Unexpected Beneficial Effect of *ortho*-Substituents on the (*S*)-Proline-Catalyzed Asymmetric Aldol Reaction of Acetone with Aromatic Aldehydes

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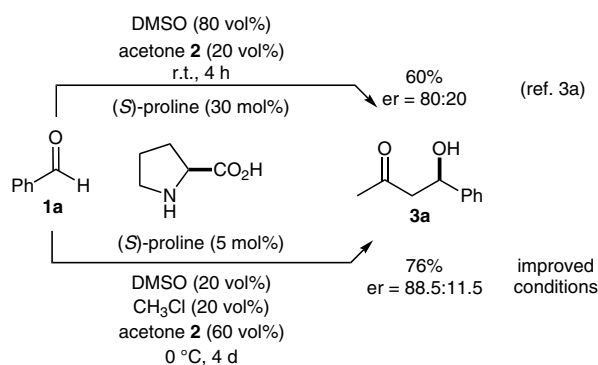*Received: 04.02.2014; Accepted: 16.02.2014*

Abstract: An intriguing effect of electronegative 2,6-substituents on the stereochemical outcome of (*S*)-proline-catalyzed aldol reactions between benzaldehyde derivatives and acetone is reported. Remarkably high enantioselectivities can be achieved with such substrates.

Key words: aldehyde, aldol reaction, asymmetric catalysis, organocatalysis, proline

Asymmetric aldol reactions are amongst the most useful carbon–carbon bond-forming reactions in organic synthesis.[1,2] The full potential of (*S*)-proline as catalyst for intermolecular aldol reactions was realized in 2000, when we reported the first organocatalytic enantioselective aldol reaction between unmodified ketones and aldehydes.[3] This report provided proof of principle for the rational use of small organic molecules as stereoselective catalysts,[4,5] at the same time highlighting the potential of organocatalysis in natural product synthesis.[6]

Aromatic aldehydes have been widely studied as substrates in amine-catalyzed aldol reactions. In our initial work,[3a] only moderate enantioselectivities were achieved (Scheme 1). We were interested in improving both yield and enantioselectivity of this reaction, by further optimizing the reaction conditions, while retaining (*S*)-proline as catalyst.

Using benzaldehyde (**1a**) as model substrate, we extensively screened different parameters such as solvent, tem-

perature, water content,[7] or amount of catalyst (see Supporting Information for details). Under our newly developed conditions, the corresponding aldol product (*R*)-**3a**[8] was obtained with 76% yield and an enantiomeric ratio of 88.5:11.5. This represents a substantial improvement compared to the results reported in our initial work (62% yield, er = 80:20; Scheme 1).[3a,9] The mixture of DMSO and CHCl$_3$ (1:1) used as cosolvent proved to be crucial, both increasing the reaction rate and minimizing side reactions, such as aldol condensation.

Interestingly, when *ortho*-substituted aromatic aldehydes were used as substrates, an increase of enantioselectivity with growing substituents was observed (Cl < Br < I; Table 1).

Table 1 Aldol Reaction of *ortho*-Halogenated Benzaldehyde Derivatives **1** with Acetone **2**[a]

Entry	Product	Yield 4 (%)	er[b]
1[c]	**4a**	78	85:15
2	**4b**	81	87.5:12.5
3	**4c**	81	91:9

[a] Reaction conditions: aldehyde **1** (0.5 mmol), acetone **2** (0.75 mL), CHCl$_3$ (0.25 mL), DMSO (0.25 mL), and (*S*)-proline (5 mol%) were stirred at 0 °C for 4 d.
[b] Determined by HPLC using a chiral stationary phase.
[c] Approximately 10% of the double aldol addition was observed by ^{1}H NMR analysis of the crude reaction mixture using an internal standard.

Scheme 1 Comparison of original and newly optimized conditions for the (*S*)-proline-catalyzed aldol reaction between benzaldehyde (**1a**) and acetone (**2**)

Yields were generally good and only traces of the corresponding enone, derived from the competitive aldol condensation pathway, could be observed. With the highly reactive 2-chlorobenzaldehyde, approximately 10% of the product resulting from double aldol addition were observed as side product (Table 1, entry 1).[10]

Based on this initial observation, we speculated that increasing the steric bulk of the benzaldehyde derivative could lead to an increased enantioselectivity. Based on this hypothesis we studied a variety of *ortho*-substituted benzaldehyde derivatives (Table 2).

