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Highly enantioselective conjugate addition of 1-bromonitroalkanes to α,β-unsaturated ketones catalyzed by 9-amino-9-deoxyepiquinine

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ABSTRACT

Asymmetric conjugate addition of 1-bromonitroalkanes to α,β-unsaturated ketones was studied using chiral primary amines as the catalysts. 9-Amino-9-deoxyepiquinine was found to be highly efficient catalyst for the transformation. 4-Bromo-4-nitroketones were obtained with excellent enantioselectivities (97–99% ee) and good yields (61–99%) for a variety of alkyl vinyl ketones. The product could be further debrominated with Bu_3SnH/AIBN to provide chiral 4-nitroketones in good yield and without loss of the optical purity.

1. Introduction

In recent years asymmetric organocatalysis has been developed to be a powerful tool for the synthesis of valuable chiral compounds.[1] A large number of asymmetric reactions have been developed catalyzed by chiral amines, thioureas (or ureas), and other chiral organic small molecules. Since initiated by MacMillan et al., the activation of α,β-unsaturated aldehydes and ketones toward conjugate addition by chiral secondary amines has been one of the most successful strategies in organocatalysis.[2] Many kinds of nucleophilic reagents were applied in the transformation, such as malonates, indoles, aldehydes, ketones, thiols, and peroxides, etc. Excellent enantioselectivities were achieved catalyzed by proline and its derivatives, MacMillan's imidazolidinones, and other chiral secondary amines. These catalysts uniquely activate the substrates by formation of the iminium cation and a LUMO lowing mechanism is well conceptualized. Although chiral secondary amines are highly efficient for activation of α,β-unsaturated aldehydes, they show inferior catalytic activities for sterically congested α,β-unsaturated ketones. Recently chiral primary amines emerged as the powerful catalysts for activation of α,β-unsaturated ketones and a number of successful examples had been reported.[3]

Nitroalkanes are important synthons in organic synthesis. Asymmetric conjugate addition of nitroalkanes to α,β-unsaturated aldehydes and ketones is a valuable method to prepare chiral γ-amino aldehydes and ketones,[4] which are useful intermediates for the synthesis of natural products and drugs. Enantioselective addition of nitroalkanes to chalcones was achieved with chiral bifunctional thiourea-amine catalysts and other metal-based chiral catalysts.[5] As the useful analogs of nitroalkanes, bromonitroalkanes provide an additional leaving group for further transformations. Ley and co-workers reported the addition of bromonitromethane to α,β-unsaturated ketones using proline tetrazole as the catalyst. The reaction provided nitrocyclopropanes in good yields and enantioselectivities.[6] Recently we[7] and the others[8] explored the asymmetric conjugate addition of bromonitroalkanes to α,β-unsaturated aldehydes catalyzed by prolinol silyl ethers. Excellent enantioselectivities and good yields were obtained in the reactions. However the method is not applicable for α,β-unsaturated ketones due to the low reactivity. Very recently, Wang and co-workers reported the enantioselective conjugate addition of 1-bromonitroalkanes to cyclic enones and chalcones catalyzed by chiral primary amines.[9] 9-Amino-9-deoxyepiquinine was found to be the efficient catalyst for the reaction. In the presence of appropriate bases, chiral nitrocyclopropanes were obtained with excellent enantioselectivities and in good yields. However alkyl vinyl ketones, such as oct-3-en-2-one, were found to be inactive in the reaction. At the same time, we also explored the asymmetric conjugate addition of 1-bromonitroalkanes to α,β-unsaturated ketones catalyzed by chiral primary amines. We found that the addition of 1-bromonitroalkanes to a variety of alkyl vinyl ketones could be achieved using 9-amino-9-deoxyepiquinine as the catalyst. Chiral bromonitroketones were

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obtained with excellent enantioselectivities and in good yields. Herein we report the results in detail.

2. Results and discussion

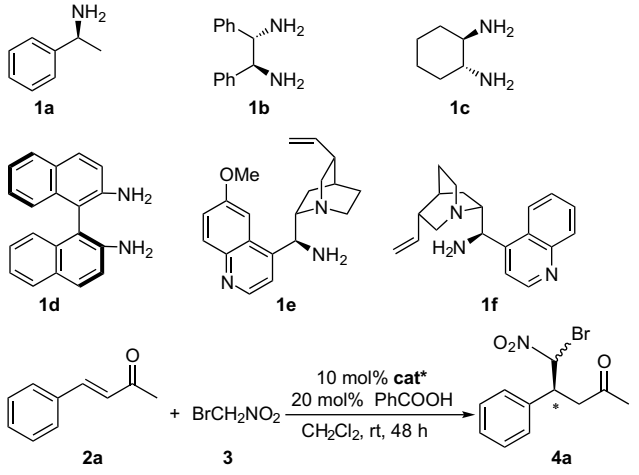
Initially chiral primary amines (**1a**–**1f**) were examined in the reaction of benzylidene acetone **2a** and bromonitromethane **3**. The results are summarized in Table 1. 2-Phenylethylamine **1a** provided the adduct **4a** in poor yield and enantioselectivity. 1,2-Diphenylethane-1,2-diamine **1b** gave **4a** with good enantioselectivity, however in low yield. Cyclohexane-1,2-diamine **1c** provided the adduct in better yield and with moderate enantioselectivity. Binaphthyl diamine **1d** was inefficient for the reaction. Further studies uncovered that chiral primary amines (**1e** and **1f**), derived from natural cinchona alkaloids, were highly efficient for the reaction (Table 1, entries 5 and 6).[10] 9-Amino-9-deoxyepiquinine **1e**, readily available from cheap quinine, provided the adduct **4a** with excellent yield and enantioselectivity. On the other hand, 9-amino-9-deoxyepicinchonidine **1f** gave another enantiomer of **4a** with excellent yield and enantioselectivity.

