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First asymmetric intermolecular bromoesterification catalyzed by chiral Brønsted acid

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ABSTRACT

The first successful enantioselective intermolecular bromoesterification was realized by using a chiral phosphoric acid as a catalyst. The reaction was optimized after screening 2-aminopyridine based basic catalysts, cinchona alkaloid based basic catalysts, and binol backbone based Brønsted acid catalysts. Up to 70% ee and a moderate yield were achieved under the optimized condition. An ion-pair mechanism has been suggested in order to explain the reaction results.

1. Introduction

The electrophilic halogenations of alkenes via a halogenium ion, such as haloetherification, halolactonization, and haloamidation are fundamental transformations in organic chemistry.[1] Haloesterification is one of the most important reactions to functionalize a double bond. The versatile product of this reaction can be employed in a wide range of diverse transformations.[2] The asymmetric halolactonization was initially accomplished either by substrate-controlled synthesis with a chiral auxiliary[3] or by a reagent-controlled reaction with a chiral halonium cation.[4] Although much effort has been undertaken, enantioselective catalytic halolactonizations have not been well developed over the past two decades.[5] In 2010, Borhan et al. made a breakthrough in the highly enantioselective chlorolactonization of 4-aryl-substituted 4-pentenoic acids catalyzed by $(DHQD)_2PHAL$ by introducing DCDPH as a chloronium source.[6] Following this work, Tang et al. reported an highly enantioselective bromolactonization of conjugated *Z*-enynes with a bifunctional cinchona-alkaloid catalyst bearing a urea moiety.[7] The enantioselective iodolactonization catalyzed by a tertiary aminourea derivative was reported by Jacobsen et al.[8] Yeung et al. have also developed an amino-thiocarbamate-catalyzed asymmetric bromolactonization of unsaturated carboxylic acids.[9] Based on molecular recognition, Fujioka et al. reported the enantioselective bromolactonization of 5-substituted 5-hexenoic acids catalyzed by a C_3-symmetric chiral trisimidazoline in the same year.[10] The successful haloesterifications have two common features: (1) all the researches focused on intramolecular haloesterifications without exception. (2) The catalysts used were designed based on chiral amines, such as alkaloid derivatives or imidazolines, which catalyzed the halolactonization either by activating halonium-cations or by interacting with a carboxyl group.

Despite recent efforts in halolactonization, the catalytic asymmetric intermolecular haloesterification remains a considerable challenge. To the best of our knowledge, there has been only one publication which recorded an attempt to catalyze the asymmetric intermolecular haloesterification up to now. However, no induced enantioselectivity was observed in this work when using chiral amine catalysts.[11] The development of such methods presents a particular challenge, due in part to the propensity of the intermediate bromonium ions to racemize by transfer between alkenes at rates that are competitive with nucleophilic capture.[12] Herein we report the first enantioselective intermolecular bromoesterification catalyzed by chiral Brønsted acids.

2. Results and discussion

We initiated our research by re-screening the alkaloid derivatives and designing new chiral amine catalysts based on aminopyridine which could recognize the carboxyl group through double hydrogen bonds.[13] Less than 10% ee was obtained after screening large numbers of chiral amines (Scheme 1); this forced us to re-evaluate our strategy of catalyst design. The first enantioselective haloesterification was achieved with a chiral titanium complex.[14] Lewis acids, such as salen-Co and salen-Cr, had been successfully employed in the asymmetric cyclic haloetherification with up to 90% ee being obtained.[15] Recently, Feng et al. reported a highly efficient haloamination reaction catalyzed by a chiral *N, N′*-dioxide–Sc(III) complex.[16] The first chiral Lewis acid catalyzed asymmetric iodolactonization was reported about 20 years ago; since then,

