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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7417–7421

Direct organocatalytic asymmetric reductive Mannich-type reactions

Gui-Ling Zhao and Armando Córdova*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

Received 18 July 2006; revised 4 August 2006; accepted 17 August 2006

Abstract—A direct asymmetric reductive Manich-type reaction that allows for the formation of three contiguous stereocenters with high chemo-, diastereo-, and enantioselectivity is presented.

The development of direct catalytic Mannich reactions has received considerable attention in recent years.[1] Such reactions have been used for the enantioselective synthesis of several important nitrogen-containing products such as amino acids, amino sugars, imino sugars, and amino alcohols.[1–12] However, there is, to our knowledge, no report of a direct catalytic asymmetric reductive Mannich-type reaction.[13] The advantage of this transformation would be that three contiguous stereocenters could be constructed via a possible organocatalytic asymmetric domino reaction sequence (Fig. 1).[14,15] Thus, by employing a metal-free asymmetric transfer hydrogenation reaction followed by a domino enantioselective Mannich-type reaction three contiguous stereocenters could possibly be assembled in a stereoselective fashion. Herein, we describe a novel amine-catalyzed direct asymmetric reductive Mannich-type reaction that furnishes the corresponding products with high chemo-, diastereo-, and enantioselectivity.

In the initial experiments, we screened different chiral amines for their ability to catalyze the List-MacMillan transfer hydrogenation reaction[16] since MacMillan's catalysts failed to catalyze the domino reductive Mannich-type reaction under our reaction conditions. To our delight, we found that chiral pyrrolidines **1** (10 mol %) catalyzed the transfer hydrogenation of aldehyde **2a** using Hantzsch ester **3** as the hydrogen source with high enantioselectivity (Table 1, entries 1 and 2).

The reactions proceeded smoothly and gave the corresponding chiral aldehydes **4** in good to high yields with 92–97% ee.[17] Encouraged by these results, we decided to perform the direct catalytic reductive Mannich-type reactions with chiral pyrrolidine **1a** as the catalyst and N-PMP-protected α-iminoglyoxylate as the electrophile (Table 2).[18]

The reactions proceeded with high chemo-, *anti*-, and enantioselectivity and gave the corresponding amino acid derivatives **5** in good yields with up to 50:1 dr and 99% ee.[19] Notably, the subsequent C–C bond-forming step led to a higher enantioselectivity of the Mannich products **5** as compared to the transfer hydrogenation products **4**. We also developed an organocatalytic enantioselective reductive Mannich protocol, which leads to other diastereomers of amino acids **5** (Scheme 1). Hence, a catalytic amount of (*R*)-proline was added to the reaction mixture together with N-PMP-protected α-iminoglyoxylate and a *syn*-selective Mannich addition was achieved with high enantioselectivity in a one-pot reaction.

For example, Mannich product **5e** was assembled in an asymmetric fashion in one-step in 80% yield with 5:1 dr and 96% ee.[20]

The absolute stereochemistry of the chiral aldehydes **4** was established by optical rotation and comparison with the literature.[16b] Hence, (*S*)-diphenylprolinols **1** catalyzed the asymmetric formation of (3*R*)-aldehydes **4a**–**4d**. The stereochemical outcome of the reaction can be explained by reaction pathway **I** (Fig. 2). Thus, efficient shielding of the *Re*-face (R = Ar) of the iminium

* Corresponding author. Tel.: +46 8 162479; fax: +46 8 154908; e-mail addresses: acordova@organ.su.se; acordova1a@netscape.net

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doi:10.1016/j.tetlet.2006.08.063

