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Article

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Memory of Chirality (MOC) Concept in Asymmetric Intermolecular Michael Addition of α-Amino Ester Enolates to Enones and Nitroalkenes

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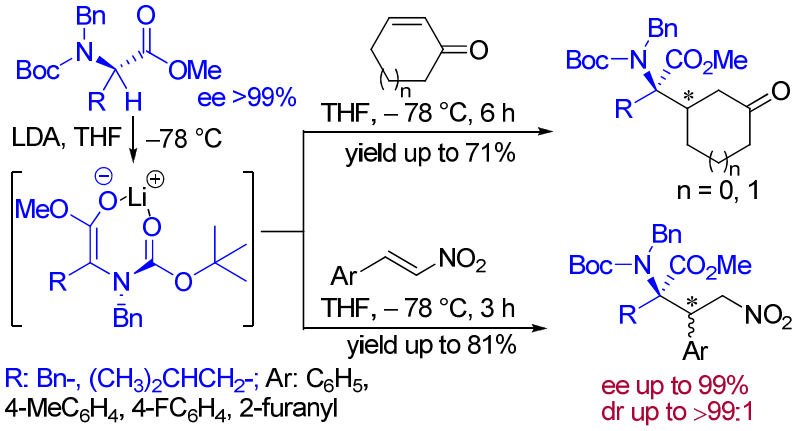


Abstract

A highly stereoselective asymmetric intermolecular conjugate addition of α-amino ester derivatives to cyclic enones via Memory of Chirality (MOC) concept in high yields with excellent diastereo- and enantioselectivity (dr >99:1, up to 99% ee) is reported. The applicability and the generality of the strategy was demonstrated by its further exploration to acyclic α,β-

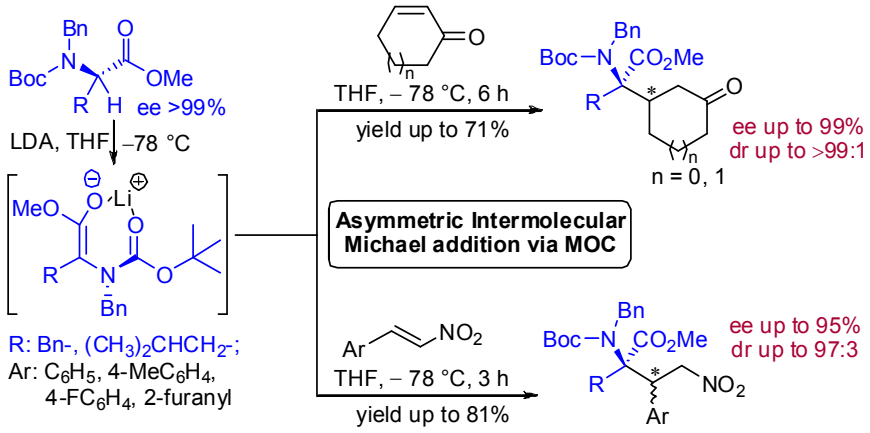
unsaturated ketone and aromatic nitroalkenes resulting in the formation of δ-keto-α-amino ester derivative and γ-nitro-α-amino ester derivatives, respectively, with excellent ee and dr.

Introduction

The asymmetric intermolecular conjugate addition is one of the key reactions in organic synthesis, especially, for accessing numerous biologically active natural products and other important compounds.[1] In most of the cases, the observed asymmetric induction is due to external chiral sources, e. g. chiral auxiliary, chiral catalysts, chiral ligands, chiral electrophiles, and chiral starting materials etc. The pioneering work by Alexakis[2] and Feringa[3] in asymmetric conjugate addition of α,β-unsaturated carbonyl compounds utilizing copper catalysis, and by Hayashi[4] employing rhodium catalyzed reactions contributed significantly in the field. Incidentally, the asymmetric intermolecular conjugate addition on nitroalkenes [5] has become an useful tool as the adducts[6] could easily be transformed into α,γ-diamino acid derivatives, an useful building blocks for biologically active peptide and other substrates.[7] Fuji and Kawabata have introduced Memory of Chirality (MOC) concept and made seminal contribution in the field of asymmetric synthesis for enantioselective construction of C-C bonds via MOC.[8] This novel concept has been explored in enolate and other chemistry for the synthesis of various biologically significant chiral compounds.[9] The MOC concept was successfully applied in intramolecular conjugate addition reactions for the synthesis of pyrrolidine, piperidine, tetrahydroisoquinoline, indoline and β-lactam derivatives with excellent enantioselectivity.[10] Very recently Kim et. al. have reported total synthesis of lepadiformine C employing asymmetric intramolecular conjugate addition via MOC concept.[11] The implementation of the MOC concept in asymmetric intermolecular conjugate addition remains largely unexplored till date except only report by Kawabata et. al. who described the total synthesis of Manzacidin A.[12] Earlier, we have

demonstrated MOC concept in imino-aldol reaction for the synthesis of nonracemic *α,β*-diamino ester derivatives and substituted aziridines.[13] In continuation of our research activities in enolate chemistry[14] using MOC concept[13], we have developed a simple protocol for intermolecular conjugate addition of axially chiral enolate **1a′–b′** generated from enantiopure *α*-amino ester derivatives **1a–b** with Michael acceptors such as cyclic *α,β*-enones, acyclic (*E*)-chalcone and aromatic nitroalkenes (Scheme 1) to furnish the corresponding addition products with high yield and excellent stereoselectivity (dr up to >99:1, up to 99% ee). Herein, we report our results in detail as an article.

Scheme 1. Asymmetric Intermolecular Conjugate Addition via MOC Concept

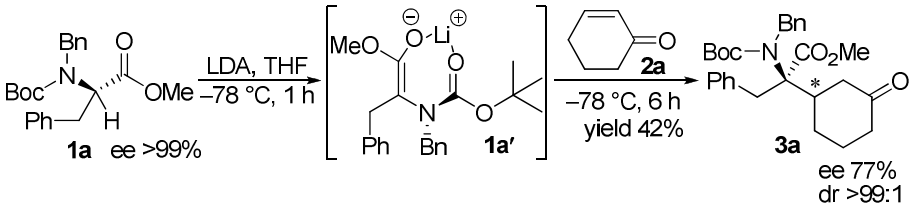


Results and Discussion

Our study began with the intermolecular conjugate addition of the enolate generated from (*S*)-*N*-benzyl-*N*-Boc phenylalanine methyl ester **1a**[13b] as the substrate with cyclohex-2-enone **2a** as the Michael acceptor. The enolate was generated from **1a** by treatment with LDA in THF at −78 °C in 1 h and reacted with cyclohex-2-enone **2a** at the same temperature for 6 h to afford the corresponding conjugate addition product **3a** as a single diastereomer in moderate yield (42%) and with good enantiomeric excess (77%) (Scheme 2, and Table 1, entry 1). Due to its existence as a mixture of rotamers, the ^{1}H NMR spectrum of the **3a** displayed broad signals. To determine

the diastereoselectivity and to resolve ^{1}H NMR spectrum, *N*-Boc group was deprotected with 4(N) HCl in ethyl acetate to give **4a** as a single diastereomer (based on ^{1}H NMR study of the crude reaction mixture) in very high yield (Scheme 4).

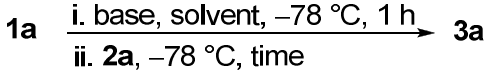
Scheme 2. Asymmetric Intermolecular Conjugate Addition of 1a with 2a via MOC Concept



To find out the optimum reaction condition for better yield and enantioselectivity, different bases, solvents, reaction time and amount of enolate were screened. The results are summarized in Table 1. When the reaction was carried out with LDA in the presence of toluene, **3a** was obtained in trace amount with poor enantiomeric excess (18% ee) (Table 1, entry 2). We then switched the base from LDA to KHMDS in different solvents. When KHMDS was employed in THF, **3a** was obtained with 31% yield and 23% ee as a single diastereomer (Table 1, entry 3). Even on applying longer reaction time (20 h) and using KHMDS in toluene, **3a** was obtained in poor yield (26%) and with 20% ee (Table 1, entry 4). When KHMDS was used in THF/toluene (1:4) solvent mixture, **3a** was obtained in 28% yield and with 12% ee, whereas using THF/toluene (4:1) mixture of solvent and KHMDS as base, yielded **3a** in lower enantioselectivity (14% ee) and poor yield (25%) (Table 1, entry 5 and 6). Other Na and Li based non-nucleophilic bases were also employed. When NaHMDS was used in THF, **3a** was formed in 22% yield and with 19% ee. Using LiHMDS instead of NaHMDS in THF furnished **3a** with a lower enantiomeric excess (23%) and yield (24%) (Table 1, entry 7 and 8). However, on using LTMP in THF, **3a** was obtained in 39% yield and with moderate enantioselectivity (65% ee) (Table 1, entry 9). Based on the optimization studies LDA and THF were selected as the base

and the solvent, respectively, for the intermolecular conjugate addition. To improve the yield and the enantioselectivity of **3a** further, next the equivalent of enolate was varied. When the reaction was carried out with 2.0 equiv. of enolate for 6 h, the yield and enantioselectivity of **3a** enhanced to 60% and 80%, respectively. Increasing the amount of the enolate further (2.5 equiv.), to our pleasure, **3a** was obtained with 71% yield and excellent ee (99%) (Scheme 3 and Table 2, entry 1). With longer reaction time (12 h), slightly improved yield (75%), but reduced ee (83%) was observed.

