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The Proline-Catalyzed Direct Asymmetric Three-Component Mannich Reaction: Scope, Optimization, and Application to the Highly Enantioselective Synthesis of 1,2-Amino Alcohols

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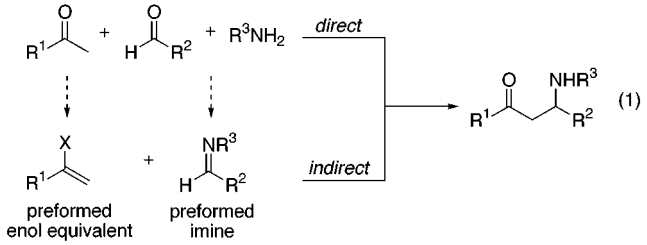
Abstract: We have developed proline-catalyzed direct asymmetric three-component Mannich reactions of ketones, aldehydes, and amines. Several of the studied reactions provide β-amino carbonyl compounds (Mannich products) in excellent enantio-, diastereo-, regio-, and chemoselectivities. The scope of each of the three components and the influence of the catalyst structure on the reaction are described. Reaction conditions have been optimized, and the mechanism and source of asymmetric induction are discussed. We further present application of our reaction to the highly enantioselective synthesis of 1,2-amino alcohols.

Introduction

The vast majority of nature's molecules, including proteins and nucleic acids and most biologically active compounds, contain nitrogen. Consequently, developing new synthetic methods for the construction of nitrogenous molecules has defined the frontiers of organic synthesis since its very beginning.[1] The Mannich reaction has long been a very useful platform for the development of such methodologies.[2] Originally, this reaction produces β-amino-carbonyl compounds from three components, an amine and two different carbonyl species. As in the related "direct aldol reaction", using unmodified carbonyl compounds in direct Mannich reactions has caused severe selectivity problems. Such limitations have been partially overcome through the development of *indirect* Mannich variants that assign the specific role of each carbonyl component in the reaction mixture. However, additional synthetic operations result from the requirement to preform intermediates such as imine and enol equivalents (eq 1).



Several asymmetric Mannich-type reactions have been described in recent years. However, catalytic enantioselective variants are rare and typically require preformation of both imine and enol equivalents.[3] We have recently discovered proline-catalyzed asymmetric three-component Mannich reactions between ketones, aldehydes, and amines that furnish Mannich products in up to 99% ee.[4] The scope of this novel catalytic asymmetric carbon−carbon-bond-forming multicomponent reaction and its application to the highly enantioselective synthesis of 1,2-amino alcohols are described herein.

Asymmetric Mannich Reactions. Mannich-type reactions that produce enantiomerically enriched products have been reported. Several indirect variants use stoichiometric amounts of chiral enol equivalents, including enamines,[5] silyl enolethers,[6] boron enolates,[7] and lithium enolates.[8] Alternatively, chiral imine equivalents have been utilized.[9] Double stereodifferentiating asymmetric Mannich-type reactions that require two different stoichiometric chiral controllers have also been developed.[10,11]

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(1) Wöhler's synthesis of (nitrogenous) urea is generally considered as the birth of of organic synthesis: Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.

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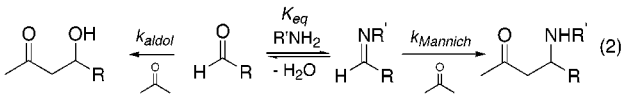
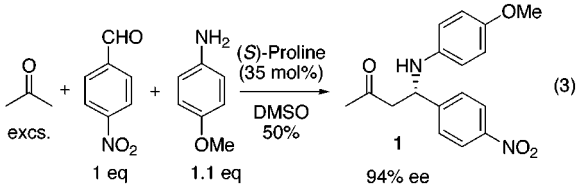
Enantioselective catalysis of the Mannich reaction is a rather new concept. First examples were described by Tomioka,[12] Kobayashi,[13] Sodeoka,[14] and Lectka.[15] All of these variants use preformed imine *and* enol equivalents combined with a metal-based catalyst.[16,17] A direct catalytic enantioselective three-component Mannich reaction of propiophenone, paraformaldehyde, and pyrrolidine has been described by Shibasaki et al.[3] However, although the product is formed in encouraging enantioselectivity (64%), the yield is poor (16%).[18]

