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COMMUNICATIONS

Published on Web 01/04/2006

Direct Asymmetric *anti*-Mannich-Type Reactions Catalyzed by a Designed Amino Acid

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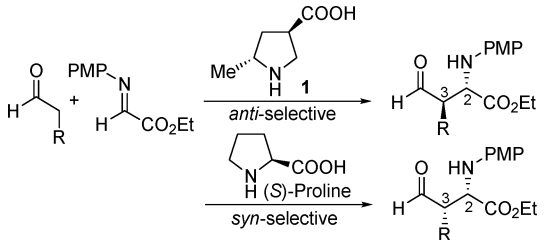
Direct catalytic asymmetric Mannich reactions are highly effective carbon−carbon bond-forming reactions that are used for the preparation of enantiomerically enriched amino acids, amino alcohols, and their derivatives.[1−7] Because of the utility of these types of synthons, the demand for Mannich reactions that selectively afford *anti*- or *syn*-products with high enantioselectivities is high. *syn*-Selective, direct, catalytic, asymmetric Mannich reactions are now common and have been performed using Zr-,[1a] Zn-,[1b−d] or Cu-derived[1e] catalysts, Brønsted acids,[2] cinchona alkaloids,[3] phase-transfer catalysts,[4] and proline and related organocatalysts.[5,6] Enantioselective *anti*-Mannich reactions are, however, considerably rarer.[1a−c,7] Even a non-asymmetric *anti* selective Mannich reaction would be of interest.[8] Thus, the development of effective enantioselective *anti*-Mannich catalysts is a challenge in contemporary asymmetric synthesis. Here we present our studies regarding a solution to this problem and disclose the design, synthesis, and evaluation of amino acid catalyst **1** as a highly diastereo- and enantioselective *anti*-Mannich catalyst for reactions involving unmodified aldehydes (Scheme 1).

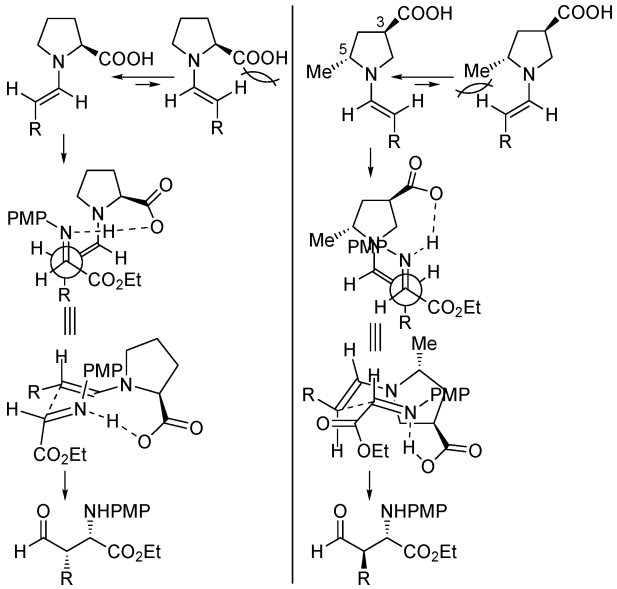
In the reaction of unmodified aldehydes with *N*-*p*-methoxyphenyl (PMP) protected imines catalyzed by the natural amino acid (*S*)-proline, (2*S*,3*S*)-*syn*-amino aldehydes are obtained with high enantioselectivities[6] (Scheme 1). Although reactions involving some pyrrolidine derivatives afford *anti*-diastereomers as their major products, the enantioselectivities obtained with these organocatalysts are moderate.[6] To design catalysts that provide *anti*-products with high levels of enantioselectivities, we revisited the key factors that control the diastereo- and enantioselectivities of (*S*)-proline-catalyzed reactions[6,9] (Scheme 2 left). Four considerations are key: (1) (*E*)-Enamine intermediates predominate. (2) The s-*trans* conformation of the (*E*)-enamine reacts in the C−C bond-forming transition state. The s-*cis* conformation results in steric interaction between the enamine and the substituent at the 2-position of the pyrrolidine ring. (3) C−C bond formation occurs at the *re* face of the enamine intermediate. This facial selection is controlled by proton-transfer from the carboxylic acid to the imine nitrogen. (4) The enamine attacks the *si* face of the (*E*)-imine. The facial selectivity of the imine is also controlled by the proton transfer that increases the electrophilicity of the imine.