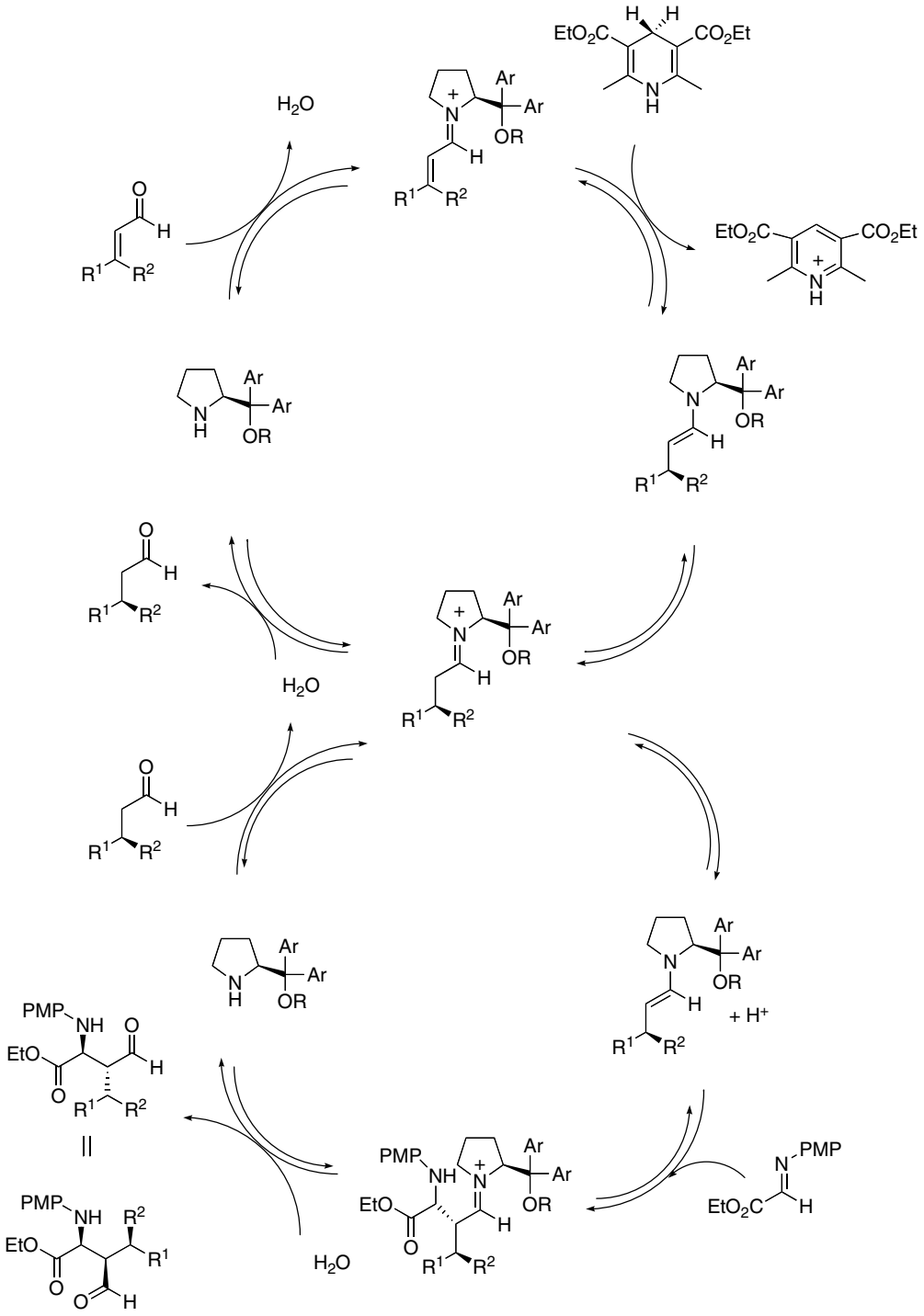


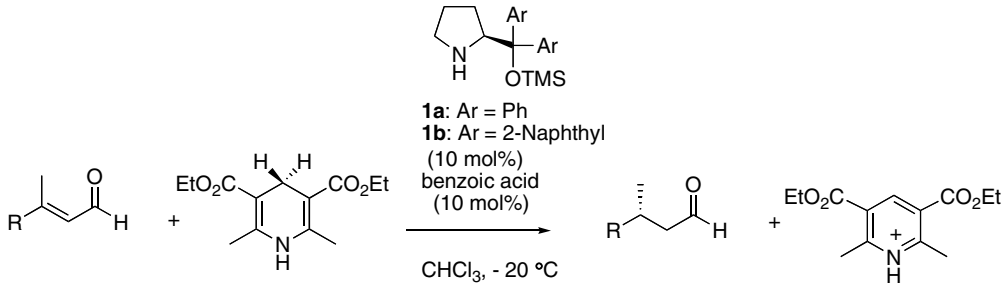
Figure 1. Catalytic cycles for the direct catalytic enantioselective reductive Mannich-type reaction.