Benzoic acid was found to be necessary for the reaction, thus a number of acid additives were further screened and the results are summarized in Table 2. Brønsted acids, such as benzoic acid, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), *p*-toluenesulfonic acid (*p*-TSA), and acetic acid, accelerated the reaction (Table 2, entries 1–5). Benzoic acid was identified as the best additive considering the excellent enantioselectivity and yield. The reaction solvents were also screened (Table 2, entries 6–13). Toluene was the preferential solvent in terms of both enantioselectivity and chemical yield. In addition the reaction was faster in toluene and complete conversion was achieved after 10 h as indicated by TLC analysis. $CHCl_3$ provided similar enantioselectivity and yield with CH_2Cl_2. Excellent enantioselectivities were also obtained in THF and Et_2O, however with lower chemical yield. More polar solvents, such as MeOH and DMF gave inferior enantioselectivity. It is noted that the diastereoselectivities of the reaction were almost consistent with different additives and solvents. The loading of catalyst was also investigated (Table 2, entries 8 and 9). While 5 mol % **1e** was used, 84% yield was achieved after 48 h. The yield was decreased to 28% while 1 mol % **1e** was used. Although the chemical yield was significantly affected by the catalyst loading, the enantioselectivities were still excellent. The fact confirmed that the background reaction without the catalyst did not occur. In a comparative experiment, nitromethane was also examined in the reaction with benzylidene acetone under optimized reaction conditions (10 mol % **1e**, 20 mol % PhCOOH, toluene, room temperature), however no reaction occurred even after 48 h. The result may be ascribed to the stronger acidity of α-proton in bromonitromethane than in nitromethane.

A variety of α,β-unsaturated ketones were examined and the results are summarized in Table 3. Excellent enantioselectivities and yields were obtained for a number of substituted benzylidene acetones. Electron-withdrawing groups and electron-donating groups at the *para*-position of the phenyl group were well tolerated (Table 3, entries 2–7). *ortho*- and *meta*-Chloro substituted benzylidene acetones also provided the product with excellent enantioselectivities and yields (Table 3, entries 8 and 9). 4-Furanyl-but-3-en-2-one and 4-thiophenyl-but-3-en-2-one were applicable in the reaction with excellent enantioselectivities and yields, however longer reaction time was necessary for these substrates (Table 3, entries 10 and 11). The reaction of β-propyl-but-3-en-2-one gave the product in 89% yield and with 98% enantioselectivity after extended reaction time (Table 3, entry 12). 1-Phenyl-pent-1-en-3-one was also suitable substrate for the reaction (Table 3, entry 13). The reaction of chalcone provided the product with excellent enantioselectivity, but in lower yield (Table 3, entry 14).

1-Bromonitroethane and 1-bromonitropropane were also examined in the reaction with benzylidene acetone. The corresponding adducts were obtained with excellent enantioselectivities and in good yields (Scheme 1). The sterically demanding 1-bromonitropropane required longer reaction time.

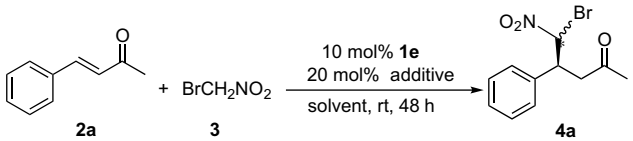
Table 1
The reaction of **2a** and **3** catalyzed by **1a**–**1f**[a]



Entry	Catalyst	Yield[b]/%	dr[c]	ee[d]/%
1	**1a**	11	57:43	36/38
2	**1b**	44	60:40	94/93
3	**1c**	53	55:45	−76/−78
4	**1d**	—	—	—
5	**1e**	95	57:43	99/99
6	**1f**	88	56:44	−97/−98

[a] The reactions were carried out at room temperature for 48 h with **2a** (0.2 mmol), **3** (0.3 mmol), **1a**–**1f** (0.02 mmol), PhCOOH (0.04 mmol), and CH_2Cl_2 (1 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral HPLC analysis.

