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# *anti*-Selective SMP-catalyzed direct asymmetric Mannich-type reactions: synthesis of functionalized amino acid derivatives

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**Abstract**—The first (*S*)-2-methoxymethylpyrrolidine (SMP)-catalyzed direct asymmetric Mannich-type reactions of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate are described. The reaction proceeded in a highly *anti*-selective manner (dr up to 19:1) with enantioselectivities between 74 and 92%. © 2002 Published by Elsevier Science Ltd.

The Mannich reaction is a key carbon–carbon bond forming reaction for the synthesis of β-amino ketones and aldehydes. The versatility of this reaction has been proven time and again in pharmaceutical chemistry and natural product syntheses.[1,2] Increasing demand for optically pure nitrogen containing synthons from the pharmaceutical industry has led to the search for asymmetric versions of this reaction. The first methods developed were non-catalytic and employed preformed enolates and enamines as nucleophiles with chiral auxiliary control.[3] Thereafter, catalytic asymmetric versions were reported that utilized preformed enolates for additions to imines.[4] Recently, several laboratories have reported the first direct asymmetric Mannich-type reactions wherein unmodified ketones are used as nucleophiles for the diastereo- and enantioselective preparation of chiral β-amino ketone compounds.[5] Recently, we extended the scope of this reaction to encompass the use of unmodified aldehydes as nucleophiles in Mannich-type reactions.[6]

The development of methodologies that provide for the directed synthesis of all possible stereoisomers is an important task in asymmetric catalysis and is still required for direct Mannich-type reactions. For example, in proline-catalyzed asymmetric Mannich-type reactions with unmodified ketones and aldehydes, two new stereocenters are created in a single step with high *syn*-diastereoselectivity.[5c–e,6] However, to the best of our knowledge, there is no report of a direct catalytic asymmetric Mannich type-reaction that provides for the selective synthesis of β-amino carbonyl compounds with *anti*-diastereoselectivity.

In our earlier studies concerning organocatalysis with amines,[7] we have reported chiral pyrrolidine derivatives that are superior to proline in the Michael and certain types of aldol reactions. Herein, we report the first direct (*S*)-2-methoxymethylpyrrolidine (SMP)-catalyzed asymmetric Mannich-type reactions with unmodified aldehydes that provides functionalized amino acid derivatives with high *anti*-selectivity and ee's up to 92%.

To address the issue of modifying the diastereoselectivity of the direct Mannich-type reaction, we performed a catalyst screen focused on pyrrolidine derivatives lacking the stereo-directing carboxylate of proline. In initial experiments, we screened for catalysts of the Mannich reaction of isovaleraldehyde (0.2 M) and *N*-PMP protected α-imino ethyl glyoxylate (0.1 M) in dioxane at room temperature. Catalyst loading was fixed at 20 mol%. Of all the catalysts screened, only ester and ether functionalized proline derivatives were catalysts of this reaction.[8] The commercially available derivative SMP[9] was the best catalyst and afforded the corresponding β-formyl functionalized leucine derivative **1a** in 48% yield, with dr >10:1 (*anti*/*syn*) and 69% ee (Eq. (1)).[10] Proton NMR analysis of the Mannich product **1a** revealed that the reaction proceeded with high *anti*-diastereoselectivity.[11] SMP has been reported to be an effective chiral auxiliary in Mannich-type reactions involving preformed SMP-enamines derived from ketones.[3a] In accord with our studies here, SMP directed formation of the *anti* product. After SMP, L-proline benzyl ester was the most effective catalyst

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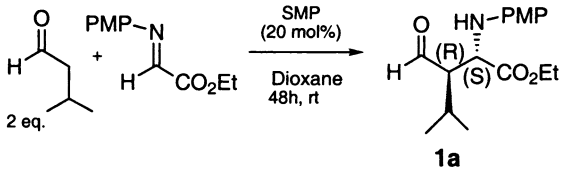
and provided **1a** in 20% yield, with dr >19:1 and 18% ee. To further optimize the SMP-catalyzed reaction a solvent screen was performed. We found that the ee of the SMP-catalyzed reaction could be increased to 82% using DMSO as a solvent.[12]




(1)