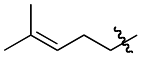
ion with *trans*-configuration led to *Si*-facial attack by the hydride, which gave the chiral enamine in transition state **II**. Next, attack on the *Si*-face of the imine with a *trans*-configuration by the chiral enamine gives the amino acid derivative (2*S*,3*R*,4*R*)-**5** with a high *anti*-selectivity.[18a]

Stabilization of the *trans*-configuration and efficient shielding of one of the faces of the chiral iminium ion and enamine, respectively, by the chiral pyrrolidine **1a** can explain the high stereoselectivity of the reaction.

In summary, we have developed a novel highly enantioselective direct organocatalytic asymmetric reductive Mannich-type reaction that furnishes three contiguous stereocenters in one step. The asymmetric reductive Mannich-type reactions which are catalyzed by simple diarylprolinol derivatives, proceed via a catalytic asymmetric domino reaction pathway and furnish amino acid

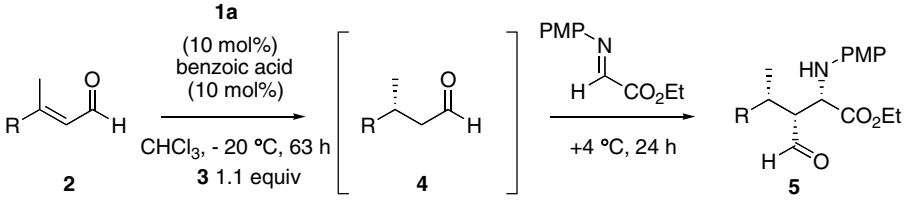
Table 1. Organocatalytic asymmetric transfer hydrogenations of aldehydes **2**



Entry	Catalyst	R	Product	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	Ph	**4a**	63	81 (99)[c]	92
2	**1b**	Ph	**4a**	63	62	90
3	**1a**	4-MeC_6H_4	**4b**	70	75	95
4	**1a**	4-BrC_6H_4	**4c**	63	58	>95
5	**1a**	2-Naphthyl	**4d**	63	75	97
6	**1a**		**4e**	63	65	n.d.[d]

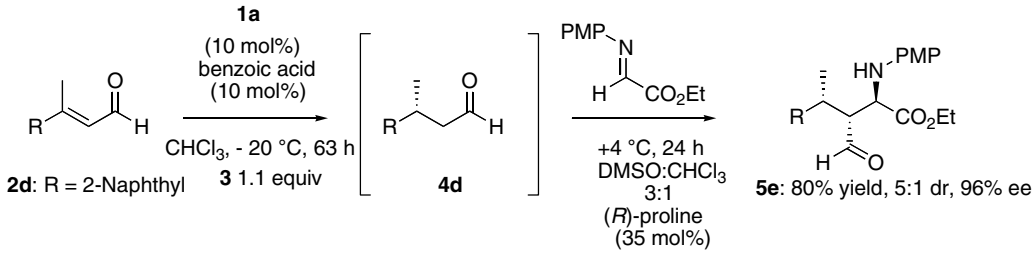
[a] Isolated yield of the pure products after silica gel chromatography.
[b] Determined by chiral-phase GC or HPLC analysis.
[c] Amount of product formed as determined by chiral-phase GC analysis.
[d] Not determined.