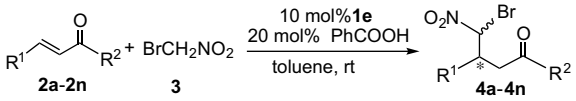
Table 2
Effects of the additives and solvents[a]



Entry	Additive	Solvent	Yield[b]/%	dr[c]	ee[d]/%
1	PhCOOH	CH_2Cl_2	95	57:43	99/99
2	TFA	CH_2Cl_2	81	57:43	96/97
3	TfOH	CH_2Cl_2	30	57:43	91/91
4	*p*-TSA	CH_2Cl_2	44	59:41	96/95
5	AcOH	CH_2Cl_2	96	57:43	98/98
6	PhCOOH	$CHCl_3$	93	56:44	>99/>99
7	PhCOOH	Toluene	95	57:43	>99/>99
8[e]	PhCOOH	Toluene	84	56:44	>99/>99
9[f]	PhCOOH	Toluene	28	56:44	>99/>99
10	PhCOOH	THF	51	59:41	98/98
11	PhCOOH	Et_2O	37	56:44	99/99
12	PhCOOH	MeOH	72	58:42	91/91
13	PhCOOH	DMF	37	56:44	80/81

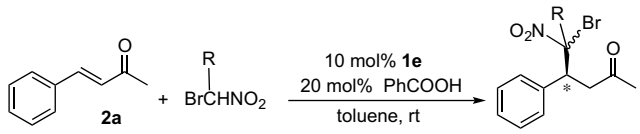
[a] The reactions were carried out at room temperature for 48 h with **2a** (0.2 mmol), **3** (0.3 mmol), **1e** (0.02 mmol), additive (0.04 mmol), and solvent (1 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral HPLC analysis.
[e] 5 mol % **1a** was used.
[f] 1 mol % **1a** was used.

Table 3
Conjugate addition of 1-bromonitromethane to α,β-unsaturated ketones catalyzed by **1e**[a]



Entry	R^1	R^2	Time/h	Yield[b]/%	dr[c]	ee[d]/%
1	Ph	Me (**2a**)	10	95	57:43	>99/>99
2	4-$MeOC_6H_4$	Me (**2b**)	10	94	57:43	>99/>99
3	4-MeC_6H_4	Me (**2c**)	9	95	56:44	99/97
4	4-ClC_6H_4	Me (**2d**)	6	97	57:43	>99/>99
5	4-BrC_6H_4	Me (**2e**)	6	99	55:45	99/nd[e]
6	4-$CF_3C_6H_4$	Me (**2f**)	6	89	61:39	99/99
7	4-$NO_2C_6H_4$	Me (**2g**)	6	90	52:48	nd[e]
8	2-ClC_6H_4	Me (**2h**)	18	92	45:55	98/98
9	3-ClC_6H_4	Me (**2i**)	12	97	54:46	>99/nd[e]
10	2-Furyl	Me (**2j**)	36	89	51:49	>99/>99
11	2-Thiophenyl	Me (**2k**)	36	94	52:48	>99/>99
12	*n*-Pr	Me (**2l**)	96	89	56:44	98/98
13	Ph	Et (**2m**)	48	90	58:42	>99/>99
14	Ph	Ph (**2n**)	96	49	63:37	98/98

[a] The reactions were carried out at room temperature with **2** (0.2 mmol), **3** (0.3 mmol), **1e** (0.02 mmol), PhCOOH (0.04 mmol), and toluene (1 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral HPLC analysis.
[e] Not determined.

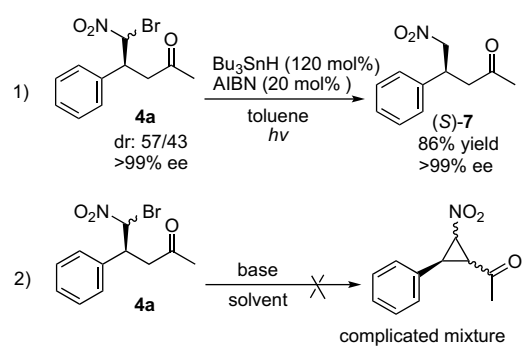


R = Me **5** (48 h, 83% yield, dr: 75/25, ee%: >99/>99)
R = Et **6** (96 h, 61% yield, dr: >99/1, ee%: >99)

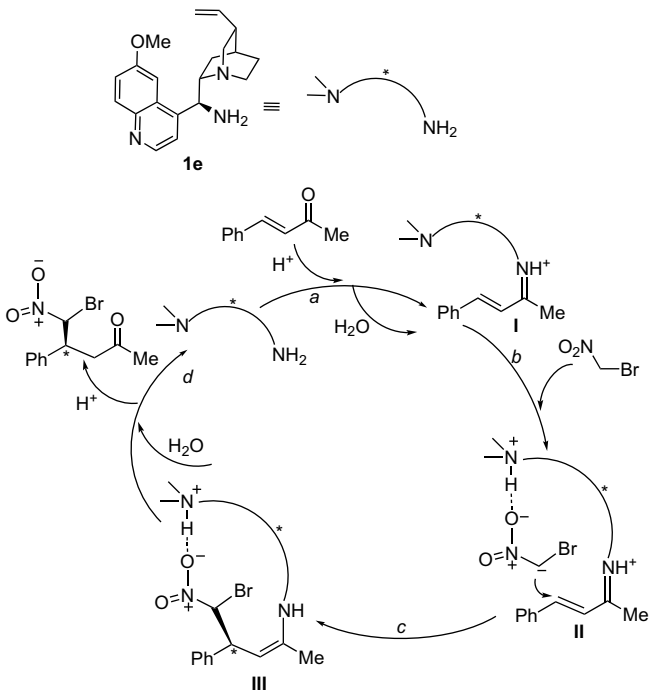
Scheme 1. The reaction of 1-bromonitroethane and 1-bromonitropropane with benzylidene acetone.

