Diastereoselectivity in the Aza-Michael Reaction of Chiral α-Methylbenzylamines with α,β-Unsaturated Carbonyl Compounds

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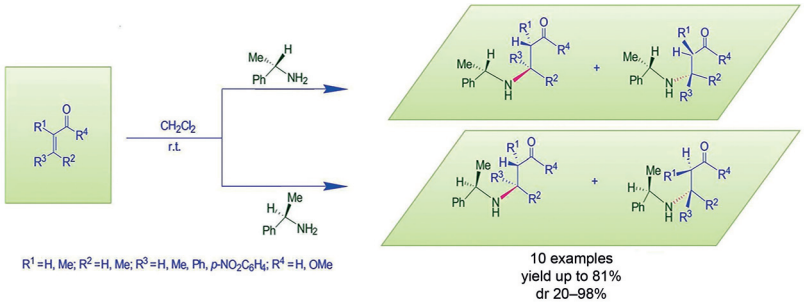


R¹ = H, Me; R² = H, Me; R³ = H, Me, Ph, *p*-NO₂C₆H₄; R⁴ = H, OMe

Received: 15.03.2018
Accepted after revision: 05.04.2018
Published online: 07.05.2018
DOI: 10.1055/s-0036-1591999; Art ID: so-2018-d0019-op

Abstract The aza-Michael reaction of (*S*)-(–)- and (*R*)-(+)-α-methylbenzylamines with *trans*-cinnamaldehyde and other α,β-unsaturated carbonyl compounds occurs with 52–98% diastereoselectivity (*de*); however, in the reaction with crotonaldehyde, the *de* is lower (20–38%). In the products obtained from the reaction with α,β-unsaturated aldehydes, the *de* could be determined on the basis of the relative intensities of the aldehydic protons of the two diastereomers. Theoretical investigations of the reaction of (*S*)-(–)-α-methylbenzylamine with *trans*-cinnamaldehyde at the DFT (B3LYP/6-31+G*) level reveal that the diastereomer formed from the attack of the amine on the *Re* face is thermodynamically more stable. The calculations also show that the aldehydic proton of this diastereomer is expected to be more deshielded, which on the basis of the ^{1}H NMR spectrum is the major product.

Keywords aza-Michael reaction, α-methylbenzylamine, diastereoselectivity, *trans*-cinnamaldehyde, DFT calculations

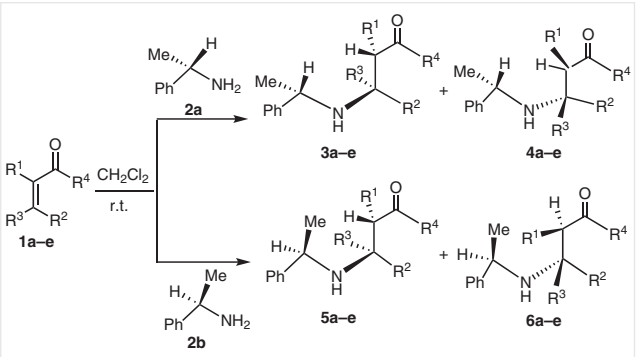
The aza-Michael reaction has emerged as one of the most powerful and reliable methods for the asymmetric synthesis of β-amino carbonyl compounds, which are important building blocks for the synthesis of a wide variety of nitrogen-containing compounds having pharmaceutical importance.[1,2]