Proline-Catalysis. Asymmetric catalysis with proline was first realized in the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[19] an enantiogroup-differentiating aldol cyclization. We have recently discovered proline-catalyzed direct asymmetric intermolecular aldol reactions of ketones with aldehydes.[20] The basis of proline-catalysis in these reactions is the facile in situ generation of chiral enolate equivalents (enamines) from ketones and aldehydes. This particular type of catalysis, *enamine catalysis*,[21] represents a way of merging enolization and enantioselective bond construction in enolate-electrophile-type reactions.[22] We expected the presumed proline enamines to not only react with carbonyl compounds in aldol reactions or with activated olefins in Michael reactions,[23,24] but also with imines in Mannich reactions. We further hoped to conduct proline-catalyzed Mannich reactions as direct three-component reactions of ketones, aldehydes, and amines without prior imine formation. Direct aldol and Mannich reactions typically compete if imines and enol equivalents are not preformed, and their rates depend on the equilibrium ratio between the aldehyde and the imine (K_{eq}) and on their respective rate constants (k_{aldol} vs $k_{Mannich}$) (eq 2).



(2)

Support for our initial reaction design involving ketones, aldehydes, and anilines came from elegant studies by Kobayashi et al.[25] In addition, we have estimated the imine/aldehyde equilibrium ratio in the reaction of *p*-nitrobenzaldehyde (0.1 M) with *p*-anisidine (0.1 M) in DMSO-d_6 from ^{1}H NMR to be around 1.[26] Therefore, both reaction pathways seemed feasible. In our initial experiment, we found (*S*)-proline to catalyze the direct asymmetric Mannich reaction of *p*-nitrobenzaldehyde, *p*-anisidine, and acetone to give the expected product (**1**) in 50% yield (eq 3).[4] The corresponding aldol product was formed as well under those conditions but in much lower yield (<20%). Most importantly, excellent enantioselectivity was observed (94% ee). This reaction constitutes the first catalytic asymmetric three-component Mannich reaction of a free aldehyde with an unmodified ketone and an amine. It is also the first organocatalytic enantioselective Mannich reaction.



(3)

Results and Discussion

Ketone Component. Other ketones can readily be used in proline-catalyzed Mannich three-component reactions with excellent results (Table 1). Reacting three different ketones (butanone, methoxyacetone, and hydroxyacetone, each 20 vol %) with *p*-anisidine (1.1 equiv) and *p*-nitrobenzaldehyde (1 equiv) furnished the desired products in high yields (92−96%) and excellent ee's of up to >99%. In addition, excellent diastereoselectivities were observed. High regioselectivities generally favoring products resulting from the higher substituted α-side of the ketone were found with oxygenated ketones, while butanone furnished a 2.5:1 regioisomeric mixture. The chemoselectivity in these reactions was also high, and essentially no aldol product was formed in all three cases.

Aldehyde Component. We have used various structurally diverse aldehydes in three-component Mannich reactions with *p*-anisidine and acetone (Table 2). In contrast to our observations in proline-catalyzed aldol reactions and in contrast to any other catalytic asymmetric Mannich reaction disclosed so far, α-unbranched aldehydes were found to be efficient substrates in these reactions. Here, acetone instead of the commonly used DMSO was used as solvent (Table 2, entries 1−5).[27] Excellent enantioselectivities yet modest yields were obtained in reactions of aromatic aldehydes.[28] α-Branched aldehydes, for example isobutyraldehyde, could also be used.

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(13) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186.
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(16) For a more recent example, see: Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271−2274.
(17) For a catalytic asymmetric vinylogous Mannich reaction, see: Martin, S. F.; Lopes, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949−8953.
(18) Very recently Jørgensen et al. developed a new catalytic asymmetric Mannich reaction of activated ketones with preformed imines. Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995−2997.
(19) (a) Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds. German Patent DE 2102623, Jul 29, 1971. (b) Eder, U.; Sauer, G.; Wiechert, R. Optically Active 1,5-Indanone and 1,6-Naphthalenedione. German Patent DE 2014757, Oct 7, 1971. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 496. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
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(21) List, B. *Synlett* **2001**, 1675−1686.
(22) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453.
(23) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425.
(24) List, B.; Castello, C. *Synlett* **2001**, 1687−1689.
(25) For example, see: Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965−1967.
(26) This equilibrium is influenced by the water concentration, and the commercially available d_6−DMSO samples we use are typically 0.1 M in H_2O.
(27) Proline can be recovered in these reactions by filtration (see Experimental Section). Alternatively, 20 vol % acetone in chloroform can be used.
(28) After our results were published, others submitted a manuscript describing related observations: Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199−201.