The product **4a** (>99% ee) was debrominated with Bu_3SnH/AIBN (Scheme 2, equation 1). Compound **7** was obtained with excellent enantioselectivity (>99% ee) and in good yield. The absolute configuration of **7** was determined as *S* by comparing the optical rotation with the reported data.[11] Analogically the absolute configuration of **4a** was assigned as *S*. On the other hand, the treatment of **4a** with various bases, such as Et_3N, DIPEA, DBU, and NMM, did not provide the expected nitrocyclopropane,[9] instead a complicated mixture was observed (Scheme 2, equation 2). The result was ascribed to the competitive intermolecular aldol reaction of **4a**.

A catalytic mechanism of the reaction is proposed (Scheme 3).[10p] The iminium cation **I** is generated from **1e** and benzylidene acetone. The acid additive is supposed to promote this step. Bromonitromethane is deprotonated by tertiary amine group of **1e** and the hydrogen bonding between the nitro group and protonated tertiary amines is formed. The resulting intermediate **II** provides a pre-organized structure and controls the enantioselectivity of the reaction. The consequent conjugate addition of bromonitroalkane anion and the tautomerization of the imine give the intermediate **III**, which is hydrolyzed to provide the product and to regenerate catalyst **1e**.



Scheme 2. Transformations of compound **4a**.



Scheme 3. Proposed catalytic mechanism.

3. Conclusion

In summary, we have developed an efficient asymmetric conjugate addition of 1-bromonitroalkanes to α,β-unsaturated ketones catalyzed by readily available 9-amino-9-deoxyepiquinine. The corresponding bromonitroketones were obtained in good yields and with excellent enantioselectivities for a variety of alkyl vinyl ketones. The product could be further debrominated with Bu_3SnH/AIBN to provide the chiral 4-nitroketone in good yield and without loss of the optical purity. Further applications of the products are currently under investigation.

4. Experimental section

4.1. General details

All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured on a Perkin Elmer digital polarimeter. Melting points were recorded on an electrothermal digital melting-point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, δ=0 ppm). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal

(δ=77.0 ppm). High resolution mass spectra were obtained with the Thermo MAT 95XP mass spectrometer. The low resolution mass spectra were obtained at the Thermo Trace GC Ultra – DSQ. Enantiomeric excesses of the products were determined by HPLC using Daicel Chiralcel AS-H, AD-H, OJ-H, and IC columns and eluting with *n*-hexane/*i*-PrOH. Compound **1e** and **1f** were prepared according to the reported procedures.[12]

4.2. Typical experimental procedure for the conjugate addition of 1-bromonitroalkanes to α,β-unsaturated ketones

9-Amino-9-deoxyepiquinine **1e** (6.5 mg, 0.02 mmol) was dissolved in toluene (1 mL). After addition of PhCOOH (4.9 mg, 0.04 mmol), the solution was stirred for 15 min at room temperature. Benzylidene acetone **2a** (29.2 mg, 0.2 mmol) was added and the mixture was stirred for another 15 min. Then 1-bromonitromethane **3** (42 mg, 0.3 mmol) was added in one portion and the reaction mixture was stirred for 10 h (monitored by TLC). The reaction solution was diluted with CH_2Cl_2 (5 mL) and washed with aqueous saturated $NaHCO_3$ (3 mL). The organic layer was dried over anhydrous sodium sulfate. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide product **4a**.

4.3. Spectral data of (bromo)nitroketones[13]

4.3.1. Compound *4a*

Major isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.29 (m, 3H), 7.25–7.21 (m, 2H), 6.25 (d, *J*=8.8 Hz, 1H), 4.18–4.11 (m, 1H), 3.21–3.03 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.3, 136.1, 129.0, 128.6, 128.1, 83.6, 46.4, 45.4, 30.4; IR (thin film) ν/cm^{-1}: 2360 (w), 2339 (w), 1715 (s), 1563 (s), 1418 (w), 1357 (m), 702 (m); HRMS (EI) calcd for $C_{11}H_{12}NO_3Br$ [M^+]: 284.9995, found: 284.9993. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=75/25, λ=220 nm, 0.5 mL/min); t_R (minor enantiomer)=17.6 min, t_R (major enantiomer)=18.4 min, >99% ee.

Minor isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.29 (m, 3H), 7.25–7.21 (m, 2H), 6.34 (d, *J*=7.2 Hz, 1H), 4.18–4.11 (m, 1H), 3.21–3.03 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.4, 135.9, 128.9, 128.3, 128.1, 84.8, 46.0, 45.1, 30.3. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=75/25, λ=220 nm, 0.5 mL/min); t_R (major enantiomer)=19.8 min, t_R (major enantiomer)=21.1 min, >99% ee.