The reaction of a nucleophile with an activated alkene having prochiral faces is accompanied by the generation of one or more stereogenic centers in one step. Thus, by manipulating the reaction environment with appropriate chiral auxiliaries, asymmetry can be induced and the desired products may be obtained with high stereoselectivity. The use of chiral nitrogen nucleophiles is one such strategy. By following this approach, (*S*)-alanine benzyl ester was used as a Michael donor and reacted with 4-oxo-4-phenyl-2-butenoate to give a mixture of diastereomers, from which the major isomer could be separated.[3] Likewise, chiral *N*-(α-methylbenzyl)hydroxylamines react with methyl enoates to afford isoxazolidinone adducts in moderate to good diastereoselectivity,[4] which could be further enhanced by using chiral crotonate acceptors under double stereodifferentiation conditions.[5] Hawkins used an atropisomeric lithiated dinaphthoazepine derivative as a chiral nitrogen nucleophile and the reaction proceeded with very high diastereoselectivity to afford β-amino esters in excellent yields.[6] Davies and co-workers developed diastereoselective conjugate additions of enantiomerically pure lithium amides to a wide range of α,β-unsaturated esters and amides, making a wide range of β-amino acids and their derivatives available.[7] They proposed a mechanistic rationale that accounted for the high diastereoselection between prochiral faces.[8] Enders and co-workers, on the other hand, employed lithiated enantiopure hydrazines as nitrogen nucleophiles, which reacted with α,β-unsaturated esters and other acceptors with a high degree of diastereoselection.[9] Likewise, Michael addition of a D-mannitol derived hydrazine to alkylidenemalonates was accomplished with high diastereoselectivities.[10] A cyclic carbamate has also been employed as a nitrogen nucleophile for its conjugate addition to nitroalkenes to afford products as single diastereomers.[11]

The Michael addition of homochiral α-methylbenzylamines to methyl crotonate[12] and some other activated alkenes[12e] has been reported earlier to occur with poor diastereoselectivity (2–19%). In all these investigations, alcohol was used as the solvent. As solvent has been found to affect diastereoselectivity in the Michael addition[13] and intramolecular Diels–Alder reactions,[14] we decided to investigate the reaction of (*S*)-(–)- and (*R*)-(+)-α-methylbenzylamines with a range of α,β-unsaturated carbonyl compounds in an aprotic solvent (dichloromethane) and found that the diastereoselectivity improved remarkably. As a result, an attempt was made to rationalize the observed diastereoselec-

tivity theoretically by computing the model reaction at the DFT level involving the attack of (*S*)-(−)-α-methylbenzylamine on the *Si* and *Re* faces of *trans*-cinnamaldehyde. The results are presented herein.

(*S*)-α-Methylbenzylamine (**2a**) and (*R*)-α-methylbenzylamine (**2b**) reacted with α,β-unsaturated carbonyl compounds (**1a–e**) in dichloromethane at room temperature (ca. 25 °C) to afford mixtures of the diastereomers **3**+**4** and **5**+**6**, respectively (Scheme 1).



1,3–6	a	b	c	d	e
R^1	H	H	H	H	Me
R^2	H	H	H	H	Me
R^3	Ph	Me	*p*-$NO_2C_6H_4$	Ph	H
R^4	H	H	H	OMe	H

Scheme 1 Reaction of (*S*)- and (*R*)-α-methylbenzylamines with α,β-unsaturated carbonyl compounds

All the products were obtained as colorless syrups, which could not be crystallized. The ^{1}H NMR spectra indicated each to be a mixture of two diastereomers. In the case of **a**,**b**,**c**, and **e**, two characteristic signals for the aldehydic protons in the range of δ ca. 9 and 8 ppm confirmed the presence of two diastereomers in each case, the relative percentages of which could be calculated on the basis of the relative intensities of these signals. The presence of two diastereomers was further corroborated by two ^{13}C NMR signals in the range of 195–160 ppm. These parts of the ^{1}H and ^{13}C NMR spectra of the product (**3a**+**4a**) obtained from the reaction of (*S*)-α-methylbenzylamine (**2a**) with *trans*-cinnamaldehyde (**1a**) are shown in Figure 1.

It may be noted that the aldehydic proton of the major diastereomer gives a double doublet (dd) at δ = 9.71 ppm ($^3J_{H-H}$ = 7.7 Hz, $^3J_{H-H}$ = 1.0 Hz) due to its coupling with the vicinal diastereotopic protons H_A and H_B. However, the aldehydic proton of the minor diastereomer gives a simple doublet at δ = 8.12 ppm ($^3J_{H-H}$ = 8.1 Hz), possibly due to the orthogonal disposition of one of the two diastereotopic protons with respect to it. In the ^{13}C NMR spectrum, signals at δ = 192.2 and 161.6 ppm are observed due to aldehydic carbon atoms of the two diastereomers.