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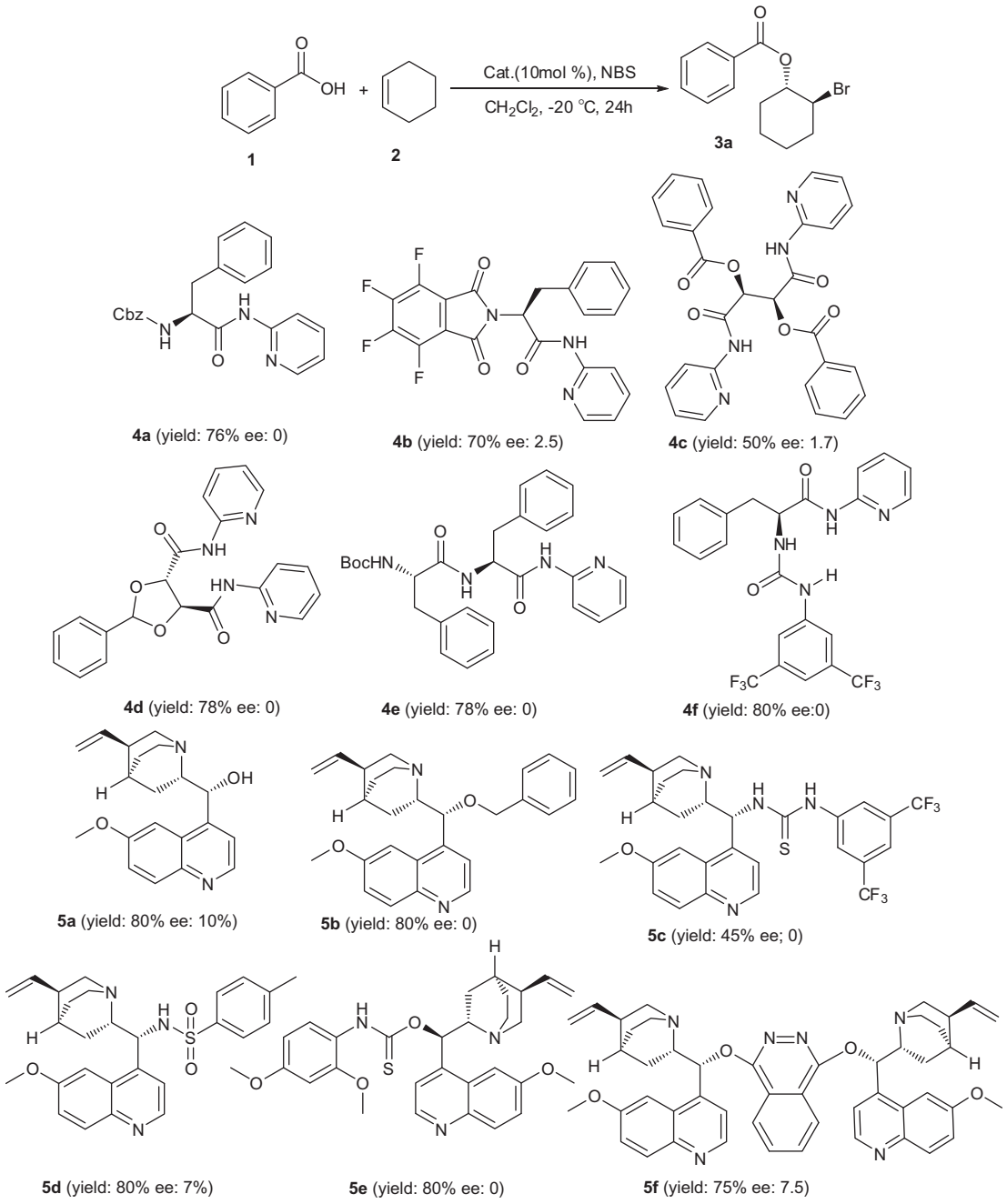


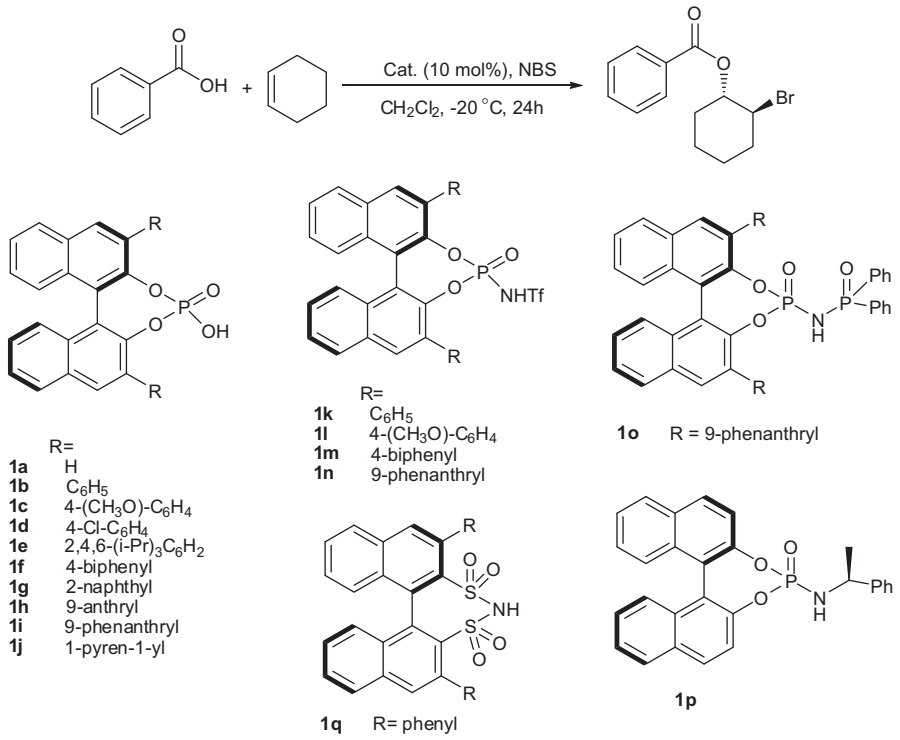
Scheme 1. Screening of catalysts derived from 2-aminopyridine and a cinchona alkaloid.

there has been only one more work using a chiral Lewis acid in a haloesterification.[5f]

Chiral phosphoric acids are one of the most widely applied Brønsted acid catalysts for a variety of organic transformations.[17] Compared to chiral metal Lewis acid catalysts, organic phosphoric acids are not only insensitive to moisture and oxygen, but also low-cost and environmentally friendly. Recently, several groups have reported the use of chiral phosphoric acids for enantioselective intramolecular bromoetherifications[5h,i] and bromoaminocyclizations.[5j] However, when they were employed to catalyze an intermolecular haloesterification, the self-haloesterification of the chiral phosphoric acids with alkene substrate could be the greatest challenge.