Table 1. Effect of Bases and Solvents on Asymmetric Intermolecular Conjugate addition[a]



entry	base	solvent	time (h)	yield **3a** (%)[b,c]	ee (%)[d] of **3a**
1	LDA	THF	6	42	77
2	LDA	Toluene	10	trace	18
3	KHMDS	THF	20	31	23
4	KHMDS	Toluene	20	26	20
5	KHMDS	THF/Toluene (1:4)	19	28	12
6	KHMDS	THF/Toluene (4:1)	18	25	14
7	NaHMDS	THF	24	22	19
8	LiHMDS	THF	24	24	23
9	LTMP	THF	11	39	65

[a]All the reactions were performed using 1.0 equiv of **1a**, 1.1 equiv of base and 1.1 equiv of **2a**. [b]Yields of isolated products (%) after column chromatographic separation. [c]The product was obtained as a single diastereomer. [d]Determined by chiral HPLC analysis using chiralpak Lux 5µ Cellulose-2 column (95:5 Hexane/Isopropanol as mobile phase and 1.0 mL/min flow rate).

The methodology was generalized with cyclopent-2-enone **2b** as a Michael acceptor and the corresponding product **3b** was obtained in good yield (67%) with excellent enantiomeric excess (91%) (Scheme 3 and Table 2, entry 2).

Scheme 3. Asymmetric Intermolecular Conjugate Addition of 1a with 2a–b

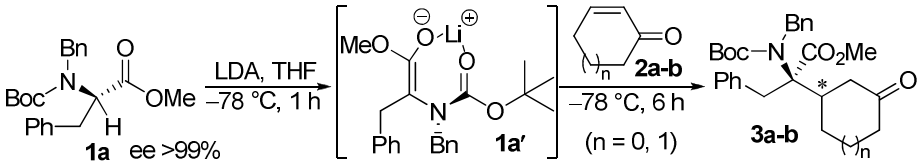
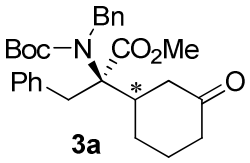
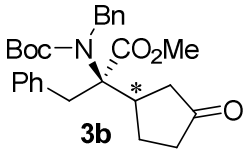


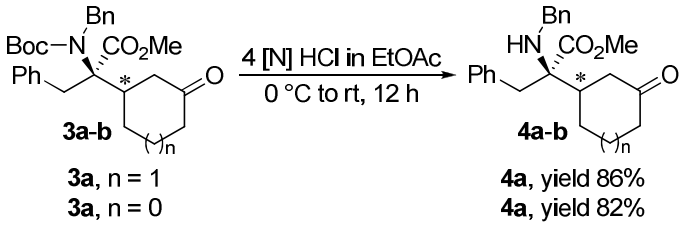
Table 2. Asymmetric Synthesis of *δ*-Keto-*α*-Amino Ester Derivatives 3a–b[a]

entry	**1**	**2**	conjugated adduct **3**	yield **3** (%)[b,c]	ee (%)[d] of **3**
1	**1a**	**2a** (n = 1)	 **3a**	71	99
2	**1a**	**2a** (n = 0)	 **3b**	67	91

[a]All the reactions were performed using 2.5 equiv of enolate of **1a** and 1.0 equiv of **2a–b**. [b]Yields of isolated products **3a–b** (%) after column chromatographic separation. [c]The products **3a–b** was obtained as a single diastereomer. [d]ee was determined from chiral HPLC analysis of **3a–b** using Chiral pak Lux 5u Cellulose-2 column (95:5 Hexane/Isopropanol as mobile phase and 1.0 mL/min flow rate).

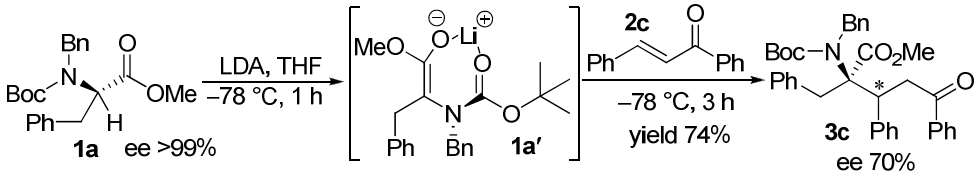
The *N*-Boc group of **3a**–**b** was deprotected using 4(N) HCl in ethyl acetate at room temperature overnight to afford **4a**–**b** with free NH group (Scheme 4).

Scheme 4. Boc Deprotection of Compounds 3a–b



To further demonstrate the scope of this methodology acyclic (*E*)-chalcone **2c** as the Michael acceptor was explored (Scheme 5). When the chiral enolate of **1a** was reacted with acyclic (*E*)-chalcone **2c** at −78 °C, the product **3c** was obtained with high yield (74%) and ee (70%) as a single diastereomer.

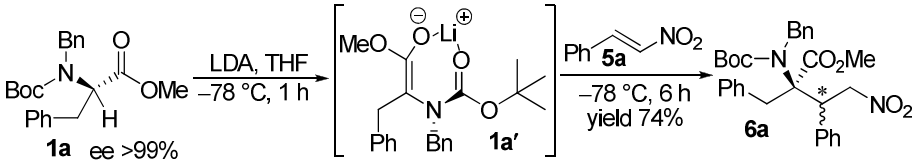
Scheme 5. Asymmetric Intermolecular Conjugate Addition of 1a with 2c



Next the scope of our protocol was further extended to *trans*-*β*-aryl nitroalkenes **5a**–**d** as the Michael acceptor. The enolate generated from **1a** by the treatment with LDA in THF at –78 °C was reacted with *trans*-*β*-nitrostyrene **5a** at the same temperature for 6 h to afford the corresponding addition product **6a** in 74% yield as a mixture of diastereomers (Scheme 6a). The broad peaks were observed in the ^{1}H NMR spectrum of **6a** at room temperature probably because of co-existence of both the rotamers as well as mixture of diastereomers. However, the formation of the product was confirmed by IR, ^{13}C{^{1}H} NMR and mass spectral analysis. To ascertain the diastereo- and enantioselectivity and to get a simplified ^{1}H NMR spectrum, the Boc group of **6a** was removed using 1:2 trifluoroacetic acid and dichloromethane to obtain the corresponding product **7a** in high yield (88%, dr 70:30) with good enantioselectivity (ee: 74% for the major isomer and 78% for the minor isomer), as shown in scheme 6b and Table 3 (entry

1). To find out the optimum condition, reaction of enolate of **1a** with **5a** was studied employing different solvents and bases, and the results are summarized in Table 3. The reaction was carried out with LDA as a base and toluene as a solvent over 10 h and a trace amount of product **6a** was obtained (Table 3, entry 2). When the intermolecular conjugate addition was studied in KHMDS as a base with different solvents (Table 3, entry 3, 4, 5 and 6), the product **6a** was obtained with the moderate yield and moderate to high diastereoselectivity but poor enantioselectivity (for both diastereomers, based on chiral HPLC analysis of **7a**) for all the cases. However, when LTMP was used as a base and THF as a solvent for 11 h, **6a** was obtained in 68% yield (Table 3, entry 7) but with moderate diastereoselectivity and enantioselectivity. Similarly, when other bases such as NaHMDS and LiHMDS were employed in THF, the product **6a** was obtained in trace amount even after the reaction was carried out for a long time (16 h) (entry 8 and 9 in Table 3). The best results were obtained with LDA in THF.

Scheme 6a. Asymmetric Intermolecular Conjugate Addition of 1a with 5a via MOC



Scheme 6b. Synthesis of Nonracemic *γ*-Nitro-*α*-Amino Ester Derivative

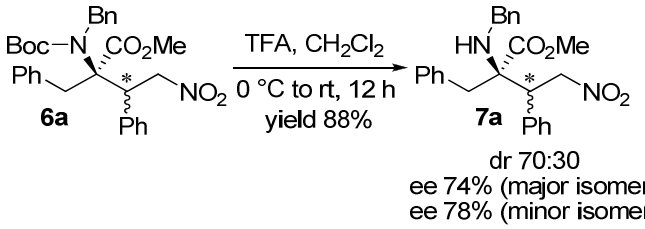
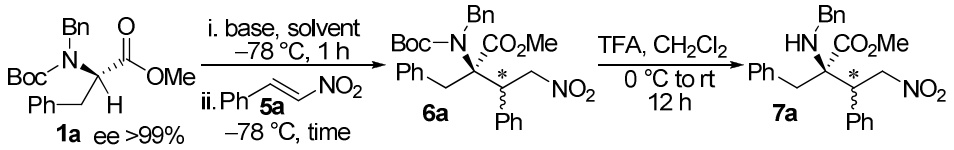


Table 3. Effect of Bases and Solvents on *trans-β*-Nitrostyrene Asymmetric Intermolecular Conjugate Addition[a]



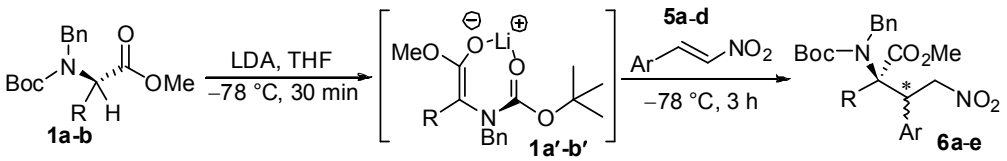
entry	base	solvent	time (h)	**6a** (%)[b]	**7a** dr[c,d]	ee (%)[e] of **7a** (major)	ee (%)[e] of **7a** (minor)
1	LDA	THF	6	74	70:30	74	78
2[f]	LDA	toluene	10	-	-	-	-
3	KHMDS	THF	3	68	74:36	54	8
4	KHMDS	toluene	10	65	78:22	20	18
5	KHMDS	THF/toluene (1:4)	5	66	81:19	42	17
6	KHMDS	THF/toluene (4:1)	5	62	79:21	40	05
7	LTMP	THF	12	68	64:36	68	70
8[f]	NaHMDS	THF	16	-	-	-	-
9[f]	LiHMDS	THF	16	-	-	-	-

[a]All the reactions were performed using 1.0 equiv of **1a**, 1.1 equiv of base and 1.1 equiv of **5a**. [b]Yields of isolated product **6a** (%) after column chromatographic separation. [c]Combined yield of both the inseparable diastereomers **7a** after column chromatographic purification and were obtained in the range of 83-88%. [d]dr based on crude ^{1}H NMR analysis of **7a**. [e]ee was determined from chiral HPLC analysis of **7a** using chiral OD-H column (95:5 hexane/isopropanol as mobile phase and 1.0 mL/min flow rate). [f]Trace amount of **6a** was obtained.

