Tetrahedron: *Asymmetry* 20 (2009) 355–361

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective conjugate addition of 1-bromonitroalkanes to α,β-unsaturated aldehydes catalyzed by chiral secondary amines

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ARTICLE INFO

Article history:
Received 9 December 2008
Accepted 13 January 2009
Available online 18 March 2009

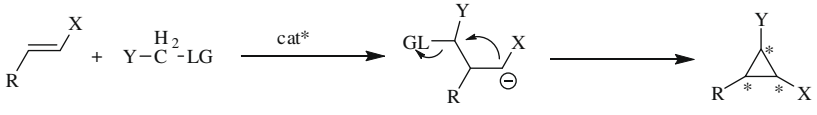
ABSTRACT

Highly enantioselective conjugate addition of bromonitromethane to α,β-unsaturated aldehydes catalyzed by chiral secondary amines has been achieved. Diphenylprolinol triethylsilyl ether was found to be the best catalyst for the reaction under MeOH/AcONa system. Various β-aryl acroleins afforded nitrocyclopropanes with excellent enantioselectivities and in good yields; however, the reaction of β-alkyl acroleins did not provide the corresponding nitrocyclopropanes. Substituted 1-bromonitromethanes, such as 1-bromonitroethane and 1-phenyl-1-bromonitromethane, were also applied in the reaction with excellent enantioselectivities and improved diastereoselectivities. The new methodology is efficient for preparing highly substituted chiral nitrocyclopropanes.

1. Introduction

Chiral cyclopropane motifs are widely found in a great number of drugs and natural products.[1] These compounds exhibit various useful biological activities, such as enzyme inhibition, insecticidal, antifungal, herbicidal, antimicrobial, antitumor, and antiviral activities.[2] Synthetic methods of chiral cyclopropanes have been extensively studied.[3] Among them, the asymmetric conjugate addition and consequent intramolecular alkylation is extremely powerful for the synthesis of chiral cyclopropanes (Scheme 1). Various Michael acceptor and nucleophilic agents with a leaving group could be applied in this transformation.[4]

Nitrocyclopropanes are a special class of cyclopropane compounds, which are presented in some natural products such as the peptidolactone hormaomycin[5] and the broad spectrum antibiotic Trovafloxacin.[6] Furthermore, nitrocyclopropanes can be converted into a wide range of useful compounds.[7] Asymmetric synthesis of nitrocyclopropanes has been developed based on the reaction of nitroalkyl carbene with alkenes,[8] conjugate addition of α-halogenated nucleophiles to nitroolefins.[9] In recent years, chiral secondary amines, for example, proline and its derivatives, imidazolidinones, have been found to be efficient catalysts for activation of α,β-unsaturated aldehydes and ketones, via a LUMO lowering mechanism.[10] Thus, the conjugate addition of 1-halogenated nitroalkanes to α,β-unsaturated aldehydes and ketones in the presence of chiral amine catalysts is also a promising method for asymmetric synthesis of nitrocyclopropanes. Ley et al. reported the first organocatalytic nitrocyclopropanation of α,β-unsaturated ketones with bromonitromethane using the proline tetrazole catalyst.[11] Córdova et al. explored the reaction of α,β-unsaturated aldehydes with bromonitromethane catalyzed by chiral secondary amines.[12] Recently, we studied the conjugate addition of 1-bromonitroalkanes to α,β-unsaturated aldehydes catalyzed by several achiral secondary amines.[13] We found that the $CHCl_3/Et_3N$ system used by Córdova et al. resulted in complicated mixtures of products, from which only low yield of nitrocyclopropanes was obtained, and instead the MeOH/AcONa system provided nitrocyclopropanes in much better yields. In addition, we also found that the substituted 1-bromonitromethanes could improve the diastereoselectivities of the reaction efficiently. Encouraged by the results, we explored the asymmetric nitrocyclopropanation of α,β-unsaturated aldehydes with 1-bromonitroalkanes using chiral secondary amines as the catalysts. Herein, our new experimental results are reported in detail.



Scheme 1. Asymmetric conjugate addition and consequent intramolecular alkylation.

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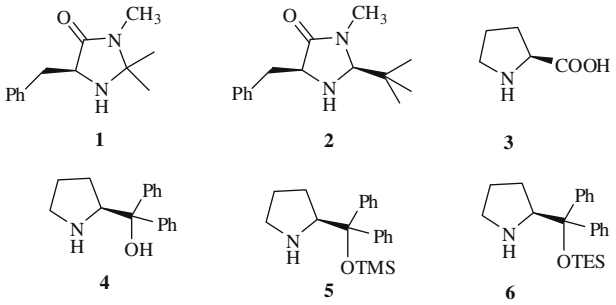
doi:10.1016/j.tetasy.2009.01.003