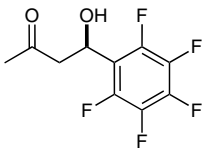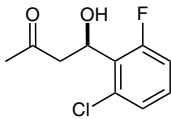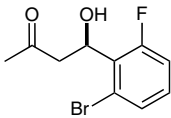**Table 2** Aldol Addition of *ortho*-Disubstituted Aromatic Aldehydes **1** with Acetone[a]
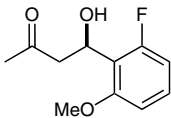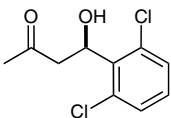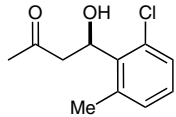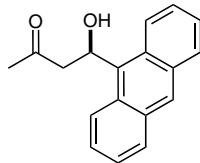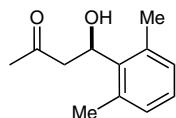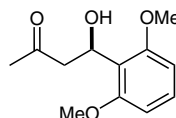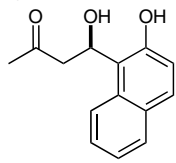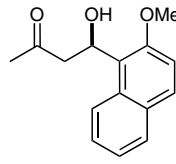
Entry	Product	Yield **5** (%)	er[b]
1	**5a**	84	93:7
2[c]	**5b**	73	97:3
3[c]	**5c**	60	98.5:1.5
4	**5d**	81	95:5
5	**5e**	82	99:1
6[c]	**5f**	69 (82)[d]	99:1

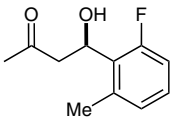**Table 2** Aldol Addition of *ortho*-Disubstituted Aromatic Aldehydes **1** with Acetone[a] (continued)

Entry	Product	Yield **5** (%)	er[b]
7	**5g**	87	99.5:0.5
8	**5h**	64	93.5:6.5
9[e]	**5i**	51	88:12
10[e]	**5j**	25[f]	98.5:1.5
11	**5k**	86	66:34
12	**5l**	60	99.5:0.5

[a] Reaction conditions: aldehyde **1** (0.5 mmol), acetone **2** (0.75 mL), CHCl₃ (0.25 mL), DMSO (0.25 mL), and (S)-proline (5 mol%) were stirred at 0 °C for 4 d.
[b] Determined by HPLC with a chiral stationary phase.
[c] Varying amounts of the double aldol product were observed by ¹H NMR analysis of the crude reaction mixture.
[d] The reaction was performed on a 94 mmol scale.
[e] 30 mol% of catalyst were used.
[f] 40% of the corresponding enone were obtained.

The pentafluorobenzaldehyde-derived aldol product **5a** was obtained with high yield and 93:7 enantiomeric ratio (Table 2, entry 1). 2-Chloro-6-fluorobenzaldehyde also reacted smoothly with the enantioselectivity increasing to

97:3 enantiomeric ratio (Table 2, entry 2). As expected, an even more pronounced effect was observed when a bromo substituent was present, and product **5c** was obtained with very high enantioselectivity (Table 2, entry 3). Surprisingly, when the effect of methyl and methoxy groups was compared, the sterically more demanding methyl substituent led to a less enantioselective reaction (Table 2, entries 4 and 5). This finding suggested that apart from the steric properties of the *ortho* substituent(s), electronic properties (presence of electronegative heteroatoms in the *ortho* substituent) might also influence the reaction outcome. When chlorine was present instead of fluorine (cf. products **5b** with **5f**, and **5d** with **5g**) higher enantioselectivities were obtained (Table 2, entries 6 and 7).

In the case of 9-anthraldehyde, aldol product **5h** was obtained with 93.5:6.5 enantiomeric ratio and moderate yield. In this particular case the solvent system employed plays an important role in the reactivity and selectivity of the process.[11] Lower enantioselectivity was obtained in the case of 2,6-dimethylbenzaldehyde (Table 2, entry 9). When we used 2,6-dimethoxybenzaldehyde, a very electron-rich and unreactive aldehyde the desired product **5j** was isolated in 25% yield and with an enantiomeric ratio of 98.5:1.5. In this case 30 mol% of catalyst were required and a considerable amount of the aldol condensation product was observed (Table 2, entry 10).

It is important to highlight that it is possible to scale up this process. High yield and identical enantioselectivity were obtained when compound **5f** was synthesized on a 94 mmol scale (Table 2, entry 6). Importantly most of the proline used could be reisolated.[12]

Finally we compared the behavior of two seemingly similar substrates, 2-hydroxy- and 2-methoxynaphthaldehyde, under our best conditions (Table 2, entries 11 and 12). The 2-hydroxynaphthaldehyde-derived aldol adduct **5k**, which is in equilibrium with its closed lactol form, has been reported to form with poor enantioselectivity (63:37 er) when using *trans*-4-OH-(*S*)-proline as catalyst.[13]

Similarly we obtained a disappointing enantiomeric ratio for **5k** (66:34). In contrast, when 2-methoxynaphthaldehyde was used, we were pleased to obtain aldol product **5l** with exceptionally high enantiomeric excess, as would be expected considering the positive effect of *ortho* substituents presented herein. This pronounced difference in enantiocontrol can be rationalized by invoking an intramolecular hydrogen bond in 2-hydroxynaphthaldehyde, which could facilitate the attack of the enamine on the aldehyde.[14] This activation stands in direct competition with the coordination of the aldehyde by the catalyst's carboxylic acid moiety, which is known to be crucial for the stereoselectivity of the process.[15] To support this proposal, we conducted the two reactions using pyrrolidine (5 mol%) as catalyst. We found that the reaction of 2-hydroxynaphthaldehyde proceeds four times faster than that of 2-methoxynaphthaldehyde, which indicates that internal activation in present in this substrate.

