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2-Pyrrolidinecarboxylic Acid Ionic Liquid as a Highly Efficient Organocatalyst for the Asymmetric One-Pot Mannich Reaction

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A novel one-pot three-component asymmetric Mannich reaction using [EMIm][Pro] (**1**) as a catalyst has been developed. By employing this new reaction system, a variety of optically active β-amino carbonyl compounds were synthesized in up to 99 % yield with up to >99 *dr* and >99 % *ee*. The reaction conditions have been optimized and the mechanism for the asymmetric induction is discussed.

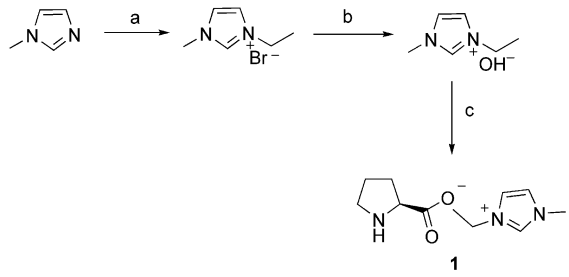
Introduction

The Mannich reaction occupies an important position in the field of organic synthesis for the construction of enantiomerically enriched β-amino carbonyl motifs such as amino acids, amino alcohols, and their derivatives.[1] It has emerged as a crucial synthetic methodology for accessing key intermediates in the synthesis of natural products as well as pharmaceutically valuable compounds.[1f,1g–11] Over the past decade, Lewis acids,[2] Lewis bases,[3] Brønsted acids,[4] and rare metal salts[5] have been investigated as catalysts in Mannich-type reactions. Recently, the development of asymmetric Mannich reactions has attracted considerable attention. Since List and co-workers[6] first reported a direct organocatalytic one-pot three-component Mannich reaction catalyzed by proline, proline-derived tetrazole,[7] acylic amino acids and their derivatives,[8] and chiral phosphoric acids[9] have also been successfully utilized as enantioselective organocatalysts in this type of transformation.

In recent years, a growing number of chiral ionic liquids (CILs) have been considered as extremely promising green reaction media,[10] not only because of their favorable properties, including reusability, nonvolatile nature and high thermal stability, but also because of their unique selectivity and reactivity, avoiding the use of expensive and/or toxic metals. Furthermore, ionic liquids have currently been employed either as catalysts or as solvents in a large number of reactions,[11] especially in direct and indirect Mannich reactions.[12] However, no CIL has been reported as a catalyst in direct or indirect asymmetric Mannich reactions.

In view of a myriad of examples employing proline as a successful organocatalyst in asymmetric Mannich reactions[13] and an increasing number of Mannich-type reactions catalyzed by ionic liquids, we proposed that the combination of proline as an effective module with ionic liquids could catalyze enantioselective Mannich reactions. Previously we reported that a CIL with (*S*)-proline as the anion [1-ethyl-3-methylimidazolium (*S*)-2-pyrrolidinecarboxylic acid salt [EMIm][Pro] (**1**)] could facilitate the asymmetric Michael addition reaction by the enamine mechanism.[14] This CIL is readily available from simple and inexpensive starting materials (proline and 1-methyl-1*H*-imidazole) and we routinely prepare it on a large scale. Herein, we disclose an efficient protocol for the direct enantioselective one-pot three-component Mannich reaction catalyzed by [EMIm]-[Pro] (**1**), which affords the corresponding adducts with high diastereo- (up to >99) and enantioselectivities (up to >99%). To the best of our knowledge, this is the first asymmetric Mannich reaction induced by a CIL and it may significantly extend the design and application of CILs in organic synthesis.

The amino acid ionic liquid [EMIm][Pro] (**1**) was easily synthesized in 70% overall yield by the published procedure[15] (Scheme 1).



Scheme 1. Synthesis of the chiral amino acid ionic liquid 1-ethyl-3-methylimidazolium (*S*)-2-pyrrolidinecarboxylic acid salt [EMIm]-[Pro] (**1**). Reagents and conditions: a) CH_3CH_2Br, $CH_3CO_2C_2H_5$, Δ, 80%; b) 201 × 7 styrene-DVB; c) proline, 70%.