4.3.2. Compound *4b*

Major isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.17–7.11 (m, 2H), 6.87–6.82 (m, 2H), 6.19 (d, *J*=8.8 Hz, 1H), 4.13–4.04 (m, 1H), 3.76 (s, 3H), 3.17–2.98 (m, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.5, 159.6, 129.3, 127.8, 114.5, 83.7, 45.6, 45.2, 30.5; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1716 (s), 1560 (s), 1517 (m), 1358 (m), 838 (w); HRMS (EI) calcd for $C_{12}H_{14}NO_4Br$ [M^+]: 315.0101, found: 315.0094. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1.0 mL/min); t_R (major enantiomer)=25.8 min, t_R (minor enantiomer)=28.6 min, >99% ee.

Minor isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.17–7.11 (m, 2H), 6.87–6.82 (m, 2H), 6.31 (d, *J*=6.4 Hz, 1H), 4.13–4.04 (m, 1H), 3.77 (s, 3H), 3.17–2.98 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.6, 159.7, 129.5, 127.7, 114.3, 85.3, 55.2, 45.8, 45.3, 30.4. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1.0 mL/min); t_R (major enantiomer)=23.2 min, t_R (minor enantiomer)=39.9 min, >99% ee.

4.3.3. Compound *4c*

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.15–7.08 (m, 4H), 6.21 (d, *J*=8.8 Hz, 1H), 4.14–4.06 (m, 1H), 3.19–3.00 (m, 2H), 2.30 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.5, 138.5, 133.0, 129.8, 128.0, 83.8, 46.2, 45.5, 30.5, 21.1; IR (thin film) ν/cm^{-1}: 3011 (m), 2923 (m), 1719 (s), 1565 (s), 1420 (m), 1355 (s), 787 (m); HRMS (EI) calcd for $C_{12}H_{14}NO_3Br$ [M^+]: 299.0152, found: 299.0151. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1.0 mL/min); t_R (major enantiomer)=22.7 min, t_R (minor enantiomer)=24.1 min, 99% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.15–7.08 (m, 4H), 6.31 (d, *J*=6.8 Hz, 1H), 4.14–4.06 (m, 1H), 3.19–3.00 (m, 2H), 2.32 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.5, 138.5, 132.9, 129.7, 128.2, 85.0, 45.7, 45.2, 30.4, 21.1. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1.0 mL/min); t_R (major enantiomer)=20.8 min, t_R (minor enantiomer)=27.9 min, 97% ee.

4.3.4. Compound *4d*

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.28 (m, 2H), 7.20–7.15 (m, 2H), 6.23 (d, *J*=8.4 Hz, 1H), 4.17–4.08 (m, 1H), 3.20–3.00 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 134.6, 134.5, 129.6, 129.2, 83.2, 45.8, 45.3, 30.4; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1700 (s), 1558 (s), 1459 (m), 1356 (m), 721 (w); HRMS (ESI) calcd for $C_{11}H_{11}NNaO_3ClBr$ [M+Na]$^+$: 341.9509, found: 341.9524. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=70/30, λ=220 nm, 0.5 mL/min); t_R (major enantiomer)=24.6 min, t_R (minor enantiomer)=26.8 min, >99% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.28 (m, 2H), 7.20–7.15 (m, 2H), 6.33 (d, *J*=6.8 Hz, 1H), 4.17–4.08 (m, 1H), 3.20–3.00 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.1, 134.5, 134.4, 129.7, 129.1, 84.6, 45.3, 45.1, 30.2. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=70/30, λ=220 nm, 0.5 mL/min); t_R (minor enantiomer)=37.4 min, t_R (major enantiomer)=38.3 min, >99% ee.

4.3.5. Compound *4e*

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.48–7.44 (m, 2H), 7.14–7.08 (m, 2H), 6.22 (d, *J*=7.2 Hz, 1H), 4.16–4.06 (m, 1H), 3.20–3.00 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 135.2, 132.2, 129.9, 122.8, 83.1, 45.9, 45.3, 30.4; IR (thin film) ν/cm^{-1}: 2361 (w), 2338 (w), 1718 (s), 1564 (s), 1410 (w), 1356 (m), 1011 (w); HRMS (EI) calcd for $C_{11}H_{11}NO_3Br_2$ [M^+]: 362.9100, found: 362.9091. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=96/4, λ=208 nm, 0.8 mL/min); t_R (minor enantiomer)=14.7 min, t_R (major enantiomer)=16.6 min, 99% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.48–7.44 (m, 2H), 7.14–7.08 (m, 2H), 6.33 (d, *J*=6.8 Hz, 1H), 4.16–4.06 (m, 1H), 3.20–3.00 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 135.0, 132.1, 130.1, 122.8, 84.5, 45.4, 45.1, 30.3.