Based on the above observations, we anticipated that enhancing the amount of the enolate and reducing the enolate generation time, both the yield and the stereoselectivity could be improved. To our great pleasure, **7a** was obtained with high dr (80:20) and excellent enantioselectivity (ee: 88% for the major and 90% for the minor diastereomers), employing 3.0 equivalents of enolate generated in 30 min at −78 °C (Table 4, entry 1). The relative stereochemistry of the major diastereomer of **7a** was confirmed by X-ray crystallographic analysis wherein the aryl and *N*-benzyl groups were found to be anti to each other (the crystal was obtained as racemate based on centrosymmetric point group) (Figure 2).[15] However, the absolute stereochemistry of the two stereocenters in the major diastereomer of **7a** was ascertained by an indirect approach. Firstly, the chiral HPLC analysis of the unreacted substrate **1a**, isolated after intermolecular conjugate addition between **1a** and **4a**, revealed the retention of original stereochemical information with only partial racemization. Secondly, the enolate generated from enantiopure **1a** on quenching with water at −78 °C resulted in recovery of the starting substrate **1a** with retention of configuration with 95% ee, whereas, the complete racemization was noticed on quenching the enolate with water at room temperature.[16] These results suggest that the base would abstract proton from the bottom face of substrate **1a** to form chiral enolate **1a'** (supported by computational studies) which on intermolecular conjugate addition with **5a** would proceed through the same face leading to the formation of the product **6a** with complete retention of configuration at the quaternary stereogenic center (C_2) as *R*. Following the anti relative stereochemistry of aryl and *N*-benzyl groups as revealed in the X-ray crystal structure of **7a** (Figure 2), the absolute configuration of the other stereocenter will become *S*. Thus, the absolute configuration of the major diastereomer **7a** is tentatively assigned as (2*R*,3*S*) which is further supported by the computational studies.[17] The generalization of our strategy was made by

studying the intermolecular Michael addition between chiral enolate of **1a'**–**b'** and various aromatic or heteroaromatic nitroalkenes **5b**–**d**. The corresponding addition products **6a**–**e** were obtained as a mixture of diastereomers (Scheme 7, Table 4). When the axial chiral enolate of **1a'** was reacted with *trans*-4-methyl-*β*-nitrostyrene **5b**, the product **6b** was obtained in good yield (76%) as a mixture of diastereomers (Table 4, entry 2). Notably, fluoro-substituted product **6c** was synthesized in good yield (75%) from the reaction of axial chiral enolate of **1a** and 4-fluoro-*β*-nitrostyrene **5c** following our protocol (Table 4, entry 3). Similarly, hetero aryl *trans*-*β*-nitrostyrene **5d** i.e., 2-(2-nitrovinyl)furan was treated with axial chiral enolate of **1a** to furnish **6d** as a mixture of diastereomers in good yield (76%) (Table 4, entry 4). After successful demonstration of the intermolecular addition with **1a'** and various aromatic *trans*-*β*-nitrostyrenes **5a**–**d**, the scope of our strategy was further extended by employing (*S*)-*N*-benzyl-*N*-Boc leucine methyl ester as the axial chiral source. When axial chiral enolate of **1b** was reacted with **5c** the corresponding intermolecular adduct, **6e** was obtained in good yield (Table 4, entry 5) as a mixture of diastereomers.

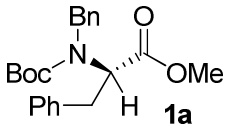
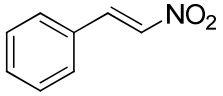
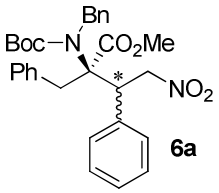
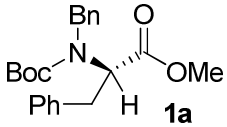
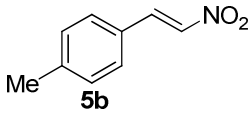
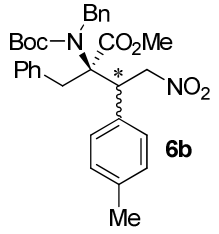
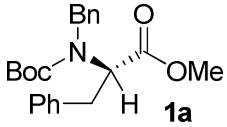
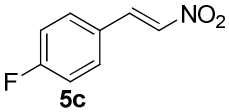
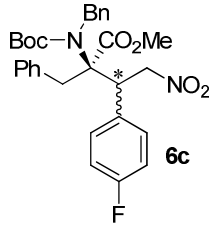
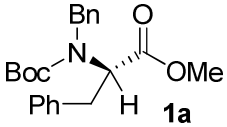
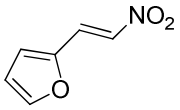
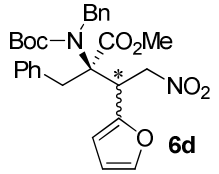
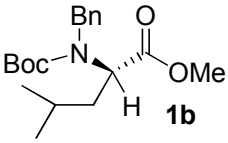
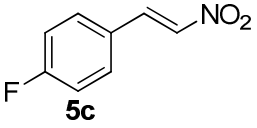
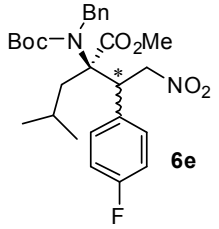
Scheme 7. Asymmetric Intermolecular Conjugate Addition of 1a–b with 5a–d



1a': R = Bn, **1b'**: R = $(CH_3)_2CHCH_2$;
5a: Ar = Ph, **5b**: Ar = 4-MeC_6H_4, **5c**: Ar = 4-FC_6H_4, **5d**: Ar = 2-furanyl

Table 4. Asymmetric synthesis of Intermolecular Conjugated Adducts 6[a]

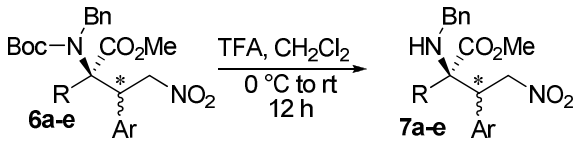
entry	substrate (**1**)	Michael acceptor (**5**)	product (**6**)	yield **6** (%)[b]

1	 **1a**	 **5a**	 **6a**	81
2	 **1a**	 **5b**	 **6b**	76
3	 **1a**	 **5c**	 **6c**	75
4	 **1a**	 **5d**	 **6d**	76
5	 **1b**	 **5c**	 **6e**	75

[a]All the reactions were performed using 3.0 equiv enolates of **1a**–**b** and 1.0 equiv of **5a**–**d**. [b]Combined yield of both the diastereomers after column chromatographic purification.

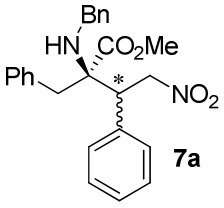
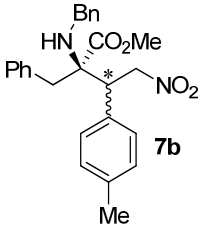
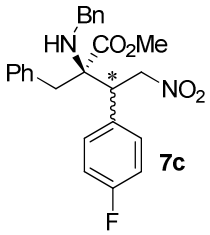
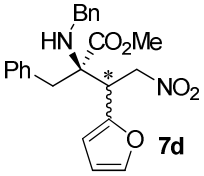
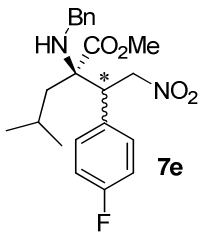
The *N*-Boc groups of **6a**–**e** were deprotected with trifluoroacetic acid and dichloromethane (1:2) to afford the corresponding products **7a**–**e** again as a mixture of diastereomers (Scheme 8 and Table 5). The major diastereomer could be obtained in pure form by fractional crystallization.[19] All the results are shown in Table 5.

Scheme 8. Boc Deprotection of Intermolecular Conjugated Adducts 6a–e



a: R = Bn, Ar = C_6H_5; **b:** R = Bn, Ar = 4-MeC_6H_4; **c:** R = Bn, Ar = 4-FC_6H_4;
d: R = Bn, Ar = 2-furanyl; **e:** R = $(CH_3)_2CHCH_2$, Ar = 4-FC_6H_4

Table 5. Synthesis of Nonracemic *γ*-Nitro-*α*-Amino Ester Derivatives 7a–e

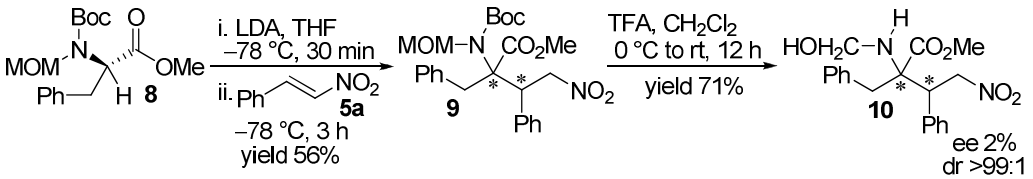
entry	product (**7**)	yield **7** (%)[a]	**7** dr[b]	ee (%)[c] of **7** major (anti)	ee (%)[c] of **7** minor (syn)
1	 **7a**	88	80:20	88	90
2	 **7b**	87	85:15	81	70
3	 **7c**	86	75:25	95	95
4	 **7d**	83	81:19	85	70
5[d]	 **7e**	86	97:3	88	-

[a]Combined yield of **7a**–**e** (%) both the diastereomers after column chromatographic purification. [b]dr determined by ^{1}H NMR of the crude reaction mixture. [c]ee was determined by chiral HPLC

analysis of **7a**–**e** using chiral OD-H column (95:5 hexane/isopropanol as mobile phase and 1.0 mL/min flow rate). [d]Minor diastereomer could not be isolated in column chromatography.