2. Results and discussions

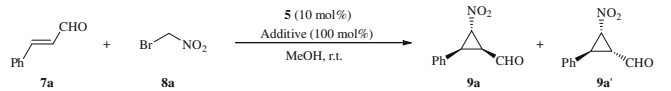
A variety of chiral secondary amines were studied in the reaction (Scheme 2). Initially, the reaction of cinnamaldehyde **7a** and bromonitromethane **8a** was examined in $CHCl_3$/Et_3N catalyzed by diphenylprolinol TMS ether **5** (the reaction conditions used by Córdova et al.).[12] The reaction afforded complicated mixtures of products, and nitrocyclopropanes **9a**/**9a**′ were obtained in only 36% GC yield and with 85% ee (Table 1, entry 5). Thus, improved reaction conditions were explored based on our previous study.[13] The reaction was re-examined in methanol with a number of acid and base additives. The results are summarized in Table 1. The reaction did not occur in the absence of additives, and benzoic acid was an inefficient additive (Table 1, entries 1–2). NaI provided the nitrocyclopropanes **9a**/**9a**′ with good enantioselectivities, however in low yield. Et_3N provided a slightly better yield, but the enantioselectivities were lower. AcONa was identified as the best additive considering the improved yield and enantioselectivities. In addition, the reaction was faster than that with other additives. The complete consumption of cinnamaldehyde was achieved after 3 h as indicated by the TLC analysis. The results undoubtedly demonstrated the superiority of MeOH/AcONa system.

The optimization of reaction solvent was studied with AcONa as the additive and the results are listed in Table 2. EtOH, ^{i}PrOH, THF, CH_2Cl_2, and $CHCl_3$ could also be used in the reaction, but lower yields were obtained in comparison with MeOH (Table 2, entries 2–4, 6, and 7 vs entry 1). CH_3CN provided nitrocyclopropanes in low yields and enantioselectivities. It is noted that the ratio of **9a**/**9a**′ increased generally with the extension of the standby time of reaction mixtures (Table 2, entries 1–7). The result suggests that **9a** is thermodynamically favorable product and that **9a**′ is kinetically favorable product.



Scheme 2. Chiral secondary amine catalysts.

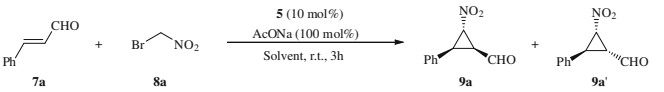
Table 1
Additive screening for the reaction of **7a** and **8a** catalyzed by **5**[a]



Entry	Additive	Time (h)	Yield[b] (%)	**9a**:**9a**′[c]	ee[d] (%) (**9a**/**9a**′)
1	—	24	Trace	ND[e]	ND
2	PhCOOH	24	Trace	ND	ND
3	NaI	24	14	70:30	83/78
4	Et_3N	24	28	57:43	66/65
5[f]	Et_3N	12	36	62:38	85/85
6	AcONa	3	76 (65[g])	60:40	89/87

[a] Cinnamaldehyde **7a** (0.25 mmol), bromonitromethane **8a** (0.26 mmol), **5** (0.025 mmol), additive (0.26 mmol), and 1.0 ml methanol were used.
[b] GC yield of combined **9a** and **9a**′.
[c] The ratios of **9a**/**9a**′ were determined by GC analysis.
[d] The ee values of **9a** and **9a**′ were determined by chiral GC.
[e] Not determined.
[f] Cinnamaldehyde **7a** (0.25 mmol), bromonitromethane **8a** (0.26 mmol), **5** (0.025 mmol), Et_3N (0.26 mmol), and 1.0 ml $CHCl_3$ were used in this case.
[g] Isolated yield of combined **9a** and **9a**′.

Table 2
Solvent screening for the reaction of **7a** and **8a**[a]

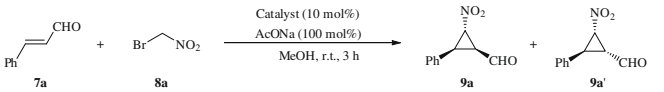


Entry	Solvent	Yield[b] (%)	**9a**:**9a**′[c]	ee[d] (%) (**9a**/**9a**′)
1	MeOH	76	60:40 (67:33)[e]	89/87
2	EtOH	66	47:53 (67:33)	84/89
3	^{i}PrOH	62	50:50 (63:37)	90/85
4	THF	59	44:56 (50:50)	83/87
5	MeCN	46	57:43 (58:42)	60/60
6	CH_2Cl_2	58	52:48 (60:40)	82/86
7	$CHCl_3$	56	50:50 (62:38)	85/87

[a] The reactions were carried out at room temperature for 3 h with cinnamaldehyde **7a** (0.25 mmol), bromonitromethane **8a** (0.26 mmol), **5** (0.025 mmol), AcONa (0.26 mmol), and 1.0 ml solvent.
[b] GC yield of combined **9a** and **9a**′.
[c] The ratios of **9a**/**9a**′ were determined by GC analysis.
[d] The ee values of **9a** and **9a**′ were determined by chiral GC.
[e] The values in parentheses were determined by GC after leaving the reaction mixtures for 24 h.

After setting up of the optimized reaction system, chiral secondary amines **1**–**6** were further examined in order to improve the enantioselectivity of the reaction, and the results are summarized in Table 3. MacMillan's catalysts **1**–**2** were inefficient for the transformation, and only trace of **9a**/**9a**′ were obtained after 3 h. Proline **3** provided moderate yield of the product, but the enantioselectivity was negligible. Diphenylprolinol **4** provided good enantioselectivity, however, in lower yield. The sterically demanding diphenylprolinol triethylsilyl ether **6** provided better yield and enantioselectivity than diphenylprolinol TMS ether **5**. Another advantage of **6** is the much better chemical stability than **5**. The color change and decomposition of **5** were observed during the storage; however **6** was highly stable even after the long-term storage. The effect of the reaction temperature on the reaction was also studied. The enantioselectivity was improved with the decrease of the reaction temperature. 96% Ee was achieved under 0 °C; however, the decrease of temperature to −20 °C did not improve the enantioselectivity furthermore (Table 3, entries 7–8). The chemical yields of **9a**/**9a**′ were almost consistent under the different reaction temperatures (Table 3, entries 6–8).