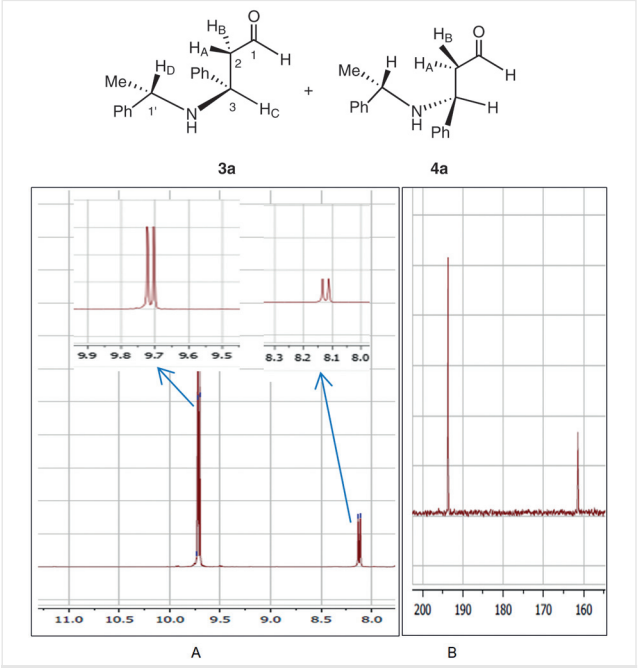


Figure 1 Parts of the ^{1}H NMR (A) and ^{13}C NMR (B) spectra of the product **3a**+**4a**

The diastereomeric excess (*de*) in the reaction of (*S*)-α-methylbenzylamine (**2a**) with **1a** was also determined by HPLC and the *de* obtained (52%) was very close to that calculated on the basis of the relative intensities of the signals of the aldehydic protons in the ^{1}H NMR spectrum (56%). The chromatogram of the mixture of the diastereomers **3a**+**4a** can be found in the Supporting Information.

Also in other cases, the *de* as determined on the basis of the ^{1}H NMR spectra ranged from 52% to 98%, except in the reaction of (*S*)- and (*R*)-α-methylbenzylamines with *trans*-crotonaldehyde (**1b**) when it was found to be 20% and 38%, respectively. The low diastereoselectivity in these cases may be attributed to the smaller size of the β-methyl group.

We attempted to rationalize the experimentally observed diastereoselectivity in the reaction of (*S*)-α-methylbenzylamine with *trans*-cinnamaldehyde theoretically by computing two model reactions initiated by the attack of the amine on *Si* and *Re* faces of the aldehyde (Figure 2).

Geometries of the products **3a** and **4a** resulting from the attack of the amine on *Si* and *Re* faces, respectively, were optimized at the B3LYP/6-31+G* level and frequency calculations were carried out at the same level. Thus, total energies of the products were calculated by summing up the respective energies with the uncorrected zero-point correction energies and are given in Table 1.

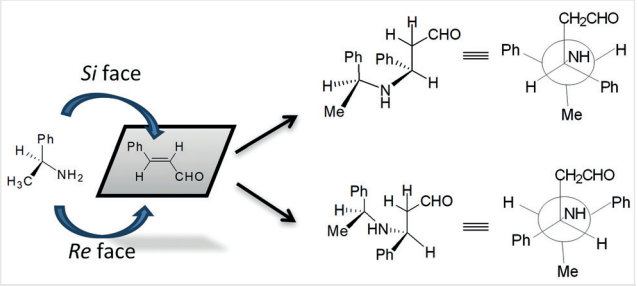


Figure 2 Attack of (*S*)-α-methylbenzylamine on *Si* and *Re* faces of *trans*-cinnamaldehyde

Table 1 Total Energies of the Two Diastereomers Resulting from the Attack of (*S*)-α-Methylbenzylamine on *Si* and *Re* Faces of *trans*-Cinnamaldehyde

Product	E (a.u.)	ZPE (a.u.)	Total energies (a.u.)	Energy difference (kcal mol^{-1})
3a	–789.236435	0.321541	–788.914894	–2.84
4a	–789.240401	0.32097	–788.919424	

We did not succeed in locating the transition structures involved in the amine attack on the *Si* and *Re* faces, and hence it has not been possible to determine which product (**3a** or **4a**) is preferred kinetically. It can be seen, however, that product **4a**, resulting from the attack on the *Re* face, is more stable than the product **3a**, formed from *Si* attack, by 2.84 kcal mol^{-1}. This corresponds to 100% *de*, which implies that the observed diastereoselectivity cannot be rationalized on the basis of the relative thermodynamic stabilities of the two products.

