Graphical Abstract

Enantioselective *anti*-Mannich reaction catalyzed by modularly designed organocatalysts

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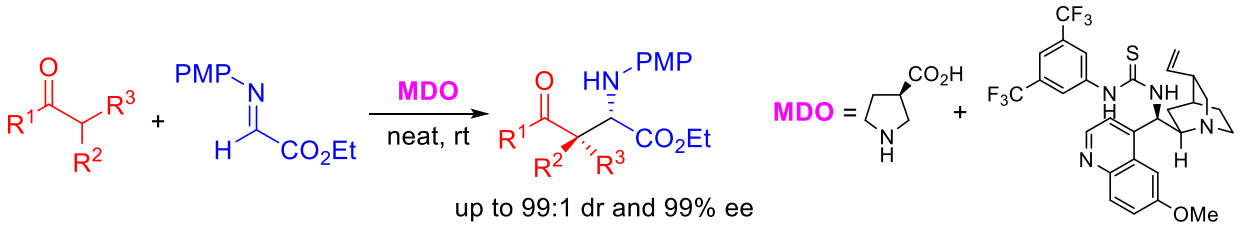

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ABSTRACT

A highly stereoselective method for achieving the *anti*-Mannich reaction of aldehydes and ketones with ethyl (4-methoxyphenylimino)acetate was realized using the modularly designed organocatalysts (MDOs) self-assembled from cinchona alkaloid derivatives and (*R*)-pyrrolidien-3-carboxylic acid in the reaction media. The desired *anti*-Mannich products were obtained in good to excellent yields (up to 93%), excellent diastereoselectivities (up to 99:1 dr), and good to high enantioselectivities (up to 99% ee).

1. Introduction

The Mannich reaction is a very important C-C bond forming reaction for the highly efficient synthesis of β-amino carbonyl compounds bearing two adjacent stereocenters.[1] The reaction can also be made diastereoselective and/or enantioselective readily by using appropriate catalysts.[1] Due to the versatility of the β-amino carbonyl compounds in organic synthesis and drug discovery, highly stereoselective methods for obtaining both the *syn*- and *anti*-Mannich products have been vigorously sought in recent decades.[1,2]

Since List[3] and Barbas[4] introduced the first organocatalyzed asymmetric direct Mannich reaction using L-proline as the catalyst, many chiral amine derivatives, most of which are derived from amino acids, such as proline, have been successfully applied as the catalysts in the direct Mannich reactions, and high diastereoselectivities and/or enantioselectivities have been achieved in many cases.[1a,b,5] Nonetheless, while amine-catalyzed asymmetric *syn*-Mannich reactions via the enamine mechanism are very common,[1a,b,5] examples of organocatalytic asymmetric *anti*-Mannich reactions are relatively limited.[6-22]

In this regard, Barbas' group reported the first *anti*-selective Mannich reaction using (*S*)-2-methoxymethylpyrrolidine (SMP) as the catalyst in 2002.[6] The *anti*-selectivity was achieved through the steric interactions between the α-methoxymethyl group on the catalyst pyrrolidine ring and the imine substrates.[6] ~~Later, the~~ same group discovered that pyrrolidine-3-carboxylic acid, which is a cyclic β-amino acid, and its derivatives are highly stereoselective catalysts for the *anti*-Mannich reactions.[7] In this case, the *anti*-selectivity was interpreted as the result of a different preferred conformation of the enamine intermediate as compared with that in the proline catalysis.[7] After these seminal reports, several different pyrrolidine derivatives were reported to produce the *anti*-Mannich products as the major stereoisomers with good to excellent stereoselectivities.[8-18] In principle, they are either the SMP-type catalysts that bearing a steric group at the α position of the pyrrolidine ring[8,9] or the pyrrolidine-3-carboxylic acid-type catalysts that bears a hydrogen bonding site at the β position of the pyrrolidine ring.[10-18] In contrast, acyclic amino acids and their derivatives have been rarely used in the *anti*-Mannich reactions.[19-21] Córdova's group reported the use of an acyclic β-amino acid for catalyzing the *anti*-Mannich reaction of ketones.[19] On the other hand, the groups of Moyano[20] and Lu[21] used acyclic α-amino acid derivatives as catalysts for the *anti*-Mannich reactions of hydroxyacetone[20] and *O*-benzyl[21a] or *O*-TBS[21b] hydroxyacetones, respectively. A totally different type of amine catalysts for the *anti*-Mannich reaction was reported by Maruoka's group. They have demonstrated that binaphthalene-based axially chiral amino sulfonamides are excellent organocatalysts for the *anti*-Mannich reactions.[22]

A few years back we introduced the modularly designed organocatalysts (MDOs),[23a] which could self-assemble under the reaction conditions from carefully designed precatalyst modules[24] through ionic interactions, for catalyzing the direct nitro-Michael reaction.[23a] Later, we[23] and others[25] have shown that these MDOs