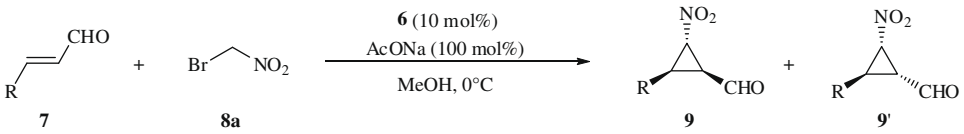
Table 3
Catalyst screening for the reaction of **7a** and **8a**[a]



Entry	Catalyst	Yield[b] (%)	**9a**:**9a**′[c]	ee[d] (%) (**9a**/**9a**′)
1	**1**	7	23:77	48/32
2	**2**	6	23:77	11/14
3	**3**	61	47:53	5/10
4	**4**	48	57:43	80/70
5	**5**	76	60:40	89/87
6	**6**	79	55:45	90/94
7[e]	**6**	79	44:56	96/96
8[f]	**6**	81	33:67	96/94

[a] The reactions were carried out at room temperature for 3 h with cinnamaldehyde **7a** (0.25 mmol), bromonitromethane **8a** (0.26 mmol), catalyst (0.025 mmol), AcONa (0.26 mmol), and 1.0 ml methanol.
[b] GC yield of combined **9a** and **9a**′.
[c] The ratios of **9a**/**9a**′ were determined by GC analysis.
[d] The ee values of **9a** and **9a**′ were determined by chiral GC.
[e] The reaction was carried out at 0 °C for 8 h.
[f] The reaction was carried out at −20 °C for 22 h.

Table 4
Reaction of α, β -unsaturated aldehydes **7** with bromonitromethane **8a** catalyzed by **6**[a]



7 8a 9 9′

Entry	7	Time (h)	Product (**9**/**9′**)[b]	Yield[c] (%)	ee[d] (%) (**9**/**9′**)
1	R = Ph **7a**	8	**9a/9a′** (55/45)	68	96/96
2	R = 4-$NO_2C_6H_4$ **7b**	9	**9b/9b′** (50/50)	63	98/92
3	R = 4-ClC_6H_4 **7c**	8	**9c/9c′** (66/34)	63	91/95
4	R = 4-$CH_3C_6H_4$ **7d**	8	**9d/9d′** (63/37)	67	94/94
5	R = 4-$OMeC_6H_4$ **7e**	16	**9e/9e′** (68/32)	61	89/96
6	R = 3-ClC_6H_4 **7f**	8	**9f/9f′** (65/35)	65	96/96
7	R = 2-ClC_6H_4 **7g**	8	**9g/9g′** (67/33)	68	88/96
8	R = 2-$OMeC_6H_4$ **7h**	8	**9h/9h′** (71/29)	61	95/89
9	R = 2-Furyl **7i**	19	**9i/9i′** (67/33)	48	89/92
10	R = 3-Pyridyl **7j**	24	**9j/9j′** (67/33)	46	88/86[e]

[a] α,β-Unsaturated aldehyde **7** (0.25 mmol), bromonitromethane **8a** (0.26 mmol), AcONa (0.26 mmol), **6** (0.025 mmol), and 1.0 ml methanol were used in the reaction.
[b] The ratios of **9**/**9′** were determined by GC analysis.
[c] Isolated yield of combined **9** and **9′**.
[d] The ee values of **9** and **9′** were determined by chiral GC or HPLC.
[e] The ee value of **9j′** was determined by chiral GC analysis of the corresponding alcohol obtained by $NaBH_4$ reduction.

A variety of α,β-unsaturated aldehydes were investigated in the reaction with bromonitromethane, and the results are summarized in Table 4. Introduction of electron-withdrawing or electron-donating substituents on the phenyl ring of cinnamaldehyde did not exert significant influence on the yield of nitrocyclopropanes (Table 4, entries 2–8); however, the enantioselectivities increased as the substituent became more electron deficient (Table 4, entries 1–4). Aldehyde **7b,** which has a 4-nitro group on the phenyl ring, provided the best enantioselectivity. On the other hand, the ratio of **9**/**9′** decreased with the introduction of more electron-deficient substituent. 3-Cl, 2-Cl, and 2-MeO substituted cinnamaldehydes also afforded excellent enantioselectivities and good yields. β-Heteroaryl- α,β-unsaturated aldehydes, such as *trans*-3-(furan-2-yl)acrolein, and *trans*-3-(pyridin-3-yl)acrolein were also applicable in the reaction. The corresponding nitrocyclopropanes were obtained with good enantioselectivities, however in lower yields (Table 4, entries 9–10). Acrolein and crotonaldehyde were examined in the reaction; however, no nitrocyclopropane products could be obtained.