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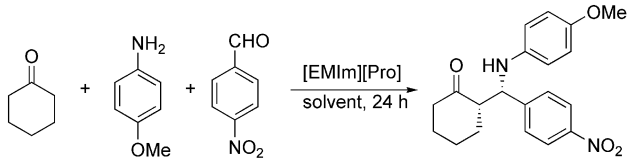
Results and Discussion

We initially examined the three-component Mannich reaction of cyclohexanone (**2a**), *p*-anisidine (**3a**), and *p*-nitrobenzaldehyde (**4a**) in CH_2Cl_2 at room temperature in the presence of 30 mol-% [EMIm][Pro] (**1**). [EMIm][Pro] (**1**) proved to be a viable catalyst for this direct Mannich reaction, affording the *syn* isomer **5a** with 78% *ee*, although the yield and *dr* were not satisfactory (Table 1, entry 1). In light of these results, we screened a variety of solvents. When the reaction was performed in DMF or DMSO, the desired product **5a** was isolated in good yield (66–78%) with excellent enantioselectivity (80–86%) within 24 h (Table 1, entries 9 and 12). Other solvents, such as THF, hexane, and [BMIm][PF_6], were found to be less satisfactory in terms of the yield and enantioselectivity (Table 1, entries 2–8). To accelerate the reaction and improve the diastereo- and enantioselectivity, we added 2 equiv. of water to the reaction mixture. As expected, the addition of excess water to the reaction mixture had a significant effect on both the diastereo- and enantioselectivity of the Mannich product. The enantioselectivity increased to 90% *ee* and the yield was 80%, albeit in roughly equal amounts of both the *syn* and *anti* isomers (Table 1, entry 13). Reducing the amount of water to 1 equiv. led to improved stereoselectivity, furnishing the corresponding product in 82% yield with an approximately 3:1 *dr* and 90% *ee* (Table 1, entry 14). Further decreasing the amount of water to 0.5 equiv. did not lead to an improvement in the ratio of diastereoisomers or the enantioselectivity. Thus, the inclusion of water in these reactions proved to be favorable for obtaining high diastereo- and enantioselectivities and enhancing the reaction rate.[16] Importantly, lowering the catalyst loading to 10 mol-% did not compromise the *ee* of the reaction (77:23 *dr*, 90% *ee*) (Table 1, entry 18).

Table 1. Examples of solvents screened for the direct asymmetric Mannich reaction of **2a**, **3a** and **4a**.[a]



2a **3a** **4a** **5a**

Entry	Catalyst [mol-%]	Solvent	Temp. [°C]	Yield [%][b]	*dr* (*syn*/*anti*)[c,d]	*ee* (*syn*) [%][d]
1	30	CH_2Cl_2	r.t.	45	56:44	78
2	30	CH_3CN	r.t.	51	51:49	78
3	30	EtOH	r.t.	65	73:27	58
4	30	THF	r.t.	35	55:45	82
5	30	hexane	r.t.	33	61:39	78
6	30	dioxane	r.t.	37	71:29	84
7	30	EtOAc	r.t.	24	66:34	82
8	30	[BMIm][PF_6]	r.t.	32	56:43	82
9	30	DMF	r.t.	66	52:48	80
10[e]	30	DMF	0	68	71:29	90
11[e]	30	DMF	–20	62	82:18	97
12	30	DMSO	r.t.	78	67:33	86
13[f]	30	DMSO	r.t.	80	56:44	90
14[g]	30	DMSO	r.t.	82	72:28	90
15[h]	30	DMSO	r.t.	85	68:32	88
16[g,e]	30	DMSO	0	73	81:19	93
17[g,e]	20	DMSO	r.t.	70	68:32	88
18[g,e]	10	DMSO	r.t.	67	77:23	90

[a] The reaction was performed using cyclohexanone (**2a**; 2 mmol, 10 equiv.), 4-nitrobenzaldehyde (**4a**; 0.22 mmol, 1.1 equiv.), *p*-anisidine (**3a**; 0.2 mmol, 1 equiv.) and **1** (0.06 mmol, 0.3 equiv.) in a solvent (0.5 mL) for 24 h. [b] Isolated yields of the product **5a** after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column. [e] After 48 h. [f] 2 equiv. of H_2O was added. [g] 1 equiv. of H_2O was added. [h] 0.5 equiv. of H_2O was added.