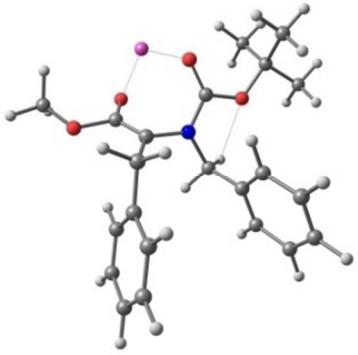
It is noteworthy that we observed high chiral induction in the present investigation and our earlier report on asymmetric imino-aldol reaction employing LDA as the base starting from our substrate (*S*)-*N*-benzyl-*N*-Boc phenylalanine methyl ester **1a**. On the contrary, Kawabata et. al. showed that KHMDS as an effective base for achieving excellent asymmetric induction using (*S*)-*N*-Boc-*N*-MOM-*α*-amino ester derivatives as the substrate via MOC concept.[9a,12] Hence, we were curious to see the outcome of the intermolecular conjugate addition reaction between (*S*)-*N*-Boc-*N*-MOM phenylalanine methyl ester derivative **8** and *trans*-*β*-nitrostyrene **5a** by using our optimized condition. Accordingly, substrate **8**[9a] was treated with LDA in THF at –78 °C for 30 min followed by reaction with *trans*-*β*-nitrostyrene **5a** at –78 °C for 3 h to furnish the corresponding intermolecular conjugated adduct **9** in moderate yield (56%). To established the stereoselectivity of this reaction the BOC group was deprotected with 1:2 trifluoroacetic acid in dichloromethane at room temperature to afford **10** with good yield (Scheme 9) as a single diastereomer (determined by ^{1}H NMR spectrum of the crude reaction mixture) with negligible enantiomeric excess (ee 2%). It is worth further mentioning that the observation is in consistent with the Kawabata's reports[9a,12] of using KHMDS as a base in obtaining good to excellent level of asymmetric induction starting from their designed substrate (*S*)-*N*-Boc-*N*-MOM-*α*-amino ester derivatives.

Scheme 9. Asymmetric Intermolecular Conjugate Addition of 8 with 5a via MOC

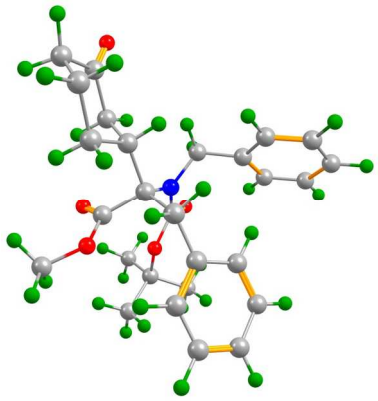


The stereochemical assignment of **3a**–**b** and **7a** were further supported by computational studies.[17] For this purpose, the structure of enolate (generated from **1a** by the treatment with LDA in THF at –78 °C) was optimized with respect to different geometry of the double bond (*E* and *Z*) and the orientation of the protecting groups (Boc and benzyl) attached to nitrogen and **1a**'*Z*1 was found to be the most stable enolate. Next, to establish the most stable product and the stereochemical assignment of **3a**–**b**, all the possible geometries of **3a**–**b** both in THF and in vacuum were modelled and optimized. For the case of **3a**, the structure **3aA** was found to be most stable whereas in the case of **3b** the structure **3bE** was found to be most stable (Figure 1). Similarly, all the different geometries possible in the case of **7a** were optimized in vacuum and in THF condition and **7aC** was found to be more stable than other geometries which is reaffirmed by the crystal structure of **7a**. Based on X-ray crystallographic analysis, experimental observation and computational studies, the absolute configuration of the major diastereomer of **7a** was tentatively confirmed (*2R,3S*).[15,17]

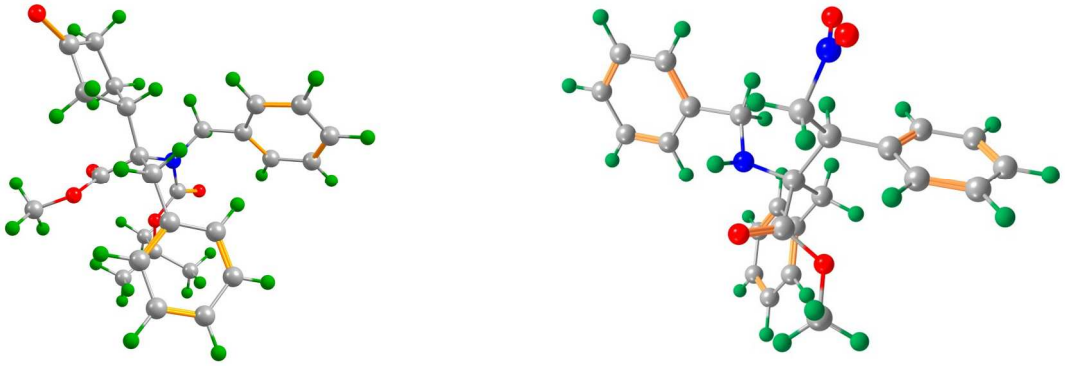
Figure 1. B3LYP/6-311+G(d) Minimized structure of **1a′**, **3a**, **3b** and **7a**



1a′-Z1

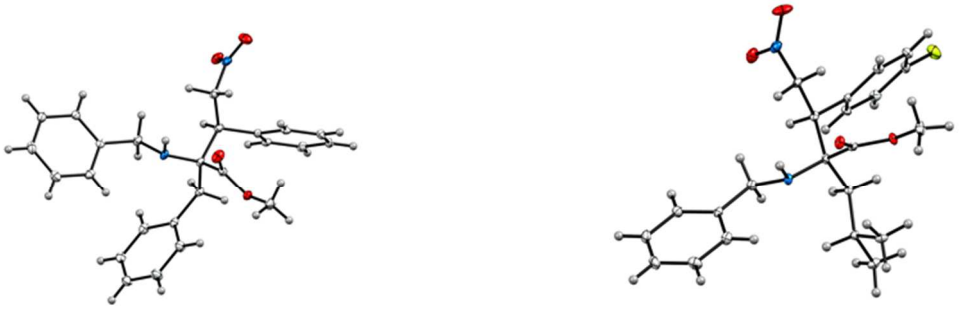


3aA



3bE **7ac**

Figure 2. X-ray crystal structure of 7a and 7e (major diastereomer)



7a **7e**

Conclusion

In conclusion, we have developed a new strategy for the intermolecular conjugate addition of (*S*)-*N*-benzyl-*N*-Boc phenylalanine methyl ester with cyclic *α,β*-enones and acyclic (*E*)-chalcone in good to excellent enantioselectivity and excellent diastereoselectivity via Memory of Chirality concept. The MOC concept was further extended for the synthesis of nonracemic *γ*-nitro-*α*-

amino ester derivatives containing adjacent quaternary and tertiary carbon stereocenters starting from (*S*)-*N*-benzyl-*N*-Boc-*α*-amino ester derivatives employing aromatic nitroalkenes as the Michael acceptors. We have demonstrated that maximum chiral induction in the conjugate addition products via MOC could be made possible employing LDA as the base. The observed stereoselectivity of the products are supported by computational studies. The absolute configuration of the major diastereomer of **7a** could be tentatively ascertained as (2*R*,3*S*). Further work is in progress.

Experimental Section

General Procedures. The analytical thin layer chromatography (TLC) was carried out for monitoring the progress of the reactions using silica gel 60 F_{254} precoated plates. Visualizations of the spots were accomplished with a UV lamp or I_2 stain. Silica gel 230–400 mesh size was used for flash column chromatographic purification using a combination of ethyl acetate and petroleum ether as the eluent. Unless otherwise mentioned, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen or argon using anhydrous solvents. Where appropriate, the solvents and all of the reagents were purified prior to use following the guidelines of Armarego and Chai.[19] (*S*)-*N*-benzyl-*N*-Boc-*α*-amino methyl esters[13] and (*S*)-*N*-MOM-*N*-Boc phenylalanine methyl ester[9a] were prepared by following the earlier reports. All of the commercial reagents were used as received without further purification unless otherwise mentioned. Proton nuclear magnetic resonance (^{1}H NMR) were recorded at 400 MHz and 500 MHz. The chemical shifts were recorded in parts per million (ppm, δ) using tetramethylsilane (δ 0.00) as the internal standard. Splitting patterns of the ^{1}H NMR are mentioned as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of doublets (td), multiplet (m) etc. Carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded at 100 MHz and 125 MHz.

HRMS were obtained using (ESI) mass spectrometer (TOF). KBr pellets were used for IR spectra of solid compounds and dichloromethane for liquied . The melting point measurements were made using a hot stage apparatus and are reported as uncorrected. The enantiomeric excess (ee) was determined by chiral HPLC using a Chiralcel OD-H, AD-H and Cellulose-2 column (detection at 254 nm) using hexane and isopropanol as the mobile phase and an UV/VIS detector. Optical rotations were measured using a 6.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]^{25}_{D}$ (*c* in g per 100 mL solvent) at 25 °C.

General experimental procedure for preparation of (*S*)-*N*-benzylated amino acid methyl ester.[13] Method **A**. To a solution of (*S*)-amino acid methyl ester hydrochloride (5.00 g, 23.18 mmol (for (*S*)-Methyl 2-(benzylamino)-3-phenylpropanoate **S1**)) in dry MeOH (40.0 mL), triethylamine (3.24 mL, 23.18 mmol) and benzaldehyde (3.53 mL, 34.77 mmol) were added. The reaction mixture was stirred at room temperature for 1.5 h, cooled to 0 °C and $NaBH_4$ (1.75 g, 46.36 mmol) was added in portions. After stirring at room temperature for additional 2 h, the solvent was evaporated to dryness and the residue was extracted with ethyl acetate and washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and solvent was evaporated. The residue was purified by flash column chromatography on silica gel (230-400 mesh) using ethyl acetate in petroleum ether as eluent.