4.3.6. Compound *4f*

Major isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.62–7.58 (m, 2H), 7.40–7.35 (m, 2H), 6.29 (d, *J*=8.4 Hz, 1H), 4.32–4.18 (m, 1H), 3.25–3.06 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.9, 140.3, 130.9 (q, J_{C-F}=32.6 Hz), 128.8, 126.1 (q, J_{C-F}=3.7 Hz), 125.1 (d, J_{C-F}=5.9 Hz), 83.0, 46.2, 45.4, 30.4; IR (thin film) ν/cm^{-1}: 2362 (w), 2338 (w), 1716 (s), 1560 (s), 1128 (s), 1115 (s), 850 (m); HRMS (EI) calcd for $C_{12}H_{11}NO_3BrF_3$ [M^+]: 352.9869, found: 352.9871. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=99/1, λ=215 nm, 0.8 mL/min); t_R (minor enantiomer)=71.9 min, t_R (major enantiomer)=86.9 min, 99% ee.

Minor isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.62–7.58 (m, 2H), 7.40–7.35 (m, 2H), 6.37 (d, J=4.4 Hz, 1H), 4.32–4.18 (m, 1H), 3.25–3.06 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.9, 140.1, 130.9 (q, J_{C-F}=32.6 Hz), 129.0, 125.9 (q, J_{C-F}=3.7 Hz), 122.4 (d, J_{C-F}=6.0 Hz), 84.2, 45.7, 45.2, 30.3. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=99/1, λ=215 nm, 0.8 mL/min); t_R (minor enantiomer)=78.7 min, t_R (major enantiomer)=93.1 min, 99% ee.

4.3.7. Compound **4g**

Major isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23–8.18 (m, 2H), 7.48–7.42 (m, 2H), 6.30 (d, J=8.4 Hz, 1H), 4.33–4.22 (m, 1H), 3.28–3.08 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.6, 147.8, 143.5, 129.4, 124.1, 82.5, 46.1, 45.2, 30.3; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1713 (s), 1562 (s), 1523 (s), 1355 (s), 857 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_3Br$ [M−NO_2]$^+$: 283.9917, found: 283.9917.

Minor isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23–8.18 (m, 2H), 7.48–7.42 (m, 2H), 6.39 (d, J=6.8 Hz, 1H), 4.33–4.22 (m, 1H), 3.28–3.08 (m, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.6, 147.9, 143.2, 129.6, 124.0, 83.8, 45.5, 45.1, 30.2.

4.3.8. Compound **4h**

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.37 (m, 1H), 7.31–7.21 (m, 3H), 6.54 (d, J=7.6 Hz, 1H), 4.69–4.60 (m, 1H), 3.27–3.13 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.1, 133.9, 133.7, 130.5, 129.7, 127.3, 82.6, 43.7, 43.0, 30.2; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1718 (s), 1563 (s), 1439 (m), 1359 (m), 1130 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_3BrCl$ [M$^+$]: 318.9605, found: 318.9608. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=95/5, λ=215 nm, 0.8 mL/min); t_R (minor enantiomer)=43.7 min, t_R (major enantiomer)=52.4 min, 98% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.37 (m, 1H), 7.31–7.21 (m, 3H), 6.42 (d, J=7.6 Hz, 1H), 4.69–4.60 (m, 1H), 3.27–3.13 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.9, 134.4, 133.9, 130.5, 129.7, 127.4, 81.5, 43.3, 43.0, 30.1. The enantiomeric excess was determined by HPLC with an OJ-H column (*n*-hexane/*i*-PrOH=95/5, λ=215 nm, 0.8 mL/min); t_R (major enantiomer)=39.5 min, t_R (minor enantiomer)=41.8 min, 98% ee.

4.3.9. Compound **4i**

Major isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–7.27 (m, 2H), 7.25–7.23 (m, 1H), 7.16–7.10 (m, 1H), 6.23 (d, J=8.4 Hz, 1H), 4.17–4.09 (m, 1H), 3.21–3.02 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.9, 138.2, 134.8, 130.3, 128.9, 128.3, 126.5, 83.2, 45.9, 45.3, 30.4; IR (thin film) ν/cm^{-1}: 2361 (w), 2342 (w), 1709 (s), 1559 (s), 1434 (m), 1352 (s), 784 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_3BrCl$ [M$^+$]: 318.9605, found: 318.9617. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=75/25, λ=208 nm, 0.5 mL/min); t_R (minor enantiomer)=10.2 min, t_R (major enantiomer)=10.8 min, >99% ee.

Minor isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–7.27 (m, 2H), 7.25–7.23 (m, 1H), 7.16–7.10 (m, 1H), 6.33 (d, J=7.2 Hz, 1H), 4.17–4.09 (m, 1H), 3.21–3.02 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 137.9, 134.7, 130.1, 128.9, 128.5, 126.7, 84.3, 45.5, 45.0, 30.3.