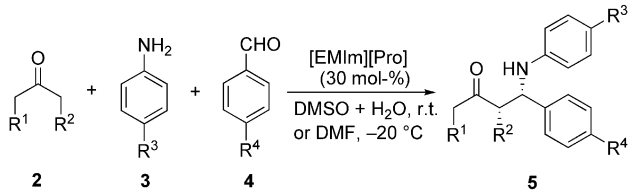
In addition, the [EMIm][Pro]-catalyzed Mannich reaction was extremely sensitive to the reaction temperature. The expected product **5a** was generated in DMF at 0 °C with approximately 3:1 *dr* and 90% *ee* (Table 1, entry 10). Reduction of the temperature to –20 °C gave the highest diastereo- and enantioselectivity (about 5:1 *dr*, 97% *ee*) (Table 1, entry 11). This is an improvement compared with the proline-catalyzed direct three-component Mannich reaction performed at room temperature[6a,6b] (50% yield, 2:1 *dr* and 84% *ee*).

Given the remarkable performance of [EMIm][Pro] (**1**) in DMF at –20 °C, we next investigated the scope of the reaction using cyclohexanone (**2a**) as the ketone donor, a set of different benzaldehyde derivatives as acceptors, and two aniline derivatives. The results are illustrated in Table 2 (entries 1–10) and show that the reaction proceeded smoothly in moderate yields (48–65%) with up to 94:6 *dr* and excellent levels of enantioselectivity (90–99%). Only trace amounts of aldol addition side-products were observed. Note that the reaction proceeded smoothly with different kinds of aromatic aldehydes bearing either electron-withdrawing or -donating groups. For example, the reaction between cyclohexanone (**2a**), *p*-methylbenzaldehyde, and aniline resulted in the formation of product **5j** with 77:23 *dr* and 91% *ee* (Table 2, entry 10).

Acyclic ketones were also examined as asymmetric Mannich donors. Excellent diastereo- (up to >99) and enantioselectivities (up to >99%) were achieved under the same reaction conditions (Table 2, entries 11 and 12). The reaction with 2-butanone (Table 2, entry 11) is highly regioselective as shown by the facts that carbon–carbon formation occurred predominantly at the more substituted α-carbon atom and no aldol product was observed in contrast to the reaction catalyzed by proline (furnished a 2.5:1 regioisomeric mixture).[6b]

To broaden the scope of this transformation, hydroxyacetone was used as a nucleophile to generate 1,2-amino alcohol derivatives. Initially, the reaction was complete within 3 h in DMSO at room temperature, typically affording only one product in higher yields and *ee* values than in DMF at –20 °C (Table 2, entries 13 and 14, 21 and 22). Under the optimized conditions, a series of aromatic aldehydes were treated with hydroxyacetone, giving rise to the corresponding amino alcohol derivatives (**5m**–**5t**) in yields of up to 99% with up to >99 *dr* and >99% *ee* (Table 2, entries 13–22). In particular, carbon–carbon bond formation

Table 2. Direct asymmetric Mannich reactions catalyzed by [EMIm][Pro] (**1**).[a]