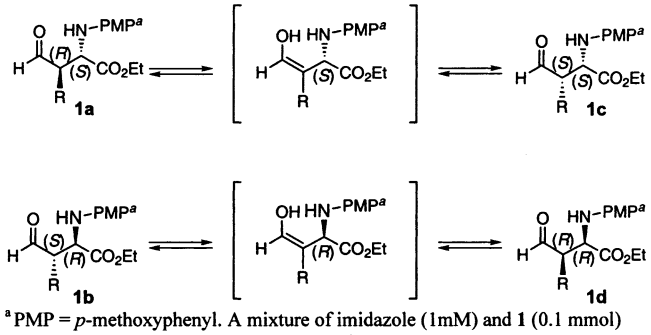
**1a**

dr >10:1, ee = 69%, yield = 48%

Encouraged by this result, several aliphatic aldehydes were reacted with *N*-PMP protected α-imino ethyl glyoxylate in DMSO as described (vide infra) to afford β-formyl functionalized amino acid derivatives **1**–**7** in moderate yield (Table 1).[13] The reactions afforded products with ee's between 74 and 92% and with a diasteromeric ratio that increased with bulkiness of the aldehyde donor in the order of Et>*n*-Bu>*i*-Pr, *n*-Pent. Significantly, aldehydes with chain lengths longer than six carbons produced a predominant diastereomer (dr >19:1) with *anti*-diastereoselectivity. Noteworthy, the reaction with the sterically demanding donor 2,2-dimethylbutyraldehyde was catalyzed by SMP to afford **2** in 57% yield, with dr >10:1 and 92% ee (entry 2),[14] whereas it was not catalyzed by L-proline. Thus, SMP can also be used as a catalyst for aldehydes that are not substrates for L-proline.

To establish the absolute configuration of the SMP-derived products, we performed an imidazole-promoted *anti–syn* isomerization of **1a** and **1b** produced by SMP and its enantiomer RMP, respectively (Scheme 1).[15] Consequently, as determined by $^1$H NMR *anti–syn* isomerization of the C-3 carbon center of **1a** changed the diastereomeric ratio to 1.1:1. Separation of the two diastereomers by chiral-phase HPLC provided known *syn*-adduct **1c** with a (2*S*,3*S*)-stereochemistry with an ee of 82%.[16] In addition, compound **1c** that had been synthesized by L-proline-catalysis was also converted (vide infra) to **1a** with a (2*S*,3*R*)-stereochemistry.[17] Furthermore, the D-proline derived *syn*-adduct **1d** was isomerized to **1b** with a (2*R*,3*S*)-stereochemistry.[18] Thus, an alternative to direct *anti* synthesis is imidazole-mediated isomerization of the proline-derived products. This route provides *anti*-diastereomers with excellent enantioselectivity, albeit reduced yields. We did not observe elimination or racemization of the C-2 carbon center of the amino acid derivatives during the reaction. Thus, SMP provides functionalized amino acid derivatives with *anti*-stereochemistry.

In the Mannich transition-state, we have assumed (*E*)-configurations of both the enamine and the imine. In the proline-catalyzed reaction (transition-state **10**), the




[a] PMP = *p*-methoxyphenyl. A mixture of imidazole (1mM) and **1** (0.1 mmol) was stirred in $CHCl_3$ at room temperature for 17h.

**Scheme 1.** Imidazole promoted isomerization of the β-formyl functionalized amino acid derivatives.

**Table 1.** SMP-catalyzed Mannich reactions of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate


| Entry | R | Yield (%)[b] | dr[c] | ee[d] | Product |
|---|---|---|---|---|---|
| 1 | *i*-Pr | 52 | 10:1 (19:1)[e] | 82 | **1a** |
| 2 | *t*-Bu | 57 | >10:1 (>19:1)[e] | 92 | **2** |
| 3 | Et | 44 | 1:1 (5:1)[e] | 75 | **3** |
| 4 | *n*-Bu | 54 | 10:1 (>10:1)[e] | 74 | **4** |
| 5 | *n*-Pent | 78 | >10:1 (>19:1)[e] | 76 | **5** |
| 6 | *n*-Hex | 68 | >19:1 (>19:1)[e] | 76 | **6** |
| 7 | *n*-$(CH_2)CH{=}CH(CH_2)_4CH_3$ *trans* | 67 | >19:1 (>19:1)[e] | 78 | **7** |

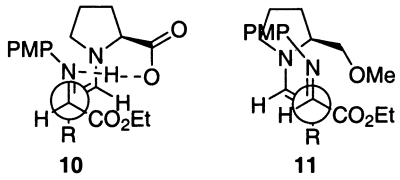
[a] PMP = *p*-methoxyphenyl. In a typical experiment, *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous DMSO ($V_{tot}$ = 5 mL), the corresponding aldehyde donor (1.0 mmol) was added followed by SMP (20 mol%) and the mixture was stirred for 2–24 h at room temperature. Following aqueous work-up with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered, and concentrated and the residue purified by column chromatography (silica, hexanes/EtOAc mixtures) to afford the corresponding Mannich addition product.

