 78.8, 64.2, 43.1, 42.8, 36.5, 34.3, 28.2, 22.5, 14.0, 10.6.

HRMS (ESI-MS) calcd. for $C_{20}H_{28}Br_4NO_3$ $[M+H^+]$: 645.8803, found 645.8804.

1v was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).

$[\alpha]^{25}_D$ = +2.87 (c 0.177, CH_2Cl_2).

4-bromobenzyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1w**)



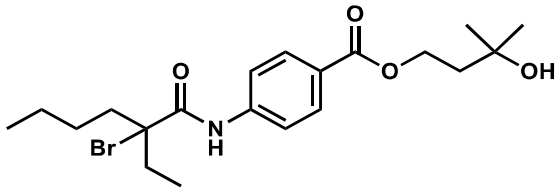
Following the general procedure above (Method C), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372 mg, 10 mmol), THF (30 mL, 0.33 M), EDC (0.88 mL, 5.0 mmol), DMAP (611.3 mg, 5.0 mmol), CH_2Cl_2 (10 mL), alcohol (1402.8 mg, 7.5 mmol) yielded the product (2.12 g, 4.2 mmol, 85%) as white solid; IR (cm^{-1}): 3347, 2956, 2873, 1685, 1592, 1522, 1406, 1377, 1317, 1271, 1242, 1174, 1114, 1069, 1013, 857, 808, 770; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.82 (brs, 1H), 8.05 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 5.30 (s, 2H), 2.33-2.21 (m, 2H), 2.09-1.97 (m, 2H), 1.61-1.52 (m, 1H), 1.38-1.31 (m, 3H), 1.08 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 165.7, 141.6, 135.1, 131.8, 131.0, 129.9, 126.0, 122.4, 119.2, 78.8, 65.9, 42.8, 36.5, 28.2, 22.5, 14.0, 10.6.

HRMS (ESI-MS) calcd. for $C_{22}H_{26}Br_2NO_3$ $[M+H^+]$: 510.0279, found 510.0280.

1w was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).

$[\alpha]^{25}_D$ = +2.77 (c 0.204, CH_2Cl_2).

3-hydroxy-3-methylbutyl 4-(2-bromo-2-ethylhexanamido)benzoate (**1x**)



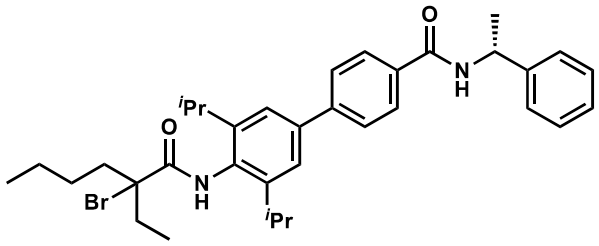
Following the general procedure above (Method C), using 2-Ethyl hexanoic acid (1.58 mL, 10 mmol), phosphorus tribromide (0.33 mL, 3.3 mmol), Bromine (0.82 mL, 16 mmol), cyclohexene (2 mL), 4-aminobenzoic acid (1372mg, 10 mmol), THF (30 mL, 0.33 M), EDC (0.88 mL, 5.0 mmol), DMAP (610.8 mg, 5.0 mmol), CH_2Cl_2 (10 mL), alcohol (0.8 mL, 7.5 mmol) yielded the product (1.76 g, 4.1 mmol, 82%) as yellow oil; IR (cm^{-1}): 3483, 3372, 2962, 2931, 2872, 1684, 1592, 1516, 1406, 1273, 1174, 1110, 854, 768, 694; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.82 (brs, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.30 (s, 2H), 2.33-2.21 (m, 2H), 2.09-1.97 (m, 2H), 1.61-1.52 (m, 1H), 1.38-1.31 (m, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.1, 166.1, 141.3, 130.8, 126.4, 119.2, 78.7, 70.0, 62.0, 42.8, 41.8, 36.4, 29.7, 28.2, 22.5, 13.9, 10.5.

HRMS (ESI-MS) calcd. for $C_{20}H_{31}BrNO_4$ $[M+H^+]$: 428.1436, found 428.1436.

1x was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).

$[\alpha]^{25}_D$ = +2.39 (c 0.391, CH_2Cl_2).

4'-(2-bromo-2-ethylhexanamido)-3',5'-diisopropyl-N-((R)-1-phenylethyl)-[1,1'-biphenyl]-4-carboxamide (**1y**)



Following the general procedure above (Method A), using 2-Ethyl hexanoic acid (0.48 mL, 3.0 mmol), phosphorus tribromide (0.15 mL, 1.1 mmol), Bromine (0.30 mL, 2.9 mmol), cyclohexene (0.70 mL), (R)-4'-amino-3',5'-diisopropyl-N-(1-phenylethyl)-[1,1'-biphenyl]-4-carboxamide (1017.6 mg, 2.50 mmol), Triethylamine (1.3 mL, 3.0 equiv.) and CH_2Cl_2 (6.0 mL, 0.4 M), yielded the product (0.97 g, 1.6 mmol, 64%) as white solid; IR (cm^{-1}): 3293, 2959, 2868, 1636, 1534, 1490, 1457, 1302, 1266, 1210, 1108, 849, 768, 697; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.20 (brs, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.43-7.36 (m, 6H), 7.31-7.28 (m, 1H), 6.35 (d, *J* = 8.1 Hz, 1H), 5.37 (quint, *J* = 7.2 Hz, 1H), 3.14 (sept, *J* = 6.9 Hz, 2H), 2.38-2.25 (m, 2H), 2.15-2.04 (m, 2H), 1.68-1.61 (m, 1H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.54-1.46 (m, 1H), 1.42-1.35 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 12H), 1.17 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.0, 166.3, 153.9, 146.5, 144.6, 143.2, 140.2, 133.3, 131.3, 128.8, 127.5, 127.4, 126.3, 122.6, 79.6, 49.3, 42.7, 36.1, 28.9, 28.5, 23.8, 22.7, 21.8, 14.0, 10.7.

HRMS (ESI-MS) calcd. for $C_{35}H_{46}BrN_2O_2$ $[M+H^+]$: 605.2743, found 605.2743.

1y was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent).

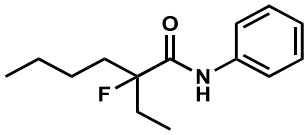
$[\alpha]^{25}_D$ = -34.98 (c 0.250, CH_2Cl_2).

Procedures and Characterization data for stereospecific fluorinations

General procedure for fluorination

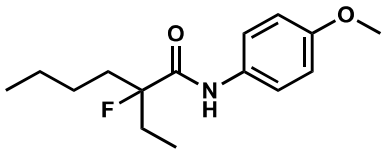
Alkyl bromide (0.20 mmol, 1.0 equiv), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol, 10 mol%), CsF (60 mg, 0.40 mmol, 2.0 equiv) and dtbbpy (5.4 mg, 2.0×10^{-2} mmol, 10 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), dried MeCN (0.4 mL) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 23 h at 20 °C. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product.

2-ethyl-2-fluoro-*N*-phenylhexanamide (**2a**)



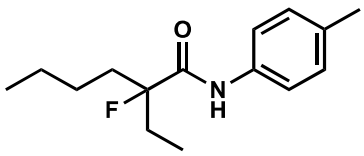
Following the general procedure above, using **1a** (59.6 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.6 mg, 2.0×10^{-2} mmol), dtbbpy (5.5 mg, 2.0×10^{-2} mmol), CsF (60.7 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2a** (42.2 mg, 89%, 99% ee) as white solid; IR (cm^{-1}): 3312, 3057, 2922, 2860, 1666, 1596, 1526, 1441, 1379, 1310, 1247, 1152, 1072, 975, 901, 864, 743; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 2.13-1.95 (m, 2H), 1.91-1.77 (m, 2H), 1.50-1.43 (m, 1H), 1.36-1.26 (m, 3H), 0.98 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2 (d, J = 20.3 Hz), 137.0, 129.2, 124.8, 119.9, 101.8 (d, J = 187.9 Hz), 36.9 (d, J = 22.2 Hz), 30.5 (d, J = 22.2 Hz), 25.3 (d, J = 3.5 Hz), 22.8, 14.0, 7.6 (d, J = 4.3 Hz); $[\alpha]^{25}_D$ = +6.12 (c 0.337, $CHCl_3$). HRMS (ESI-MS) calcd. for $C_{14}H_{21}FNO$ [$M+H^+$]: 238.1607, found 238.1607.

2-ethyl-2-fluoro-*N*-(4-methoxyphenyl)hexanamide (**2b**)



Following the general procedure above, using **1b** (65.4 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.2 mg, 2.0×10^{-2} mmol), dtbbpy (5.3 mg, 2.0×10^{-2} mmol), CsF (60.6 mg, 0.40 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2b** (49.3 mg, 92%, >99% ee) as white solid; IR (cm^{-1}): 3311, 2956, 2926, 2860, 1659, 1597, 1513, 1412, 1247, 1164, 1031, 977, 872, 818, 715; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H), 2.12-1.94 (m, 2H), 1.90-1.76 (m, 2H), 1.50-1.43 (m, 1H), 1.36-1.25 (m, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.9 (d, J = 19.9 Hz), 156.8, 130.1, 121.7, 114.3, 101.8 (d, J = 187.7 Hz), 55.6, 36.8 (d, J = 22.2 Hz), 30.4 (d, J = 22.7 Hz), 25.3 (d, J = 3.0 Hz), 22.7, 13.9, 7.6 (d, J = 4.2 Hz); $[\alpha]^{25}_D$ = +4.19 (c 0.186, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{23}FNO_2$ [$M+H^+$]: 268.1713, found 268.1713.

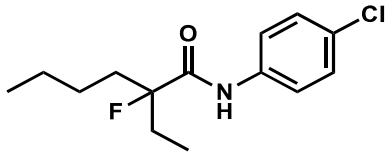
2-ethyl-2-fluoro-*N*-(p-tolyl)hexanamide (**2c**)



Following the general procedure above, using **1c** (62.2 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.4 mg, 2.0×10^{-2} mmol), dtbbpy (5.8 mg, 2.0×10^{-2} mmol), CsF (60.7 mg, 0.40 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2c** (41.8 mg, 83%, 90% ee) as white solid; IR (cm^{-1}): 3314, 2956, 2926, 2872, 1661, 1594, 1521, 1406, 1309, 1247, 1156, 975, 871, 807, 709; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, J

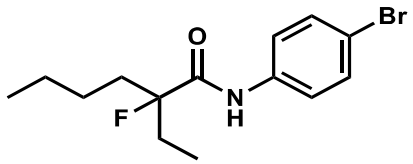
= 9.1 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 2.33 (s, 3H), 2.12-1.94 (m, 2H), 1.90-1.75 (m, 2H), 1.49-1.42 (m, 1H), 1.36-1.25 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1 (d, *J* = 20.0 Hz), 134.5, 134.4, 129.6, 120.0, 101.8 (d, *J* = 188.4 Hz), 36.9 (d, *J* = 22.3 Hz), 30.5 (d, *J* = 22.2 Hz), 25.3 (d, *J* = 3.1 Hz), 22.8, 20.9, 14.0, 7.6 (d, *J* = 4.3 Hz); $[\alpha]^{25}_D$ = +4.29 (c 0.250, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{23}FNO$ [M+H$^+$]: 252.1764, found 252.1764.

N-(4-chlorophenyl)-2-ethyl-2-fluorohexanamide (**2d**)



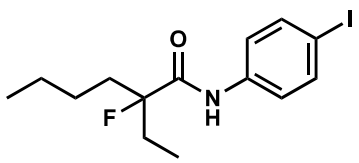
Following the general procedure above, using **1d** (66.5 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.4 mg, 2.0×10^{-2} mmol), dtbbpy (5.5 mg, 2.0×10^{-2} mmol), CsF (60.4 mg, 0.40 mmol), and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2d** (44.6 mg, 82%, 95% ee) as white solid; IR (cm^{-1}): 3310, 2958, 2926, 2874, 1670, 1590, 1514, 1399, 1300, 1243, 1154, 1089, 1014, 976, 870, 815, 705, 678; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 2.11-1.93 (m, 2H), 1.91-1.76 (m, 2H), 1.52-1.40 (m, 1H), 1.35-1.23 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3 (d, *J* = 20.3 Hz), 135.5, 129.8, 129.1, 121.2, 101.8 (d, *J* = 188.6 Hz), 36.8 (d, *J* = 22.1 Hz), 30.4 (d, *J* = 22.4 Hz), 25.3 (d, *J* = 3.0 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +5.89 (c 0.409, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{20}ClFNO$ [M+H$^+$]: 272.1217, found 272.1217.

N-(4-bromophenyl)-2-ethyl-2-fluorohexanamide (**2e**)



Following the general procedure above, using **1e** (75.8 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.4 mg, 2.0×10^{-2} mmol), dtbbpy (5.4 mg, 2.0×10^{-2} mmol), CsF (91.1 mg, 0.60 mmol), and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2e** (81.4 mg, 89%, 97% ee) as white solid; IR (cm^{-1}): 3310, 2958, 2927, 2873, 1671, 1587, 1513, 1456, 1395, 1243, 1154, 1073, 1011, 977, 813, 705; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 2.11-1.93 (m, 2H), 1.91-1.76 (m, 2H), 1.50-1.42 (m, 1H), 1.36-1.23 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4 (d, *J* = 20.2 Hz), 136.0, 132.1, 121.5, 117.4, 101.8 (d, *J* = 188.2 Hz), 36.8 (d, *J* = 22.1 Hz), 30.4 (d, *J* = 22.4 Hz), 25.3 (d, *J* = 3.0 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +7.67 (c 0.346, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{20}BrFNO$ [M+H$^+$]: 316.0712, found 316.0713.

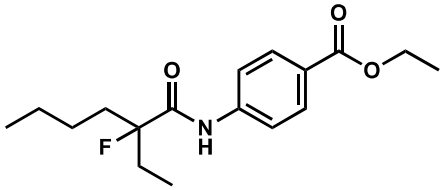
2-ethyl-2-fluoro-*N*-(4-iodophenyl)hexanamide (**2f**)



Following the general procedure above, using **1f** (85.0 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol), dtbbpy (5.3 mg, 2.0×10^{-2} mmol), CsF (60.8 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2f** (66.2 mg, 91%, >99% ee) as white solid; IR (cm^{-1}): 3305, 2954, 2924, 2871, 1669, 1584, 1508, 1457, 1392, 1303, 1281, 1239, 1153, 1006, 976, 869, 810, 706; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 2.10-1.92

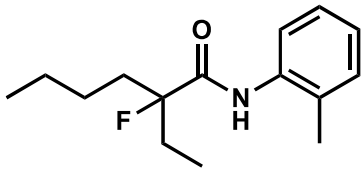
(m, 2H), 1.90-1.71 (m, 2H), 1.49-1.41 (m, 1H), 1.34-1.22 (m, 3H), 0.96 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4 (d, J = 20.2 Hz), 138.1, 136.7, 121.8, 101.8 (d, J = 188.2 Hz), 88.1, 36.8 (d, J = 22.1 Hz), 30.4 (d, J = 22.7 Hz), 25.3 (d, J = 3.0 Hz), 22.7, 13.9, 7.6 (d, J = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +7.36 (c 0.492, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{14}H_{20}IFNO$ [M+H$^+$]: 364.0574, found 364.0574.

ethyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2g**)



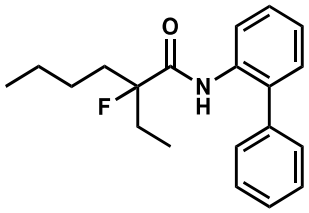
Following the general procedure above, using **1g** (77.2 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.7 mg, 2.0×10^{-2} mmol), dtbbpy (5.5 mg, 2.0×10^{-2} mmol), CsF (61.0 mg, 0.40 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2g** (54.0 mg, 87%, 90% ee) as white solid; IR (cm^{-1}): 3324, 2963, 2926, 2859, 1709, 1672, 1593, 1518, 1409, 1267, 1176, 1101, 974, 850, 766; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.24 (d, J = 8.9 Hz, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.12-1.97 (m, 2H), 1.95-1.78 (m, 2H), 1.50-1.42 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.36-1.25 (m, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (d, J = 20.2 Hz), 166.1, 140.9, 130.9, 126.6, 119.0, 101.9 (d, J = 188.2 Hz), 61.0, 36.8 (d, J = 21.5 Hz), 30.4 (d, J = 22.7 Hz), 25.3 (d, J = 3.1 Hz), 22.7, 14.4, 13.9, 7.6 (d, J = 4.8 Hz); $[\alpha]^{25}_D$ = +5.91 (c 0.220, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{17}H_{25}FNO_3$ [M+H$^+$]: 310.1818, found 310.1818.

2-ethyl-2-fluoro-*N*-(o-tolyl)hexanamide (**2h**)



Following the general procedure above, using **1h** (62.3 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol), bpy (3.3 mg, 2.0×10^{-2} mmol), CsF (91.4 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2h** (42.9 mg, 81%, >99% ee) as white solid; IR (cm^{-1}): 3297, 2964, 2926, 2873, 1667, 1585, 1518, 1450, 1291, 1257, 1155, 980, 922, 841, 747, 709; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.2 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 2.30 (s, 3H), 2.17-1.98 (m, 2H), 1.93-1.79 (m, 2H), 1.57-1.46 (m, 1H), 1.39-1.30 (m, 3H), 1.02 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1 (d, J = 19.9 Hz), 134.9, 130.6, 128.8, 126.9, 125.4, 122.6, 102.1 (d, J = 188.2 Hz), 36.9 (d, J = 21.9 Hz), 30.5 (d, J = 22.6 Hz), 25.4 (d, J = 2.9 Hz), 22.8, 17.7, 14.0, 7.6 (d, J = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +6.76 (c 0.213, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{23}FNO$ [M+H$^+$]: 252.1764, found 252.1764.

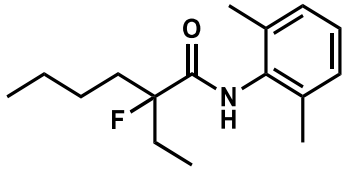
N-([1,1'-biphenyl]-2-yl)-2-ethyl-2-fluorohexanamide (**2i**)



Following the general procedure above, using **1i** (74.7 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.4 mg, 2.0×10^{-2} mmol), bpy (2.8 mg, 2.0×10^{-2} mmol), CsF (91.2 mg, 0.60 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2i** (54.6 mg, 87%, 96% ee) as white solid; IR (cm^{-1}): 3409, 2956, 2928, 2871, 1691, 1583, 1521, 1448, 1153, 1009, 971, 856, 754, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.33 (d, J = 8.2 Hz, 1H),

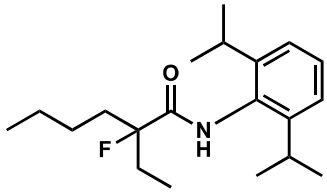
8.20 (d, J = 8.7 Hz, 1H), 7.48 (t, J = 7.1 Hz, 2H), 7.44-7.36 (m, 4H), 7.30 (dd, J = 1.4, 7.6 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 2.07-1.89 (m, 2H), 1.82-1.64 (m, 2H), 1.37-1.20 (m, 4H), 0.90 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1 (d, J = 20.1 Hz), 137.8, 133.9, 132.9, 130.2, 129.3, 129.0, 128.4, 128.1, 124.8, 121.3, 101.6 (d, J = 189.0 Hz), 36.9 (d, J = 22.1 Hz), 30.5 (d, J = 22.5 Hz), 25.3 (d, J = 2.9 Hz), 22.7, 14.0, 7.5 (d, J = 4.1 Hz); $[\alpha]^{25}_D$ = -23.50 (c 0.334, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{25}FNO$ [M+H$^+$]: 314.1920, found 314.1920.

N-(2,6-dimethylphenyl)-2-ethyl-2-fluorohexanamide (**2j**)



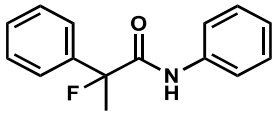
Following the general procedure above, using **1j** (65.7 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.8 mg, 2.0×10^{-2} mmol), dtbbpy (5.8 mg, 2.0×10^{-2} mmol), CsF (60.6 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2j** (46.5 mg, 88%, >99% ee) as white solid; IR (cm^{-1}): 3223, 2954, 2927, 2871, 1664, 1512, 1466, 1378, 1263, 1220, 1155, 982, 876, 764, 723; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.1 Hz, 1H), 7.13-7.08 (m, 3H), 2.26 (s, 6H), 2.15-1.99 (m, 2H), 1.98-1.80 (m, 2H), 1.59-1.52 (m, 1H), 1.48-1.40 (m, 1H), 1.38-1.32 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2 (d, J = 20.5 Hz), 135.2, 133.1, 128.4, 127.4, 102.3 (d, J = 188.0 Hz), 36.8 (d, J = 21.3 Hz), 30.4 (d, J = 22.6 Hz), 25.6 (d, J = 3.1 Hz), 22.8, 18.9, 14.0, 7.8 (d, J = 4.2 Hz); $[\alpha]^{25}_D$ = +10.29 (c 0.287, $CHCl_3$). HRMS (ESI-MS) calcd. for $C_{16}H_{25}FNO$ [M+H$^+$]: 266.1920, found 266.1920.

N-(2,6-diisopropylphenyl)-2-ethyl-2-fluorohexanamide (**2k**)



Following the general procedure above, using **1k** (76.7 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.3 mg, 2.0×10^{-2} mmol), dtbbpy (5.8 mg, 2.0×10^{-2} mmol), CsF (61.2 mg, 0.40 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2k** (56.2 mg, 87%, 91% ee) as white solid; IR (cm^{-1}): 3265, 2957, 2866, 1659, 1508, 1457, 1380, 1257, 1154, 979, 793, 735; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, J = 8.1 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.7 Hz, 2H), 3.11 (sept, J = 6.9 Hz, 2H), 2.16-2.01 (m, 2H), 1.98-1.82 (m, 2H), 1.58-1.52 (m, 1H), 1.46-1.31 (m, 3H), 1.21 (d, J = 6.8 Hz, 12H), 1.07 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3 (d, J = 21.0 Hz), 146.1, 130.2, 128.4, 123.5, 102.3 (d, J = 187.1 Hz), 36.7 (d, J = 22.3 Hz), 30.3 (d, J = 22.8 Hz), 28.7, 25.6 (d, J = 3.0 Hz), 23.7, 22.9, 14.0, 7.6 (d, J = 4.7 Hz); $[\alpha]^{25}_D$ = +8.41 (c 0.186, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{33}FNO$ [M+H$^+$]: 322.2546, found 322.2546.

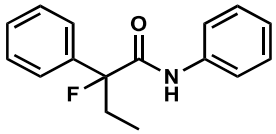
2-fluoro-*N*,2-diphenylpropanamide (**2l**)



Following the general procedure above, using **1l** (51.8 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.3 mg, 2.0×10^{-2} mmol), dtbbpy (5.4 mg, 2.0×10^{-2} mmol), CsF (60.8 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2a** (31.5 mg, 61%, 83% ee) as white solid; IR (cm^{-1}): 3346, 3057, 2947, 1671, 1596, 1525, 1496, 1438, 1374, 1319, 1252, 1118, 1069, 1027, 936, 886, 850, 752, 730, 689; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (d, J = 5.0 Hz, 1H), 759 (d, J = 7.0 Hz, 2H), 756 (d, J = 7.4 Hz, 2H),

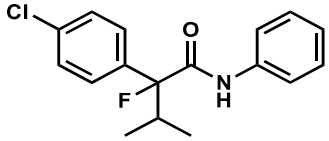
7.40-7.30 (m, 5H), 7.12 (t, J = 7.5 Hz, 1H), 2.01 (d, J = 23.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.3 (d, J = 21.0 Hz), 139.5 (d, J = 22.1 Hz), 137.0, 129.1, 128.7 (d, J = 1.62 Hz), 128.6, 124.9, 124.5 (d, J = 9.1 Hz), 119.9, 98.6 (d, J = 186.9 Hz), 25.6(d, J = 23.5 Hz); $[\alpha]^{25}_D$ = +58.8 (c 0.259, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{15}FNO$ $[M+H^+]$: 244.1138, found 244.1138.

2-fluoro-*N*,2-diphenylbutanamide (**2m**)



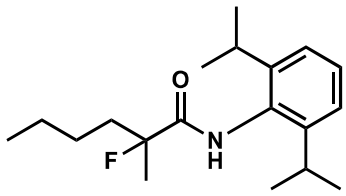
Following the general procedure above, using **1l** (55.3 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol), dtbbpy (5.6 mg, 2.0×10^{-2} mmol), CsF (60.9 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2a** (40.1 mg, 77%, 94% ee) as white solid; IR (cm^{-1}): 3378, 2974, 2941, 2882, 2108, 1739, 1672, 1596, 1522, 1492, 1438, 1319, 1305, 1238, 1128, 1071, 1030, 1003, 963, 937, 905, 864, 810, 759, 724, 689, 669; ^{1}H NMR (500 MHz, $CDCl_3$) δ:8.17 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.34-7.30 (m, 3H), 7.11 (t, J = 7.5 Hz, 1H), 2.53-2.40 (m, 1H), 2.27-2.16 (m,1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.9 (d, J = 21.3 Hz), 138.6 (d, J = 22.2 Hz), 137.0, 128.2 (d, J = 2.0 Hz), 128.5, 124.8, 124.7 (d, J = 10.0 Hz), 120.0, 101.2 (d, J = 191.1 Hz), 32.1 (d, J = 22.8 Hz), 7.7 (d, J = 3.9 Hz);$[\alpha]^{25}_D$ = +76.3 (c 0.177, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{16}H_{17}FNO$ $[M+H^+]$: 258.1294, found 258.1294.

2-(4-chlorophenyl)-2-fluoro-3-methyl-*N*-phenylbutanamide (**2n**)



Following the general procedure above, using **1n** (64.5 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.6 mg, 2.0×10^{-2} mmol), dtbbpy (5.4 mg, 2.0×10^{-2} mmol), CsF (61.1 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2a** (54.3 mg, 89%, 98% ee) as white solid; IR (cm^{-1}):3287, 3065, 2971, 2935, 2876, 1670, 1596, 1526, 1489, 1442, 1399, 1316, 1250, 1181, 1145, 1090, 1039, 1012, 968, 909, 883, 825, 783, 750, 688.; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.6 Hz, 1H), 7.57-7.52 (m, 4H), 7.35-7.30 (m, 4H), 7.12 (t, J = 7.4 Hz, 1H), 2.75 (dsep, J = 6.9, 34.1 Hz, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.8 (d, J = 20.8 Hz), 136.8, 136.6 (d, J = 22.6 Hz), 134.3, 129.2, 128.6, 126.2 (d, J = 11.9 Hz), 125.1, 120.1, 102.7 (d, J = 196.7 Hz), 36.0 (d, J = 22.2 Hz), 16.9 (d, J = 4.0 Hz), 15.6 (d, J = 3.6 Hz); $[\alpha]^{25}_D$ = -42.7(c 0.105, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{17}H_{18}ClFNO$ $[M+H^+]$: 306.1061, found 306.1060.

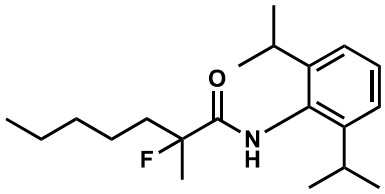
N-(2,6-diisopropylphenyl)-2-fluoro-2-methylhexanamide (**2o**)



Following the general procedure above, using **1o** (73.4 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.3 mg, 2.0×10^{-2} mmol), dtbbpy (5.8 mg, 2.0×10^{-2} mmol), CsF (61.2 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2o** (53.4 mg, 87%, 77% ee, 92%, 98% ee (3 equiv of CsF at 80°C)) as white solid; IR (cm^{-1}): 3262, 2956, 1661, 1515, 1456, 1223, 1054, 929, 796; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 3.06 (sept, J = 6.9 Hz, 2H), 2.17-2.03 (m, 1H), 1.90-1.80 (m, 1H), 1.66 (d, J = 22.6 Hz, 6H), 1.61-1.55 (m, 1H), 1.46-1.35 (m, 3H), 1.21 (t, J = 6.9 Hz, 6H), 1.20 (d, J = 6.9 Hz, 6H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

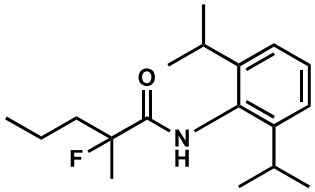
δ: 171.9 (d, J = 21.0 Hz), 146.2, 130.1, 128.5, 123.5, 100.0 (d, J = 185.9 Hz), 37.7 (d, J = 21.8 Hz), 28.7, 25.6 (d, J = 3.0 Hz), 24.3 (d, J = 24.0 Hz), 23.7, 23.6, 22.8, 14.1; $[\alpha]^{25}_{D}$ = +10.99 (c 0.512, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{19}H_{31}FNO$ [M+H$^+$]: 308.2390, found 308.2390.

N-(2,6-diisopropylphenyl)-2-fluoro-2-methylheptanamide (**2p**)



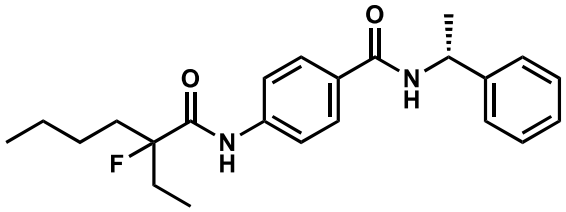
Following the general procedure above, using **1p** (76.2 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.3 mg, 2.0×10^{-2} mmol), dtbbpy (5.8 mg, 2.0×10^{-2} mmol), CsF (61.2 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2p** (55.2 mg, 86%, 72% ee, 90%, 94% ee (3 equiv of CsF at 80°C)) as white solid; IR (cm^{-1}): 3253, 2958, 1660, 1514, 1214, 1158, 1056, 797; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 3.06 (sept, J = 6.9 Hz, 2H), 2.17-2.03 (m, 1H), 1.88-1.78 (m, 1H), 1.66 (d, J = 22.6 Hz, 3H), 1.61-1.55 (m, 1H), 1.48-1.40 (m, 1H), 1.35-1.31 (m, 4H), 1.20 (t, J = 6.9 Hz, 6H), 1.19 (d, J = 6.9 Hz, 6H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9 (d, J = 19.7 Hz), 146.2, 130.1, 128.5, 123.5, 100.0 (d, J = 184.0 Hz), 38.0 (d, J = 21.9 Hz), 31.8, 28.7, 24.4 (d, J = 23.9 Hz), 23.6, 23.1 (d, J = 24.0 Hz), 22.6, 14.0; $[\alpha]^{25}_{D}$ = -10.34 (c 0.553, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{33}FNO$ [M+H$^+$]: 322.2546, found 322.2546.

N-(2,6-diisopropylphenyl)-2-fluoro-2-methylpentanamide (**2q**)



Following the general procedure above, using **1q** (71.0 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol), dtbbpy (5.7 mg, 2.0×10^{-2} mmol), CsF (61.0 mg, 0.40 mmol),TEMPO (47.0 mg, 0.30 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2p** (56.4 mg, 96%, 96% ee) as white solid; IR (cm^{-1}):3264.8, 3069.7, 2956.5, 2869.3, 1660.9, 1591.1, 1508.0, 1458.1, 1365.7, 1325.8, 1255.8, 1210.0, 1162.2, 1052.3, 945.6, 893.2, 849.5, 797.7, 741.4, 702.8.; ^{1}H NMR (500 MHz, $CDCl_3$) δ:7.60 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 3.04 (sep, J = 6.9 Hz, 2H), 2.13-2.01 (m, 1 H), 1.87-1.78 (m, 1 H), 1.67 (d, J =22.3 Hz, 3H), 1.62-1.56 (m, 1 H), 1.52-1.41 (m, 1 H), 1.21 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 6H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:172.0 (d, J =20.4 Hz,), 146.2, 130.2, 128.6, 123.6, 100.3 (d, J = 182.6 Hz), 40.2 (d, J = 21.5 Hz), 28.8, 24.3 (d, J = 24.2 Hz), 23.7, 23.6, 16.7(d, J = 3.9 Hz), 14.3 ; $[\alpha]^{25}_{D}$ = -9.30 (c 0.106, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{29}FNO$ [M+H$^+$]: 294.2233, found 294.2233.

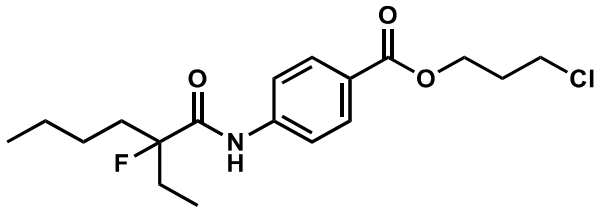
4-(2-ethyl-2-fluorohexanamido)-*N*-((*R*)-1-phenylethyl)benzamide (**2r**)



Following the general procedure above, using **1r** (89.4 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.7 mg, $2.0\times10^{-}$

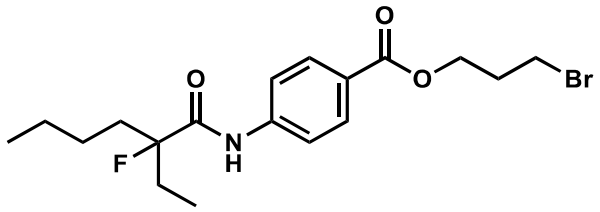
$^{-2}$ mmol), bpy (3.4 mg, 2.0×10^{-2} mmol), CsF (92.0 mg, 0.60 mmol) and dried MeCN (0.4 mL) at 80°C for 23 h, yielded the product **2r** (34.4 mg, 44%, 87% ee) as white solid; IR (cm^{-1}): 3319, 3032, 2926, 2849, 1671, 1623, 1573, 1505, 1448, 1405, 1310, 1271, 1243, 1185, 1155, 1088, 1014, 975, 881, 839, 758, 697, 654; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.39-7.33 (m, 4H), 7.28-7.25 (m, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.32 (quint, *J* = 7.1 Hz, 1H), 2.10-1.95 (m, 2H), 1.93-1.77 (m, 2H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.49-1.42 (m, 1H), 1.35-1.24 (m, 3H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5 (d, *J* = 20.8 Hz), 165.8, 143.2, 139.8, 130.5, 128.8, 128.1, 127.5, 126.3, 119.4, 101.8 (d, *J* = 188.6 Hz), 49.3, 36.7 (d, *J* = 22.0 Hz), 30.6 (d, *J* = 23.6 Hz), 30.3, 25.3 (d, *J* = 3.0 Hz), 22.7, 21.8, 13.9, 7.6 (d, *J* = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = -46.2 (c 0.115, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{23}H_{30}FN_2O_2$ [M+H$^+$]: 385.2291, found 385.2291.

3-chloropropyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2s**)



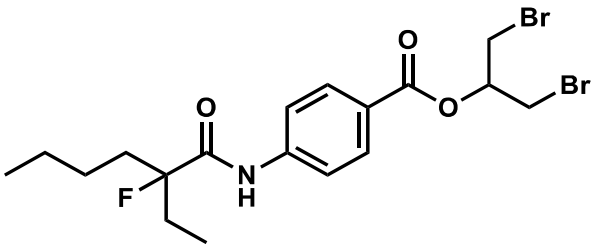
Following the general procedure above, using **1s** (84.2 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.6 mg, 2.0×10^{-2} mmol), bpy (3.3 mg, 2.0×10^{-2} mmol), CsF (91.0 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2s** (65.6 mg, 91%, >99% ee) as white solid; IR (cm^{-1}): 3339, 2958, 2930, 2872, 1694, 1592, 1520, 1407, 1267, 1246, 1174, 1108, 1017, 973, 855, 767; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 4.46 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.23 (quint, *J* = 6.2 Hz, 2H), 2.11-1.95 (m, 2H), 1.93-1.77 (m, 2H), 1.48-1.40 (m, 1H), 1.37-1.22 (m, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.4 Hz), 165.8, 141.2, 130.9, 126.0, 119.1, 101.8 (d, *J* = 188.3 Hz), 61.7, 41.3, 36.8 (d, *J* = 22.1 Hz), 31.8, 30.4 (d, *J* = 22.5 Hz), 25.3 (d, *J* = 3.0 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +6.94 (c 0.250, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{26}ClFNO_3$ [M+H$^+$]: 358.1585, found 358.1585.

3-bromopropyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2t**)



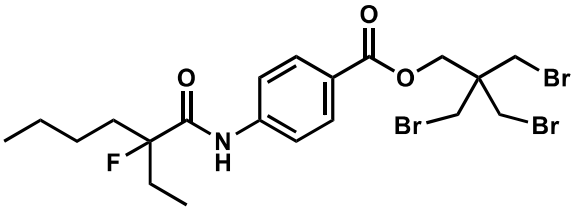
Following the general procedure above, using **1t** (92.6 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.5 mg, 2.0×10^{-2} mmol), bpy (3.3 mg, 2.0×10^{-2} mmol), CsF (91.0 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2t** (68.4 mg, 85%, >99% ee) as white solid; IR (cm^{-1}): 3324, 2952, 2925, 2858, 1708, 1675, 1593, 1518, 1453, 1409, 1325, 1276, 1180, 1112, 976, 845, 764; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 8.9 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 4.45 (t, *J* = 6.0 Hz, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.32 (quint, *J* = 6.3 Hz, 2H), 2.11-1.96 (m, 2H), 1.94-1.78 (m, 2H), 1.49-1.42 (m, 1H), 1.35-1.23 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6 (d, *J* = 20.4 Hz), 165.8, 141.2, 130.9, 126.0, 119.1, 101.8 (d, *J* = 188.3 Hz), 62.7, 36.7 (d, *J* = 21.9 Hz), 31.9, 30.4 (d, *J* = 22.4 Hz), 29.5, 25.3 (d, *J* = 3.0 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.3 Hz); Optical rotation $[\alpha]^{25}_D$ = +6.55 (c 0.417, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{26}BrFNO_3$ [M+H$^+$]: 402.1080, found 402.1079.

1,3-dibromopropan-2-yl-4-(2-ethyl-2-fluorohexanamido)benzoate (**2u**)



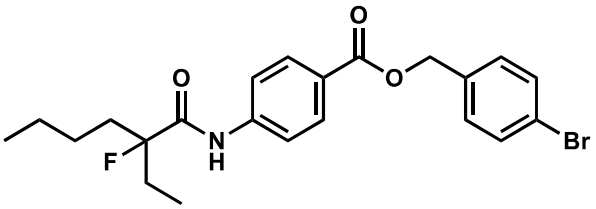
Following the general procedure above, using **1u** (108.0 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.6 mg, 2.0×10^{-2} mmol), bpy (3.1 mg, 2.0×10^{-2} mmol), CsF (91.0 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2u** (80.7 mg, 84%, >99% ee) as white solid; IR (cm^{-1}): 3275, 2933, 1718, 1669, 1593, 1519, 1411, 1263, 1163, 1102, 1019, 973, 848, 763, 693; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 9.4 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 5.36 (quint, *J* = 5.2 Hz, 1H), 3.78-3.71 (m, 4H), 2.12-1.78 (m, 4H), 1.50-1.42 (m, 1H), 1.36-1.23 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.3 Hz), 164.7, 141.6, 131.4, 125.1, 119.2, 101.8 (d, *J* = 188.7 Hz), 71.3, 36.8 (d, *J* = 22.3 Hz), 31.5, 30.4 (d, *J* = 22.8 Hz), 25.3 (d, *J* = 2.9 Hz), 22.7, 13.9, 7.5 (d, *J* = 4.3 Hz); Optical rotation $[\alpha]^{25}_D$ = +6.10 (c 0.414, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{25}Br_2FNO_3$ $[M+H^+]$: 480.0185, found 480.0187.

3-bromo-2,2-bis(bromomethyl)propyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2v**)



Following the general procedure above, using **1v** (130.1 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.3 mg, 2.0×10^{-2} mmol), bpy (3.1 mg, 2.0×10^{-2} mmol), CsF (91.4 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2v** (110.6 mg, 94%, >99% ee) as white solid; IR (cm^{-1}): 3342, 2956, 2928, 2870, 1686, 1592, 1519, 1407, 1264, 1173, 1098, 972, 854, 764; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 9.4 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 4.45 (s, 2H), 3.63 (s, 6H), 2.11-1.78 (m, 2H), 1.49-1.42 (m, 1H), 1.35-1.24 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.4 Hz), 165.0, 141.6, 131.0, 125.2, 119.3, 101.8 (d, *J* = 188.6 Hz), 64.2, 43.1, 36.8 (d, *J* = 21.9 Hz), 34.3, 30.4 (d, *J* = 22.4 Hz), 25.3 (d, *J* = 2.9 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.4 Hz); Optical rotation $[\alpha]^{25}_D$ = +3.84 (c 0.343, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{28}Br_3FNO_3$ $[M+H^+]$: 585.9603, found 585.9604.

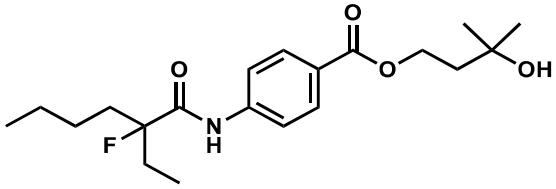
4-bromobenzyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2w**)



Following the general procedure above, using **1w** (103.0 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.2 mg, 2.0×10^{-2} mmol), bpy (3.4 mg, 2.0×10^{-2} mmol), CsF (91.4 mg, 0.60 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2w** (74.0 mg, 82%, >99% ee) as white solid; IR (cm^{-1}): 3311, 2965, 2926, 2859, 1717, 1670, 1595, 1520, 1487, 1408, 1370, 1272, 1172, 1123, 1068, 1010, 976, 846, 798, 764; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 9.1 Hz, 1H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.8 Hz,

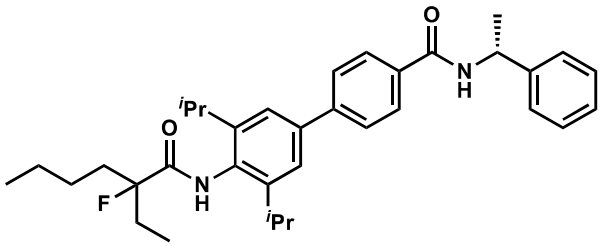
2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 5.30 (s, 2H), 2.12-1.94 (m, 2H), 1.93-1.77 (m, 2H), 1.51-1.41 (m, 1H), 1.36-1.23 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.1 Hz), 165.7, 141.3, 135.1, 131.8, 131.1, 129.9, 125.9, 122.3, 119.2, 101.8 (d, *J* = 189.1 Hz), 65.9, 36.8 (d, *J* = 22.1 Hz), 30.5 (d, *J* = 22.4 Hz), 25.3 (d, *J* = 2.4 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.1 Hz); Optical rotation $[\alpha]^{25}_D$ = +6.18 (c 0.199, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{22}H_{26}BrFNO_3$ [M+H$^+$]: 450.1080, found 450.1081.

3-hydroxy-3-methylbutyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**2x**)



Following the general procedure above, using **1x** (85.5 mg, 0.20 mmol, >99% ee), $CuBr_2$ (4.8 mg, 2.0×10^{-2} mmol), dtbbpy (5.3 mg, 2.0×10^{-2} mmol), CsF (61.0 mg, 0.40 mmol) and dried MeCN (0.4 mL) at room temperature for 23 h, yielded the product **2x** (56.9 mg, 77%, 90% ee) as viscous oil; IR (cm^{-1}): 3329, 2961, 2930, 2872, 1693, 1593, 1522, 1408, 1274, 1246, 1174, 1111, 973, 857, 769; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 4.48 (t, *J* = 6.8 Hz, 2H), 2.10-1.92 (m, 2H), 1.97 (t, *J* = 6.9 Hz, 2H), 1.89-1.76 (m, 3H), 1.48-1.41 (m, 1H), 1.33-1.22 (m, 2H), 1.30 (s, 6H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.2 Hz), 166.1, 141.1, 130.9, 126.3, 119.2, 101.8 (d, *J* = 189.0 Hz), 70.1, 62.0, 41.8, 36.8 (d, *J* = 22.1 Hz), 30.4 (d, *J* = 22.5 Hz), 29.8, 25.3 (d, *J* = 2.8 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.2 Hz); Optical rotation $[\alpha]^{25}_D$ = +8.23 (c 0.150, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{31}FNO_4$ [M+H$^+$]: 368.2237, found 368.2237.

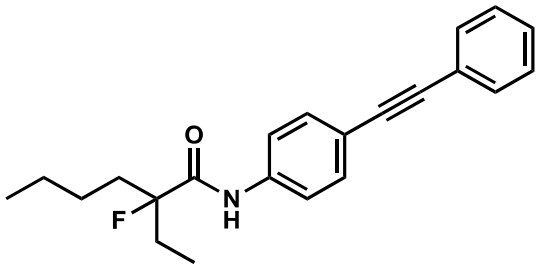
4'-(2-ethyl-2-fluorohexanamido)-3',5'-diisopropyl-*N*-((*R*)-1-phenylethyl)-[1,1'-biphenyl]-4-carboxamide (**2y**)



Following the general procedure above, using **1y** (60.4 mg, 0.10 mmol, >99% ee), $CuBr_2$ (2.1 mg, 1.0×10^{-2} mmol), dtbbpy (2.8 mg, 1.0×10^{-2} mmol), CsF (30.5 mg, 0.20 mmol) and dried MeCN (0.2 mL) at 80°C for 23 h, yielded the product **2y** (39.1 mg, 72%, 89% ee) as white solid; IR (cm^{-1}): 3275, 2959, 2868, 1637, 1494, 1458, 1303, 1266, 1147, 976, 848, 750, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.38-7.34 (m, 4H), 7.30-7.26 (m, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 5.37 (quint, *J* = 7.2 Hz, 1H), 3.17 (sept, *J* = 6.9 Hz, 2H), 2.15-2.01 (m, 2H), 1.99-1.83 (m, 2H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.60-1.54 (m, 1H), 1.49-1.35 (m, 3H), 1.27 (d, *J* = 6.8 Hz, 12H), 1.09 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6 (d, *J* = 20.6 Hz), 166.5, 146.7, 144.6, 143.2, 140.2, 133.2, 130.2, 128.8, 127.59, 127.52, 127.4, 126.3, 122.7, 102.3 (d, *J* = 186.7 Hz), 49.3, 36.7 (d, *J* = 21.9 Hz), 30.3 (d, *J* = 22.4 Hz), 28.9, 25.6 (d, *J* = 3.3 Hz), 23.8 (d, *J* = 4.5 Hz), 22.9, 21.8, 14.1, 7.6 (d, *J* = 4.7 Hz); Optical rotation $[\alpha]^{25}_D$ = -35.3 (c 0.145, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{35}H_{46}FN_2O_2$ [M+H$^+$]: 545.3543, found 545.3545.

3. Applications

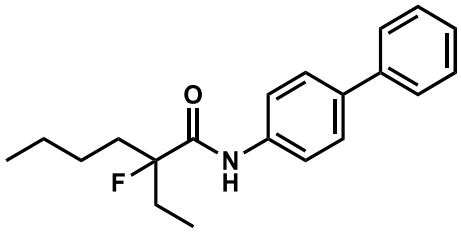
2-ethyl-2-fluoro-*N*-(4-(phenylethynyl)phenyl)hexanamide (**4**)



Procedures and Characterization data of Sonogashira coupling

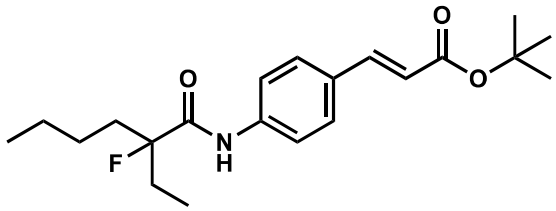
2f (0.10 mmol, 1.0 equiv), $PdCl_2$ (2.0×10^{-2} mmol, 20 mol%), PPh_3 (4.0×10^{-2} mmol, 40 mol%), CuI (5.0×10^{-3} mmol, 5 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), Phenylacetylene (0.15 mmol, 1.5 equiv.), Et_3N (0.15 mmol, 1.5 equiv.), THF (0.30 mL) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 17 h at 70 °C. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **4** (62.9 mg, 93%, >99% ee) as white solid; IR (cm^{-1}): 3312, 2957, 2924, 2860, 1666, 1582, 1516, 1405, 1308, 1242, 1153, 1069, 975, 871, 827, 750, 686; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.15 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.54-7.52 (m, 4H), 7.37-7.31 (m, 3H), 2.13-1.95 (m, 2H), 1.93-1.76 (m, 2H), 1.51-1.44 (m, 1H), 1.37-1.26 (m, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3 (d, J = 20.3 Hz), 136.9, 132.5, 131.6, 128.4, 128.3, 123.3, 119.6, 119.5, 101.8 (d, J = 188.6 Hz), 89.3, 89.1, 36.8 (d, J = 21.9 Hz), 30.5 (d, J = 22.6 Hz), 25.3 (d, J = 2.9 Hz), 22.7, 13.9, 7.6 (d, J = 4.2 Hz); $[\alpha]^{25}_D$ = +14.02 (c 0.092, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{22}H_{25}FNO$ $[M+H^+]$: 338.1920, found 338.1922.

N-([1,1'-biphenyl]-4-yl)-2-ethyl-2-fluorohexanamide (**5**)



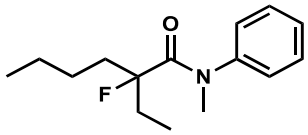
2f (0.10 mmol, 1.0 equiv), $PhB(OH)_2$ (0.20 mmol, 2.0 equiv.), $PdCl_2$(dppf) (3.0×10^{-3} mmol, 3 mol%), K_2CO_3 (0.30 mmol, 3.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), 1,4-dioxane/H_2O = 6/1 (0.40 mL) was added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 21 h at 80 °C. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **5** (52.5 mg, 85%, 93% ee) as white solid; IR (cm^{-1}): 3315, 2955, 2928, 2871, 1668, 1590, 1508, 1403, 1313, 1288, 1247, 1155, 1073, 1006, 977, 871, 830, 756, 687; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.17 (d, J = 10.6 Hz, 1H), 7.69 (dt, J = 1.9, 8.6 Hz, 2H), 7.61-7.57 (m, 4H), 7.45 (t, J = 7.4 Hz, 2H), 7.36-7.33 (m, 1H), 2.14-1.98 (m, 2H), 1.92-1.79 (m, 2H), 1.52-1.45 (m, 1H), 1.38-1.29 (m, 3H), 1.01 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3 (d, J = 19.8 Hz), 140.5, 137.8, 136.2, 128.9, 127.8, 127.3, 127.0, 120.2, 101.9 (d, J = 188.4 Hz), 36.9 (d, J = 22.2 Hz), 30.5 (d, J = 22.4 Hz), 25.3 (d, J = 3.0 Hz), 22.8, 14.0, 7.6 (d, J = 4.2 Hz); $[\alpha]^{25}_D$ = +11.70 (c 0.171, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{20}H_{25}FNO$ $[M+H^+]$: 314.1920, found 314.1922.

tert-butyl (*E*)-3-(4-(2-ethyl-2-fluorohexanamido)phenyl)acrylate (**6**)



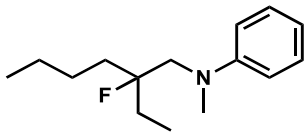
2e (0.20 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.0×10^{-2} mmol, 20 mol%), P(*o*-tol)$_3$ (8.0×10^{-2} mmol, 40 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), ^{t}Bu-acrylate (0.26 mmol, 1.3 equiv.), Et_3N (0.20 mL) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 2 h at 100 °C. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **6** (60.7 mg, 83%, >99% ee) as white solid; IR (cm^{-1}): 3329, 2958, 292, 2871, 1702, 1673, 1636, 1587, 1514, 1411, 1306, 1244, 1209, 1144, 975; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 2.10-1.94 (m, 2H), 1.90-1.78 (m, 2H), 1.53 (s, 9H), 1.48-1.42 (m, 1H), 1.34-1.25 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.4 (d, *J* = 20.3 Hz), 166.4, 142.7, 138.5, 131.1, 128.9, 120.0, 119.4, 101.7 (d, *J* = 188.2 Hz), 80.5, 36.8 (d, *J* = 21.9 Hz), 30.4 (d, *J* = 22.6 Hz), 28.2, 25.3 (d, *J* = 2.9 Hz), 22.7, 13.9, 7.5 (d, *J* = 4.2 Hz); $[\alpha]^{25}_D$ = +11.59 (c 0.122, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{21}H_{31}FNO_3$ [M+H$^+$]: 364.2288, found 364.2290.