Table 1. Three-Component Mannich Reactions with Different Ketones (PMP = *p*-Methoxyphenyl, Ar = *p*-$O_2NC_6H_4$)

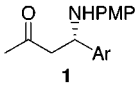
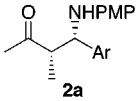
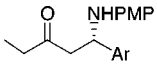
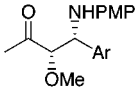
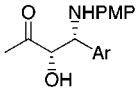
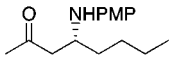
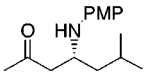
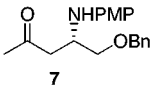
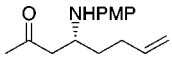
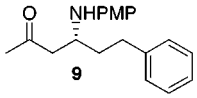
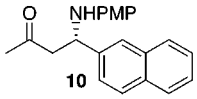
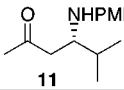
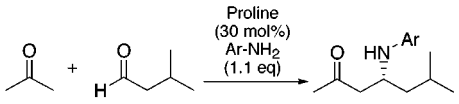
Ketone	Products	Yield %	de %	ee %
	 **1**	50	-	94
	 **2a**	96 (2a : 2b = 2.5:1)	>95	99
	 **2b**		-	94
	 **3**	93	>95	98
	 **4**	92	>95	>99

Table 2. Three-Component Mannich Reactions with Different Aldehydes

Entry	Product	Yield %	ee %
1	 **5**	74	73
2	 **6**	90	93
3	 **7**	82	75
4	 **8**	60	80
5	 **9**	80	93
6	 **10**	35	96
7	 **11**	56	70

Amine Component. The amine component is crucial to the synthetic utility of Mannich productst. A desirable feature is an easily removable, "traceless" nitrogen substituent to allow for further manipulations at the amine portion. We have studied four different aniline derivatives: *p*-anisidine, *o*-anisidine, *p*-chloroaniline, and *o*-aminophenol (Table 3). Clearly, yields and ee's are optimal with *p*-anisidine, which introduces the *p*-methoxyphenyl (PMP) group into the product. The PMP group can be removed under oxidative conditions (vide infra); *p*-anisidine can therefore be considered a synthetic ammonia equivalent in these reactions.

Table 3. Tested Aniline Derivatives



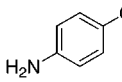
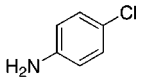
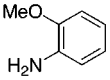
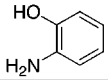
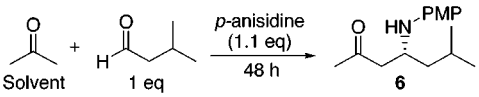
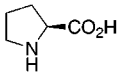
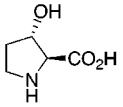
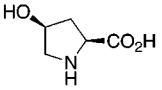
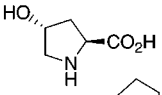
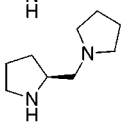
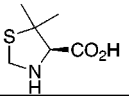
Entry	Ar-NH_2	Yield %	ee %
1		90	93
2		55	84
3		43	< 10
4		51	< 10

Table 4. Selection of Studied Catalysts



Entry	Catalyst (35 mol%)	Yield %	ee %
1		90	93
2		56	76
3		22	12
4		22	15
5		26	0
6		60	16

Catalyst. In our earlier studies of amine-catalyzed direct asymmetric aldol reactions we noticed that, although several other catalysts could be identified, proline typically gave superior results regarding yield and enantioselectivity.[20] Although we investigated only a limited number of catalysts so far, the trend seems to be similar in the Mannich reaction. Of the commercially available proline derivatives we studied in the reaction leading to ketone **6**, proline is clearly the best (Table 4).

Reaction Optimization. We studied the effect of catalyst loading and ketone-donor amount on reaction time, yield, and ee. While the use of a relatively large amount (35 mol %) of inexpensive proline in our original study may be justified,