When 10% of the simplest chiral phosphoric acid **1a** (Scheme 2) was employed in the intermolecular bromoesterification between benzoic acid and cyclohexene, 21% of *trans*-2-bromocyclohexyl benzoate was produced while less than 3% product was obtained in the background reaction (Table 1, entries 1 and 2), which indicated that phosphoric acid **1a** was able to catalyze the bromoesterification between benzoic acid and cyclohexene, even though no enantioselectivity was detected. This result is noteworthy since the catalyst **1a** itself could react with cyclohexene to give the bromoesterification product in 78% yield under the same reaction conditions. Thus, a series of chiral phosphoric acids **1b**–**1j** with different 3,3′-substituted BINOL backbones were used in the reaction (Scheme 2), and their catalytic results are illustrated in Table 1 (entries 2–11).

The best result obtained was with the 9-phenanthryl substituted chiral Brønsted acid **1i**, which gave the bromoesterification product with 31% enantioselectivity and 23% yield (Table 1, entry



Scheme 2. Chiral Brønsted acids employed in intermolecular bromoesterification.

Table 1
Catalytic result of bromoesterification with catalysts **1a**–**1q**

Entry	Cat	Yield (%)	ee %	Entry	Cat	Yield (%)	ee %
1	NO	3	0	10	**1i**	23	31
2	**1a**	21	0	11	**1j**	19	13
3	**1b**	20	11	12	**1k**	19	0
4	**1c**	18	10	13	**1l**	15	0
5	**1d**	21	11	14	**1m**	18	0
6	**1e**	21	13	15	**1n**	26	0
7	**1f**	19	15	16	**1o**	16	0
8	**1g**	21	11	17	**1p**	13	0
9	**1h**	20	0	18	**1q**	0	0

10). Chiral phosphoramides have displayed better catalytic ability in many asymmetric reactions when compared with phosphoric acid catalysts because of their enhanced acidity.[18] The introduction of an NHTf group into the phosphoryl moiety may decrease the catalyst's self-bromoesterification due to the large steric hindrance, and so the yield of the desired intermolecular bromoesterification product increases. However, when chiral phosphoramides **1k**–**1n** (Scheme 2) were employed in our reaction, no enantioselectivity was observed, and at the same time, the yields of all these reaction were much less than those of the reactions catalyzed by the corresponding chiral phosphoric acids (Table 1, entries 12–15). Similar results were obtained by using bulky phosphoramides and chiral disulfonimide (**1o**–**1q**, Scheme 2). These data indicated that increasing the acidity and steric hindrance of the catalyst did not improve neither the yield nor the enantioselectivity of the intermolecular bromoesterification. After screening different chiral Brønsted acids, we found the best catalyst to be the chiral phosphoric acid **1i**.

Various solvents including CH_2Cl_2, $CHCl_3$, toluene, ethyl ether, and mixed solvents were evaluated; the CH_2Cl_2/cyclohexane (1:3) mixture was identified as the best solvent system. Next, we optimized the reaction temperature and found that decreasing the temperature to −40 °C increased the enantioselectivity to