General experimental procedure for preparation of (*S*)-*N*-benzyl-*N*-Boc amino acid methyl esters (1a–b).[13] Method **B**. To a solution of (*S*)-*N*-benzylated amino acid methyl esters (5.00 g, 18.56 mmol (for **1a**)) in dry CH_2Cl_2, di-*tert*-butyl dicarbonate (5.12 mL, 22.27 mmol) and triethylamine (2.85 mL, 20.42 mmol) were added at 0 °C and the mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored with TLC), the reaction mixture was quenched with 0.5 M aqueous HCl and the aqueous layer was extracted with

CH_2Cl_2. The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (230-400 mesh) using ethyl acetate in petroleum ether as eluent to afford the pure products (**1a**–**b**).

General procedure for the intermolecular conjugate addition of (*S*)-*N*-benzyl-*N*-Boc-α-amino methyl ester (1a) with various cyclic- and acyclic enones (2a–c). Method **C**. To a solution of diisopropylamine (0.15 mL, 1.04 mmol) in 2.0 mL dry THF was added *n*-BuLi (1.6 M in hexane, 0.66 mL, 1.05 mmol) at 0 °C and stirred for 30 min. It was cooled to −78 °C and a solution of (*S*)-*N*-benzyl-*N*-*tert*-butoxycarbonyl phenylalanine methyl ester (**1a**, 387.9 mg, 1.05 mmol) in 3.0 mL dry THF was added to it and allowed to stir for 1 h. Cyclic- and acyclic enone (**2a**–**c**) (40 mg, 0.42 mmol (for **2a**)) dissolved in 0.5 mL dry THF was slowly added into the reaction mixture and stirring was continued at the same temperature for 6 h. After completion of the reaction (monitored with TLC), it was quenched with aqueous saturated ammonium chloride solution and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to afford the pure products (**3a**–**c**).

General method for removal of Boc group from intermolecular conjugate adduct (3a–b). Method **D**. 4(N) HCl in ethyl acetate (3.1 mL) was added to the intermolecular conjugate adduct (**3a**–**b**) (100.0 mg, 0.21 mmol (for **3a**)) at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of the reaction (monitored with TLC), it was neutralized with aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate (3 × 4.0 mL). The

combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to afford the pure products (**4a**–**b**).

General procedure for the intermolecular conjugate addition of (*S*)-*N*-benzyl-*N*-Boc-α-amino methyl ester derivatives (1a–b) with various *trans*-*β*-aromatic nitroalkenes (5a–d). Method **E**. To a solution of diisopropylamine (0.15 mL, 0.81 mmol) in 2.0 mL dry THF was added *n*-BuLi (1.6 M in hexane, 0.50 mL, 0.81 mmol) at 0 °C and stirred for 30 min. It was cooled to −78 °C and a solution of (*S*)-*N*-benyl-*N*-*tert*-butoxycarbonyl-α-amino methyl ester derivatives (**1a**–**b**) (299.3 mg, 0.81 mmol) in 3.0 mL dry THF was added to it and allowed to stir for 30 min. *Trans*-*β*-aromatic nitroalkenes (**5a**–**d**) (40.0 mg, 0.27 mmol (for **5a**)) dissolved in 1.0 mL dry THF was slowly added into the reaction mixture and stirring was continued at the same temperature for 3 h. After completion of the reaction (monitored with TLC), it was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to afford the pure products (**6a**–**e**).

General method for removal of Boc group from intermolecular conjugate adduct (6a–e). Method **F**. To a solution of intermolecular conjugate adduct (**6a**–**e**) (90.0 mg, 0.17 mmol (for **6a**)) in dry CH_2Cl_2 (2.0 mL), trifluoroacetic acid (0.9 mL) was added at 0 °C and the mixture was stirred at room temperature overnight. After completion of the reaction (monitored with TLC), it was neutralized with aqueous saturated $NaHCO_3$ solution and extracted with of CH_2Cl_2 (3 × 3.0

mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to afford the pure products as a mixture of diastereomers (**7a–e**). Diastereoselectivity was determined by ^{1}H NMR spectrum of the crude reaction mixture. In the case of substrates **7a**, **7b**, **7d**, the diastereomeric mixtures were not separated by column chromatography and their ee was determined by chiral HPLC analysis of diastereomeric mixtures. However, when the mixture of diastereomers obtained after column chromatography was dissolved in minimum amount of HPLC grade ethanol followed by sonication and allowed to cool at low temperature (−20 °C) to obtain the major diastereomer in pure form. The mother liquor mostly contained the minor diastereomer along with some amount of the major isomer and hence the minor isomer could not be obtained in pure form. In the case of **7c**, diastereomers were not separated and it was obtained only as the mixture of diastereomers. In the case of **7e**, the major diastereomer was separated by column chromatography. However, the minor diastereomer was not isolated in pure form.

(*S*)-Methyl 2-(benzylamino)-3-phenylpropanoate[20] (S2). The general method **A** described above was followed when the (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride (**S1**, 5.00 g, 23.18 mmol) was reacted with triethylamine (3.24 mL, 23.18 mmol), benzaldehyde (3.53 mL, 34.77 mmol) followed by sodium borohydride (1.75 g, 46.36 mmol to afford (*S*)-methyl 2-(benzylamino)-3-phenylpropanoate[20] (**S2**) as a colorless liquid in 90% (5.61 g, 20.86 mmol) yield; R_f: 0.40 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3321, 3062, 3027, 2949, 2845, 1735, 1603, 1495, 1453, 1343, 1198, 1170, 1129, 1076, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 1H), 2.96 (dd, J = 6.4, 1.4 Hz, 2H), 3.54 (t, J = 6.6 Hz, 1H), 3.61–3.64 (m,

4H), 3.81 (d, J = 13.2 Hz, 1H), 7.15–7.17 (m, 2H), 7.20–7.29 (m, 8H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 39.9, 51.8, 52.1, 62.2, 126.8, 127.2, 128.3, 128.54, 128.59, 129.4, 137.4, 139.7, 175.2; HRMS (ESI) for $C_{17}H_{20}NO_2$, $(M+H)^+$ found 270.1490, calcd 270.1494.

(*S*)-Methyl 2-(benzylamino)-4-methylpentanoate[21] **(S4).** The general method **A** described above was followed when the (*S*)-methyl 2-amino-4-methylpentanoate hydrochloride (**S3**, 2.50 g, 13.76 mmol) was reacted with triethylamine (1.92 mL, 13.76 mmol), benzaldehyde (2.10 mL, 20.64 mmol) followed by sodium borohydride (1.04 g, 27.42 mmol) to afford (*S*)-methyl 2-(benzylamino)-4-methylpentanoate[21] (**S4**) as a colorless liquid in 78% (2.52 g, 10.73 mmol) yield; R_f: 0.56 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3337, 3063, 3028, 2961, 2874, 1732, 1604, 1495, 1454, 1434, 1386, 1367, 1333, 1236, 1196, 1178, 1149, 1075, 1027; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5, 3H), 0.91 (d, J = 6.6 Hz, 3H), 1.44–1.49 (m, 2H), 1.71 (s, 1H), 1.74–1.80 (m, 1H), 3.30 (t, J = 6.8 Hz, 1H), 3.60 (d, J = 12.9 Hz, 1H), 3.71 (s, 3H), 3.80 (d, J = 12.9 Hz, 1H), 7.22– 7.33 (m, 5H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 22.3, 22.9, 25.0, 43.0, 51.8, 52.3, 59.4, 127.2, 128.4, 128.5, 140.1, 176.7; HRMS (ESI) for $C_{14}H_{22}NO_2$, $(M+H)^+$ found 236.1655, calcd 236.1651.

(*S*)-Methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate[20] **(1a).** The general method **B** described above was followed when the (*S*)-methyl 2-(benzylamino)-3-phenylpropanoate (**S2**, 5.00 g, 18.56 mmol) was reacted with di-*tert*-butyl dicarbonate (5.12 mL, 22.27 mmol) and triethylamine (2.85 mL, 20.42 mmol) at 0 °C and the mixture was stirred at room temperature for 24 h to afford **1a**[20] as a colorless liquid in 78% (5.34 g, 14.48 mmol) yield; R_f: 0.61 (15% ethyl acetate in petroleum ether); $[\alpha]^{25}_{D}$ = −112.67 (c 0.450, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3064, 3029, 2950, 2977, 1744, 1698, 1605, 1496, 1454, 1427, 1392, 1366, 1314, 1278, 1278, 1250, 1164, 1129, 1079, 1046, 1030, 1002; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) for

mixture of rotamers δ 28.5, 35.8, 36.7, 51.4, 51.7 52.0, 60.9, 61.2, 76.9, 81.0, 126.6, 126.7, 127.1, 127.4, 127.7, 128.3, 128.5, 128.6, 128.8, 129.4, 137.3, 138.1, 138.2, 155.2, 155.4, 171.5, 171.6; HRMS (ESI) for $C_{22}H_{27}NNaO_4$, $(M+Na)^+$ found 392.1834, calcd 392.1838.

(*S*)-Methyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-4-methylpentanoate[21] (1b). The general method **B** described above was followed when the (*S*)-methyl 2-(benzylamino)-4-methylpentanoate (**S3**, 2.40 g, 10.21 mmol) was reacted with di-*tert*-butyl dicarbonate (2.81 mL, 12.25 mmol) and triethylamine (1.57 mL, 11.23 mmol) at 0 °C and the mixture was stirred at room temperature for 24 h to afford **1b**[21] as a colorless liquid in 72% (2.46 g, 10.21 mmol) yield; R_f: 0.50 (15% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = −54.711 (*c* 2.25, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3065, 3030, 2957, 2870, 1744, 1697, 1605, 1496, 1454, 1434, 1406, 1392, 1366, 1318, 1247, 1202, 1165, 1075, 1048, 1030; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) for mixture of rotamers δ 22.1, 22.8, 24.9, 25.0, 28.4, 38.6, 39.4, 49.4, 50.4, 52.0, 57.0, 57.7, 80.7, 127.0, 127.4, 128.3, 128.5, 138.3, 139.2, 156.0, 156.1, 172.6, 172.9; HRMS (ESI) for $C_{19}H_{29}NNaO4$, $(M+Na)^+$ found 358.1991, calcd 358.1994.