2-ethyl-2-fluoro-*N*-methyl-*N*-phenylhexanamide (**7**)



2a (0.25 mmol, 1.0 equiv), NaH (34.1 mg, 1.42 mmol, 5.7 equiv) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%) and cooling at 0°C, dried DMF (0.50 mL), MeI (1.25 mmol, 5.0 equiv) were added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere for 23 h at 20 °C. After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **7** (54.1 mg, 94%, >99% ee) as viscous oil; IR (cm^{-1}): 2957, 2929, 2872, 1640, 1594, 1494, 1458, 1378, 1270, 1119, 1029, 970, 773, 731, 698; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.36 (m, 2H), 7.32-7.28 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 3.28 (brs, 3H), 2.08-1.93 (m, 2H), 1.70-1.60 (m, 2H), 1.43-1.24 (m, 4H), 0.95-0.88 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3 (d, *J* = 21.2 Hz), 144.7, 128.9, 127.3, 126.9, 102.2 (d, *J* = 194.9 Hz), 40.5, 38.2 (d, *J* = 22.4 Hz), 31.7 (d, *J* = 22.9 Hz), 25.8 (d, *J* = 2.5 Hz), 22.8, 14.0, 8.1 (d, *J* = 3.8 Hz); $[\alpha]^{25}_D$ = -30.20 (c 0.166, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{22}FNNaO$ [M+Na$^+$]: 274.1583, found 274.1584.

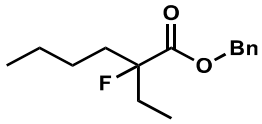
N-(2-ethyl-2-fluorohexyl)-*N*-methylaniline (**8**)



7 (0.20 mmol, 1.0 equiv) was added under air to a dried flask equipped with a stir bar. After flashing nitrogen gas (purity 99.95%) and cooling at 0°C, 1M boran THF solution (4.00 mmol, 20.0 equiv) was added by dried syringe and the resulting mixture was vigorously stirred for 15 h at 90 °C. After this time, the resulting solution was quenched with water. Then, 1M HCl was added and the mixture was stirred for 10 min at 20°C. After this time, sat. $NaHCO_3$ was added to pH 8-9, stirred for 30 min at 20°C and extracted CH_2Cl_2. The

solution obtained was filtered through anhydrous Na_2SO_4, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **8** (30.5 mg, 89%, 93% ee) as viscous oil; IR (cm^{-1}): 2935, 2870, 1598, 1504, 1458, 1374, 1193, 1140, 1110, 1033, 989, 949, 859, 745, 690; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.22 (dd, *J* = 1.8, 7.2 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 6.70 (dt, *J* = 1.0, 6.3 Hz, 1H), 3.50 (d, *J* = 2.6 Hz, 1H), 3.45 (d, *J* = 1.6 Hz, 1H), 2.98 (s, 3H), 1.79-1.57 (m, 4H), 1.38-1.27 (m, 4H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.5, 129.1, 116.5, 112.3, 101.6 (d, *J* = 172.9 Hz), 58.8 (d, *J* = 21.1 Hz), 39.8 (d, *J* = 3.3 Hz), 34.1 (d, *J* = 22.8 Hz), 27.4 (d, *J* = 24.0 Hz), 25.6 (d, *J* = 6.6 Hz), 23.2, 14.0, 7.8 (d, *J* = 7.3 Hz); $[\alpha]^{25}_D$ = -6.18 (c 0.195, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{24}FNNa$ [M+Na$^+$]: 260.1790, found 260.1791.

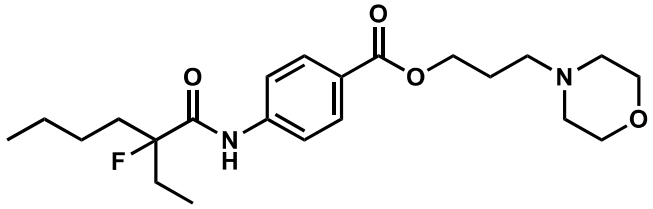
benzyl 2-ethyl-2-fluorohexanoate (**9**)



Hydrolysis: 7 (0.20 mmol, 1.0 equiv) was added under air to a flask equipped with a stir bar. After flashing nitrogen gas (purity 99.95%), 1M HBr/AcOH solution (0.8 mL), EtOH/water (0.4 mL, 1/1) were added by syringe and the resulting mixture was vigorously stirred for 22 h at 100 °C. After this time, the resulting solution was quenched with water. The crude product was obtained after EtOAc extraction followed by evaporation.

Esterification: BnBr (0.4 mmol, 2 equiv), K_2CO_3 (0.4 mmol, 2 equiv), and DMF (0.8 mL) the resulting crude mixture The solution obtained was filtered through anhydrous Na_2SO_4, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **9** (86.7 mg, 86%, 99% ee) as viscous oil; IR (cm^{-1}): 2956, 2930, 1757, 1734, 1455, 1240, 1209, 1139, 979, 696; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37-7.31 (m, 5H), 5.21 (d, *J* = 1.4 Hz, 2H), 1.96-1.73 (m, 4H), 1.48-1.39 (m, 1H), 1.30-1.22 (m, 2H), 1.15-1.07 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7 (d, *J* = 6.5 Hz), 135.5, 128.6, 128.57, 128.51, 98.8 (d, *J* = 187.5 Hz), 67.0, 37.0 (d, *J* = 2.5 Hz), 30.6 (d, *J* = 3.1 Hz), 25.4 (d, *J* = 3.5 Hz), 22.7, 13.9, 7.6 (d, *J* = 4.8 Hz); HRMS (ESI-MS) calcd. for $C_{15}H_{22}FO_2$ [M+H$^+$]: 253.1604, found 253.1604.

3-morpholinopropyl 4-(2-ethyl-2-fluorohexanamido)benzoate (**10**)



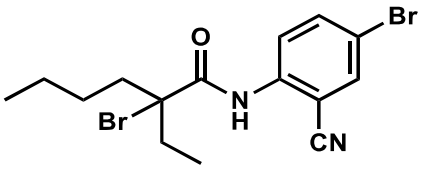
2t (0.075 mmol, 1.0 equiv) was added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), morpholine (0.15 mmol, 2.0 equiv.) and dried DMF (0.15 mL) were sequentially added by syringe and the resulting mixture vigorously stirred under nitrogen atmosphere at room temperature for 23 h. After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product **10** (22.7 mg, 74%, 91% ee) as white solid; IR (cm^{-1}): 3338, 2955, 2859, 2811, 1693, 1593, 1521, 1458, 1407, 1270, 1174, 1112, 1015, 973, 860, 769, 696; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 9.1 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 4.37 (t, *J* = 6.6 Hz, 2H), 3.73 (t, *J* = 4.6 Hz, 4H), 2.54-2.50 (m, 6H), 2.11-1.93 (m, 4H), 1.92-1.77 (m, 2H), 1.49-1.40 (m, 1H), 1.35-1.23 (m, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7 (d, *J* = 20.4 Hz), 166.0, 141.0, 130.9, 126.3, 119.1, 101.8 (d, *J* = 189.5 Hz), 66.8, 63.2, 55.6, 53.6, 36.8 (d, *J* = 22.3 Hz), 30.4 (d, *J* = 22.6 Hz), 25.8, 25.3 (d, *J* = 3.1 Hz), 22.7, 13.9, 7.5 (d, *J* = 4.3 Hz); Optical rotation $[\alpha]^{25}_D$ = +5.79 (c 0.137, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{22}H_{34}FN_2O_4$ [M+H$^+$]: 409.2503, found 409.2503.

Synthesis of chiral fluorinated NTR1

2-Ethyl hexanoic acid (10 mmol, 1.0 equiv.), and PBr_3 (0.33 mL, 3.3 mmol) were sequentially added under air to a vial equipped with a stir bar, rubber cap, and aluminum cover cap under nitrogen atmosphere (purity 99.95%). The resulting mixture vigorously stirred under nitrogen atmosphere for 1 h at 90˚C. After this time, Br_2 (0.82mL, 16 mmol) was added to the reaction mixture and the temperature was raised up 110 °C. When the temperature was reached at 110 °C, inside pressure was released via needle. After releasing the pressure, the resulting mixture vigorously stirred under nitrogen atmosphere for 3 h at 110 °C. Next, additional Br_2 (if necessary) was added to the mixture to complete the reaction. After stirring for 3 h at 110 °C, the mixture was cooled to room temperature and cyclohexene (2.0 mL, 40.0 mmol) was added to the mixture. The resulting crude α-bromo acid bromide was used for the next step.

α-bromo acid bromide synthesized above, Et_3N (4.2 mL, 30 mmol) were sequentially added to CH_2Cl_2 (10 mL, 1.0 M), then 2-amino-5-bromobenzonitrile (10 mmol, 1.0 equiv.) was dropped into the mixture at 0 ºC. The resulting mixture vigorously stirred overnight at room temperature. After this time, the contents of the flask were washed with saturated aqueous $Na_2S_2O_3$ (20 mL × 3), saturated aqueous $NaHCO_3$ (20 mL × 3) and brine (20 mL × 1). The combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by flash chromatography, eluting hexane-EtOAc to afford the racemic alkyl bromide **1z**. Chiral alkyl bromide was obtained after chiral separation with chiral column.

2-bromo-*N*-(4-bromo-2-cyanophenyl)-2-ethylhexanamide (**1z**)

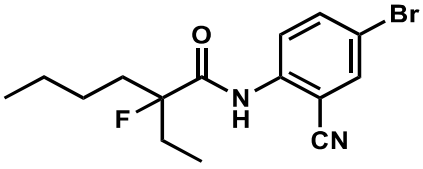


Following the general procedure above, using 2-Ethyl hexanoic acid (1.6 mL, 10 mmol), phosphorus tribromide (0.32 mL, 3.3 mmol), Bromine (0.9 mL, 16 mmol), cyclohexene (2 mL), 2-amino-5-bromobenzonitrile (1969.4 mg, 10 mmol), Triethylamine (4.7 mL, 3.0 equiv.) and CH_2Cl_2 (20 mL, 0.5 M), yielded the product (3.02 g, 8.9 mmol, 89%) as yellow oil; IR (cm^{-1}): 3342, 2956, 2931, 2871, 2223, 1684, 1572, 1507, 1465, 1392, 1288, 1248, 1200, 1146, 1118, 1081, 880, 828; ^1H NMR (500 MHz, $CDCl_3$) δ: 9.27 (brs, 1H), 8.30 (d, J = 9.6 Hz, 1H), 7.72-7.70 (m, 2H), 2.32-2.20 (m, 2H), 2.10-1.99 (m, 2H), 1.63-1.56 (m, 1H), 1.38-1.29 (m, 3H), 1.08 (t, J = 8.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.6, 139.2, 137.2, 134.6, 122.2, 117.1, 114.7, 104.6, 77.6, 42.7, 36.3, 28.2, 22.5, 13.9, 10.5.
HRMS (ESI-MS) calcd. for $C_{15}H_{19}Br_2N_2O$ $[M+H^+]$: 400.9864, found 400.9865.

1z was prepared from corresponding carboxylic acid according to general procedure. Enantiomers were separated by YMC CHIRAL ART Amylose-SA (flow rate: 21.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent).

$[\alpha]^{25}_D$ = -4.99 (c 0.241, CH_2Cl_2).

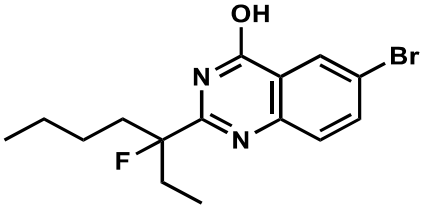
N-(4-bromo-2-cyanophenyl)-2-ethyl-2-fluorohexanamide (**11**)



Alkyl bromide **1z** (1005.5 mmol, 1.0 equiv), 2,2-bpy (38.7 mg, 0.25 mmol, 10 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), $CuBr_2$ (56.5 mg, 0.25 mmol, 10 mol%), CsF (1143.0 mg, 7.5 mmol, 3.0 equiv) and dried MeCN (6 mL) were added by syringe, and the resulting mixture vigorously stirred under nitrogen atmosphere for 23 h at 20 °C. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **11**. (785.5 mg, 92%, 99% ee) as white solid; IR (cm^{-1}): 3267, 2959, 2925, 2860, 2232, 1675, 1570, 1508, 1482, 1390, 1288, 1238, 1154, 1116, 980, 848, 827, 687;

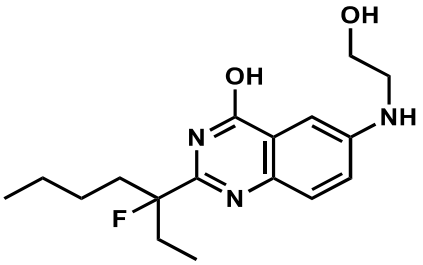
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.64 (d, *J* = 10.0 Hz, 1H), 8.31 (d, *J* = 6.2 Hz, 1H), 7.72-7.69 (m, 2H), 2.09-1.79 (m, 4H), 1.54-1.43 (m, 1H), 1.35-1.22 (m, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0 (d, *J* = 21.0 Hz), 138.5, 137.2, 134.6, 122.8, 117.0, 114.5, 104.7, 101.6 (d, *J* = 189.1 Hz), 36.6 (d, *J* = 22.2 Hz), 30.3 (d, *J* = 22.6 Hz), 25.2 (d, *J* = 3.0 Hz), 22.7, 13.9, 7.5 (d, *J* = 4.3 Hz); Optical rotation $[\alpha]^{25}_{D}$ = -2.51 (c 0.457, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{19}BrFN_2O$ [M+H$^+$]: 341.0665, found 341.0666.

6-bromo-2-(3-fluoroheptan-3-yl)quinazolin-4-ol (**12**)



Alkyl fluoride **11** (2.3 mmol, 1.0 equiv) was added under air to a dram vial equipped with a stir bar and a screw cap. Then, EtOH (11.5 mL) and 30% H_2O_2 solution were added by syringe. NaOH (113.1 mg, 2.8 mmol, 1.2 equiv.) was added and the resulting mixture vigorously stirred for 20 h at reflux (85°C). After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **12** (379.5 mg, 48%, 99% ee) as white solid; IR (cm^{-1}): 3175, 3101, 2953, 2868, 1675, 1602, 1459, 1409, 1330, 1291, 1159, 976, 886, 831; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (brs, 1H), 8.42 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 2.23-1.95 (m, 4H), 1.48-1.39 (m, 1H), 1.34-1.24 (m, 2H), 1.17-1.08 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.4, 156.3 (d, *J* = 25.4 Hz), 147.7 (d, *J* = 2.6 Hz), 137.9, 129.4, 129.2, 122.5, 120.5, 100.2 (d, *J* = 178.7 Hz), 38.1 (d, *J* = 22.2 Hz), 31.7 (d, *J* = 22.5 Hz), 25.1 (d, *J* = 3.3 Hz), 22.7, 13.9, 7.4 (d, *J* = 4.9 Hz); Optical rotation $[\alpha]^{25}_{D}$ = -16.87 (c 0.334, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{15}H_{19}BrFN_2O$ [M+H$^+$]: 341.0665, found 341.0665.

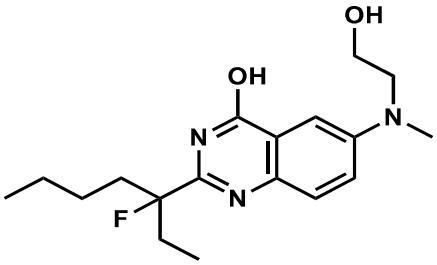
2-(3-fluoroheptan-3-yl)-6-((2-hydroxyethyl)amino)quinazolin-4-ol (**13**)



12 (1.1 mmol, 1.0 equiv), CuI (20.6 mg, 0.11 mmol), L-proline (12.9 mg, 0.11 mmol), K_3PO_4 (467.1 mg, 2.2 mmol) were added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), dried DMSO (1.1 mL) and 2-aminoethan-1-ol (91.1 mg, 0.60 mmol) were added by syringe and the resulting mixture vigorously stirred at 100°C for overnight. After this time, the resulting solution was quenched with water and extracted Et_2O. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **13** (176.0 mg, 50%, 99% ee) as yellow oil; IR (cm^{-1}): 3340, 3188, 3067, 2955, 2928, 2871, 1651, 1621, 1493, 1458, 1373, 1062, 829, 752; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (brs, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.07 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.37 (t, *J* = 5.2 Hz, 2H), 2.18-1.89 (m, 4H), 1.41-1.33 (m, 1H), 1.24 (sext, *J* = 7.5 Hz, 2H), 1.15-1.06 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.1, 151.4 (d, *J* = 26.1 Hz), 147.4, 140.9, 128.5, 122.9, 121.9, 104.8, 100.1 (d, *J* = 177.7 Hz), 60.8, 46.0, 38.2 (d, *J* = 21.9 Hz), 31.7 (d, *J* = 22.5 Hz), 25.1 (d, *J* =

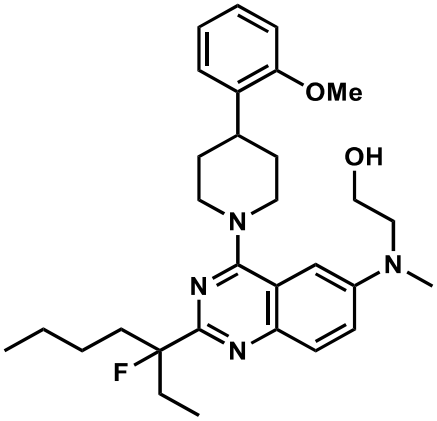
3.2 Hz), 22.7, 13.9, 7.5 (d, J = 4.7 Hz); Optical rotation $[\alpha]^{25}_{D}$ = -14.52 (c 0.179, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{17}H_{25}FN_3O_2$ [M+H$^+$]: 322.1931, found 322.1932.

2-(3-fluoroheptan-3-yl)-6-((2-hydroxyethyl)(methyl)amino)quinazolin-4-ol (**14**)



13 (0.60 mmol, 1.0 equiv) and $NaBH_3CN$ (191.9 mg, 3.0 mmol) were added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), MeOH (1.2 mL), AcOH (AcOH was added until the solution pH was reached at 4.) and formaldehyde solution (0.24 mL, 3.0 mmol) were added by syringe and the resulting mixture vigorously stirred at room temperature for 2 h. After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH to afford the fluorinated product **14** (191.8 mg, 95%, 99% ee) as yellow solid; IR (cm^{-1}): 3189, 2929, 2871, 1653, 1617, 1502, 1376, 1343, 1045, 974, 820, 785; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.35 (brs, 1H), 7.58 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 3.0 Hz, 1H), 7.32 (dd, J = 3.0, 9.1 Hz, 1H), 3.88 (t, J = 5.6 Hz, 2H), 3.61 (t, J = 5.6 Hz, 2H), 3.10 (s, 3H), 2.22-1.93 (m, 4H), 1.78 (brs, 1H), 1.46-1.37 (m, 1H), 1.32-1.24 (m, 2H), 1.18-1.09 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.0 (d, J = 16.6 Hz), 151.4 (d, J = 7.7 Hz), 151.1 (d, J = 7.8 Hz), 148.4 (d, J = 27.6 Hz), 139.7 (d, J = 19.8 Hz), 128.3 (d, J = 8.4 Hz), 121.8 (d, J = 10.5 Hz), 120.6 (d, J = 51.0 Hz), 105.5 (d, J = 19.4 Hz), 100.0 (d, J = 178.0 Hz), 60.2 (d, J = 153.4 Hz), 54.0 (d, J = 205.5 Hz), 39.0 (d, J = 31.6 Hz), 38.2 (d, J = 22.1 Hz), 31.7 (d, J = 22.5 Hz), 25.2 (d, J = 3.2 Hz), 22.7, 13.9, 7.5 (d, J = 4.6 Hz); Optical rotation $[\alpha]^{25}_{D}$ = -15.74 (c 0.297, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{18}H_{27}FN_3O_2$ [M+H$^+$]: 336.2087, found 336.2088.

2-((2-(3-fluoroheptan-3-yl)-4-(4-(2-methoxyphenyl)piperidin-1-yl)quinazolin-6-yl)(methyl)amino)ethan-1-ol (**15**)



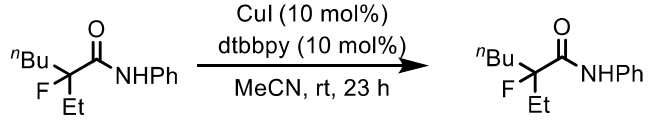
14 (0.55 mmol, 1.0 equiv) and BOP (366.9 mg, 0.83 mmol) were added under air to a dram vial equipped with a stir bar and a screw cap. After flashing nitrogen gas (purity 99.95%), MeCN (1.1 mL) and DBU (334.9 mg, 2.2 mmol) were added by syringe and the resulting mixture stirred for 5 min. Then, 4-(2-methoxyphenyl)piperidine (105.1 mg, 0.55 mmol) was added by syringe and the resulting mixture stirred at room temperature for 20 h. After this time, the resulting solution was quenched with water and extracted EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with

CH_2Cl_2/MeOH to afford the fluorinated product **15** (274.2 mg, 98%, 99% ee) as yellow solid; IR (cm^{-1}): 3303, 2928, 1603, 1540, 1491, 1457, 1360, 1236, 1051, 838, 747; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 9.5 Hz, 1H), 7.43 (dd, *J* = 2.5, 9.3 Hz, 1H), 7.24-7.21 (m, 1H), 7.17 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.72 (d, *J* = 12.9 Hz, 2H), 3.88 (t, *J* = 5.5 Hz, 2H), 3.85 (s, 3H), 3.60 (t, *J* = 5.4 Hz, 2H), 3.40 (t, *J* = 12.2 Hz, 3H), 3.08 (s, 3H), 2.25-2.04 (m, 2H), 2.06 (d, *J* = 14.7 Hz, 3H), 1.93-1.84 (m, 2H), 1.53-1.44 (m, 1H), 1.32-1.23 (m, 2H), 1.13-1.04 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9, 159.3 (d, *J* = 24.7 Hz), 156.9, 148.1, 137.8, 132.9, 127.5, 126.5, 124.9, 122.2, 120.7, 114.9, 110.6, 103.8, 100.0 (d, *J* = 181.1 Hz), 59.8, 55.4, 54.9, 50.7 (d, *J* = 9.4 Hz), 38.9, 38.1 (d, *J* = 21.9 Hz), 35.6, 32.1 (d, *J* = 12.3 Hz), 31.8 (d, *J* = 22.7 Hz), 25.4 (d, *J* = 3.2 Hz), 22.8, 14.0, 7.7 (d, *J* = 4.5 Hz); Optical rotation $[\alpha]^{25}_D$ = +12.56 (c 0.236, CH_2Cl_2). HRMS (ESI-MS) calcd. for $C_{30}H_{42}FN_4O_2$ [M+H$^+$]: 509.3292, found 509.3293.

Control experiments

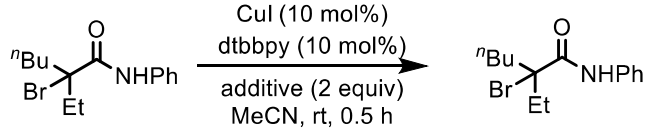
#1: Stability test (Results) **1a** is stable for Cu^{II}. **1a** is unstable for Cu^{I} and CsF. **2a** is stable.

#1-1: Stability of **2a** in the presence of CuI



2a (100% ee) → **2a** >99%, >99% es

#1-2: Stability of **1a** in the presence of CuI



1a (100% ee) → **1a**

Run	additive	**1a** (yield /es)
1	none	99% / 73%
2	none (9 h)	99% / 41%
3	none (23 h)	78% / 4%
4	none ($CuBr_2$ instead of CuI, 23 h)	90% / 99%
5	CsF	79% / 19%
6	CsBr	99% / 82%
7	Cs_2CO_3	99% / 90%
8	CaOAc	99% / 98%

General procedure for control experiments (#1-1)

2a (0.10 mmol, 1.0 equiv, >99% ee), CuI (1.9 mg, 1.0×10^{-2} mmol, 10 mol%), and dtbbpy (2.7 mg, 1.0×10^{-2} mmol, 10 mol%) were added into a 5 mL screw-vial under air. Then, dried MeCN (0.2 mL) was added under N_2 atmosphere. The mixture was stirred at room temperature for 23 h. After 23 hours, the reaction mixture was diluted with AcOEt and filtered. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to recovery of **2a**. Enantio excess of **2a** was determined by HPLC analysis with Daicel CHIRALPAK IA-3.

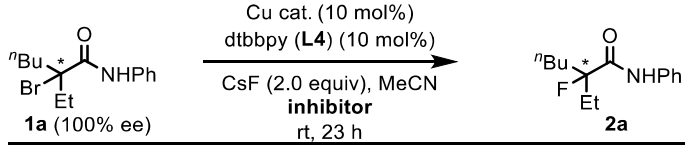
General procedure for control experiments (#1-2)

1a (0.10 mmol, 1.0 equiv, >99% ee), CuI (1.9 mg, 1.0×10^{-2} mmol, 10 mol%), and dtbbpy (2.7 mg, 1.0×10^{-2} mmol, 10 mol%) were added into a 5 mL screw-vial under air. Then, dried MeCN (0.2 mL) was added under N_2 atmosphere. The mixture was stirred at room temperature for 0.5 h. After 0.5 hours, the reaction mixture was diluted with AcOEt and filtered. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to recovery of **1a**. Enantio excess of **1a** was determined by HPLC analysis with Daicel CHIRALPAK IA-3.

#2: Inhibitor test

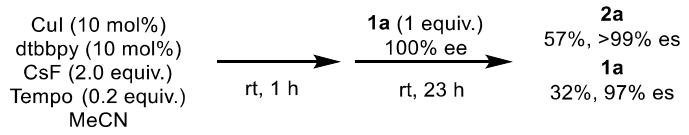
#2-1: Effect of inhibitor

(Results: Tempo is not an inhibitor but oxidant for Cu^{I}.)



Run	Cu cat.	inhibitor (equiv.)	**2a** (yield /es)	**1a** (yield /es)
1	CuI	none	71% / 4%	-
2	CuBr	none	58% / 2%	-
3	$CuBr_2$	none	89% / 98%	-
4	CuI	Tempo (0.2)	95% / 41%	23% / 64%
5	CuI	Tempo (1.5)	77% / >99%	58% / >99%

#2-2: Role of Tempo



General procedure for control experiments (#2-1)

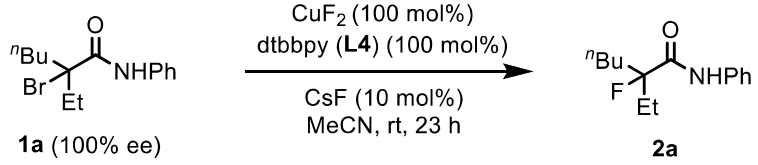
1a (0.10 mmol, 1.0 equiv., >99% ee), Cu cat. (1.0×10^{-2} mmol, 10 mol%), and dtbbpy (2.7 mg, 1.0×10^{-2} mmol, 10 mol%) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. In glove box, CsF (30 mg, 0.20 mmol, 2.0 equiv), TEMPO as additive and dried MeCN (0.2 mL) were added and the resulting mixture vigorously stirred at room temperature for 23 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **2a**.

General procedure for control experiments (#2-2)

CuI (1.9 mg, 1.0×10^{-2} mmol, 10 mol%), dtbbpy (2.7 mg, 1.0×10^{-2} mmol, 10 mol%), CsF (30 mg, 0.20 mmol, 2.0 equiv), TEMPO (3.1 mg, 2.0×10^{-2} mmol, 20 mol%), and dried MeCN (0.2 mL) were sequentially added to a dram vial equipped with a stir bar and a screw cap and the resulting mixture vigorously stirred at room temperature for 1 h in glove box. Then, **1a** (0.10 mmol, 1.0 equiv., >99% ee) was added and the resulting mixture stirred at room temperature for 23 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the desired product **2a**.

#3: Reactivity of CuF_2

(Results: CuF_2 is active in the presence of Cs salt.)



1a (100% ee) **2a**

Run	Variation from standard conditions	**2a** (yield /es)
1	without CsF	0% / -
2	none	62% / 99%
3	bpy istead of dtbbpy (1 equiv)	62% / 99%
4	without Ligand	0% / -
5	with Tempo (1 equiv)	68% / 99%
6	Cs_2CO_3 instead of CsF	54% / >99%
7	CsOAc instead of CsF	51% / >99%
8	AgF, K_3PO_4, $CuBr_2$, or DABCO instead of CsF	3-17% / -

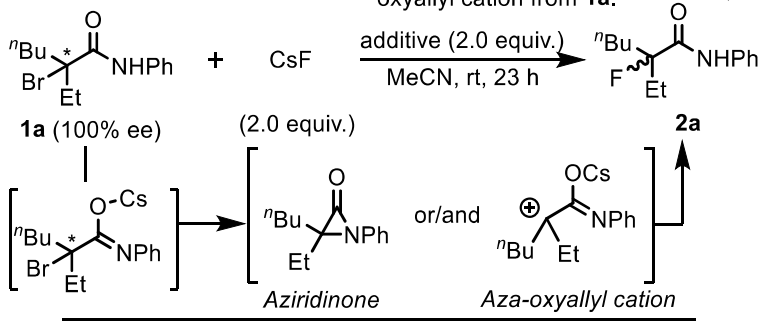
General procedure for control experiments (#3)

1a (0.10 mmol, 1.0 equiv., >99% ee), CuF_2 (10.2 mg, 0.10 mmol, 1.0 equiv.), and dtbbpy (26.8 mg, 0.10 mmol, 1.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar and a screw cap. In glove box, CsF (1.5 mg, 1.0×10^{-2} mmol, 10 mol%), and dried MeCN (0.2 mL) were added and the resulting mixture vigorously stirred at room temperature for 23 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **2a**.

#4: Role of CsF

#4-1: Without Cu catalyst

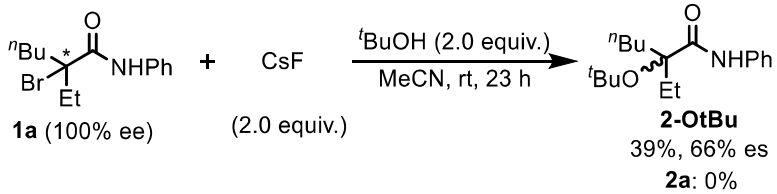
(Results: Deprotonation of amide with CsF. CsF generates aziridinone or aza-oxyallyl cation from **1a**.)



1a (100% ee)

Entry	additive	Isolated yield	*es*	Memo
1	none	37%	26%	**1a**: 28%, 96% es
2	Cs_2CO_3	52%	35%	Elimination: 11%

#4-2: With ^{t}BuOH



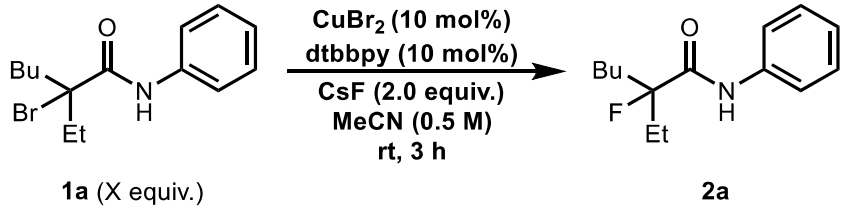
1a (100% ee)

2-OtBu
39%, 66% es
2a: 0%

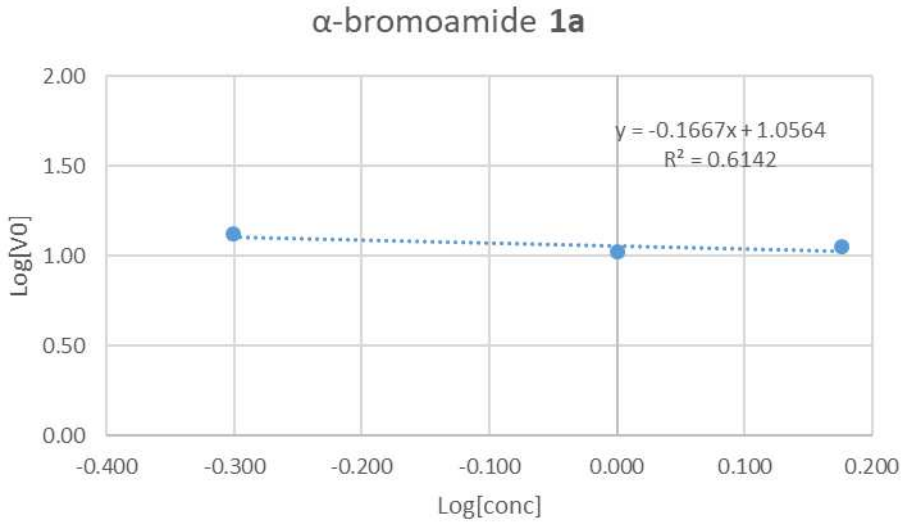
General procedure for control experiments (#4-1)
1a (0.10 mmol, 1.0 equiv., >99% ee) was added under air to a dram vial equipped with a stir bar and a screw cap. In glove box, CsF (30 mg, 0.20 mmol, 2.0 equiv), Cs_2CO_3 (65.2 mg, 0.20 mmol, 2.0 equiv) as additive and dried MeCN (0.2 mL) were added and the resulting mixture vigorously stirred at room temperature for 23 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the fluorinated product **2a**.

General procedure for control experiments (#4-1)
1a (0.10 mmol, 1.0 equiv., >99% ee) was added under air to a dram vial equipped with a stir bar and a screw cap. In glove box, CsF (30 mg, 0.20 mmol, 2.0 equiv), ^{t}BuOH (14.8 mg, 0.20 mmol, 2.0 equiv) and dried MeCN (0.2 mL) were sequentially added and the resulting mixture vigorously stirred at room temperature for 23 h. After this time, the contents of the flask were filtered through the plug of silica gel, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the desired product **2-OtBu**. Enantio excess of **2-OtBu** was determined by HPLC analysis with Daicel CHIRALPAK IA-3.

The order of each component in the reaction
All kinetic studies were carried out under the general procedure for **1a**.
All yields were detected by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.
A. Order in **1a**.

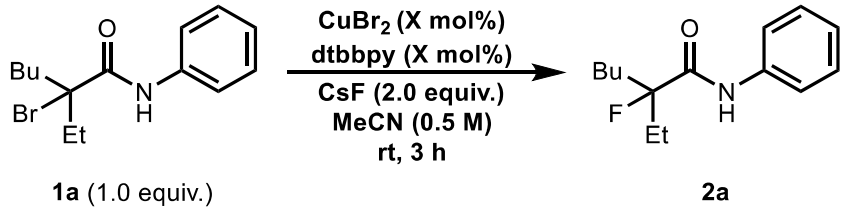


1a (X equiv.) **2a**

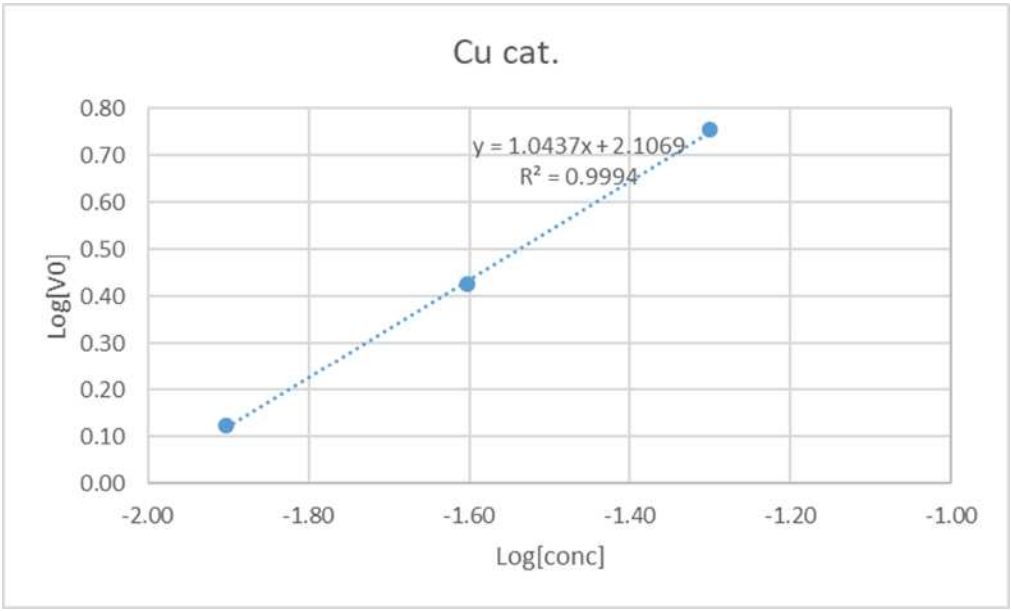


x	1.0	2.0	3.0
concentration	0.5	1.00	1.50
yield/2a	39.8	31.6	33.6
log[conc]	-0.301	0.00	0.18
log[V_0]	1.12	1.02	1.05

B. Order in Catalyst.

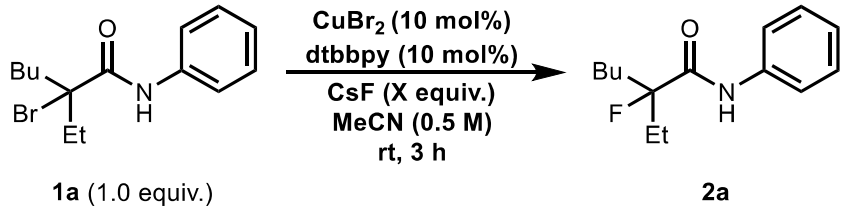


1a (1.0 equiv.) **2a**

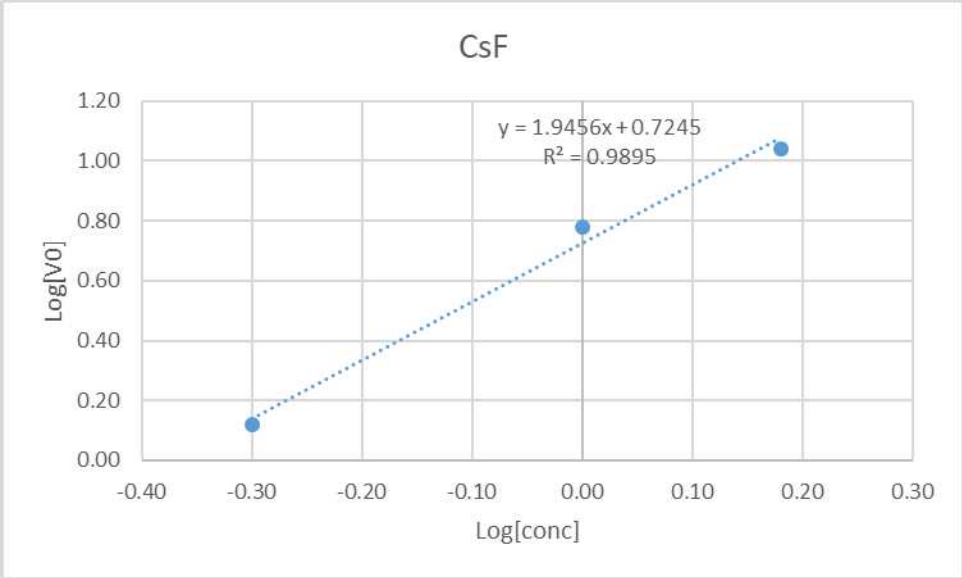


x	2.5	5.0	10.0
concentration	0.0125	0.025	0.05
yield/2a	4	8	17
log[conc]	-1.90	-1.60	-1.30
log[Vo]	0.12	0.43	0.75

C. Order in CsF.



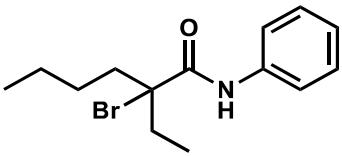
1a (1.0 equiv.) **2a**

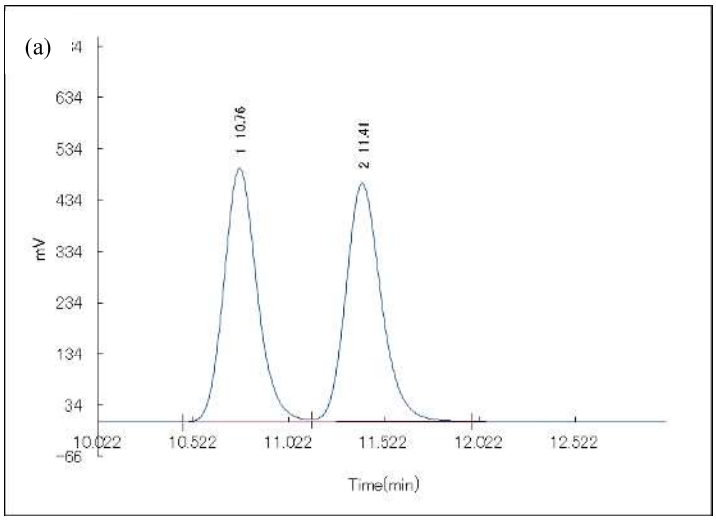


x	1.0	2.0	3.0
concentration	0.5	1	1.5
yield/2a	4	18	33
log[conc]	-0.30	0.00	0.18
log[Vo]	0.12	0.78	1.04

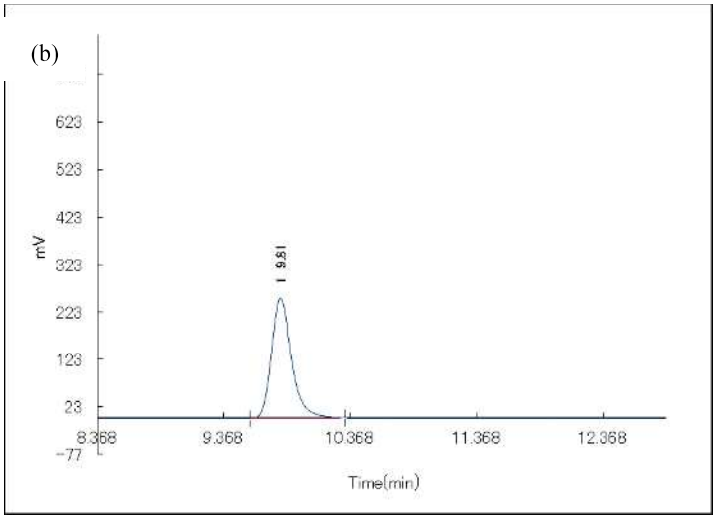
5. HPLC profiles

(1a)





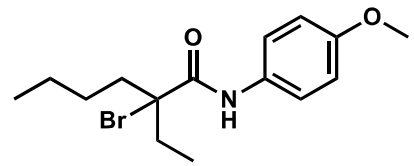
retention time (min)	Area (%)
10.76	49.9583
11.41	50.0417

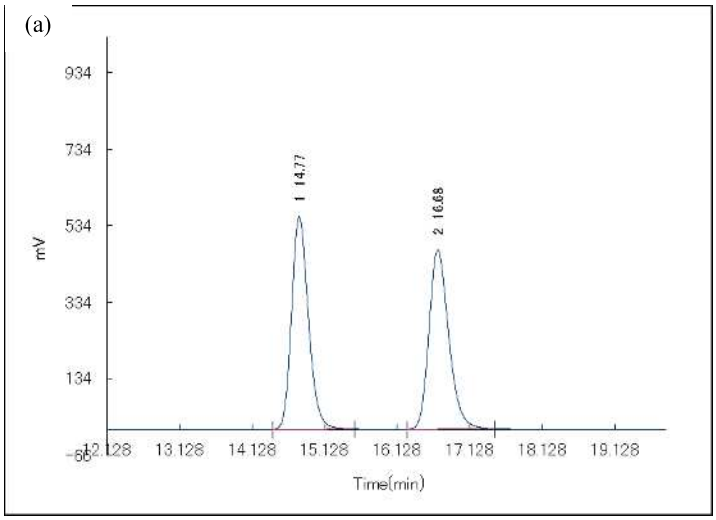


retention time (min)	Area (%)
9.81	100

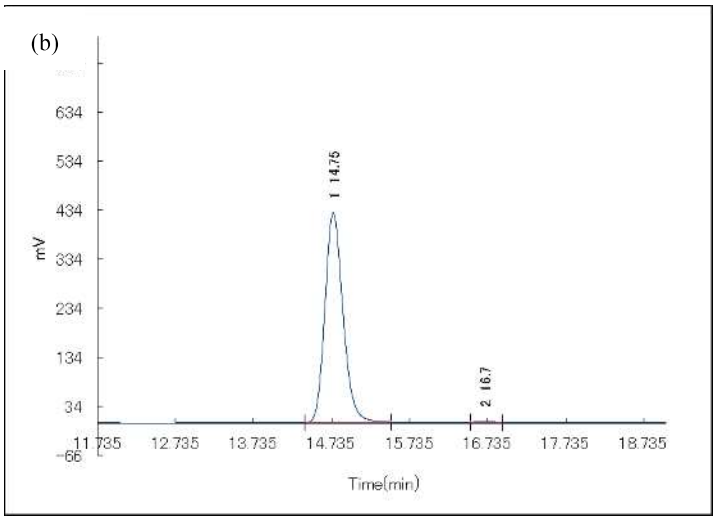
Supporting Figure 1a Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1a** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1b**)





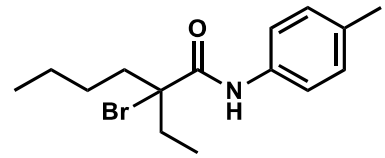
retention time (min)	Area (%)
14.77	50.2962
16.68	49.7038

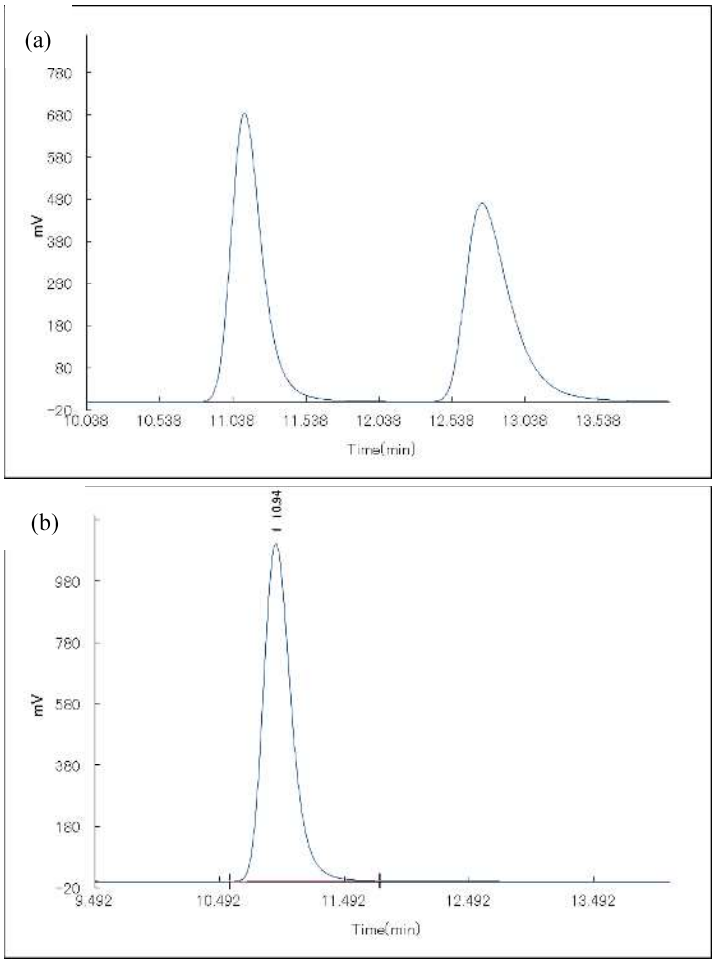


retention time (min)	Area (%)
14.75	99.634
16.7	0.366

Supporting Figure 1b Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1b** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1c**)



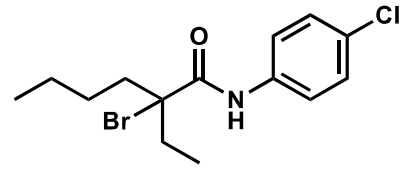


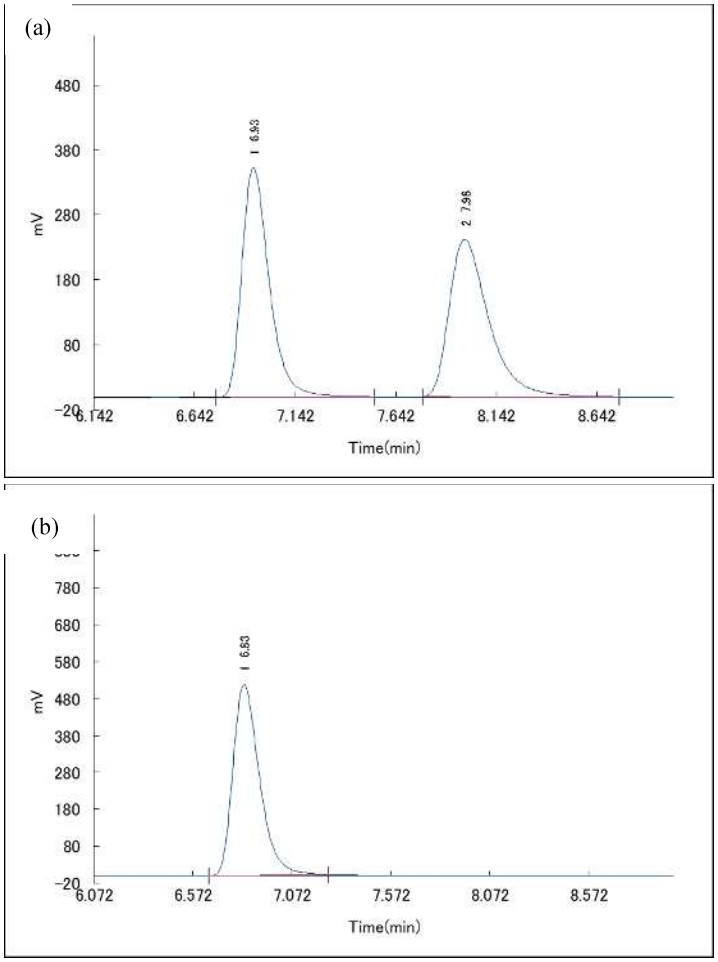
retention time (min)	Area (%)
11.12	50.0967
12.74	49.9033

retention time (min)	Area (%)
10.94	100

Supporting Figure 1c Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **S3** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1d**)



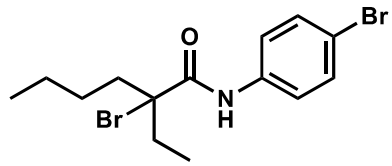


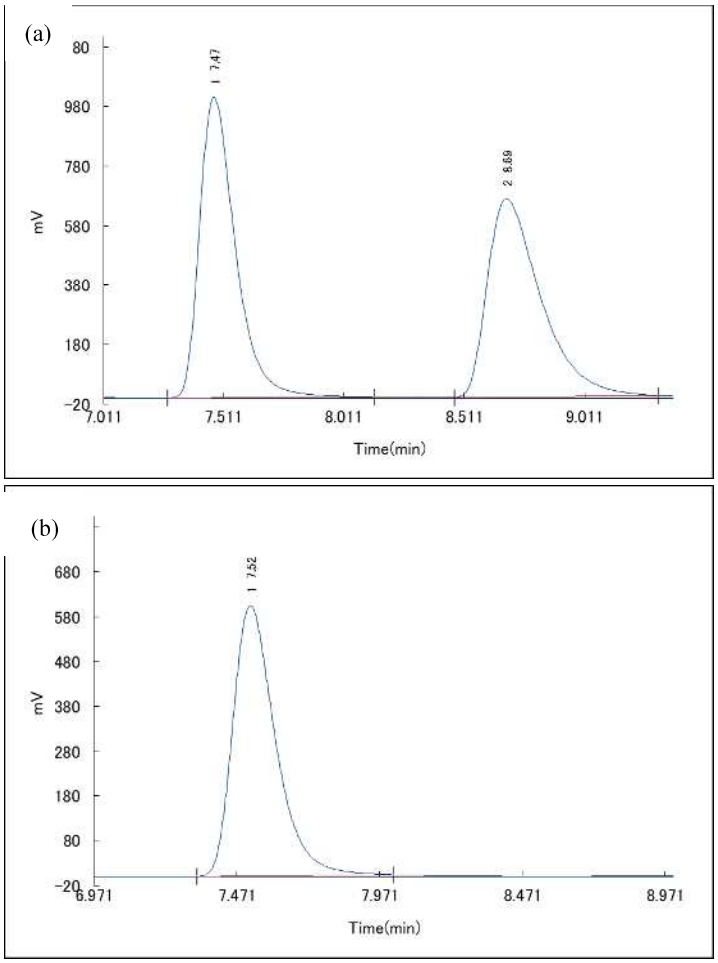
retention time (min)	Area (%)
6.93	50.3126
7.98	49.6874

retention time (min)	Area (%)
6.83	100

Supporting Figure 1d Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1d** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1e**)