4.3.10. Compound **4j**

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.33 (m, 1H), 6.33–6.28 (m, 1H), 6.27 (d, J=7.2 Hz, 1H), 6.24–6.22 (m, 1H), 4.37–4.27 (m, 1H), 3.17–2.99 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0, 148.7, 142.9, 110.8, 109.3, 81.8, 42.9, 40.3, 30.2; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1719 (s), 1566 (s), 1355 (s), 744 (m); HRMS (ESI) calcd for $C_9H_{11}NO_4Br$ [M+H]$^+$: 275.9871, found: 275.9873. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1 mL/min); t_R (minor enantiomer)=15.0 min, t_R (major enantiomer)=18.4 min, >99% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.33 (m, 1H), 6.33–6.28 (m, 1H), 6.36 (d, J=5.6 Hz, 1H), 6.24–6.22 (m, 1H), 4.37–4.27 (m, 1H), 3.17–2.99 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.1, 149.0, 142.9, 110.6, 109.5, 82.6, 42.9, 40.3, 30.2. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1 mL/min); t_R (major enantiomer)=21.3 min, t_R (major enantiomer)=23.7 min, >99% ee.

4.3.11. Compound **4k**

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.24 (m, 1H), 6.98–6.92 (m, 2H), 6.31 (d, J=8.0 Hz, 1H), 4.56–4.41 (m, 1H), 3.24–3.06 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.2, 137.6, 127.7, 127.2, 126.0, 83.2, 46.4, 41.9, 30.4; IR (thin film) ν/cm^{-1}: 2360 (w), 2339 (w), 1718 (s), 1565 (s), 1355 (m), 708 (m); HRMS (EI) calcd for $C_9H_{10}NO_3BrS$ [M$^+$]: 290.9559, found: 290.9565. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1 mL/min); t_R (minor enantiomer)=16.4 min, t_R (major enantiomer)=18.4 min, >99% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.24 (m, 1H), 6.98–6.92 (m, 2H), 6.45 (d, J=5.6 Hz, 1H), 4.56–4.41 (m, 1H), 3.24–3.06 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.3, 138.0, 127.5, 127.0, 125.9, 85.2, 46.6, 41.6, 30.3. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=90/10, λ=220 nm, 1 mL/min); t_R (major enantiomer)=22.5 min, t_R (minor enantiomer)=26.6 min, >99% ee.

4.3.12. Compound **4l**

Major isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.19 (d, J=4.8 Hz, 1H), 2.90–2.76 (m, 2H), 2.63–2.55 (m, 1H), 2.17 (s, 3H), 1.50–1.26 (m, 4H), 0.95–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.7, 85.4, 43.9, 39.6, 32.3, 30.2, 19.7, 13.8; IR (thin film) ν/cm^{-1}: 2361 (w), 2340 (w), 1718 (s), 1564 (s), 1358 (m); HRMS (ESI) calcd for $C_8H_{14}NNaO_3Br$ [M+Na]$^+$: 274.0055, found: 274.0055. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=85/15, λ=208 nm, 0.5 mL/min); t_R (minor enantiomer)=12.1 min, t_R (major enantiomer)=12.4 min, 98% ee.

Minor isomer: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.30 (d, J=4.8 Hz, 1H), 2.90–2.76 (m, 2H), 2.63–2.55 (m, 1H), 2.18 (s, 3H), 1.50–1.26 (m, 4H), 0.95–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.3, 85.2, 43.7, 39.4, 33.0, 30.2, 20.0, 13.7. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=85/15, λ=208 nm, 0.5 mL/min); t_R (minor enantiomer)=11.0 min, t_R (major enantiomer)=11.4 min, 98% ee.

4.3.13. Compound **4m**

Major isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.82 (m, 2H), 7.25–7.20 (m, 2H), 6.26 (d, J=8.8 Hz, 1H), 4.20–4.13 (m, 1H), 3.18–3.00 (m, 2H), 2.47–2.25 (m, 2H), 1.01–0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.2, 136.2, 129.1, 128.6, 128.2, 83.7, 46.5, 44.3, 36.6, 7.5; IR (thin film) ν/cm^{-1}: 2361 (w), 2339 (w), 1711 (s), 1559 (s), 1354 (m), 756 (w); HRMS (EI) calcd for $C_{12}H_{14}NO_3Br$ [M$^+$]: 299.0152, found: 299.0143. The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH=75/25, λ=208 nm, 0.3 mL/min); t_R (major enantiomer)=16.7 min, t_R (minor enantiomer)=18.8 min, >99% ee.

Minor isomer: white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.82 (m, 2H), 7.25–7.20 (m, 2H), 6.35 (d, J=7.2 Hz, 1H), 4.20–4.13 (m, 1H), 3.18–3.00 (m, 2H), 2.47–2.25 (m, 2H), 1.01–0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.2, 136.1, 128.9, 128.3, 128.2, 84.8, 46.1, 43.9, 36.5, 7.5. The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH=75/25, λ=208 nm, 0.3 mL/min); t_R (major enantiomer)=17.5 min, t_R (minor enantiomer)=18.2 min, >99% ee.