(2*R*)-Methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-2-(3-oxocyclohexyl)-3-phenylpropanoate (3a). The general method **C** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 387.9 mg, 1.05 mmol) was reacted with cyclohex-2-enone (**2a**, 40.0 mg, 0.42 mmol) at −78 °C for 6 h to afford **3a** (138.0 mg, 0.30 mmol) in 71% yield as a thick liquid; R_f: 0.48 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +5.085 (*c* 0.236, CH_2Cl_2); Optical purity was determined by Chiral HPLC analysis (Chiralpak Lux 5u Cellulose-2 column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; ee 99%; T_R 1: 24.3 min (major), T_R 2: 33.3 min (minor); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3030, 2975, 1736, 1696, 1604, 1496, 1453, 1389, 1366, 1253, 1159, 1086, 1030; ^1H NMR (500

MHz, $CDCl_3$) δ 1.25–1.50 (m, 11H), 1.94 (bs, 1H), 2.064–2.11 (m, 2H), 2.18–2.25 (m, 2H), 2.35–2.38 (m, 2H), 2.95 (d, J = 13.1 Hz, 1H), 3.18 (d, J = 13.7 Hz, 1H), 3.58 (d, J = 13.7 Hz, 1H), 3.72 (s, 3H), 3.96 (bs, 1H), 7.08–7.10 (m, 2H), 7.15–7.18 (m, 1H), 7.26–7.27 (m, 7H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 24.7, 27.3, 28.1, 37.8, 41.2, 42.2, 45.6, 49.7, 51.8, 71.2, 80.9, 125.8, 126.3, 127.4, 128.2, 128.4, 128.6, 130.7, 135.9, 140.2, 155.9, 171.5, 210.6; HRMS (ESI-TOF) for $C_{28}H_{39}N_2O_5$, $(M+NH_4)^+$ found 483.2850, calcd 483. 2859.

(2*R*)-Methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-2-(3-oxocyclopentyl)-3-phenylpropanoate (3b). The general method **C** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 454.4 mg, 1.23 mmol) was reacted with cyclopent-2-enone (**2b**, 40.0 mg, 0.49 mmol) at −78 °C for 6 h to afford **3b** (150.0 mg, 0.33 mmol) in 67% yield as a thick liquid; R_f: 0.47 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +22.356 (*c* 0.416, CH_2Cl_2); Optical purity was determined by chiral HPLC analysis (Chiralpak Lux 5u Cellulose-2 column), hexane-isopropanol 95:5, flow rate 1.0 mL/min; ee 91%; T_R 1: 40.8 min (major),), T_R 2: 62.0 min (minor). IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3029, 2975, 1742, 1693, 1604, 1496, 1453, 1384, 1366, 1254, 1216, 1159, 1088, 1031; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.94–2.09 (m, 4H), 2.21–2.28 (m, 2H), 2.64–2.69 (m, 1H), 2.78–2.80 (m, 1H), 3.07 (d, J = 13.7 Hz, 1H), 3.63–3.65 (m, 1H), 3.78 (s, 3H), 4.07 (bs, 1H), 7.09–7.11 (m, 2H), 7.17–7.19 (m, 1H), 7.26–7.30 (m, 7H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 24.7, 28.0, 38.6, 39.1, 40.9, 42.5, 49.2, 52.1, 69.9, 81.0, 125.7, 126.3, 127.4, 128.2, 128.6, 130.5, 135.8, 140.2, 155.9, 172.0, 217.1; HRMS (ESI-TOF) for $C_{27}H_{34}NO_5$, $(M+H)^+$ found 452.2438, calcd 452.2437.

(*R*)-Methyl 2-benzyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-5-oxo-3,5-diphenylpentanoate (3c). The general procedure described above was followed when the enolate of (*S*)-methyl 2-

(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 177.3 mg, 0.48 mmol) was reacted with (*E*)-chalcone (**2c**, 40.0 mg, 0.19 mmol) at −78 °C for 3h to afford **3c** (80.0 mg, 0.14 mmol) in 74% yield as a semi solid; R_f: 0.53 (30% ethyl acetate in petroleum ether); $[\alpha]^{25}_{D}$ = +5.085 (*c* 0.236, CH_2Cl_2); Optical purity was determined by Chiral HPLC analysis (Chiralpak AD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; ee 70%; T_R 1: 24.3 min (major), T_R 2: 33.3 min (minor); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 2953, 2924, 2853, 1735, 1700, 1604, 1510, 1496, 1453, 1387, 1367, 1345, 1304, 1249, 1208, 1162, 1123, 1093, 1046, 1018; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.45 (m, 9H), 3.00 (bs, 1H), 3.53–3.83 (m, 8H), 4.49 (bs, 1H), 6.86 (bs, 1H), 7.05–7.13 (m, 4H), 7.22–7.46 (m, 15H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 28.2, 39.0, 42.2, 44.4, 48.0, 51.9, 71.2, 80.9, 125.9, 126.0, 127.1, 127.5, 127.8, 127.9, 128.1, 128.4, 128.5, 130.33, 130.37, 131.1, 132.6, 136.6, 137.1, 139.8, 140.3, 156.3, 172.6, 197.8; HRMS (ESI-TOF) for $C_{37}H_{43}N_2O_5$, $(M+NH_4)^+$ found 595.3173, calcd 595.3172.

(2*R*)-Methyl 2-(benzylamino)-2-(3-oxocyclohexyl)-3-phenylpropanoate (4a). The general method **D** described above was followed when intermolecular conjugate adduct **3a** (100 mg, 0.21 mmol) was reacted with 4(N) HCl in ethyl acetate (3.1 mL) to afford **4a** (64.0 mg, 0.18 mmol) in 86% yield as a thick liquid; R_f: 0.48 (30% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3361, 3061, 3028, 2949, 2862, 1712, 1602, 1495, 1453, 1346, 1316, 1079, 1029; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39–1.51 (m, 2H), 1.90 (bs, 1H), 2.05–2.08 (m, 1H), 2.12–2.15 (m, 1H), 2.18–2.26 (m, 2H), 2.35–2.41 (m, 2H), 2.57 (d, J = 14.3 Hz, 1H), 3.08 (d, J = 14.3 Hz, 1H), 3.24 (d, J = 14.3 Hz, 1H), 3.716–3.718 (m, 3H), 3.75–3.83 (m, 2H), 7.21–7.28 (m, 6H), 7.30–7.31 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 25.1, 26.3, 37.8, 41.4, 43.91, 43.95, 47.5, 52.0, 68.4, 126.9, 127.2, 128.1, 128.4, 128.6, 130.2, 136.6, 140.2, 174.4, 211.4; HRMS (ESI-TOF) for $C_{23}H_{28}NO_3$, $(M+H)^+$ found 366.2063, calcd 366.2069.

(2*R*)-Methyl 2-(benzylamino)-2-(3-oxocyclopentyl)-3-phenylpropanoate (4b). The general method **D** described above was followed when intermolecular conjugate adduct **3b** (100.0 mg, 0.22 mmol) was reacted with 4(N) HCl in ethyl acetate (3.2 mL) to afford **4b** (65.0 mg, 0.18 mmol) in 82 % yield as a thick liquid; R_f: 0.47 (30% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3354, 3086, 3061, 3028, 2951, 2924, 2852, 1740, 1603, 1495, 1454, 1404, 1365, 1255, 1211, 1162, 1080, 1029; ^{1}H NMR (500 M Hz, $CDCl_3$) δ 1.72 (bs, 1H), 1.82–1.88 (m, 1H), 2.07–2.18 (m, 2H), 2.28–2.42 (m, 3H), 2.63 (bs, 1H), 3.07 (d, J = 14.9 Hz, 1H), 3.24–3.32 (m, 1H), 3.73 (s, 3H), 3.73–3.82 (m, 1H), 3.92 (d, J = 12.0 Hz, 1H), 7.23–7.30 (m, 6H), 7.31–7.36 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 24.3, 38.8, 39.0, 41.0, 42.5, 48.1, 52.0, 68.1, 127.1, 127.4, 128.3, 128.5, 128.7, 130.3, 136.4, 140.2, 174.5, 218.0; HRMS (ESI-TOF) for $C_{22}H_{26}NO_3$, $(M+H)^+$ found 352.1913, calcd 352.1911.

(*R*)-Methyl 2-benzyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-4-nitro-3-phenylbutanoate (6a). The general method **E** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 299.30 mg, 0.81 mmol) was reacted with *trans*-*β*-nitrostyrene (**5a**, 40.0 mg, 0.27 mmol) at −78 °C for 3 h to afford **6a** as a mixture of diastereomers (115.0 mg, 0.22 mmol) in 81% yield as thick liquid where the diastereomers were not separated through flash column chromatography; R_f: 0.40 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3031, 2977, 1818, 1745, 1692, 1603, 1554, 1496, 1454, 1380, 1367, 1251, 1156, 1086, 1031; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 28.2, 38.5, 48.6, 49.9, 51.9, 52.2, 70.0, 81.6, 81.7, 125.80, 125.88, 126.6, 127.7, 127.9, 128.3, 128.6, 128.7, 128.9, 129.0, 129.74, 129.79, 130.7, 131.0, 134.4, 135.3, 135.6, 136.0, 139.5, 156.1, 170.7; HRMS (ESI-TOF) for $C_{30}H_{34}N_2NaO_6$, $(M+Na)^+$ found 541.2313, calcd 541.2315.