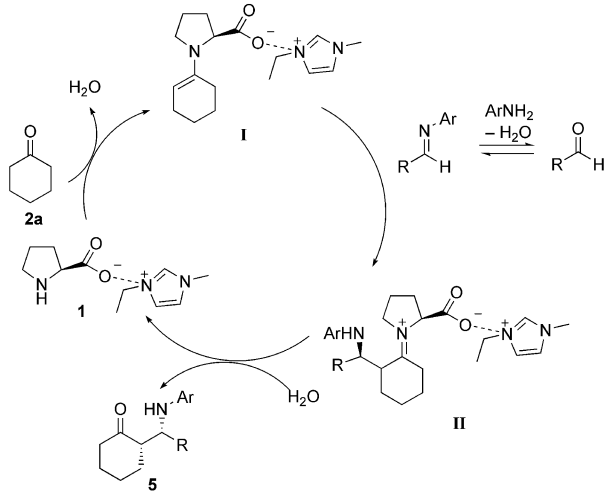
Entry	Ketone	R^3	R^4	Product	Temp. [°C]	Time [h]	Yield [%][b]	*dr* (*syn*/*anti*)[c,d]	*ee* (*syn*)[%][d]
1	**2a**	OMe	NO_2	**5a**	–20	48	62	82:18	97
2	**2a**	OMe	CN	**5b**	–20	48	65	54:46	90
3	**2a**	H	NO_2	**5c**	–20	36	56	74:26	95
4	**2a**	H	Cl	**5d**	–20	36	49	92:8	98
5	**2a**	H	CN	**5e**	–20	18	53	86:14	98
6	**2a**	H	F	**5f**	–20	36	48	89:11	96
7	**2a**	H	H	**5g**	–20	36	59	94:6	99
8	**2a**	H	Br	**5h**	–20	36	57	87:13	97
9	**2a**	H	CF_3	**5i**	–20	18	58	80:20	99
10	**2a**	H	CH_3	**5j**	–20	36	48	77:23	91
11	R^1 = H, R^2 = CH_3	OMe	NO_2	**5k**	–20	72	60	98:2	97
12	R^1 = CH_3, R^2 = CH_3	H	NO_2	**5l**	–20	48	49	>99	>99
13	R^1 = H, R^2 = OH	OMe	CN	**5m**	r.t.	3	97	95:5	99
14	R^1 = H, R^2 = OH	OMe	CN	**5m**	–20	12	90	97:3	97
15	R^1 = H, R^2 = OH	OMe	NO_2	**5n**	r.t.	3	78	94:6	95
16	R^1 = H, R^2 = OH	H	NO_2	**5o**	r.t.	3	88	91:9	96
17	R^1 = H, R^2 = OH	OMe	Cl	**5p**	r.t.	3	98	95:5	98
18	R^1 = H, R^2 = OH	OMe	F	**5q**	r.t.	3	92	94:6	97
19	R^1 = H, R^2 = OH	OMe	H	**5r**	r.t.	3	98	91:9	93
20	R^1 = H, R^2 = OH	OMe	CH_3	**5s**	r.t.	3	96	93:7	93
21	R^1 = H, R^2 = OH	OMe	Br	**5t**	r.t.	3	99	>99	98
22	R^1 = H, R^2 = OH	OMe	Br	**5t**	–20	12	91	>99	97

[a] Reaction conditions: see the Exp. Sect. [b] Isolated yields after column chromatography. [c] Determined by ^{1}H NMR spectroscopy chiral-phase HPLC. [d] Determined by chiral-phase HPLC using a Daicel Chiralpak AD-H column.

with hydroxyacetone selectively occurred at the carbon bearing the hydroxy group. Furthermore, most compounds exhibited higher stereoselectivities and yields than proline under mild conditions.[6b]

The absolute configurations of the Mannich products were determined by ^{1}H NMR analysis, from the chiral-phase HPLC retention times as well as by comparison with the literature.[6a,6b]

On the basis of the previous mechanism for proline-catalyzed Mannich reactions, we reasoned that this asymmetric Mannich reaction could also proceed by an enamine pathway because nucleophilic addition of the in situ generated enamine would be faster to an imine than to an aldehyde.[6a,6b] As shown in Scheme 2, the reaction starts with enamine **I** activation of the cyclohexanone by the proline anion and an electrostatic interaction with the imidazolium moiety of the catalyst. In a second pre-equilibrium, the aldehyde and the aniline form an imine. Then enamine-activated **I** reacts with the imine to form **II** via transition state **A**. The last step is a dehydration reaction to afford the correcponding product **5** (Figure 1). The catalyst **1** is regenerated in the subsequent step. The stereochemical results can be explained by the plausible transition state **A**. Because additional water is added and the reaction is conducted in wet solvents, the transition state is stabilized by hydrogen-bonding between the nitrogen atom of the imine and the nitrogen atom of the imidazolium moiety of the catalyst. A switch of the facial selectivity is disfavored because of steric repulsion between the Ar group of the imine and the imidazolium moiety of the catalyst.



Scheme 2. Proposed mechanism for the **1**-catalyzed asymmetric one-pot Mannich reaction.

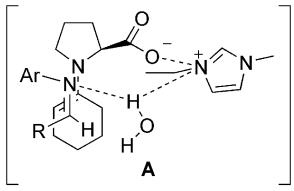


Figure 1. Proposed structure of transition state A.