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are highly efficient catalysts for many important C-C bond forming reactions, such as Michael, Mannich, hetero-Diels-Alder, Biginelli, and aldol reactions. Most recently, we also demonstrated that MDOs could be used as excellent catalysts for the asymmetric diastereodivergent reactions.[26] In 2013 we showed that MDOs self-assembled from L-proline and cinchona alkaloid thioureas were highly reactive and stereoselective catalysts for the *syn*-Mannich reactions between ethyl (4-methoxyphenylimino)acetate and aldehydes or ketones.[23f] In terms of both the reactivity and the stereoselectivity, remarkable synergistic effects of combining the two precatalyst modules to form the MDO were clearly demonstrated by the control experiments.[23f] Encouraged by these results, we wondered whether we could use similar effects to improve the *anti*-Mannich reactions, which, as summarized above, is more challenge to achieve than the *syn*-Mannich reaction. Herein we wish to disclose our detailed study of using novel MDOs self-assembled from (*R*)-pyrrolidine-3-carboxylic acid and cinchona alkaloid thioureas for the highly stereoselective *anti*-Mannich reaction of aldehydes and ketones with ethyl (4-methoxyphenylimino)acetate.

2. Results and discussions

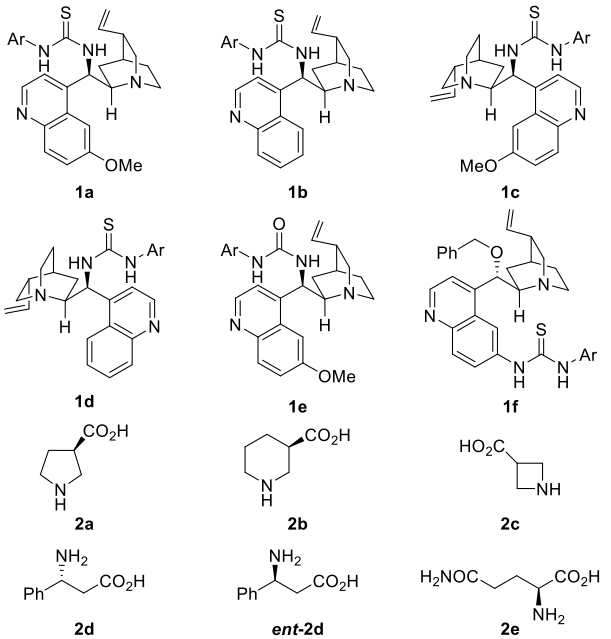
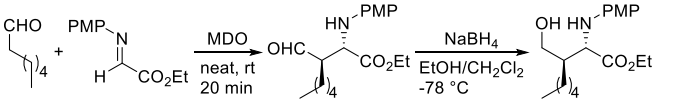


Figure 1. Precatalyst modules screened in the *anti*-Mannich reaction [Ar = 3,5-$(CF_3)_2C_6H_3$-]

Using heptanal (**3a**) and ethyl (4-methoxyphenylamino)-acetate (**4a**) as the model substrates, we initially screened the MDOs formed in situ in the reaction media from the precatalyst modules of the cinchona alkaloid and amino acid derivatives (Figure 1) to identify the best MDO for the *anti*-Mannich reaction. Based on our previous findings,[23f] the reaction was carried out under neat conditions at room temperature. The results are summarized in Table 1. It should be pointed out that, in order to facilitate the ee value determination, the initial Mannich product **5a** was reduced to the corresponding γ-alcohol **6a**. When the quinidine-derived thiourea **1a** and (*R*)-pyrrolidine-3-carboxylic acid (**2a**, 5 mol % each) were used to form the MDO in situ, the desired *anti*-Mannich product **5a** was obtained in 90% yield as an essentially pure enantiomer (99% ee) with a dr of 99:1 (entry 1). Similar to the *syn*-Mannich reaction previously realized by us using the MDO self-assembled from L-proline and the quinidine-derived thiourea (**1a**),[23f] a high product

Table 1. Catalyst screening for the *anti*-Mannich reaction[a]



3a 4a 5a 6a

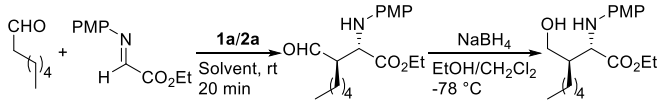
Entry	MDO		Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	**1a**	**2a**	90	99:1	99
2	**1a**	--	0	--	--
3	--	**2a**	80	90:10	85
4	**1b**	**2a**	78	92:8	99
5	**1c**	**2a**	83	90:10	99
6	**1d**	**2a**	83	95:5	98
7	**1e**	**2a**	83	96:4	96
8	**1f**	**2a**	87	86:14	96
9	**1a**	**2b**	49	83:17	96
10	**1a**	**2c**	34	76:24	12[e]
11	**1a**	**2d**	0	--	--
12	**1a**	***ent*-2d**	0	--	--
13	**1a**	**2e**	0	--	--

[a]Unless noted otherwise, all reactions were carried out with **3a** (0.24 mmol, 1.2 equiv), **4a** (0.20 mmol) and the specified catalyst modules (0.010 mmol, 5 mol % each) under neat conditions at room temperature (25 °C) for 20 min. [b]Yield of the isolated product **6a** after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture of the direct Mannich reaction. [d]Determined by HPLC analysis of the reduced product **6a** on a ChiralPak IC column. The absolute stereochemistry of products **5a** and **6a** was determined by comparing the measured optical rotation of compound **5a** with that reported in the literature (Ref. 7c). [e]The opposite enantiomer was obtained as the major product.