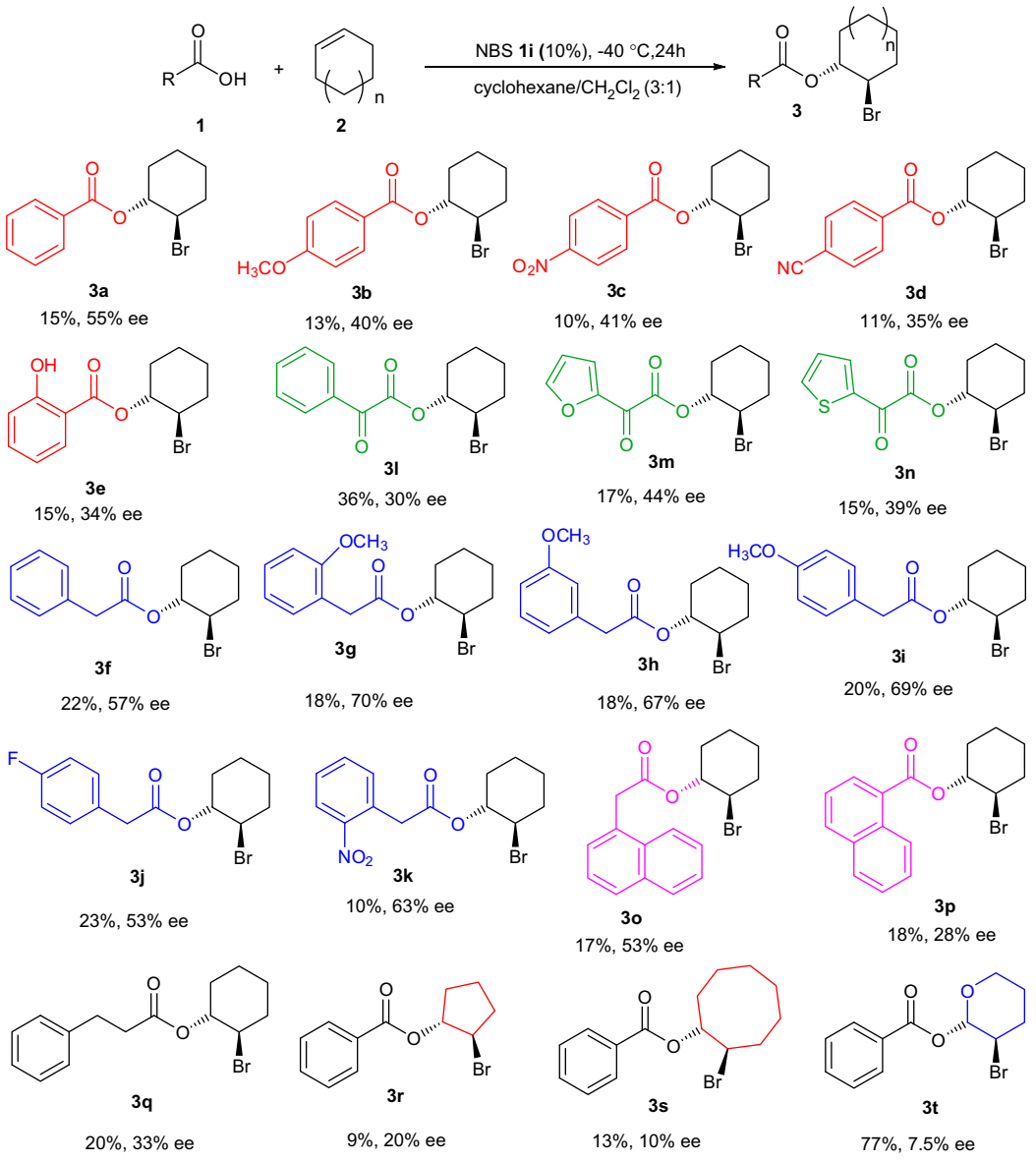
Table 2
Optimization of the reaction condition

Entry	Halogen	Cat (%)	Yield (%)	ee (%)
1	NBS	10	15	55
2	NCS	10	—	—
3	NIS	10	35	0
4	DBDMH	10	80	0
5	NBP	10	8	38

55% ee. However, lowering the temperature further did not increase the enantioselectivity but slightly decreased the yield. Different types of halogen sources including *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), *N*-bromophthalimide (NBP), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) were tested, but none of them were found to be better than NBS in terms of ee (Table 2, entries 2–5).

Under the optimized condition, we explored the scope of the asymmetric intermolecular bromoesterification catalyzed by chiral phosphoric acid **1i**. Benzoic acid derivatives with different substitutions were thus investigated (Scheme 3).

All of the reactions were performed smoothly with moderate ee values. Benzoic acid derivatives **3a**–**3e** with electron donating or electron withdrawing groups, gave lower ee values compared to benzoic acids (Scheme 3). The more acidic α-keto acids **3l**–**3m** were evaluated next (Scheme 3), and gave similar results to those obtained with benzoic acids. When 2-arylacetic acids **3f**–**3j** were used in the intermolecular bromoesterification, much better enantioselectivities were obtained (Scheme 3). Meanwhile, a clear correlation became obvious between the electronic properties of the aryl ring and the stereoselectivity: the 2-arylacetic acids **3g**–**3i** with electron donating groups (Scheme 3) afforded higher enantioselectivities than those with electron withdrawing groups (**3j** and **3k**, Scheme 3). The highest enantioselectivity of 70% ee was obtained when 2-(2-methoxyphenyl)acetic acid **3g** was reacted with cyclohexene (Scheme 3). When one more methylene



Scheme 3. Substrate scope in the catalytic intermolecular bromoesterification reaction.

group was inserted into the 2-phenylacetic acid, the enantioselectivity decreased dramatically (**3q**, Scheme 3). Sterically hindered acids were also investigated, but the steric effect appeared to have a negative influence on the ee values (**3o**–**3p**, Scheme 3). Changing the ring size of the cyclic-olefin resulted in a decrease of the ee values (**3r**–**3s**, Scheme 3). When an oxygenated cyclohexene was applied to the reaction, only α-bromo-β-benzoate tetrahydropyran **3t** was obtained with a high yield (Scheme 3).

The absolute configuration of **3a** was assigned according to the literature.[19] On the basis of the experimental data and literatures,[20,5h] a reaction mechanism was proposed (Fig. 1). The reaction could be initiated by transferring the bromonium ion from NBS to cyclohexene; the basic *N*-succinimide anion then forms an ion pair complex with the positively charged bromonium ion. The nucleophilic oxygen atom on the phosphate group interacts with the acid substrate through a hydrogen bond, which thus induces nucleophilic attack on the cyclic bromonium ion by the carboxyl group in a chiral environment (**TS**, Fig. 1). The proton of the acid substrate is left to the phosphate group to regenerate the chiral phosphoric catalyst. In the ion pair intermediate (**ip-M**, Fig. 1), the oxygen of the phosphate group could also attack the cyclic bromonium ion to give the self-bromoesterification by-product, which could result in a decline of the catalytic loading and thus decrease the reaction yield. The interaction between the chiral phosphoric acid catalyst and the acid substrate in the transition state (**TS**, Fig. 1) explains the disappearance of the enantioselectivity when phosphoramides were employed in the same reaction. We speculate that the bulky NHTf group blocked the connection between the catalyst and the acid substrate.

