Chiral Zwitterions from Vicinal Diamines: Effective and Recoverable Asymmetric Enamine Catalysts

Yupu Qiao, Long Zhang, Sanzhong Luo,* Jin-Pei Cheng

Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. of China
Fax +86(10)62554446; E-mail: luosz@iccas.ac.cn

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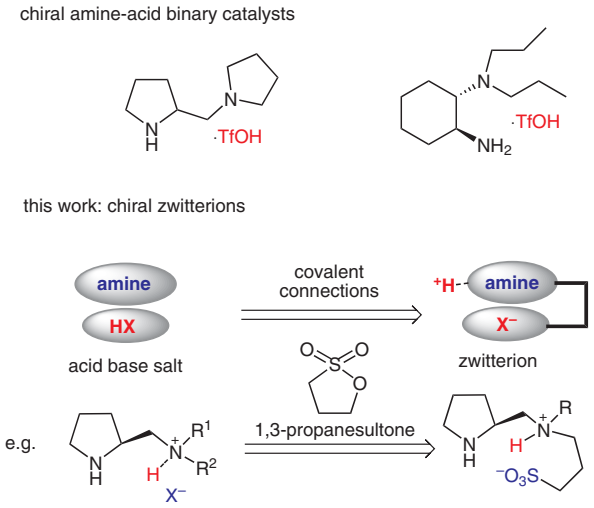
Abstract: A series of chiral zwitterionic vicinal diamines were designed and synthesized. The zwitterionic catalysts demonstrated good reactivity and enantioselectivity in asymmetric enamine-based transformations and could be readily recycled and reused for four times.

Key words: chiral zwitterion, organocatalysts, enamine, catalyst immobilization

The use of chiral amine–Brønsted acid conjugates has been proved to be a powerful strategy for both enamine- and iminium-based catalysis as evidenced by the prevalence of chiral pyrrolidine diamines in asymmetric organocatalysis.[1] Recently, chiral primary amine–Brønsted acid conjugates, particularly those from vicinal diamines, have also been found to be viable bifunctional amino catalysts for a range of transformations.[2] In the typical chiral diamine–acid conjugate systems, it has been known that the acids not only facilitate the aminocatalytic cycle, but also play essential role in stereocontrol with the protonated amino group normally serving as the critical H-bond interacting moiety (Scheme 1).[1d] Therefore, the judicious selections of acid, chiral amine, and their combinations become very crucial for effective catalysis. Though endowed with combinatorial flexibility, the bi-/multicomponent catalytic systems pose considerable challenges for mechanism studies and also lack of convenience for synthetic manipulations. As a continuation to our effort in this area,[2,3] we herein present an alternative zwitterion strategy for the amine–acid catalysis. In this strategy, the amine and acid moieties are covalently connected and the resulting zwitterion would function similarly like its acid–base ion-pair counterpart as a H-bonding donor. Our studies indicate that such chiral zwitterions are indeed viable amino catalyst with additional advantages such as readily recyclability and reusability due to their zwitterionic nature.

The zwitterion organocatalysts could be synthesized following a simple two-step procedure.[4] First, the ring-opening reaction of 1,3-propanesultone or 2-sulfobenzoic anhydride and secondary amines gave the N-protected zwitterion products which were then subject to deprotection with Pd/C to afford the final product with high purity.[5] The zwitterionic-type product could be easily purified via a simply filtration–wash procedure and no chromatography was needed in this process. Unlike the chiral amine–Brønsted acid conjugates which are often syrup-type materials, the chiral zwittertions are obtained as white powders and can be conveniently handled.[6] In addition, the zwitterions are barely soluble in less polar solvent such as diethyl ether, ethyl acetate, and THF but well soluble in high polar solvent such as DMF, DMSO, particularly the environmentally benign PEG and ionic liquids, a beneficial property for biphasic catalysis.



Scheme 1 Catalyst design strategy

The asymmetric direct Michael addition between isobutyraldehyde and β-nitrostyrene was selected as a benchmark for testing our zwitterions.[7] As shown in Table 1, only trace product could be obtained with pyrrolidine-amide catalyst **3a** (Scheme 2, Table 1, entry 1). However, when using secondary-secondary diamine zwitterions **3b** as the catalyst, the Michael product could be formed with 36% yield and 54% ee in 48 hours (Table 1, entry 2). To our delight, significant improvements on both stereoselectivity and yield were observed when using secondary-tertiary diamine zwitterions as the catalyst (Table 1, entries 3–5). The best results (24 h, 80% yield, 78% ee) were achieved with catalyst **3e** which bears an isopentyl group (Table 1, entry 5). Compared with the common ion-pair catalyst **4** (Table 1, entry 6), the zwitterions catalyst **3e** demonstrated a slightly higher activity while maintained