Conclusions

We have reported herein the first employment of CIL [EMIm][Pro] (**1**) as a catalyst for the one-pot three-component asymmetric Mannich reaction with excellent chemo-, regio-, and enantioselectivities either under mild conditions or at a low temperature. The desired products were isolated in up to 99% yield and with up to >99 *dr* and >99% *ee*. Additionally, this catalyst is readily prepared from rather inexpensive starting materials and the reactions could be conducted in wet solvent without an inert atmosphere. The proposed mechanism and transition state have been discussed on the basis of the stereochemistry of the corresponding Mannich products. Hence, the study demonstrates that [EMIm][Pro] is a promising organocatalyst for the synthesis of enantioenriched β-amino carbonyl molecules. Further investigations of this novel transformation and the synthetic applications of [EMIm][Pro] are underway.

Experimental Section

General: Commercial reagents were used as received unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded with either a Bruker-DPX 400 or AV-400 spectrometer. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard. Coupling constants (J) are given in Hz. HRMS data were recorded with an IonSpec FT-ICR mass spectrometer with an ESI source. HPLC analysis was performed with a Shimadzu CTO-10AS instrument using a Chiralpak AD-H column purchased from Daicel Chemical Industries. All Mannich products are known compounds (see Table 3 and footnotes) and exhibited spectroscopic and analytical data in agreement with their structures. The configurations of the products were assigned by comparison with literature data (Table 3).

Synthesis of Amino Acid Ionic Liquid [EMIm][Pro] (1):[15] Under vigorous stirring, freshly distilled bromoethane (58.2 g, 0.53 mol) was added dropwise over 1 h to a solution of 1-methylimidazole (20.6 g, 0.25 mol) in ethyl acetate (60 mL). The mixture, already turbid, was heated at reflux for 6 h. When the reaction was cooled to room temp., it was filtered and the white solid filtrate ([EMIm]-Br) was washed twice with ethyl acetate (20 mL, each). After recrystallization from a mixture of acetonitrile and ether acetate, [EMIm]Br was dried on a Rotavapor for 1 h at 70 °C under 0.1 mbar of pressure: Yield: 38.4 g of white solid (80%). Then an aqueous solution of 1-ethyl-3-methylimidazolium hydroxide ([EMIm]OH) was prepared from[EMIm]Br (9.55 g, 0.05 mol) using an anion-exchange resin (201 × 7 Styrene-DVB). An aqueous solution of [EMIm]OH was added dropwise to a slight excess of an aqueous proline (6.9 g, 0.06 mol) solution. After stirring for 24 h at room temp., water was evaporated at 50 °C under vacuum. Acetonitrile (90 mL) and methanol (10 mL) were added to the residue and the mixture was stirred vigorously. The excess proline was then filtered. The filtrate was evaporated to remove the solvents and the product [EMIm][Pro] was dried in vacuo for 24 h at 80 °C; yield 9.84 g (87.5%). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 9.67 (s, 1 H, imidazole), 7.87 (s, 1 H, imidazole), 7.79 (s, 1 H, imidazole), 4.25 (q, J = 10.17 Hz, 2 H, N-CH_2), 3.90 (s, 3 H, N-CH_3), 3.32 (br., 1 H, CH pyrrolidine), 2.97–3.05 (m, 1 H, CH pyrrolidine), 2.72 (br., 1 H, CH pyrrolidine), 1.83–1.90 (m, 1 H, CH pyrrolidine), 1.69–1.74 (m, 1 H, CH pyrrolidine), 1.53–1.59 (m, 2 H, CH_2 pyrrolidine), 1.42 (t, J = 7.30, 7.30 Hz, 3 H, CH_3-CH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 176.0, 136.9, 123.5, 121.9, 61.8, 46.4, 44.0, 35.5, 30.6, 25.3, 15.1 ppm. ESI-MS: calcd. for $C_6H_{11}N_2^+$ 111.09 [M]$^+$; found 111.21; calcd. $C_5H_8NO_2^-$ 114.06 [M]$^-$; found 114.21.

General Procedure for One-Pot Three-Component Asymmetric Mannich Reaction for Solvent Screening: See Table 1. A 25 mL round-bottomed flask was charged with *p*-anisidine (25 mg, 0.2 mmol), 4-nitrobenzaldehyde (33 mg, 0.22 mol), [EMIm][Pro] (**1**; 13 mg, 0.06 mol), and solvent (0.5 mL). After being stirred vigorously for 1 h at room temperature until the imine had formed, as monitored by TLC, cyclohexanone (0.2 mL, 2 mmol) was added to the mixture. When the reaction was finished, the reaction mixture was worked up by adding saturated ammonium chloride and then extracted with AcOEt. The organic layers were washed with water, dried with Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/hexane, 1:2) to afford the adducts as a *syn*/*anti* mixture. The *anti* and *syn* diastereomers could not be discriminated by TLC.