Table 2. Direct catalytic enantioselective reductive Mannich-type reactions



Entry	R	Product	Yield[a] (%)	Dr[b]	ee[c] (%)
1	Ph	**5a**	69	16:1	99
2	4-MeC_6H_4	**5b**	54	>10:1	96
3	4-BrC_6H_4	**5c**	58	10:1	>95
4	2-Naphthyl	**5d**	70	50:1	97

[a] Isolated yield of the pure products after silica gel chromatography.
[b] *anti*:*syn* Ratio as determined by NMR analysis of the crude product.
[c] Determined by chiral-phase HPLC analyses. PMP = *p*-methoxyphenyl.



Scheme 1. Direct catalytic enantioselective reductive Mannich-type reaction with **1a** and (*R*)-proline as the catalysts.

derivatives in good yields with up to 50:1 dr and up to 99% ee. Further studies on the development of direct catalytic enantioselective reductive intermolecular C–C bond-forming reactions and their application in catalytic asymmetric domino- and cascade-reactions are ongoing.

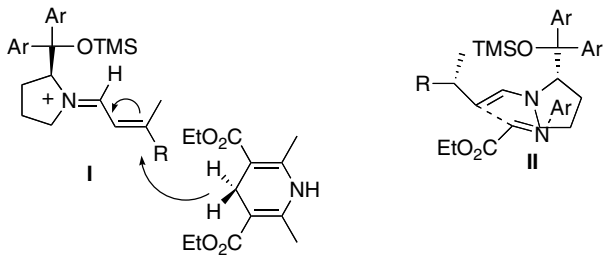


Figure 2. Proposed reaction pathway **I** and transition state **II** for the protected diarylprolinol catalyzed direct asymmetric reductive Mannich-type reaction.

Acknowledgements

We gratefully acknowledge the Swedish National Research Council, Carl-Trygger Foundation, Lars-Hierta Foundation, and Medivir AB for financial support.

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17. A solution of aldehyde **2** (0.5 mmol) and catalyst **1a** (16 mg, 10 mol %) in $CHCl_3$ (2 mL) was cooled to −20 °C. To this solution was added benzoic acid (6 mg, 0.05 mmol, 10 mol %) and Hantzsch ester (140 mg, 0.55 mmol). The reaction mixture was stirred at −20 °C for 63 h, after which the solvent was removed and the residue was purified by silica gel column chromatography (Et_2O/pentane mixtures) to give **4**.
18. Both enantiomers of α,α-diphenylprolinol and α,α-di(2-naphthyl)prolinol are commercially available and TMS protected in one step. For the use of protected diarylprolinols in *anti*-selective Mannich type reactions see: (a) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760; (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296; See also: (c) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794; (d) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703; (e) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964; (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (g) Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 99.
19. A solution of aldehyde **2** (0.5 mmol) and catalyst **1a** (16 mg, 10 mol %) in $CHCl_3$ (2 mL) was cooled to −20 °C. To this solution was added benzoic acid (6 mg, 0.05 mmol, 10 mol %) and Hantzsch ester (140 mg, 0.55 mmol). The resulting yellow suspension was stirred at −20 °C for 63 h. Next, the reaction temperature was increased to +4 °C and N-PMP-protected α-iminoglyoxylate (34 mg, 0.17 mmol) was added. The reaction mixture was stirred for 24 h at +4 °C. Next, the solvent was removed and the residue was purified by silica-gel column chromatography

