

# A new class of metal-free catalysts for direct diastereo- and regioselective Mannich reactions in aqueous media

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**Abstract**—Camphor sulfonic acid is an efficient catalyst for Mannich reactions of benzaldehyde, aniline and various ketones in aqueous media, with diastereo- or regioselectivities. Meanwhile, three sulfonated amino acids can catalyze the same type of reactions effectively with high diastereo- or regioselectivities.

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Mannich-type reaction is a classic protocol to synthesize  $\beta$ -amino carbonyl compounds and has been investigated extensively. The first asymmetric Mannich reaction was diastereoselective and involved the addition of preformed enolates and enamines to preformed imines.<sup>1</sup> With the increasing interests in developing environmental benign reactions, the atom-economic catalytic process that employs unmodified carbonyl donor, amine, and acceptor aldehyde as an idealized Mannich-type reaction is attracting more and more attention.<sup>1</sup> Only very recently, the first catalytic asymmetric 3-component Mannich-type reaction using free aldehydes and ketones was reported, in which L-proline was used as a catalyst and the reaction was carried out in DMSO.<sup>2</sup>

Using metal-free small molecules as catalysts has been another strategy to develop green organic reactions.<sup>3</sup> The reported metal-free catalysts used for Mannich-type reactions include DBSA,<sup>4</sup> polymer-supported sulfonic acid,<sup>5</sup> L-proline,<sup>2</sup> and chiral phosphoric acid derivatives.<sup>6</sup> Reactions catalyzed by the latter two in organic media show high enantioselectivities.

Kobayashi et al. reported the first asymmetric Mannich reaction catalyzed by chiral Lewis acid in aqueous media,<sup>7</sup> in which  $ZnF_2$  and a chiral diamine were used as the catalysts for the diastereoselective and enantioselective Mannich-type condensation of a hydrazono ester with

silyl enol ethers. Herein, as part of our systematic searching for the potential application of natural chiral compounds, especially amino acids, in asymmetric syntheses carried out in aqueous media,<sup>8</sup> we wish to report the first direct 3-component diastereo-controlled Mannich-type reactions catalyzed by a series of metal-free catalysts, using water as the only solvent. The catalysts used in this study include D-camphor sulfonic acid (D-CSA) and sulfonated amino acids, as shown in Figure 1.

Initially, the catalytic effect of the commercially available D-CSA in the amount of 10 mmol% for the condensation reaction of benzaldehyde, aniline, and cyclohexanone in aqueous media was evaluated. The reaction proceeded smoothly to afford the Mannich condensation products in good yield with the *anti* isomer as the only product. Encouraged by the result, the effect of sulfonated amino acids was evaluated and the results were presented in Table 1. It showed that, in all cases, the  $\beta$ -amino carbonyl adduct was obtained in excellent yields with the *anti* isomer as the dominant

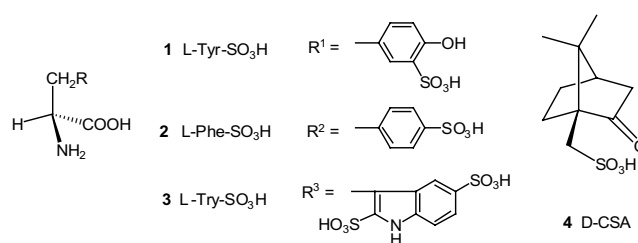


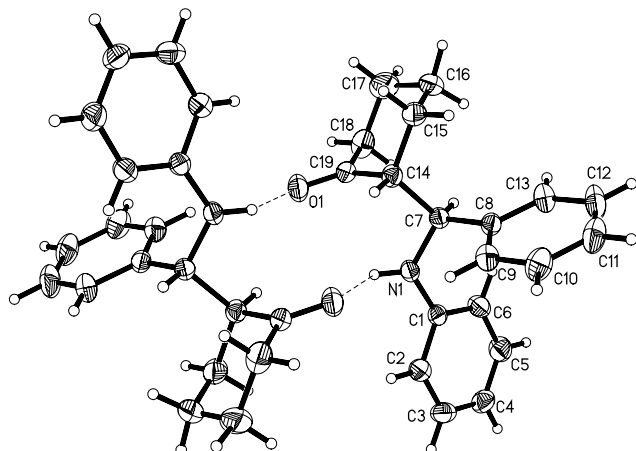
Figure 1. The Brønsted-acid catalysts.