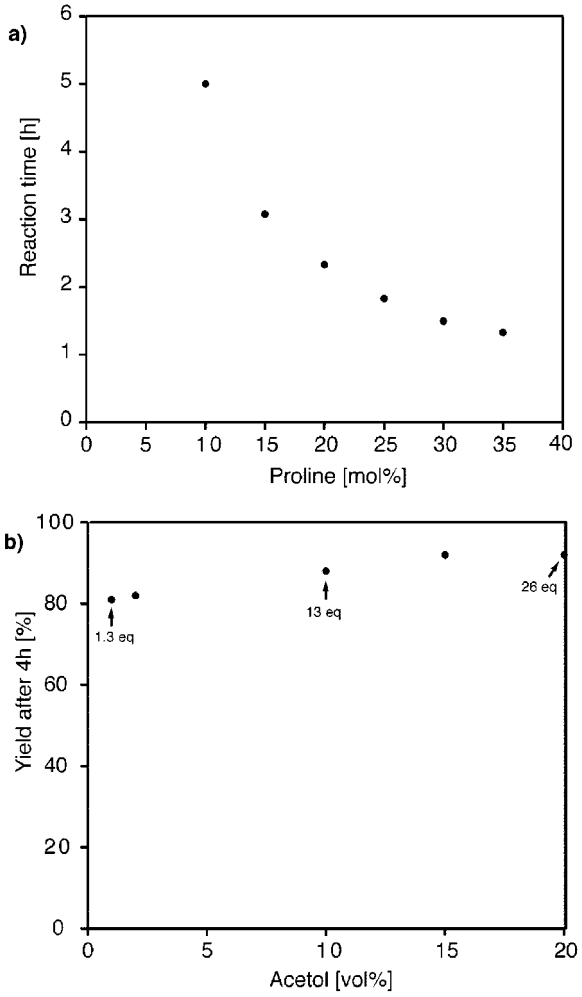
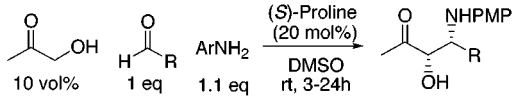
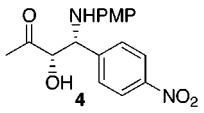
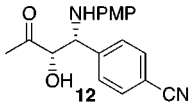
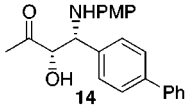
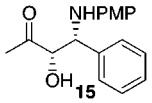
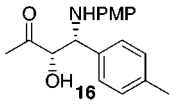
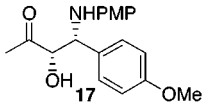
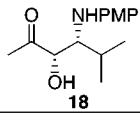


Figure 1. Optimization of catalyst loading and ketone amount in the reaction of *p*-nitrobenzaldehyde with *p*-anisidine and hydroxyacetone (acetol). (a) Variation of catalyst concentration. Conditions: 1 equiv of aldehyde, 1.1 equiv of *p*-anisidine, 10 vol % acetol/DMSO. (b) Variation of acetol concentration. Conditions: 1 equiv of aldehyde, 1.1 equiv of *p*-anisidine, 20 mol % proline.

Table 5. Catalytic Enantioselective Synthesis of *syn*-1,2-Amino Alcohols



Entry	Product	Yield %	dr	ee %
1	 **4**	92	20:1	>99
2	 **12**	88	15:1	99
3	 **13**	90	15:1	98
4	 **14**	79	8:1	94
5	 **15**	83	9:1	93
6	 **16**	85	5:1	86
7	 **17**	88	3:1	61
8	 **18**	57	17:1	65

reducing catalyst loading would certainly constitute an improvement. In addition, we originally used a large excess of the ketone donor, which again may be justified in the case of inexpensive and readily available ketones but might be considered problematic if more expensive and complex ketones should need to be employed. To improve these two parameters we studied the reaction of hydroxyacetone with *p*-nitrobenzaldehyde and *p*-anisidine to give Mannich product **4** (Figure 1). We found that the amount of proline can effectively be reduced to 10 mol % while still obtaining the product in good yield (>90%) and in a reasonable reaction time (<5 h). Moreover, the required amount of hydroxyacetone could be dramatically reduced. We found 1.3 equiv (1 vol %) to be sufficient for obtaining the product in excellent enantioselectivity and good yield after 4 h (Figure 1).[29] While we have not studied other ketones in these optimization reactions, we anticipate that lower ketone concentrations may generally be used. This assumption is supported by experiments of Kobayashi et al. who conducted three-component Mannich reactions with 1 equiv each of ketone, aldehyde, and amine.[25] Our standard reaction conditions have been modified according to these results, and we now conveniently use 20 mol % proline and 10 vol % hydroxyacetone.

Highly Enantioselective Synthesis of 1,2-Amino Alcohols.[30] Among the most effective and enantioselective proline-catalyzed Mannich reactions are those that involve hydroxyacetone as the donor. The corresponding aldol reactions provided anti-diols in excellent diastereo- and enantioselectivities.[20b] In contrast, we found proline-catalyzed Mannich reactions with hydroxyacetone to typically furnish *syn*-1,2-amino alcohols in high chemo-, regio-, diastero-, and enantioselectivities and in good yields. In particular, the reactions using aromatic aldehydes provide the products in useful selectivities (Table 5).