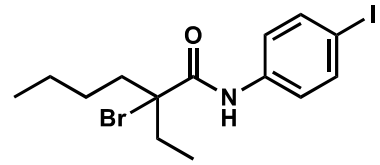


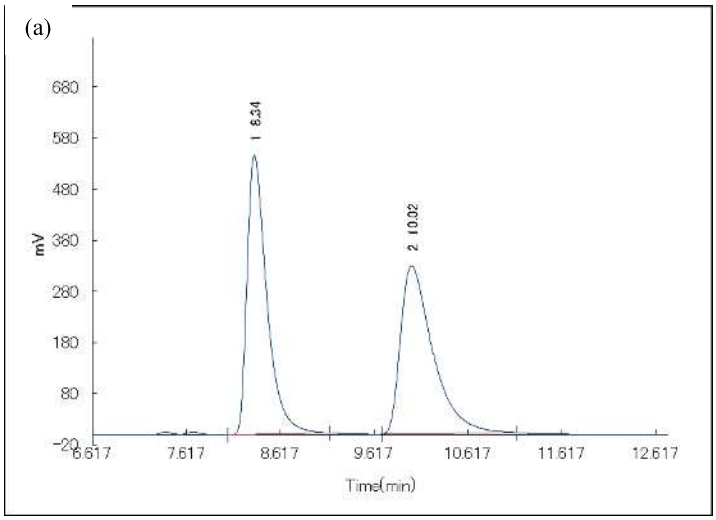
retention time (min)	Area (%)
7.47	50.5275
8.69	49.4725

retention time (min)	Area (%)
7.52	100

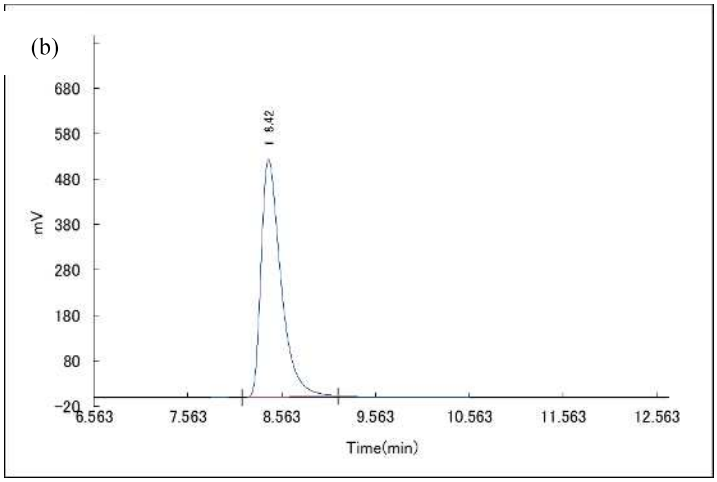
Supporting Figure 1e Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1e** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(1f)





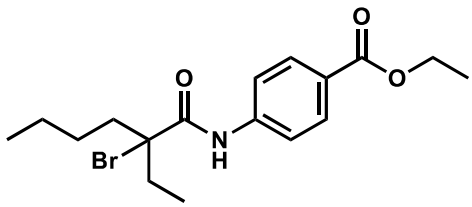
retention time (min)	Area (%)
8.34	50.3486
10.02	49.6514

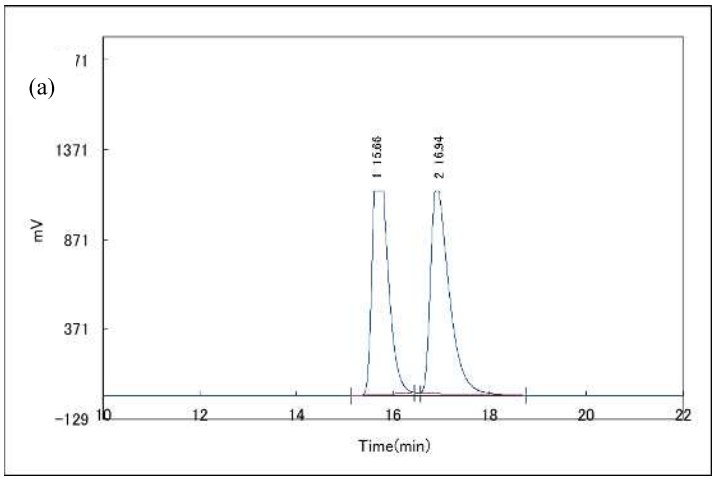


retention time (min)	Area (%)
8.42	100

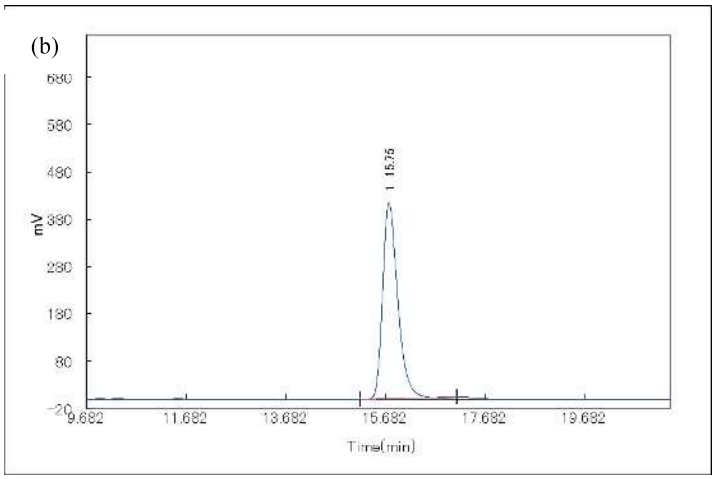
Supporting Figure 1f Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1f** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1g**)





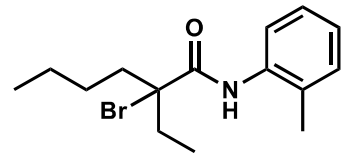
retention time (min)	Area (%)
15.66	47.9
16.94	52.1

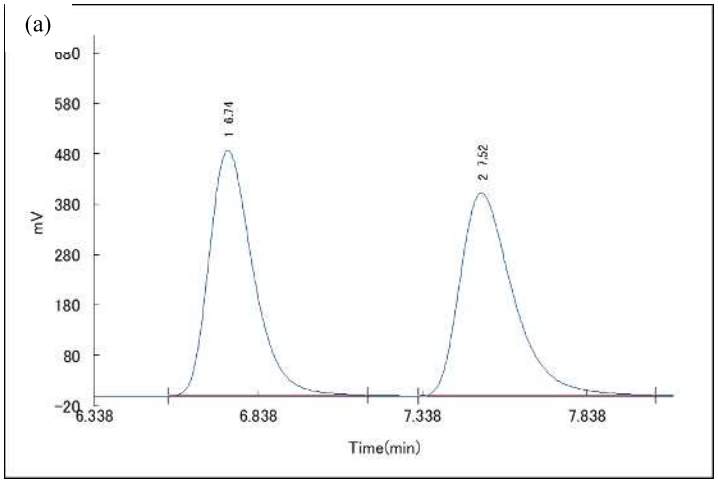


retention time (min)	Area (%)
15.75	100

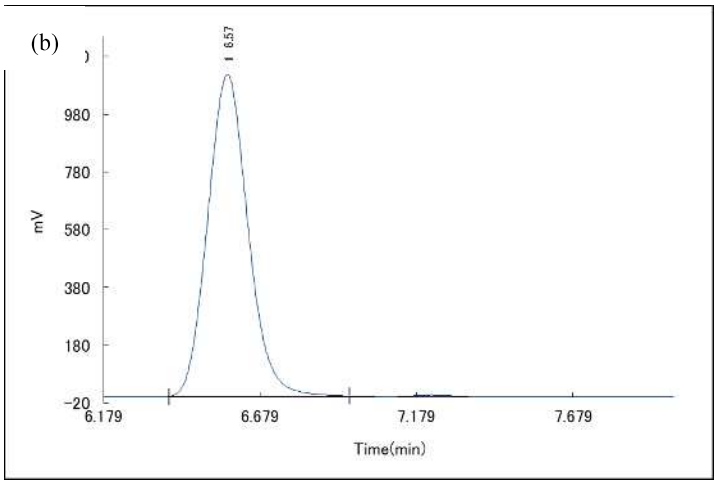
Supporting Figure 1g Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1g** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1h**)





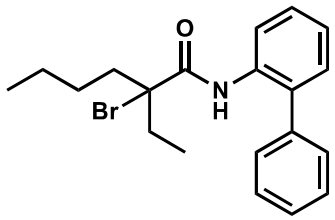
retention time (min)	Area (%)
6.74	50.0396
7.52	49.9604

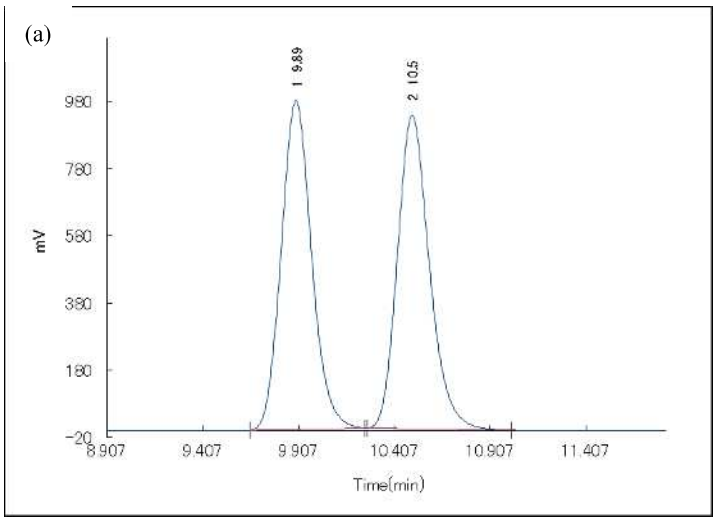


retention time (min)	Area (%)
6.57	100

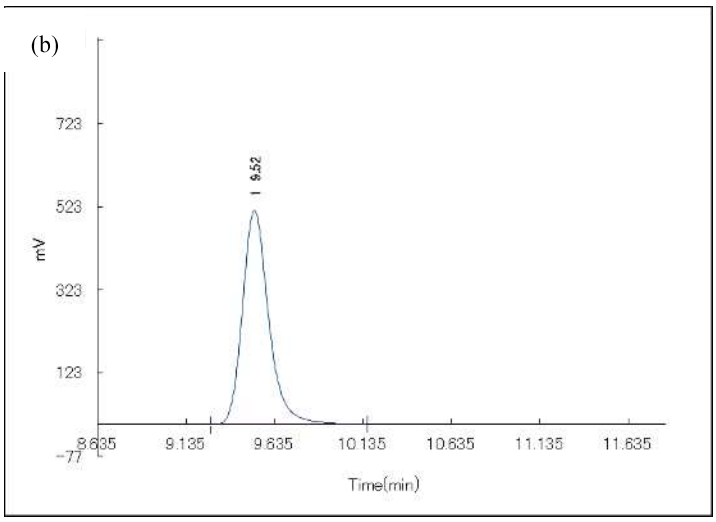
Supporting Figure 1h Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1h** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(1i)





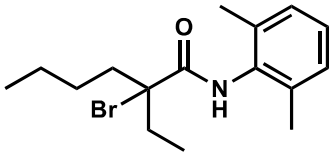
retention time (min)	Area (%)
9.89	49.9207
10.5	50.0793

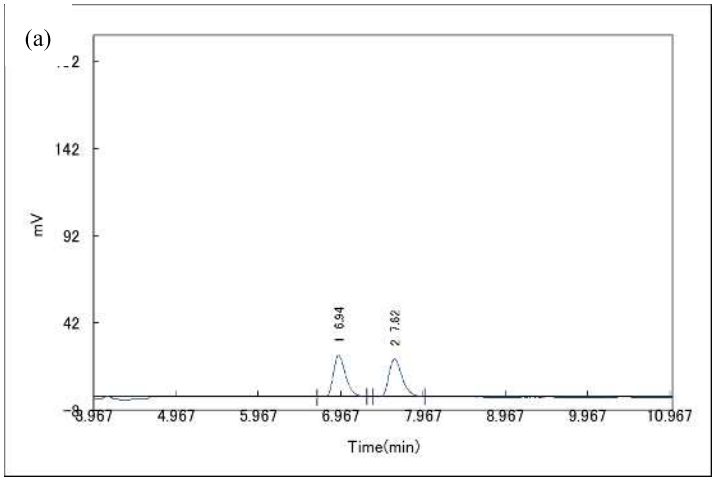


retention time (min)	Area (%)
9.52	100

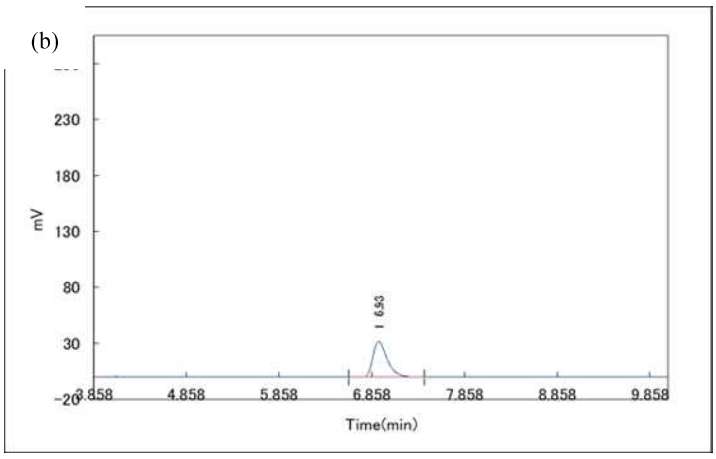
Supporting Figure 1i Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched 1i using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1j**)





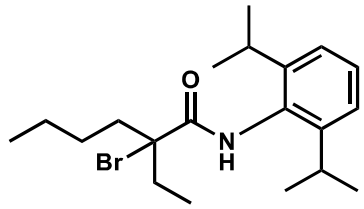
retention time (min)	Area (%)
6.94	50
7.62	50

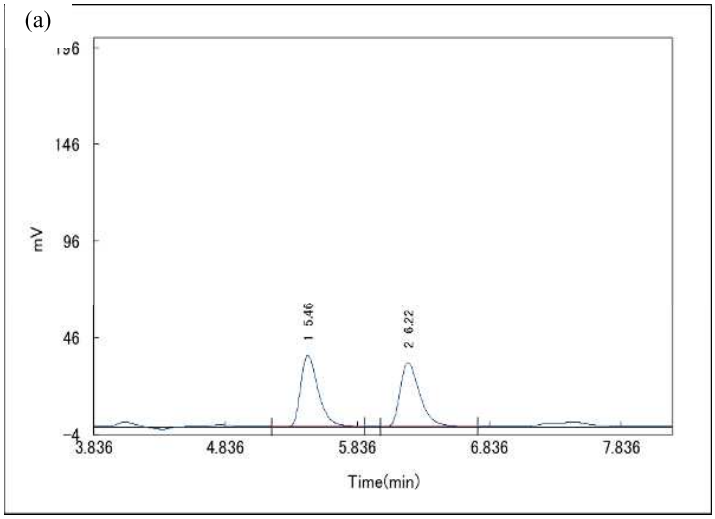


retention time (min)	Area (%)
6.93	100

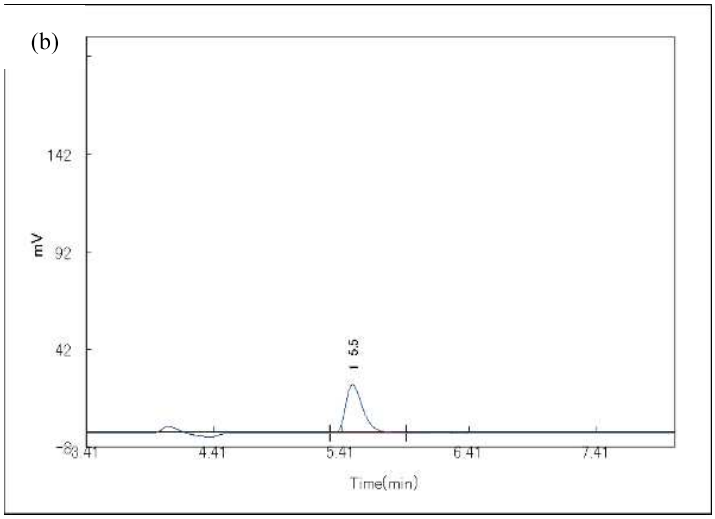
Supporting Figure 1j Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1j** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1k**)





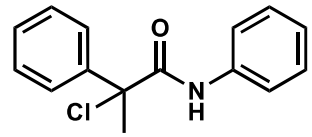
retention time (min)	Area (%)
5.46	49.8
6.22	50.2

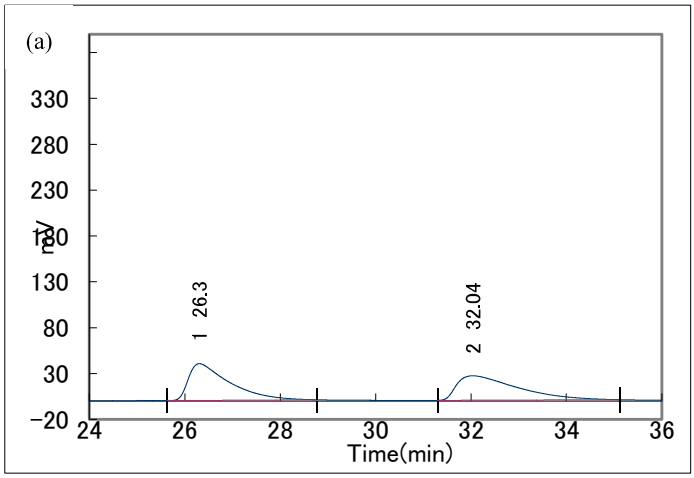


retention time (min)	Area (%)
5.5	100

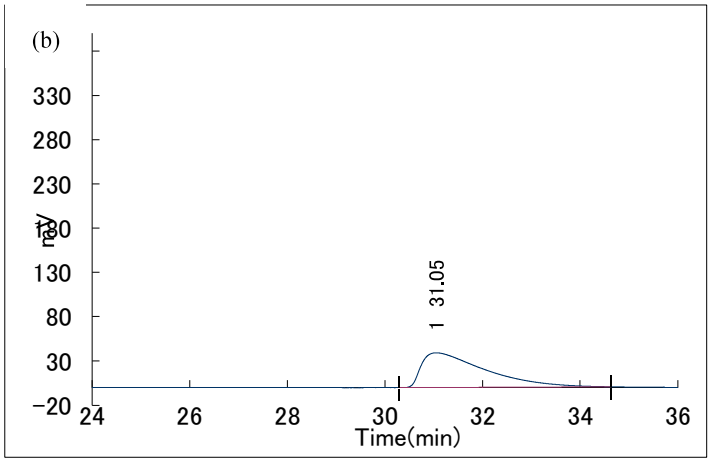
Supporting Figure 1k Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1k** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**1l**)





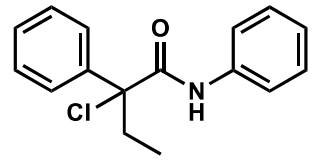
retention time (min)	Area(%)
26.3	50.4413
32.04	49.5587

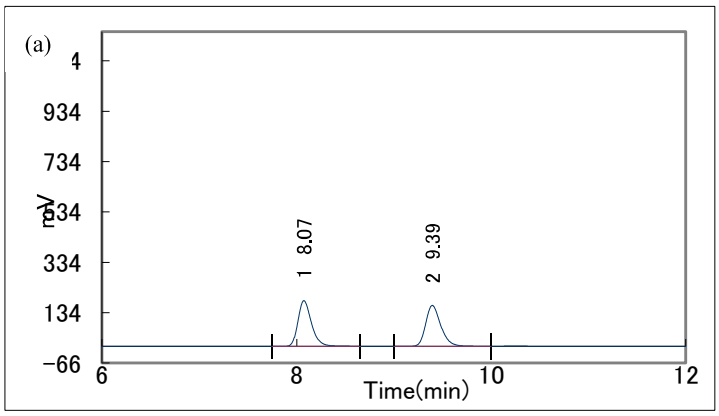


retention time (min)	Area(%)
31.05	100

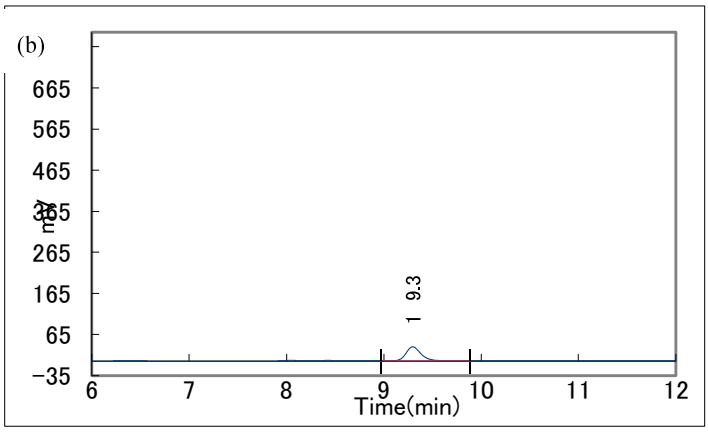
Supporting Figure 1l Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1l** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1m**)





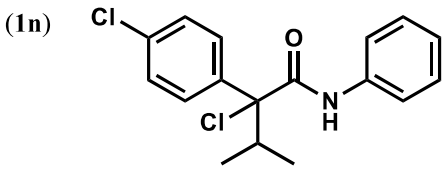
retention time (min)	Area(%)
8.07	50.2299
9.39	49.7701

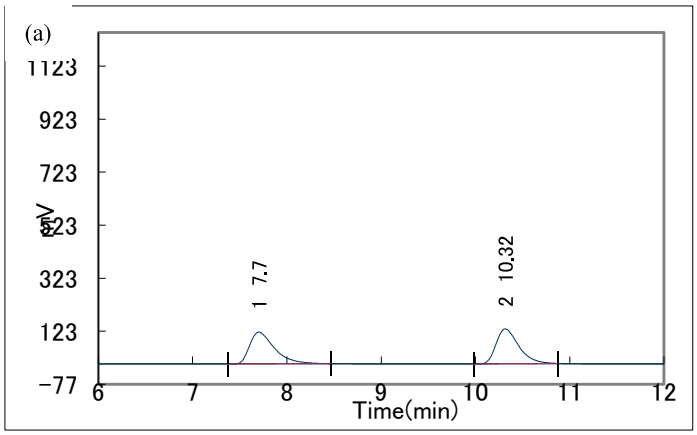


retention time (min)	Area(%)
9.3	100

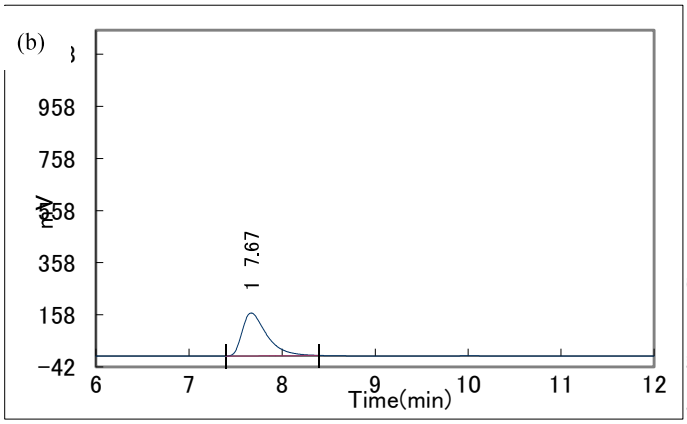
Supporting Figure 1m Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1m** using YMC CHIRAL ART Amylose-SA (flow rate: 1.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1n**)





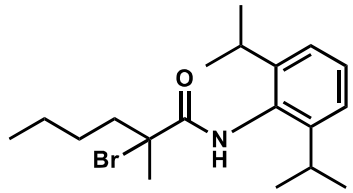
retention time (min)	Area(%)
7.7	50.0766
10.32	49.9234

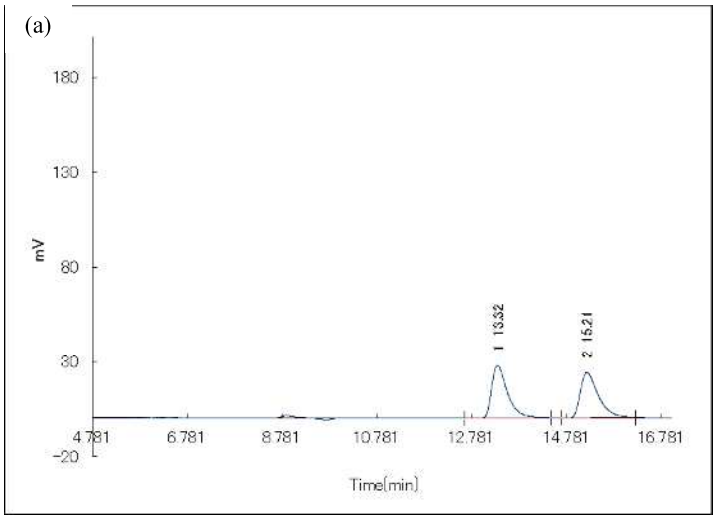


retention time (min)	Area(%)
7.67	100

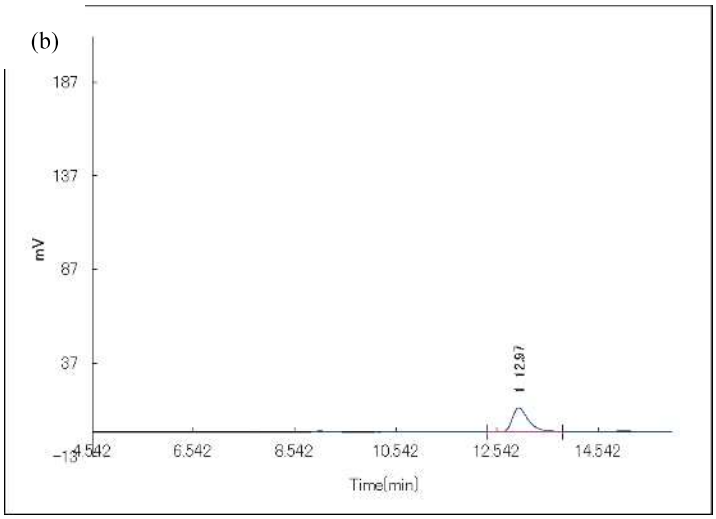
Supporting Figure 1n Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1n** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1o**)





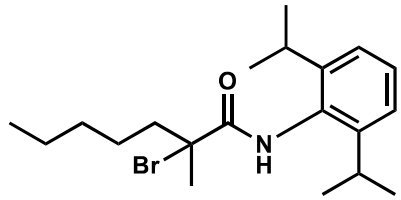
retention time (min)	Area (%)
13.32	50.5035
15.21	49.4965



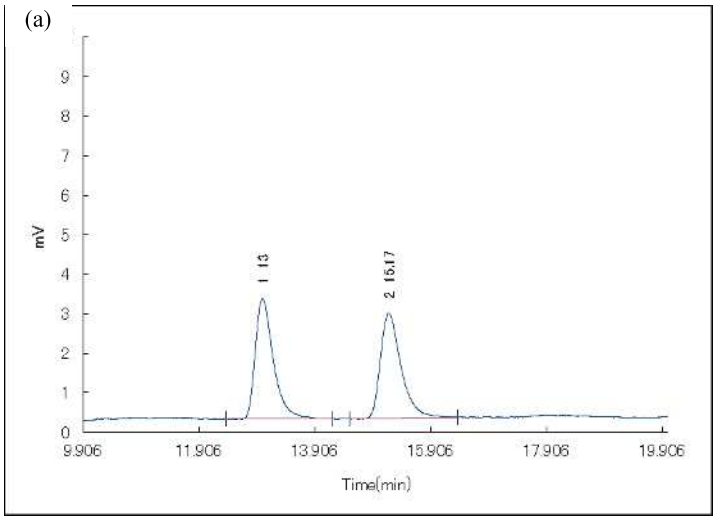
retention time (min)	Area (%)
12.97	100

Supporting Figure 1o Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1o** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1p**)

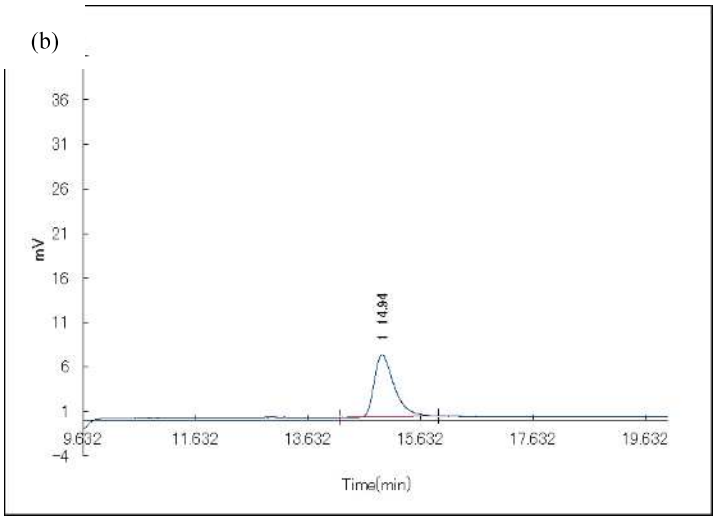


(a)



retention time (min)	Area (%)
13	50.2673
15.17	49.7327

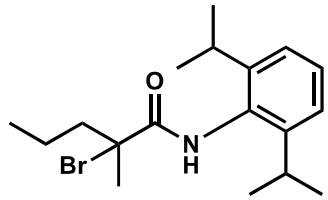
(b)

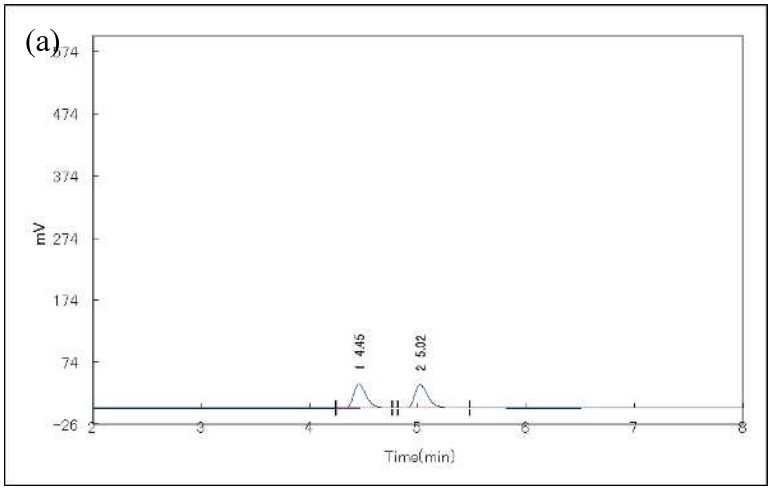


retention time (min)	Area (%)
14.94	100

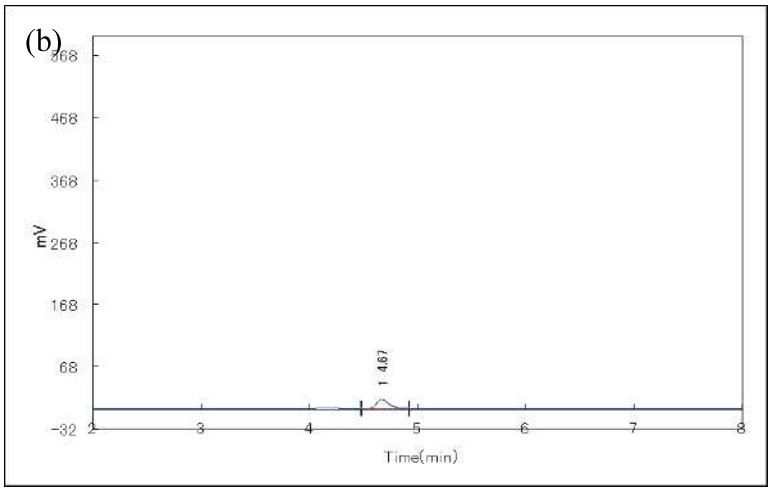
Supporting Figure 1p Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1p** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**1q**)





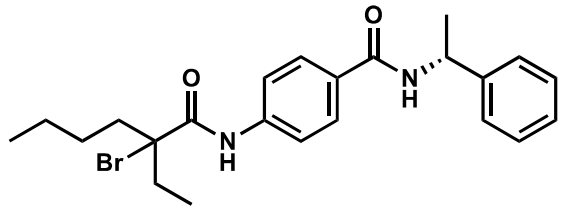
Retention time (min)	Area (%)
4.45	50.3
5.02	49.7

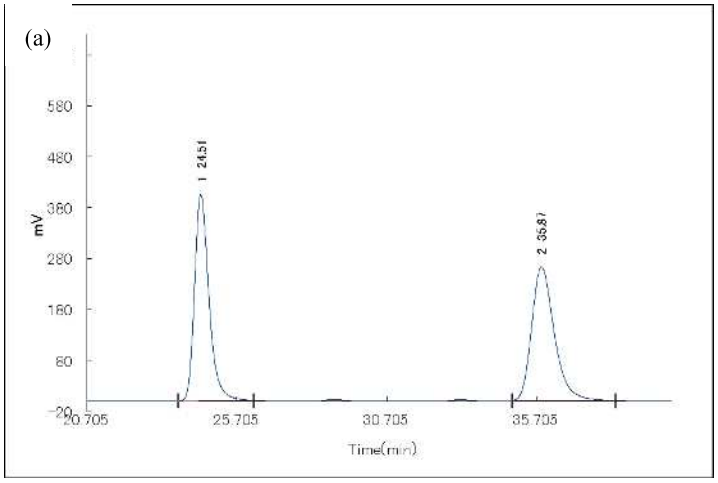


Retention time (min)	Area (%)
4.67	100.0
--	--

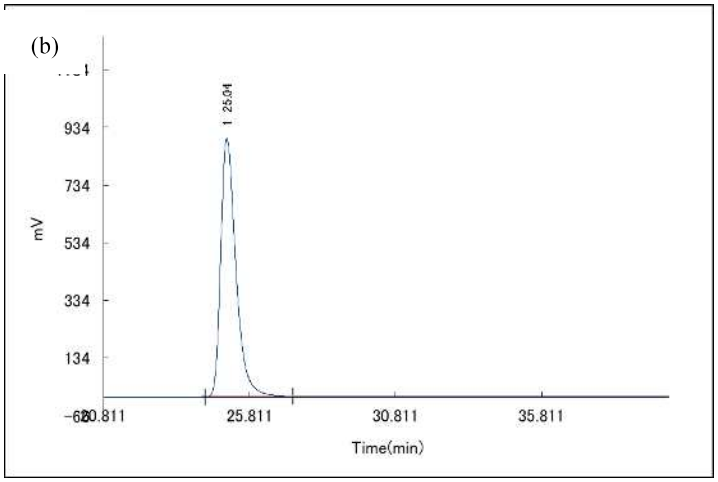
Supporting Figure 1q Chiral HPLC profiles of (a) racemic and (b, c) enantiomerically enriched **1q** using Daicel. CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/ Isopropylalchol = 99.5/0.5 as an eluent monitored at 254 nm).

(**1r**)





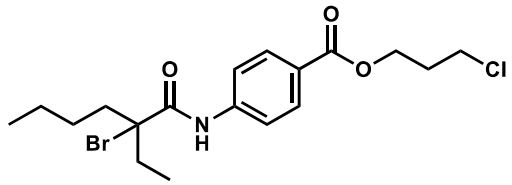
retention time (min)	Area (%)
24.51	49.556
35.87	50.444

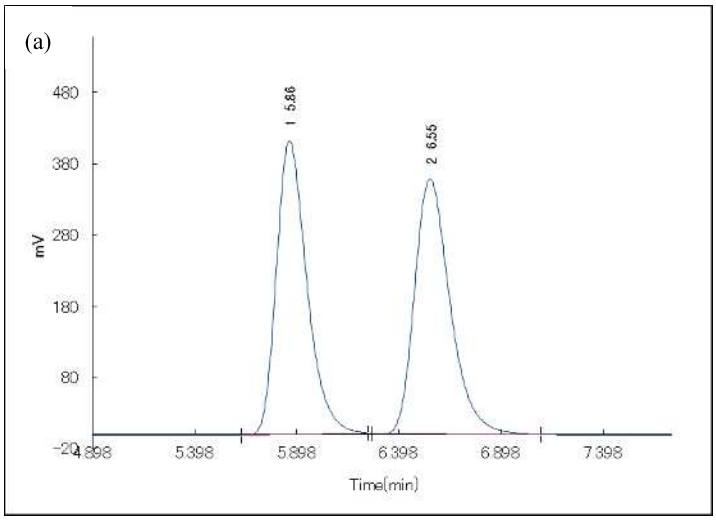


retention time (min)	Area (%)
25.04	100

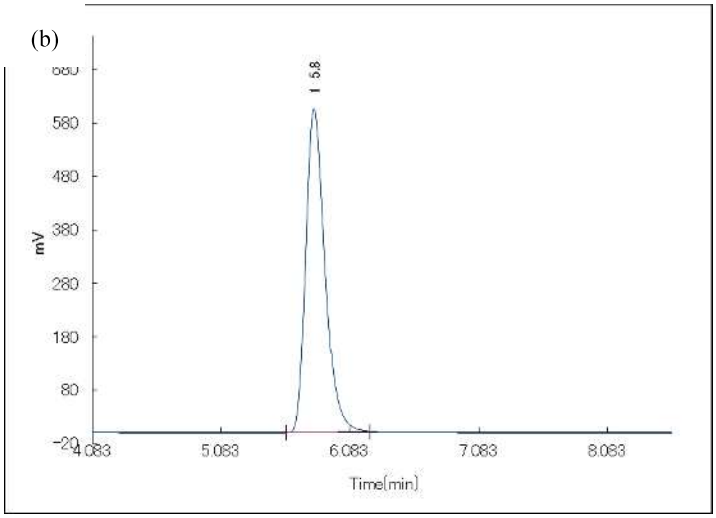
Supporting Figure 1r Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1r** using YMC CHIRAL ART Amylose-SA (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

(1s)





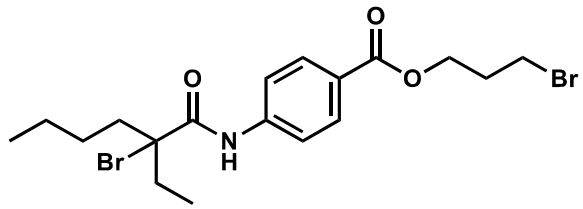
retention time (min)	Area (%)
5.86	49.7404
6.55	50.2596



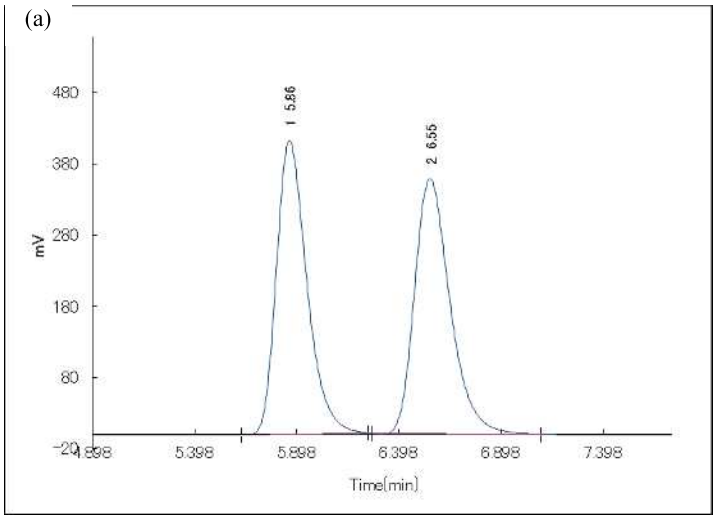
retention time (min)	Area (%)
5.8	100

Supporting Figure 1s Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1s** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 80/20 as an eluent monitored at 254 nm).

(**1t**)

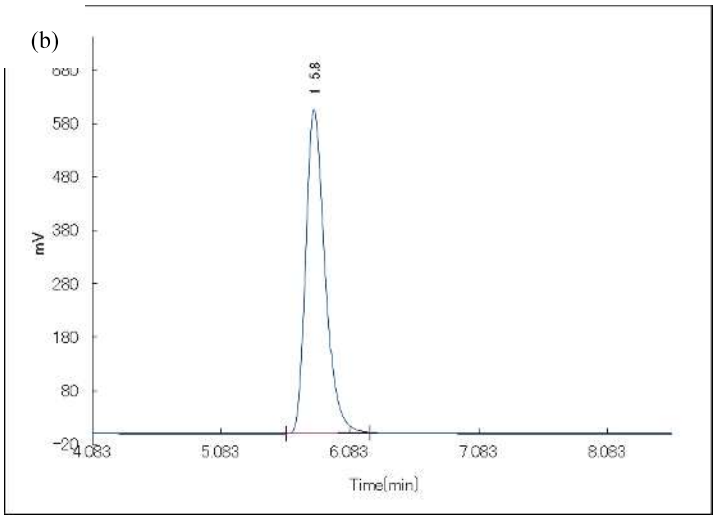


(a)



retention time (min)	Area (%)
5.86	49.7404
6.55	50.2596

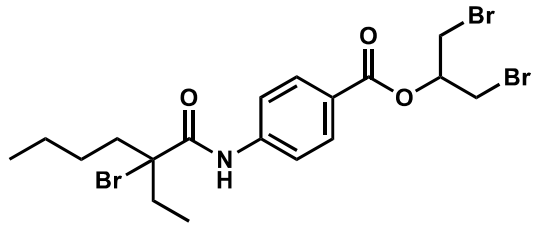
(b)

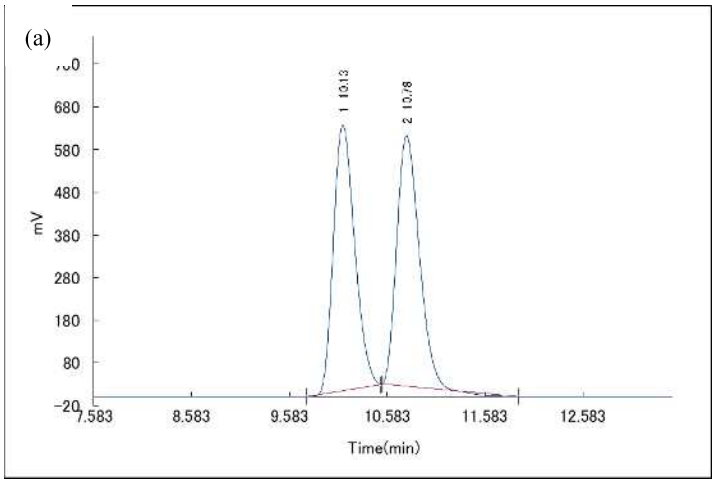


retention time (min)	Area (%)
5.8	100

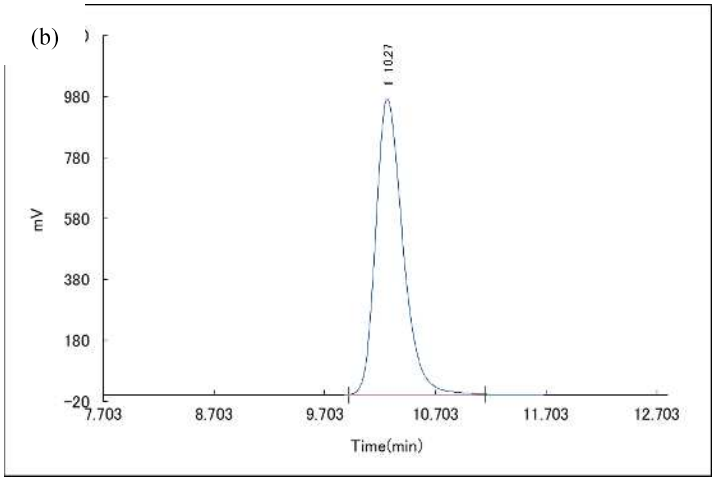
Supporting Figure 1t Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1t** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 80/20 as an eluent monitored at 254 nm).

(**1u**)





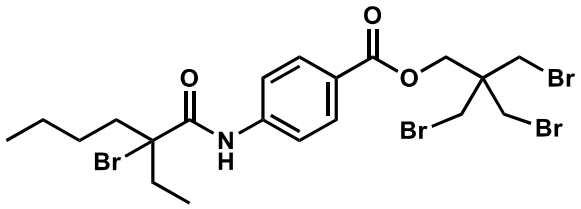
retention time (min)	Area (%)
10.13	50.2775
10.78	49.7225



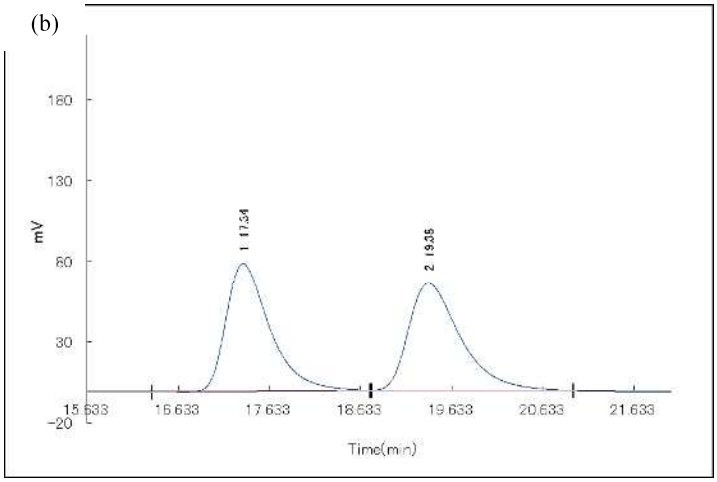
retention time (min)	Area (%)
10.27	100

Supporting Figure 1u Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1u** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

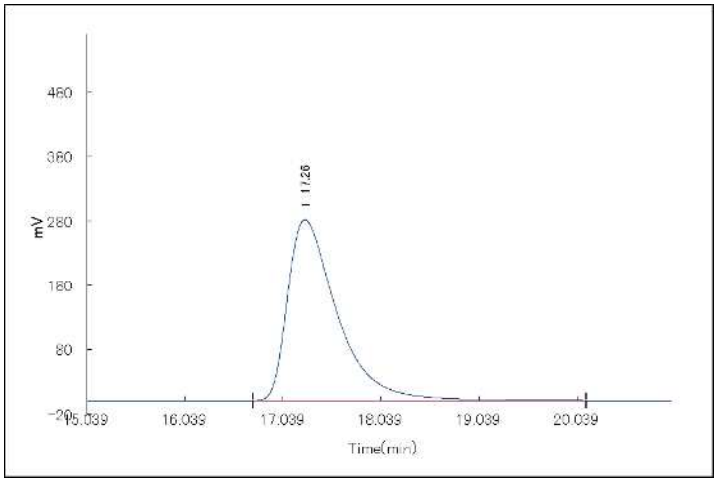
(**1v**)



(b)



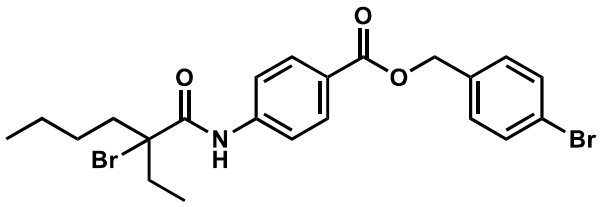
retention time (min)	Area (%)
17.34	50.2356
19.38	49.7644

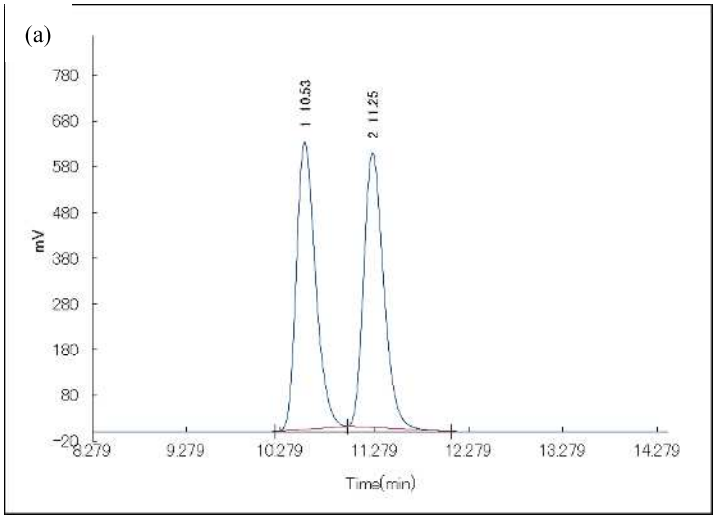


retention time (min)	Area (%)
17.26	100

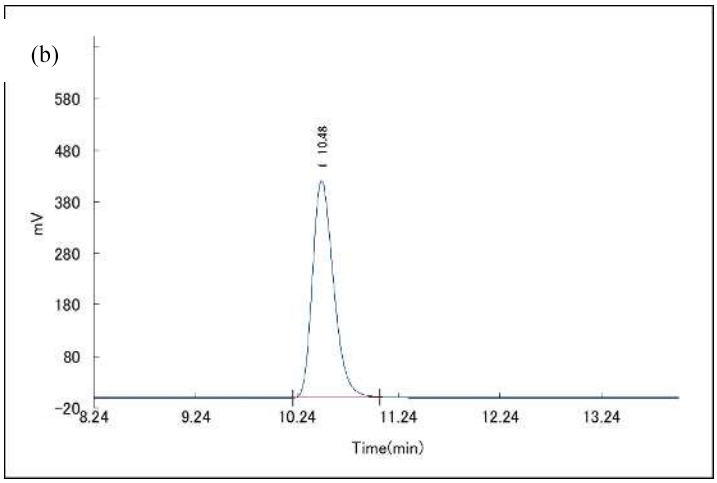
Supporting Figure 1v Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1v** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent monitored at 254 nm).