3. Conclusion

In conclusion, we have presented the first successful example of enantioselective intermolecular bromoesterification by using chiral Brønsted acids as catalysts. Up to 70% ee was achieved by a 9-phenanthryl substituted chiral phosphoric acid catalyst, but self-bromoesterification of the catalyst meant that the product was obtained in low yield. The proposed ion pair mechanism provides new ideas with regards to catalyzing and controlling the stereoselectivity of the haloesterification reactions. Further

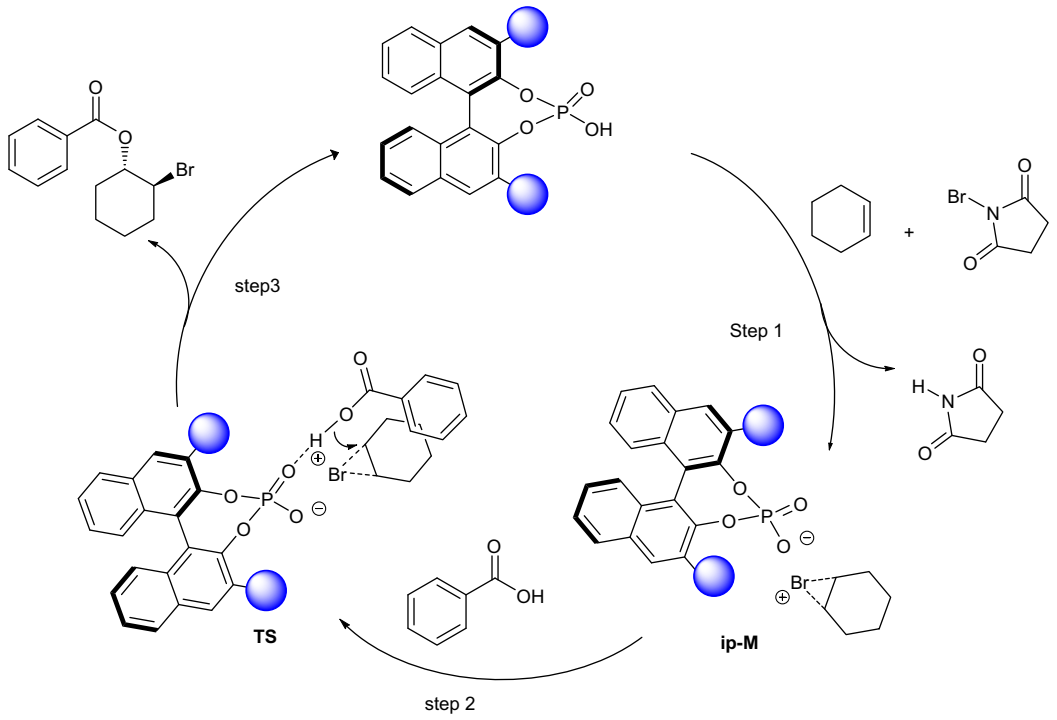


Figure 1. The proposed mechanism.

investigation of the reaction mechanism and the development of new Brønsted acid catalysts for haloesterification are currently underway in our laboratory.

4. Experimental

All reactions that required anhydrous conditions were carried out by standard procedures under a nitrogen atmosphere. Commercially available reagents from Alfa Aesar and Aldrich were used as received. The solvents were dried by distillation over the appropriate drying reagents. Enantiomeric excesses (ee) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with a UV detector at 254 and 280 nm. ^{1}H NMR spectra were recorded on commercial instruments (300 or 150 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR spectra were collected on commercial instruments (300 or 600 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0).

4.1. General procedure for the intermolecular bromoesterification

To a solution of acid **1** (0.2 mmol) in CH_2Cl_2, cyclohexane (0.5 mL: 1.5 mL), catalyst **1i** (14 mg, 0.02 mmol), and NBS (44.5 mg, 0.25 mmol) were added sequentially, the reaction solution was stirred at −40 °C for 30 min followed by gradually adding olefin **2** (0.2 mmol) in 10 min. The reaction mixture was stirred at −40 °C for 48 h and directly purified by flash column chromatography eluting with ethyl acetate and hexane.

4.1.1. 2-Bromocyclohexyl 4-methoxybenzoate) 3b

Yellowish oil, $[\alpha]_D^{20} = +2.5$ (*c* 0.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, 2H, *J* = 8.64 Hz), 6.92 (d, 2H, *J* = 8.82 Hz), 5.10 (m, 1H), 4.15 (m, 1H), 3.86 (s, 3H), 2.41 (m, 1H), 2.27 (m, 1H), 1.97 (m, 1H), 1.82 (m, 2H), 1.42 (m, 1H), 1.24 (m, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.33, 163.47, 131.76, 122.67, 113.63, 76.00, 55.44, 52.78, 35.49, 31.08, 25.38, 23.27. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}BrO_3$[M+Na]$^+$: 335.0253, found: 335.0257. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 11.9 min, t_{R2} = 13.9 min.