yield was achieved in just 20 min without the need to use a large excess of the aldehyde. Control experiments conducted with the individual module (i.e., **1a** or **2a** individually) as the catalyst under identical conditions showed either no reactivity (for **1a**, entry 2) or much worse reactivity and stereoselectivity (for **2a**, entry 3). These results clearly demonstrate that MDO do form under the reaction conditions and are responsible for the observed synergistic effects. Similar to the MDO assembled from **1a** and **2a**, the MDO assembled from cinchonine thiourea (**1b**) and **2a** also produced product **5a** in a high dr (92:8) with an excellent ee value (99% ee), but the yield was slightly lower (78%, entry 4). Very similar results were also obtained for the MDOs self-assembled from quinine thiourea (**1c**) and **2a** and cinchonidine thiourea (**1d**) and **2a** (entries 5 and 6). Nonetheless, a slightly lower ee value (96% ee) was obtained from the MDO of the quinidine-derived urea (**1e**) and **2a** (entry 7). Likewise, the MDO self-assembled from the quinidine-derived C_6'-thiourea (**1f**) and **2a** also led to a product with lower dr (86:14) and ee value (96% ee, entry 8). Thus, this screen identified quinidine thiourea (**1a**) as the best stereocontrolling module[23a] in terms of both the product yield and the stereoselectivities.

Next, additional amino acid derivatives were screened as the reaction-center module[23a] using **1a** as the stereocontrolling module. Unsatisfactory diastereoselectivity (83:17 dr) was obtained from the MDO assembled from **1a** and (*R*)-piperidine-3-carboxylic acid (**2b**), which is also a cyclic β-amino acid. Moreover, the product yield was also poor (49%, entry 9). Similarly, poor yield (34%), diastereoselectivity (76:24 dr), and ee value (12% ee) were also obtained when the MDO formed from **1a** and azetidine-3-carboxylic acid (**2c**) was applied (entry

Table 2. Effects of solvent and temperature on the *anti*-Mannich reaction[a]



3a **4a** **5a** **6a**

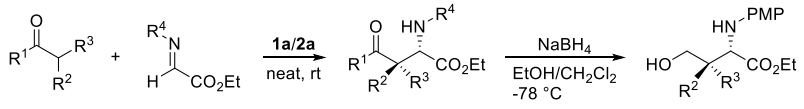
Entry	Solvent	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%)[d]
1	neat	90	99:1	99
2	toluene	81	99:1	99
3	benzene	62	88:12	99
4	xylene	81	91:9	99
5	hexane	72	95:5	92
6	THF	87	96:4	96
7	CH_2Cl_2	82	97:3	99
8	CH_3CN	56	90:10	98
9	DMF	72	95:5	98
10[e]	neat	68	80:20	99
11[f]	neat	73	91:9	96

[a]Unless noted otherwise, all reactions were carried out with **3a** (0.24 mmol, 1.2 equiv.) and the imine **4a** (0.20 mmol) in the presence of (*R*)-pyrrolidine-3-carboxylid acid (**1a**, 0.010 mmol, 5 mol %) and quinidine thiourea (**2a**, 0.010 mmol, 5 mol %) in the specified solvent (0.5 mL) at room temperature (ca. 25 °C). [b]Yield of the isolated product **6a** after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture of the direct Mannich reaction. [d]Determined by HPLC analysis of the reduced product **6a** on a ChiralPak IC column. The absolute stereochemistry of products **5a** and **6a** was determined by comparing the measured optical rotation of compound **5a** with that reported in the literature (Ref. 7c). [e]The reaction was carried out at 50 °C. [f]The reaction was carried out at 0 °C.

10). In addition, the opposite enantiomer was obtained as the major product in this case. Although the enantioselectivity of this MDO is poor, it should be pointed out that this result actually unequivocally reveals that the stereocontrolling module (i.e., **1a**) indeed contributes to the overall stereoselectivity of this reaction, since azetidine-3-carboxylic acid (**2c**) is in fact an achiral compound, which cannot impart any product ee value by itself. In contrast to cyclic β-amino acids, MDOs formed from **1a** and acyclic β-amino acids, such as (*R*)-3-amino-3-phenylpropanoic acid (**2d**, entry 11) and (*S*)-3-amino-3-phenylpropanoic acid (***ent*-2d**, entry 12), did not furnish any product. Similarly, the MDO of **1a** and an α-amino acid, L-glutamine (**2e**), did not give any product, either (entry 13). Thus, this screening identified (*R*)-pyrrolidine-3-carboxylic acid (**2a**) as the best reaction-center module.