(**1w**)





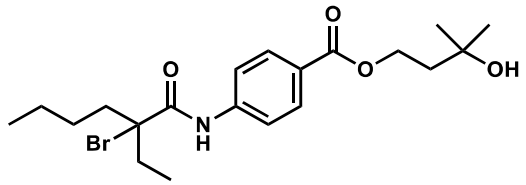
retention time (min)	Area (%)
10.53	50.1536
11.25	49.8464

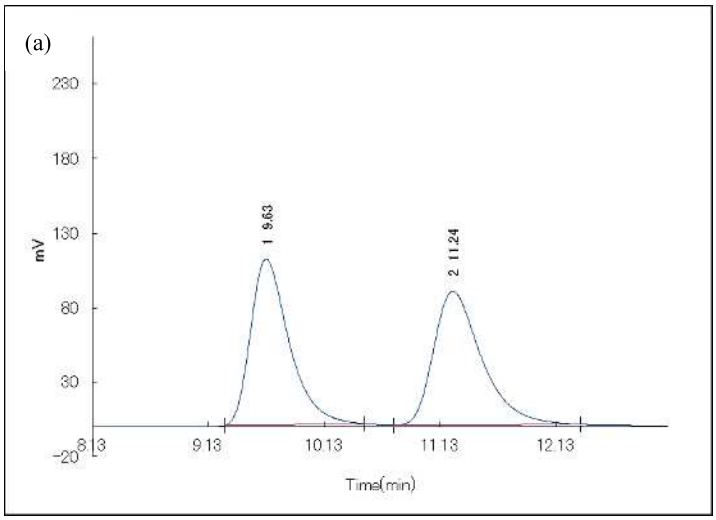


retention time (min)	Area (%)
10.48	100

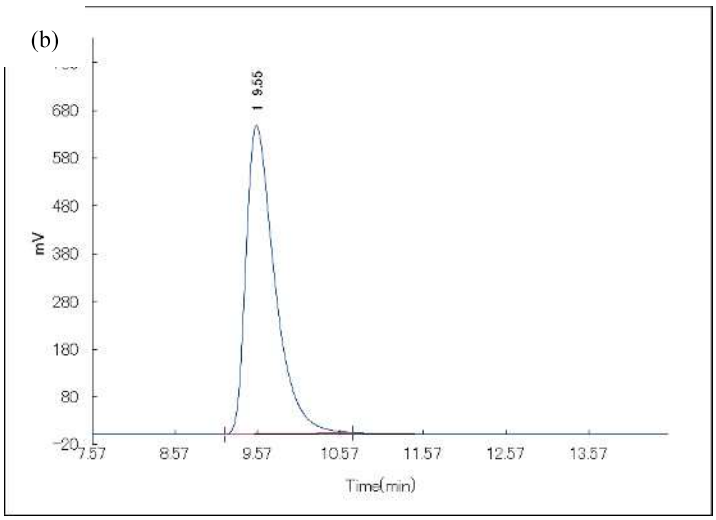
Supporting Figure 1w Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1w** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

(**1x**)





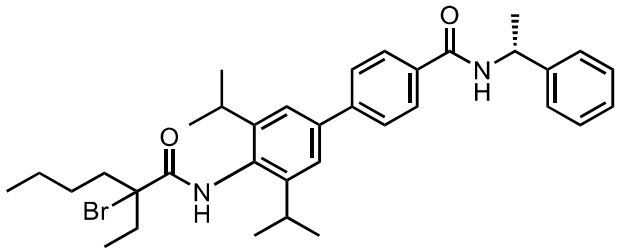
retention time (min)	Area (%)
9.63	49.9024
11.24	50.0976

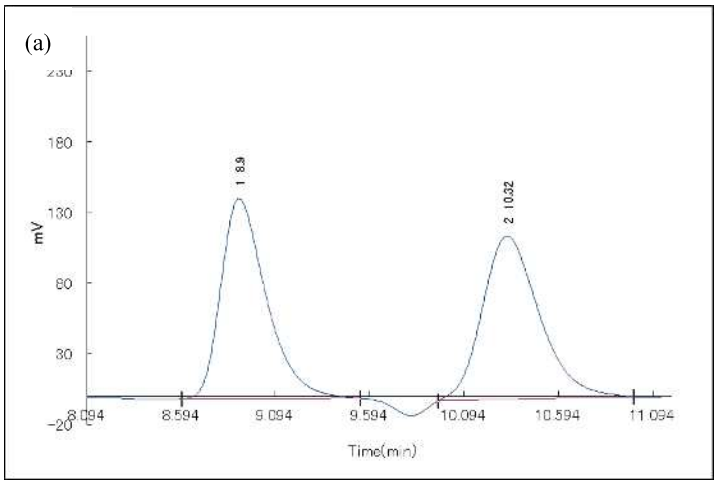


retention time (min)	Area (%)
9.55	100

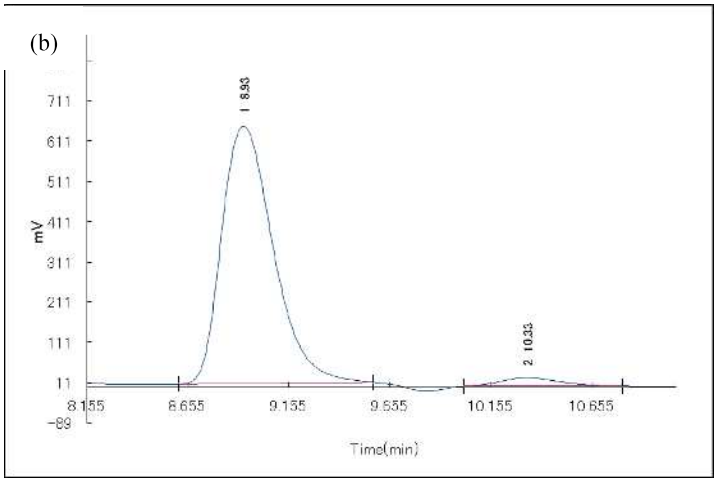
Supporting Figure 1x Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1x** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

(**1y**)





retention time (min)	Area (%)
8.9	49.439
10.32	50.561

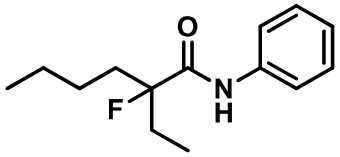


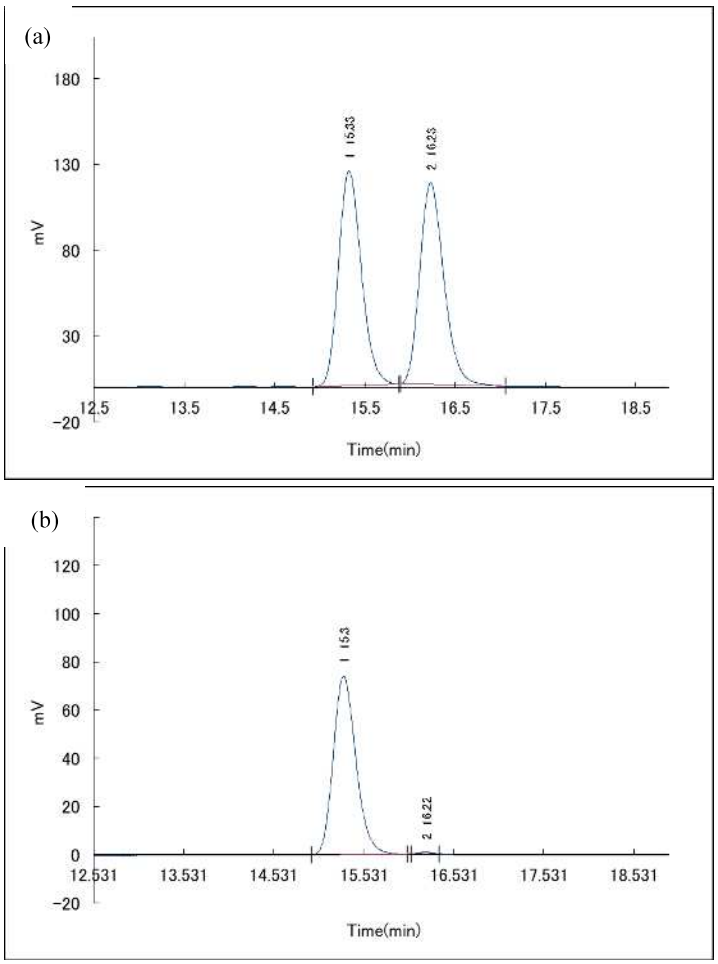
retention time (min)	Area (%)
8.93	96.444
10.33	3.556

Supporting Figure 1y Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1y** using Daicel CHIRALPAK IC-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 70/30 as an eluent monitored at 254 nm).

Chiral HPLC Profile

(2a)



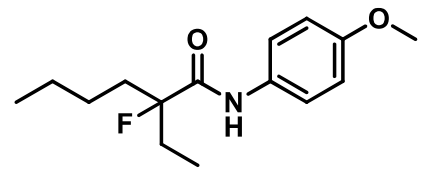


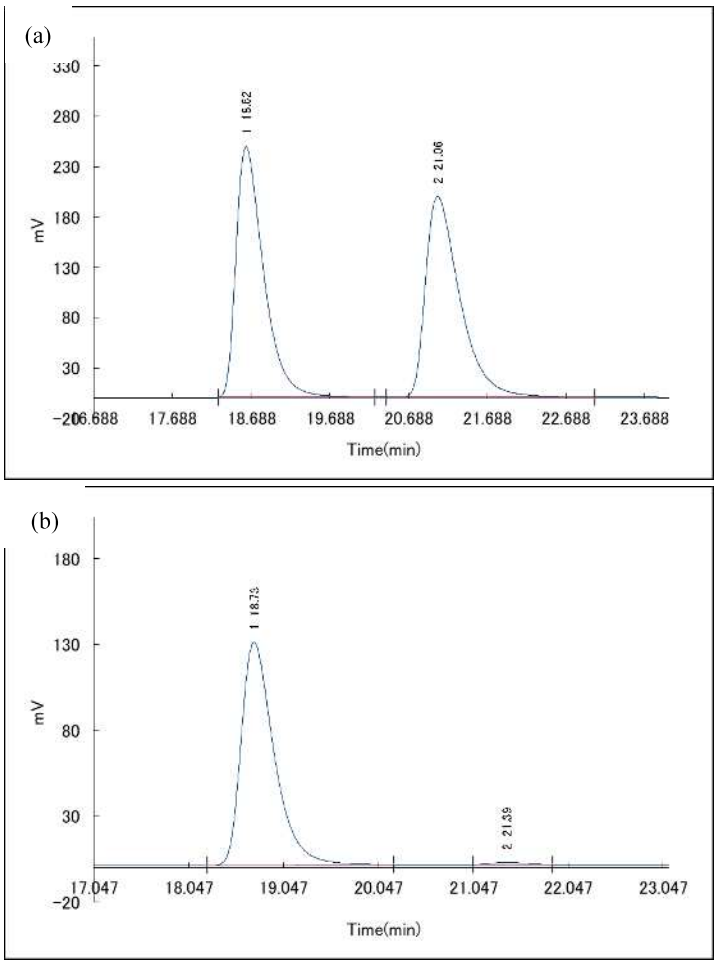
retention time (min)	Area (%)
15.33	50.2135
16.23	49.7865

retention time (min)	Area (%)
15.3	99.5044
16.22	0.4956

Supporting Figure 2a Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2a** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2b)



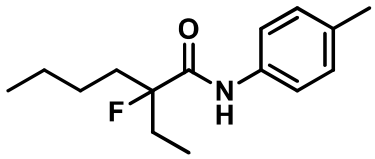


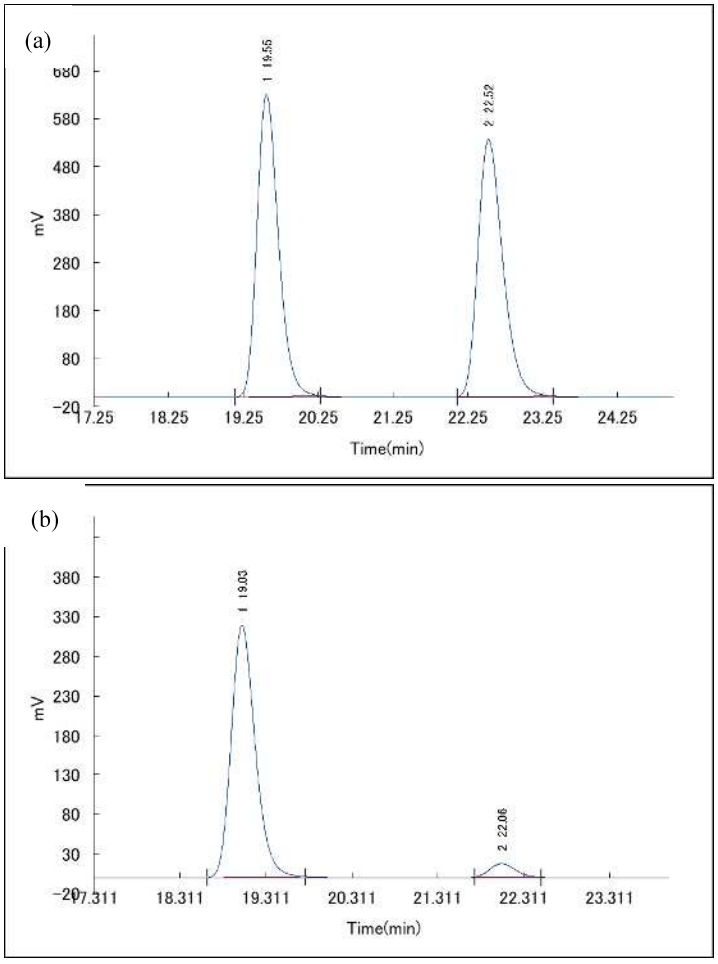
retention time (min)	Area (%)
18.62	50.0053
21.06	49.9947

retention time (min)	Area (%)
18.73	98.9509
21.39	1.0491

Supporting Figure 2b Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2b** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**2c**)



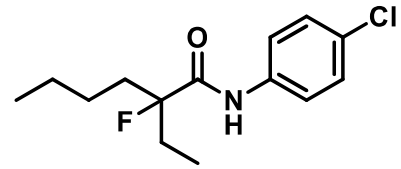


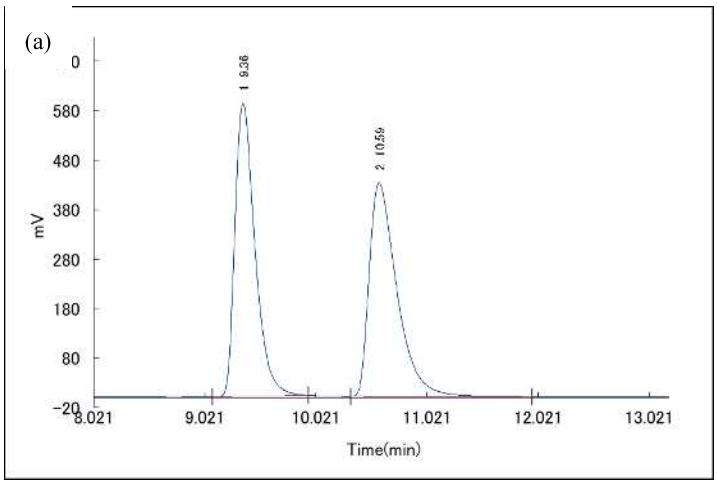
retention time (min)	Area (%)
19.55	50.2624
22.52	49.7376

retention time (min)	Area (%)
19.03	94.7012
22.06	5.2988

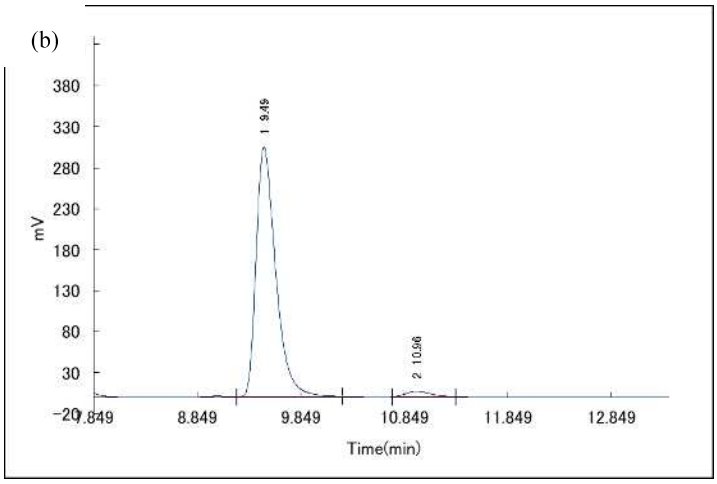
Supporting Figure 2c Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2c** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2d)





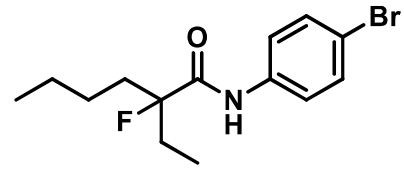
retention time (min)	Area (%)
9.36	49.8133
10.59	50.1867

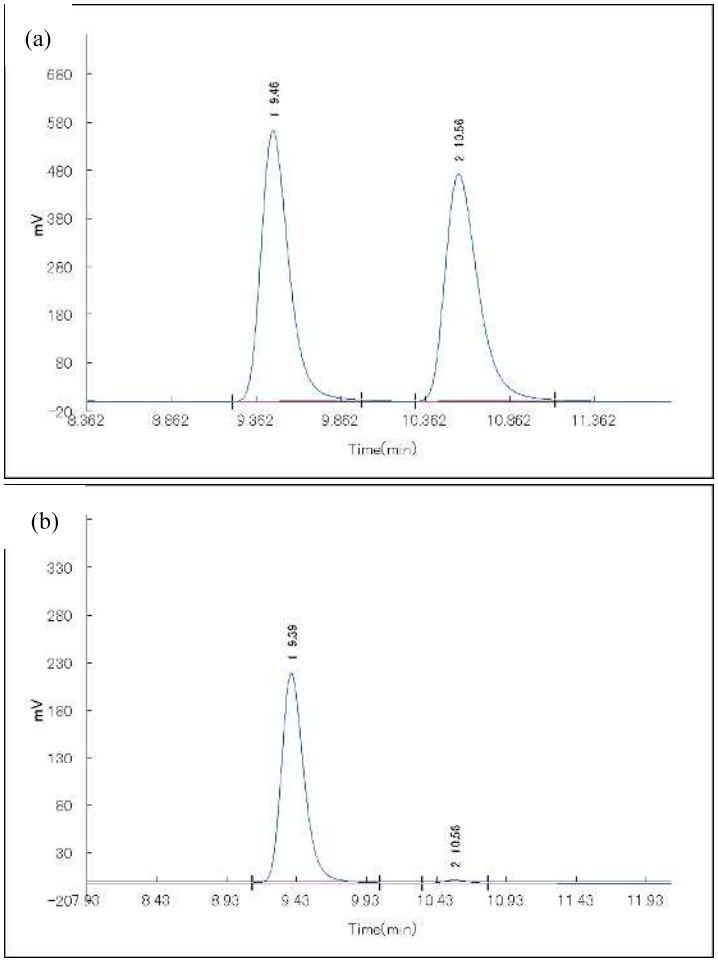


retention time (min)	Area (%)
9.49	97.348
10.96	2.652

Supporting Figure 2d Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2d** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2e)



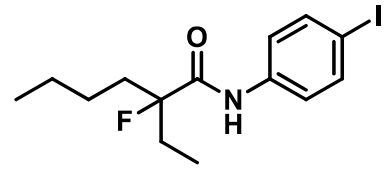


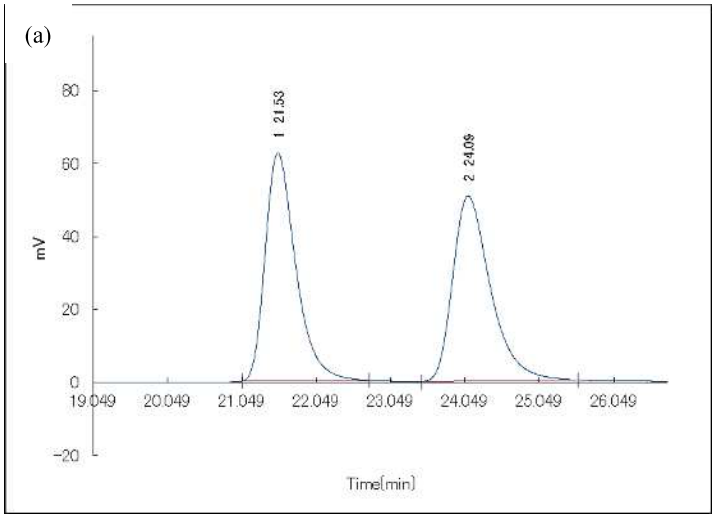
retention time (min)	Area (%)
9.46	50.2288
10.56	49.7712

retention time (min)	Area (%)
9.39	98.5319
10.56	1.4681

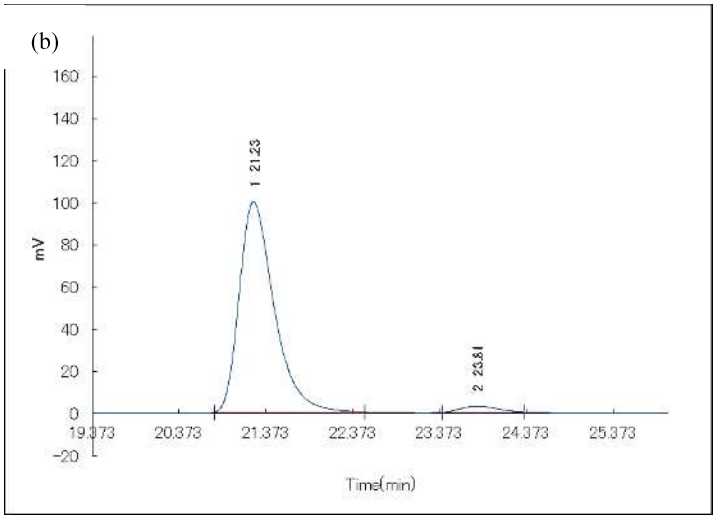
Supporting Figure 2e Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2e** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2f)





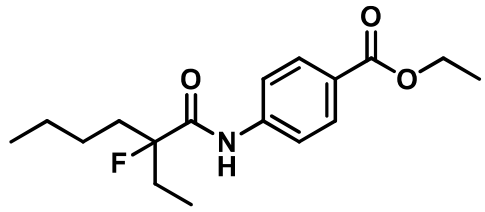
retention time (min)	Area (%)
21.53	49.86
24.09	50.14

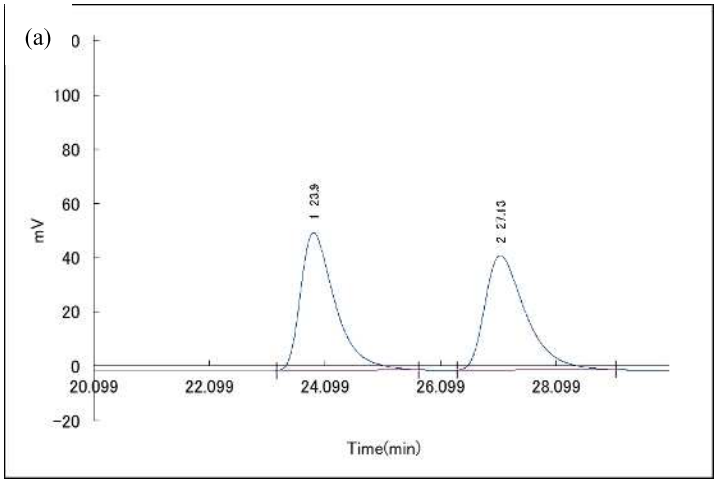


retention time (min)	Area (%)
21.23	97.1761
23.81	2.8239

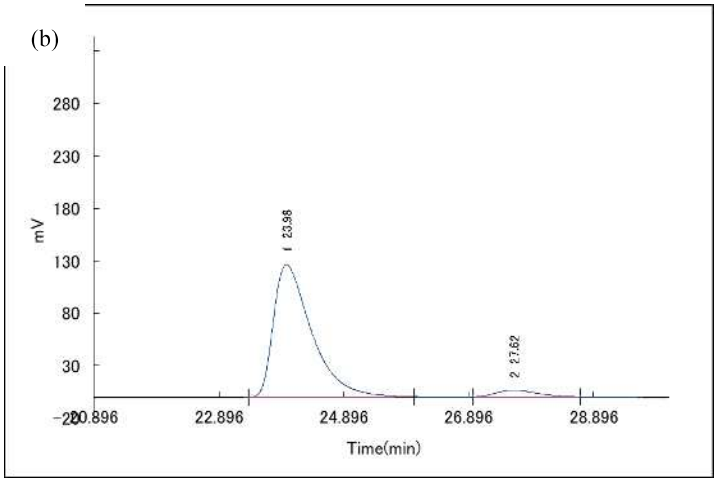
Supporting Figure 2f Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2f** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2g)





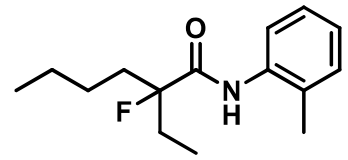
retention time (min)	Area (%)
23.9	50.4535
27.13	49.5465

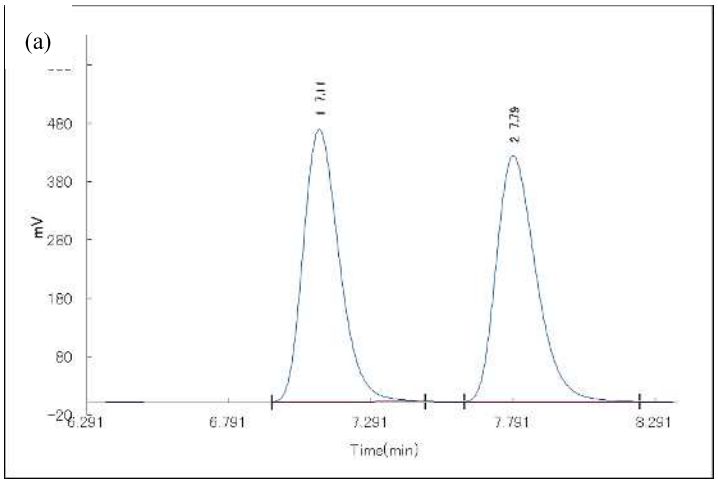


retention time (min)	Area (%)
23.98	94.7797
27.62	5.2203

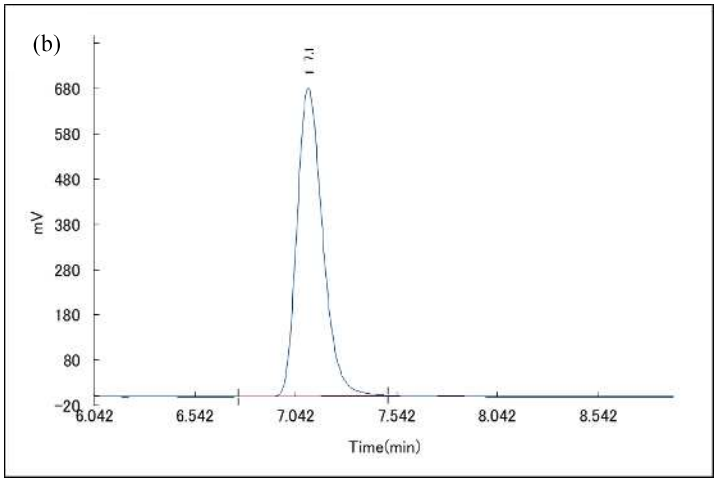
Supporting Figure 2g Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2g** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2h)





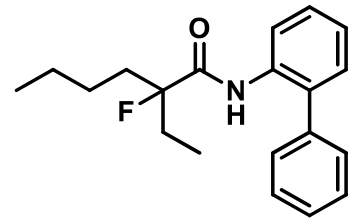
retention time (min)	Area (%)
7.11	50.0502
7.79	49.9498

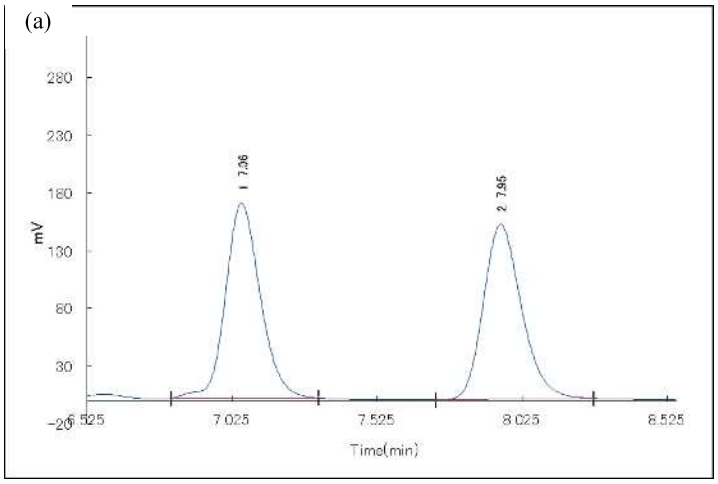


retention time (min)	Area (%)
7.1	100

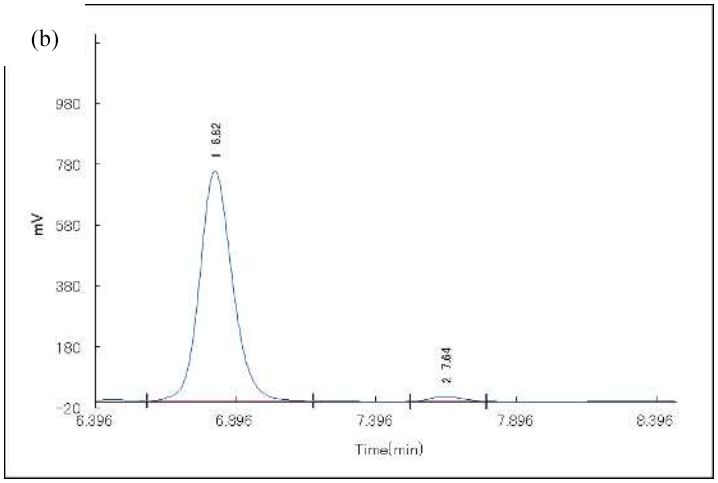
Supporting Figure 2h Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2h** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2i)





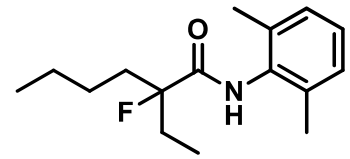
retention time (min)	Area (%)
7.06	50.4712
7.95	49.5288

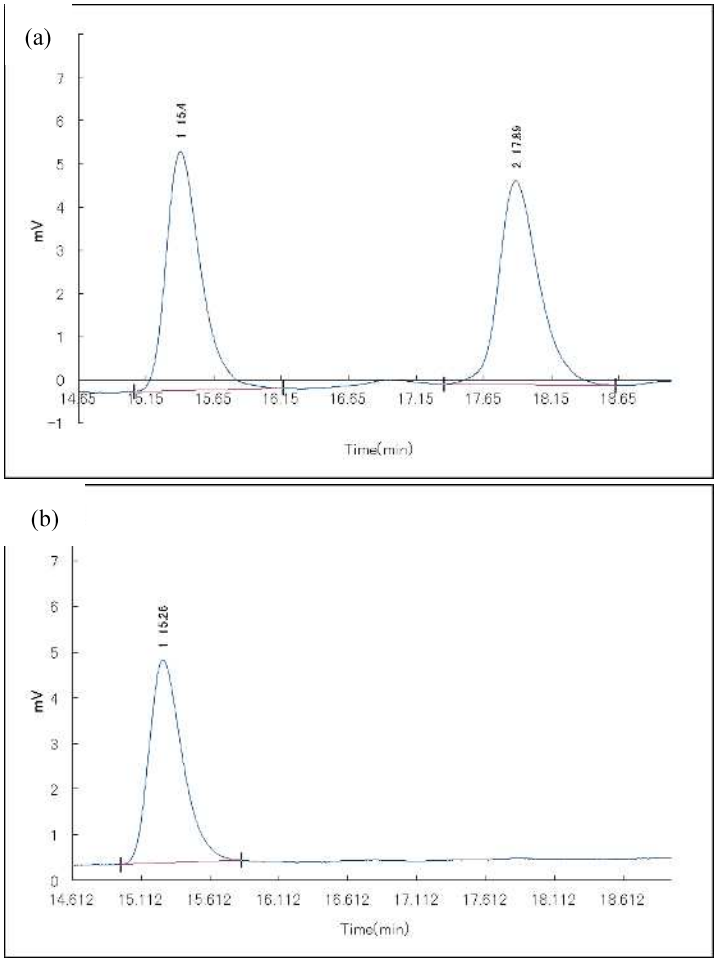


retention time (min)	Area (%)
6.82	98.0463
7.64	1.9537

Supporting Figure 2i Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2i** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2j)



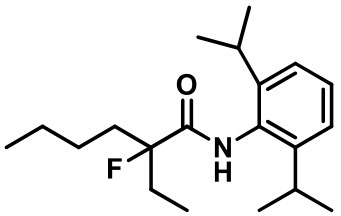


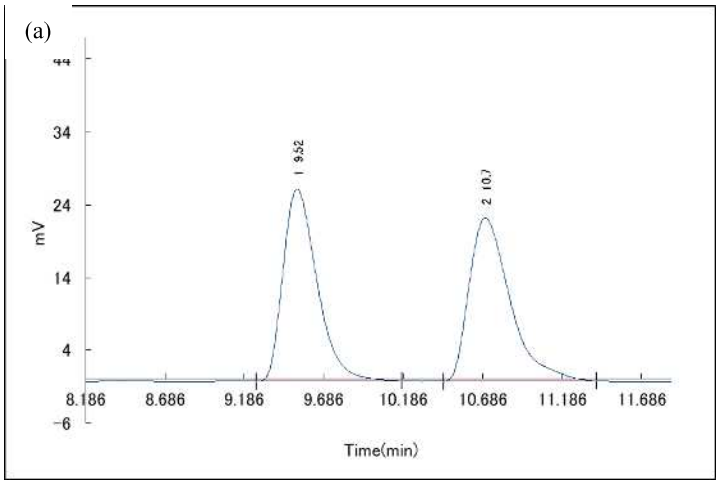
retention time (min)	Area (%)
15.4	50.153
17.89	49.847

retention time (min)	Area (%)
15.26	100

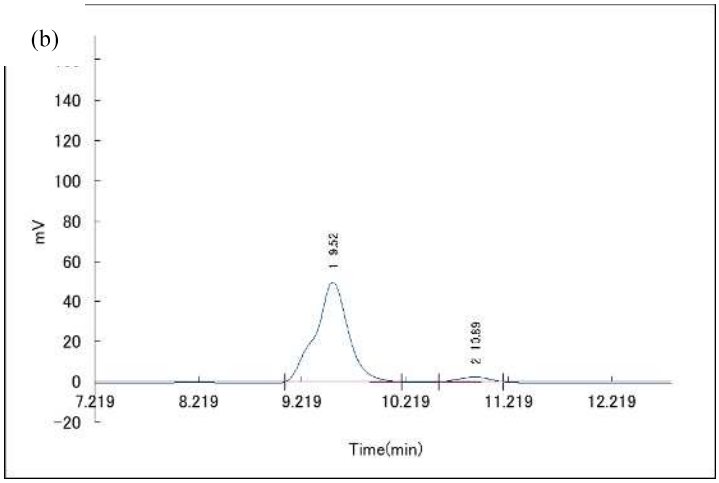
Supporting Figure 2j Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2j** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**2k**)





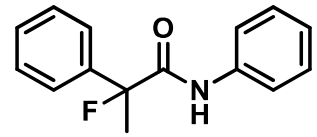
retention time (min)	Area (%)
9.52	49.4215
10.7	50.5785

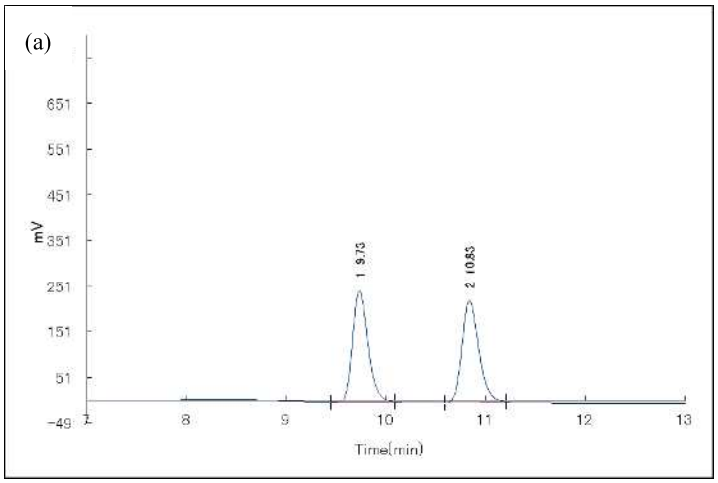


retention time (min)	Area (%)
9.52	95.7526
10.89	4.2474

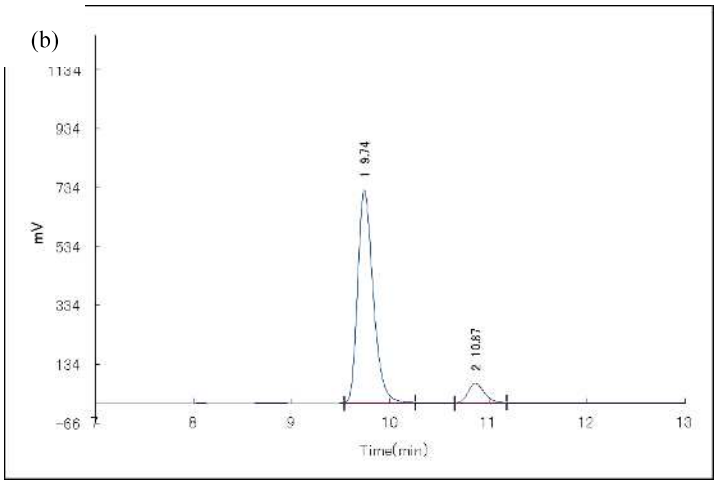
Supporting Figure 2k Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2k** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2l)





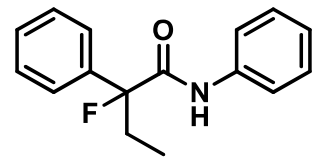
retention time (min)	Area (%)
9.73	49.9858
10.83	50.0142

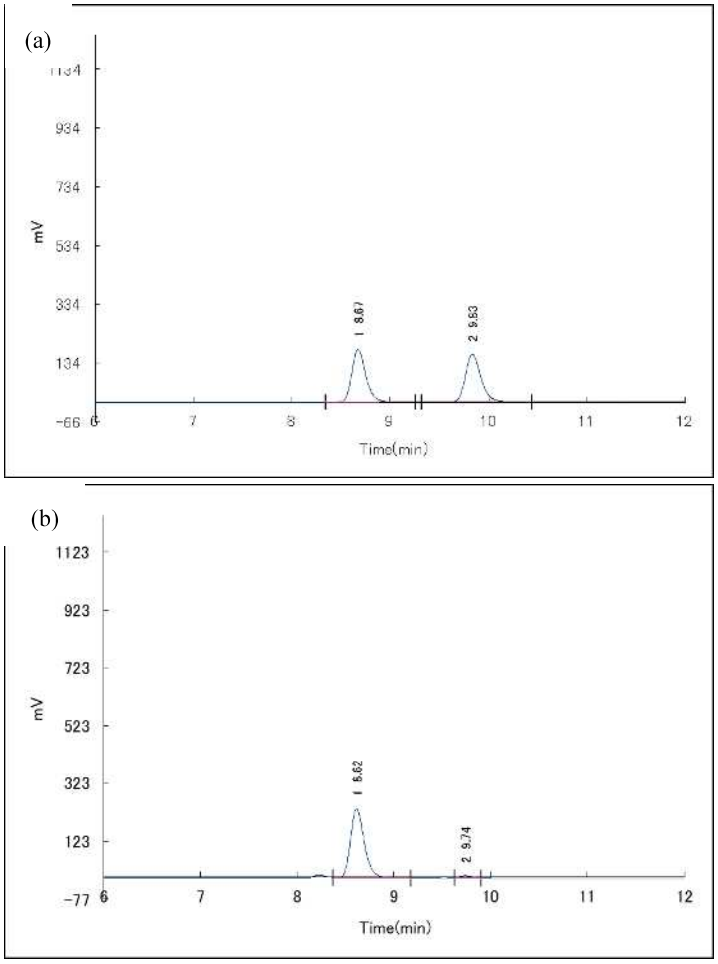


retention time (min)	Area (%)
9.74	91.1601
10.87	8.8399

Supporting Figure 2l Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2l** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 97/3 as an eluent monitored at 254 nm).

(2m)



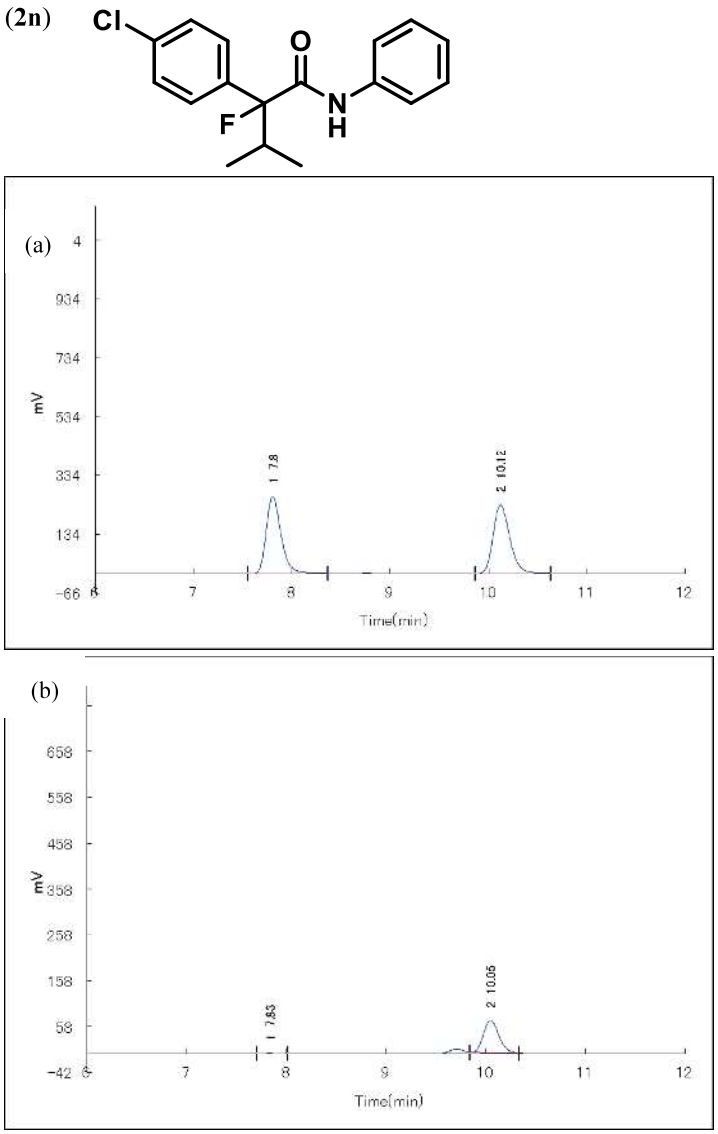


retention time (min)	Area (%)
8.67	50.1149
9.83	49.8851

retention time (min)	Area (%)
8.62	97.593
9.74	2.407

Supporting Figure 2m Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2m** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 97/3 as an eluent monitored at 254 nm).

(2n)

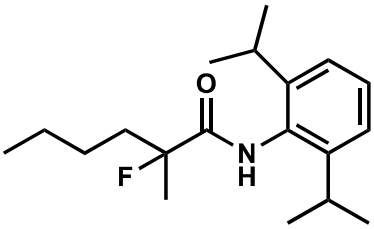


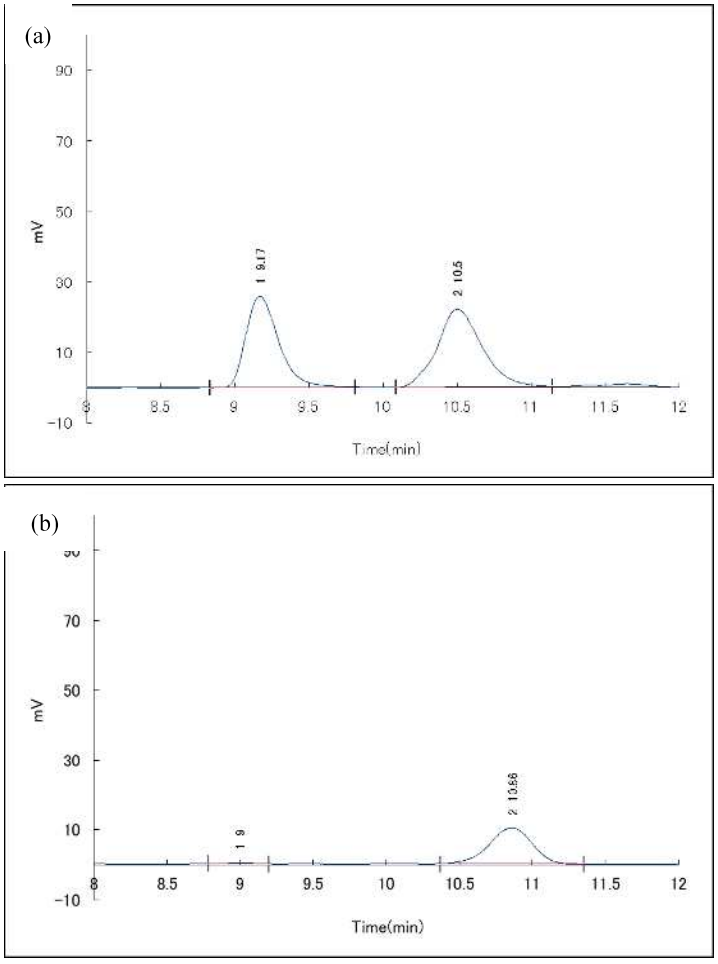
retention time (min)	Area (%)
7.80	49.8644
10.12	50.1356

retention time (min)	Area (%)
7.83	1.0499
10.05	98.9501

Supporting Figure 2n Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2n** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 97/3 as an eluent monitored at 254 nm).

(**2o**)



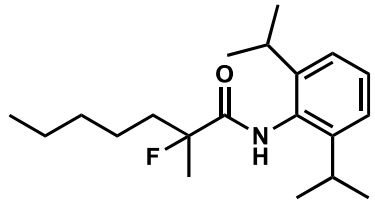


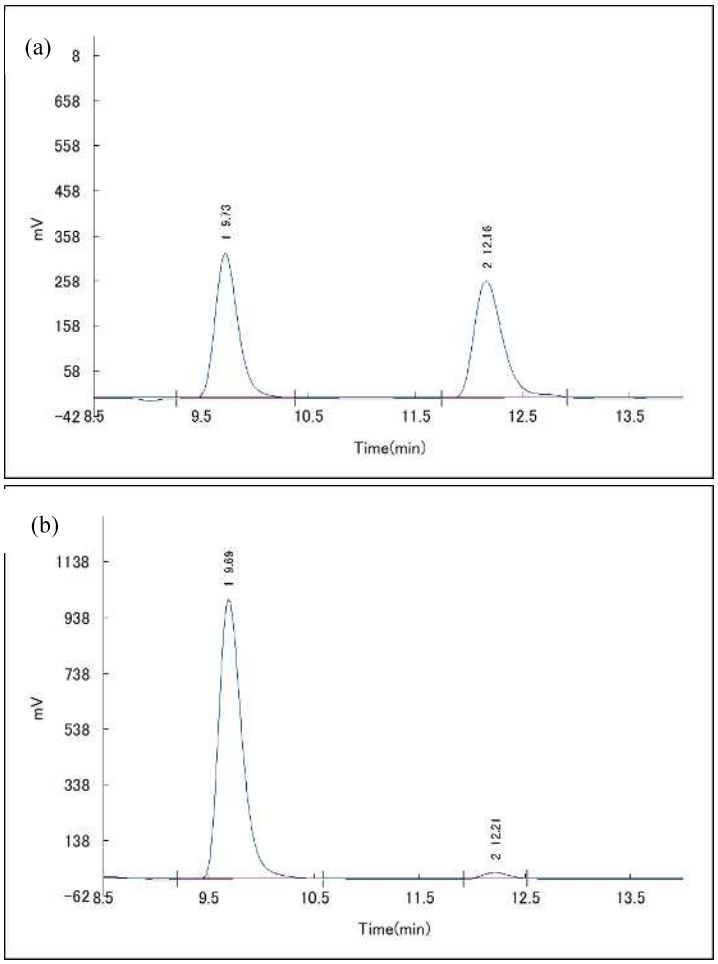
retention time (min)	Area (%)
9.17	46.0722
10.5	53.9278

retention time (min)	Area (%)
9.00	1.4811
10.86	98.5189

Supporting Figure 2o Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2o** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**2p**)



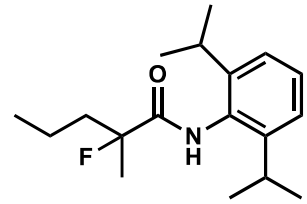


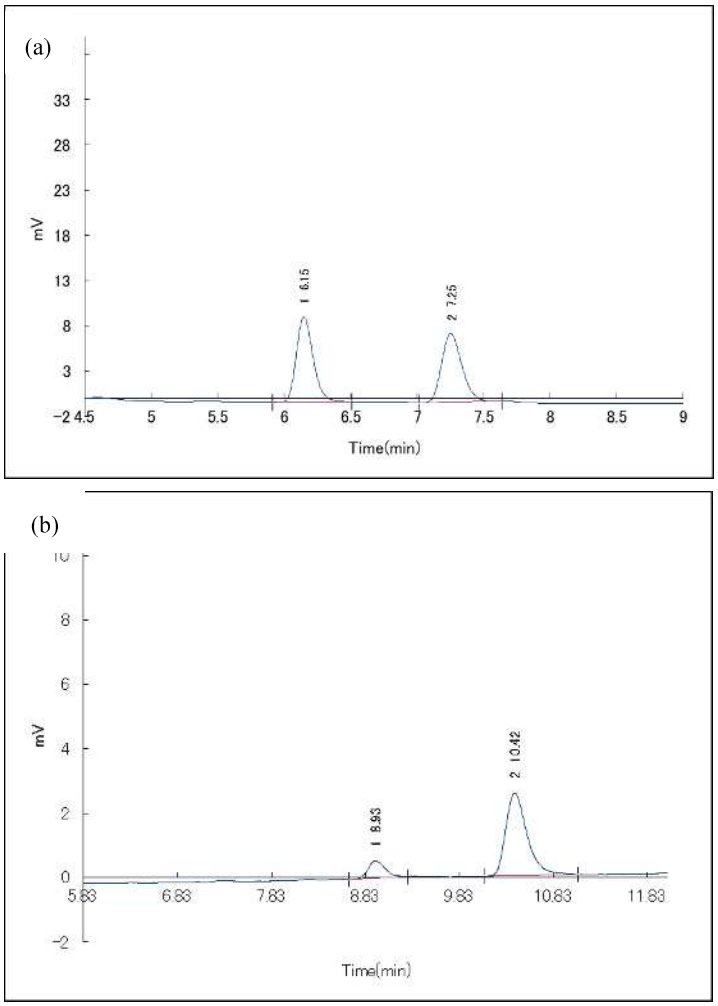
retention time (min)	Area (%)
9.73	49.8811
12.16	50.1189

retention time (min)	Area (%)
9.69	97.7124
12.21	2.2876

Supporting Figure 2p Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2p** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(2q)



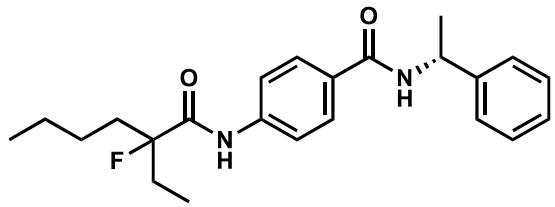


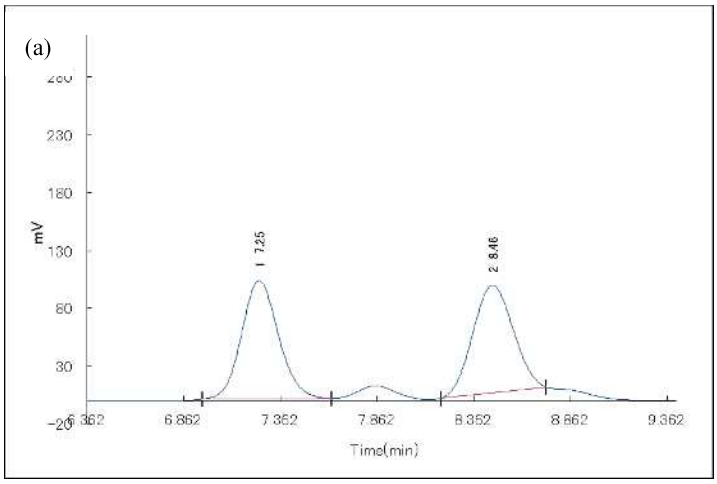
retention time (min)	Area (%)
6.15	50.9946
7.25	49.0054

retention time (min)	Area (%)
8.93	13.7932
10.42	86.2068

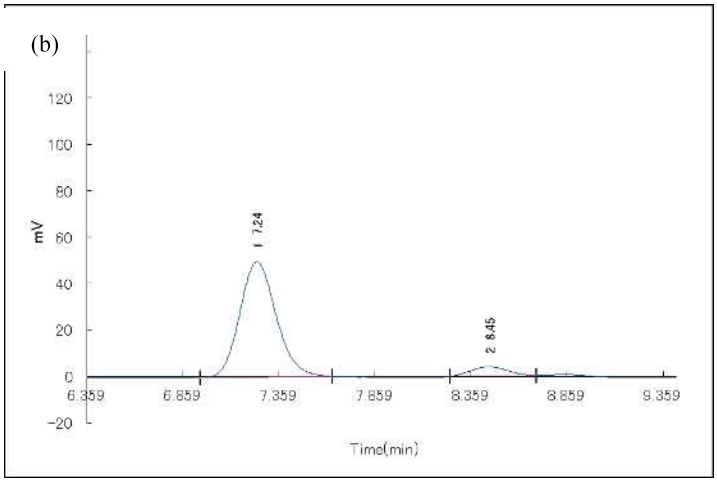
Supporting Figure 2q Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2q** using Daicel CHIRALPAK IC-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 97/3 as an eluent monitored at 254 nm).