[b] Yield of isolated pure compound after column chromatography.

[c] dr = *anti*/*syn* as determined by NMR of the isolated product.

[d] The ee values of products **1a**–**7** were determined by chiral-phase HPLC analyses.

[e] dr = *anti*/*syn* as determined by NMR of the product after extraction.




[a] PMP = *p*-methoxyphenyl.

**Scheme 2.** Plausible transition-states.[a]

*si*-face of the imine is attacked by the enamine's *si*-face with a potential hydrogen bond from proline's carboxylate assisting in fixing the relative topicity of the attack. Lacking the stereodirecting carboxylate of proline, the topicity of the SMP catalyzed reaction is altered (transition-state **11**). In the SMP-catalyzed reaction the *si*-face of the imine is selectively attacked by the *re*-face of the enamine drawing the ethereal oxygen closer to the imine nitrogen, which if protonated, may provide for a favorable coulombic interaction (Scheme 2).[19] This attractive force could compensate for potential steric interactions between the pyrrolidine group of SMP and the PMP protecting group of the imine.

In conclusion, we have developed the 2-methoxymethylpyrrolidine-catalyzed direct asymmetric Mannich-type reaction with unmodified aldehydes and *N*-PMP protected α-imino ethyl glyoxylate that provides both enantiomeric forms of β-formyl functionalized amino acid derivatives. The reaction proceeds with high *anti*-diastereoselectivity and enantioselectivities up to 92%. This study indicates that the popular and highly successful chiral-auxiliary SMP can be used in a catalytic manner. Further development of this methodology is underway and will be reported in due course.

## Acknowledgements

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## References

1. (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1; (b) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044; (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (d) Denmark, S.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p. 93; (e) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH, New York, 1997.
2. The first example of the application of the Mannich reaction to natural product synthesis is attributed to Robinson in his synthesis of tropinone. See: Robinson, R. *J. Chem. Soc.* **1917**, 762.
3. See for example: (a) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *42*, 1963; (b) Palomo, C.; Oiarbide, M.; Gonzales-Rego, M. C.; Sharma, A. K.; Garcia, J. M.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063; (c) Enders, D.; Ward, D.; Adam, J.; Raabe G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981; (d) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *39*, 5287; (e) Seebach, D.; Betschart, C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593; (f) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215; (g) Arendt, M.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2639.
4. (a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450; (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180; (c) Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520; (d) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 2060; (e) Ferraris, D.; Yong, B.; Dudding, T.; Leckta, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548; (f) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67; (g) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143.
5. (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857; (b) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995; (c) Notz, W.; Saktihvel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199; (d) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336; (e) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842.
6. Córdova, A.; Watanabe, S.-i.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1866.
7. (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395; (b) Saktihvel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260; (c) Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951; (d) Betancort, J. M.; Saktihvel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 4441; (e) Betancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737; (f) Córdova, A.; Notz, W.; Barbas, C. F., III *J. Org. Chem.* **2002**, *67*, 301.
8. Screened catalysts: SMP, L-prolinol, (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, (*S*)-1-(2-pyrrolidinylmethyl)-piperidine, L-proline benzyl ester, L-proline benzyl ester HCl salt, L-proline methyl ester HCl salt.
9. This proline-derived amine was developed by Enders et al. as a chiral auxiliary and is commercially available in both enantiomeric forms. For an excellent review of its use in asymmetric synthesis, see: Enders, D.; Klatt, M. *Synthesis* **1996**, 1403.
10. L-Prolinol, (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, (*S*)-1-(2-pyrrolidinylmethyl)piperidine and the hydrochloric salts of proline methyl or benzyl esters were not catalysts of this reaction.
11. *Ethyl (2S,3R)-3-formyl-2-(p-methoxyphenylamino)-4-methylpentanoate (**Ia**)*: $^1$H NMR (250 MHz): $\delta$ 1.08 (d, 3H, $J=7.0$ Hz, $CHCH_3$), 1.12 (d, 1H, $J=7.0$ Hz, $CHCH_3$), 1. 21 (t, 3H, $OCH_2CH_3$), 2.11 (m, 1H), 2.59 (m, 1H), 3.74 (s, 3H, $OCH_3$), 3.85 (bs, 1H, ArN*H*CH), 4.15 (m, 2H, $OCH_2CH_3$), 4.36 (bs, 1H), 6.66 (d, 2H, $J=7.0$