With the best MDO self-assembled from **1a** and **2a**, we further optimized the reaction conditions. The results are summarized in Table 2. First some common organic solvents were screened (entries 2-9). As the results in Table 2 show, in general, results obtained from organic solvents are inferior in terms of both product yield and stereoselectivities as compared to those obtained under neat conditions (entry 1). Among these organic solvents, the best results were obtained in toluene, in which

Table 3. Substrate Scope of the *anti*-Mannich Reaction[a]



3 **4** **5** **6**

4a: R^4 = PMP
4b: R^4 = Ts

R^1 = H. R^4 = PMP

Entry	R^1	R^2	R^3	R^4	Time (min)	Product	Yield (%)[b]	dr (*anti*:*syn*)[c]	ee (%)[d]
1	H	$CH_3(CH_2)_4$-	H	PMP	20	**6a**	93	99:1	99
2	H	CH_3-	H	PMP	20	**6b**	88	99:1	90
3	H	$CH_3(CH_2)_2$-	H	PMP	20	**6c**	90	95:5	89
4	H	$CH_3(CH_2)_6$-	H	PMP	20	**6d**	91	99:1	86
5	H	$CH_3(CH_2)_9$-	H	PMP	20	**6e**	83	95:5	82
6	H	$PhCH_2$	H	PMP	40	**6f**	86	94:6	92
7	H	$(CH_3)_2CH$-	H	PMP	20	**6g**	92	96:4	94
8	H	CH_3-	CH_3-	PMP	40	**6h**	81	---	18
9	H	$CH_3(CH_2)_4$-	H	Ts	40	**6i**	89[e]	81:19	5
10	Me	$CH_3(CH_2)_2$-	H	PMP	1800	**5j**	76[e]	80:20	84[f]
11		-$(CH_2)_4$-	H	PMP	120	**5k**	90[e]	92:8	86[f]
12		-$(CH_2)_2OCH_2$-	H	PMP	60	**5l**	78[e]	70:30	44[f]
13		-$(CH_2)_5$-	H	PMP	1440	**5m**	85[e]	84:16	59[f]
14		-$(CH_2)_3$-	H	PMP	--	**5n**	0	--	--

[a]Unless noted otherwise, all reactions were carried out with **3** (0.24 mmol, 1.2 equiv.), **4** (0.20 mmol) in the presence of (*R*)-pyrrolidine-3-carboxylid acid (**1a**, 0.010 mmol, 5 mol %) and quinidine thiourea (**2a**, 0.010 mmol, 5 mol %) under neat conditions at room temperature (25 °C). [b]Unless otherwise noted, yield refers to that of the isolated product **6** after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture of the direct Mannich reaction. [d]Determined by HPLC analysis of the purified product on a ChiralPak IC column. Unless otherwise indicated, the absolute stereochemistry of products **6** was similarly assigned based on that of product **6a** according to the reaction mechanism. [e]Yield of the isolate product **5** after column chromatography. [f]The absolute stereochemistry of product **5k** was determined by comparing the measured optical rotation with that reported in the literature (Ref. 7a). The absolute stereochemistry of the other ketone Mannich products was similarly assigned based on the reaction mechanism.

exactly the same level of stereoselectivities as those obtained under neat conditions were obtained, except that the product yield was slightly lower (81% vs. 90%, entry 2). Thus, solvent-free conditions proved to be the optimal conditions for this MDO-catalyzed *anti*-Mannich reaction. When the reaction was carried out under neat conditions at 50 °C (entry 10) and 0 °C (entry 11), both the product dr and yield dropped.

Next, the reaction scope was established under the optimized reaction conditions. Again, to facilitate the ee value determination via the HPLC analysis, the Mannich products of aldehydes and **4a** and **4b** were further reduced to the corresponding γ-alcohols (**6a**-**i**). In contrast, the Mannich products of ketones and **4a** (**5j**-**m**) were directly analyzed by HPLC. The results are summarized in Table 3. As the data in Table 3 show, besides the *anti*-Mannich product of heptanal (**6a**, entry 1), the desired *anti*-Mannich products of other straight chain aliphatic aldehydes, such as those of propanal (**6b**, entry 2), pentanal (**6c**, entry 3), nonanal (**6d**, entry 4), dodecanal (**6e**, entry 5), and hydrocinnamaldehyde (**6f**, entry 6), were all obtained in high yields, excellent diastereoselectivities, and good to high ee values. Similarly, the branched isovaleraldehyde also produced the corresponding *anti*-Mannich product **6g** in a high yield with excellent stereoselectivities (entry 7). Nonetheless, while the sterically more hindered isobutyraldehyde also produced the corresponding Mannich product **6h** in a good yield, the product ee value dropped dramatically to only 18% (entry 8). Similarly, the *anti*-Mannich product **6i**, which is the reaction product of **3a** and the *N*-tosyl imine **4b**, was obtained in a good yield with a good diastereoselectivity but a poor ee value (entry 9). Comparing this result with that in entry 1, it is evident that the PMP protecting group on the imine is essential for maintaining the high ee values of the *anti*-Mannich products, most likely because of the hydrogen bonding between the imine nitrogen atom and the catalyst. When an acyclic ketone, 2-hexanone, was employed as the substrate, the desired *anti*-Mannich product **5j** was obtained in a good yield with a moderate dr (80:20) and a good ee value (entry 10). As for cyclic ketones, cyclohexanone yielded the desired *anti*-Mannich product **5k** in a high yield with a high dr and a good ee value (entry 11). However, the *anti*-Mannich product of tetrahydropyran-4*H*-one **5l** was obtained in much poorer dr and ee values (entry 12). Also, the reaction with cycloheptanone gave the desired *anti*-Mannich product **5m** in only moderate yield, dr, and ee values (entry 13). There has been no report on using cyclopentanone in *anti*-Mannich reaction till now. We tried this substrate with **4a** under the MDO catalysis, and, as expected, no desired *anti*-Mannich product was obtained (entry 14).