*4.3.14. Compound **4n***

Major isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95–7.89 (m, 2H), 7.60–7.55 (m, 1H), 7.48–7.43 (m, 2H), 7.34–7.28 (m, 5H), 6.39 (d, J=8.4 Hz, 1H), 4.42–4.35 (m, 1H), 3.76–3.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.9, 136.5, 136.3, 133.5, 129.0, 128.7, 128.6, 128.3, 128.0, 84.1, 46.8, 40.9; IR (thin film) ν/cm^{-1}: 2349 (w), 2325 (w), 1680 (s), 1561 (s), 1350 (m), 747 (m); HRMS (EI) calcd for $C_{16}H_{14}OBr$ $[M-NO_2]^+$: 301.0223, found: 301.0221. The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH=90/10, λ=208 nm, 1 mL/min); t_R (major enantiomer)=13.5 min, t_R (minor enantiomer)=17.5 min, 98% ee.

Minor isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95–7.89 (m, 2H), 7.60–7.55 (m, 1H), 7.48–7.43 (m, 2H), 7.34–7.28 (m, 5H), 6.49 (J=6.4 Hz, 1H), 4.42–4.35 (m, 1H), 3.76–3.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.0, 136.4, 136.2, 133.6, 128.9, 128.8, 128.6, 128.5, 128.0, 85.1, 46.3, 40.5. The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH=90/10, λ=208 nm, 1 mL/min); t_R (major enantiomer)=10.9 min, t_R (minor enantiomer)=14.8 min, 98% ee.

*4.3.15. Compound **5***

Major isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.29 (m, 3H), 7.23–7.21 (m, 2H), 4.21 (dd, J=9.2, 4.0 Hz, 1H), 3.32–3.24 (m, 2H), 2.19 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.2, 136.0, 129.2, 128.6, 128.5, 98.7, 51.5, 45.9, 30.3, 29.5; IR (thin film) ν/cm^{-1}: 2360 (w), 2339 (w), 1717 (s), 1553 (s), 1357 (m), 741 (w); HRMS (EI) calcd for $C_{12}H_{14}NO_3Br$ $[M^+]$: 299.0152, found: 299.0148. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=90/10, λ=208 nm, 0.8 mL/min); t_R (minor enantiomer)=9.4 min, t_R (major enantiomer)=10.2 min, >99% ee.

Minor isomer: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33–7.29 (m, 3H), 7.23–7.21 (m, 2H), 4.33 (dd, J=10.0, 3.6 Hz, 1H), 3.19–3.05 (m, 2H), 2.19 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=203.8, 135.5, 129.4, 128.7, 128.5, 101.5, 50.4, 46.1, 30.2, 29.1. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=90/10, λ=208 nm, 0.8 mL/min); t_R (minor enantiomer)=12.4 min, t_R (major enantiomer)=13.7 min, >99% ee.

*4.3.16. Compound **6***

Yellow oil. $[\alpha]_D^{20}$=+14.0 (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30–7.27 (m, 3H), 7.25–7.22 (m, 2H), 4.21 (dd, J=8.4, 6.0 Hz, 1H), 3.24–3.23 (m, 2H), 2.09 (s, 3H), 2.57–2.48 (m, 1H), 2.19–2.10 (m, 1H), 1.08 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.4, 136.3, 129.2, 128.5, 111.0, 51.0, 46.6, 35.7, 30.5, 10.1; IR (thin film) ν/cm^{-1}: 2349 (w), 2339 (w), 1721 (s), 1557 (s), 1418 (w), 1357 (m), 816 (w); HRMS (EI) calcd for $C_{13}H_{16}NO_3Br$ $[M^+]$: 313.0308, found: 313.0309. The enantiomeric excess was determined by HPLC with an IC column (*n*-hexane/*i*-PrOH=75/25, λ=208 nm, 0.5 mL/min); t_R (minor enantiomer)=10.0 min, t_R (major enantiomer)=11.1 min, >99% ee.

4.4. Experimental procedure for the debromination of 4a[14]

Under nitrogen atmosphere, a solution of **4a** (57.2 mg, 0.2 mmol, dr: 57:43, ee: >99%/>99%), Bu_3SnH (65 μL, 0.24 mmol), and AIBN (6.7 mg, 0.04 mmol) in dry toluene (1.5 mL) was sealed in a quartz tube. The solution was irradiated with a UV lamp for 10 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to give **7** as a white solid (35.6 mg, 86% yield). $[\alpha]_D^{20}$=+2.0 (c 3.0, $CHCl_3$); mp: 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.27 (m, 3H), 7.23–7.21 (m, 2H), 6.70 (dd, J=6.8, 12.4 Hz, 1H), 4.60 (dd, J=8.0, 12.0 Hz, 1H), 4.05–3.97 (m, 1H), 2.92 (d, J=6.8 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=205.4, 138.8, 129.0, 127.9, 127.3, 79.4, 46.1, 39.0, 30.3; IR (thin film) ν/cm^{-1}: 2360 (w), 2339 (w), 1714 (s), 1547 (s), 1361 (m), 758 (m); MS (EI): 161 $[M-NO_2]^+$. The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH=75/25, λ=208 nm, 0.8 mL/min); t_R (major enantiomer)=15.9 min, t_R (minor enantiomer)=21.8 min, >99% ee.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.055.

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