(*R*)-Methyl 2-benzyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-4-nitro-3-p-tolylbutanoate (6b). The general method **E** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 277.1 mg, 0.75 mmol) was reacted with *trans*-4-methyl-*β*-nitrostyrene (**5b**, 40.0 mg, 0.25 mmol) at −78 °C for 3 h to afford **6b** as a mixture of diastereomers (101.0 mg, 0.19 mmol) in 76% yield as thick liquid where the diastereomers were not separated through flash column chromatography; R_f: 0.41 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3031, 2978, 1800, 1745, 1693, 1604, 1554, 1515, 1496, 1454, 1381, 1368, 1307, 1252, 1210, 1157, 1085, 1030; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 21.3, 28.3, 28.4, 38.7, 48.1, 49.9, 51.9, 52.2, 81.6, 125.8, 125.9, 126.0, 126.6, 127.6, 127.9, 128.3, 128.6, 128.7, 128.9, 129.7, 130.1, 130.7, 131.0, 132.8, 134.5, 138.4, 138.5, 139.5, 139.9, 156.2, 156.5, 170.8; HRMS (ESI-TOF) for $C_{31}H_{36}N_2NaO_6$, $(M+Na)^+$ found 555.2471, calcd 555.2477.

(*R*)-Methyl 2-benzyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-3-(4-fluorophenyl)-4-nitrobutanoate (6c). The general method **E** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 266.0 mg, 0.72 mmol) was reacted with *trans*-4-fluoro-*β*-nitrostyrene (**5c**, 40.0 mg, 0.24 mmol) at −78 °C for 3 h to afford **6c** as a mixture of diastereomers (98.0 mg, 0.18 mmol) in 75% yield as thick liquid where the diastereomers were not separated through flash column chromatography; R_f: 0.39 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3064, 3032, 2977, 2928, 1798, 1745, 1693, 1605, 1554, 1511, 1496, 1454, 1382, 1368, 1250, 1229, 1108, 1085, 1030, 1007; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 28.2, 28.4, 38.7, 47.9, 49.9, 52.0, 52.3, 81.7, 81.9, 115.9, 116.2, 125.80, 125.88, 126.7, 127.7, 128.0, 128.4, 128.6, 128.7, 128.8, 128.9, 130.6, 130.9, 131.3, 131.8, 134.2, 135.3, 139.3, 139.5, 156.1, 156.5, 162.8 (d, $^1J_{C-F}$

= 240.0 Hz), 170.6; HRMS (ESI-TOF) for $C_{30}H_{37}FN_3O_6$, $(M+NH_4)^+$ found 554.2666, calcd 554.2664.

(*R*)-Methyl 2-benzyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-4-nitrobutanoate (6d). The general method **E** described above was followed when the enolate of (*S*)-methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-phenylpropanoate (**1a**, 321.4 mg, 0.87 mmol) was reacted with 2-(2-nitrovinyl)furan (**5d**, 40.0 mg, 0.29 mmol) at −78 °C for 3 h to afford **6d** as a mixture of diastereomers (111.9 mg, 0.22 mmol) in 76% yield as thick liquid where the diastereomers were not separated through flash column chromatography; R_f: 0.38 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3063, 3032, 2977, 1798, 1744, 1690, 1604, 1554, 1497, 1454, 1391, 1368, 1272, 1253, 1199, 1158, 1086, 1031, 1015; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 28.2, 40.7, 42.5, 48.5, 52.0, 52.3, 69.1, 75.8, 81.5, 82.4, 111.11, 111.17, 125.7, 125.8, 126.61, 126.69, 127.9, 128.4, 128.6, 128.83, 128.89, 130.7, 131.0, 134.2, 139.5, 140.1, 143.1, 150.2, 156.4, 170.3; HRMS (ESI-TOF) for $C_{28}H_{36}N_3O_7$, $(M+NH_4)^+$ found 526.2551, calcd 526.2553.

(*S*)-Methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)-2-(1-(4-fluorophenyl)-2-nitroethyl)-4-methylpentanoate (6e). The general method **E** described above was followed when the enolate of (*S*)-methyl-2-(benzyl(*tert*-butoxycarbonyl)amino)-4-methylpentanoate (**1b**, 241.5 mg, 0.72 mmol) was reacted with *trans*-4-fluoro-*β*-nitrostyrene (**5c**, 40.0 mg, 0.24 mmol) at −78 °C for 3 h to afford **6e** as a mixture of diastereomers (90.5 mg, 0.18 mmol) in 75% yield as thick liquid where the diastereomers were not separated through flash column chromatography; R_f: 0.40 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 2967, 2930, 2872, 1737, 1691, 1605, 1556, 1511, 1497, 1466, 1453, 1384, 1368, 1349, 1274, 1253, 1229, 1162, 1128, 1108, 1073, 1031; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 23.2, 24.3, 24.9,

28.0, 28.4, 41.2, 42.0, 47.2, 47.9, 52.2, 68.1, 81.3, 115.8, 116.0, 125.7, 126.5, 128.2, 132.1, 139.6, 156.0, 162.7 (d, $^{1}J_{C-F}$ = 246.8 Hz), 173.0; HRMS (ESI-TOF) for $C_{27}H_{39}FN_3O_6$, $(M+NH_4)^+$ found 520.2823, calcd 520.2820.

Methyl 2-benzyl-2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-4-nitro-3-phenylbutanoate (9). The general method **E** described above was followed when the enolate of (*S*)-methyl 2-(*tert*-butoxycarbonyl(methoxymethyl)amino)-3-phenylpropanoate (**8**, 261.94 mg, 0.81 mmol) was reacted with *trans*-*β*-nitrostyrene (**5a**, 40.0 mg, 0.27 mmol) at −78 °C for 3 h to afford **9** (70.0 mg, 0.15 mmol) in 56 % yield as thick liquid. R_f: 0.44 (30% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (CH_2Cl_2, cm^{-1}) 3064, 3032, 2954, 2924, 2853, 1745, 1709, 1603, 1584, 1554, 1495, 1455, 1434, 1409, 1392, 1369, 1296, 1255, 1208, 1179, 1081, 1033; ^{1}H NMR (500 MHz, $CDCl_3$) for mixture of rotamers δ 1.25–1.47 (m, 12H), 3.23–3.30 (m, 5H), 3.60 (s, 1H), 3.84 (s, 3H),4.33 (bs, 2H), 4.76 (bs, 1H), 5.50 (bs, 1H), 7.17–7.38 (m, 11H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 28.2, 28.4, 38.7, 48.7, 52.0, 52.3, 55.8, 70.0, 78.1, 82.1, 127.3, 127.9, 128.6, 128.7, 128.9, 129.4, 129.9, 130.8, 130.9, 134.9, 136.0, 155.5, 171.0; HRMS (ESI-TOF) for $C_{25}H_{32}N_2NaO_7$, $(M+Na)^+$ found 495.2103, calcd 495.2107.

(2*R*,3*S*)-Methyl 2-benzyl-2-(benzylamino)-4-nitro-3-phenylbutanoate (7a major diastereomer). The general method **F** described above was followed when intermolecular conjugate adduct **6a** (90.0 mg, 0.17 mmol) was reacted with trifluoroacetic acid (0.9 mL) in dry CH_2Cl_2 (2.0 mL) at 0 °C and mixture was stirred at room temperature overnight to afford **7a** as a mixture of inseparable diastereomers in semi-solid form with 88% overall yield (64.0 mg, 0.15 mmol) with dr 80:20 (based on ^{1}H NMR analysis of crude reaction mixture). Optical purity was determined by Chiral HPLC analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 88%, T_R 1: 15.46 min (major), T_R 2: 35.15 min

(minor) and for the minor diastereomer, ee 90%, T_R 1: 12.44 min (minor), T_R 2: 20.06 min (major). The mixture of diastereomers was dissolved in minimum amount of HPLC grade ethanol followed by sonication and allowed to cool at low temperature (−20 °C) to obtain the major diastereomer **7a** in pure solid form. mp 70–73 °C; R_f: 0.40 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +4.800 (*c* 0.250, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3358, 3061, 3029, 2950, 1731, 1602, 1551, 1495, 1453, 1434, 1377, 1213, 1093, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ 1.99 (bs, 1H), 3.09 (d, J = 14.8 Hz, 1H), 3.20 (d, J = 14.9 Hz, 1H), 3.63 (s, 3H), 3.84 (d, J = 12.0 Hz, 1H), 3.95–4.01 (m, 2H), 4.83–4.88 (m, 1H), 5.15 (dd, J = 4.0, 13.1 Hz, 1H), 7.17–7.35 (m, 15H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 38.5, 47.5, 50.1, 52.1, 68.6, 77.1, 127.2, 127.5, 128.3, 128.5, 128.75, 128.77, 128.79, 129.4, 130.3, 135.8, 136.0, 139.5, 173.3; HRMS (ESI-TOF) for $C_{25}H_{27}N_2O_4$, $(M+H)^+$ found 419.1978, calcd 419.1971.

(*2R*,*3S*)-Methyl 2-benzyl-2-(benzylamino)-4-nitro-3-p-tolylbutanoate (7b major diastereomer). The general method **F** described above was followed when intermolecular conjugate adduct **6b** (80.0 mg, 0.15 mmol) was reacted with trifluoroacetic acid (0.75 mL) in dry CH_2Cl_2 (1.5 mL) at 0 °C and the mixture was stirred at room temperature overnight to afford **7b** as a mixture of diastereomers in semi-solid form with 87% overall yield (58.0 mg, 0.13 mmol) with dr 85:15 (based on ^1H NMR analysis of crude reaction mixture). Optical purity was determined by Chiral HPLC analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 81%, T_R 1: 16.15 min (major), T_R 2: 31.01 min (minor) and for the minor diastereomer, ee 70%, T_R 1: 11.75 min (minor), T_R 2: 20.75 min (major). The mixture of diastereomers was dissolved in minimum amount of HPLC grade ethanol followed by sonication and allowed to cool at low temperature (−20 °C) to obtain the major diastereomer **7b** in pure solid form. mp 71–73 °C; R_f: 0.41 (20% ethyl acetate in petroleum

ether); $[\alpha]^{25}_{D} = -18.400$ (*c* 0.250, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3352, 3028, 2924, 2855, 1734, 1603, 1553, 1515, 1495, 1453, 1435, 1377, 1209, 1120, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (bs, 1H), 2.32 (s, 3H), 3.08 (d, J = 14.8 Hz, 1H), 3.20 (d, J = 14.9 Hz, 1H), 3.63 (s, 3H), 3.83 (d, J = 12.0 Hz, 1H), 3.93–3.97 (m, 2H), 4.80–4.85 (m, 1H), 5.14 (dd, J = 3.4, 13.1 Hz, 1H), 7.04–7.06 (m, 2H), 7.11–7.12 (m, 2H), 7.21–7.34 (m, 10H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ 21.3, 38.5, 47.6, 49.8, 52.1, 68.6, 77.2, 127.2, 127.5, 128.3, 128.72, 128.79, 129.3, 129.5, 130.4, 132.6, 136.1, 138.2, 139.6, 173.4; HRMS (ESI) for $C_{26}H_{29}N_2O_4$, $(M+H)^+$ found 433.2127, calcd 433.2127.