A single crystal was obtained from a solution of **9b**/**9b′** in EtOAc/petroleum ether (*V*/*V* = 1/10).[14] X-ray diffraction analysis uncovered that the crystal was formed from the **9b′** (Fig. 1). The absolute configuration was determined as (1*S*,2*R*,3*S*). Analogically the compound **9b** was proposed to have (1*S*,2*S*,3*S*) absolute configuration. The result is consistent with the conclusion obtained via chemical transformations by Córdova and co-workers.[12]

In our previous study, substituted bromonitromethanes were found to provide better diastereoselectivities,[13] and thus 1-bromonitroalkanes **8b**–**8e** were examined in the reaction with cinnamaldehyde **7a**. The results are summarized in Table 5.

1-Bromonitroethane **8b** provided the corresponding nitrocyclopropanes in moderate yield and with excellent enantioselectivities (Table 5, entry 2). The ratio of **9k**/**9k′** was decreased to 14/86. 1-Bromonitropropane **8c** gave low yield of product (Table 5, entry 3). 1-Bromo-1-phenylnitromethane **8d** provided exclusively **9m′** with 99% ee and in good yield (Table 5, entry 4). The reaction of ethyl 2-bromonitroacetate **8e** afforded a complicated reaction mixture, from which no nitrocyclopropane was isolated.

The observed enantioselectivities and diastereoselectivities of the reactions can be rationalized based on a simple working model (Scheme 3). The iminium cation **I** is generated from cinnamaldehyde and **6**. The *re* face of double bond is efficiently shielded by bulk diphenylmethyl group of **6**. The bromonitroalkane anion attacks **I** from the *si* face to provide **II**. The consequent intramolecular alkylation of **II** provides the nitrocyclopropane product **9′**. The epimerization of **9′** under the reaction conditions affords **9**. While a substituent exists in the 1-bromonitromethane (R′ ≠ H), the epimerization of **9′** is inhibited, and the reaction provides **9′** as the major product.

3. Conclusion

In conclusion, the asymmetric conjugate addition of bromonitromethane to α,β-unsaturated aldehydes has been developed. Diphenylprolinol triethylsilyl ether was identified as the best catalyst for the reaction. Excellent enantioselectivities and good yields were achieved for a number of β-aryl acroleins under MeOH/AcONa system. Substituted 1-bromonitromethanes, such as 1-bromonitroethane and 1-phenyl-1-bromonitromethane, also provided excellent enantioselectivities and improved diastereoselectivities. The reaction is efficient for preparing highly substituted chiral nitrocyclopropanes.

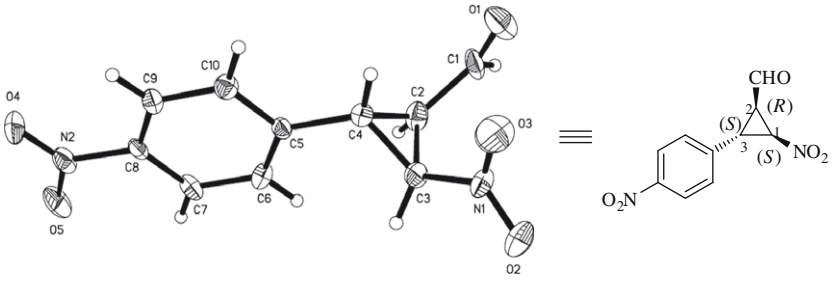
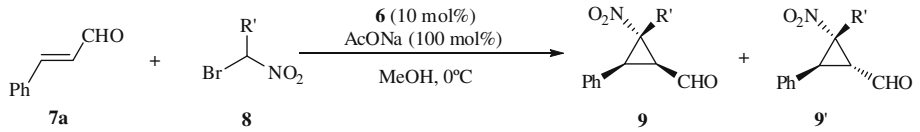


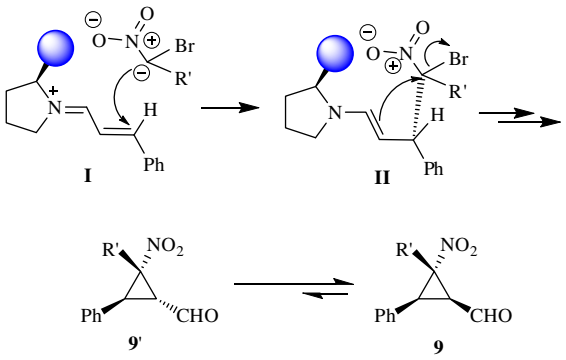
Figure 1. X-ray structure of the nitrocyclopropane **9b′**.

Table 5
Reaction of 1-bromonitroalkanes **8** with cinnamaldehyde **7a** catalyzed by **6**[a]



Entry	8	Time (h)	Product (**9**/**9′**)[b]	Yield[c] (%)	ee[d] (%) (**9**/**9′**)
1	R′ = H **8a**	8	**9a**/**9a′** (55/45)	68	96/96
2	R′ = CH_3 **8b**	12	**9k**/**9k′** (14/86)	65	95/98[e]
3	R′ = Et **8c**	12	**9l**/**l′** (4/96)	28[f]	—[g]
4	R′ = Ph **8d**	12	**9m**/**9m′** (<1/99)	63	—/99
5	R′ = COOEt **8e**	12	—[h]	—	—

[a] Cinnamaldehyde **7a** (0.25 mmol), 1-bromonitroalkane **8** (0.26 mmol), AcONa (0.26 mmol), **6** (0.025 mmol), and 1.0 ml methanol were used in the reaction.
[b] The ratios of **9a**/**9a′**, **9k**/**9k′**–**9m**/**9m′** were determined by GC analysis.
[c] Isolated yield of combined **9** and **9′**.
[d] The ee values were determined by chiral GC.
[e] The ee value of **9k′** was determined by chiral GC analysis of the corresponding alcohol **10′**, obtained by $NaBH_4$ reduction of **9k′**.
[f] The yield was determined by ^{1}H NMR.
[g] The ee values of **9l** and **9l′** were not determined.
[h] No nitrocyclopropane products could be isolated.