4.1.2. 2-Bromocyclohexyl 4-nitrobenzoate 3c

Brown oil, $[\alpha]_D^{20} = +1.6$ (*c* 0.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, 2H, *J* = 9.9 Hz), 8.24 (d, 2H, *J* = 9.8 Hz), 5.15 (m, 1H), 4.15 (m, 1H), 2.45 (m, 1H), 2.30 (m, 1H), 2.04 (m, 1H), 1.98 (m, 2H), 1.54 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 163.77, 150.63, 135.52, 130.85, 123.55, 52.38, 35.81, 31.39, 25.65, 23.35; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}BrNO_4$ [M+Na]$^+$: 349.9996, found: 349.9998. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 13.5 min, t_{R2} = 14.1 min.

4.1.3. 2-Bromocyclohexyl 4-cyanobenzoate 3d

White powder, mp 65–68 °C, $[\alpha]_D^{20} = +4.8$ (*c* 0.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (d, 2H, *J* = 17.7 Hz), 7.76 (d, 2H, *J* = 17.6 Hz), 5.16 (m, 1H), 4.12 (m, 1H), 2.40 (m, 1H), 2.27 (m, 1H), 1.92 (m, 3H), 1.36 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.01, 134.08, 132.22, 130.24, 117.96, 116.49, 76.81, 52.40, 35.77, 31.35, 25.62, 23.41; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}BrO_2$[M+Na]$^+$ = 330.0100, found = 330.0103. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 85:15, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 12.7 min, t_{R2} = 13.2 min.

4.1.4. 2-Bromocyclohexyl 2-hydroxybenzoate 3e

White powder, mp 59–64 °C, $[\alpha]_D^{20} = +3.5$ (*c* 0.1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 10.72 (s, 1H), 7.89–7.86 (m, 1H), 7.47–7.45 (m, 1H), 6.97–6.87 (m, 2H), 5.15–5.14 (m, 1H), 4.15–4.14 (m, 1H), 2.28–1.93 (m, 1H), 1.84–1.81 (m, 1H), 1.77–1.56 (m, 2H), 1.53–1.26 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.74, 148.83, 138.82, 132.66, 113.54, 52.58, 35.51, 31.34, 25.65, 23.75; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{15}BrO_3[M+Na]^+$ = 321.0310, found = 321.0293. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 85:15, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 15.7 min, t_{R2} = 18.2 min.

4.1.5. 2-Bromocyclohexyl 2-phenylacetate 3f

Colorless oil, $[\alpha]_D^{20} = +11.0$ (*c* 0.15, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.38 (m, 5H), 4.90 (m, 1H), 3.95 (m, 1H), 3.67 (t, 2H), 2.26 (m, 1H), 2.12 (m, 1H), 1.83 (m, 1H), 1.71 (m, 2H), 1.42–1.25 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.53, 133.96, 129.32, 128.51, 127.05, 76.15, 52.54, 41.49, 35.47, 30.95, 25.36, 23.18. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}BrO_2$ $[M+Na]^+$: 319.0304, found: 319.0306. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 98:2, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 13.4 min, t_{R2} = 14.3 min.

4.1.6. 2-Bromocyclohexyl 2-(2-methoxyphenyl)acetate 3g

Colorless oil, $[\alpha]_D^{20} = +6.2$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 1H), 7.20 (d, 1H, *J* = 6.0 Hz), 6.91 (t, 1H, *J* = 12.0 Hz), 6.86 (d, 1H, *J* = 6.0 Hz), 4.92 (m, 1H), 3.97 (m, 1H), 3.81 (s, 3H), 3.65 (s, 2H), 2.29 (m, 1H), 2.12 (m, 1H), 1.85 (m, 1H), 1.70 (m, 2H), 1.37 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.82, 157.55, 130.90, 128.49, 123.11, 120.45, 110.36, 75.71, 55.37, 52.52, 36.19, 35.23, 30.68, 25.15, 23.05. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}BrO_3$ $[M+Na]^+$: 349.0410, found: 349.0412. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 6.4 min, t_{R2} = 7.9 min.

4.1.7. 2-Bromocyclohexyl 2-(3-methoxyphenyl)acetate 3h

Colorless oil, $[\alpha]_D^{20} = +10.2$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.24 (m, 1H), 6.87 (m, 1H), 6.81 (m, 1H), 4.91 (m, 1H), 3.96 (m, 1H), 3.80 (s, 3H), 3.64 (m, 2H), 2.32 (m, 1H), 2.10 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.36(m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.40, 159.71, 135.36, 129.46, 121.69, 114.86, 112.78, 76.19, 55.23, 52.56, 41.52, 35.50, 30.96, 25.38, 23.19. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}BrO_3[M+Na]^+$: 349.0410, found: 349.0412. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 8.0 min, t_{R2} = 8.9 min.