Hz, Ar*H*), 6.77 (d, 2H, $J=7.0$ Hz, Ar*H*), 9.75 (d, 1H, $J=3.3$ Hz, CHC*H*O); $^{13}$C NMR (125 MHz): $\delta$ 203.6, 173.4, 153.5, 140.7, 116.2, 115.1, 61.7, 59.9, 57.5, 55.9, 27.8, 21.6, 19.5, 14.4; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda=254$ nm); $t_R$ (major) = 7.00 min; $t_R$ (minor) = 10.84 min; $[\alpha]_D=-16.5$ (*c* 1.2, $CH_2Cl_2$). HRMS calcd for $C_{16}H_{23}NO_4$ (M+Na$^+$): 316.1519. Found: 316.1521.

12. Reactions performed in THF, EtOH, EtOAc and $CH_3CN$ were very slow.
13. In a typical experiment, *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous dioxane or DMSO and the corresponding aldehyde donor (1.0 mmol) was added, followed by SMP (20 mol%). The total volume of the reaction mixture was 5 mL. After stirring for 2–24 h at room temperature, the mixture was worked-up by addition of half-saturated ammonium chloride solution and extraction with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate mixtures) to afford the corresponding Mannich addition product. The ee's of all products were determined by chiral-phase HPLC analysis.
14. *Ethyl (2S,3R)-3-formyl-2-(p-methoxyphenylamino)-4,4-dimethylpentanoate* (**2**): $^1$H NMR (250 MHz): $\delta$ 1.15 (s, 9H, $J=7.0$ Hz, CHC$H_3$), 1. 19 (t, 3H, OCH$_2$C$H_3$), 2.77 (dd, $J=7.8$ Hz, $J=3.3$ Hz, 1H), 3.74 (s, 3H, OC$H_3$), 3.85 (bs, 1H, ArN*H*CH), 4.15 (m, 2H, OC$H_2$CH$_3$), 4.34 (dd, $J=18.3$ Hz, $J=6.6$ Hz, 1H), 6.65 (d, 2H, $J=9.7$ Hz, Ar*H*), 6.77 (d, 2H, $J=9.7$ Hz, Ar*H*), 9.76 (d, 1H, $J=3.3$ Hz, CHC*H*O); $^{13}$C NMR (125 MHz): $\delta$ 203.3, 173.6, 153.4, 140.7, 116.1, 115.1, 62.8, 61.6, 56.5, 55.9, 33.4, 29.2, 14.3; HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda=254$ nm); $t_R$ (major) = 11.78 min; $t_R$ (minor) = 16.22 min; $[\alpha]_D=-22$ (*c* 2.3, $CH_2Cl_2$). HRMS calcd for $C_{17}H_{25}NO_4$ (M+H$^+$): 308.1856. Found: 308.1858.
15. Ward, D. E.; Sales, M.; Sasmal, P. K. *Org. Lett.* **2001**, *3*, 3671.
16. NMR was in accordance with the previously reported (2*S*,3*S*)-enantiomer **1c** (Ref. 6). HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH = 99:1, flow rate 1.0 mL/min, $\lambda=254$ nm); $t_R=8.82$ min. The (2*R*,3*R*)-enantiomer **1d** has a $t_R=13.24$ min under the same HPLC conditions.
17. Imidazole promoted *anti–syn* isomerization of **1c** with an ee of 93% and a dr of 10:1 provided a diastereomeric mixture with a *anti*/*syn* ratio of 1:1.1. Removal of imidazole by column chromatography provided **1a** in 95% yield with a dr of 3:1 and an ee of 93%.
18. Imidazole promoted *anti–syn* isomerization of **1c** with an ee of 93% and a dr of 10:1 provided a diastereomeric mixture with a *anti*/*syn* ratio of 1:1.1. Removal of imidazole by column chromatography provided **1a** in 95% yield with a dr of 3:1 and an ee of 93%.
19. Electrostatic interactions of this type have been postulated in non-catalytic asymmetric Mannich-type reactions with preformed SMP enamines. See: Ref. 1b and Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689.