Scheme 3. Working model of asymmetric reaction of 1-bromonitroalkanes with cinnamaldehyde.

4. Experimental

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 Model 341 digital polarimeter. Melting points were recorded on an electrothermal digital melting-point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts in ^{1}H 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 or SHIMADZU LCMS-IT-TOF mass spectrometer. The low-resolution mass spectra were obtained with the Thermo Trace GC Ultra—DSQ II and Agilent 6120 (Quadrapole LC–MS) mass spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, and w = weak). GC yields and enantiomeric excesses of most nitrocyclopropane products were determined by GC (Agilent 6890N) with a Varian capillary column CP-Chirasil-DexCB (25 m × 0.25 mm, 0.25 μm, # CP7502). Enantiomeric excesses of other nitrocyclopropane products were determined by HPLC using a Daicel Chiralcel AS-H column and eluting with ^{n}-hexane/^{i}-PrOH. The X-ray crystallographic data were obtained with the Bruker Smart Apex II CCD X-ray diffractometer.

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

A mixture of diphenylprolinol triethylsilyl ether **6** (0.025 mmol) and cinnamaldehyde **7** (0.25 mmol) in 1.0 ml methanol was stirred for 5 min at room temperature, and was cooled to 0 °C. After 1-bromonitroalkane **8** (0.26 mmol) and AcONa (0.26 mmol) were added, the reaction mixture was stirred for 8–24 h at 0 °C. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide nitrocyclopropanes **9** and **9′** as inseparable mixtures.

4.3. Spectroscopic data of nitrocyclopropanes 9[15]

4.3.1. Compound 9a

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (d, J = 3.2 Hz, 1H), 7.35–7.26 (m, 5H), 5.33 (dd, J = 4.8, 3.6 Hz, 1H), 3.85 (dd, J = 11.2, 4.8 Hz, 1H), 3.42 (dt, J = 11.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0, 130.2, 128.9, 128.7, 126.8, 62.4, 38.5, 36.1; IR (thin film) ν/cm^{-1}: 2855 (w), 1714 (s), 1634 (m), 1548 (s), 1499 (w), 1364 (s), 698 (m); HRMS (EI) calcd for $C_{10}H_9NO_3$ (M^+): 191.0582, found: 191.0585. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 125 °C for 78 min, then 150 °C for 40 min); t_R (major enantiomer) = 69.0 min, t_R (minor enantiomer) = 72.7 min, 96% ee.

4.3.2. Compound 9a′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (d, J = 4.8 Hz, 1H), 7.42–7.17 (m, 5H), 4.82 (dd, J = 8.4, 4.8 Hz, 1H), 4.00 (dd, J = 8.0, 4.8 Hz, 1H), 2.71 (ddd, J = 8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 133.2, 129.1, 128.53, 128.45, 66.5, 39.2, 32.5. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 125 °C for 78 min, then 150 °C for 40 min); t_R (major enantiomer) = 69.0 min, t_R (minor enantiomer) = 72.7 min, 96% ee.

4.3.3. Compound 9b

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 5.35 (dd, J = 4.8, 4.0 Hz, 1H), 3.90 (dd, J = 11.2, 4.8 Hz, 1H), 3.62 (ddd, J = 11.2, 3.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 147.8, 140.4, 127.9, 124.4, 62.4, 38.0, 35.7; IR (thin film) ν/cm^{-1}: 2855 (w), 1713 (s), 1604 (m), 1552 (s), 1519 (s), 1348 (s), 856 (m); HRMS (EI) calcd for $C_{10}H_8N_2O_5$ (M^+): 236.0433, found: 236.0435. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 220 nm, 1.0 ml/min); t_R (major enantiomer) = 60.2 min, t_R (minor enantiomer) = 66.8 min, 98% ee.

4.3.4. Compound 9b′

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 4.88 (dd, J = 8.4, 4.8 Hz, 1H), 4.08 (dd, J = 7.8, 4.4 Hz, 1H), 2.79 (ddd, J = 8.0, 8.0, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 147.9, 137.4, 129.9, 124.0, 66.0, 38.9, 31.4. The enantiomeric excess was determined by HPLC with an AS-H column (^{n}-hexane/^{i}-PrOH = 75/25, λ = 220 nm, 1.0 ml/min); t_R (major enantiomer) = 33.1 min, t_R (minor enantiomer) = 38.8 min, 92% ee.