From the results of our current study and our earlier study with the MDOs self-assembled from L-proline,[23f] it is clear that the stereochemistry outcome of the Mannich reactions is mainly controlled by the reaction-center modules used (i.e., the amino acids), since the same relative and absolute configuration of the Mannich products were obtained from the amino acids and the corresponding MDOs formed from those amino acids. On the other hand, the cinchona alkaloid thioureas (i.e., the stereocontrolling modules of the MDOs) help improve the reactivity of the reaction-center modules greatly, especially under such solvent-free conditions, and their stereoselectivities.

3. Conclusions

In summary, we have demonstrated that the MDO self-assembled from (*R*)-pyrrolidine-3-carboxylic acid and quinidine thiourea is a highly efficient catalyst for the *anti*-Mannich reaction of aldehydes and ketones with ethyl (4-methoxyphenylimino)acetate. Under solvent-free conditions, the desired *anti*-Mannich products may be obtained in good to high yields (up to 93%) and good to excellent diastereoselectivities (up to 99:1) and ee values (up to 99%) in short reaction times without the need of using large excesses of the aldehyde or ketone substrates. Combing the current method with the method we developed earlier for the *syn*-Mannich products,[23f] we have achieved a facile diastereodivergent synthesis[26c] of the desired Mannich products using the MDOs.

4. Experimental

4.1. General methods.

All reactions were carried out in oven-dried glassware. Solvents were dried using standard protocols. Aldehydes and ketones were freshly distilled before use. Ethyl (4-methoxyphenylimino)acetate (**4a**) was prepared following the known procedure.[27] Precatalyst modules **1a**-**1d**,[28] **1e**,[29] and **1f**[30] were synthesized following the reported procedures. Precatalyst modules **2a**-**2e** were commercially available. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz, respectively) spectra were recorded at 25 °C using $CDCl_3$ as the solvent.

4.2. General Procedure for the anti-Mannich Reaction.

Quinidine-derived thiourea **1a** (5.9 mg, 0.010 mmol, 5 mol %) and (*R*)-pyrrolidine-3-carboxylic acid (**2a**, 1.2 mg, 0.010 mmol, 5 mol %) were added to heptanal (**3a**, 27.4 mg, 0.24 mmol) while stirring at rt (Note: If the reaction was conducted in a solvent, precatalysts **1a** and **2a** were first taken in 0.5 mL of the corresponding solvent and the mixture was stirred for 15 min before the addition of aldehyde.). The mixture was further stirred at room temperature for 10 min, and then the imine **4a** (41.4 mg, 0.20 mmol) was added. Upon the completion (monitored by TLC), the reaction was quenched by adding aqueous ammonium chloride (2.0 mL). The mixture was then extracted with ethyl acetate (2.0 mL × 2). The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated. The crude reaction mixture was transferred to a column packed with silica gel and hexane and eluted with a 90:10 hexane/EtOAc mixture to yield product **5a** (61.8 mg, 96%) as a colorless gummy liquid, which was further reduced using sodium borohydride (11.3 mg, 0.30 mmol) in dichloromethane (1.0 mL) and ethanol (0.25 mL) at -78 °C for 45 min. Upon the completion of the reaction (monitored by TLC), the mixture was quenched with aq. $NaHCO_3$ (2.0 mL) and extracted with dichloromethane (2.0 mL × 2). The extracts were washed with brine (2.0 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the the crude reaction mixture was transferred to a column packed with silica gel and hexane and eluted with 30% ethyl acetate in hexane to yield product **6a** (60.4 mg, 93%) as a yellow oil.

*4.2.1. Ethyl(2S,3R)-3-(hydroxymethyl)-2-[(4 methoxyphenyl)amino]octanoate (**6a**)*

Yellow oil; 60.4 mg, 93% yield; 99:1 dr, 99% ee, $[\alpha]^{25}{}_D$ = -17.3 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 – 6.63 (m, 4H), 4.16 (qt, *J* = 7.1, 1.3 Hz, 2H), 4.04 (dd, *J* = 6.4, 1.1 Hz, 1H), 3.88 – 3.69 (m, 6H), 2.07 (q, *J* = 4.8, 4.0 Hz, 1H), 1.45 – 1.25 (m, 9H), 1.22 (td, *J* = 7.1, 1.1 Hz, 3H), 0.89 (td, *J* = 7.0, 1.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.19, 175.08, 156.51, 142.73, 115.67, 114.80, 61.44, 57.03, 55.60, 53.89, 31.60, 26.91, 31.60, 26.91, 25.62, 22.27, 14.09, 13.86. ν_{max} (neat, cm^{-1}): 3268, 2927, 1726, 1618, 1510, 1411, 1368, 1236. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{30}NO_4$ ($[M+H]^+$): 324.2169; Found: 324.2173. Enantiomeric excess of **6a** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column

(75:25 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 7.1 min; minor enantiomer: t_R = 6.2 min.