(toluene/EtOAc = 20/1) to give amino acid derivatives **5** as oils. It should be mentioned that products **5** can epimerize during silica gel column chromatography. To overcome this, the aldehyde moiety of products **5** can be reduced with $NaBH_4$ to the corresponding alcohol. Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, $J = 7.2$ Hz, 3H), 1.42 (d, $J = 6.9$ Hz, 3H), 3.24 (ddd, $J = 10.2$, 3.9, 2.7 Hz, 1H), 3.40 (dd, $J = 10.2$, 6.9 Hz, 1H), 3.72 (s, 3H), 3.73–3.75 (m, 1H), 3.90 (br s, 1H), 4.04 (q, $J = 7.2$ Hz, 2H), 6.32 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 9.0$ Hz, 2H), 7.17–7.33 (m, 5H), 9.96 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.4, 38.4, 55.7, 58.2, 59.5, 61.5, 114.7, 116.1, 127.2, 127.8, 129.0, 140.9, 143.6, 153.2, 172.9, 203.8. The ee was determined by HPLC on Daicel Chiralpak As with *iso*-hexane/*i*-PrOH (97:3) as the eluent: major isomer: $t_R = 26.272$ min; minor isomer: $t_R = 50.809$ min; $[\alpha]_D^{25}$ −14.6 (*c* 1.0, $CHCl_3$). HRMS(ESI) the exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}NO_4$) requires *m*/*z* 356.1862, found *m*/*z* 356.1864. Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, $J = 7.2$ Hz, 3H), 1.38 (d, $J = 6.6$ Hz, 3H), 2.35 (s, 3H), 3.19 (ddd, $J = 10.2$, 4.5, 2.4 Hz, 1H), 3.36 (dd, $J = 10.2$, 6.9 Hz, 1H), 3.72 (s, 3H), 3.73–3.74 (m, 1H), 3.90 (br s, 1H), 4.04 (q, $J = 7.2$ Hz, 2H), 6.34 (d, $J = 8.7$ Hz, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 7.08–7.19 (m, 4H), 9.94 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.4, 21.2, 38.0, 55.8, 58.2, 59.6, 61.5, 114.7, 116.1, 127.7, 129.6, 135.7, 140.5, 141.0, 153.1, 173.0, 203.9. The ee was determined by HPLC on Daicel Chiralpak As with *iso*-hexane/*i*-PrOH (97:3) as the eluent: major isomer: $t_R = 23.161$ min; minor isomer: $t_R = 43.670$ min; $[\alpha]_D^{25}$ −24.9 (*c* 1.0, $CHCl_3$). Compound **5d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, $J = 7.2$ Hz, 3H), 1.51 (d, $J = 7.2$ Hz, 3H), 3.34 (ddd, $J = 10.4$, 4.4, 2.0 Hz, 1H), 3.58 (dd, $J = 10.4$, 6.8 Hz, 1H), 3.70 (s, 3H), 3.88 (br s, 1H), 3.99 (dq, $J = 7.2$, 2.4 Hz, 2H), 3.99–4.02 (m, 1H), 6.30 (d, $J = 9.2$ Hz, 2H), 6.61 (d, $J = 9.2$ Hz, 2H), 7.38 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.46–7.50 (m, 2H), 7.61 (s, 1H), 7.70–7.73 (m, 1H), 7.82–7.85 (m, 2H), 10.01 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.2, 38.5, 55.8, 58.2, 59.5, 61.5, 114.7, 116.0, 125.5, 126.0, 126.4, 126.9, 127.7, 127.9, 128.4, 128.8, 132.7, 133.6, 140.8, 153.1, 172.9, 203.8. The ee was determined by HPLC on Daicel Chiralpak As with *iso*-hexane/*i*-PrOH (97:3) as the eluent: major isomer: $t_R = 37.666$ min; minor isomer: $t_R = 61.701$ min; $[\alpha]_D^{25}$ −20.4 (*c* 1.0, $CHCl_3$).

20. A solution of aldehyde **2d** (98 mg, 0.5 mmol) and catalyst **1a** (16 mg, 10 mol %) in $CHCl_3$ (0.5 mL) was cooled to −20 °C. To this solution was added benzoic acid (6 mg, 0.05 mmol, 10 mol %) and Hantzsch ester (140 mg, 0.55 mmol). The resulting yellow suspension was stirred at −20 °C for 63 h. The mixture was warmed to +4 °C and DMSO (1.5 mL) was added. Then D-proline (20 mg, 0.175 mmol, 35 mol %) and N-PMP-protected α-iminoglyoxylate (34 mg, 0.17 mmol) was added. The reaction mixture was stirred for 24 h at +4 °C. Next, the reaction mixture was washed with water and extracted with EtOAc. The organic phase was collected and dried over Na_2SO_4. The solvent was removed and the crude product was purified by silica gel column chromatography (toluene/EtOAc = 20/1) to give a mixture of **5e** (5:1, 55 mg, yield 80%).