4.3.5. Compound 9c

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 6.8 Hz, 2H), 7.18 (d, J = 6.4 Hz, 2H), 5.26 (dd, J = 3.8, 2.8 Hz, 1H), 3.78 (dd, J = 8.8, 3.6 Hz, 1H), 3.44 (dt, J = 8.8, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 134.4, 130.1, 129.0, 128.7, 62.4, 38.3, 35.6; IR (thin film) ν/cm^{-1}: 2924 (m), 2854 (m), 1714 (s), 1551 (s), 1495 (m), 1364 (m), 1094 (m), 1015 (m), 827 (m); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0192. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 49.6 min, t_R (minor enantiomer) = 58.6 min, 91% ee.

4.3.6. Compound 9c′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, J = 4.0 Hz, 1H), 7.34 (d, J = 6.8 Hz, 2H), 7.12 (d, J = 6.8 Hz, 2H), 4.77 (dd, J = 6.6, 4.0 Hz, 1H), 3.95 (dd, J = 6.0, 4.0 Hz, 1H), 2.66 (ddd, J = 6.4, 6.4, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 134.5, 131.8, 129.3, 128.2, 66.3, 38.9, 31.7. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 77.5 min, t_R (minor enantiomer) = 84.0 min, 95% ee.

4.3.7. Compound 9d

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (d, J = 2.8 Hz, 1H), 7.17–7.09 (m, 4H), 5.27 (dd, J = 3.8, 3.2 Hz, 1H), 3.80 (dd, J = 8.8, 4.0 Hz, 1H), 3.37 (dt, J = 9.2, 2.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 138.5, 129.6, 128.6, 126.7, 62.5, 38.6, 36.0, 21.1; IR (thin film) ν/cm^{-1}: 2925 (w), 1715 (s), 1549 (s), 1456 (w), 1363 (s), 1122 (m), 807 (w); HRMS (EI) calcd for $C_{11}H_{11}NO_3$ (M^+): 205.0739, found: 205.0737. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 24.7 min, t_R (minor enantiomer) = 25.9 min, 94% ee.

4.3.8. Compound 9d′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (d, J = 4.0 Hz, 1H), 7.21–7.00 (m, 4H), 4.76 (dd, J = 6.4, 3.6 Hz, 1H), 3.95 (dd, J = 6.2, 3.6 Hz, 1H), 2.66 (ddd, J = 6.4, 6.4, 4.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 138.6, 129.8, 128.5, 127.2, 62.7, 39.3, 32.4, 29.7. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 34.1 min, t_R (minor enantiomer) = 36.2 min, 94% ee.

4.3.9. Compound 9e

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (d, J = 3.2 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.25 (dd, J = 4.8, 3.6 Hz, 1H), 3.78 (dd, J = 11.2, 4.8 Hz, 1H), 3.78 (s, 3H), 3.36 (dt, J = 11.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 159.6, 129.9, 122.1, 114.4, 62.7, 55.26, 38.7, 35.8; IR (thin film) ν/cm^{-1}: 2926 (m), 2852 (m), 1714 (s), 1613 (m), 1549 (s), 1517 (s), 1366 (m), 1251 (m), 1180 (m), 834 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ (M^+): 221.0688, found: 221.0685. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 56.2 min, t_R (minor enantiomer) = 60.3 min, 89% ee.

4.3.10. Compound 9e′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, J = 4.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.74 (dd, J = 8.0, 4.8 Hz, 1H), 3.94 (dd, J = 8.0, 4.8 Hz, 1H), 3.80 (s, 3H), 2.64 (ddd, J = 8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 159.8, 128.0, 125.1, 114.6, 66.6, 55.35, 39.3, 32.2. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 82.0 min, t_R (minor enantiomer) = 87.4 min, 96% ee.

4.3.11. Compound 9f

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, J = 2.8 Hz, 1H), 7.29–7.12 (m, 4H), 5.28 (dd, J = 4.8, 3.6 Hz, 1H), 3.80 (dd, J = 11.2, 4.8 Hz, 1H), 3.46 (dt, J = 11.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 135.18, 132.2, 130.2, 129.1, 128.85, 127.0, 62.2, 38.2, 35.6; IR (thin film) ν/cm^{-1}: 2925 (w), 2852 (w), 1714 (m), 1636 (s), 1549 (m), 1364 (m), 1082 (w), 784 (w); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0195. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 140 °C); t_R (major enantiomer) = 74.9 min, t_R (minor enantiomer) = 77.0 min, 96% ee.

4.3.12. Compound 9f′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (d, J = 4.4 Hz, 1H), 7.33–7.06 (m, 4H), 4.79 (dd, J = 8.4, 4.8 Hz, 1H), 3.96 (dd, J = 7.8, 4.8 Hz, 1H), 2.69 (ddd, J = 8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6, 135.22, 134.9, 130.5, 128.89, 127.1, 125.1, 66.1, 38.8, 31.7. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 140 °C); t_R (major enantiomer) = 108.8 min, t_R (minor enantiomer) = 118.5 min, 96% ee.

4.3.13. Compound 9g

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (d, J = 2.0 Hz, 1H), 7.38–7.25 (m, 4H), 5.22 (dd, J = 4.0, 3.2 Hz, 1H), 3.73 (dd, J = 8.6, 3.6 Hz, 1H), 3.56 (ddd, J = 8.8, 2.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.1, 134.7, 130.5, 129.9, 127.9, 127.3, 127.0, 62.8, 37.6, 34.7; IR (thin film) ν/cm^{-1}: 2925 (m), 2853 (m), 1715 (s), 1550 (s), 1479 (m), 1441 (m), 1364 (s), 1131 (w), 755 (m); HRMS (EI) calcd for $C_{10}H_8ClNO_3$ (M^+): 225.0193, found: 225.0190. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 28.8 min, t_R (minor enantiomer) = 27.4 min, 88% ee.