The *syn*-diastereoselectivity and absolute configuration of the products were assigned on the basis of the X-ray structural analysis of Mannich product **15** (Figure 2).

These Mannich reactions can be considered a regiospecific alternative to the Sharpless asymmetric aminohydroxylation

(29) Trost et al. have made similar observations in direct asymmetric aldol reactions of α-hydroxylated ketones: Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368.

(30) For an excellent review on the synthesis of 1,2-amino alcohols, see: Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576.

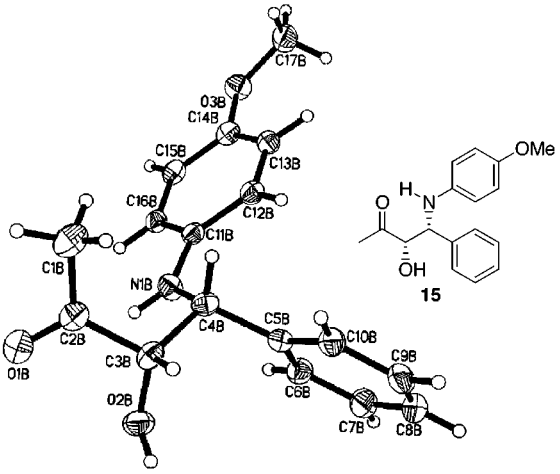
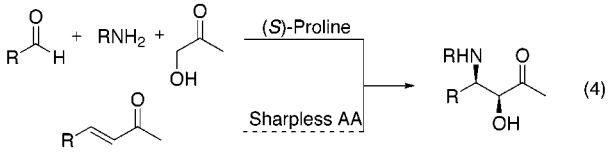
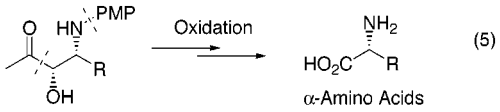


Figure 2. X-ray structure of amino ketone **15** (ORTEP view). The atoms are drawn at 50% probability.

reaction (AA). The AA of α,*β*-unsaturated ketones is, to the best of our knowledge, unknown (eq 4).[31]



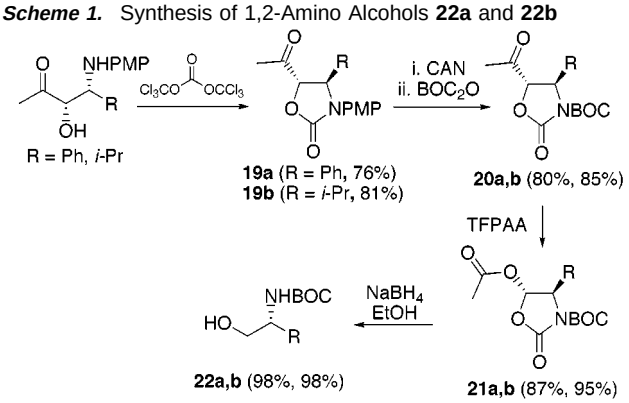
An important utility of the obtained enantiomerically enriched *syn*-1,2-amino alcohols would be their use in a synthesis of α-amino acid derivatives. In principle, such a synthesis would involve two straightforward oxidations: an oxidative α-hydroxy ketone (glycol-type) cleavage[32] and an oxidative removal of the aromatic nitrogen substituent (eq 5).



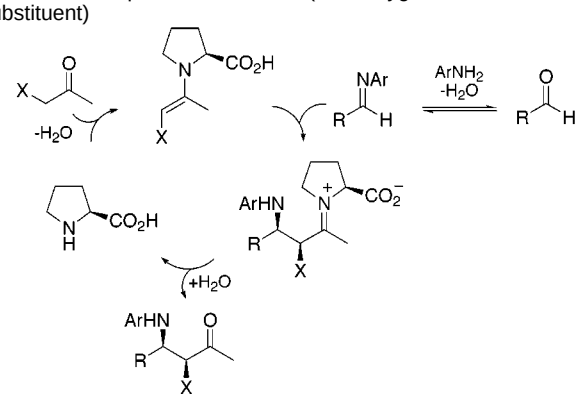
Not unexpectedly, a simple one-pot procedure accomplishing both oxidations in a single operation could not be realized. However, we have developed a novel sequence that leads from hydroxyacetone-Mannich products to *N*-BOC-protected 1,2-amino alcohols **22** in four steps (Scheme 1).