(**2r**)





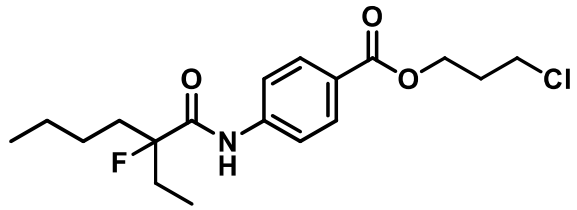
retention time (min)	Area (%)
7.25	50.1599
8.46	49.8401

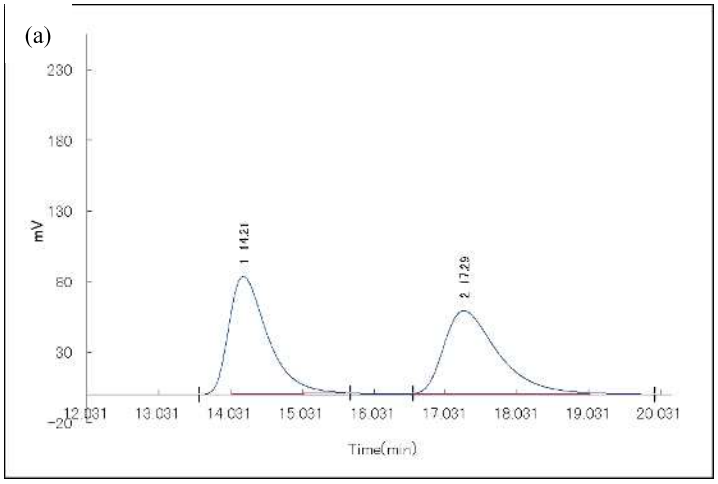


retention time (min)	Area (%)
7.24	92.7242
8.45	7.2758

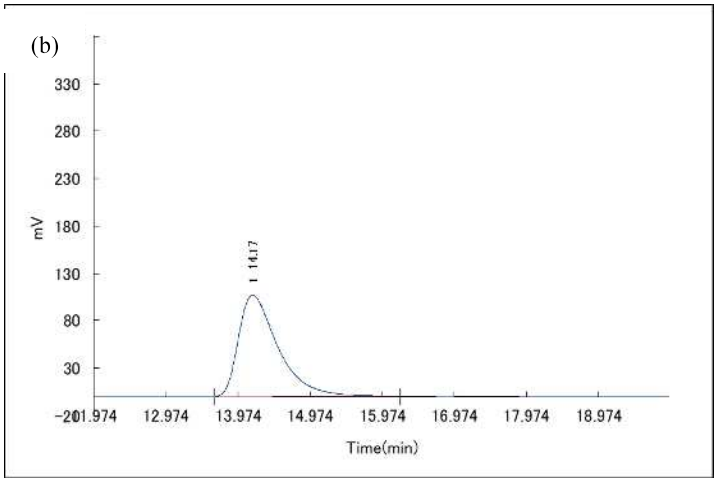
Supporting Figure 2r Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2r** using YMC CHIRAL ART Amylose-SA (flow rate: 1.5 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

(**2s**)





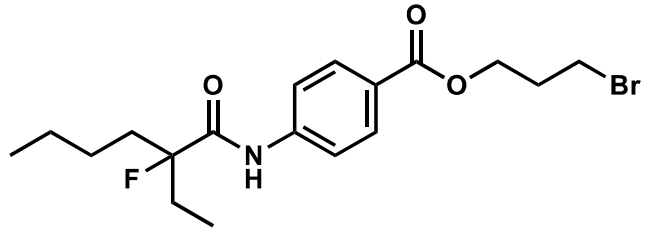
retention time (min)	Area (%)
14.21	50.1024
17.29	49.8976

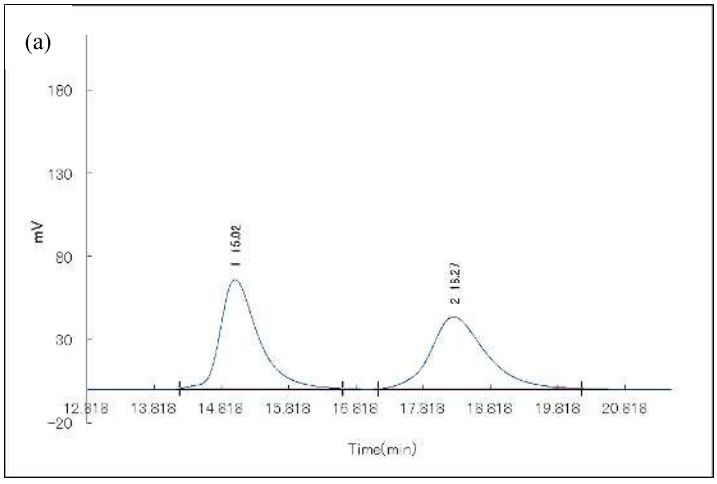


retention time (min)	Area (%)
14.17	100

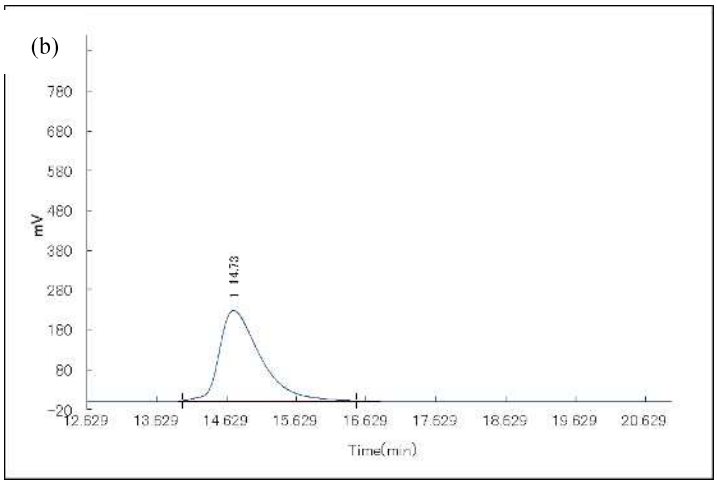
Supporting Figure 2s Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2s** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent monitored at 254 nm).

(**2t**)





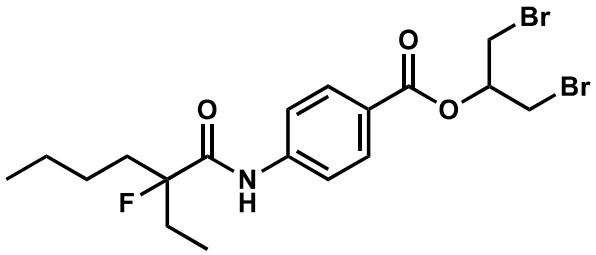
retention time (min)	Area (%)
15.02	50.9688
18.27	49.0312

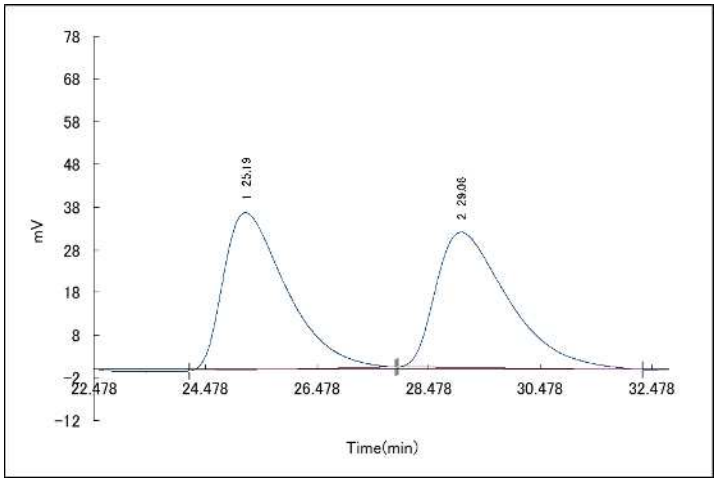


retention time (min)	Area (%)
14.73	100

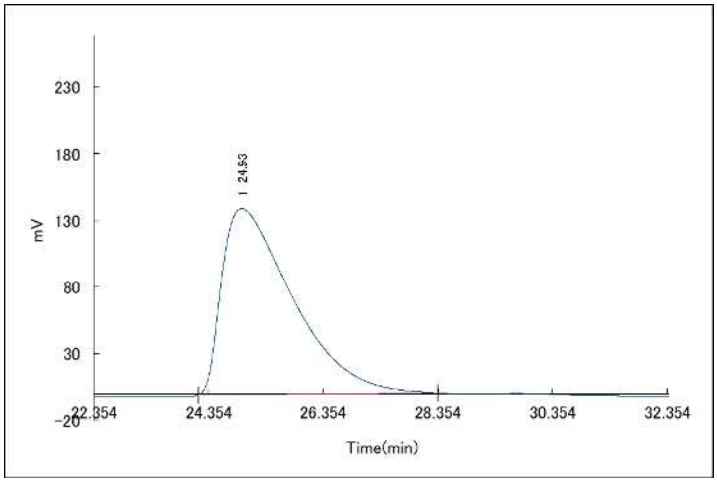
Supporting Figure 2t Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2t** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent monitored at 254 nm).

(2u)





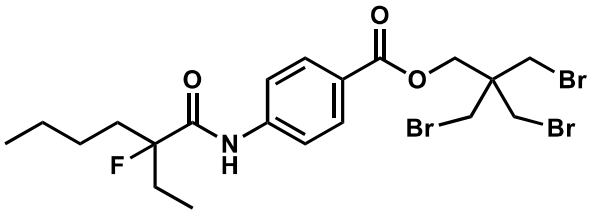
retention time (min)	Area (%)
25.19	50.3569
29.06	49.6431

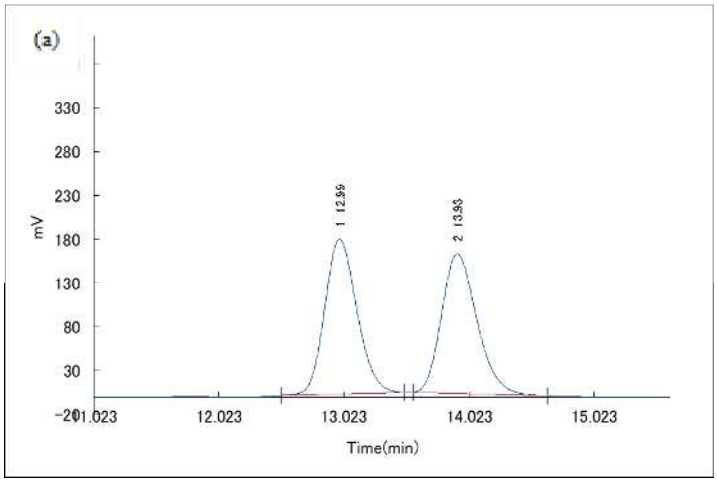


retention time (min)	Area (%)
24.93	100

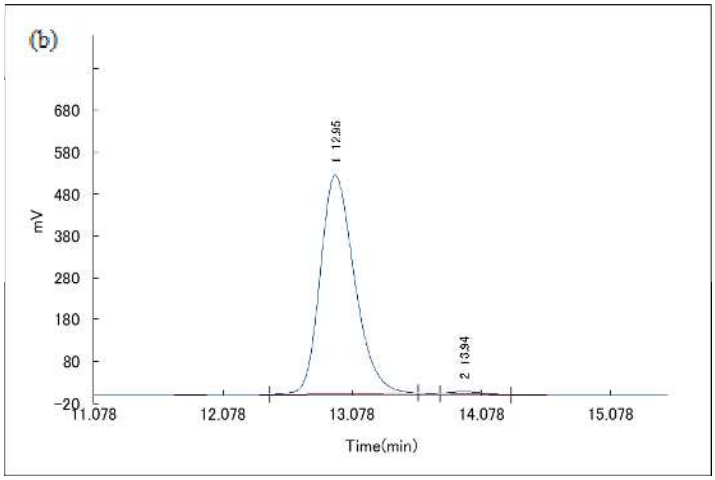
Supporting Figure 2u Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2u** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent monitored at 254 nm).

(**2v**)





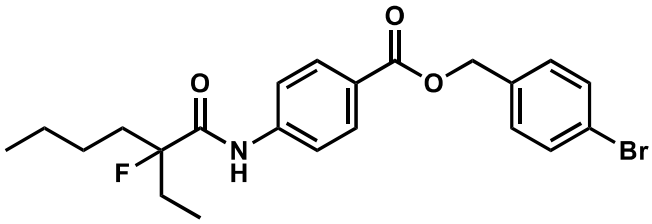
retention time (min)	Area (%)
12.99	50.2088
13.93	49.7912

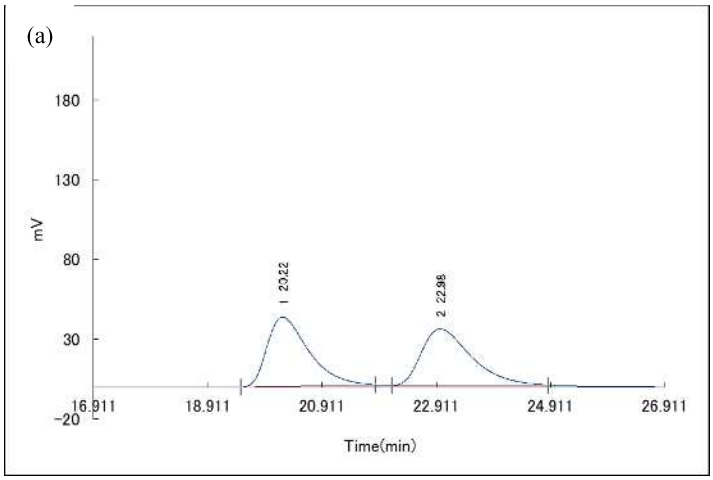


retention time (min)	Area (%)
12.95	99.1963
13.94	0.8037

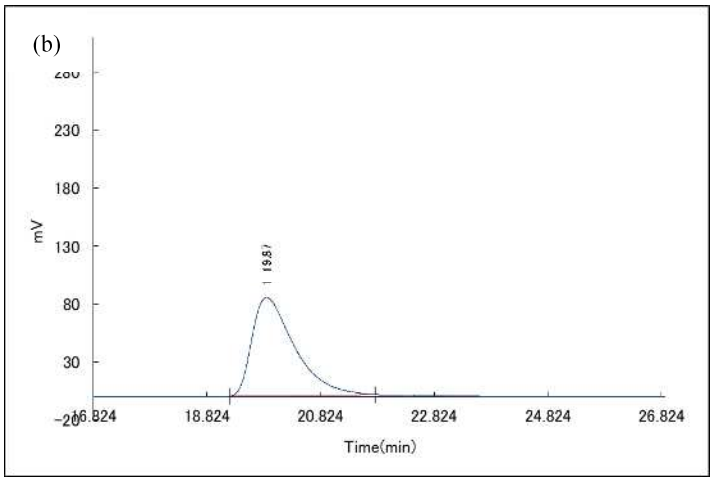
Supporting Figure 2v Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2v** using Daicel CHIRALPAK IC-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 95/5 as an eluent monitored at 254 nm).

(**2w**)





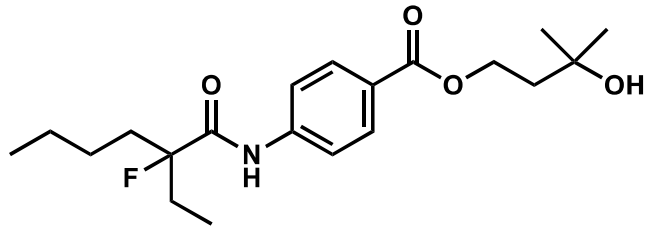
retention time (min)	Area (%)
20.22	50.6791
22.98	49.3209

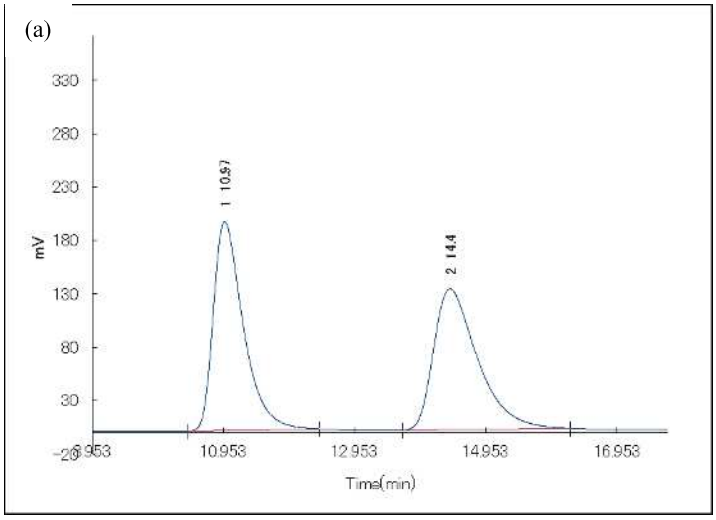


retention time (min)	Area (%)
19.87	100

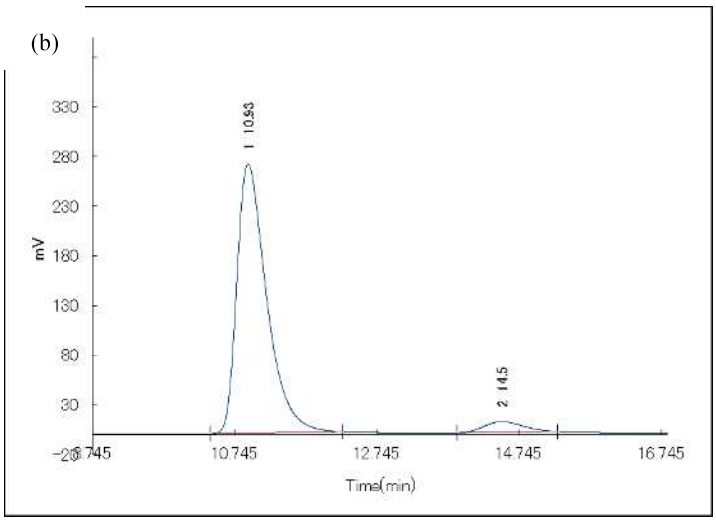
Supporting Figure 2w Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2w** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 as an eluent monitored at 254 nm).

(**2x**)





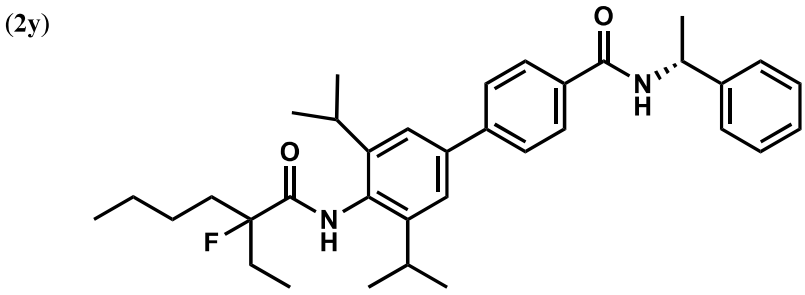
retention time (min)	Area (%)
10.97	50.3495
14.4	49.6505

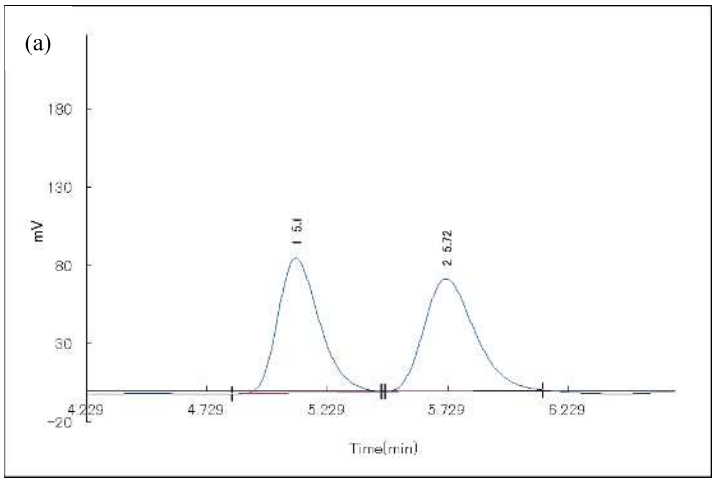


retention time (min)	Area (%)
10.93	95.088
14.5	4.912

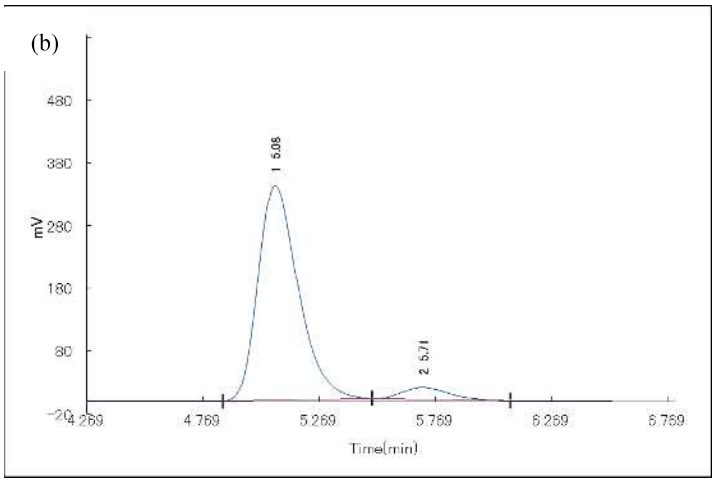
Supporting Figure 2x Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2x** using YMC CHIRAL ART Amylose-SA (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 70/30 as an eluent monitored at 254 nm).

(**2y**)





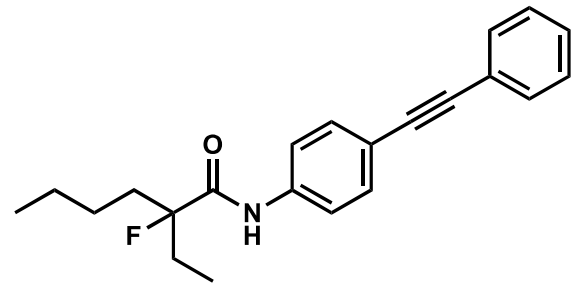
retention time (min)	Area (%)
5.1	49.6805
5.72	50.3195

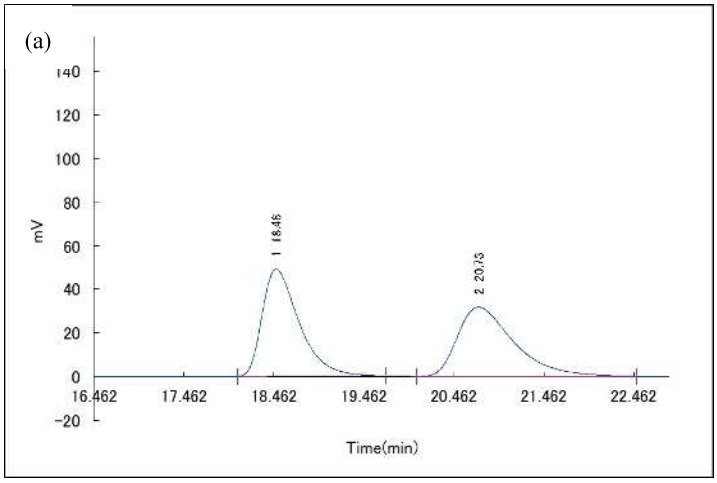


retention time (min)	Area (%)
5.08	94.1187
5.71	5.8813

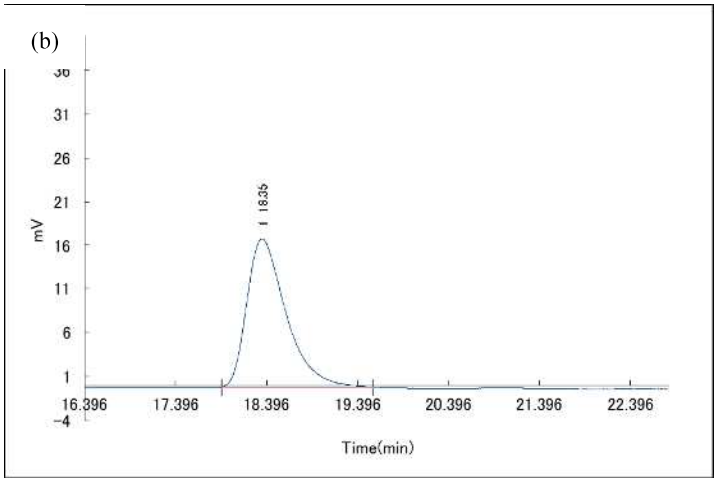
Supporting Figure 2y Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **2y** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 70/30 as an eluent monitored at 254 nm).

(**4**)





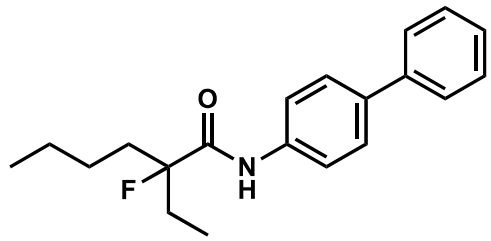
retention time (min)	Area (%)
18.48	50.44
20.73	49.56

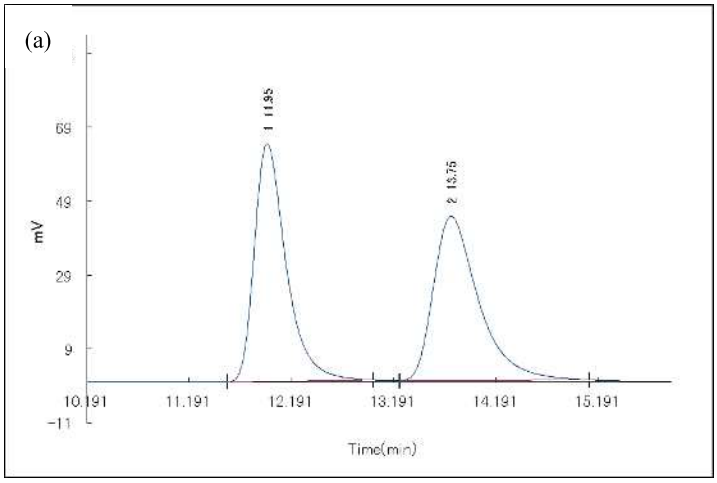


retention time (min)	Area (%)
18.35	100

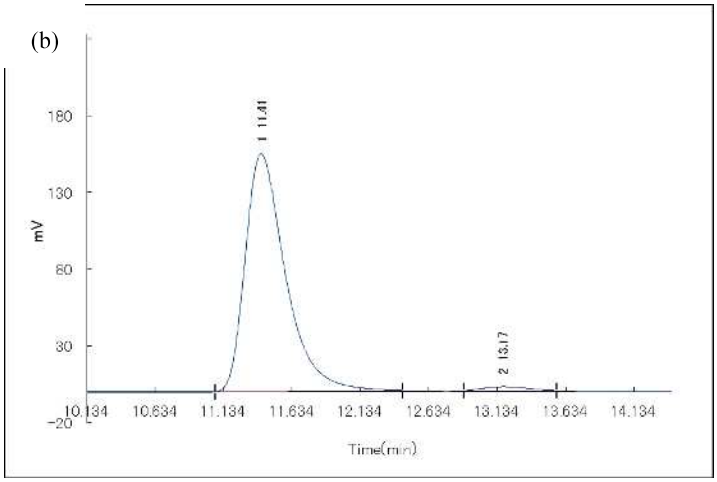
Supporting Figure 4 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **4** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc/ = 99/1 (additive *i*-PrOH 0.5%)) as an eluent monitored at 254 nm).

(**5**)





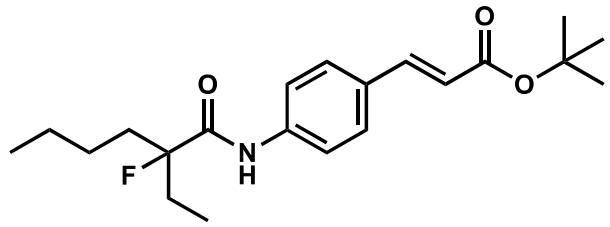
retention time (min)	Area (%)
11.95	50.4639
13.75	49.5361

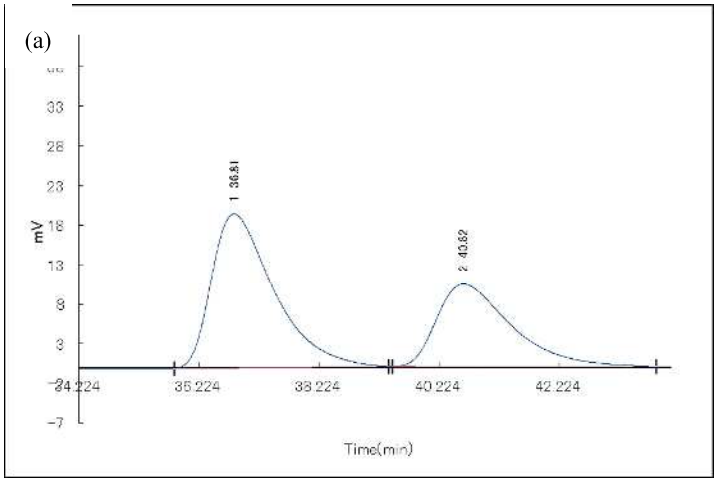


retention time (min)	Area (%)
11.41	98.2133
13.17	1.7867

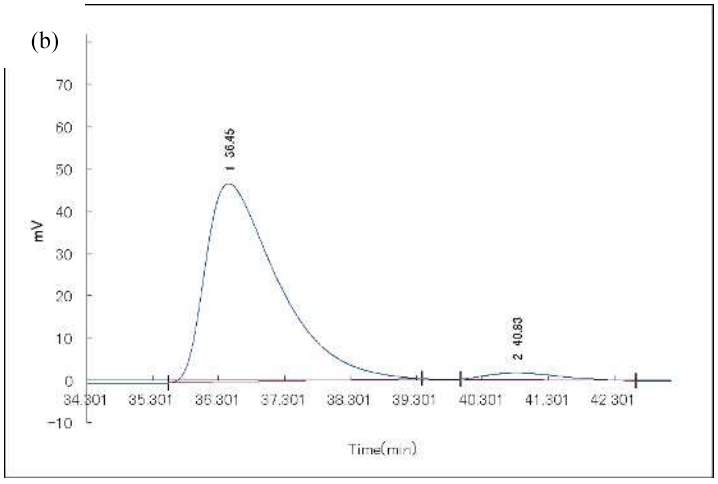
Supporting Figure 5 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **5** using Daicel CHIRALPAK ID-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**6**)





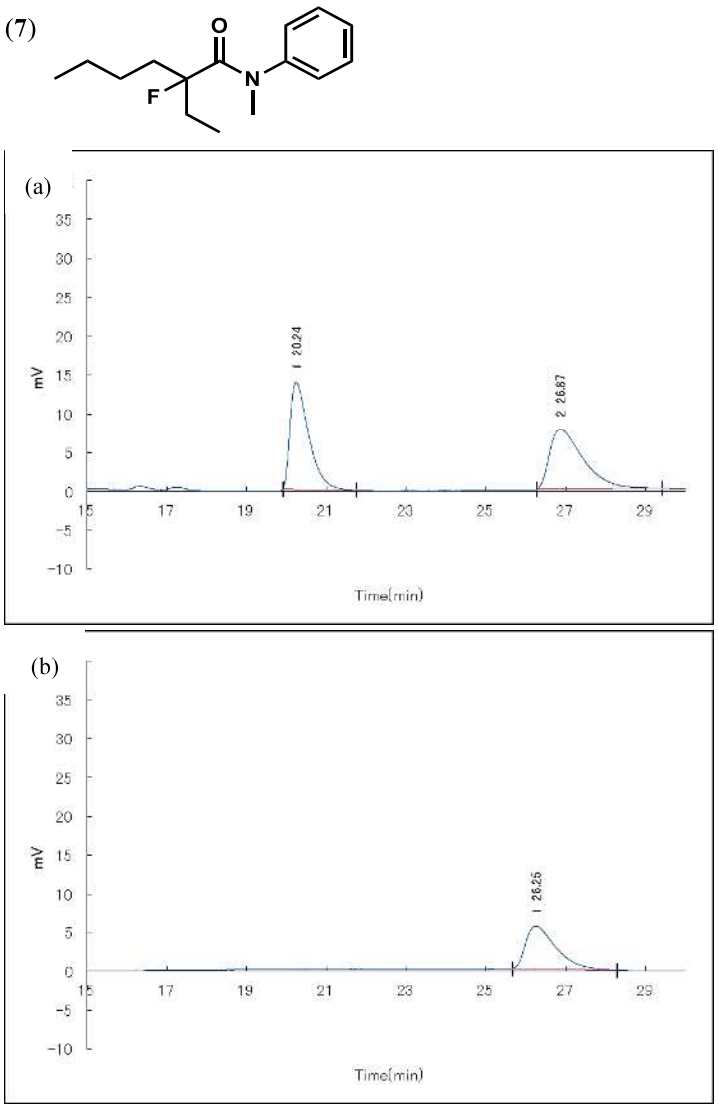
retention time (min)	Area (%)
36.81	61.0798
40.62	38.9202



retention time (min)	Area (%)
36.45	96.8347
40.83	3.1653

Supporting Figure 6 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **6** using Daicel CHIRALPAK ID-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(7)

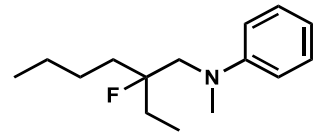


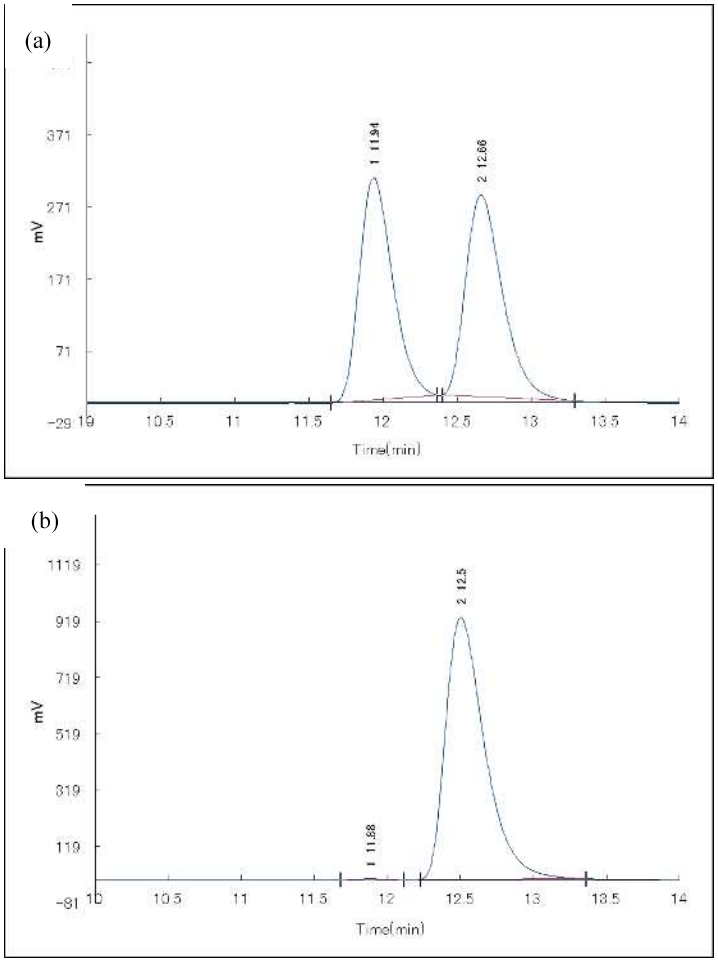
retention time (min)	Area (%)
20.24	50.1734
26.87	49.8266

retention time (min)	Area (%)
26.25	100

Supporting Figure 7 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **7** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**8**)



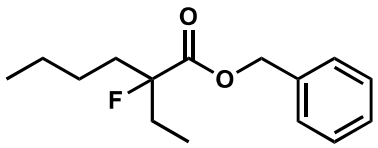


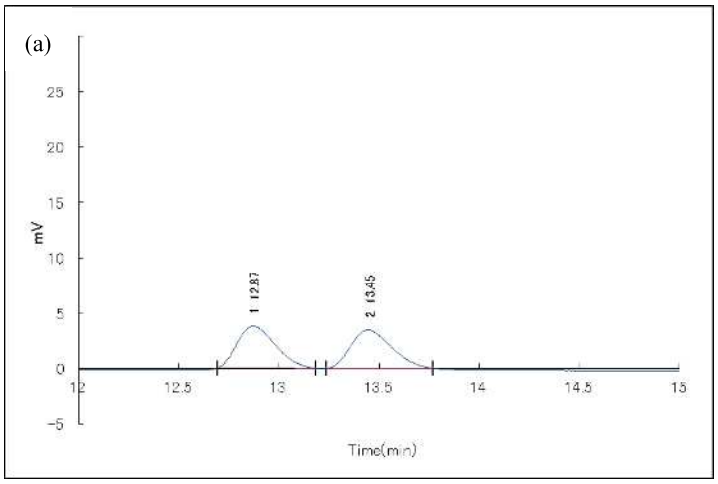
retention time (min)	Area (%)
11.94	49.9883
12.66	50.0117

retention time (min)	Area (%)
11.88	0.276
12.50	99.724

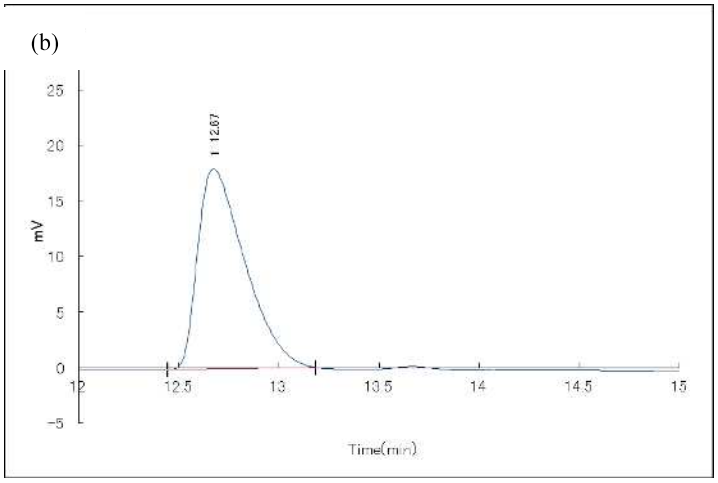
Supporting Figure 8 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **8** using Daicel CHIRALPAK IA-3 (flow rate: 0.5 mL/min, *n*-hexane/DCM = 99/1 as an eluent monitored at 254 nm).

(**9**)





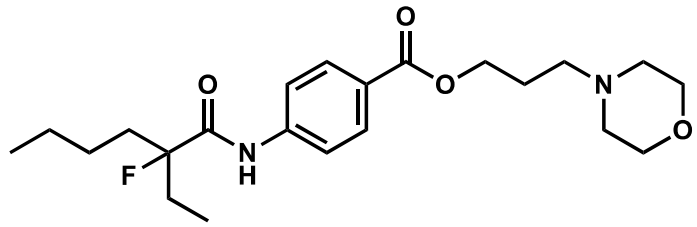
retention time (min)	Area (%)
12.87	50.3021
13.45	49.6979

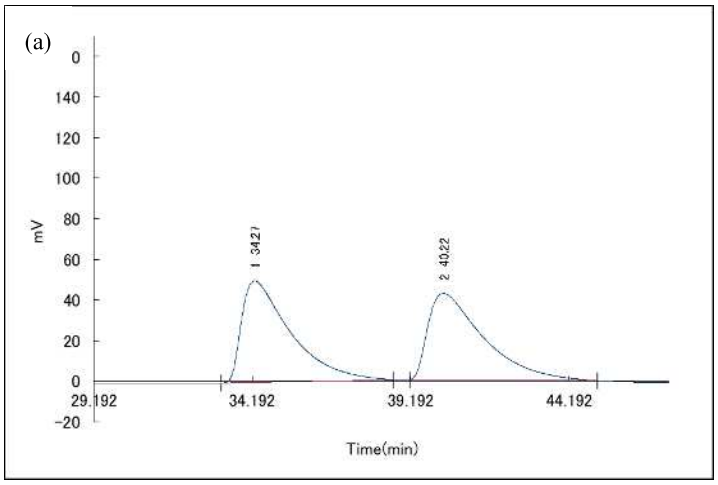


retention time (min)	Area (%)
12.67	100

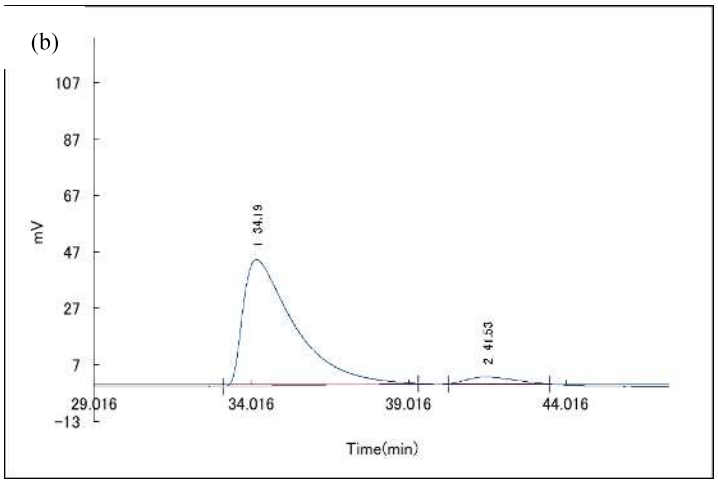
Supporting Figure 9 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **9** using Daicel CHIRALPAK IC-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 as an eluent monitored at 254 nm).

(**10**)





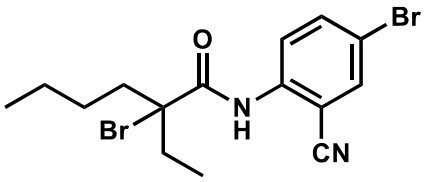
retention time (min)	Area (%)
34.27	50.7924
40.22	49.2076

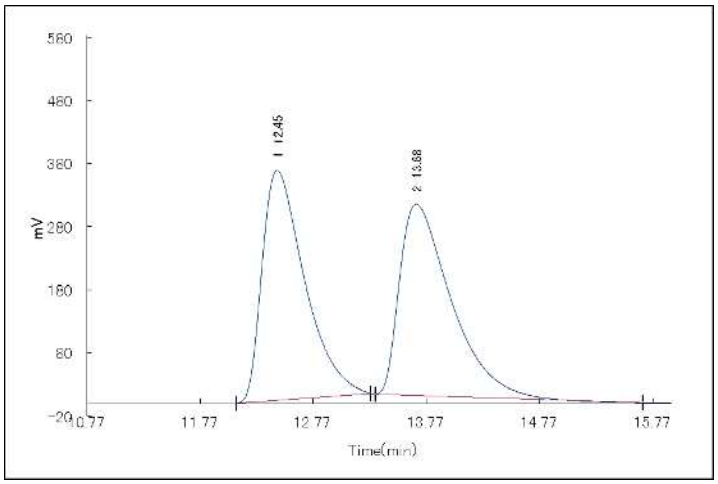


retention time (min)	Area (%)
34.19	95.338
41.53	4.662

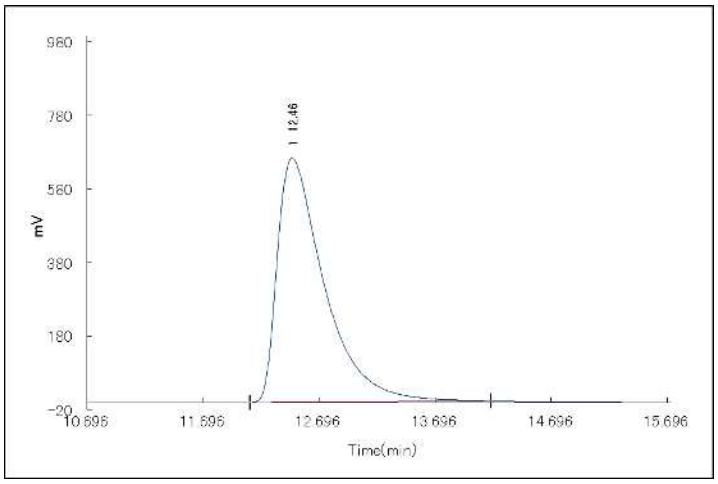
Supporting Figure 10 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **10** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 90/10 (additive *i*-PrOH 1.0%)) as an eluent monitored at 254 nm).

(**1z**)





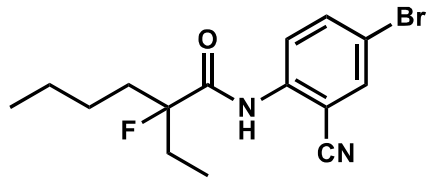
retention time (min)	Area (%)
12.45	49.8646
13.68	50.1354

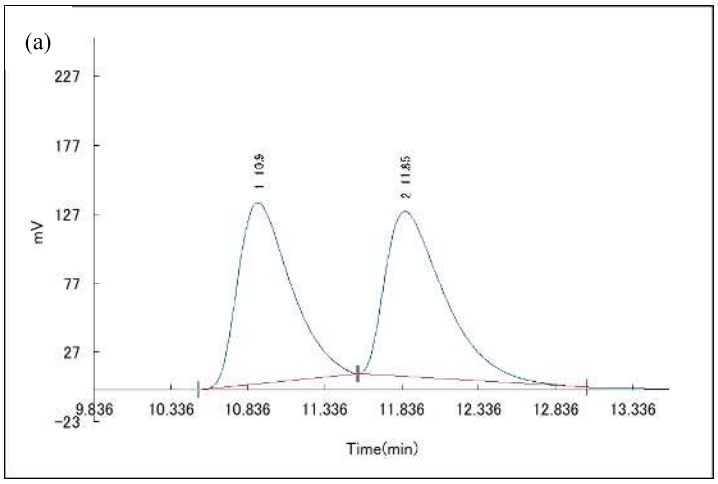


retention time (min)	Area (%)
12.46	100

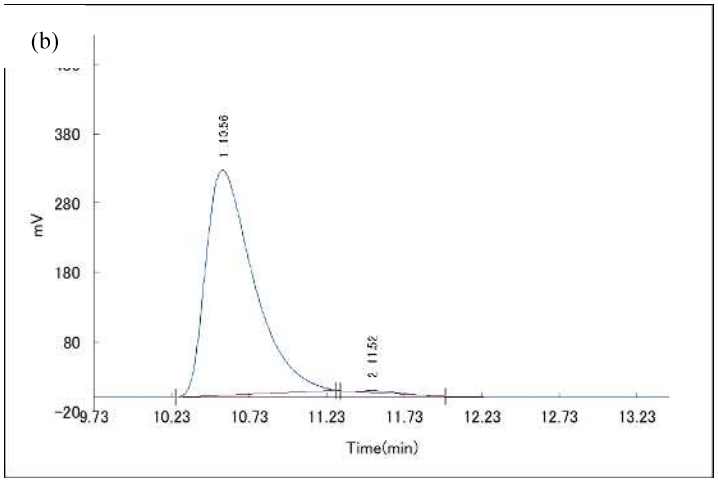
Supporting Figure 1z Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **1z** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 (additive *i*-PrOH 0.5%)) as an eluent monitored at 254 nm).

(**11**)





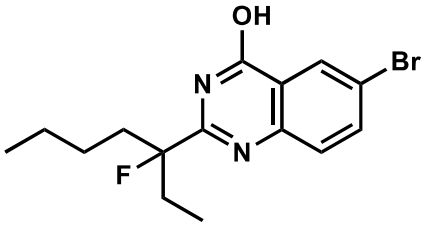
retention time (min)	Area (%)
10.9	49.5731
11.85	50.4269

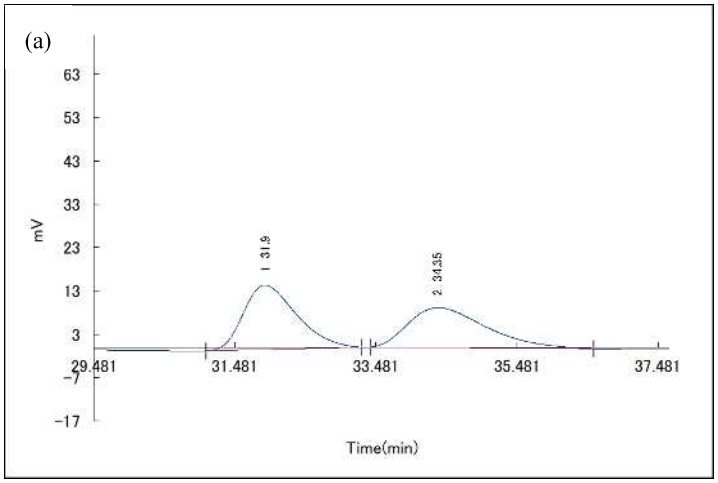


retention time (min)	Area (%)
10.56	99.4867
11.52	0.5133

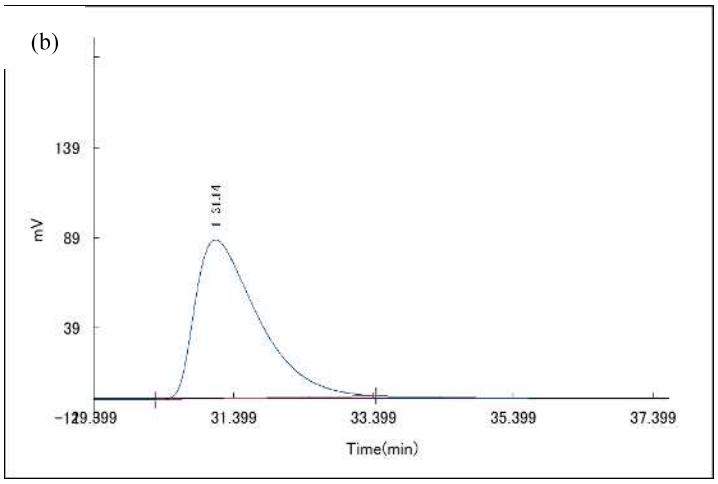
Supporting Figure 11 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **11** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 99/1 as an eluent monitored at 254 nm).

(**12**)





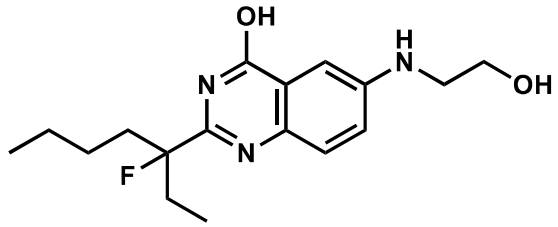
retention time (min)	Area (%)
31.9	52.2895
34.35	47.7105

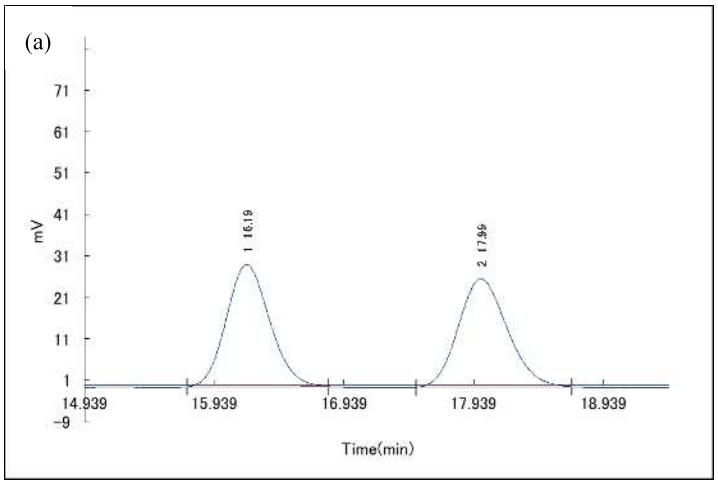


retention time (min)	Area (%)
31.14	100

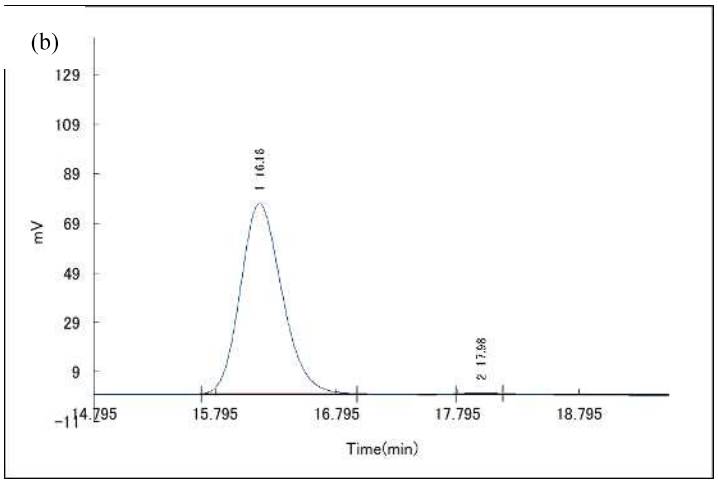
Supporting Figure 12 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **12** using Daicel CHIRALPAK IA-3 (flow rate: 1.0 mL/min, *n*-hexane/EtOAc = 99/1 (additive *i*-PrOH 1.0%)) as an eluent monitored at 254 nm).

(**13**)





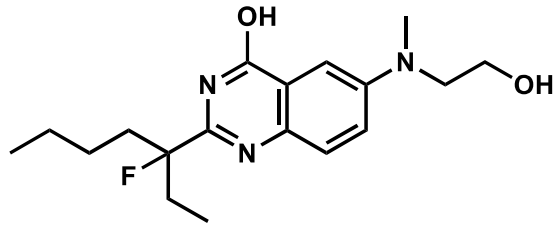
retention time (min)	Area (%)
16.19	50.0841
17.99	49.9159

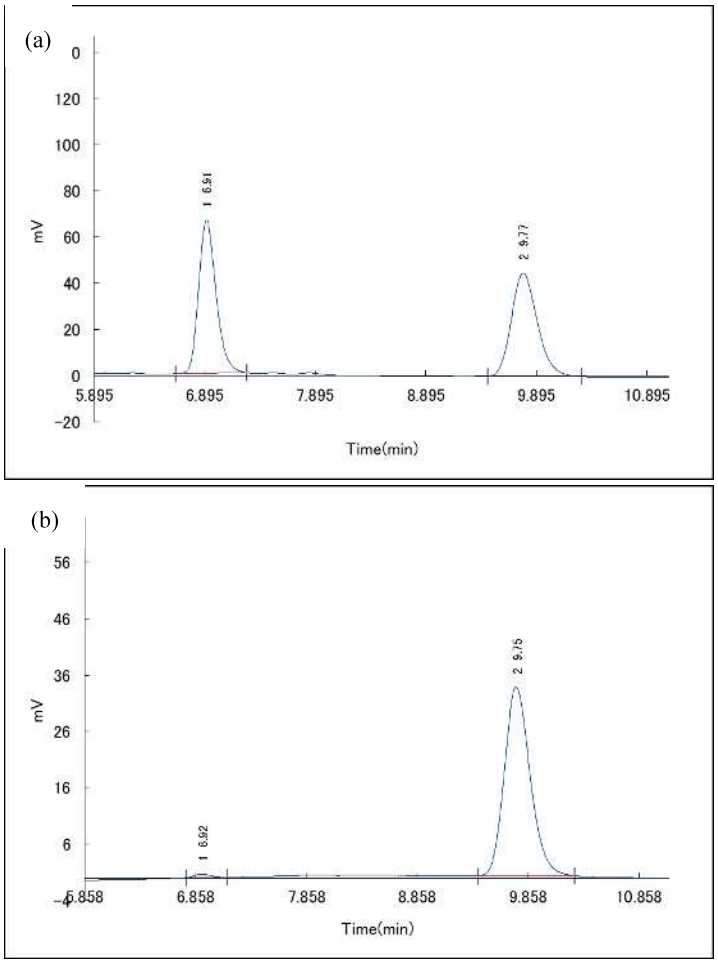


retention time (min)	Area (%)
16.16	99.6808
17.98	0.3192

Supporting Figure 13 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **13** using Daicel CHIRALPAK IA-3 (flow rate: 1.2 mL/min, *n*-hexane/*i*-PrOH = 80/20 as an eluent monitored at 254 nm).