4.3.14. Compound 9g′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, J = 3.6 Hz, 1H), 7.45–7.08 (m, 4H), 4.75 (dd, J = 6.4, 4.0 Hz, 1H), 4.13 (dd, J = 6.4, 4.0 Hz, 1H), 2.65 (ddd, J = 6.6, 6.6, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.2, 135.4, 131.0, 129.7, 128.6, 128.2, 127.2, 65.8, 38.1, 31.0. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 46.9 min, t_R (minor enantiomer) = 50.2 min, 96% ee.

4.3.15. Compound 9h

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (d, J = 3.2 Hz, 1H), 7.33–6.84 (m, 4H), 5.15 (dd, J = 4.8, 3.6 Hz, 1H), 3.82 (s, 3H), 3.62 (dd, J = 10.8, 4.8 Hz, 1H), 3.38 (dt, J = 10.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.9, 157.5, 129.9, 129.7, 120.5, 118.7, 110.5, 62.6, 55.3, 37.8, 31.9; IR (thin film) ν/cm^{-1}: 2841 (w), 1714 (s), 1604 (m), 1547 (s), 1498 (m), 1364 (s), 1252 (s), 1025 (m), 755 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_4$ (M^+): 221.0688, found: 221.0683. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 140 °C); t_R (major enantiomer) = 62.8 min, t_R (minor enantiomer) = 64.9 min, 89% ee.

4.3.16. Compound 9h′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (d, J = 5.2 Hz, 1H), 7.33–6.84 (m, 4H), 4.86 (dd, J = 8.0, 5.2 Hz, 1H), 4.02 (dd, J = 8.0, 4.8 Hz, 1H), 3.84 (s, 3H), 2.73 (ddd, J = 8.0, 8.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3, 157.9, 129.9, 127.6, 121.3, 120.6, 110.7, 65.9, 55.4, 38.2, 29.5. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 140 °C); t_R (major enantiomer) = 86.9 min, t_R (minor enantiomer) = 91.9 min, 95% ee.

4.3.17. Compound 9i

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, J = 4.0 Hz, 1H), 7.34–7.33 (m, 1H), 6.35–6.34 (m, 2H), 5.28 (dd, J = 4.2, 4.0 Hz, 1H), 3.67 (dd, J = 10.8, 4.4 Hz, 1H), 3.32 (dt, J = 10.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.4, 144.7, 142.9, 111.0, 110.2, 61.8, 38.1, 28.1; IR (thin film) ν/cm^{-1}: 2924 (m), 2855 (m), 2361 (w), 1716 (s), 1550 (s), 1506 (w), 1365 (s), 1014 (m), 742 (s); HRMS (ESI) calcd for $C_8H_6NO_4$ $[M-H]^-$: 180.0297, found: 180.0305. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 125 °C); t_R (major enantiomer) = 22.4 min, t_R (minor enantiomer) = 24.3 min, 89% ee.

4.3.18. Compound 9i′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, J = 4.8 Hz, 1H), 7.34–7.33 (m, 1H), 6.38–6.36 (m, 2H), 4.90 (dd, J = 8.2, 4.4 Hz, 1H), 3.97 (dd, J = 7.6, 4.4 Hz, 1H), 2.80 (ddd, J = 8.0, 7.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 146.2, 142.7, 111.1, 108.9, 64.8, 37.5, 25.9. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 125 °C); t_R (major enantiomer) = 26.7 min, t_R (minor enantiomer) = 28.7 min, 92% ee.

4.3.19. Compound 9j

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (d, J = 2.0 Hz, 1H), 8.56–8.55 (m, 2H), 7.55–7.52 (m, 1H), 7.28–7.24 (m, 1H), 5.30 (dd, J = 5.0, 4.0 Hz, 1H), 3.79 (dd, J = 11.0, 4.8 Hz, 1H), 3.54 (ddd, J = 11.0, 3.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 150.1, 149.5, 136.1, 126.3, 123.4, 62.0, 37.8, 33.9; IR (thin film) ν/cm^{-1}: 2924 (w), 2854 (w), 2349 (m), 1710 (s), 1547 (s), 1413 (w), 1364 (s), 1026 (w), 710 (s); HRMS (ESI) calcd for $C_9H_9N_2O_3$ $[M+H]^+$: 193.0613, found: 193.0605. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 47.0 min, t_R (minor enantiomer) = 50.6 min, 88% ee.

4.3.20. Compound 9j′

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, J = 4.8 Hz, 1H), 8.51–8.49 (m, 2H), 7.47–7.44 (m, 1H), 7.31–7.28 (m, 1H), 4.85 (dd, J = 8.4, 4.8 Hz, 1H), 3.98 (dd, J = 7.6, 4.8 Hz, 1H), 2.72 (ddd, J = 8.0, 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6, 149.7, 148.5, 134.1, 129.2, 123.7, 65.8, 38.3, 29.7. The enantiomeric excess of **9j′** was determined after reducing to the corresponding alcohol. The enantiomeric excess of the corresponding alcohol was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 165 °C); t_R (major enantiomer) = 44.3 min, t_R (minor enantiomer) = 48.9 min, 86% ee.