4.1.8. 2-Bromocyclohexyl 2-(4-methoxyphenyl)acetate 3i

Colorless oil, $[\alpha]_D^{20} = +14.2$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.21 (d, 2H, *J* = 6.0 Hz), 6.86 (d, 2H, *J* = 6.0 Hz), 4.90 (m, 1H), 3.96 (m, 1H), 3.79 (s, 3H), 3.59 (m, 2H), 2.31 (m, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.71 (m, 2H), 1.36 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.85, 158.70, 130.34, 126.06, 113.96, 76.07, 55.26, 52.59, 40.58, 35.48, 30.96, 25.37, 23.18. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}BrO_3$ $[M+Na]^+$: 349.0410, found: 349.0412. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 95:5, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 11.7 min, t_{R2} = 12.5 min.

4.1.9. 2-Bromocyclohexyl 2-(4-fluorophenyl) acetate 3j

Yellowish oil, $[\alpha]_D^{20} = +10.2$ (*c* 0.20, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, 2H, *J* = 6.0 Hz), 7.00 (d, 2H, *J* = 6.0 Hz), 4.90 (m, 1H), 3.96 (m, 1H), 3.62 (m, 2H), 2.32 (m, 1H), 2.10 (m, 1H), 1.86 (m, 1H), 1.72 (m, 2H), 1.35 (m, 3H). ^{13}C NMR NMR (150 MHz, $CDCl_3$) δ: 170.37, 161.22, 130.91, 130.86, 129.64, 115.42, 115.28, 76.35, 52.58, 40.61, 35.61, 31.11, 25.48, 23.25. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}BrFO_2$ $[M+Na]^+$ = 337.0210, found = 349.0216. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 7.4 min, t_{R2} = 8.0 min.

4.1.10. 2-Bromocyclohexyl 2-(2-nitrophenyl) acetate 3k

Yellowish oil, $[\alpha]_D^{20} = +2.2$ (*c* 0.07, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, 1H, *J* = 6.0 Hz), 7.60 (m, 1H), 7.48 (m, 1H), 7.39 (d, 1H, *J* = 6.0 Hz), 4.90 (m, 1H), 4.08 (m, 2H), 3.94 (m, 1H), 2.32 (m, 1H), 2.16 (m, 1H), 1.84 (m, 1H), 1.71 (m, 2H), 1.36 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.91, 148.81, 133.55, 133.41, 129.73, 128.60, 125.26, 75.35, 52.37, 39.85, 35.40, 30.85, 25.29, 23.13. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}BrO_4$ $[M+Na]^+$: 364.0155, found: 364.0155. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 90:10, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 7.9 min, t_{R2} = 8.5 min.

4.1.11. 2-Bromocyclohexyl 2-oxo-2-phenylacetate 3l

Colorless oil, $[\alpha]_D^{20} = +7.1$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, 2H, *J* = 7.6 Hz), 7.88 (m, 1H), 7.52 (d, 2H, *J* = 7.5 Hz), 5.23 (m, 1H), 4.06 (m, 1H), 2.43 (m, 1H), 2.23 (m, 1H), 1.93 (m, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.35 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 186.32, 163.07, 134.94, 132.37, 130.20, 128.90, 76.80, 51.89, 35.81, 31.29, 25.52, 23.35. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{15}BrO_3$ $[M+Na]^+$: 333.0097, found = 333.0096. Enantiomeric excess was determined by HPLC (Daicel Chirapak OJ-H, hexane/*iso*-propanol = 95:5, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 11.6 min, t_{R2} = 13.1 min.

4.1.12. 2-Bromocyclohexyl 2-(furan-2-yl)-2-oxoacetate 3m

Off white solid, mp 65–68 °C, $[\alpha]_D^{20} = +2.2$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.77 (m, 2H), 6.68 (d, 1H, *J* = 6.0 Hz), 5.15 (m, 1H), 4.10 (m, 1H), 2.48 (m, 1H), 2.22 (m, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1.57 (m, 1H), 1.48 (m, 1H), 1.35 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.09, 160.29, 149.75, 149.53, 124.80, 113.01, 78.50, 51.79, 35.73, 31.06, 25.47, 23.33; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}BrO_4[M+Na]^+$ = 323.0145, found = 323.0139. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 95:5, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 15.3 min, t_{R2} = 16.8 min.

4.1.13. 2-Bromocyclohexyl 2-oxo-2-(thiophen-2-yl)acetate 3n

Green solid, mp 58–62 °C, $[\alpha]_D^{20} = +7.7$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.17 (m, 1H), 7.83 (m, 1H), 7.21 (m, 1H), 5.18 (m, 1H), 4.09 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.59 (m, 2H), 1.49 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 176.50, 160.91, 139.22, 137.42, 137.37, 128.71, 78.51, 51.81, 35.72, 31.09, 25.47, 23.34; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}BrO_3S[M+Na]^+$ = 338.9661, found = 338.9665. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 95:5, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 12.5 min, t_{R2} = 13.5 min.