(**14**)



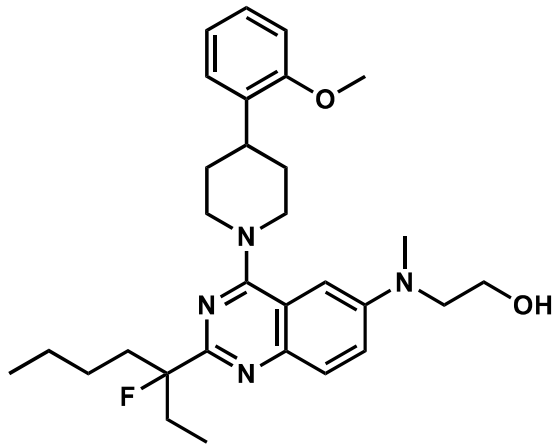


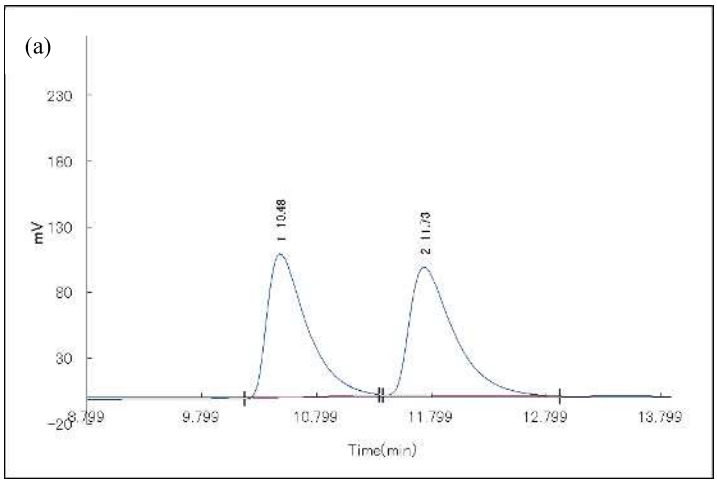
retention time (min)	Area (%)
6.91	49.9683
9.77	50.0317

retention time (min)	Area (%)
6.92	1.0764
9.75	98.9236

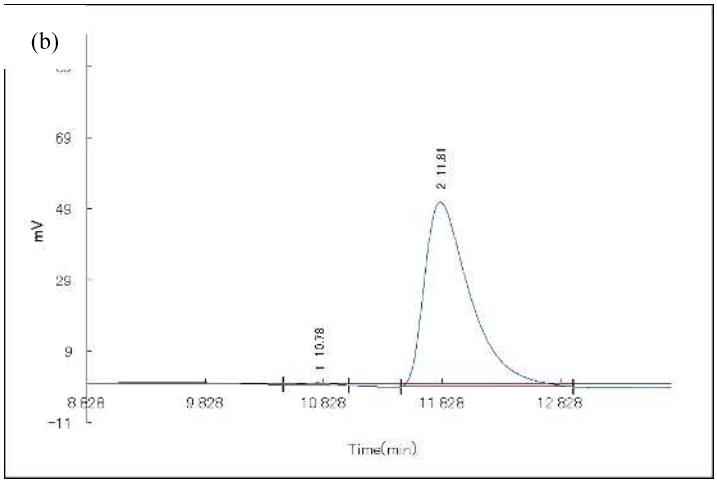
Supporting Figure 14 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **14** using Daicel CHIRALPAK IA-3 (flow rate: 1.2 mL/min, *n*-hexane/*i*-PrOH = 80/20 as an eluent monitored at 254 nm).

(**15**)





retention time (min)	Area (%)
16.19	50.0841
17.99	49.9159



retention time (min)	Area (%)
16.16	99.6808
17.98	0.3192

Supporting Figure 15 Chiral HPLC profiles of (a) racemic and (b) enantiomerically enriched **15** using Daicel CHIRALPAK ID-3 (flow rate: 1.0 mL/min, *n*-hexane/*i*-PrOH = 85/15 as an eluent monitored at 254 nm).

Chapter 6 Oxazaborolidinone: steric coverage effect of Lewis acidic boron center in Suzuki-Miyaura couplings

6.1 Introduction

Organic boronic acid is a very useful reagent used in various synthetic reactions such as Suzuki-Miyaura coupling.[1] In Suzuki-Miyaura coupling using organic boronic acid, transmetalation is a very important factor.

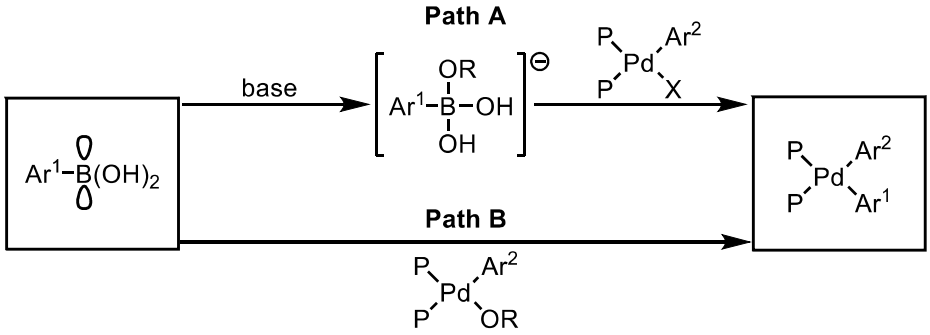
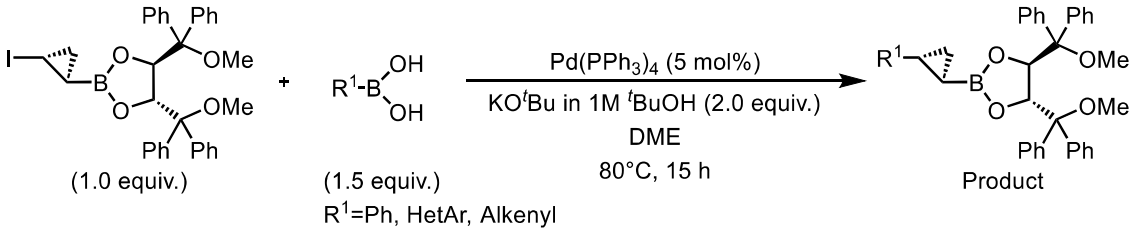


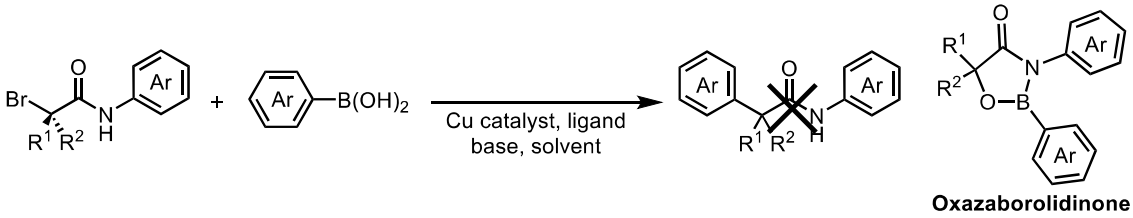
Figure 1 Transmetalation mechanism

Research has been conducted since 1998 to elucidate the mechanism of this transmetalation,[2] and two paths have been proposed (Figure 1). Base acts on the boron p-orbital of boronic acid, ate complex is formed (path A). On the other hand, oxygen in palladium complex coordinates to boron p-orbital (path B). In order for transmetalation to proceed efficiently, it is necessary to control the reactivity of the boron *p*-orbital. In order to regulate the reactivity of the boron *p*-orbital, methods of controlling the reactivity with a protecting group have been taken. Many examples of Suzuki-Miyaura coupling using boron reagent using electronic control methods have been reported.[3,4] However, there are few examples of Suzuki-Miyaura coupling of boron reagents using steric control methods.



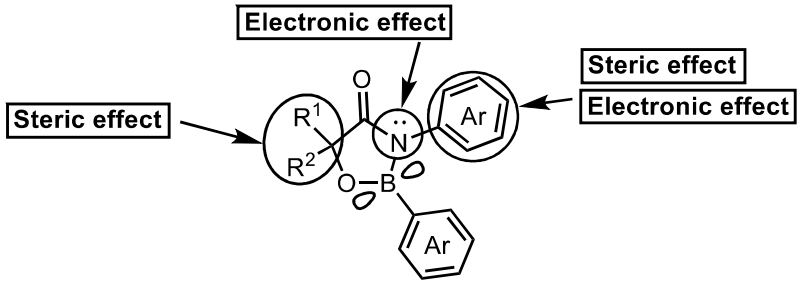
Scheme 1 Pietruszka group's report in 2004

Chemoselective Suzuki-Miyaura coupling by using steric hindered substituent as protector of boron p-orbital was reported by Pietruszka group in 2004 (Scheme 1).[5]



Scheme 2 Formation of oxazaborolidinone in the presence of Cu catalyst

As a result of examining whether the Suzuki-Miyaura coupling between arylboronic acid and α-bromoamide proceeds in the presence of copper catalyst, the desired phenyl adduct could not be obtained at all, and this oxazaborolidinone was obtained (Scheme 2). Since the reaction of oxazazaborolidinone with α-bromoamide did not progress, I thought that this oxazaborolidinone could be used.

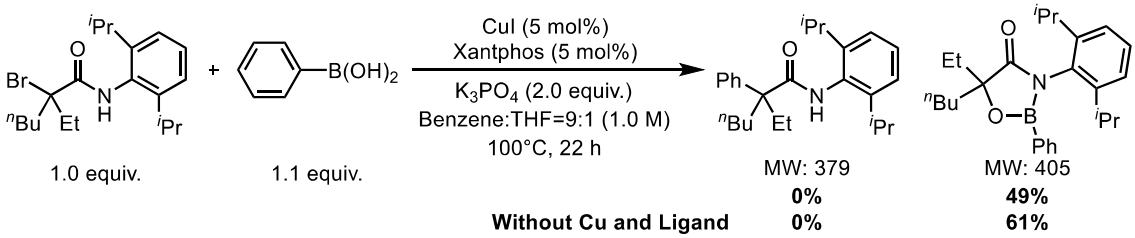


Scheme 3 Oxazaborolidinone

Looking at the structure of oxazaborolidinone, there are many elements that can adjust the reactivity, and I thought that it would be possible to freely control the reactivity and stability of organoboron reagents (Scheme 3). In this study, I developed oxazaborolidinone as a new boron reagent, and investigated the unstable boron reagent Suzuki-Miyaura coupling and iterative coupling to confirm the characteristics of oxazaborolidinone.

6.2 Results and discussion

6.2.1 Preliminary experiments



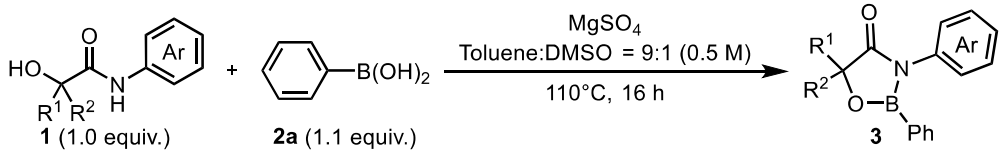
Scheme 4 Preliminary experiments

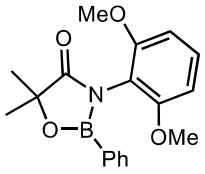
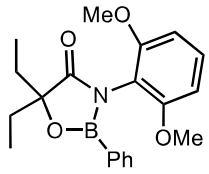
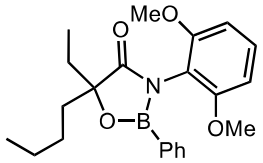
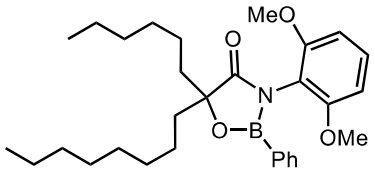
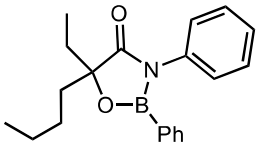
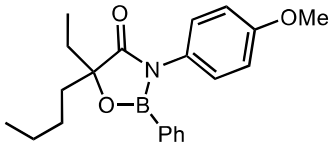
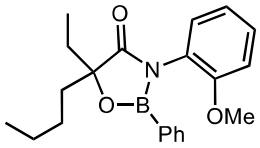
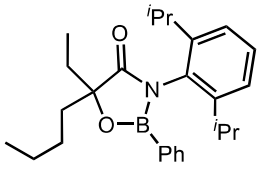
At first, I examined Suzuki-Miyaura coupling between α-bromoamide and phenyl boronic acid in the presence of Cu catalyst. As a result, phenyl added product was not obtained at all, but oxazaborolidinone was obtained in 49% yield. Then, when I conducted the reaction in the absence of

Cu catalyst, the yield of oxazaborolidinone improved. GC-MS analysis and TLC information showed that oxazaborolidinone is a high-temperature-stable compound and can be isolated without tailing against silica gel chromatography.

6.2.2 Synthesis of various oxazaborolidinones

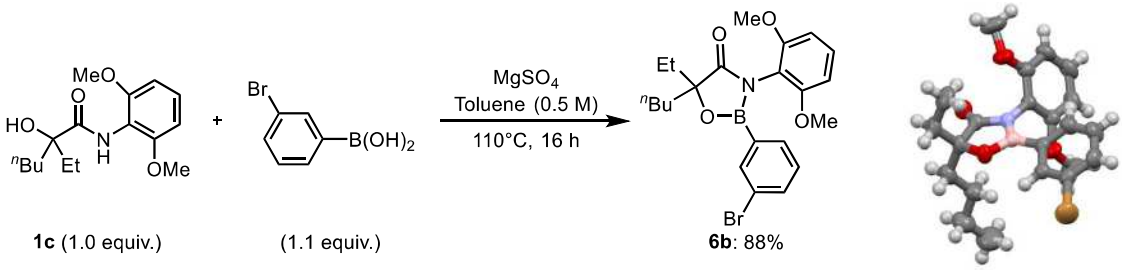
Table 1 Synthesis of various oxazaborolidinones



Yield of oxazaborolidinone			
			
3a	**3b**	**3c**	**3d**
--	89%[a]	95%[a]	70%
			
3e	**3f**	**3g**	**3h**
34%	53%	64%	81%

[a]Without DMSO.

In previous Burke's report, MIDA (N-methyliminodiacetic acid) protected boron reagents were synthesized by Dean-Sterk method.[3c] Inspired by this Burke's reported method, I also tried to synthesize oxazaborolidinone **3** by dehydration condensation between α-hydroxyamide **1** and aryl boronic acid **2a** (Table 1). First, the steric effect of the alkyl chain at the carbonyl α-position was also investigated. As a result, **3a** with small steric hindrance could not be synthesized with low stability, but **3b-3d** could be synthesized with high yields. Oxazaborolidinone **3c** was obtained in 95% isolated yield. Next, oxazaborolidinone having phenyl group (**3e**), *p*-methoxyphenyl group (**3f**), and *o*-methoxyphenyl group (**3g**) were obtained with moderate yield due to low stability of oxazaborolidinone. Finally, oxazaborolidinone having diisopropyl group with very large steric hindrance was obtained in high yield.



Scheme 5 Synthesis of oxazaborolidinone **6b** and single-crystal X-ray structural analysis

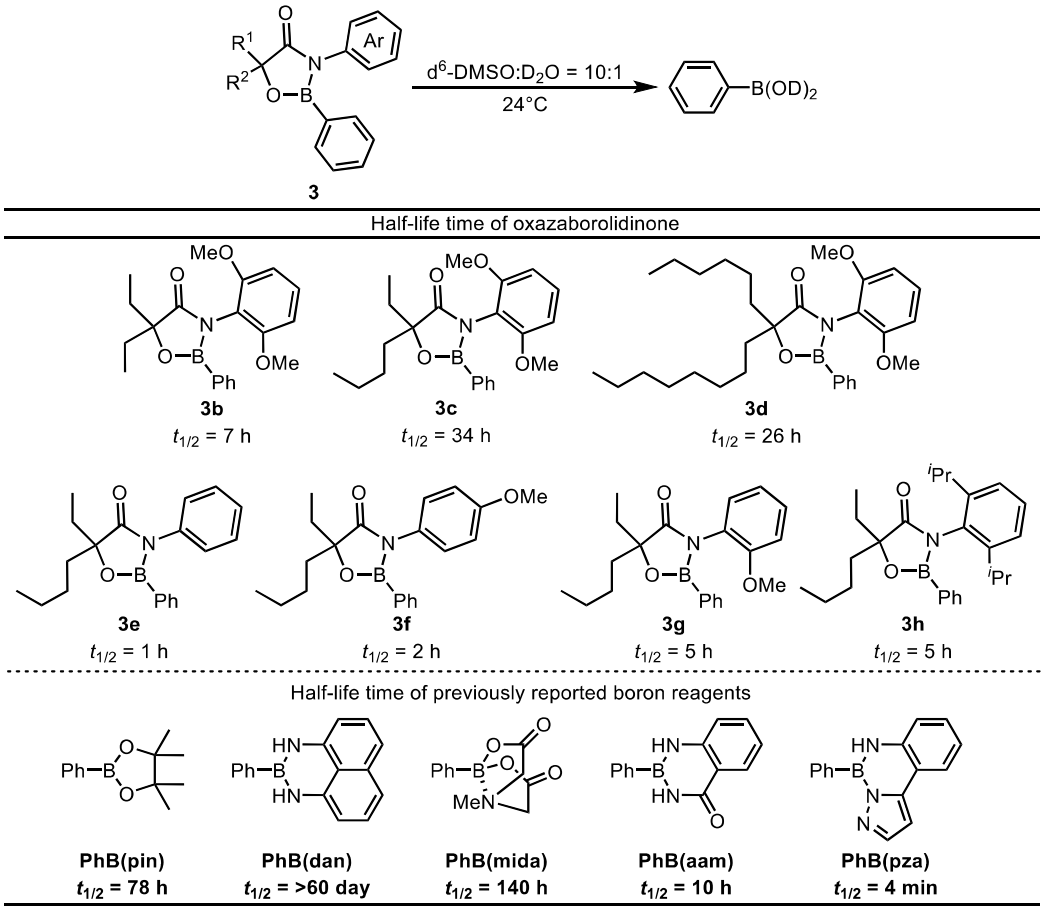
By dehydration condensation of α-hydroxyamide **1c** and m-bromophenyl boronic acid in toluene at 110°C for 16 h, oxazaborolidinone **6b** was obtained in 88% yield. Then, Oxazaborolidinone **6b** was used for single crystal X-ray structural analysis. Looking at this structure, it was suggested that the boron *p*-orbital may be covered with an alkyl chain at the carbonyl α-position and dimethoxy group of amide aryl group.

6.2.3 Stability Comparison of oxazaborolidinone

In order to efficiently proceed with the Suzuki-Miyaura coupling of heteroaryl-,[6] vinyl-,[7] and alkyl-boron reagents,[8] it is important to slowly release boronic acid by hydrolysis of stabilized protected boron reagents. In addition, in iterative coupling of a boron reagents having a halogen substituent, it is important to be able to control the activation or deactivation of the boron p-orbital. Therefore, I conducted two experiments to confirm the stability of oxazaborolidinone. The first experiment was to investigate the stability of protected boron reagents in a half-life measurement experiment to measure the rate of boronic acid release by measuring ^{1}H NMR at room temperature in DMSO aqueous solution.[9] The second experiment was to investigate the stability of the protecting group in the reactivity comparison with boronic acid in the Buchwald Suzuki-Miyaura coupling under anhydrous conditions.[10]

6.2.3.1 Half-life time measurements of masked boron reagents

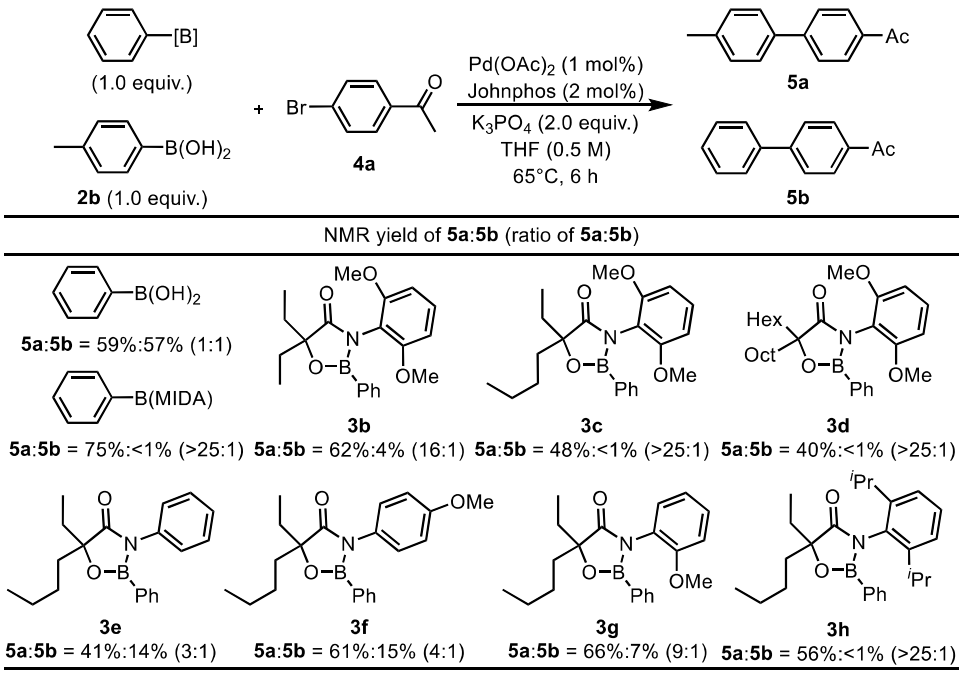
Table 2 Half-life time of masked boron reagents



The previously reported boron reagents PhB(aam), PhB(pin), and PhB(mida) have half-lives of 10, 78, and 140 hours, respectively. Also, PhB(dan) is quite stable against water, while PhB(pza) is hardly stable against water.[9] I conducted the measurement of half-life time of oxazaborolidinone (Table 2). **3a**, which has a small steric hindrance of the alkyl chain at carbonyl α-position, has a half-life of 7 h, and as the steric hindrance of the alkyl chain increases, the half-life also increases, with **3c** being 34 h and the longest half-life time among oxazaborolidinones. Next, oxazaborolidinones having phenyl- (**3e**) and *p*-methoxyphenyl-substituent (**3f**) have a very short half-life time. Also, oxazaborolidinone **3g** with *o*-methoxyphenyl substituent has a half-life time of 5 h. Contrary to my prediction, oxazaborolidinone, which has a very bulky diisopropylphenyl group, also has a short half-life of 5 h.

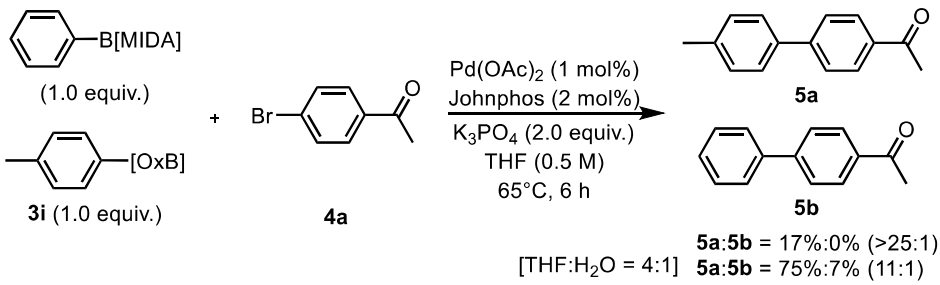
6.2.3.2 The reactivity comparison with boronic acid in the Buchwald S-M coupling under anhydrous conditions

Table 3 The reactivity comparison in the Buchwald S-M coupling under anhydrous conditions



The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Stoichiometric quantities of phenyl-substituted oxazaborolidinones (**3**) and *p*-tolylboronic acid (**2b**) were reacted with p-bromoacetophenone (**4a**) under Buchwald's anhydrous SMC conditions (Table 3).[10] Under these conditions, the reactivity of aryl boronic acids (**2a** and **2b**) was the same. Burke's MIDA boronate gave 75% of **5a** and <1% of **5b**, which indicates a good blocking effect of MIDA backbone. I next tested a series of my oxazaborolidinones (**3b-3h**). Diethyl substituted **3b** yielded 62% of **5a** and 4% of **5b**, but more hindered **3c** and **3d** exhibited excellent blocking effects (**5a**:**5b** = 48%:<1%, 40%:<1%, respectively). Structures of *N*-substituent are also important. Sterically less hindered **3e** and **3f** gave low ratios, and slightly hindered *N*-ortho-anisyl substituted **3g** was 66% of **5a** and 7% of **5b**. These reactivities from **3e-3g** could be attributed to the generation of small amounts of water from **2b**. The resulting water reacted with oxazaborolidinone to release a reactive aryl boronic acid, which indicated that covering the boron atom in oxazaborolidinone (**3e-3g**) was not enough. Although half-life of **3h** ($t_{1/2}$=5 h) was shorter than **3c** ($t_{1/2}$=34 h), blocking effect in SMC was good. As the results, sterically bulky *N*-3,5-dimethoxyphenyl substituted **3c** was significantly advantageous due to long half-life, good synthetic yield (Table 2), and almost perfect inhibition of SMC (Table 3).

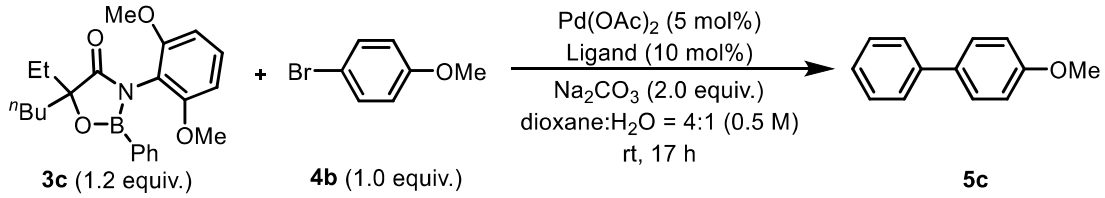


Scheme 6 Competition of PhB(mida) vs. oxazaborolidinone **3i**

Subsequently, the reactivity of mida-protected boron reagent and oxazabororidinone **3i** was compared (Scheme 6). The reactivity of PhB(mida) and oxazaborolidinone **3i** was compared with 4-acetylbromobenzene **4a** under Buchwald's anhydrous SMC conditions. As a result, only the product **5a** with which oxazasabolidinone **3i** reacted was produced. Then, Suzuki-Miyaura coupling under hydrous conditions. This result showed that **5a**:**5b** was produced at a yield of 75%:7%, that oxazabororidinone was easier to deprotect than mida, and that it was highly reactive with Suzuki-Miyaura coupling.

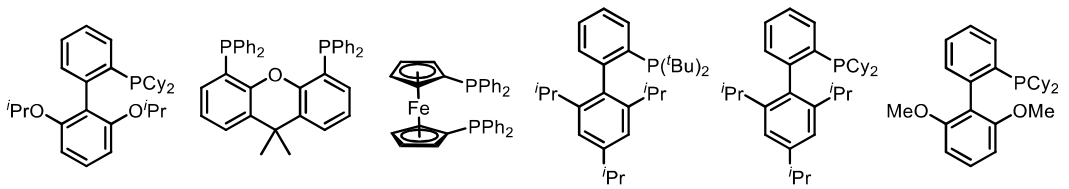
6.2.4 Optimization of reaction conditions for C-B cross-coupling

Table 4 Screening of ligands.



3c (1.2 equiv.) **4b** (1.0 equiv.) **5c**

Entry	Ligand	NMR yield of **5c**
1[a]	L1	>99% (91%)
2	L1	56% (50%)
3	L2	0%
4	L3	6%
5	PPh_3	trace
6	PCy_3	32%
7	L4	44%
8	L5	47%
9	L6	50%



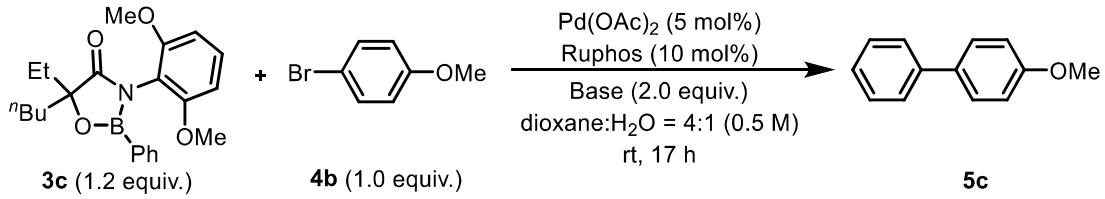
L1: Ruphos **L2**: Xantphos **L3**: DPPF **L4** **L5**: Xphos **L6**: Sphos

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated product yields are shown in parentheses. [a]80°C.

To obtain information about effects of ligand in the reaction of Suzuki-Miyaura cross-coupling between oxazaborolidinone **3c** and 4-bromoanisole **4b** (Table 4). First, when Ruphos (**L1**) as a ligand was used and the reaction occurred at 80°C, coupling product **5c** was obtained quantitatively (entry 1). When the reaction at room temperature was conducted, the product was produced in 56% NMR yield (entry 2). Next, I investigated about the effects of various phosphine ligand. However, the product

yield was not improved when using bidentate (entry 3,4) or monodentate (entry 5-9) phosphine ligands. As a result of ligand examination, Ruphos was determined as the optimal ligand.

Table 5 Screening of bases and time.



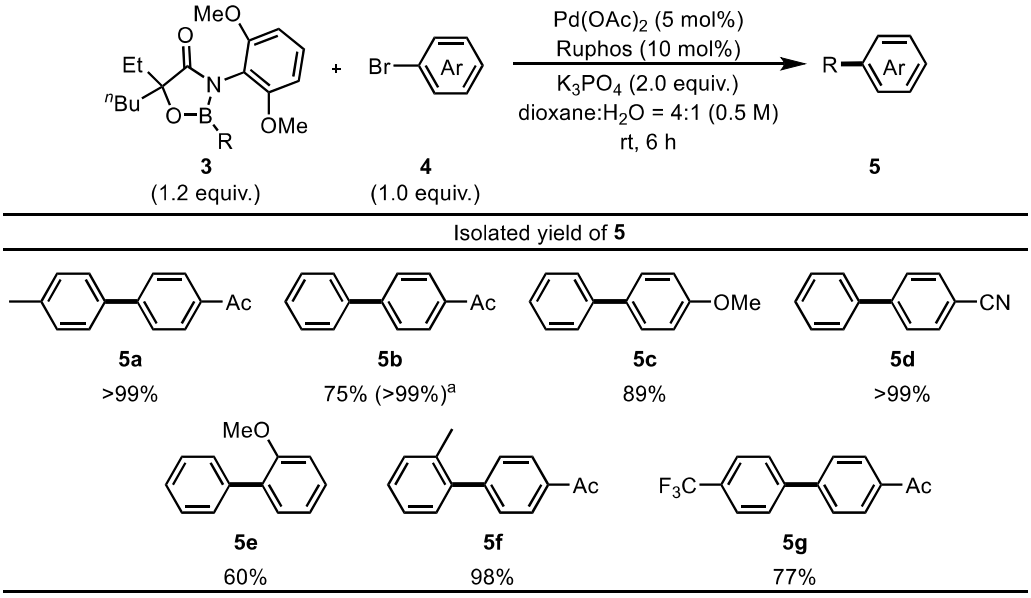
Entry	Base	NMR yield of **5c**
1	Na_2CO_3	56% (50%)
2	$NaHCO_3$	trace
3	K_2CO_3	77% (69%)
4	Cs_2CO_3	85% (76%)
5	K_3PO_4	>99% (95%)
6	KOAc	4%
7	CsOAc	4%
8	KO*t*Bu	>99% (93%)
9	NaOH	84%
10	DABCO	40%
11[a]	K_3PO_4	>99% (89%)
12[b]	K_3PO_4	84%
13[c]	K_3PO_4	29%

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated product yields are shown in parentheses. [a]6 h. [b]3 h. [c]1 h.

Next, I investigated about the effects of base (Table 5). When, the reaction using $NaHCO_3$ (entry 2) or acetate (entry 6,7) was conducted, trace amount of product was obtained. Next, the yield of coupling product was improved when a stronger base than Na_2CO_3 was used for example K_2CO_3, Cs_2CO_3, K_3PO_4, KO^{t}Bu and NaOH. As a result, the product was obtained in 95% isolated yield, when K_3PO_4 as a base was used (entry 5). However, DABCO as organic base did not gave good results (entry 10). Then, I investigated about the reaction time. As a result, I found that 6 h was the optimal time (entry 11). However, the product yield was decreased when the reaction was conducted for 1 h or 3 h.

6.2.5 Substrate scope for C-B bond cross-coupling

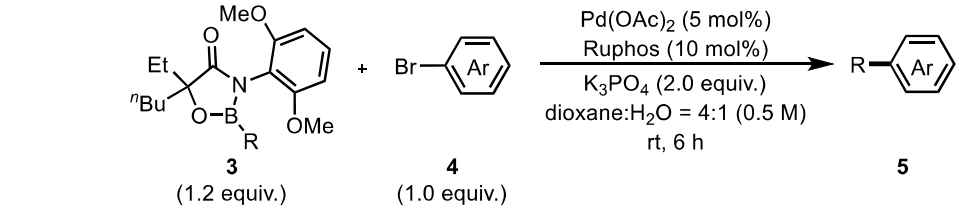
Table 6 Substrate scope with stable boron reagents

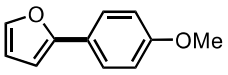
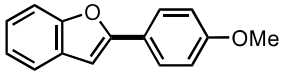
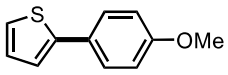
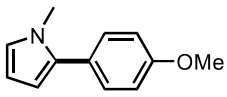
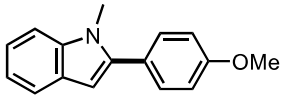
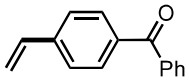
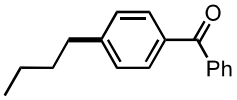


[a]**3** (1.5 equiv.) and Na_2CO_3 instead of K_3PO_4 were used at 80°C for 17 h.

First, I examined substrate scope with stable boron reagents (Table 6). Aryl bromide with electron-deficient and electron-donating substituents at para-position could be used, and it was possible to obtain coupling products **5a-5d** with excellent yields. However, when aryl bromide having methoxy group at ortho position was used, **5e** was obtained in moderate yield. Next, the coupling product **5f** was produced in 98% isolated yield but when using aryl oxazaborolidinone having trifluoromethyl group, the coupling product **5g** was obtained in 77% yield.

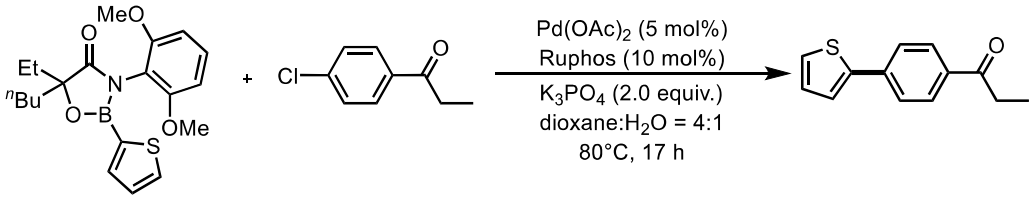
Table 7 Substrate scope with unstable boron reagents



Isolated yield of **5**			
			
5h	**5i**	**5j**	
>99%[a]	84%[a]	96%	
			
5k	**5l**	**5m**	**5n**
89%	96%	93%[b]	85%[c]

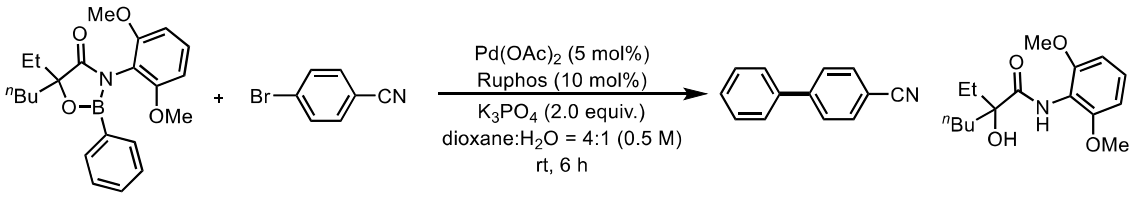
[a]**3** (1.5 equiv.) and Na_2CO_3 instead of K_3PO_4 were used at 80°C for 17 h. [b]**3** (1.5 equiv.) was used at 100°C for 2 h. [c]**3** (2.0 equiv.) was used at 100°C for 19 h.

Next, I examined substrate scope with unstable boron reagents (Table 7). In this study using 2-furyl- and 2-benzofuryl-oxazaborolidinone, the conditions were changed, but coupling products were obtained with high yields (**5h**, **5i**). Also, the coupling product (**5j-5l**) could be obtained with excellent yield when I conducted the reaction using 2-thienyl-, 2-pyrrole- and 2-indole-oxazaborolidinone. Vinyl and *n*butyl-oxaborolidinone could be synthesized, and the Suzuki-Miyaura coupling using these oxazaborolidinones required a temperature of 100°C, but the coupling product (**5m**, **5n**) could be obtained in high yield.



Scheme 7 Suzuki-Miyaura coupling between 2-thienyl oxazaborolidinone and aryl chloride

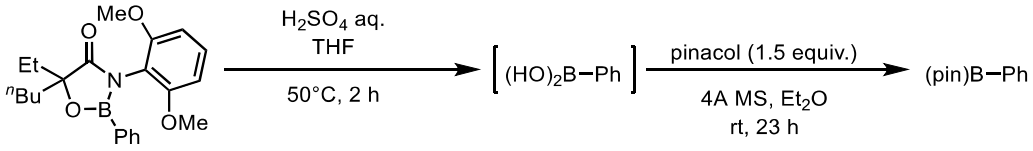
Subsequently, I conducted Suzuki-Miyaura coupling between 2-thienyl oxazaborolidinone and aryl chloride required a temperature of 80°C (Scheme 7). As a result, the coupling product **5m** could be obtained in 96% yield.



3c (1.2 equiv.) **4c** (1.0 equiv.) **5d** >99% **1c** >99%

Scheme 8 Recovery of α-hydroxyamide **1c**

After performing a coupling reaction using oxazaborolidinone **3c** and 4-bromocyanobenzene **4c**, α-hydroxyamide **1c** can be completely recovered (Scheme 8). When the recovered α-hydroxyamide **1c** can be reacted with phenylboronic acid **2a**, **3c** can be synthesized without problems, and **1c** can be reused many times.



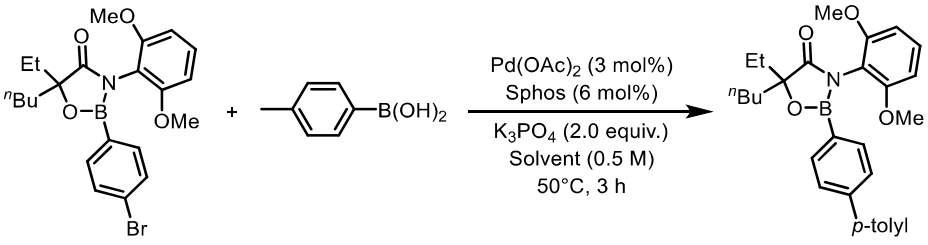
3c **2a**: >99% (NMR) **2a'**: 74%

Scheme 9 Confirmation of boronic acid production by hydrolysis

Subsequently, by hydrolysis deprotection of oxazaborolidinone **3c** under acidic conditions, it was confirmed that boronic acid **2a** was quantitatively generated at ^{1}H NMR followed by the reaction with pinacol (Scheme 9). As a result, Ph-Bpin **2a'** was obtained in 74% isolated yield. This result suggested that boronic acid is generated by hydrolytic deprotection of oxazaborolidinone.

6.2.6 Optimization of reaction conditions for C-Br coupling

Table 8 Screening of solvents



6a **2b** (1.5 equiv.) **7a**

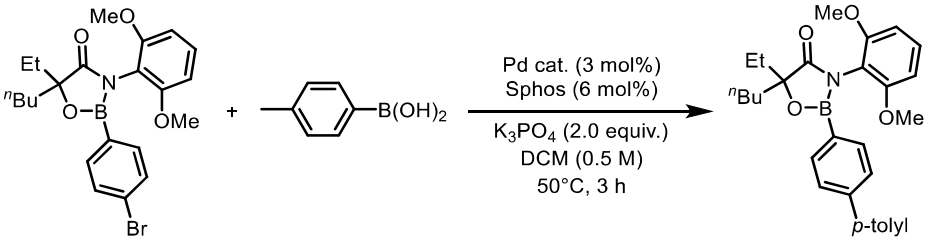
Entry	Solvent	NMR yield of **7a**	Memo
1	THF	72%	-
2	MeCN	8%	-
3	Toluene	75%	-
4	DCM	78%	**6a** 15%^{NMR}
5	MeOH	0%	deprotection 43%^{NMR}

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

I investigated about the effects of solvent (Table 8). When the reaction was performed in THF, Toluene or DCM, the desired product **7a** was obtained in 72%-78% NMR yield (entry 1,3,4). In these studies,

it was difficult to isolate product **7a** by column chromatography. *p*-tolyl oxazaborolidinone was detected in the reaction in MeCN (entry 2). The reaction in MeOH did not yield any coupling product **7a**, and the deprotection of the boron reagent proceeded in 43% yield (entry 5). As a result, I determined that DCM was used as the optimum solvent.

Table 9 Screening of Pd catalysts



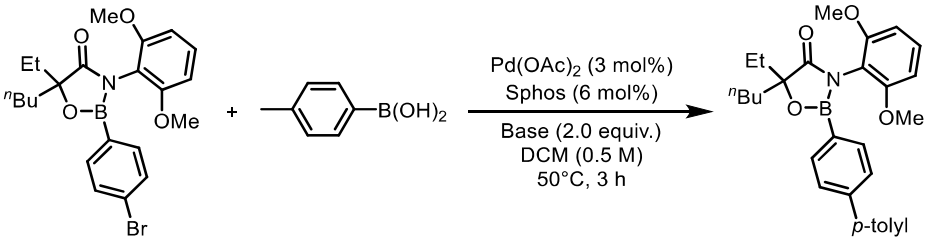
6a **2b** (1.5 equiv.) **7a**

Entry	Pd cat.	NMR yield of **7a**	Memo
1	$Pd(OAc)_2$	78%	**6a** 15%^{NMR}
2	$PdCl_2$	11%	-
3	$Pd_2(dba)_3CHCl_3$	0%	no reaction
4	$Pd(PPh_3)_4$	54%	**6a** 25%^{NMR}

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

To obtain information about the effects of Pd catalyst (Table 9). When the reaction was performed using $PdCl_2$, the desired product **7a** was obtained in 11% NMR yield (entry 2). *p*-tolyl oxazaborolidinone was detected in this reaction. Probably, HCl caused by ligand exchange has a negative effect. The reaction using $Pd_2(dba)_3CHCl_3$ did not proceed (entry 3). On the other hand, $Pd(PPh_3)_4$ was able to proceed with the reaction, but only in moderate yield (entry 4).

Table 10 Screening of bases.



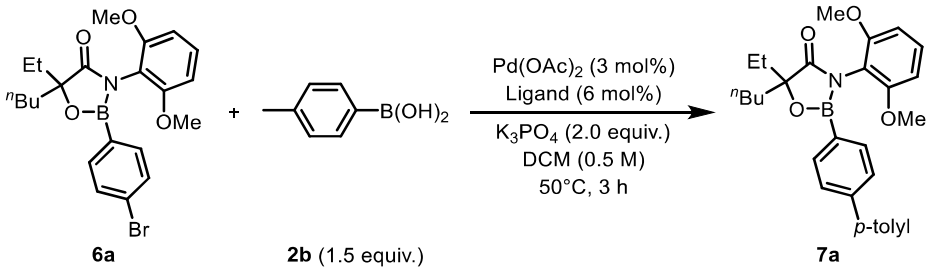
6a **2b** (1.5 equiv.) **7a**

Entry	Base	NMR yield of **7a**	Memo
1	K_3PO_4	78%	**6a** 15%^{NMR}
2	Cs_2CO_3	27%	-
3	Na_2CO_3	0%	no reaction
4	CsOAc	72%	**6a** 28%^{NMR}
5	KOAc	63%	**6a** 29%^{NMR}
6	NaOAc	10%	**6a** 76%^{NMR}
7	LiOAc	0%	no reaction
8	^{t}BuOK	11%	**6a** 42%^{NMR}
9	DABCO	0%	deprotection 47%^{NMR}

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

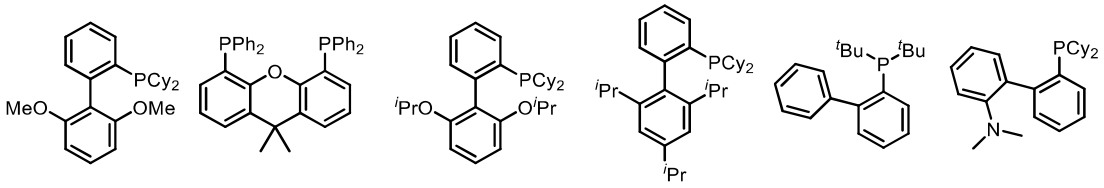
Next, I investigated about the effects of base (Table 10). Carbonate for example Cs_2CO_3 and Na_2CO_3 did not give good result (entry 2,3). As the basicity of acetate decreased, the yield of the product **7a** tended to decrease (entry 4-7). The reaction using ^{t}BuOK gave the coupling product **7a** in 11% NMR yield (entry 8). However, when DABCO as an organic base was used, the product **7a** could not be obtained at all, and deprotection proceeded (entry 9).

Table 11 Screening of ligands



6a **2b** (1.5 equiv.) **7a**

Entry	Ligand	NMR yield of **7a**	Memo
1	Sphos	78%	**6a** 15%^{NMR}
2	Xantphos	0%	no reaction
3	Ruphos	67%	**6a** 12%^{NMR}
4	Xphos	75%	**6a** 22%^{NMR}
5	**L1**	67%	**6a** 16%^{NMR}
6	**L2**	58%	**6a** 18%^{NMR}, deprotection 8%^{NMR}
7	*rac*-BINAP	31%	**6a** 42%^{NMR}, deprotection 15%^{NMR}
8	PPh_3	63%	**6a** 8%^{NMR}
9	PCy_3	0%	**6a** 71%^{NMR}
10[a]	Sphos	78%	**6a** 71%^{NMR}
11[a,b]	Sphos	>99% (98%)	-
12[a,b,c]	Sphos	>99% (98%)	-
13[a,b,c,d]	Sphos	>99%	-



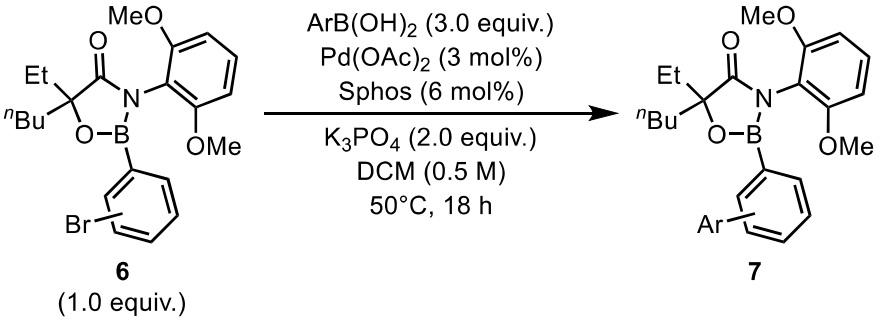
Sphos Xantphos Ruphos Xphos **L1** **L2**

The product yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated product yields are shown in parentheses. [a]18 h. [b]**2b** (3.0 equiv.) was used. [c]Room temperature. [d]7 mol% of $Pd(OAc)_2$ and 14 mol% of Sphos were used.

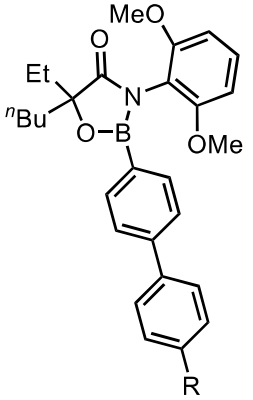
Subsequently, I investigated about the effects of ligand (Table 11). When xantphos as a bidentate ligand or tricyclohexylphosphine was used, **7a** could not be obtained (entry 2,9). However, using dicyclohexylarylphosphine (entry 3,4,6), ligand **L1** (entry 5) or PPh_3 (entry 8), **7a** was obtained in moderate yield. When the reaction was conducted using *rac*-BINAP, **7a** was obtained in 31% yield and the deprotected product was also obtained in 15% yield (entry 7). As the results of ligand examination, I determined Sphos as the optimal ligand. Next, I examined the reaction conditions. As a result, when the reaction was performed by increasing aryl boronic acid **2b** to 3 equivalents, **7a** was quantitatively obtained and isolated (entry 11). Also, when the reaction was carried out at room temperature, the product yield did not decrease (entry 12).

6.2.7 Substrate scope for C-Br bond Suzuki-Miyaura coupling

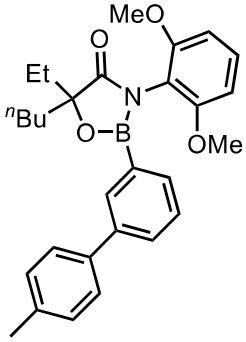
Table 12 Substrate scope for C-Br bond Suzuki-Miyaura coupling



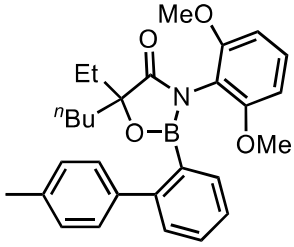
Isolated yield of **7**



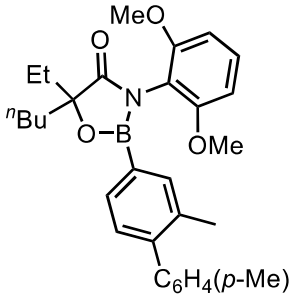
7a (R = Me): 98%
7b (R = OMe): 84%[a]
7c (R = COOMe): 78%[a]



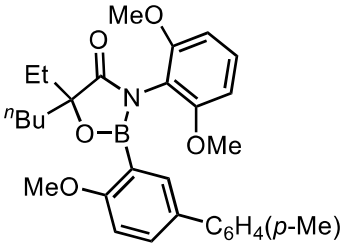
7d
96%



7e
0% (68%)[b]



7f
96%



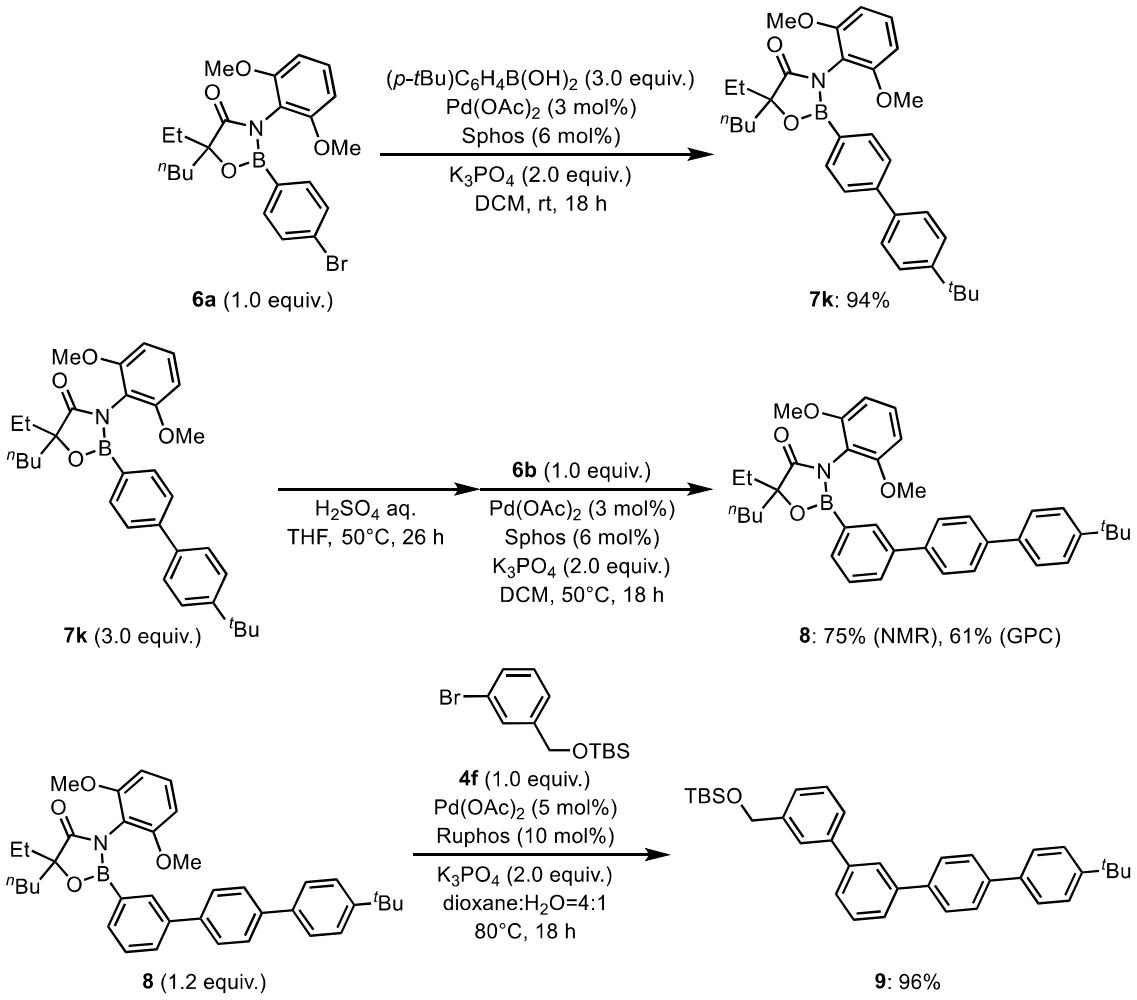
7g
77%

[a]$Pd(OAc)_2$ (7 mol%) and Sphos (14 mol%) were used at room temperature. [b]Toluene was used instead of DCM at 110°C.