Treatment of Mannich products **15** and **18** with triphosgene gave crystalline oxazolidinones **19a** (R = Ph) and **19b** (R = *i*-Pr). After exchanging the PMP group with BOC to give carbamates **20a,b**, a Baeyer−Villiger oxidation with trifluoroperacetic acid (TFPAA)[33] cleanly gave acetals **21a,b**. Reduction furnished *N*-BOC-phenylglycinol (**22a**) and *N*-BOC-valinol (**22b**) in excellent yields.[34] The overall process starting from the Mannich products gave *N*-BOC-protected 1,2-amino alcohols **22a** and **22b** in 52 and 64% yield, respectively, and without any noticeable racemization as confirmed by optical rotation and HPLC analysis.

Scheme 1. Synthesis of 1,2-Amino Alcohols **22a** and **22b**



Scheme 2. Proposed Mechanism (X = Oxygen or Carbon Substituent)



Mechanism. The most plausible mechanism of the proline-catalyzed three-component Mannich reaction is depicted in Scheme 2. Accordingly, the ketone reacts with proline to give an enamine. In a second preequilibrium between the aldehyde and the aniline, an imine is formed. Imine and enamine then react to give after hydrolysis the enantiomerically enriched Mannich product. This mechanism is similar to the one we proposed for the proline-catalyzed aldol reaction with the only difference being that the aldehyde is first converted into an imine before reacting with the presumed proline enamine.

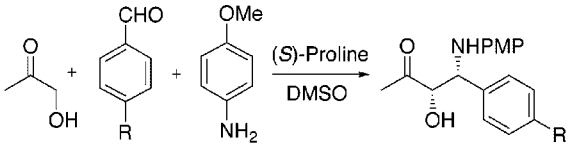
In the reactions of hydroxyacetone with different *p*-substituted aromatic aldehydes we discovered a strong effect of the electronic properties of the aromatic moiety on the stereoselectivity. The enantioselectivity correlates well with Hammett σ_p-values, and a linear Hammett plot was obtained. The reaction constant ρ for the proline-catalyzed three-component Mannich reaction was determined to be 1.36 ($R^2 = 0.95$) (Figure 3).[35,36]

(31) (a) Li, G.; Chang, H.-T; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. (b) Review: O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329.

(32) For elegant examples of such α-hydroxy ketone cleavages, see: (a) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499−2506. (b) Reference 8.

(33) TFPAA was prepared in situ from urea-hydrogen peroxide and trifluoroacetic anhydride, see: Ziegler, F. E.; Metcalf, C. A., III; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1993**, *115*, 2581−2589 and references therein. *m*-CPBA was less efficient in these reactions.

(34) For an elegant alternative approach to aryl glycinols using the Sharpless AA, see: Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217. O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519−2526. For selected other methods for the synthesis of 2-substituted 2-amino ethanols, see: (a) Reduction of α-amino acids: Smith, G. A.; Gawley, R. E. *Org. Synth.* **1985**, *63*, 136−139. Meyers, A. I.; McKennon, M. J. *J. Org. Chem.* **1993**, *58*, 3568−3571. (b) From glycol aldehyde hydrazones: Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219−1222. Enders, D.; Reinhold, U. *Liebigs Ann.* **1996**, 11−26. (c) Other auxiliary methodologies: Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051−2054. Youn, S. W.; Choi, J. Y.; Kim, Y. H. *Chirality* **2000**, *12*, 404−407. (d) Optical resolution: Morita, T.; Nagasawa, Y.; Yahiro, S.; Matsunaga, H.; Kunieda, T. *Org. Lett.* **2001**, *3*, 897−899. Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275−1294. (e) Curtius rearrangement of *β*-hydroxy acids: Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742−2748.



R	σ_p	Yield %	dr	ee %	er
NO_2	0.81	92	20:1	>99	332
CN	0.70	88	15:1	99	199
Br	0.26	90	15:1	98	99
Ph	0.05	79	8:1	94	32
H	0	83	9:1	93	28
Me	-0.14	85	5:1	86	13