NMR spectroscopy has been used to determine absolute configuration.[15] In one such strategy, a secondary alcohol was derivatized with α-methoxy-α-trifluoromethylphenylacetic acid or a similar aryl group containing carboxylic acid. Two stereoisomers could be differentiated on the basis of the ^{1}H NMR shielding or deshielding of the substituent group present on the chiral center caused by the phenyl ring.[16] The geometries of the two diastereomers formed from the attack of (*S*)-α-methylbenzylamine on *Si* and *Re* faces of *trans*-cinnamaldehyde optimized at the B3LYP/6-31+G* level are shown in Figure 3.

Notably, the aldehydic protons in **3a** and **4a** fall in the shielding and deshielding zones of the phenyl ring, respectively. If these observations are viewed in correlation with the ^{1}H NMR spectrum of the mixture of **3a** and **4a** discussed earlier, the diastereomer **4a** formed from the attack of the amine on the *Re* face of cinnamaldehyde can be concluded to be the major product, which is also thermodynamically more stable, as shown by DFT calculations.

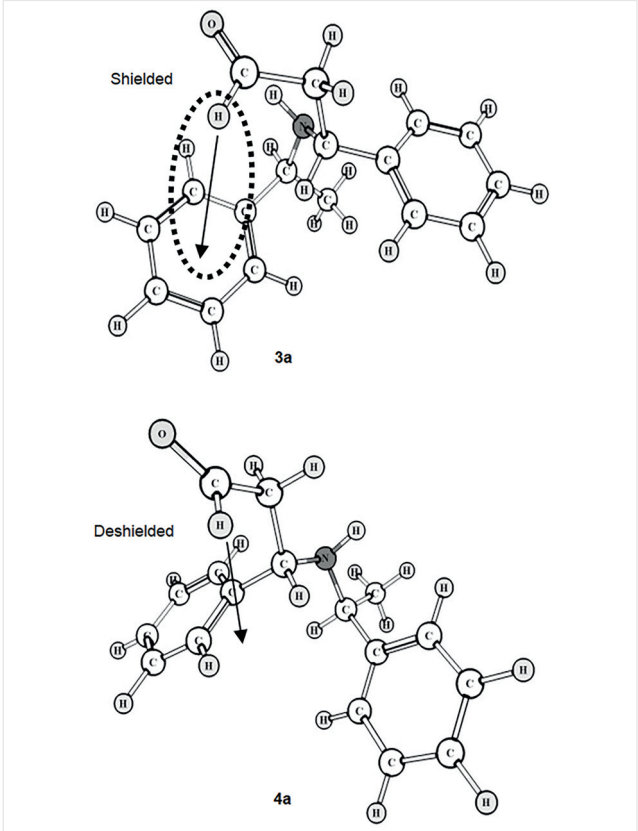


Figure 3 Optimized geometries of the diastereomers formed from the attack of (*S*)-α-methylbenzylamine on *Si* (**3a**) and *Re* (**4a**) faces of *trans*-cinnamaldehyde

In conclusion, the reaction of chiral α-methylbenzylamines with α,β-unsaturated carbonyl compounds in dichloromethane occurs with moderate to very high diastereoselectivity, with *de* ranging from 52% to 98%, except in the reaction of (*S*)- and (*R*)-α-methylbenzylamines with *trans*-crotonaldehyde when the *de* were found to be 20% and 38%, respectively. The low diastereoselectivity in these cases may be attributed to the smaller size of the β-methyl group. It was possible to determine *de* in the reaction with cinnamaldehyde and other α,β-unsaturated aldehydes on the basis of the relative intensities of the aldehydic protons of the two diastereomers. Theoretical investigations at the DFT level along with the ^{1}H NMR data indicate that the diastereomer resulting from the attack of the amine on the *Re* face of *trans*-cinnamaldehyde is the major diastereomer.