*4.2.2. Ethyl(2S,3R)-4-hydroxy-2-[(4-methoxyphenyl)amino]-3-methylbutanoate (**6b**)*

Colorless oil; 47.2 mg, 88% yield; 99:1 dr, 90% ee, $[\alpha]^{25}_D$ = -26.2 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 – 6.74 (m, 2H), 6.75 – 6.68 (m, 2H), 4.24 – 4.09 (m, 2H), 3.95 (d, *J* = 7.4 Hz, 1H), 3.82 – 3.62 (m, 6H), 2.16 (pd, *J* = 7.1, 4.8 Hz, 1H), 1.31 – 1.15 (m, 4H), 1.03 – 0.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.28, 153.67, 140.12, 116.84, 114.77, 66.91, 63.06, 61.09, 55.62, 38.36, 14.25, 13.75. ν_{max} (neat, cm^{-1}): 3366, 2849, 1733, 1596, 1378, 1233. HRMS (ESI) *m/z* calcd. for $C_{14}H_{22}NO_4$ ($[M+H]^+$): 268.1543; Found: 268.1553. Enantiomeric excess of **6b** was determined by chiral stationary phase HPLC analysis using a ChiralPak IB column (95:5 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 34.9 min; minor enantiomer t_R = 25.9 min.

*4.2.3. Ethyl (2S,3R)-3-(hydroxymethyl)-2-[(4-methoxyphenyl)amino]hexanoate (**6c**)*

Yellow oil; 53.4 mg, 90% yield; 95:5 dr, 89% ee, $[\alpha]^{25}_D$ = -34.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 – 6.58 (m, 4H), 4.17 (h, *J* = 5.4 Hz, 2H), 4.04 (t, *J* = 5.4 Hz, 1H), 3.89 – 3.56 (m, 6H), 2.07 (qt, *J* = 7.9, 3.9 Hz, 1H), 1.48 – 1.28 (m, 4H), 1.22 (q, *J* = 11.5, 9.3 Hz, 3H), 1.02 – 0.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.57, 153.66, 140.11, 116.765, 114.80, 63.87, 61.99, 61.12, 55.66, 30.43, 20.26, 14.21, 14.19. ν_{max} (neat, cm^{-1}): 3386, 2953, 1723, 1465, 1377, 1200. HRMS (ESI) *m/z* calcd. for $C_{16}H_{26}NO_4$ ($[M+H]^+$): 296.1856; Found: 296.1860. Enantiomeric excess of **6c** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (85:15 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 16.4 min; minor enantiomer: t_R = 15.7 min.

*4.2.4. Ethyl (2S,3R)-3-(hydroxymethyl)-2-[(4-methoxyphenyl)amino]decanoate (**6d**)*

Colorless oil; 70 mg, 91% yield; 99:1 dr, 86% ee, $[\alpha]^{25}_D$ = -39.8 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, *J* = 0.7 Hz, 4H), 4.15 (qd, *J* = 7.1, 0.6 Hz, 2H), 4.03 (d, *J* = 6.5 Hz, 1H), 3.89 – 3.63 (m, 6H), 2.05 (d, *J* = 2.4 Hz, 1H), 1.36 – 1.25 (m, 10H), 1.24 – 1.17 (m, 5H), 0.93 – 0.79 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.80, 154.40, 121.89, 117.84, 114.74, 114.22, 63.62, 62.84, 61.27, 55.61, 42.81, 31.78, 29.69, 29.14, 28.23, 27.04, 22.63, 14.08, 14.09. ν_{max} (neat, cm^{-1}): 3281, 2918, 1733, 1596, 1463, 1378, 1233. HRMS (ESI) *m/z* calcd. for $C_{20}H_{34}NO_4$ ($[M+H]^+$): 352.2482; Found: 352.2489. Enantiomeric excess of **6d** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 28.3 min; minor enantiomer t_R = 26.4 min.

*4.2.5. Ethyl (2S,3R)-3-(hydroxymethyl)-2-[(4-methoxyphenyl)amino]tridecanoate (**6e**)*

Yellow oil; 65.2 mg, 83% yield; 95:5 dr, 82% ee, $[\alpha]^{25}_D$ = -42.6 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 – 6.72 (m, 2H), 6.71 – 6.64 (m, 2H), 4.24 – 4.11 (m, 2H), 4.03 (d, *J* = 6.4 Hz, 1H), 3.88 – 3.66 (m, 5H), 2.03 (d, *J* = 7.5 Hz, 1H), 1.44 – 1.07 (m, 22H), 1.01 – 0.76 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.95, 153.30, 140.81, 116.32, 114.77, 64.18, 61.78, 61.07, 55.67, 43.17, 31.90, 29.77, 29.60, 29.50, 29.33, 28.26, 27.09, 22.69, 14.25, 14.14. ν_{max} (neat, cm^{-1}): 3358, 2923, 1731, 1508, 1464, 1370, 1238. HRMS (ESI) *m/z* calcd. for $C_{23}H_{40}NO_4$ ($[M+H]^+$): 394.2952; Found: 394.2958. Enantiomeric excess of **6e** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 12.6 min, minor enantiomer: t_R = 11.8 min.