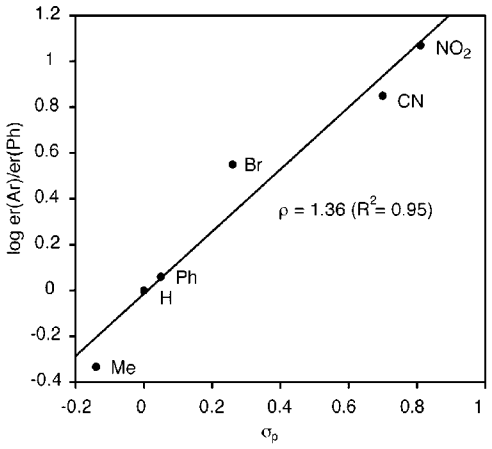
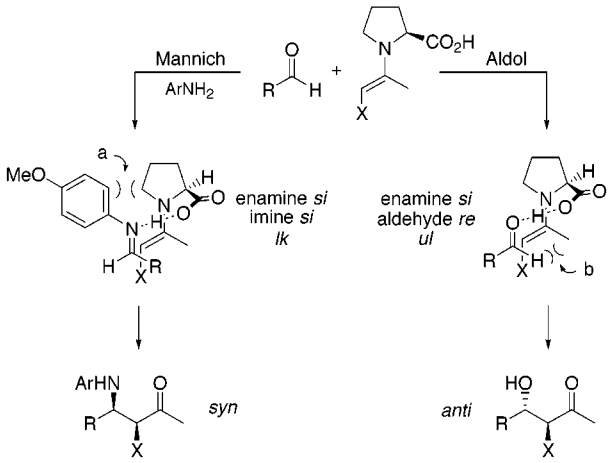


Figure 3. Substituent effect on enantioselectivity.

Our results suggest negative charge formation in the enantioselectivity-determining step, which is consistent with the proposed nucleophilic addition of an enamine to an imine. The observation that higher ee's were obtained with more reactive aldehydes (imines) has previously been made by Noyori et al. in β-amino-alcohol-catalyzed additions of dialkylzincs to benzaldehyde derivatives.[37]

A main difference between proline-catalyzed aldol and Mannich reactions concerns the stereoselectivity. Typically, aldols result from a *re*-enantiofacial attack on the aldehyde, whereas Mannich products are formed via *si*-face attack on an imine. Moreover, if substituted ketone donors are used, in the aldol reaction, *anti*-diastereoselectivity is typically observed while excellent *syn*-selectivity was found in the corresponding Mannich reactions. Consequently, the enamine-enantiofaciality (*si*, if the substituent X is of highest priority) is the same in both reactions, but the electrophile-faciality is reversed resulting in *like* topicity (*lk*) in the Mannich reaction and in *unlike* topicity (*ul*) in the aldol reaction.[38] That both enamine and imine may adopt both (*E*)- and (*Z*)-configurations complicates an analysis of the entire *sortiment* of plausible transition states.[39] In our originally proposed mechanism, we employed (*Z*)-imines to account for the reversed enantioselectivity. However, while

Scheme 3. Opposite Enantiofacial Selectivities and Topicities in Aldol and Mannich Transition States



imines may undergo (*E*)−(*Z*) isomerization,[40] and (*Z*)-imines have been implicated earlier in related transition states,[7] typically they are present in only low equilibrium concentrations. On the basis of these considerations we have developed advanced transition-state models that explain the contrasting stereoselectivities of proline-catalyzed aldol and Mannich (Scheme 3).

Accordingly, in the Mannich transition state we assume (*E*)-configurations of both the proline enamine and the imine. The *si*-face of the imine is selectively attacked by the enamine to allow for protonation of its lone pair and compensation of negative charge formation. Attack of the imine *re*-face would result in unfavorable steric interactions between the pyrrolidine and aromatic ring (Scheme 3, arrow a). These interactions do not exist in the aldol reaction, and steric repulsion between aldehyde and enamine carbon substituents dominates (Scheme 3, arrow b).

Conclusions

Scope, optimization, and application of the proline-catalyzed direct asymmetric three-component Mannich reaction have been described herein. The development of this reaction constitutes a major advancement over prior asymmetric Mannich reaction technologies. Of the several important improvements, a few are mentioned in the following: (1) Our reaction is the first organocatalytic asymmetric Mannich reaction. (2) It is also the first catalytic asymmetric three-component Mannich reaction that uses free aldehydes instead of preformed imine equivalents or paraformaldehyde. (3) The reaction is broad in scope, and several different aldehydes, including the important class of α-unbranched aldehydes, may be used. (4) Exceptionally high enantio-, diastereo-, regio-, and chemoselectivities have been obtained. (5) The reactions are operationally simple and use an inexpensive and nontoxic catalyst that is available in both enantiomeric forms.