Subsequently, I examined substrate scope of C-Br Suzuki-Miyaura coupling using halogen substituted oxazaborolidinone **6** (Table 12). At first, the coupling products **7a**, **7d** were obtained with excellent yield between oxazaborolidinone **6a**, **6b** and *p*-tolyl boronic acid **2b**. Next, I conducted the coupling using boronic acid **2c** with electron-donating substituent and boronic acid **2d** with electron-deficient substituent. As a result, the coupling product (**7b**, **7c**) was produced in high yield required

an increasing palladium catalyst load and a temperature at room temperature. The *o*-bromophenyl oxazaborolidinone **6c** did not react at 50°C, but when the temperature was raised to 110°C, the coupling product was obtained in 68% yield. Even if a substituent was present at the ortho position of the bromo group, the coupling proceeded without any problems, and the product was obtained with excellent yield. Finally, when oxazaborolidinone with electron-donating substituent **6e** was used, the coupling product **7g** could be obtained with moderate yield.

6.2.8 Iterative coupling



Scheme 10 Iterative Suzuki-Miyaura coupling

I carried out the iterative Suzuki-Miyaura coupling (Scheme 10). At first, the coupling product **7k** was obtained in 94% yield when oxazaborolidinone **6a** and *p-tert*-butyl phenyl boronic acid were used. The obtained coupling product **7k** was hydrolyzed with an aqueous sulfuric acid solution at 50°C for 26 h and coupled with oxazazaborolidinone **6b**. As a result, the product **8** was obtained in 75% NMR yield and 61% GPC yield. Finally, I conducted C-B bond Suzuki-Miyaura coupling between **8** and aryl bromide **4f** at 80°C for 18 h, quarteraryl compound **9** could be obtained in 96% isolated yield.

6.3 Conclusion

In conclusion, I have developed masked organoboronic acid, OxB, in which the boron atom is protected by both steric and electronic effect. A back born (alpha-hydroxycarboxamide) of OxB has bulky alpha-alkyl groups and a carboxamide group possessing both electronic and steric effect. This subtle effect softly covers boron p-orbital. And this property easily re-opens the reactivity of organoboron compound for SMC. For example, 2-heterocyclic, vinyl, and alkyl borons are inherently unstable but OxB stabilized them and undergoes SMC efficiently. My masking concept may be extended to a variety of coupling of stabilized unstable organoboronic acid or iterative coupling reactions including various cross-couplings.

6.4 Reference

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6.5 Experimental section

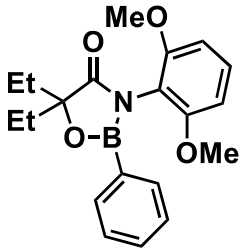
General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick) were used; for column chromatography Silica *Flash*® P60 (SiliCycle, 40-63 μm) was used. Visualization was accomplished by UV light (254 nm), ^{1}H and ^{13}C NMR spectra were obtained using a JEOL 500 MHz NMR spectrometer. Chemical shifts for ^{1}H NMR were described in parts per million (chloroform as an internal standard $\delta = 7.26$) in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard ($\delta = 77.16$), unless otherwise noted. ^{11}B NMR spectra were obtained using a JEOL 500 MHz NMR spectrometer and referenced to an external standard of ($BF_3{\cdot}Et_2O$). High resolution mass analyses (HRMS) were obtained using an ACQUITY UPLC/ TOF-MS for ESI. Infrared spectra were recorded on Agilent Technologies Cary 630 FTIR. Anhydrous solvents were purchased from Kanto Chemical Co., Ltd. Other chemicals were purchased from TCI, Aldrich, and Wako and directly used without further purification.

Measurement of half-life time of oxazaborolidinone

To a solution of PhOxB **3** (0.020 mmol) and dibenzylether as internal standard in DMSO-d_6 (0.70 mL) was added D_2O (0.07 mL) at room temperature. Conversion of PhOxB **3** was monitored by ^{1}H NMR spectroscopy.

Stability of OxB **3b**

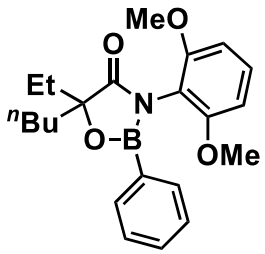


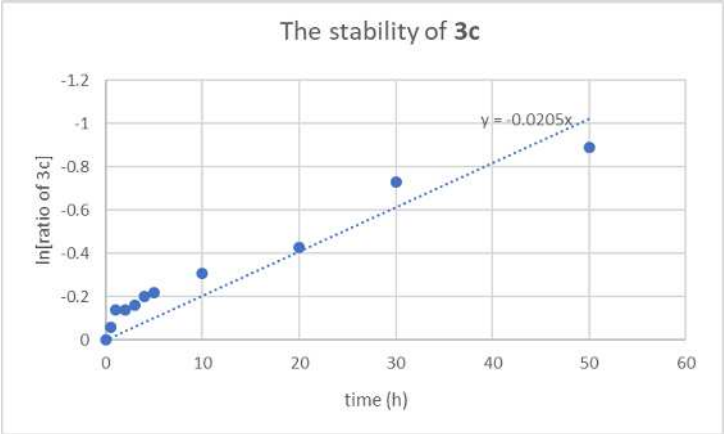
$\ln(50/100) = -0.1064 \times x$

$x = 6.5$ h

Half-life time of oxazaborolidinone **3b** was 7 h.

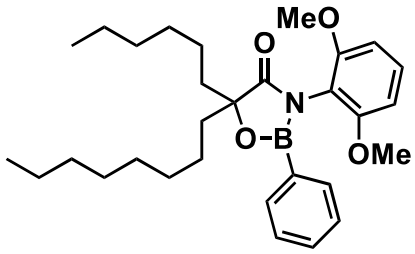
Stability of OxB **3c**

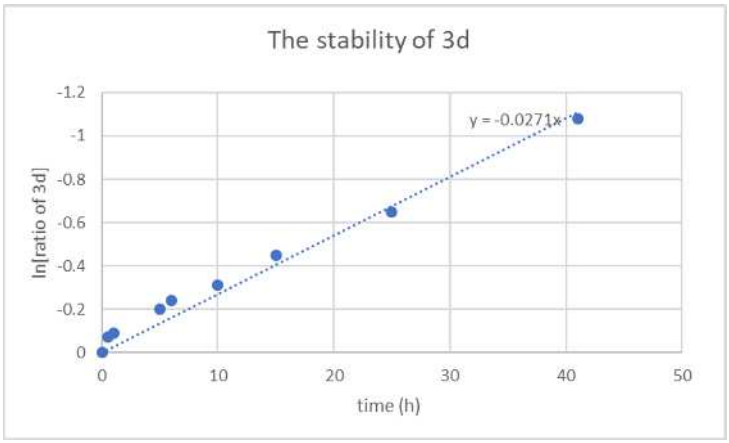




ln(50/100) = -0.0205×x
x = 33.8 h
Half-life time of oxazaborolidinone **3c** was 34 h.

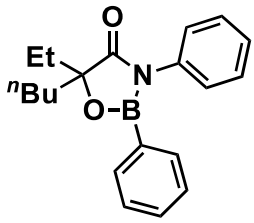
Stability of OxB **3d**

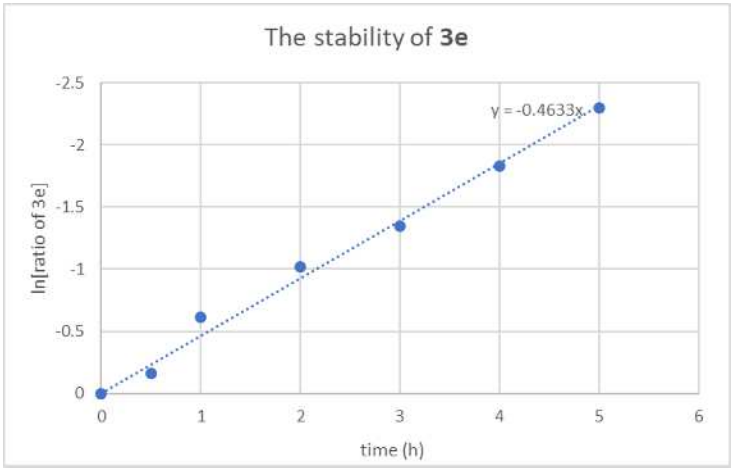




ln(50/100) = -0.0271×x
x = 25.5 h
Half-life time of oxazaborolidinone **3d** was 26 h.

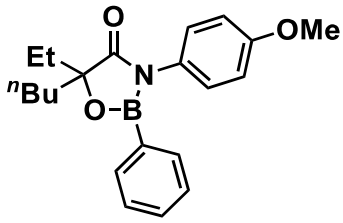
Stability of OxB **3e**

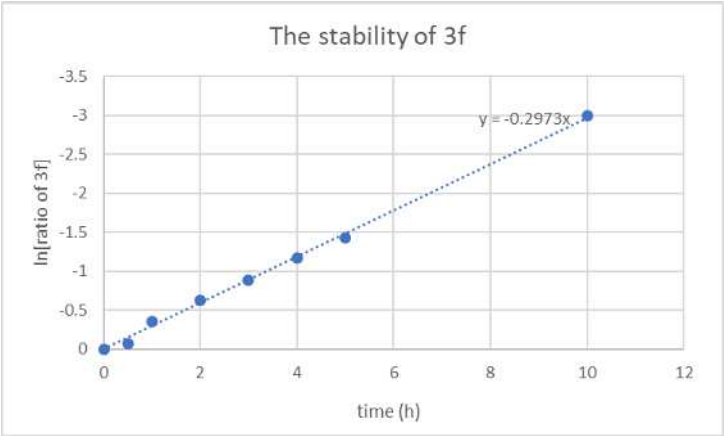




ln(50/100) = -0.4633×x
x = 1.4 h
Half-life time of oxazaborolidinone **3e** was 1 h.

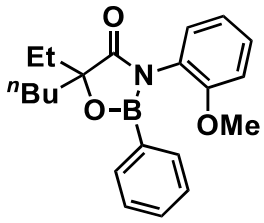
Stability of OxB **3f**

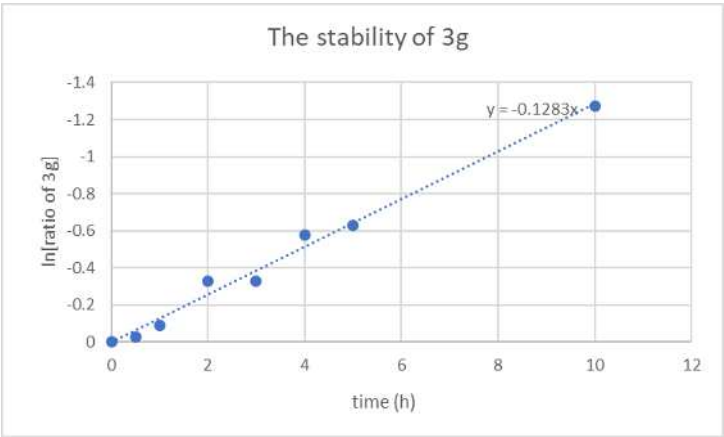




ln(50/100) = -0.2973×x
x = 2.3 h
Half-life time of oxazaborolidinone **3f** was 2 h.

Stability of OxB **3g**

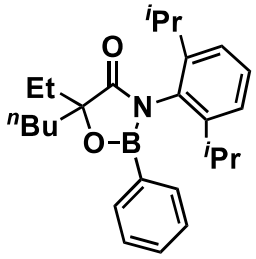


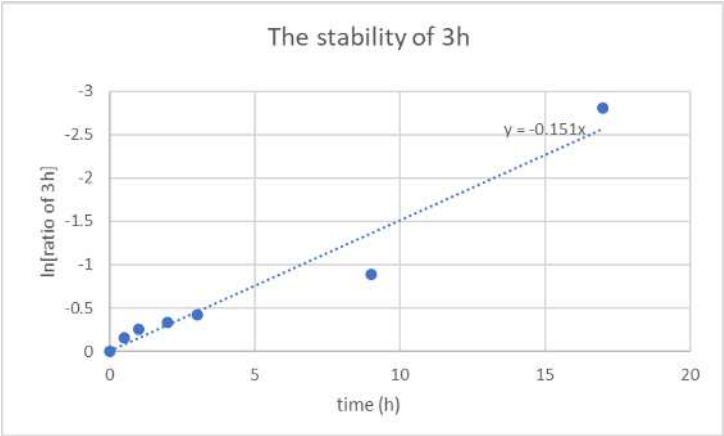


ln(50/100) = -0.1283×x
x = 5.4 h

Half-life time of oxazaborolidinone **3g** was 5 h.

Stability of OxB **3h**





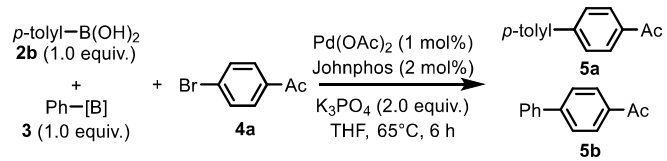
ln(50/100) = -0.151×x
x = 4.5 h

Half-life time of oxazaborolidinone **3h** was 5 h.

Competition studies

Competition studies (Ph[B] vs. p-tolyl boronic acid)

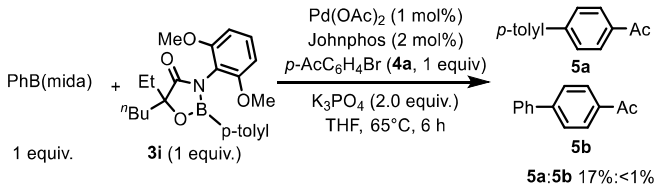
Ph[B] **3** (1.0 equiv.), p-tolyl boronic acid **2b** (1.0 equiv.), 4-bromoacetophenone **4a** (0.5 mmol), $Pd(OAc)_2$ (1 mol%) and Johnphos (2 mol%) were sequentially added under air to a dram vial equipped with a stir bar. K_3PO_4 (2.0 equiv.) and THF (0.5 M) were added in a glove box, removed from the glove box and the resulting mixture was vigorously stirred for 6 h at 65°C. After this time, the reaction mixture was extracted with AcOEt and filtered through a plug of silica gel. After removal of the solvent in vacuum, the filtrate was then analyzed by ^1H NMR (internal standard: tetrachloroethane).



Run / **3** / Yield (%) (**5a**:**5b**)								
1	$PhB(OH)_2$ (**2a**)[b]	59:57	4	**3c**	48:<1	7	**3f**	61:15
2	PhB(mida)[b]	79:<1	5	**3d**	40:<1	8	**3g**	66: 7
3	**3b**	62: 4	6	**3e**	41:14	9	**3h**	56:<1

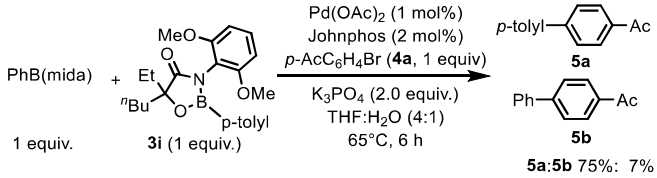
Competition of p-tolyl[OxB] 3i vs. PhB(mida) under Buchwald's anhydrous SMC conditions

The general procedure was followed using 3i (0.5 mmol) and PhB(mida) (0.5 mmol).



Competition of p-tolyl[OxB] 3i vs. PhB(mida) in the presence of water

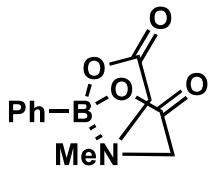
p-tolyl[OxB] **3i** (1.0 equiv.), PhB(mida) (1.0 equiv.), 4-bromoacetophenone **4a** (0.5 mmol), $Pd(OAc)_2$ (1 mol%) and Johnphos (2 mol%) were sequentially added under air to a dram vial equipped with a stir bar. K_3PO_4 (2.0 equiv.) and THF (0.8 mL) were added in a glove box, removed from the glove box. Then, water (0.2 mL) was added by syringe and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for 6 h at 65℃. After this time, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the filtrate was then analyzed by ^1H NMR (internal standard: tetrachloroethane).



General procedure for synthesis of PhB(mida)

N-methyliminodiacetic acid (1.0 equiv.) and boronic acid (1.1 equiv.) and $MgSO_4$ (1.1 equiv.) were sequentially added under air to a dram vial equipped with a stir bar. Toluene:DMSO=9:1 (0.25 M) was added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for overnight at 110℃. After this time, the reaction mixture was filtered with AcOEt. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired product.

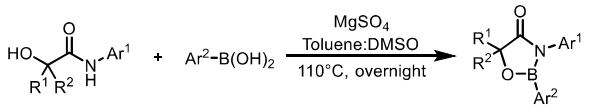
4-methyl-8-phenyldihydro-4l4,8l4-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborole-2,6(3H,5H)-dione[1]

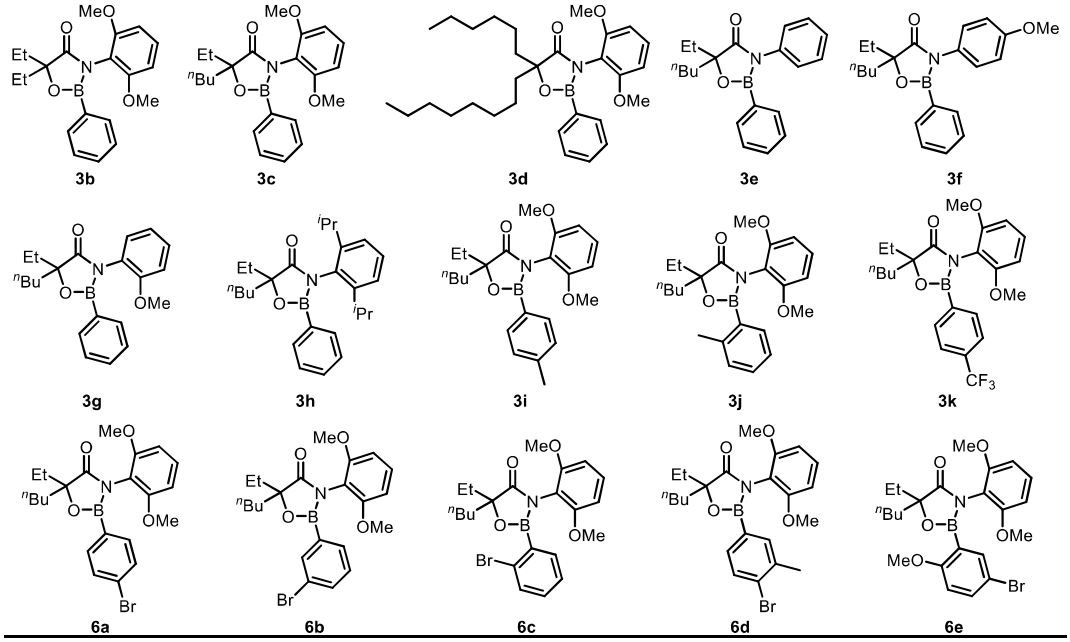


Using *N*-methyliminodiacetic acid (146.4 mg, 1.0 mmol), phenyl boronic acid **2a** (122.5 mg, 1.0 mmol), $MgSO_4$ (132.4 mg, 1.1 mmol) and toluene:DMSO=9:1 (0.25 M) at 110℃ for overnight, yielded the product (175.7 mg, 75%) as pale solid; ^1H NMR (500 MHz, CD_3CN) δ: 7.46 (m, 2H), 7.37 (m, 3H), 4.04 (d, J = 16.8 Hz, 2H), 3.86 (d, J = 16.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ: 168.6, 132.4, 129.3, 127.9, 61.8, 47.5; ^{11}B NMR (160 MHz, CD_3CN) δ: 10.52.

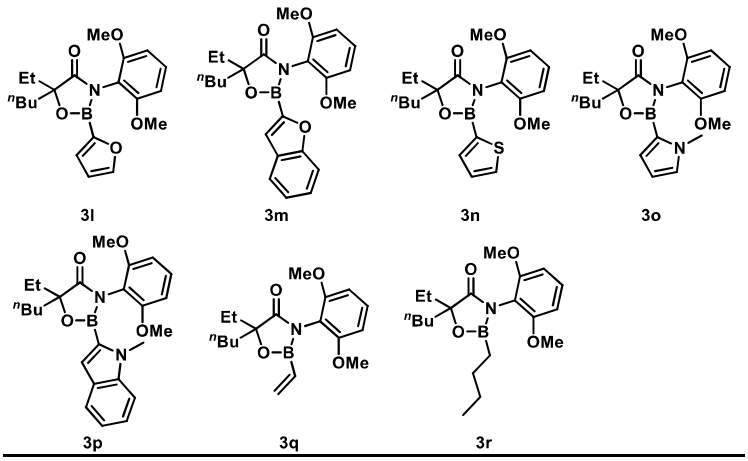
General procedures and Characterization data of oxazaborolidinones

Synthesis of oxazaborolidinone by condensation method





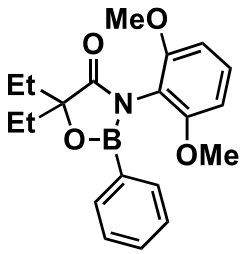
Synthesis of oxazaborolidinone by Grignard method



General procedure for synthesis of oxazaborolidinone by condensation method

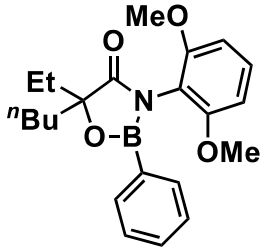
The corresponding α-hydroxyamide (1.0 equiv.) and boronic acid (1.1 equiv.) and $MgSO_4$ (1.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar. Toluene:DMSO=9:1 (0.5 M) was added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for 16 h at 110°C. After this time, the reaction mixture was filtered with AcOEt. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **3**.

3-(2,6-dimethoxyphenyl)-5,5-diethyl-2-phenyl-1,3,2-oxazaborolidin-4-one (**3b**)



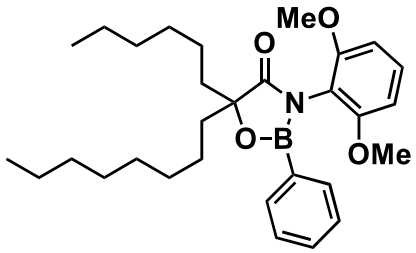
Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxybutanamide **1b** (215.0 mg, 0.80 mmol), phenyl boronic acid **2a** (107.6 mg, 0.88 mmol), $MgSO_4$ (112.0 mg, 0.93 mmol) and toluene (1.6 mL) at 110°C for 16 h, yielded the product **3b** (253.4 mg, 89%) as white solid; IR (cm^{-1}): 2973, 1729, 1592, 1505, 1475, 1431, 1369, 1258, 1161, 1105, 1026, 945, 889, 771, 700; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 8.5 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 3.69 (s, 6H), 2.00-1.93 (m, 2H), 1.90-1.83 (m, 2H), 0.98 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.1, 156.0, 134.0, 131.5, 129.0, 127.8, 114.2, 104.4, 87.7, 55.9, 30.7, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.82.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-phenyl-1,3,2-oxazaborolidin-4-one (**3c**)



Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (57.3 mg, 0.19 mmol), phenyl boronic acid **2a** (25.3 mg, 0.21 mmol), $MgSO_4$ (25.3 mg, 0.21 mmol) and toluene (0.38 mL) at 110°C for 16 h, yielded the product **3c** (69.9 mg, 95%) as white solid; IR (cm^{-1}): 2960, 2927, 2843, 1723, 1592, 1504, 1476, 1432, 1358, 1255, 1157, 1112, 892, 769; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (d, J = 8.1 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 7.31-7.25 (m, 3H), 6.63 (d, J = 8.5 Hz, 2H), 3.69 (d, J = 5.4 Hz, 6H), 2.00-1.81 (m, 4H), 1.46-1.29 (m, 4H), 0.98 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.2, 156.1 (d, J = 4.1 Hz), 134.0, 131.5, 129.0, 127.8, 114.2, 104.4 (d, J = 3.1 Hz), 87.4, 55.9 (d, J = 9.4 Hz), 37.6, 30.9, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.81.

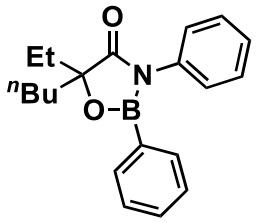
3-(2,6-dimethoxyphenyl)-5-hexyl-5-octyl-2-phenyl-1,3,2-oxazaborolidin-4-one (**3d**)



Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-hexyl-2-hydroxydecanamide **1d** (203.8 mg, 0.50 mmol), phenyl boronic acid **2a** (67.1 mg, 0.55 mmol), $MgSO_4$ (94.1 mg, 0.78 mmol) and toluene:DMSO=9:1 (1.0 mL) at 110°C for 16 h, yielded the product **3d** (172.7 mg, 70%) as yellow oil; IR (cm^{-1}): 2923, 2852, 1734, 1595, 1506, 1477, 1437, 1358, 1256, 1111, 891, 772; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.51 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 8.2 Hz, 1H), 7.32-

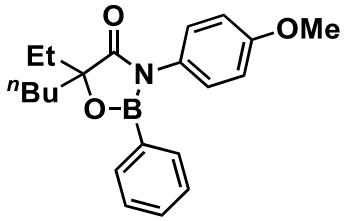
7.28 (m, 3H), 6.63 (d, J = 8.6 Hz, 2H), 3.69 (s, 6H), 1.91-1.79 (m, 4H), 1.41-1.26 (m, 20H), 0.85 (t, J = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.4, 156.0, 134.0, 131.5, 129.0, 127.8, 114.1, 104.4, 87.1, 55.9, 38.1, 32.0 (d, J = 8.6 Hz), 29.8 (d, J = 3.3 Hz), 29.4 (d, J = 11.8 Hz), 23.1 (d, J = 7.3 Hz), 22.7 (d, J = 10.0 Hz), 14.2 (d, J = 3.6 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.54.

5-butyl-5-ethyl-2,3-diphenyl-1,3,2-oxazaborolidin-4-one (**3e**)



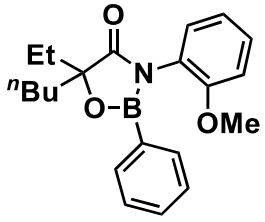
Following the general procedure (condensation method), using 2-ethyl-2-hydroxy-N-phenylhexanamide **1e** (153.0 mg, 0.65 mmol), phenyl boronic acid **2a** (86.6 mg, 0.71 mmol), $MgSO_4$ (92.2 mg, 0.77 mmol) and toluene:DMSO=9:1 (1.3 mL) at 110°C for 16 h, yielded the product **3e** (71.3 mg, 34%) as orange oil; IR (cm^{-1}): 2958, 2925, 2860, 1734, 1600, 1499, 1437, 1358, 1217, 1160, 1126, 889, 752; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53 (dd, J = 1.4, 8.2 Hz, 2H), 7.47-7.43 (m, 3H), 7.40-7.37 (m, 1H), 7.30 (t, J = 7.9 Hz, 2H), 7.19-7.17 (m, 2H), 2.01-1.83 (m, 4H), 1.46-1.41 (m, 1H), 1.38-1.25 (m, 3H), 0.96 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.5, 136.3, 134.9, 132.0, 129.5, 127.9, 127.8, 127.3, 87.0, 37.2, 30.7, 25.3, 22.8, 14.1, 7.6; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.33.

5-butyl-5-ethyl-3-(4-methoxyphenyl)-2-phenyl-1,3,2-oxazaborolidin-4-one (**3f**)



Following the general procedure (condensation method), using 2-ethyl-2-hydroxy-N-(4-methoxyphenyl)hexanamide **1f** (655.4 mg, 2.47 mmol), phenyl boronic acid **2a** (332.9 mg, 2.72 mmol), $MgSO_4$ (327.4 mg, 2.72 mmol) and toluene:DMSO=9:1 (4.94 mL) at reflux (110°C) for 16 h, yielded the product **3f** (456.6 mg, 53%) as yellow oil; IR (cm^{-1}): 2957, 2933, 2872, 1729, 1601, 1511, 1438, 1358, 1245, 1160, 1029, 892, 815, 754; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.12-7.09 (m, 2H), 6.98-6.96 (m, 2H), 3.86 (s, 3H), 2.00-1.84 (m, 4H), 1.48-1.24 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.8, 158.9, 134.9, 131.9, 129.0, 128.3, 127.9, 114.7, 86.9, 55.5, 37.2, 30.7, 25.3, 22.8, 14.0, 7.6; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.52.

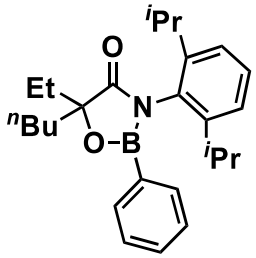
5-butyl-5-ethyl-3-(2-methoxyphenyl)-2-phenyl-1,3,2-oxazaborolidin-4-one (**3g**)



Following the general procedure (condensation method), using 2-ethyl-2-hydroxy-N-(2-methoxyphenyl)hexanamide **1g** (432.5 mg, 1.63 mmol), phenyl boronic acid **2a** (218.9 mg, 1.79 mmol), $MgSO_4$ (190 mg, 1.58 mmol) and toluene:DMSO=9:1 (3.30 mL) at reflux (110°C) for 16 h, yielded the product **3g** (365.3 mg, 64%) as yellow oil; IR (cm^{-1}): 2956, 2933, 2872, 1733, 1600, 1503,

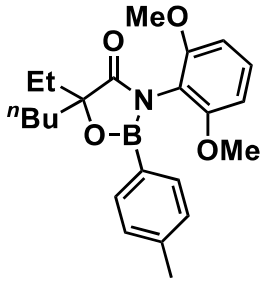
1438, 1358, 1248, 1159, 1025, 893, 748; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.39-7.35 (m, 1H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.15-7.12 (m, 1H), 7.04-6.99 (m, 2H), 3.67 (d, *J* = 7.4 Hz, 3H), 2.00-1.82 (m, 4H), 1.47-1.26 (m, 4H), 0.99-0.95 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.5, 154.8, 134.3, 131.7, 129.3, 129.1 (d, *J* = 5.9 Hz), 127.9, 125.4, 121.0, 112.0, 87.2, 55.5 (d, *J* = 7.4 Hz), 37.4 (d, *J* = 14.2 Hz), 30.8 (d, *J* = 16.7 Hz), 25.4, 22.9 (d, *J* = 10.9 Hz), 14.2 (d, *J* = 24.5 Hz), 7.5 (d, *J* = 32.4 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.49.

5-butyl-3-(2,6-diisopropylphenyl)-5-ethyl-2-phenyl-1,3,2-oxazaborolidin-4-one (**3h**)



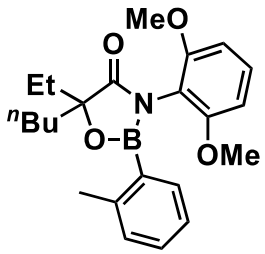
Following the general procedure (condensation method), using N-(2,6-diisopropylphenyl)-2-ethyl-2-hydroxyhexanamide **1h** (166.1 mg, 0.52 mmol), phenyl boronic acid **2a** (71.5 mg, 0.59 mmol), $MgSO_4$ (80.6 mg, 0.67 mmol) and toluene:DMSO=9:1 (1.04 mL) at 110°C for 16 h, yielded the product **3h** (170.3 mg, 81%) as viscous oil; IR (cm^{-1}): 2960, 2869, 1731, 1600, 1356, 1159, 1127, 798; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43-7.39 (m, 4H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 2.91 (sept, *J* = 6.9 Hz, 2H), 1.99-1.89 (m, 4H), 1.53-1.33 (m, 4H), 1.16 (dd, *J* = 2.9, 6.9 Hz, 6H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.96 (dd, *J* = 4.6, 6.9 Hz, 6H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 184.0, 145.4 (d, *J* = 3.5 Hz), 134.6, 132.1, 131.8, 128.7, 127.9, 124.1, 86.9, 37.2, 30.9, 28.8 (d, *J* = 6.3 Hz), 25.6, 24.6 (d, *J* = 7.8 Hz), 23.4 (d, *J* = 4.3 Hz), 23.0, 14.1, 7.7; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.95.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(p-tolyl)-1,3,2-oxazaborolidin-4-one (**3i**)



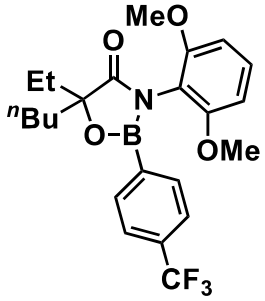
Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (177.5 mg, 0.6 mmol), *p*-tolyl boronic acid **2b** (90.0 mg, 0.66 mmol), $MgSO_4$ (55.8 mg, 0.46 mmol) and toluene (1.2 mL) at 110°C for 16 h, yielded the product **3i** (210.0 mg, 88%) as white solid; IR (cm^{-1}): 2937, 1726, 1593, 1506, 1478, 1400, 1358, 1257, 1162, 1109, 892, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.5 Hz, 2H), 3.69 (d, *J* = 4.1 Hz, 6H), 2.32 (s, 3H), 1.99-1.79 (m, 4H), 1.45-1.29 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 156.1 (d, *J* = 3.9 Hz), 141.9, 134.1, 128.9, 128.7, 114.3, 104.4 (d, *J* = 2.9 Hz), 87.3, 55.9 (d, *J* = 9.6 Hz), 37.6, 30.9, 25.4, 22.9, 21.8, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.02.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(o-tolyl)-1,3,2-oxazaborolidin-4-one (**3j**)

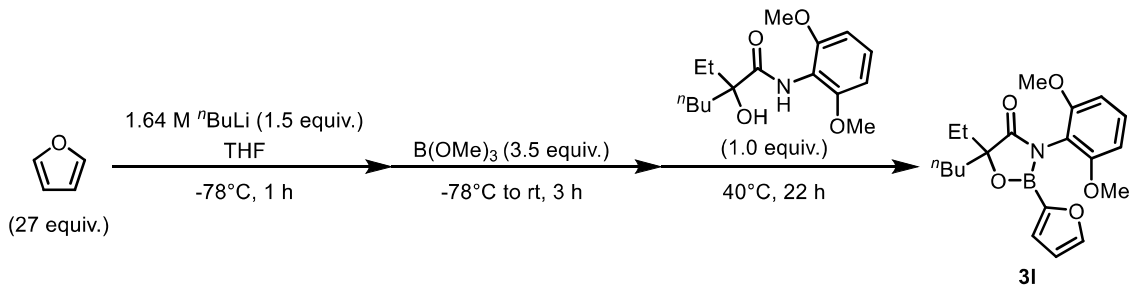


Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (176.8 mg, 0.6 mmol), *o*-tolyl boronic acid **2c** (89.4 mg, 0.66 mmol), $MgSO_4$ (57.8 mg, 0.48 mmol) and toluene (1.2 mL) at 110°C for 16 h, yielded the product **3j** (196.8 mg, 83%) as white solid; IR (cm^{-1}): 2966, 2939, 1729, 1593, 1504, 1474, 1357, 1254, 1159, 1106, 890, 765; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.22-7.11 (m, 4H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.53 (dd, *J* = 2.4, 8.5 Hz, 2H), 3.67 (d, *J* = 10.0 Hz, 6H), 2.45 (s, 3H), 1.99-1.82 (m, 4H), 1.51-1.32 (m, 4H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 182.7, 155.7 (d, *J* = 2.7 Hz), 142.5, 133.0, 130.0, 129.5, 128.6, 124.5, 114.2, 104.4 (d, *J* = 4.3 Hz), 88.0, 55.8 (d, *J* = 9.6 Hz), 37.5, 30.8, 25.5, 22.9, 22.1, 14.3, 7.5; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 35.49.

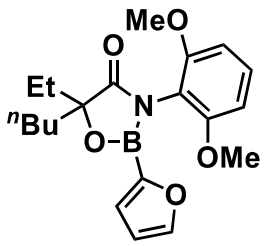
5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-oxazaborolidin-4-one (**3k**)



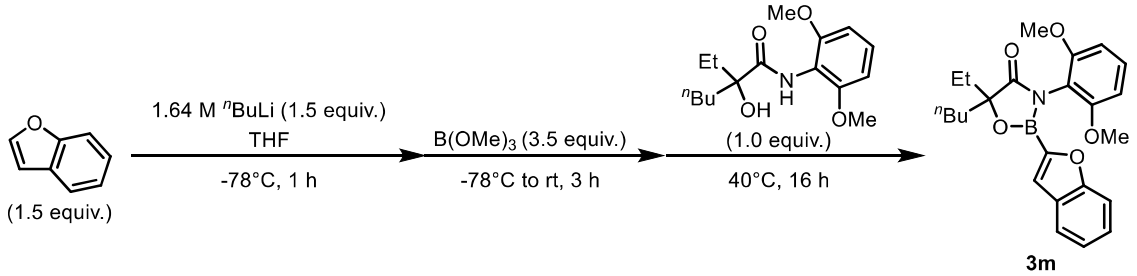
Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (177.4 mg, 0.6 mmol), *p*-trifluoromethyl boronic acid **2d** (125.1 mg, 0.66 mmol), $MgSO_4$ (60.7 mg, 0.50 mmol) and toluene (1.2 mL) at 110°C for 16 h, yielded the product **3k** (237.4 mg, 88%) as white solid; IR (cm^{-1}): 2955, 2930, 1730, 1594, 1507, 1480, 1404, 1366, 1319, 1258, 1161, 1104, 1060, 1016, 892, 835, 773; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.32 (t, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 3.70 (d, *J* = 4.0 Hz, 6H), 1.99-1.81 (m, 4H), 1.43-1.31 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.0, 155.9 (d, *J* = 4.4 Hz), 134.2, 133.0 (q, *J* = 32.3 Hz), 129.2, 124.0 (q, *J* = 271.9 Hz), 124.4 (q, *J* = 3.7 Hz), 113.6, 104.4 (d, *J* = 3.3 Hz), 87.9, 55.9 (d, *J* = 9.2 Hz), 37.5, 30.8, 25.4, 22.8, 14.2, 7.3; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.67.



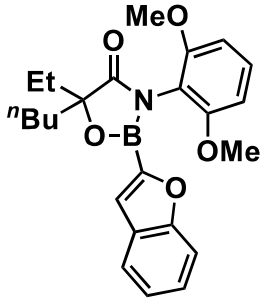
5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(furan-2-yl)-1,3,2-oxazaborolidin-4-one (**3l**)



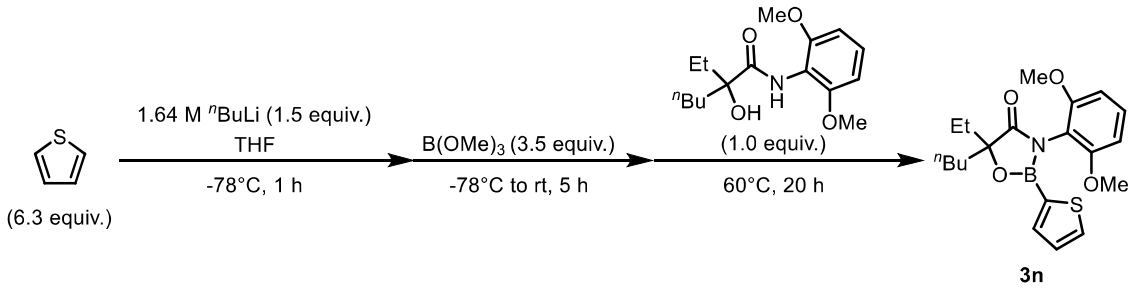
Using furan (4 mL), ^{n}BuLi (1.8 mL, 3.0 mmol), $B(OMe)_3$ (0.9 mL, 8.1 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (590.5 mg, 2.0 mmol), yielded the product **3l** (145.0 mg, 20%) as yellow solid; IR (cm^{-1}): 2938, 1733, 1572, 1507, 1477, 1394, 1346, 1257, 1166, 1111, 1013, 925, 756; ^{1}H NMR (500 MHz, CD_3CN) δ: 7.68 (brs, 1H), 7.35 (t, J = 8.5 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.43 (d, J = 3.6 Hz, 1H), 6.38-6.37 (m, 1H), 3.68 (d, J = 4.7 Hz, 6H), 1.83-1.76 (m, 4H), 1.36-1.28 (m, 4H), 0.90-0.86 (m, 6H); ^{13}C NMR (125 MHz, d_6-acetone) δ: 181.0, 156.2 (d, J = 4.2 Hz), 148.2, 129.0, 124.1, 113.8, 110.5, 104.4 (d, J = 2.7 Hz), 87.3, 55.5 (d, J = 5.8 Hz), 37.3, 30.6, 25.2, 22.6, 13.6, 6.8; ^{11}B NMR (160 MHz, d_6-acetone) δ: 29.82.



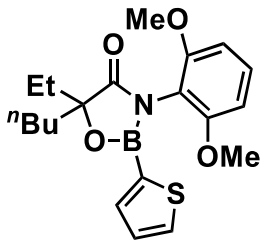
2-(benzofuran-2-yl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**3m**)



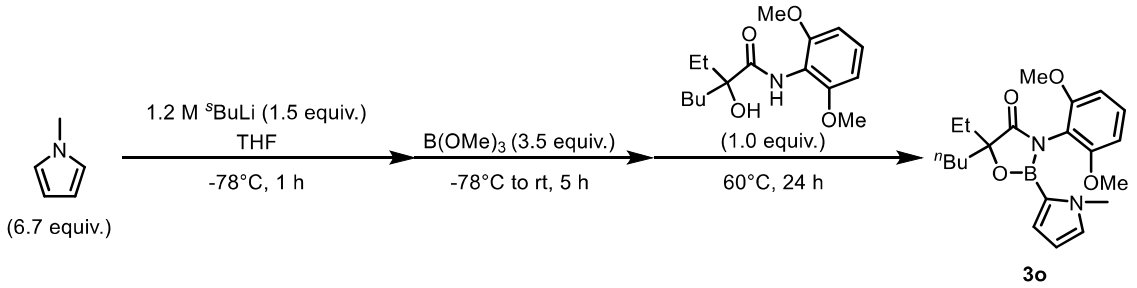
Using benzofuran (0.32 mL, 3.0 mmol), ^{n}BuLi (1.8 mL, 3.0 mmol), $B(OMe)_3$ (0.8 mL, 7.0 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (591.4 mg, 2.0 mmol), yielded the product **3m** (206.0 mg, 24%) as yellow oil; IR (cm^{-1}): 2937, 1734, 1593, 1561, 1506, 1476, 1358, 1323, 1256, 1165, 1109, 940, 753; ^{1}H NMR (500 MHz, CD_3CN) δ: 7.55 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.42-7.36 (m, 2H), 7.22 (t, J = 7.0 Hz, 1H), 6.78-6.76 (m, 3H), 3.69 (d, J = 4.2 Hz, 6H), 1.88-1.81 (m, 4H), 1.41-1.28 (m, 4H), 0.93 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ: 181.8, 157.2, 156.1 (d, J = 3.9 Hz), 129.5, 127.1, 126.8, 123.1, 122.3, 120.4, 113.2, 111.6, 104.6 (d, J = 1.5 Hz), 88.2, 55.7 (d, J = 3.3 Hz), 37.1, 30.5, 25.3, 22.5, 13.5, 6.7; ^{11}B NMR (160 MHz, CD_3CN) δ: 30.65.



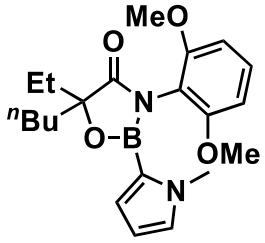
5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(thiophen-2-yl)-1,3,2-oxazaborolidin-4-one (**3n**)



Using thiophene (0.5 mL, 6.3 mmol), ^{n}BuLi (1.0 mL, 1.5 mmol), $B(OMe)_3$ (0.6 mL, 5.4 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (294.4 mg, 1.0 mmol), yielded the product **3n** (228.1 mg, 59%) as brown solid; IR (cm^{-1}): 3067, 2960, 2930, 1726, 1593, 1506, 1477, 1421, 1360, 1304, 1256, 1108, 769; ^{1}H NMR (500 MHz, CD_3CN) δ: 7.69 (d, J = 4.7 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.30 (d, J = 3.5 Hz, 1H), 7.12-7.10 (m, 1H), 6.73 (d, J = 8.6 Hz, 2H), 3.67 (d, J = 5.6 Hz, 6H), 1.87-1.78 (m, 4H), 1.41-1.29 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ: 182.1, 156.3 (d, J = 3.3 Hz), 137.5, 134.1, 129.6, 128.6, 113.4, 104.6 (d, J = 1.3 Hz), 87.7, 55.7 (d, J = 2.6 Hz), 37.2, 30.7, 25.3, 22.6, 13.6, 6.8; ^{11}B NMR (160 MHz, CD_3CN) δ: 31.81.

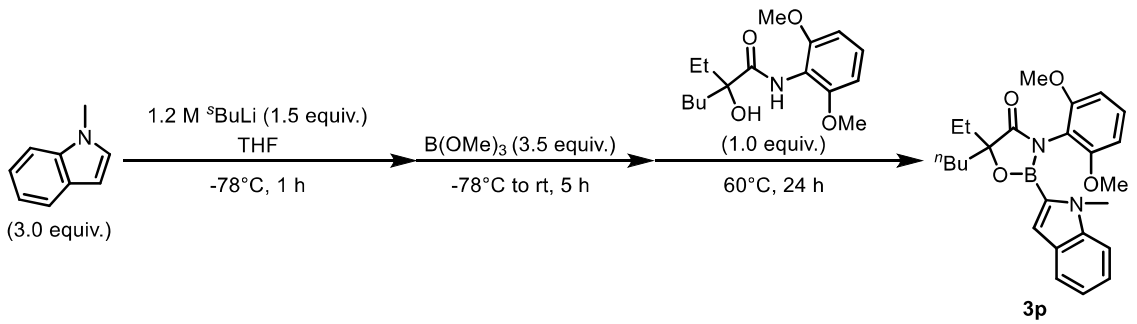


5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(1-methyl-1H-pyrrol-2-yl)-1,3,2-oxazaborolidin-4-one (**3o**)

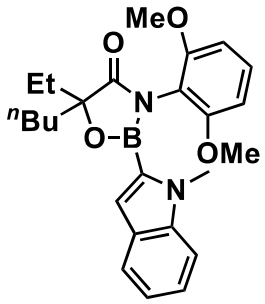


Using N-methylpyrrole (0.6 mL, 6.7 mmol), ^{s}BuLi (1.3 mL, 1.5 mmol), $B(OMe)_3$ (0.4 mL, 3.6 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (295.1 mg, 1.0 mmol), yielded the

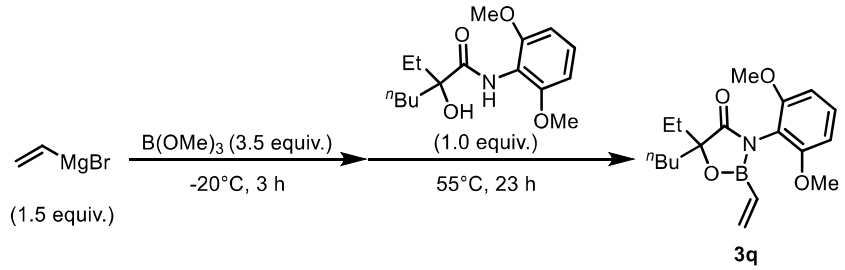
product **3o** (80.7 mg, 21%) as white solid; IR (cm^{-1}): 2962, 2937, 1731, 1595, 1532, 1506, 1477, 1417, 1361, 1338, 1258, 1111, 772, 739; ^{1}H NMR (500 MHz, CD_3CN) δ: 7.34 (t, *J* = 8.4 Hz, 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 5.87 (dd, *J* = 2.3, 3.8 Hz, 1H), 5.75 (dd, *J* = 1.6, 3.9 Hz, 1H), 3.86 (s, 3H), 3.67 (d, *J* = 5.9 Hz, 6H), 1.83-1.75 (m, 4H), 1.42-1.28 (m, 4H), 0.93-0.87 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ: 182.0, 156.2 (d, *J* = 1.9 Hz), 129.8, 129.1, 122.6, 114.5, 108.4, 104.5, 87.1, 55.6 (d, *J* = 2.0 Hz), 37.3, 36.5, 30.7, 25.4, 22.6, 13.6, 6.8; ^{11}B NMR (160 MHz, CD_3CN) δ: 30.62.



5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(1-methyl-1H-indol-2-yl)-1,3,2-oxazaborolidin-4-one (**3p**)

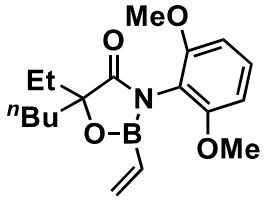


Using N-methyl indole (0.4 mL, 3.0 mmol), ^{s}BuLi (1.3 mL, 1.5 mmol), $B(OMe)_3$ (0.5 mL, 4.5 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (295.6 mg, 1.0 mmol), yielded the product **3p** (73.7 mg, 17%) as white solid; IR (cm^{-1}): 2963, 1734, 1596, 1509, 1478, 1367, 1259, 1111, 917, 777, 732; ^{1}H NMR (500 MHz, CD_3CN) δ: 7.41-7.36 (m, 3H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 1H), 4.02 (s, 3H), 3.68 (d, *J* = 7.1 Hz, 6H), 1.87-1.79 (m, 4H), 1.43-1.31 (m, 4H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ: 182.0, 156.1, 140.3, 129.3, 127.5, 123.9, 121.4, 119.5, 114.3, 110.0, 104.7, 87.8, 55.7 (d, *J* = 2.3 Hz), 37.2, 32.1, 30.6, 25.4, 22.6, 13.5, 6.8; ^{11}B NMR (160 MHz, CD_3CN) δ: 31.83.

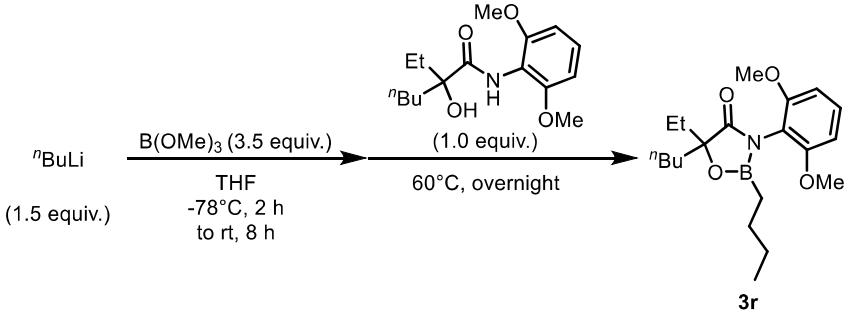


3q

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-vinyl-1,3,2-oxazaborolidin-4-one (**3q**)

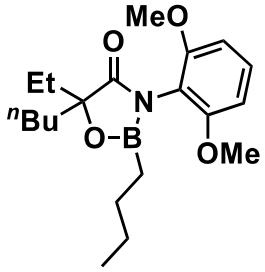


Using vinylmagnesium bromide (1.5 mL, 1.5 mmol), $B(OMe)_3$ (0.4 mL, 3.6 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (296.5 mg, 1.0 mmol), yielded the product **3q** (18.5 mg, 6%) as yellow solid; IR (cm^{-1}): 3071, 2940, 2836, 1733, 1594, 1506, 1477, 1430, 1392, 1257, 1112, 970, 769; ^1H NMR (500 MHz, CD_3CN) δ: 7.29 (t, J = 8.6 Hz, 1H), 6.68 (d, J = 8.4 Hz, 2H), 5.99-5.93 (m, 2H), 5.76 (dd, J = 14.5, 19.3 Hz, 1H), 3.71 (d, J = 4.4 Hz, 6H), 1.79-1.70 (m, 4H), 1.33-1.23 (m, 4H), 0.89-0.84 (m, 6H); ^{13}C NMR (125 MHz, CD_3CN) δ: 182.1, 155.9 (d, J = 3.7 Hz), 136.8, 129.0, 113.4, 104.4, 87.1, 55.6 (d, J = 2.6 Hz), 37.1, 30.5, 25.2, 22.5, 13.5, 6.7; ^{11}B NMR (160 MHz, CD_3CN) δ: 32.64.