Commercially available amines, aldehydes and dichloromethane were purchased from Sigma–Aldrich. Dichloromethane was freshly dried and distilled.

IR spectra were recorded on NaCl plate with a Perkin–Elmer Precisely FT-IR spectrometer. NMR spectra were recorded with a Jeol Resonance-400 MHz spectrometer; ^{1}H NMR at a frequency of 400 MHz and ^{13}C NMR at a frequency of 100 MHz using TMS as the internal ref-

erence. High-resolution mass spectra (HRMS) were recorded with a Waters Xevo G2-S Q Tof instrument with UPLC. HPLC was carried out with a Waters-2998 instrument with photodiode array detector and pump-515 (hexane/2-propanol, 99:1).

Procedures

To a solution of **1** (**1a**, 1.03 g, 0.99 mL, 7.75 mmol; **1b**, 0.54 g, 0.64 mL, 7.75 mmol; **1c**, 0.91 g, 7.75 mmol; **1d**, 1.26 g,7.75 mmol; **1e**, 0.65 g, 0.75 mL, 7.75 mmol) in dichloromethane (10 mL) in a 100 mL RB flask was added dropwise, a solution of 1 equiv of amine (**2a**,**b** 0.94 g, 1 mL, 7.75 mmol) in dichloromethane (5 mL) at r.t. with continuous stirring. After addition was complete, the reaction mixture was stirred for another 3–4 h. The solvent was removed under reduced pressure to afford a syrupy residue.

Computational Methods

All calculations were carried out using Gaussian 03 software[17] within the density functional theory (DFT) framework.[18] Geometry optimizations were performed at the B3LYP/6-31+G* level.[19] Stationary points were analyzed by frequency calculations at the same level to confirm their character as local minima. To distinguish between different diastereomers, absolute configurations have been assigned on the basis of theoretical analysis.

(3*R*,1′*S*)- and (3*S*,1′*S*)-3-(α-Methylbenzyl)amino-3-phenylpropanals 3a+4a

Yield: 1.59 g (81%); *de*: 56%; colorless syrup.

IR (NaCl): 3420 (N-H st.), 1626 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 1.0 Hz, 1 H, C*H*O, major diastereomer), 8.12 (d, $^3J_{HH}$ = 8.5 Hz, 1 H, C*H*O, minor diastereomer), 7.62–6.95 (unresolved m, 20 H, ArH), 4.50 (dq, $^3J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 6.6 Hz, 2 H, H_D), 1.78 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2 H, H_A), signals for H_B and H_C merged with that of H_A, 1.63 (dd, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.8 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2 (*C*=O, major), 161.6 (*C*=O, minor), 142.0–125.0 (aromatic carbon atoms), 67.2 (*C*3), 57.7 (*C*1′), 21.1 (CH_3).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{19}NO$: 253.1466; found: 253.1439.

(3*R*,1′*R*)- and (3*S*,1′*R*)-3-(α-Methylbenzyl)amino-3-phenylpropanals (5a+6a)

Yield: 1.57 g (80%); *de*: 96%; colorless syrup.

IR (NaCl): 3420 (N-H st.), 1633 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, C*H*O, major diastereomer), 9.35 (unresolved d, 1 H, C*H*O, minor diastereomer), 7.64–7.41 (unresolved m, 20 H, aromatic protons), 4.30 (dq, $^3J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 6.0 Hz, 2 H, H_D), 2.36 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2 H, H_A), signals for H_B and H_C merged, 1.42 (dd, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.2 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.59 (*C*=O, major), 161.6 (*C*=O, minor), 141–126 (aromatic carbon atoms), 67.2 (*C*3), 57.7 (*C*1′), 21.1 (CH_3).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{19}NO$: 253.1466; found: 253.1443.

(3*S*,1′*S*)- and (3*R*,1′*S*)-3-(α-Methylbenzyl)aminobutanals (3b+4b)

Yield: 1.53 g (78%); *de*: 38%; colorless syrup.