4.3.21. Compound 9k

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.29 (d, J = 6.0 Hz, 1H), 7.41–7.18 (m, 5H), 3.89 (d, J = 11.2 Hz, 1H), 3.27 (dd, J = 11.2, 5.6 Hz, 1H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 130.2, 129.4, 128.9, 128.4, 69.0, 39.7, 38.9, 12.8; IR (thin film) ν/cm^{-1}: 2921 (s), 2851 (s), 1713 (s), 1539 (s), 1450 (m), 1390 (w), 1351 (m), 1113 (m), 699 (m); HRMS (EI) calcd for $C_{11}H_{11}NO_3$ (M^+): 205.0739, found: 205.0736. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 130 °C); t_R (major enantiomer) = 27.8 min, t_R (minor enantiomer) = 30.6 min, 95% ee.

4.3.22. Compound 9k′

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, J = 4.4 Hz, 1H), 7.39–7.20 (m, 5H), 4.19 (d, J = 8.0 Hz, 1H), 2.61 (dd, J = 8.0, 4.4 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 131.8, 129.8, 128.9, 128.4, 72.5, 41.4, 37.2, 16.6. The enantiomeric excess of **9i′** was determined after reducing to the corresponding alcohol **10′**.

4.3.23. Compound 9l′

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, J = 4.4 Hz, 1H), 7.38–7.23 (m, 5H), 4.13 (d, J = 8.0 Hz, 1H), 2.65 (dd, J = 8.0, 4.0 Hz, 1H), 1.68 (q, J = 7.6 Hz, 2H), 0.94 (t, J = 8.0 Hz, 3H); MS (EI) m/e = 219.1 (M^+), 190.1, 173.0, 145.0, 131.0, 128.0, 115.0, 105.0, 91.0, 76.9, 65.0, 51.0, 39.0, 29.0.

4.3.24. Compound 9m′

White solid. $[\alpha]_D^{20} = +17.0$ (c 1.0, $CHCl_3$); Mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (d, J = 4.0 Hz, 1H), 7.37–7.15 (m, 8H), 6.89–6.86 (m, 2H), 4.31 (d, J = 8.0 Hz, 1H), 3.23 (dd, J = 8.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 131.6, 131.3, 130.3, 129.0, 128.7, 128.5, 128.1, 127.9, 80.1, 40.2, 37.0; IR (thin film) ν/cm^{-1}: 2924 (w), 1703 (s), 1549 (s), 1448 (m), 1338 (m), 1127 (m), 1043 (m), 712 (m); HRMS (EI) calcd for $C_{16}H_{13}NO_3$ (M^+): 267.0895, found: 267.0890. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 150 °C); t_R (major enantiomer) = 48.2 min, t_R (minor enantiomer) = 52.5 min, 99% ee.

4.4. Reduction of 9k/9k′ with $NaBH_4$

A mixture of **9k/9k′** (dr = 14/86) (10 mg) and $NaBH_4$ (8 mg) was mixed in ethanol (1 ml). After stirring for 15 min at room temper-

ature, the solution was treated with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 ml × 2). The organic layer was separated and filtered through a silica gel plug. Alcohol **10**/**10′** was obtained after evaporation of the solvent.

4.4.1. Compound 10

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5H), 3.94 (dd, J = 11.6, 6.8 Hz, 1H), 3.53 (dd, J = 11.8, 8.4 Hz, 1H), 3.55 (d, J = 10.8 Hz, 1H), 2.77 (ddd, J = 10.8, 8.4, 6.8 Hz, 1H), 1.77 (s, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 129.9, 128.8, 127.7, 67.2, 58.9, 36.8, 34.6, 12.3; IR (thin film) ν/cm^{-1}: 3421(s), 2926 (w), 1604 (w), 1531 (s), 1449 (m), 1390 (m), 1353 (m), 1118 (m), 1031 (m), 699 (m); HRMS (EI) calcd for $C_{11}H_{13}NO_3$ (M^+): 207.0895, found: 207.0891.

4.4.2. Compound 10′

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5H), 4.17 (dd, J = 12.2, 5.6 Hz, 1H), 3.95 (dd, J = 12.0, 8.4 Hz, 1H), 3.56 (d, J = 8.4 Hz, 1H), 2.15 (ddd, J = 8.4, 8.4, 5.6 Hz, 1H), 2.08 (s, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.1, 128.7, 128.6, 127.8, 70.0, 59.9, 36.2, 36.1, 17.1. The enantiomeric excess was determined by GC using a Varian capillary column CP-Chirasil-DexCB (carrier: N_2, constant flow: 3.7 ml/min, oven temperature: 140 °C); t_R (major enantiomer) = 65.1 min, t_R (minor enantiomer) = 70.3 min, 98% ee.

Acknowledgments

We thank the National Natural Science Foundation of China (No. 20772160), NCET plan of Ministry of Education of China, Guangzhou Bureau of Science and Technology for the financial support of this study.

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14. The crystallographic data (excluding structure factors) of **9b′** are deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 710653. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
15. The diastereoisomers **9** and **9′** are inseparable by column chromatography. Their ^{1}H NMR and ^{13}C NMR data were obtained by analyzing the NMR spectra of **9**/**9′** mixtures. However IR and MS spectroscopic data could not be assigned individually for them.