The stereoselective formation of the *anti*-products necessitates a reversal in the facial selectivity of either the enamine or the imine, compared to the proline-catalyzed reactions. A pyrrolidine derivative bearing substituents at 2- and 4-positions (or at 3- and 5-positions) (Scheme 2, right) was hypothesized to be an *anti*-Mannich catalyst. The steric features of a substituent at the 5-position of the pyrrolidine can be used to fix the conformation of the enamine

Scheme 1



Scheme 2



(see point 2 above). This substituent can presumably be any functional group that cannot initiate proton transfer to the imine. The acid functionality was then placed at the distal 3-position of the ring, to affect control of enamine and imine face selection in the transition state (see points 3 and 4). To avoid steric interactions between the substituent at the 5-position of the new catalyst and the imine in the transition state, the substituents at 3- and 5-positions should be in the *trans* configuration.

On the basis of these considerations, a new catalyst (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (RR35, **1**) was designed. The major transition state of the Mannich reaction catalyzed by **1** is presented in Scheme 2 (right). Computational studies of the **1**-catalyzed reaction of propionaldehyde and *N*-PMP-protected α-imino methyl glyoxylate using HF/6-31G* level of theory[10] were used to test our design prior to synthesis. The catalyst was predicted to give 95:5 *anti*:*syn* diastereoselectivity and ∼98% ee for the formation of the (2*S*,3*R*)-product (Table 1, entry 1).

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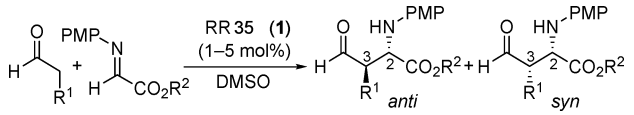
10.1021/ja056984f CCC: $33.50

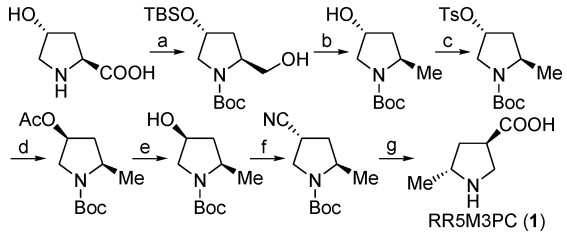
Table 1. RR35 (**1**)-Catalyzed Mannich-Type Reactions[a]



entry	R^1	R^2	time (h)	product	yield (%)	dr[b] *anti:syn*	ee[c] (%)
1[d]	Me	Me	-	–	–	95:5	98
2	Me	Et	1	**2**	70	94:6	>99[e]
3	*i*-Pr	Et	3	**3**	85	98:2	99
4	*n*-Bu	Et	0.5	**4**	54	97:3	99
5[f,g]	*n*-Bu	Et	1	**4**	71	97:3	99
6[f,h]	*n*-Bu	Et	2	**4**	57	97:3	>99
7	*n*-Pent	Et	3	**5**	80	97:3	>99
8[i]	$CH_2CH{=}CH_2$	Et	3	**6**	72	96:4	>97
9	*i*-Pr	*i*-Pr	1	**7**	92	97:3	98
10	*n*-Pent	*i*-Pr	1	**8**	85	96:4	>99

[a] Typical conditions: To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1 equiv) and aldehyde (0.5 mmol, 2 equiv) in anhydrous DMSO (2.5 mL), catalyst RR35 (**1**) (0.0125 mmol, 0.05 equiv, 5 mol % to the imine) was added and the mixture was stirred at room temperature. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR. [c] The ee of the (2*S*,3*R*)-*anti*-product was determined by chiral-phase HPLC analysis. [d] Indicates computational predictions using methods described in the text. [e] The ee was determined by HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine. [f] The reaction was performed in a doubled scale. [g] Catalyst **1** (2 mol %) was used. [h] Catalyst **1** (1 mol %) was used. [i] The reaction was performed with doubled concentration for each reactant and catalyst **1**.