General Procedure for the Catalytic Asymmetric Mannich Reaction at Room Temperature: See Table 2. A 25 mL round-bottomed flask was charged with *p*-anisidine or aniline (0.2 mmol, 1 equiv.), aldehyde (0.22 mol, 1.1 equiv.), [EMIm][Pro] (**1**) (0.06 mol, 0.3 equiv.), H_2O (0.2 mmol, 1 equiv.), and DMSO (0.5 mL). After being stirred vigorously for 1 h at room temperature until the imine had formed, as monitored by TLC, ketone (2 mmol, 10 equiv.) was added to the mixture. When the reaction was finished, the reaction mixture was worked up by adding saturated ammonium chloride and then extracted with AcOEt. The organic layers were washed with water, dried with Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/hexane, 1:2) to afford the adducts as a *syn*/*anti* mixture. The *anti* and *syn* diastereomers could not be discriminated by TLC.

General Procedure for the Catalytic Asymmetric Mannich Reaction at –20 °C: See Table 2. A 25 mL round-bottomed flask was charged with *p*-anisidine or aniline (0.2 mmol, 1 equiv.), aldehyde (0.22 mol, 1.1 equiv.), [EMIm][Pro] (**1**; 0.06 mol, 0.3 equiv.), and DMF (0.5 mL). After being stirred vigorously for 1 h at room temperature until the imine had been consumed, as monitored by TLC, the reaction mixture was cooled to –20 °C and ketone (2 mmol, 10 equiv.) was added to the mixture. When the reaction was finished, the reaction mixture was worked up by adding saturated ammonium chloride and then extracted with AcOEt. The organic layers were washed with water, dried with Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography (ethyl acetate/hexane, 1:2) to afford the adducts as a *syn*/*anti* mixture. The *anti* and *syn* diastereomers could not be discriminated by TLC.

Table 3. Selected ^{1}H NMR spectroscopic data for diastereoisomers and HPLC data for enantiomers of Mannich adducts.

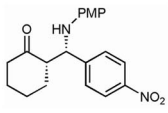
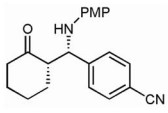
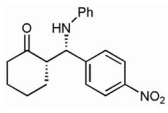
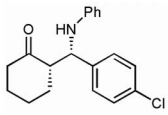
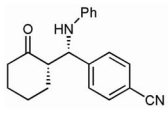
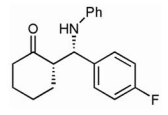
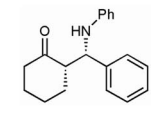
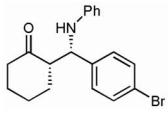
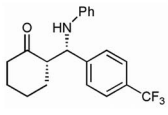
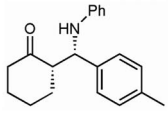
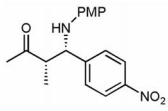
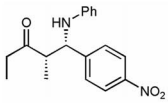
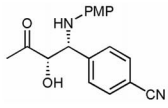
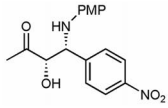
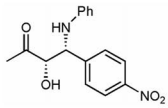
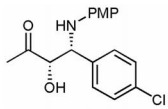
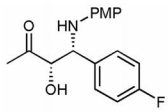
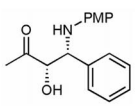
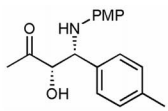
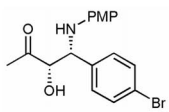
Entry	Product (2*S*,1'*R*)	^{1}HNMR ($CDCl_3$)		HPLC condition (λ = 254 nm)		*syn*	*anti*
		O=C–*CH* [ppm]	NH–*CH* [ppm]	Column	Heptane/*i*PrOH flow [mL/min]	t_R major / t_R minor [min]	t_R major / t_R minor [min]
1[8a,9c,17a]	 **5a**	2.83 (m)	4.78 (d, *J* = 4.3 Hz)	AD-H	75:25 1	19.3 / 17.9	15.8 / 14.1
2[17a]	 **5b**	2.80 (m)	4.73 (d, *J* = 4.1 Hz)	AD-H	95:5 1	105.6 / 60.7	101.5 / 63.8
3[9c]	 **5c**	2.84 (m)	4.85 (d, *J* = 4.4 Hz)	AD-H	80:20 1	17.3 / 12.3	14.8 / 9.9
4[9c]	 **5d**	2.82 (m)	4.75 (d, *J* = 4.4 Hz)	AD-H	95:5 1	13.8 / 10.6	17.1 / 12.9
5[9c]	 **5e**	2.79 (m)	4.79 (d, *J* = 4.0 Hz)	AD-H	95:5 1	57.0 / 52.1	54.9 / 30.2
6[9c]	 **5f**	2.82 (m)	4.75 (d, *J* = 4.1 Hz)	AD-H	90:10 1	11.7 / 8.7	9.5 / 7.4
7[9c]	 **5g**	2.75 (m)	4.73 (d, *J* = 4.1 Hz)	AD-H	90:10 1	10.8 / 8.5	9.3 / 8.2
8[9c]	 **5h**	2.75 (m)	4.71 (d, *J* = 4.1 Hz)	AD-H	95:5 1	19.0 / 13.9	14.9 / 11.8
9[9c]	 **5i**	2.81 (m)	4.82 (d, *J* = 4.0 Hz)	AD-H	90:10 1	8.9 / 7.1	7.2 / 6.4
10[9c]	 **5j**	2.84 (m)	4.76 (d, *J* = 4.3 Hz)	AD-H	90:10 1	8.9 / 7.4	7.6 / 6.7