**Keywords:** Direct Mannich reaction; Metal-free catalyst; Aqueous media; Sulfonated amino acid; Camphor sulfonic acid.

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**Table 1.** Catalytic results for reactions of benzaldehyde, aniline, and cyclohexanone

Entry	Catalysts	Time (hr)	Yield	Product <sup>a</sup>	de (%)
1	D-CSA	5	91	<b>8a</b> <sup>b</sup>	100
2	L-Tyr-SO <sub>3</sub> H	5	90	<b>8a, 8b</b> <b>8a:8b</b> = 95:5	90
3	L-Try-SO <sub>3</sub> H	5	88	<b>8a, 8b</b> <b>8a:8b</b> = 97:3	94
4	L-Phe-SO <sub>3</sub> H	5	90	<b>8a</b>	100
5	1,5nds	5	78	<b>8a, 8b</b> <b>8a:8b</b> = 72:28	44
6	bpds	5	73	<b>8a, 8b</b> <b>8a:8b</b> = 82:18	64
7	L-Tyr	5	nd	nd	

<sup>a</sup> Determined by <sup>1</sup>H NMR.<sup>b</sup> With ee% of 8% established by HPLC with chiral column Daicel Chiralpak AS-RH.**Figure 2.** Crystal structure of the *anti* isomer of compound **8**, showing the racemic dimer linked by hydrogen bonds.

diastereoisomer. The structure of the *anti* isomer is further confirmed by X-ray crystallography,<sup>9</sup> as shown in Figure 2. The *anti* isomers formed racemic dimer via hydrogen bonds between the amino and carbonyl groups.

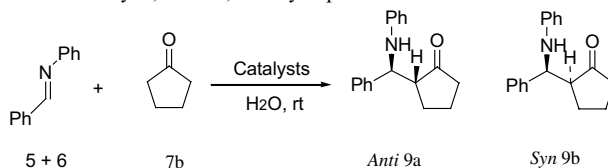
In order to identify the structural factor contribution to the stereoselectivities, the catalytic effect of achiral aromatic sulfonic acids, namely, naphthalene-1,5-disulfonic acid (1,5nds) and 4,4'-biphenyldisulfonic acids (bpds), as well as L-tyrosine were investigated and the results were shown as entries 5–7 in Table 1. Both 1,5nds and bpds produced high yields but moderate diastereoselectivities, which were comparable to the catalytic results reported for the achiral catalyst DBSA.<sup>4</sup> L-Tyrosine did not catalyze the Mannich-type reaction under the reaction conditions evaluated, indicating that carboxylic acid is not acidic enough to activate the reaction. Therefore, both sulfonic acid and the chiral nature of the reaction media were crucial for effective and high diastereoselective catalytic results.

3-Component reaction of benzaldehyde, aniline, and cyclopentanone did not produce the desired adduct, probably due to the polyaminoalkylation of cyclopentanone. Therefore, another procedure was adopted, in which benzaldehyde and aniline were first mixed to produce imine in situ before ketone was added, and the desired adduct was generated with moderate yields and excellent diastereoselectivities, as shown in Table 2.

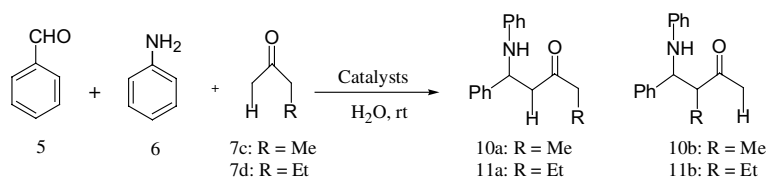
Finally, the regioselectivities of these Brønsted acids were examined and the results shown in Table 3. In all cases, the C–C bond was formed by the less-substituted carbon atom of the asymmetric ketones, and **10a** or **11a** was obtained as the major product, which is consistent with what was reported for DBSA.<sup>4</sup>

The reaction process could be considered to proceed via an iminium salt generated by benzaldehyde, aniline and the Brønsted acid, as shown in Scheme 1. It should be noted that in aqueous media, the oxygen atoms of the sulfonate group are hydrogen bonding acceptors while the hydrogen atoms of the amino group are hydrogen bonding donors. The strong hydrogen bonds formed between these groups could dominant the intermolecular interaction in aqueous solution, create an asymmetrical environment enhancing the enantioselectivities,<sup>3,6</sup> and consequently produce the detectable (yet low) enantioselectivity observed in entry 1.