*4.2.6. Ethyl (2S,3R)-3-benzyl-4-hydroxy-2-[(4-methoxyphenyl)amino]butanoate (**6f**)*

Colorless oil; 63.6 mg, 86% yield; 94:6 dr, 92% ee, $[\alpha]^{25}_D$ = -28.3 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.16 (m, 5H), 6.81 – 6.71 (m, 2H), 6.68 – 6.59 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.08 (d, *J* = 5.6 Hz, 1H), 3.84 – 3.60 (m, 4H), 2.91 – 2.61 (m, 2H), 2.39 (dqd, *J* = 9.9, 6.3, 3.6 Hz, 1H), 1.33 – 1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.99, 153.09, 140.93, 139.32, 129.14, 128.52, 126.37, 115.97, 114.77, 62.97, 61.18, 60.57, 55.68, 55.65, 44.75, 34.66, 14.26. ν_{max} (neat, cm^{-1}): 3292, 2932, 2838, 1731, 1508, 1453, 1332, 1256. HRMS (ESI) *m/z* calcd. for $C_{20}H_{26}NO_4$ ($[M+H]^+$) 344.1856; Found: 344.1865. Enantiomeric excess of **6f** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 16.6 min; minor enantiomer: t_R = 19.2 min.

*4.2.7. Ethyl (2S,3R)-3-(hydroxymethyl)-2-[(4-methoxyphenyl)amino]-4-methylpentanoate (**6g**)*

Yellow oil; 54.4 mg, 92% yield; 96:4 dr, 94% ee, $[\alpha]^{25}_D$ = -34.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75 (qd, *J* = 9.2, 3.0 Hz, 4H), 4.24 – 4.01 (m, 3H), 3.85 (t, *J* = 4.0 Hz, 2H), 3.74 (d, *J* = 4.0 Hz, 3H), 1.85 (q, *J* = 5.7 Hz, 2H), 1.30 – 1.12 (m, 4H), 1.00 (ddd, *J* = 21.6, 6.8, 3.8 Hz, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.91, 153.72, 140.09, 116.91, 114.76, 62.05, 61.91, 61.08, 55.64, 48.66, 21.40, 18.74, 14.19. ν_{max} (neat, cm^{-1}): 3373, 2953, 1727, 1512, 1369, 1237. HRMS (ESI) *m/z* calcd. for $C_{16}H_{26}NO_4$ ($[M+H]^+$): 296.1856; Found: 296.1863. Enantiomeric excess of **6g** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (92.5:7.5 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 35.6 min; minor enantiomer: t_R = 39.6 min.

*4.2.8. Ethyl (S)-4-hydroxy-2-[(4-methoxyphenyl)amino]-3,3-dimethylbutanoate (**6h**)*

Yellow oil; 46.0 mg, 81% yield; 18% ee, $[\alpha]^{25}_D$ = -42.6 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 – 6.74 (m, 2H), 6.74 – 6.68 (m, 2H), 4.28 – 4.05 (m, 2H), 3.93 (s, 1H), 3.74 (s, 3H), 3.62 – 3.48 (m, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 24.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.20, 153.61, 140.77, 116.96, 114.75, 71.75, 65.82, 65.79, 60.96, 55.65, 55.61, 38.38, 22.63, 20.16, 14.27. ν_{max} (neat, cm^{-1}): 3375, 2932, 1723, 1511, 1465, 1368, 1235. HRMS (ESI) *m/z* calcd. for $C_{15}H_{24}NO_4$ ($[M+H]^+$): 282.1700, Found: 281.1704. Enantiomeric excess of **6h** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 14.6 min; minor enantiomer t_R = 11.8 min.

*4.2.9. Ethyl (2S,3R)-3-(hydroxymethyl)-2-[(4-methylphenyl)sulfonamido]octanoate (**6i**)*

Colorless oil; 54 mg, 89% yield; 81:19 dr, 5% ee, $[\alpha]^{25}_D$ = 33.7 (c = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (dq, *J* = 8.6, 2.1 Hz, 2H), 7.38 – 7.17 (m, 2H), 3.89 (dd, *J* = 11.2, 2.9

Hz, 1H), 3.66 – 3.45 (m, 1H), 3.29 (t, *J* = 6.5 Hz, 1H), 2.42 (d, *J* = 2.8 Hz, 2H), 1.54 – 1.35 (m, 3H), 1.30 – 0.95 (m, 12H), 1.00 – 0.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.99, 138.52, 129.48, 127.01, 61.08, 56.06, 42.64, 33.62, 32.02, 31.65, 29.05, 28.08, 27.10, 25.58, 22.55, 22.49, 14.08. ν_{max} (neat, cm^{-1}): 3390, 2953, 2856, 1723, 1465, 1377, 1330. HRMS (ESI) *m/z* calcd. for $C_{18}H_{30}NO_5S$ $[M+H]^+$): 372.1829; Found: 372.1834. Enantiomeric excess of **6i** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 34.1 min; minor enantiomer: t_R = 29.6 min.