4.1.14. 2-Bromocyclohexyl 2-(naphthalen-1-yl)acetate 3o

Colorless oil, $[\alpha]_D^{20} = +5.0$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, 1H, *J* = 6.0 Hz), 7.84 (m, 1H), 7.79 (m, 1H), 7.55 (m, 1H), 7.49 (m, 1H), 4.92 (m, 1H), 4.11 (m, 2H), 3.98 (m, 1H), 2.23 (m, 1H), 2.07 (m, 1H), 1.81 (m, 1H), 1.67 (m, 2H), 1.31 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.54, 133.34, 132.15, 130.53, 128.68, 128.05, 128.02, 126.28, 125.75, 125.44, 12.97, 76.20, 52.46, 39.27, 35.33, 30.81, 25.23, 23.08. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}BrO_2[M+Na]^+$: 369.0461, found = 369.0452. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 95:5, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 9.4 min, t_{R2} = 11.3 min.

4.1.15. 2-Bromocyclohexyl 1-naphthoate 3p

White solid, mp 85–88 °C, $[\alpha]_D^{20} = +4.8$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.93 (d, 1H, *J* = 7.0 Hz), 8.22 (d, 1H, *J* = 6.0 Hz), 8.03 (d, 1H, *J* = 6.0 Hz), 7.90 (d, 1H, *J* = 6.0 Hz), 7.64–7.25 (m, 3H), 5.28 (m, 1H), 4.21 (m, 1H), 2.48–2.36 (m, 2H), 2.01 (m, 1H), 1.97 (m, 2H), 1.83 (m, 2H), 1.53 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.53, 133.84, 133.31, 131.37, 130.16, 128.51, 127.73, 127.36, 126.23, 125.83, 124.54, 76.58, 52.86, 35.81, 31.41, 25.61, 23.46; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}BrO_2[M+Na]^+$ = 349.0304, found = 335.0311. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 99:1, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 24.5 min, t_{R2} = 24.7 min.

4.1.16. 2-Bromocyclohexyl 3-phenylpropanoate 3q

White solid, mp 95–98 °C, $[\alpha]_D^{20} = +8.5$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.19 (m, 2H), 7.15–7.11 (m, 3H), 4.85–4.82 (m, 1H), 4.00–3.96 (m, 1H), 2.96–2.88 (m, 2H), 2.64–2.54 (m, 2H), 2.34–2.31 (m, 1H), 2.01–1.90 (m, 2H), 1.73–1.70 (m, 1H), 1.54–1.48 (m, 1H), 1.42–1.34 (m, 1H), 1.28–1.18 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.90, 140.44, 128.46, 128.29, 126.24, 75.83, 52.82, 35.96, 35.60, 31.16, 30.98, 25.49, 23.28; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}BrO_2[M+Na]^+$ = 333.0562, found = 333.0524. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 99:1, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 19.5 min, t_{R2} = 24.7 min.

4.1.17. 2-Bromocyclopentyl benzoate 3r

White solid, mp 67–68 °C, $[\alpha]_D^{20} = +3.7$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (m, 2H), 7.56 (m, 1H), 7.41 (m, 2H), 5.52 (m, 1H), 4.37 (m, 1H), 2.44–2.39 (m, 2H), 2.15–1.87 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.60, 133.14, 129.99, 129.62, 128.41, 82.67, 52.94, 34.66, 29.54, 21.81; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}BrO_2[M+Na]^+$ = 291.0131, found = 291.0129. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 98:2, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 7.5 min, t_{R2} = 8.1 min.

4.1.18. 2-Bromocyclooctyl benzoate 3s

White solid, mp 79–82 °C, $[\alpha]_D^{20} = +5.8$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, 2H, *J* = 6.0 Hz), 7.55 (t, 1H, *J* = 7.0 Hz), 7.45 (t, 1H, *J* = 6.0 Hz), 5.43 (m, 1H), 4.49 (m, 1H), 2.33 (m, 1H), 2.15 (m, 1H), 1.92 (m, 3H), 1.61 (m, 1H), 1.49 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.73, 132.94, 130.4, 129.7, 128.36, 76.81, 57.35, 32.22, 31.70, 25.88, 25.46, 25.41, 24.68; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}Br2O_4[M+Na]^+$ = 333.0461, found = 333.0466. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 98:2, flow rate 0.8 mL/min, UV = 280 nm): t_{R1} = 8.2 min, t_{R2} = 8.4 min.

4.1.19. 3-Bromotetrahydro-2*H*-pyran-2-ylbenzoate 3t

White solid, mp 68–70 °C, $[\alpha]_D^{20} = +2.8$ (*c* 0.10, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (m, 2H), 7.57 (m, 1H), 7.44 (m, 2H), 6.14 (d, *J* = 8.6 Hz, 1H), 4.21 (m, 1H), 4.19–4.03 (m, 2H), 3.84–3.82 (m, 1H), 2.51–2.48 (m, 1H), 2.13–2.04 (m, 2H), 1.68–1.57 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.56, 133.53, 129.92, 129.44, 128.51, 94.82, 64.25, 47.08, 29.96, 22.91; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}BrO_3[M+Na]^+$ = 306.9940, found = 306.9935. Enantiomeric excess was determined by HPLC (Daicel Chirapak AD-H, hexane/*iso*-propanol = 98:2, flow rate 0.5 mL/min, UV = 280 nm): t_{R1} = 20.1 min, t_{R2} = 22.7 min.

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