Scheme 3 [a]



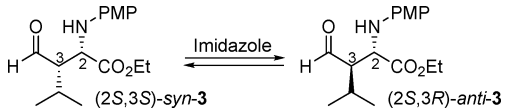
[a] (a) Known procedures (see Supporting Information); (b) (i) MsCl, Et_3N, (ii) $LiBHEt_3$, (iii) TBAF, 94% (3 steps); (c) TsCl, pyridine, 58%; (d) NH_4OAc, 99%; (e) NaOH, 93%; (f) (i) MsCl, Et_3N, (ii) NaCN, 58% (2 steps); (g) (i) HCl, (ii) Dowex 50WX8, 90% (2 steps).

RR35 (**1**)[11] was synthesized (Scheme 3), and Mannich reactions involving a variety of unmodified aldehydes were studied (Table 1). In accord with the design principles and in quantitative agreement with the computational predictions, the reactions catalyzed by **1** afforded *anti*-amino aldehyde products in excellent diastereo- and enantioselectivities.[12] With 5 mol % catalyst loading, the reaction rates with catalyst **1** were approximately 2- to 3-fold faster than the corresponding proline-catalyzed reactions that afford the *syn*-products. The high catalytic efficiency of **1** allowed the reactions to be catalyzed with only 1 or 2 mol % to afford the desired products in reasonable yields within a few hours (Table 1, entries 5 and 6).

Imidazole isomerization[13] of the *anti*-**3** product obtained from the **1**-catalyzed reaction and of the (2*S*,3*S*)-*syn*-**3** product obtained from the (*S*)-proline-catalyzed reaction[6] confirmed that the major *anti*-product generated from the **1**-catalyzed reaction had a (2*S*,3*R*) configuration. (Scheme 4).

The relative contributions of the carboxylic acid and methyl group of **1** in directing the stereochemical outcome of the reaction were assessed. Computational studies involving the derivative lacking the 5-methyl group, (*S*)-3-pyrrolidinecarboxylic acid, indicate that the methyl group contributes ∼1 kcal/mol toward the *anti*-diastereoselectivity. That is, the result in entry 1 of Table 1 changes to 82:18 *anti*:*syn* dr and 92% ee when transition states with the unmethylated catalyst are located. This unmethylated catalyst was also tested in an actual reaction, for the case where R^1 = *i*-Pr. This derivative afforded (2*R*,3*S*)-*anti*-**3** in 95:5 *anti*:*syn* dr and 93% ee, which is a drop of ∼0.6 kcal/mol from the **1**-catalyzed reaction with the same substrate (Table 1, entry 3).

Scheme 4



An efficient organocatalyst RR35 (**1**) for *anti*-Mannich-type reactions has been developed.[14] This catalyst has been demonstrated to be useful for the synthesis of amino acid derivatives with excellent *anti*-diastereoselective control and high enantioselectivities under mild conditions. Further studies on the full scope of this Mannich catalyst, computational studies, and other reactions catalyzed by it and its derivatives will be reported soon.

Acknowledgment. This study was supported by The Skaggs Institute for Chemical Biology and the National Institute of General Medical Sciences, National Institutes of Health (GM36700 to K.N.H.).

Supporting Information Available: Experimental procedures and spectral and chromatographic data. This material is availablefree of charge via the Internet at http://pubs.acs.org.

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(12) DMSO provided the best *anti* selectivity and enantioselectivity of the solvents tested for the RR35-catalyzed Mannich reaction to afford *anti*-**3**. Reactions in DMF (*anti*:*syn* = 97:3, 97% ee), CH_3CN (96:4, 96% ee), EtOAc (94:6, 96% ee), and dioxane (97:3, 95% ee) were as efficient with respect to reaction rate as in DMSO.

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JA056984F