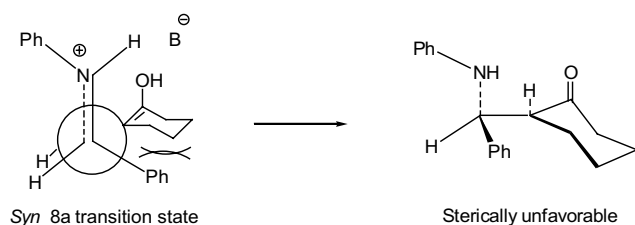
In summary, we have identified a new group of small organic molecules which can catalyze the 3-component Mannich-type reaction with moderate to high yields and high stereoselectivities, with water as the only solvent at room temperature. Amino acids are readily obtained chiral organic compounds. However, only recently, with L-proline catalyzed successfully a series of organic reactions,<sup>2,10</sup> the use of natural amino acids as chiral source for asymmetric catalysts attracted people's attention.<sup>11</sup> Our result reported herein shows that amino acid derivatives can be served as effective

**Table 2.** Catalytic results for reactions of benzaldehyde, aniline, and cyclopentanone

Entry	Catalysts	Time (hr)	Yield	Product <sup>a</sup>	de (%)
8	D-CSA	1	60	<b>9a</b>	100
9	L-Tyr-SO <sub>3</sub> H	1	60	<b>9a</b>	100
10	L-Try-SO <sub>3</sub> H	1	58	<b>9a, 9b</b> <b>9a:9b</b> = 97:3	94
11	L-Phe-SO <sub>3</sub> H	1	60	<b>9a, 9b</b> <b>9a:9b</b> = 92:8	84

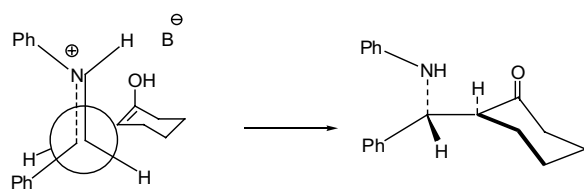
<sup>a</sup> Determined by <sup>1</sup>H NMR.**Table 3.** Reactions of benzaldehyde, aniline, and 2-butanone, 2-pentanone

Entry	Catalyst	R	Time (hr)	Yield (%)	Product <sup>a</sup>
12	D-CSA	Me	24	75	<b>10a</b>
13	L-Tyr-SO <sub>3</sub> H	Me	24	65	<b>10a, 10b</b> <b>10a:10b</b> = 90:10 <sup>b</sup>
14	L-Try-SO <sub>3</sub> H	Me	24	70	<b>10a, 10b</b> <b>10a:10b</b> = 80:20 <sup>b</sup>
15	L-Phe-SO <sub>3</sub> H	Me	24	72	<b>10a, 10b</b> <b>10a:10b</b> = 87:13 <sup>b</sup>
16	D-CSA	Et	24	68	<b>11a</b>
17	L-Tyr-SO <sub>3</sub> H	Et	24	68	<b>11a</b>
18	L-Try-SO <sub>3</sub> H	Et	24	68	<b>11a</b>
19	L-Phe-SO <sub>3</sub> H	Et	24	68	<b>11a</b>

<sup>a</sup> Determined by <sup>1</sup>H NMR.<sup>b</sup> The de% of **10b** is around 20% with the *syn* isomer as the major product.

Syn 8a transition state

Sterically unfavorable



Anti 8a transition state

**Scheme 1.** Proposed catalytic transition state for the *syn* and *anti* isomers. B<sup>-</sup> represents the de-protonated Brønsted acid.

catalysts for reactions carried out in aqueous media. It is remarkable that in entries 1, 4, 8, 9, 12, 16–19, the reactions are diastereo- or regiocontrolled, with one isomer as the only product.

### Acknowledgements

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.174. Crystallographic data (excluding structure factors) for the structures in this paper has been

deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 239849. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 0 1223 336033 or email: deposit@ccdc.cam.ac.uk).

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9. Crystal data for the *anti* isomer of **8**,  $M_w = 279.37$ , monoclinic, space group  $P2_1/n$ ,  $a = 10.309(4)$ ,  $b = 10.726(4)$ ,  $c = 14.263(5)$  Å,  $\beta = 95.076(7)^\circ$ ,  $V = 1570.8(10)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho_{\text{calcd}} = 1.181$  g cm<sup>-3</sup>,  $F(000) = 600$ , MoK $\alpha$  radiation,  $\mu = 0.072$  mm<sup>-1</sup>. Reflections collected 9776, unique 3809,  $R(\text{int}) = 0.0159$ ,  $R_1 = 0.0527$ ,  $wR_2 = 0.1516$  for strong reflections with  $I > 2\sigma(I)$ ,  $\text{Gof} = 1.022$ .
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