A possible rationalization of the effect exerted by *ortho* substituents is depicted in Figure 1. The steric demand of the substituent(s) is expected to result in an increasingly perpendicular orientation of the aromatic ring and the aldehyde moiety. When comparing the Houk–List transition state models leading to the major (**A**) and minor (**B**) enantiomers,[16] a steric clash between the *ortho* substituent(s) and the incoming enamine is present in **B**. In addition to this steric factor, when R contains an electronegative heteroatom, the charge densities on this atom and on the carboxylate moiety of the catalyst will lead to an additional electronic repulsion in the disfavored transition state **B**. In concert, these effects lead to the substantial increase of enantioselectivity reported in this study.
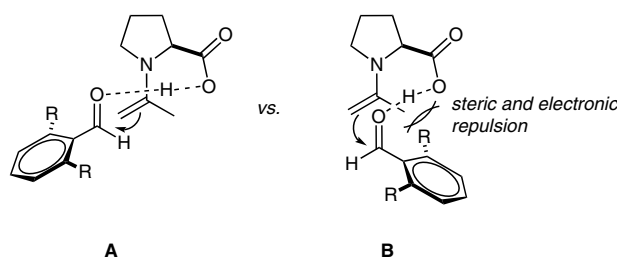

Figure 1   Rationalization of the observed effect of *ortho* substituents

In summary we have found a remarkable effect on the enantiocontrol of the aldol reaction between acetone and aromatic aldehydes caused by *ortho* substituents on the aldehyde. Using (*S*)-proline as catalyst *ortho*,*ortho*-disubstituted aromatic aldehydes react smoothly with acetone yielding the corresponding aldol adducts with exceptional enantioselectivities. A rationalization of the observed effect based on both the steric and electronic properties of the substituents was provided and is in agreement with the widely accepted stereochemical model for this type of reactions.

(*S*)-Proline (0.025 mmol) was added to a solution of the corresponding aldehyde **1** (0.5 mmol) in acetone (0.75 mL), CHCl$_3$ (0.25 mL), and DMSO (0.25 mL) and was stirred at 0 °C for 4 d. After this time, H$_2$O was added to the reaction mixture, which was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The hydroxy ketone was isolated by column chromatography (silica, hexane–EtOAc).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Mahrwald, R. In *Modern Aldol Reactions*; Wiley-VCH: Weinheim, **2004**.

(2) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(3) (a) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573.

(4) For recent reviews, see: (a) Berkessel, A.; Gröger, H. In *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**. (b) List, B. *Chem. Commun.* **2006**, 819. (c) Dalko, P. I. In *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(5) Some selected examples of designed catalysts: (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (b) Szöllősi, G.; London, G.; Baláspiri, L.; Somlai, C.; Bartók, M. *Chirality* **2003**, *15*, 90. (c) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (d) Guo, H.-M.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2005**, 1450. (e) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, 4287. (f) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (g) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (h) Guizetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754. (i) Raj, M.; Vishnumaya Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097.

(6) Wasser, M. In *Asymmetric Organocatalysis in Natural Product Syntheses*; Springer: Wien, **2012**.

(7) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891.

(8) The absolute stereochemistry was assigned by comparison of the specific rotation with the one reported in the literature: Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319.

(9) Aromatic aldehydes commonly used in asymmetric aldol transformations were also tested, obtaining moderate yields and enantioselectivities. See Supporting Information, compounds **3b–j**.

(10) (a) Gryko, D.; Lipinski, R. *Eur. J. Org. Chem.* **2006**, 3864. (b) Luo, S.; Li, J.; Xu, H.; Zhang, L.; Cheng, J.-P. *Org. Lett.* **2007**, *9*, 3675. (c) Hu, S.; Jiang, T.; Zhang, Z.; Zhu, A.; Han, B.; Song, J.; Xie, Y.; Li, W. *Tetrahedron Lett.* **2007**, *48*, 5613.

(11) Compound **5h** has been described previously in literature obtained from the (*S*)-proline-catalyzed aldolization. It was obtained in 10% yield after 2 d of reaction time using 30 mol% of catalyst, see: Zhou, Y.; Shan, Z. *J. Org. Chem.* **2006**, *71*, 9510.

(12) 87% of (*S*)-proline was reisolated and reused in different experiments, maintaining its catalytic activity.

(13) Ramachary, D. B.; Sakthidevi, R. *Chem. Eur. J.* **2009**, *15*, 4516.

(14) Ji, C.; Peng, Y.; Huang, C.; Wang, N.; Jiang, Y. *Synlett* **2005**, 986.

(15) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755.

(16) (a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (b) Bahamanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.