IR (NaCl): 3395 (N-H st.), 1657 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 1.0 Hz, 1 H, C*H*O, major diastereomer), 8.31 (unresolved d, 1 H, C*H*O, minor diastereomer), 7.99–7.29 (unresolved m, 10 H, aromatic protons), 4.49 (dq, $^3J_{HH}$ =10.0 Hz, $^3J_{HH}$ = 6.0 Hz, 2 H, H_D), 2.39 (dd, $^2J_{HH}$ =16.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2 H, H_A), 1.92 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2 H, H_B), signal for H_C merged, 1.49 (dd, $^3J_{HH}$ = 6.0 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1 (*C*=O, major), 162.4 (*C*=O, minor), 129–124 (aromatic carbon atoms), 69.1 (*C*3), 59.8 (*C*1′), 22.7 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO$: 192.1388; found: 192.1310.

(3*S*,1′*R*)- and (3*R*,1′*R*)-3-(α-Methylbenzyl)aminobutanals (5b+6b)

Yield: 1.51 g (77%); *de*: 20%; colorless syrup.

IR (NaCl): 3400 (N-H st.), 1657 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 1.0 Hz, 1 H, C*H*O, major diastereomer), 8.42 (unresolved d, 1 H, C*H*O, minor diastereomer), 7.99–6.40 (unresolved m, 10 H, aromatic protons), 4.33 (dq, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 6.0 Hz, 2 H, H_D), 2.63 (dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 8.0 Hz, 2 H, H_A), 1.92 (dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 8.0 Hz, 2 H, H_B), signal for H_C merged, 1.49 (dd, $^3J_{HH}$ = 6.0, 6 H, CH_3).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 187.1 (*C*=O, major), 161.6 (*C*=O), 127–124 (aromatic carbon atoms), 76.1 (*C*2), 67.0 (*C*3), 57.7 (*C*1′), 22.5 (CH_3).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{17}NO$: 191.1310; found: 191.1361.

(3*R*,1′*S*)- and (3*S*,1′*S*)-3-(α-Methylbenzyl)amino-3-(4-nitrophenyl)propanals (3c+4c)

Yield: 1.47 g (61%); *de*: 61%; colorless syrup.

IR (NaCl): 3398 (N-H st.), 1597 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, C*H*O, major diastereomer), 8.17 (d, $^3J_{HH}$ = 8.1 Hz, 1 H, C*H*O, minor diastereomer), 7.61–6.59 (unresolved m, 18 H, aromatic protons), 4.49 (q, $^3J_{HH}$ = 6.7 Hz, 2 H, H_D), 2.24 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2 H, H_A), 1.61 (unresolved dd, 2 H, H_B), 1.42 (unresolved dd, 2 H, H_C), 1.28 (d, $^3J_{HH}$ = 6.7 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.2 (*C*=O, major), 172.6 (*C*=O, minor), 148–122 aromatic carbons, 62.5 (*C*3), 55.5 (*C*1′), 28.2 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1395; found: 299.1317.

(3*R*,1′*R*)- and (3*S*,1′*R*)-3-(α-Methylbenzyl)amino-3-(4-nitrophenyl)propanals (5c+6c)

Yield: 1.33 g (68%); *de*: 52%; colorless syrup.

IR (NaCl): 3401 (N-H st.), 1601 (C=O st.) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, $^3J_{HH}$ = 8.0 Hz, C*H*O, 1 H, major diastereomer), 8.13 (unresolved d, 1 H, C*H*O, minor diastereomer), 7.52–6.49 (unresolved m, 18 H, aromatic protons), 4.55 (q, $^3J_{HH}$ = 6.6 Hz, 2 H, H_D), 2.62 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 8.5 Hz, 2 H, H_A), signals for H_B and H_C merged, 1.45 (d, $^3J_{HH}$ = 6.6 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.5 (*C*=O major), 162.1 (*C*=O, minor), 144–127 (aromatic carbon atoms), 66.1 (*C*3), 56.3 (*C*1′), 22.7 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1395; found: 299.1379.

(3*R*,1′*S*)- and (3*S*,1′*S*)-Methyl 3-(α-Methylbenzyl)amino-3-phenylpropanoate (3d+4d)

Yield: 1.43 g (73%); colorless syrup.