Table 3. *(Continued)*.

Entry	Product (2*S*,1'*R*)	^{1}HNMR ($CDCl_3$)		HPLC condition (λ = 254 nm)		*syn*	*anti*
		O=C–*CH* [ppm]	NH–*CH* [ppm]	Column	Heptane/*i*PrOH flow [mL/min]	t_R major / t_R minor [min]	t_R major / t_R minor [min]
11[8a,6b]	 **5k**	4.76 (d, *J* = 5.0 Hz)	4.76 (d, *J* = 5.0 Hz)	AD-H	90:10 1	25.0 / 20.8	19.5 / 24.1
12[4e]	 **5l**	4.61 (d, *J* = 5.1 Hz)	4.09 (d, *J* = 6.8 Hz)	AD-H	90:10 1	13.5 / 11.6	12.6 / 10.7
13[6b,17b]	 **5m**	4.79 (d, *J* = 2.0 Hz)	4.63 (d, *J* = 4.5 Hz)	AD-H	85:15 1	28.5 / 26.4	34.0 / 21.4
14[6b,17b]	 **5n**	5.03 (d, *J* = 2.3 Hz)	4.43 (d, *J* = 2.3 Hz)	AD-H	85:15 1	34.5 / 38.6	27.5 / 22.5
15[17b]	 **5o**	5.09 (d, *J* = 2.0 Hz)	4.40 (d, *J* = 2.0 Hz)	AD-H	85:15 1	19.7 / 18.4	17.4 / 12.4
16[17b]	 **5p**	4.87 (d, *J* = 2.0 Hz)	4.38 (d, *J* = 1.9 Hz)	AD-H	85:15 1	14.9 / 12.7	14.5 / 10.9
17[17b]	 **5q**	4.80 (d, *J* = 2.5 Hz)	4.32 (d, *J* = 2.5 Hz)	AD-H	85:15 1	14.9 / 11.9	14.1 / 10.9
18[6b,17b]	 **5r**	4.81 (d, *J* = 2.6 Hz)	4.34 (d, *J* = 2.6 Hz)	AD-H	85:15 1	14.9 / 10.6	12.9 / 11.8
19[6b,17b]	 **5s**	5.42 (d, *J* = 1.6 Hz)	4.54 (d, *J* = 1.6 Hz)	AD-H	85:15 1	14.4 / 10.5	13.2 / 11.1
20 [6b,17b]	 **5t**	4.79 (d, *J* = 2.3 Hz)	4.32 (d, *J* = 2.3 Hz)	AD-H	85:15 0.6	26.6 / 22.9	19.6 / 25.8

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