Experimental Section

General Experimental Procedure for Mannich Reactions with Different Ketones (Table 1). A suspension of (*S*)- or (*R*)-proline (40 mg, 0.35 mmol), *p*-anisidine (135 mg, 1.1 mmol), and an aldehyde (1.0 mmol) in 8 mL of DMSO and 2 mL of the ketone (acetone,

(35) The result with *p*-anisaldehyde (R = OMe) has been excluded.
(36) (a) Hammet, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96. (b) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 1−261.
(37) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605−3614.
(38) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413−1423.
(39) Hoffmann, R. *Angew. Chem., Int. Ed.* **2001**, *30*, 3337−3340.
(40) (a) Bjoergo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1081−1084. (b) Kessler, H. *Tetrahedron* **1974**, *30*, 1861−1870.

2-butanone, methoxyacetone, or hydroxyacetone) was stirred at room temperature for 12 h. The reactions were worked up by adding phosphate-buffered saline (PBS) solution (pH 7.4), extracting with ethyl acetate, drying the organic layer with $MgSO_4$, and purifying the crude product by column chromatography with hexane/ethyl acetate mixtures.

General Experimental Procedure for the Synthesis of Mannich Products from Acetone (Table 2). A suspension of (*S*)- or (*R*)-proline (40 mg, 0.35 mmol), *p*-anisidine (135 mg, 1.1 mmol), and an aldehyde (1.0 mmol) in 10 mL of DMSO/acetone (4:1) (procedure A), in pure acetone (procedure B), or in $CHCl_3$/acetone (4:1) (procedure C) was stirred at room temperature for 12−48 h. In procedures A and C, the reactions were worked up by adding phosphate-buffered saline (PBS) solution (pH 7.4), extracting with ethyl acetate, drying the organic layer with $MgSO_4$, and purifying the crude product by column chromatography with hexane/ethyl acetate mixtures. In procedure B, the reactions were worked up by filtration to recover >80% of proline, concentration, and column chromatography with hexane/ethyl acetate mixtures.

General Experimental Procedure for the Synthesis of Mannich Products from Hydroxyacetone (Table 5). A suspension of (*S*)- or (*R*)-proline (23 mg, 0.2 mmol, 20 mol %), *p*-anisidine (135 mg, 1.1 mmol), and an aldehyde (1.0 mmol) in 10 vol % hydroxyacetone/DMSO (9 mL) was stirred at room temperature for 3−16 h. The reactions were worked up by adding saturated aqueous ammonium chloride solution and extracting with hexane/ethyl acetate = $^2/_3$ (2 × 15 mL). The organic layers were washed once with water (15 mL), dried ($MgSO_4$), filtered, and concentrated to furnish after column chromatography (hexane/ethyl acetate = $^3/_1$) the pure *syn*-products (**4**, **12**−**18**). Diastereoselectivities were determined from the raw ^{1}H NMR spectrum of the reaction mixture.

Synthesis of (*R*)-4-(4-Methoxy-phenylamino)-6-methyl-heptan-2-one (6) as a Representative Experiment. A suspension of (*S*)-proline (40 mg, 0.35 mmol), *p*-anisidine (135 mg, 1.1 mmol), and isovaleraldehyde (1.0 mmol) in 10 mL of acetone was stirred at room temperature for 18 h. The mixture was filtered to recover ca. 35 mg of proline. Concentration of the filtrate followed by column chromatography (15% ethyl acetate/hexanes) gave Mannich product **6** as a clear oil (224 mg, 0.9 mmol, 90%). HRMS (MALDI): calcd for MNa^+ 272.1626, found 272.1630. IR: 2954, 1708, 1513, 1240. $t_r(R) = 6.5$ min, $t_r(S) = 7.3$ min, ee = 93% (Chiralcel AS, $\lambda = 315$ nm, 10% *i*PrOH/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 1.33 (m, 1H), 1.47 (m, 1H), 1.75 (m, 1H), 2.12 (s, 3H), 2.54 (dd, $J = 6.6$, 16.7 Hz, 1H), 2.66 (dd, $J = 5.3$, 16.7 Hz, 1H), 3.73 (s, 3H), 3.81 (m, 1H), 6.58 (m, 2H), 6.76 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 22.2, 22.9, 24.9, 31.0, 44.6, 48.0, 48.9, 55.7, 114.8, 114.9, 141.3, 152.0, 208.4.

Acknowledgment. Support by R. A. Lerner and the Scripps Research Institute is gratefully acknowledged. We thank Raj K. Chadha for X-ray structural analyses and the M. G. Finn group for sharing chemicals.

Supporting Information Available: Full experimental details and characterization of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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