IR (NaCl): 3415 (N-H st.), 1637 (C=O st.), 1174 (C-O st.) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–6.50 (unresolved m, 20 H, aromatic protons), 4.65 (q, $^3J_{HH}$ = 7.6 Hz, 2 H, H_D), 3.69 (s, 3 H, OCH_3, major), 3.68 (s, 3 H, OCH_3, minor), 1.89 (dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 7.7 Hz, 2 H, H_A), 1.45 (dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 7.6 Hz, 2 H, H_B), signal for H_C merged.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8 (*C*=O), 148–129 aromatic carbons, 55.01 (O-*C*H_3), 22.9 (*C*H_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}NO_2$: 284.1650; found: 284.1673.

(3*R*,1′*R*)- and (3*S*,1′*R*)-Methyl 3-(α-Methylbenzyl)amino-3-phenylpropanoate (5d+6d)

Yield: 1.47 g (75%); colorless syrup.

IR (NaCl): 3413 (N-H st.), 1637 (C=O st.), 1174 (C-O st.) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–6.50 (unresolved m, 20 H, aromatic protons), 4.25 (q, $^3J_{HH}$ = 8.2 Hz, 2 H, H_D), 3.79 (s, 3 H, OCH_3, major), 3.78 (s, 3 H, OCH_3, minor), 1.99 (unresolved dd, 2 H, H_A), 1.49 (unresolved dd, 2 H, H_B), H_C merged, 1.37 (d, $^3J_{HH}$ = 6.8 Hz, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5 (*C*=O), 145–125 aromatic carbons, 51.72 (O-*C*H_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}NO_2$: 284.1650; found: 284.1604.

(2*S*,3*S*,1′*S*)- and (2*R*,3*R*,1′*S*)-2-Methyl-3-(α-methylbenzyl)aminobutanals (3e+4e)

Yield: 1.37 g (70%); *de*: 66%: colorless syrup.

IR (NaCl): 3409 (N-H st.), 1629 (C=O st.) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.91 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, C*H*O, major diastereomer), 8.61 (unresolved d, 1 H, C*H*O, minor diastereomer), 7.50–6.01 (unresolved m, 10 H, aromatic protons), 4.41 (q, $^3J_{HH}$ = 8.0 Hz, 2 H, H_D), 2.60 (unresolved q, 2 H, H_A), 1.86 (d, $^3J_{HH}$ = 8.0 Hz, 6 H, C(2)CH_3), 1.52 (d, $^3J_{HH}$ = 8.2 Hz, 6 H, C(3)CH_3), 1.32 (d, $^3J_{HH}$ = 7.8 Hz, 6 H, C(1′)CH_3), 0.91 (unresolved q, 2 H, H_C).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5 (*C*=O, major), 169.4 (*C*=O, minor), 144–124 aromatic carbons, 57.0 (*C*3), 50.2 (*C*1′), 26.2 ((C2)*C*H_3), 23.9 ((C1′)*C*H_3).

HRMS (ESI): *m*/*z* [M-H]$^+$ calcd for $C_{13}H_{18}NO$: 204.1388; found: 204.1353.

(2*S*,3*S*,1′*R*)- and (2*R*,3*R*,1′*R*)-2-Methyl-3-(α-methylbenzyl)aminobutanals (5e+6e)

Yield: 1.39 g (71%); *de*: 42%; colorless syrup.

IR (NaCl): 3377 (N-H st.), 1628 (C=O st.) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, C*H*O, major diastereomer), 8.06 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, C*H*O, minor diastereomer),7.75–6.55 (unresolved m, 10 H, aromatic protons), 4.38 (unresolved, dq, 2 H, H_D), 2.51 (unresolved q, 2 H, H_A), 1.61 (unresolved d, 6 H, C(2)CH_3), 1.50 (d, $^3J_{HH}$ = 8.0 Hz, 6 H, C(3)CH_3), 1.35 (d, $^3J_{HH}$ = 8.0 Hz, 6 H, C(1′)CH_3), 1.31 (unresolved q, 2 H, H_C).

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{19}NO$: 205.1466; found: 205.1481.

Acknowledgment

The authors thank the authorities of The IIS (deemed to be university) for providing necessary facilities.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591999.

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