3r

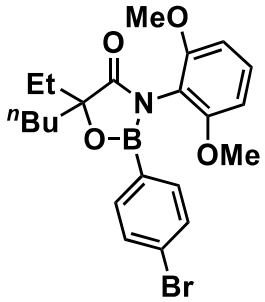
2,5-dibutyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**3r**)



Using ^{n}BuLi (0.9 mL, 1.5 mmol), $B(OMe)_3$ (0.4 mL, 3.5 mmol) and N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (295.8 mg, 1.0 mmol), yielded the product **3r** (87.0 mg, 24%) as viscous oil; IR (cm^{-1}): 2931, 2870, 1732, 1595, 1506, 1477, 1381, 1256, 1111, 772; ^1H NMR (500 MHz, CD_3CN) δ: 7.27 (t, J = 8.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 2H), 3.72 (d, J = 4.3 Hz, 6H), 1.76-1.66 (m, 4H), 1.33-1.20 (m, 8H), 0.89 (t, J = 7.1 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H), 0.79-0.75 (m, 5H); ^{13}C NMR (125 MHz, CD_3CN) δ: 181.9, 155.9 (d, J = 3.4 Hz), 128.8, 113.6, 104.3 (d, J = 1.3 Hz), 87.0, 55.6 (d, J = 3.9 Hz), 37.1, 30.4, 25.3, 25.2, 24.9, 22.6, 13.5, 13.1, 6.7; ^{11}B NMR (160 MHz, CD_3CN)

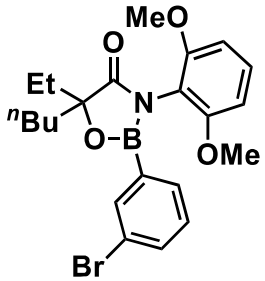
δ: 37.94.

2-(4-bromophenyl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**6a**)



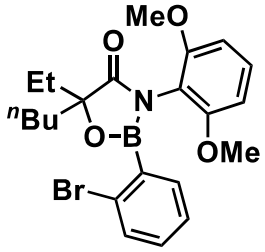
Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (592.3 mg, 2.0 mmol), (4-bromophenyl)boronic acid (442.5 mg, 2.2 mmol), $MgSO_4$ (268.3 mg, 2.2 mmol) and toluene (4.0 mL) at reflux (110°C) for 16 h, yielded the product **6a** (837.4 mg, 91%) as white solid; IR (cm^{-1}): 2949, 1729, 1586, 1506, 1480, 1395, 1357, 1258, 1161, 1110, 1009, 890, 769, 717; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39 (dd, *J* = 8.5, 23.8 Hz, 4H), 7.31 (t, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 3.70 (d, *J* = 3.9 Hz, 6H), 1.99-1.79 (m, 4H), 1.43-1.28 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.1, 155.9 (d, *J* = 4.5 Hz), 135.5, 131.1, 129.2, 126.7, 113.8, 104.4 (d, *J* = 3.1 Hz), 87.6, 55.9 (d, *J* = 9.7 Hz), 37.5, 30.8, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.96.

2-(3-bromophenyl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**6b**)



Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (236.8 mg, 0.8 mmol), (3-bromophenyl)boronic acid (176.6 mg, 0.88 mmol), $MgSO_4$ (190.2 mg, 1.58 mmol) and toluene (1.6 mL) at 110°C for 16 h, yielded the product **6b** (323.0 mg, 88%) as white solid; IR (cm^{-1}): 2965, 2920, 1731, 1593, 1506, 1478, 1411, 1351, 1258, 1108, 901; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.74 (brs, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 3.71 (d, *J* = 4.9 Hz, 6H), 1.99-1.79 (m, 4H), 1.43-1.30 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.0, 155.9 (d, *J* = 4.0 Hz), 136.8, 134.5, 132.2, 129.6, 129.2, 122.5, 113.6, 104.4 (d, *J* = 3.3 Hz), 87.8, 55.9 (d, *J* = 9.3 Hz), 37.5, 30.8, 25.3, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.17.

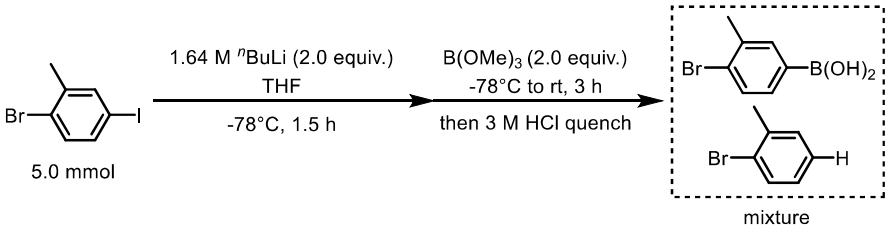
2-(2-bromophenyl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**6c**)



Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-

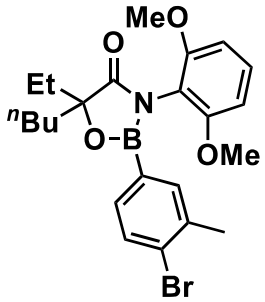
hydroxyhexanamide **1c** (236.5 mg, 0.8 mmol), (2-bromophenyl)boronic acid (175.9 mg, 0.88 mmol), $MgSO_4$ (73.8 mg, 0.61 mmol) and toluene (1.6 mL) at 110°C for 16 h, yielded the product **6c** (296.5 mg, 80%) as white solid; IR (cm^{-1}): 2965, 2939, 1731, 1591, 1504, 1474, 1427, 1362, 1254, 1106, 1028, 890, 768; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.46 (d, J = 7.9 Hz, 1H), 7.18-7.12 (m, 4H), 6.50 (dd, J = 1.9, 8.5 Hz, 2H), 3.69 (d, J = 8.0 Hz, 6H), 2.01-1.82 (m, 4H), 1.62-1.55 (m, 1H), 1.48-1.31 (m, 3H), 1.06 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 182.3, 155.6 (d, J = 3.3 Hz), 134.1, 132.1, 131.3, 128.6, 126.1, 126.0, 113.4, 104.2 (d, J = 4.0 Hz), 88.8, 55.8 (d, J = 9.8 Hz), 37.5, 30.8, 25.4, 22.8, 14.3, 7.6; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 35.50.

The synthesis of (4-bromo-3-methylphenyl)boronic acid



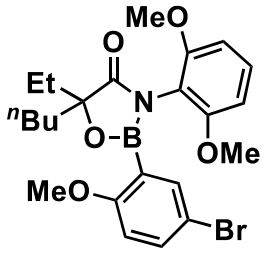
(4-bromo-3-methylphenyl)boronic acid was synthesized with reference to previous report.[16]

2-(4-bromo-3-methylphenyl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**6d**)



Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (147.7 mg, 0.5 mmol), mixture of (4-bromo-3-methylphenyl)boronic acid and 1-bromo-2-methylbenzene, $MgSO_4$ (98.5 mg, 0.82 mmol) and toluene:DMSO=9:1 (1.0 mL) at 110°C for 16 h, yielded the product **6d** (94.8 mg, 40%) as white solid; IR (cm^{-1}): 2939, 1725, 1590, 1506, 1477, 1395, 1356, 1256, 1196, 1164, 1105, 1026, 766, 713; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.31 (t, J = 8.5 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 3.70 (d, J = 5.2 Hz, 6H), 2.31 (s, 3H), 1.99-1.79 (m, 4H), 1.43-1.29 (m, 4H), 0.96 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.0, 156.0 (d, J = 4.1 Hz), 137.3, 136.4, 132.6, 132.0, 129.2, 129.1, 113.9, 104.4 (d, J = 3.1 Hz), 87.6, 55.9 (d, J = 9.3 Hz), 37.5, 30.9, 25.4, 22.93, 22.90, 14.3, 7.3; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.68.

2-(5-bromo-2-methoxyphenyl)-5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**6e**)



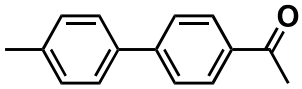
Following the general procedure (condensation method), using N-(2,6-dimethoxyphenyl)-2-ethyl-2-hydroxyhexanamide **1c** (473.3 mg, 1.6 mmol), (5-bromo-2-methoxyphenyl)boronic acid (408.3 mg, 1.77 mmol), $MgSO_4$ (123.9 mg, 1.03 mmol) and toluene (3.2 mL) at reflux (110°C) for 16 h, yielded the product **6e** (631.4 mg, 80%) as white solid; IR (cm^{-1}): 2953, 2934, 2838, 1729, 1593, 1507, 1476, 1395, 1344, 1256, 1160, 1109, 1030, 802, 769; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 2.6 Hz, 1H), 7.38 (dd, *J* = 2.6, 8.7 Hz, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 2H), 3.67 (d, *J* = 5.6 Hz, 6H), 3.44 (s, 3H), 1.99-1.79 (m, 4H), 1.52-1.32 (m, 4H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 182.5, 162.0, 155.6 (d, *J* = 3.6 Hz), 136.8, 134.3, 128.3, 114.7, 112.7, 112.0, 104.3 (d, *J* = 3.4 Hz), 88.0, 55.8 (d, *J* = 9.8 Hz), 55.3, 37.5, 30.8, 25.3, 22.8, 14.3, 7.3; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.53.

General procedures and Characterization data of Suzuki-Miyaura coupling

General procedure for Suzuki-Miyaura cross-coupling

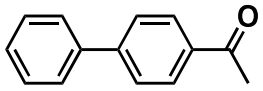
Oxazaborolidinone (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), Ruphos (10 mol%), and K_3PO_4 (2.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar. The corresponding bromoarene (1.0 equiv.) and 1,4-dioxane:H_2O=4:1 (0.5 M) were added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for 6 h at room temperature. After this time, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **5**.

1-(4'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (**5a**)[2]



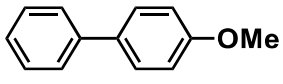
Following the general procedure above, using **3i** (94.7 mg, 0.24 mmol), 1-(4-bromophenyl)ethan-1-one (39.9 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 1.0×10^{-2} mmol), Ruphos (9.7 mg, 2.0×10^{-2} mmol), K_3PO_4 (84.4 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5a** (42.0 mg, >99%) as white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 2.64 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.9, 145.8, 138.3, 137.0, 135.6, 129.7, 129.0, 127.2, 127.0, 26.7, 21.2.

1-([1,1'-biphenyl]-4-yl)ethan-1-one (**5b**)[3]



Following the general procedure above, using **3c** (57.2 mg, 0.15 mmol), 1-(4-bromophenyl)ethan-1-one (19.8 mg, 0.1 mmol), $Pd(OAc)_2$ (1.5 mg, 6.7×10^{-3} mmol), Ruphos (4.8 mg, 1.0×10^{-2} mmol), Na_2CO_3 (20.8 mg, 0.2 mmol) and 1,4-dioxane:H_2O=4:1 (0.2 mL) at 80°C for 17 h, yielded the product **5b** (22.2 mg, >99%) as white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.64-7.62 (m, 2H), 7.49-7.46 (m, 2H), 7.42-7.39 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.9, 145.8, 139.9, 135.9, 129.07, 129.03, 128.3, 127.39, 127.33, 26.7.

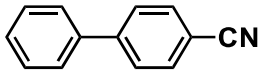
4-methoxy-1,1'-biphenyl (**5c**)[4]



Following the general procedure above, using **3c** (91.5 mg, 0.24 mmol), 1-bromo-4-methoxybenzene (37.5 mg, 0.20 mmol), $Pd(OAc)_2$ (2.6 mg, 1.2×10^{-2} mmol), Ruphos (9.5 mg, 2.0×10^{-2} mmol), K_3PO_4 (84.3 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5c** (32.8 mg, 89%) as white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.55 (dd, *J* = 1.3, 8.3 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7,

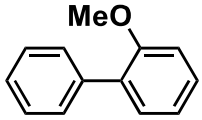
114.3, 55.4.

[1,1'-biphenyl]-4-carbonitrile (**5d**)[5]



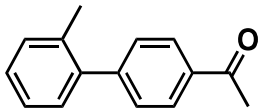
Following the general procedure above, using **3c** (91.4 mg, 0.24 mmol), 4-bromobenzonitrile (36.1 mg, 0.2 mmol), $Pd(OAc)_2$ (2.3 mg, 1.0×10^{-2} mmol), Ruphos (9.5 mg, 2.0×10^{-2} mmol), K_3PO_4 (84.8 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5d** (36.2 mg, >99%) as yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 8.4, 23.2 Hz, 4H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 8.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.7, 139.2, 132.7, 129.2, 128.7, 127.8, 127.3, 119.0, 111.0.

2-methoxy-1,1'-biphenyl (**5e**)[6]



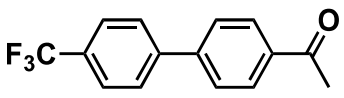
Following the general procedure above, using **3c** (91.5 mg, 0.24 mmol), 1-bromo-2-methoxybenzene (37.6 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 1.0×10^{-2} mmol), Ruphos (9.2 mg, 2.0×10^{-2} mmol), K_3PO_4 (84.9 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5e** (22.2 mg, 60%) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 9.5 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.36-7.33 (m, 3H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.5, 138.6, 131.0, 130.8, 129.6, 128.7, 128.0, 127.0, 120.9, 111.3, 55.6.

1-(2'-methyl-[1,1'-biphenyl]-4-yl)ethan-1-one (**5f**)[7]



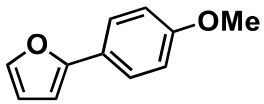
Following the general procedure above, using **3j** (95.6 mg, 0.24 mmol), 1-(4-bromophenyl)ethan-1-one (40.3 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 1.0×10^{-2} mmol), Ruphos (9.5 mg, 2.0×10^{-2} mmol), K_3PO_4 (85.0 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5f** (41.9 mg, 98%) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 3H), 7.23 (d, *J* = 7.2 Hz, 1H), 2.65 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.0, 147.0, 140.8, 135.6, 135.2, 130.6, 129.6, 129.5, 128.3, 128.0, 126.0, 26.7, 20.5.

1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one (**5g**)[8]



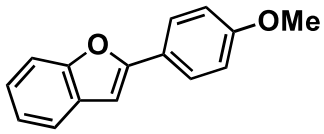
Following the general procedure above, using **3k** (108.3 mg, 0.24 mmol), 1-(4-bromophenyl)ethan-1-one (39.8 mg, 0.2 mmol), $Pd(OAc)_2$ (2.4 mg, 1.0×10^{-2} mmol), Ruphos (9.0 mg, 2.0×10^{-2} mmol), K_3PO_4 (85.0 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5g** (40.6 mg, 77%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.2 Hz, 2H), 7.73 (s, 4H), 7.70 (d, *J* = 8.3 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.7, 144.2, 143.4, 136.6, 130.3 (d, *J* = 32.4 Hz), 129.1, 127.7, 127.5, 126.0 (q, *J* = 3.8 Hz), 124.2 (d, *J* = 271.9 Hz), 26.8.

2-(4-methoxyphenyl)furan (**5h**)[9]



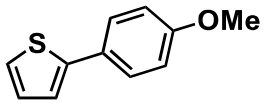
Following the general procedure above, using **3l** (49.7 mg, 0.13 mmol), 1-bromo-4-methoxybenzene (17.2 mg, 0.09 mmol), $Pd(OAc)_2$ (1.1 mg, 4.9×10^{-3} mmol), Ruphos (4.0 mg, 8.6×10^{-3} mmol), Na_2CO_3 (19.3 mg, 0.18 mmol) and 1,4-dioxane:H_2O=4:1 (0.18 mL) at 80°C for 17 h, yielded the product **5h** (19.5 mg, >99%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 9.0 Hz, 2H), 7.43-7.42 (m, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 3.5 Hz, 1H), 6.45-6.44 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.0, 154.1, 141.4, 125.3, 124.1, 114.1, 111.6, 103.4, 55.4.

2-(4-methoxyphenyl)benzofuran (**5i**)[10]



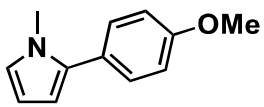
Following the general procedure above, using **3m** (130.6 mg, 0.3 mmol), 1-bromo-4-methoxybenzene (36.7 mg, 0.2 mmol), $Pd(OAc)_2$ (2.3 mg, 1.0×10^{-2} mmol), Ruphos (9.9 mg, 2.0×10^{-2} mmol), Na_2CO_3 (42.9 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at 80°C for 17 h, yielded the product **5i** (36.9 mg, 84%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 9.1 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.25-7.20 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.89 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.0, 156.1, 154.8, 129.6, 126.5, 123.8, 123.4, 122.9, 120.6, 114.3, 111.0, 99.7, 55.4.

2-(4-methoxyphenyl)thiophene (**5j**)[11]



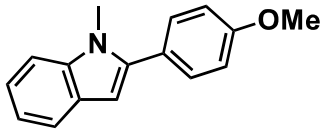
Following the general procedure above, using **3n** (94.8 mg, 0.24 mmol), 1-bromo-4-methoxybenzene (38.0 mg, 0.2 mmol), $Pd(OAc)_2$ (2.5 mg, 1.0×10^{-2} mmol), Ruphos (9.8 mg, 2.0×10^{-2} mmol), K_3PO_4 (84.9 mg, 0.4 mmol) and 1,4-dioxane:H_2O=4:1 (0.4 mL) at room temperature for 6 h, yielded the product **5j** (37.1 mg, 96%) as yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 9.0 Hz, 2H), 7.22-7.19 (m, 2H), 7.06-7.04 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.2, 144.4, 128.0, 127.39, 127.32, 123.9, 122.1, 114.3, 55.4.

2-(4-methoxyphenyl)-1-methyl-1H-pyrrole (**5k**)[12]



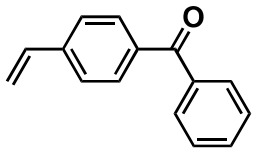
Following the general procedure above, using **3o** (53.6 mg, 0.14 mmol), 1-bromo-4-methoxybenzene (22.6 mg, 0.12 mmol), $Pd(OAc)_2$ (1.5 mg, 6.7×10^{-3} mmol), Ruphos (5.5 mg, 1.2×10^{-2} mmol), K_3PO_4 (50.9 mg, 0.24 mmol) and 1,4-dioxane:H_2O=4:1 (0.24 mL) at room temperature for 6 h, yielded the product **5k** (20.0 mg, 89%) as viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 6.21-6.17 (m, 2H), 3.85 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.7, 134.4, 130.1, 126.0, 123.1, 113.8, 108.0, 107.6, 55.4, 35.0.

2-(4-methoxyphenyl)-1-methyl-1H-indole (**5l**)[13]



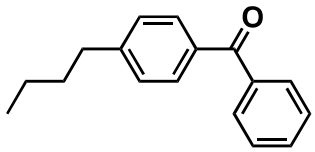
Following the general procedure above, using **3p** (40.3 mg, 0.08 mmol), 1-bromo-4-methoxybenzene (11.7 mg, 0.06 mmol), $Pd(OAc)_2$ (1.0 mg, 4.5×10^{-3} mmol), Ruphos (3.4 mg, 7.3×10^{-3} mmol), K_3PO_4 (25.8 mg, 0.12 mmol) and 1,4-dioxane:H_2O=4:1 (0.12 mL) at room temperature for 6 h, yielded the product **5l** (14.2 mg, 96%) as white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.50 (brs, 1H), 3.88 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.5, 141.5, 138.2, 130.7, 128.0, 125.3, 121.4, 120.3, 119.8, 114.0, 109.6, 101.0, 55.4, 31.1.

phenyl(4-vinylphenyl)methanone (**5m**)[14]



Following the general procedure above, using **3q** (27.1 mg, 0.08 mmol), (4-bromophenyl)(phenyl)methanone (13.6 mg, 0.05 mmol), $Pd(OAc)_2$ (1.0 mg, 4.5×10^{-3} mmol), Ruphos (2.5 mg, 5.4×10^{-3} mmol), K_3PO_4 (21.0 mg, 0.1 mmol) and 1,4-dioxane:H_2O=4:1 (0.1 mL) at 100°C for 2 h, yielded the product **5m** (10.1 mg, 93%) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81-7.78 (m, 4H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.52-7.47 (m, 4H), 6.79 (dd, *J* = 10.8, 18.6 Hz, 1H), 5.90 (d, *J* = 17.6 Hz, 1H), 5.41 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 141.6, 137.8, 136.7, 136.1, 132.4, 130.6, 130.0, 128.3, 126.1, 116.7.

(4-butylphenyl)(phenyl)methanone (**5n**)[15]



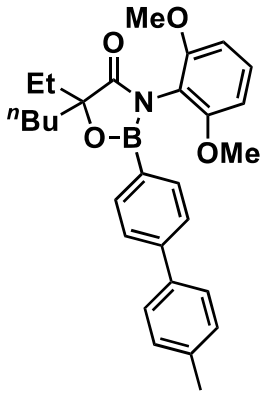
Following the general procedure above, using **3r** (72.3 mg, 0.2 mmol), (4-bromophenyl)(phenyl)methanone (26.1 mg, 0.1 mmol), $Pd(OAc)_2$ (1.3 mg, 5.8×10^{-3} mmol), Ruphos (4.6 mg, 9.9×10^{-3} mmol), K_3PO_4 (42.6 mg, 0.2 mmol) and 1,4-dioxane:H_2O=4:1 (0.1 mL) at 100°C for 19 h, yielded the product **5n** (20.3 mg, 85%) as viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.64 (quin, *J* = 7.6 Hz, 2H), 1.42-1.34 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.9, 148.3, 138.0, 135.1, 132.2, 130.4, 130.0, 128.4, 128.3, 35.8, 33.4, 22.4, 14.0.

General procedures and Characterization data of C-Br bond Suzuki-Miyaura coupling

General procedure for C-Br bond Suzuki-Miyaura coupling

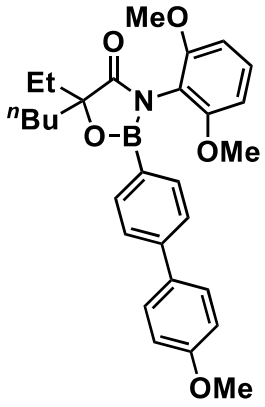
Oxazaborolidinone **6** (1.0 equiv.), the corresponding boronic acid (3.0 equiv.), $Pd(OAc)_2$ (3 mol%) and Sphos (6 mol%) were sequentially added under air to a dram vial equipped with a stir bar. Next, K_3PO_4 (2.0 equiv.) and DCM (0.5 M) were added in the glove box, and the resulting mixture was stirred for 18 h at 50°C. After this time, the reaction mixture was filtered with AcOEt. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired products **7**.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4'-methyl-[1,1'-biphenyl]-4-yl)-1,3,2-oxazaborolidin-4-one (**7a**)



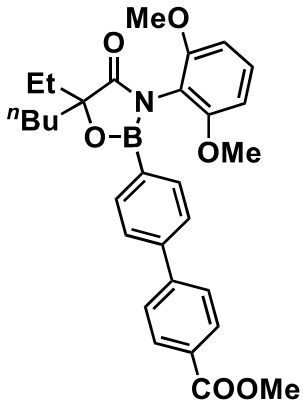
Following the general procedure above, using **6a** (92.6 mg, 0.2 mmol), *p*-tolyl boronic acid **2b** (81.0 mg, 0.6 mmol), $Pd(OAc)_2$ (1.4 mg, 6.0×10^{-3} mmol), Sphos (5.7 mg, 1.4×10^{-2} mmol), K_3PO_4 (85.1 mg, 0.4 mmol) and DCM (0.4 mL) at room temperature for 18 h, yielded the product **7a** (92.6 mg, 98%) as yellow oil; IR (cm^{-1}): 2959, 2931, 1734, 1593, 1477, 1361, 1257, 1110, 802, 772; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.33-7.29 (m, 1H), 7.24-7.22 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 3.72 (d, *J* = 4.6 Hz, 6H), 2.38 (s, 3H), 1.99-1.81 (m, 4H), 1.46-1.31 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 156.2 (d, *J* = 3.9 Hz), 144.2, 137.9, 137.6, 134.6, 129.6, 129.1, 127.1, 126.4, 114.3, 104.5 (d, *J* = 3.0 Hz), 87.5, 56.0 (d, *J* = 8.8 Hz), 37.7, 31.0, 25.5, 23.0, 21.2, 14.4, 7.5; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.66.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4'-methoxy-[1,1'-biphenyl]-4-yl)-1,3,2-oxazaborolidin-4-one (**7b**)



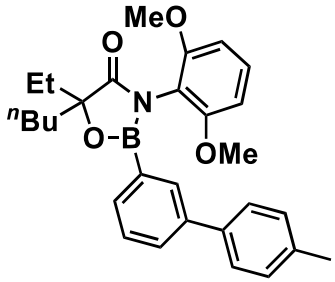
Following the general procedure above, using **6a** (92.6 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid **2c** (89.8 mg, 0.6 mmol), $Pd(OAc)_2$ (3.4 mg, 1.5×10^{-2} mmol), Sphos (11.5 mg, 2.8×10^{-2} mmol), K_3PO_4 (85.2 mg, 0.4 mmol) and DCM (0.4 mL) at room temperature for 18 h, yielded the product **7b** (82.9 mg, 84%) as yellow oil; IR (cm^{-1}): 2937, 2837, 1731, 1596, 1505, 1477, 1397, 1360, 1247, 1162, 1111, 1037, 820, 730; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 3.72 (d, *J* = 4.9 Hz, 6H), 2.00-1.82 (m, 4H), 1.50-1.30 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.2, 159.5, 156.1 (d, *J* = 3.9 Hz), 143.8, 134.6, 133.2, 129.0, 128.2, 126.0, 114.3, 114.2, 104.4 (d, *J* = 3.0 Hz), 87.4, 56.0 (d, *J* = 9.6 Hz), 55.4, 37.6, 30.9, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.23.

methyl 4'-(5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-4-oxo-1,3,2-oxazaborolidin-2-yl)-[1,1'-biphenyl]-4-carboxylate (**7c**)



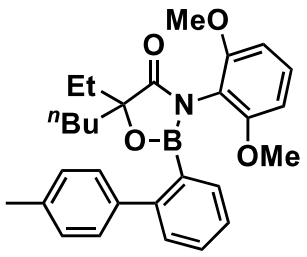
Following the general procedure above, using **6a** (46.0 mg, 0.1 mmol), (4-(methoxycarbonyl)phenyl)boronic acid **2d** (54.9 mg, 0.3 mmol), $Pd(OAc)_2$ (1.8 mg, 7.0×10^{-3} mmol), Sphos (5.4 mg, 1.4×10^{-2} mmol), K_3PO_4 (42.2 mg, 0.2 mmol) and DCM (0.2 mL) at room temperature for 18 h, yielded the product **7c** (40.2 mg, 78%) as yellow solid; IR (cm^{-1}): 2941, 1710, 1596, 1505, 1477, 1363, 1275, 1255, 1102, 831, 770; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.4 Hz, 4H), 7.55 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 8.4 Hz, 1H), 6.66 (d, J = 8.5 Hz, 2H), 3.93 (s, 3H), 3.72 (d, J = 5.4 Hz, 6H), 2.01-1.83 (m, 4H), 1.48-1.31 (m, 4H), 1.00 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.2, 167.0, 156.1 (d, J = 4.0 Hz), 145.2, 142.8, 134.6, 130.2, 129.3, 129.1, 127.1, 126.7, 114.1, 104.5 (d, J = 3.0 Hz), 87.6, 56.0 (d, J = 9.3 Hz), 52.2, 37.6, 30.9, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.13.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4'-methyl-[1,1'-biphenyl]-3-yl)-1,3,2-oxazaborolidin-4-one (**7d**)



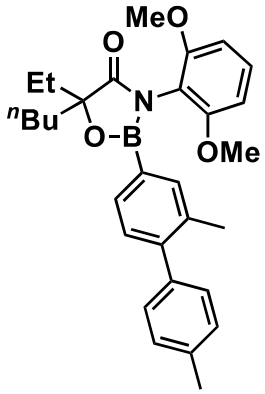
Following the general procedure above, using **6b** (230.6 mg, 0.5 mmol), *p*-tolyl boronic acid **2b** (203.7 mg, 1.5 mmol), $Pd(OAc)_2$ (3.7 mg, 1.6×10^{-2} mmol), Sphos (12.4 mg, 3.0×10^{-2} mmol), K_3PO_4 (212.3 mg, 1.0 mmol) and DCM (1.0 mL) at 50°C for 18 h, yielded the product **7d** (227.2 mg, 96%) as yellow oil; IR (cm^{-1}): 2937, 1731, 1595, 1505, 1477, 1397, 1355, 1256, 1109, 771; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.35-7.31 (m, 4H), 7.20 (d, J = 7.9 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 3.70 (d, J = 5.2 Hz, 6H), 2.38 (s, 3H), 2.01-1.81 (m, 4H), 1.45-1.31 (m, 4H), 0.99 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 156.1 (d, J = 3.7 Hz), 140.1, 138.0, 137.1, 132.65, 132.61, 129.9, 129.5, 129.0, 128.3, 126.8, 114.2, 104.4 (d, J = 3.2 Hz), 87.6, 56.0 (d, J = 9.7 Hz), 37.6, 30.9, 25.4, 22.9, 21.2, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.83.

5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4'-methyl-[1,1'-biphenyl]-2-yl)-1,3,2-oxazaborolidin-4-one (**7e**)



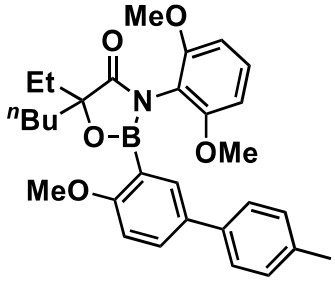
Following the general procedure above, using **6c** (108.7 mg, 0.24 mmol), *p*-tolyl boronic acid **2b** (96.3 mg, 0.71 mmol), $Pd(OAc)_2$ (1.8 mg, 8.0×10^{-3} mmol), Sphos (5.9 mg, 1.4×10^{-2} mmol), K_3PO_4 (101.3 mg, 0.48 mmol) and DCM (0.47 mL) at 110°C for 18 h, yielded the product **7e** (75.4 mg, 68%) as white solid; IR (cm^{-1}): 2954, 2932, 1723, 1593, 1505, 1475, 1357, 1255, 1108, 818, 762; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, J = 7.5 Hz, 1H), 7.37 (dd, J = 1.5, 7.5 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.25-7.21 (m, 3H), 7.11-7.08 (m, 3H), 6.40 (t, J = 8.2 Hz, 2H), 3.56 (d, J = 1.7 Hz, 6H), 2.38 (s, 3H), 1.85-1.73 (m, 4H), 1.37-1.20 (m, 4H), 0.92-0.87 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 182.6, 155.5 (d, J = 6.6 Hz), 146.3, 140.1, 136.3, 133.1, 129.8, 128.9, 128.7, 128.5, 128.3, 125.9, 113.4, 103.9 (d, J = 3.8 Hz), 87.7, 55.4 (d, J = 12.3 Hz), 37.1, 30.4, 25.3, 22.9, 21.2, 14.2, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 35.96.

5-butyl-3-(2,6-dimethoxyphenyl)-2-(2,4'-dimethyl-[1,1'-biphenyl]-4-yl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**7f**)



Following the general procedure above, using **6d** (94.8 mg, 0.2 mmol), *p*-tolyl boronic acid **2b** (82.0 mg, 0.6 mmol), $Pd(OAc)_2$ (1.3 mg, 6.0×10^{-3} mmol), Sphos (5.6 mg, 1.4×10^{-2} mmol), K_3PO_4 (84.9 mg, 0.4 mmol) and DCM (0.4 mL) at 50°C for 18 h, yielded the product **7f** (93.2 mg, 96%) as yellow oil; IR (cm^{-1}): 2935, 1733, 1595, 1506, 1478, 1396, 1360, 1258, 1110, 811, 770; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, J = 3.1 Hz, 1H), 7.36-7.32 (m, 2H), 7.24-7.19 (m, 4H), 7.16-7.14 (m, 1H), 6.68 (d, J = 8.4 Hz, 2H), 3.76-3.74 (m, 6H), 2.42 (s, 3H), 2.24 (s, 3H), 2.06-1.84 (m, 4H), 1.56-1.34 (m, 4H), 1.05-1.02 (m, 3H), 0.96-0.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 156.2 (d, J = 3.6 Hz), 145.2, 138.7, 136.8, 136.3, 134.7, 131.5, 129.5, 129.0, 128.9, 114.3, 104.4 (d, J = 2.6 Hz), 87.4, 56.0 (d, J = 9.1 Hz), 37.7, 31.0, 25.5, 23.0, 21.3, 20.6, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 33.95.

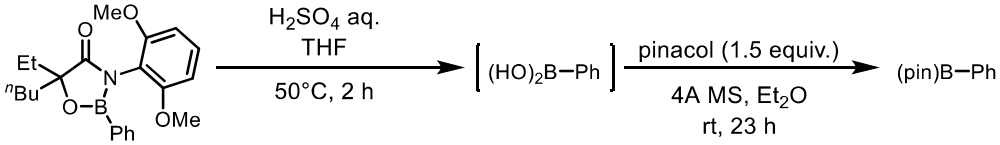
5-butyl-3-(2,6-dimethoxyphenyl)-5-ethyl-2-(4-methoxy-4'-methyl-[1,1'-biphenyl]-3-yl)-1,3,2-oxazaborolidin-4-one (**7g**)



Following the general procedure above, using **6e** (245.9 mg, 0.5 mmol), *p*-tolyl boronic acid **2b** (203.9 mg, 1.5 mmol), $Pd(OAc)_2$ (3.5 mg, 1.6×10^{-2} mmol), Sphos (12.7 mg, 3.1×10^{-2} mmol), K_3PO_4 (212.3 mg, 1.0 mmol) and DCM (1.0 mL) at 50°C for 18 h, yielded the product **7g** (194.3 mg, 77%) as white solid; IR (cm^{-1}): 2929, 2856, 1739, 1593, 1475, 1394, 1343, 1256, 1109, 1021, 908, 809, 771; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 2.4 Hz, 1H), 7.51 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.19 (t, *J* = 8.5 Hz, 3H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.57-6.55 (m, 2H), 3.65 (d, *J* = 8.8 Hz, 6H), 3.59 (s, 3H), 2.36 (s, 3H), 2.00-1.81 (m, 4H), 1.46-1.33 (m, 4H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 182.8, 162.6, 155.8 (d, *J* = 2.9 Hz), 138.0, 136.3, 133.2, 132.8, 130.3, 129.4, 128.2, 126.5, 115.0, 110.4, 104.4 (d, *J* = 5.8 Hz), 87.9, 55.9 (d, *J* = 9.7 Hz), 55.4, 37.5, 30.9, 25.3, 22.9, 21.1, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 35.43.

General procedures and Characterization data of deprotection, coupling with aryl chloride and iterative coupling

#1 Deprotection

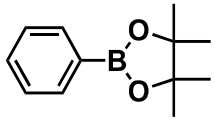


3c **2a**: >99% (NMR) **2a'**: 74%

General procedure for deprotection and synthesis of PhBpin **2a'**

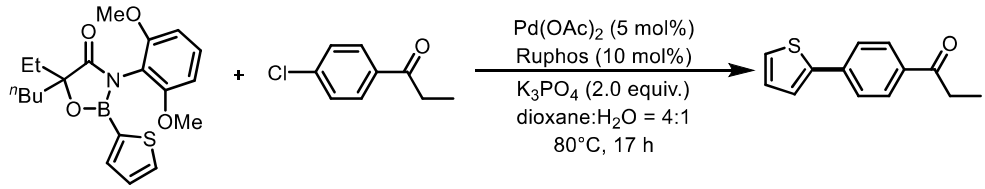
Oxazaborolidinone **3c** (1.0 equiv.), H_2O (15 equiv.) and THF (0.5 M) were added under air to a dram vial equipped with a stir bar. Next, H_2SO_4 (5.0 equiv.) was added at 0°C under air, and the resulting mixture was stirred for 2 h at 50°C. After this time, the reaction mixture was extracted with AcOEt and dried with anhydrous Na_2SO_4. After removal of the solvent in vacuum, NMR measurements were performed to calculate the yield of boronic acid **2a** (NMR solvent: d_6-DMSO:D_2O = 10:1, internal standard: dibenzyl ether). After NMR measurements, the mixture was extracted with AcOEt and dried with anhydrous Na_2SO_4. After removal of the solvent in vacuum, pinacol (1.5 equiv.), 4A MS and Et_2O (0.33 M) were added under air. The mixture was stirred at room temperature for 23 h. After this time, the reaction mixture was filtered with AcOEt. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired product **2a'**.

4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**2a'**)[17]



Following the general procedure above, using **3c** (190.7 mg, 0.5 mmol), H_2SO_4 (0.13 mL, 2.5 mmol), H_2O (0.14 mL, 7.5 mmol), THF (1 mL) at 50°C for 2 h, then pinacol (88.6 mg, 0.75 mmol), 4A MS and Et_2O (1.5 mL) at room temperature for 23 h, yielded the product **2a'** (75.3 mg, 74%) as viscous oil; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 1.35 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.8, 131.3, 127.8, 83.8, 24.9.

#2 Coupling with aryl chloride

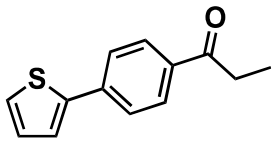


3n (1.2 equiv.) (1.0 equiv.) **5o:** 96%

General procedure for synthesis of **5o**

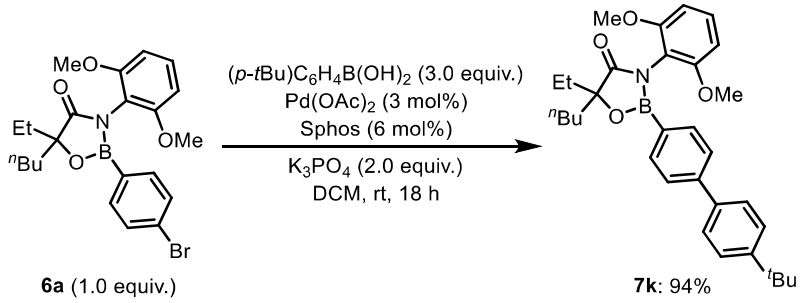
Oxazaborolidinone **3n** (1.2 equiv.), 1-(4-chlorophenyl)propan-1-one (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), Ruphos (10 mol%), and K_3PO_4 (2.0 equiv.) were sequentially added under air to a dram vial equipped with a stir bar. Next, 1,4-dioxane:H_2O=4:1 (0.5 M) was added by syringe, and the resulting mixture was vigorously stirred under nitrogen atmosphere [charged by general N_2 (99.95%) gas flow] for 17 h at 80°C. After this time, the reaction mixture was extracted with AcOEt and dried with anhydrous $MgSO_4$. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired product **5o**.

1-(4-(thiophen-2-yl)phenyl)propan-1-one (**5o**)[18]

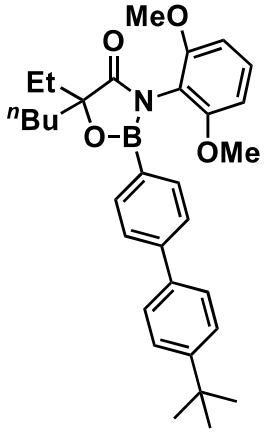


Following the general procedure above, using **3n** (171.1 mg, 0.44 mmol), 1-(4-chlorophenyl)propan-1-one (60.2 mg, 0.36 mmol), $Pd(OAc)_2$ (4.5 mg, 2.0×10^{-2} mmol), Ruphos (16.4 mg, 3.5×10^{-2} mmol), K_3PO_4 (152.4 mg, 0.72 mmol) and 1,4-dioxane:H_2O=4:1 (0.72 mL) at 80°C for 17 h, yielded the product **5o** (74.0 mg, 96%) as white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.43 (dd, J = 1.1, 3.7 Hz, 1H), 7.37 (dd, J = 1.1, 5.1 Hz, 1H), 7.12 (dd, J = 3.6, 5.0 Hz, 1H), 3.02 (q, J = 7.3 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.1, 143.1, 138.6, 135.6, 128.8, 128.4, 126.4, 125.7, 124.6, 31.8, 8.3.

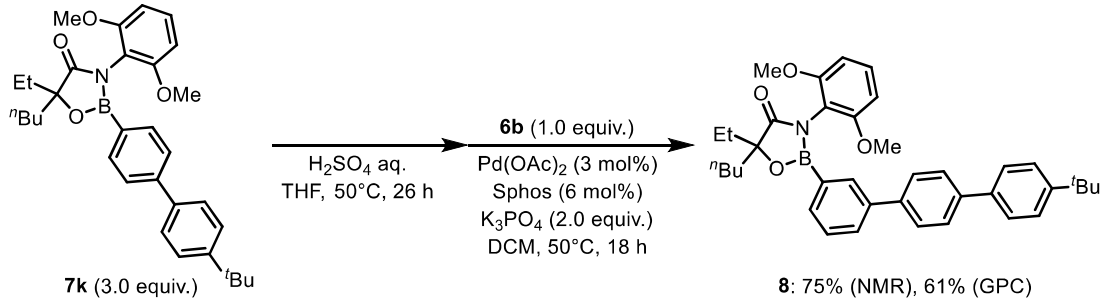
#3 Iterative coupling



5-butyl-2-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**7k**)



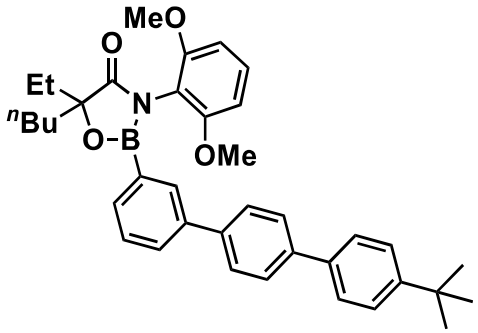
Following the general procedure for C-Br bond Suzuki-Miyaura coupling, using **6a** (230.4 mg, 0.5 mmol), (4-(tert-butyl)phenyl)boronic acid **2e** (268.5 mg, 1.5 mmol), $Pd(OAc)_2$ (3.4 mg, 1.5×10^{-2} mmol), Sphos (12.4 mg, 3.0×10^{-2} mmol), K_3PO_4 (214.3 mg, 1.0 mmol) and DCM (1.0 mL) at room temperature for 18 h, yielded the product **7k** (242.9 mg, 94%) as yellow oil; IR (cm^{-1}): 2955, 2867, 1733, 1595, 1506, 1477, 1360, 1256, 1162, 1110, 819, 730; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, J = 8.5 Hz, 2H), 7.51 (dd, J = 2.8, 8.7 Hz, 4H), 7.44 (d, J = 8.7 Hz, 2H), 7.32 (t, J = 8.5 Hz, 1H), 6.66 (d, J = 8.5 Hz, 2H), 3.72 (d, J = 4.8 Hz, 6H), 2.01-1.81 (m, 4H), 1.48-1.35 (m, 4H), 1.35 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.2, 156.1 (d, J = 3.7 Hz), 150.8, 144.0, 137.9, 134.5, 129.0, 126.8, 126.4, 125.8, 114.3, 104.5 (d, J = 2.9 Hz), 87.4, 56.0 (d, J = 9.4 Hz), 37.6, 34.6, 31.4, 30.9, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.34.



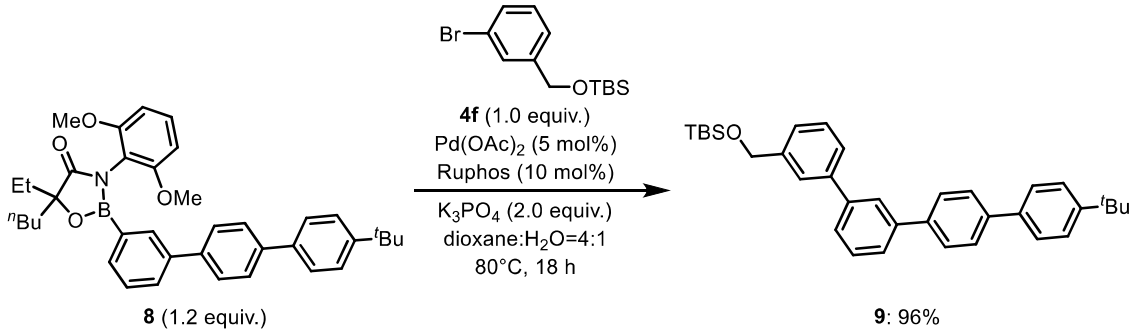
Oxazaborolidinone **7k** (3.0 equiv.), H_2O (15.0 equiv.) and THF (0.5 M) were added under air to a dram vial equipped with a stir bar. Next, H_2SO_4 (15.0 equiv.) was added at 0°C under air, and the

resulting mixture was stirred for 26 h at 50°C. After this time, the reaction mixture was extracted with AcOEt and dried with anhydrous Na_2SO_4. After removal of the solvent in vacuum, the residue was dried under reduced pressure for 6 hours. After 6 h, oxazaborolidinone **6b** (1.0 equiv.), boronic acid by deprotection from **7k**, $Pd(OAc)_2$ (3 mol%) and Sphos (6 mol%) were sequentially added under air to a dram vial equipped with a stir bar. Next, K_3PO_4 (2.0 equiv.) and DCM (0.5 M) were added in the glove box, and the resulting mixture was stirred for 18 h at 50°C. After this time, the reaction mixture was filtered with AcOEt. After removal of the solvent in vacuum, the residue was purified with silica gel column chromatography to give desired product **8**.

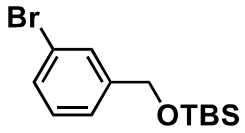
5-butyl-2-(4"-(tert-butyl)-[1,1':4',1"-terphenyl]-3-yl)-3-(2,6-dimethoxyphenyl)-5-ethyl-1,3,2-oxazaborolidin-4-one (**8**)



Using **7k** (385.1 mg, 0.75 mmol), H_2SO_4 (0.2 mL, 3.75 mmol), H_2O (0.07 mL, 3.75 mmol) and THF (1.5 mL) at 50°C for 26 h, then **6b** (115.0 mg, 0.25 mmol), $Pd(OAc)_2$ (1.6 mg, 7.5×10^{-3} mmol), Sphos (6.1 mg, 1.5×10^{-2} mmol), K_3PO_4 (106.1 mg, 0.5 mmol) and DCM (0.5 mL) at 50°C for 18 h, yielded the product **8** (89.0 mg, 61%) as white solid; IR (cm^{-1}): 2955, 2867, 1732, 1595, 1502, 1477, 1356, 1256, 1161, 1109, 824, 770; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (brs, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.55-7.51 (m, 5H), 7.41-7.34 (m, 2H), 6.70 (d, J = 8.6 Hz, 2H), 3.73 (d, J = 7.2 Hz, 6H), 2.06-1.86 (m, 4H), 1.51-1.37 (m, 4H), 1.41 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 183.3, 156.2 (d, J = 3.5 Hz), 150.5, 140.0, 139.8, 139.5, 137.8, 132.9, 132.7, 130.0, 129.1, 128.4, 127.4, 127.3, 126.7, 125.9, 114.3, 104.5 (d, J = 2.7 Hz), 87.6, 56.0 (d, J = 9.1 Hz), 37.6, 34.6, 31.5, 31.0, 25.4, 22.9, 14.3, 7.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ: 34.34.



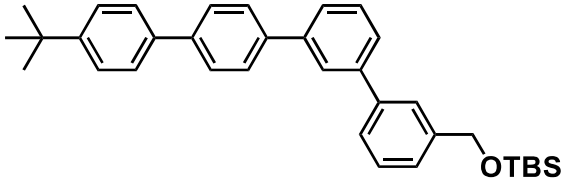
1-(4-bromophenyl)ethan-1-one (**4f**)



4f was synthesized with reference to previous report.[19]
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (brs, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 4.71 (s, 2H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:

143.9, 130.0, 129.8, 129.1, 124.5, 122.5, 64.2, 26.0, 18.4, -5.2.

tert-butyl((4'''-(tert-butyl)-[1,1':3',1'':4'',1'''-quaterphenyl]-3-yl)methoxy)dimethylsilane (**9**)



Following the general procedure for Suzuki-Miyaura cross-coupling, using **8** (79.0 mg, 0.13 mmol), 1-(4-bromophenyl)ethan-1-one **4f** (33.1 mg, 0.11 mmol), $Pd(OAc)_2$ (1.2 mg, 5.5×10^{-3} mmol), Ruphos (5.2 mg, 1.1×10^{-2} mmol), K_3PO_4 (46.5 mg, 0.22 mmol) and 1,4-dioxane:H_2O=4:1 (0.22 mL) at 80°C for 18 h, yielded the product **9** (53.7 mg, 96%) as white solid; IR (cm^{-1}): 2952, 2925, 2855, 1498, 1464, 1360, 1252, 1096, 1002, 823, 782, 700; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.86 (s, 1H), 7.73-7.68 (m, 4H), 7.63-7.58 (m, 5H), 7.55-7.53 (m, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 4.83 (s, 2H), 1.38 (s, 9H), 0.97 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.5, 142.1, 141.9, 141.4, 141.1, 140.2, 139.8, 137.8, 129.3, 128.8, 127.6, 127.4, 126.8, 126.2, 126.1, 126.0, 125.9, 125.8, 125.2, 125.0, 65.0, 34.6, 31.4, 26.1, 18.5, -5.0.

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Conclusion

The tetrasubstituted alkyl compounds are carbon compounds with four bulky substituents except for hydrogen atom. The tetrasubstituted carbon moieties are common structures of various bioactive molecules, and the development of efficient tetrasubstituted carbon moiety construction methods is a very important issue. Nucleophilic substitution reaction is unlikely to occur due to steric hindrance between alkyl halide and nucleophile, and elimination reaction that are not much affected by the steric hindrance are preferred. Therefore, it is very difficult to synthesize tetrasubstituted alkyl compounds by nucleophilic substitution reaction. In the radical reaction, radical species are highly active, so it has become possible to overcome the effects of steric hindrance between haloalkanes and substrates. With the development of radical chemistry, the problem of steric hindrance has been alleviated, but there are still problems.

Problem 1

When aiming for the synthesis of complex compounds, there may be situations where compounds having multiple leaving groups are used to react, but if there are leaving groups with similar reactivity, it is difficult to selectively activate only one of them, and both leaving groups are likely to react.

Problem 2

It is difficult to reflect the stereochemistry of chiral starting material in the product when free radical species are generated. Due to the planar free radical species, racemization proceeds when the substrate is introduced.

Solution to problem 1

In chapter 3, the photoredox-catalyzed enamide Heck-type tertiary alkylation via carbon-carbon bond cleavage of cyclohexadienone derivatives was developed. I have developed a method of using the cyclohexadienone moiety as a new active group and found that it can be activated in the presence of visible light catalyst. Also, by using the difference in the activation energy of the leaving group, C-C bond cleavage of cyclohexadienone could be applied to chemoselective coupling.

Solution to problem 2

In chapter 4, I have developed stereopecific hydroxylations of chiral α-bromocarboxamides. The reaction occurred in a retentive manner via an aziridinone intermediate. Also, in chapter 5, I developed stereospecific fluorination in the presence of Cu catalyst. In this reaction, the stereoretentive product could be obtained. I suggested that the reaction proceeds via in-cage radical species produced by the action of copper catalyst. Both stereospecific tertiary alkylation reactions do not proceed through free radical species with planarity.

Thus, I was able to develop several methods for the synthesis of tetrasubstituted carbon compounds in this paper

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Acknowledgement

I would like to express my deepest gratitude to Prof. Nishikata, who gave me a great deal of guidance as my supervisor in carrying out this research. In addition, Prof. Kamimura, Prof. Kawamoto, Prof. Onimura, and Prof. Yamabuki provided appropriate advice as chief and co-examiners in the preparation of this paper. I would like to express my deepest gratitude here. Lastly, I would like to express my sincere gratitude to the members of the Nishikata Laboratory for their great advice and cooperation in carrying out this research. I would like to express my gratitude here.