*4.2.10. Ethyl (2S,3R)-3-acetyl-2-[(4-methoxyphenyl)amino]hexanoate (**5j**)*[7b]

Colorless oil; 47.8 mg, 76% yield; 80:20 dr, 84% ee, $[\alpha]^{25}_D$ = -36.5 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (ddd, *J* = 9.4, 4.9, 2.1 Hz, 2H), 6.73 – 6.60 (m, 2H), 4.21 – 4.10 (m, 3H), 3.76 (t, *J* = 1.9 Hz, 3H), 3.10 – 2.97 (m, 1H), 2.53 (ddd, *J* = 7.5, 5.4, 2.0 Hz, 2H), 1.63 – 1.50 (m, 3H), 1.27 – 1.16 (m, 5H), 0.92 (td, *J* = 7.4, 5.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.19, 172.59, 152.74, 140.99, 115.24, 114.89, 77.29, 77.03, 76.78, 61.31, 60.71, 55.74, 54.39, 43.90, 30.94, 29.93, 29.04, 27.21, 24.26, 14.18. ν_{max} (neat, cm^{-1}): 3335, 2957, 1727, 1699, 1510, 1464, 1362, 1286. HRMS (ESI) *m/z* calcd. for $C_{17}H_{26}NO_4$ ($[M+H]^+$): 308.1856; Found: 308.1861. Enantiomeric excess of **5j** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 8.8 min; minor enantiomer: t_R = 11.3 min.

*4.2.11. Ethyl (S)-2-[(4-methoxyphenyl)amino]-2-[(R)-2-oxocyclohexyl]acetate (**5k**):*[7b]

Colorless oil; 59.4 mg, 90% yield; 92:8 dr, 86% ee, $[\alpha]^{25}_D$ = +32.8 (c = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 – 6.69 (m, 2H), 6.70 – 6.54 (m, 2H), 4.28 – 4.04 (m, 2H), 3.98 (d, *J* = 4.1 Hz, 1H), 3.74 (d, *J* = 2.4 Hz, 3H), 3.21 – 3.03 (m, 1H), 2.60 – 2.23 (m, 2H), 2.23 – 2.01 (m, 2H), 2.02 – 1.83 (m, 2H), 1.88 – 1.56 (m, 3H), 1.36 – 1.15 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.00, 173.10, 152.74, 142.15, 115.64, 115.61, 114.74, 61.22, 59.18, 59.01, 55.79, 55.62, 53.62, 41.85, 30.56, 26.87, 24.57, 14.25, 14.18, 14.10. Enantiomeric excess of **5k** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 17.5 min; minor enantiomer: t_R = 16.3 min.

*4.2.12. Ethyl (S)-2-[(4-methoxyphenyl)amino]-2-[(S)-4-oxotetrahydro-2H-pyran-3-yl]acetate (**5l**):*[7b]

Colorless oil; 54 mg, 78% yield; 70:30 dr, 44% ee, $[\alpha]^{25}_D$ = +46.3 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 – 6.74 (m, 2H), 6.74 – 6.58 (m, 2H), 4.34 – 3.97 (m, 6H), 3.97 – 3.85 (m, 1H), 3.86 – 3.77 (m, 1H), 3.74 (d, *J* = 2.2 Hz, 3H), 3.25 (dt, *J* = 9.5, 5.2 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.48 (dt, *J* = 14.9, 3.9 Hz, 1H), 1.30 – 1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.19, 172.15, 153.19, 141.27, 116.22, 115.91, 114.82, 70.07, 69.58, 68.07, 67.84, 61.54, 61.49, 56.64, 55.68, 54.45, 53.84, 42.09, 42.03. Enantiomeric excess of **5l** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 19.2 min; minor enantiomer: t_R = 17.9 min.

*4.2.13. Ethyl (S)-2-[(4-methoxyphenyl)amino]-2-[(R)-2-oxocycloheptyl]acetate (**5m**)*[7b]

Yellow oil; 54.4 mg, 85% yield; 84:16 dr, 59% ee, $[\alpha]^{25}_D$ = +35.8 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 4.18 (t, *J* = 7.1 Hz, 2H), 3.76 (d, *J* = 1.5 Hz, 3H), 3.11 – 3.00 (m, 1H), 2.56 (d, *J* = 3.7 Hz, 2H), 2.19 (s, 1H), 2.10 – 1.86 (m, 4H), 1.57 (dd, *J* = 11.3, 2.6 Hz, 2H), 1.48 – 1.33 (m, 2H), 1.28 – 1.20 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.20, 172.60, 152.74, 140.99, 115.24, 114.89, 77.29, 77.03, 76.78, 61.31, 60.71, 55.74, 54.39, 43.90, 30.94, 29.93, 29.04, 27.21, 24.26, 14.18, 14.15. Enantiomeric excess of **5m** was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (80:20 hexanes/*i*-PrOH at 1.0 mL/min, λ = 254 nm), major enantiomer: t_R = 17.7 min; minor enantiomer: t_R = 15.2 min.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/

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