(*R*)-Methyl 2-benzyl-2-(benzylamino)-3-(4-fluorophenyl)-4-nitrobutanoate (7c mixture of diastereomers). The general method **F** described above was followed when intermolecular conjugate adduct **6c** (80.0 mg, 0.15 mmol) was reacted with trifluoroacetic acid (0.75 mL) in dry CH_2Cl_2 (1.5 mL) at 0 °C and the mixture was stirred at room temperature overnight to afford **7c** as a mixture of inseparable diastereomers in liquid form with 86% overall yield (58 mg, 0.13 mmol) with dr 75:25 (based on ^1H NMR analysis of crude reaction mixture). Optical purity was determined by Chiral HPLC analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 95%, T_R 1: 20.96 min (major), T_R 2: 43.65 min (minor) and for the minor diastereomer, ee 95%, T_R 1: 17.08 min (minor), T_R 2: 33.32 min (major). R_f: 0.39 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}): 3031, 2929, 2977, 1798, 1605, 1553, 1511, 1496, 1454, 1368, 1227, 1158, 1107, 1086, 1031; ^1H NMR (500 MHz, $CDCl_3$) for major of diastereomer δ 1.99 (bs, 1H), 3.08 (d, J = 14.8 Hz, 1H), 3.17 (d, J = 14.9 Hz, 1H), 3.63 (s, 3H), 3.84 (d, J = 12.0 Hz, 1H), 3.94–4.00 (m, 2H), 4.78–4.83 (m, 1H), 5.13 (dd, J = 4.0, 13.2 Hz, 1H), 6.98–7.03 (m, 2H), 7.15–7.35 (m, 12H); ^{13}C{^1H} NMR (125 MHz, $CDCl_3$) for mixture of diastereomers δ 38.3, 38.5, 47.6, 47.8, 49.4, 49.5, 52.2, 52.4, 68.5, 77.2,

77.3, 115.6, 115.7, 115.8, 115.9, 127.3, 127.5, 127.6,128.0, 128.2, 128.82, 128.85, 130.24, 130.28, 130.01, 131.08, 131.13, 131.19, 131.56, 131.58, 135.5, 135.8, 139.42, 139.49, 163.3, 163.7, 173.3, 174.0; HRMS (ESI) for $C_{25}H_{26}FN_2O_4$, $(M+H)^+$ found 437.1872, calcd 437.1877.

(*2R*,*3S*)-Methyl 2-benzyl-2-(benzylamino)-3-(furan-2-yl)-4-nitrobutanoate (7d major diastereomer). The general method **F** described above was followed when intermolecular conjugate adduct **6d** (90.0 mg, 0.18 mmol) was reacted with trifluoroacetic acid (0.90 mL) in dry CH_2Cl_2 (2.0 mL) at 0 °C and the mixture was stirred at room temperature overnight to afford **7d** as a mixture of diastereomers in semi-solid form with 83% overall yield (63.0 mg, 0.15 mmol) with dr 80:20 (based on ^{1}H NMR analysis of crude reaction mixture. Optical purity was determined by Chiral HPLC analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 85%, T_R 1: 12.26 min (major), T_R 2: 30.24 min (minor) and for the minor diastereomer, ee 70%, T_R 1: 11.19 min (minor), T_R 2: 14.83 min (major). The mixture of diastereomers was dissolved in minimum amount of HPLC grade ethanol followed by sonication and allowed to cool at low temperature (−20 °C) to obtain the major diastereomer **7d** in pure solid form. mp 81–84 °C; R_f: 0.38 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +37.000 (*c* 0.100, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3351, 3030, 2953, 2924, 2853, 1732, 1603, 1555, 1496, 1454, 1434, 1376, 1204, 1148, 1083, 1015; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (bs, 1H), 3.04 (d, J = 14.3 Hz, 1H), 3.28 (d, J = 14.3 Hz, 1H), 3.70 (s, 3H), 3.78 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 12.0 Hz, 1H), 4.34 (dd, J = 2.8, 10.3 Hz, 1H), 4.71–4.76 (m, 1H), 4.81–4.84 (m, 1H), 6.24 (d, J = 2.8 Hz, 1H), 6.33–6.34 (m, 1H), 7.24–7.34 (m, 10H), 7.39 (d, J = 1.7 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 38.1, 44.1, 47.5, 52.5, 68.2, 75.2, 110.0, 110.8, 127.4, 127.5, 128.1, 128.6, 128.7, 130.4, 135.7, 139.6, 142.9, 149.6, 173.6; HRMS (ESI-TOF) for $C_{23}H_{25}N_2O_5$, $(M+H)^+$ found 409.1763, calcd 409.1763.

(*R*)-Methyl 2-(benzylamino)-2-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-4-methylpentanoate (7e major diastereomer). The general method **F** described above was followed when intermolecular conjugate adduct **6e** (80.0 mg, 0.15 mmol) was reacted with trifluoroacetic acid (0.75 mL) in dry CH_2Cl_2 (1.5 mL) at 0 °C and the mixture was stirred at room temperature overnight to afford **7e** major diastereomer in pure solid form with 86% overall yield (54.0 mg, 0.13 mmol) with dr 97:3 (based on ^{1}H NMR analysis of crude reaction mixture). Optical purity was determined by Chiral HPLC analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 88%, T_R 1: 11.43 min (major), T_R 2: 21.52 min (minor). mp 91–94 °C; R_f: 0.40 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ =−20.727 (*c* 0.275, CH_2Cl_2); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3361, 3029, 2956, 2870, 1728, 1604, 1554, 1510, 1453, 1436, 1377, 1302, 1228, 1163, 1140, 1106, 1072, 1028; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.54–1.61 (m, 2H), 1.79–1.82 (m, 2H), 2.14 (bs, 1H), 3.64 (s, 3H), 3.77–3.88 (m, 2H), 3.97 (dd, J = 3.6, 11.4 Hz, 1H), 4.75–4.81 (m, 1H), 5.05 (dd, J = 3.2, 12.8 Hz, 1H), 6.99 (t, 8.4 Hz, 2H), 7.16–7.19 (m, 2H), 7.25–7.37 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 22.9, 24.5, 24.9, 42.0, 46.7, 50.2, 51.9, 66.8, 76.9, 115.4, 115.6, 127.6, 128.2, 128.8, 131.10, 131.18, 131.51, 131.54, 139.7, 162.6 (d, $^1J_{C–F}$ = 248.1 Hz), 173.9; HRMS (ESI-TOF) for $C_{22}H_{28}FN_2O_4$, $(M+H)^+$ found 403.2033, calcd 403.2033.

Methyl 2-benzyl-2-(hydroxymethylamino)-4-nitro-3-phenylbutanoate (10). The general method **F** described above was followed when intermolecular conjugate adduct **9** (50.0 mg, 0.11 mmol) was reacted with trifluoroacetic acid (0.5 mL) in dry CH_2Cl_2 (1.5 mL) at 0 °C and the mixture was stirred at room temperature overnight to afford **10** as major diastereomer in pure form as a thick liquid in 71% overall yield (28.0 mg, 0.078 mmol) with dr >99:1 (based on ^{1}H NMR analysis of crude reaction mixture). Optical purity was determined by Chiral HPLC

analysis (Chiralpak OD-H column), hexane−isopropanol 95:5, flow rate = 1.0 mL/min; for the major diastereomer, ee 2%, T_R 1: 60.99 min (minor), T_R 2: 74.53 min (major). R_f: 0.42 (30% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ 3341, 3029, 2952, 2923, 2853, 1734, 1551, 1495, 1455, 1434, 1379, 1299, 1215, 1157, 1122, 1096, 1032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (bs, 2H), 2.96 (d, J = 16.0 Hz, 1H), 3.20 (d, J = 15.4 Hz, 1H), 3.48 (s, 3H), 3.91–4.03 (m, 3H), 4.93–5.04 (m, 2H), 7.05–7.10 (m, 2H), 7.15–7.19 (m, 4H), 7.25–7.31 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 35.5, 45.4, 51.7, 52.4, 64.9, 76.8, 125.7, 126.9, 127.0, 128.3, 128.5, 128.80, 128.88, 132.9, 135.9, 174.0; HRMS (ESI-TOF) for $C_{19}H_{21}N_2O_4$, $(M+H-H_2O)^+$ found 341.1503, calcd 341.1501.

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of the compounds, HPLC chromatograms for ee determination, X-ray crystallography data (CIF) of **7a** (CCDC 1558403) and **7e** (CCDC

1558404) and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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15. See the Supporting Information for details of X-ray crystallographic analysis of **7a**, **7e**.

16. See Supporting Information (Figure S74 to S79) for more details.

17. See the Supporting Information for details of the computational studies (Table S5, S6 and S7).

18. Although both the diastereomers could not be separated by column chromatography, the major diastereomer precipitates out from the solution when the mixture of diastereomers was treated with HPLC grade ethanol followed by sonication and allowed to cool at low temperature

(−20 °C). The mother liquor contained mostly the minor diastereomer along with some amount of the major isomer and hence the minor isomer could not be obtained in pure form.

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