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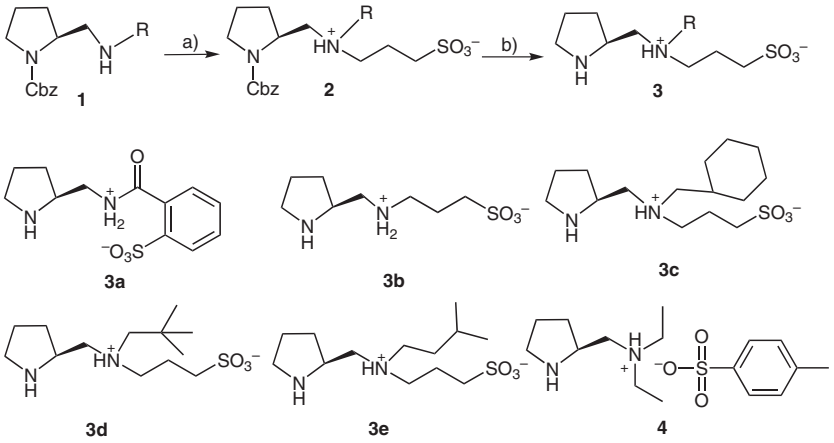
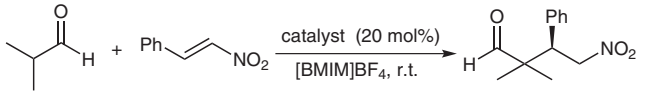


Scheme 2 *Reagents and conditions*: a) R = H: for **3a**, 2-sulfobenzoic anhydride, toluene, r.t.; for **3b**, 1,3-propanesultone, toluene, r.t.; R = alkyl group: 1,3-propanesultone, toluene, reflux; b) Pd/C, H_2, MeOH–H_2O (1:1).

the same enantioselectivity, thus verifying the viability of the zwitterions catalytic strategy. Furthermore, the chiral zwitterionic catalyst could be easily recycled and reused. After each run, catalyst **3e** could be recycled by precipitation with diethyl ether. The recycled catalyst was directly used in the next run upon removing the residue organic solvent. It is found that the zwitterions could be reused at least four times while maintaining high enantioselectivity with slightly decreased activity (Table 1, entries 7–9).

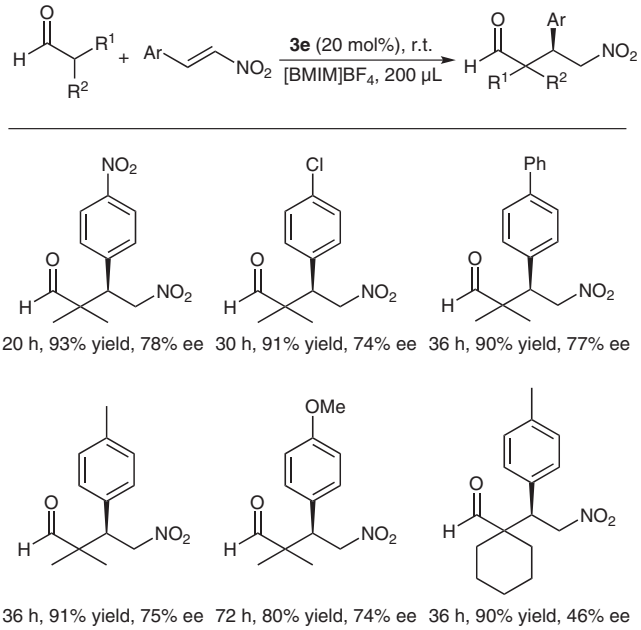
Encouraged by these results, we next examined the scope of the reaction with a series of α,α-disubstituted aldehyde donors and nitroolefins using catalyst **3e**. The results were summarized in Scheme 3. As shown, the reaction worked very well when using isobutyraldehyde as a donor producing the desired Michael products in high yields and good enantioselectivities. Both electron-rich and electron-deficient nitrostyrenes could be employed in this reaction. Cyclohexanecarboxaldehyde could also be used as the Michael donor, and the Michael adduct was obtained in 90% yield with 44% ee.

Table 1 Catalyst Screening and Recycling[a]



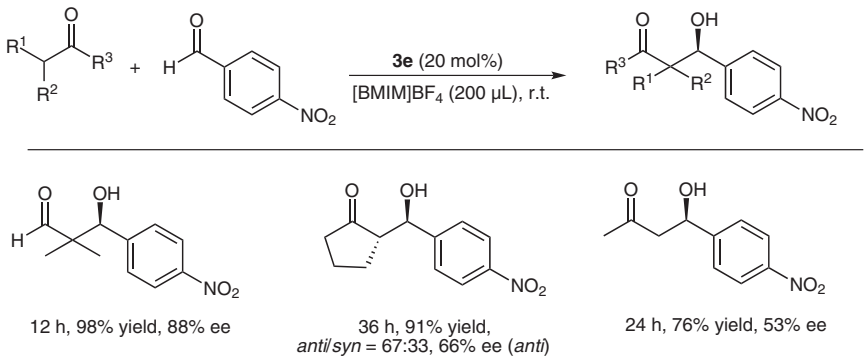
Entry	Catalyst[b]	Time (h)	Yield (%)	ee (%)[c]
1	**3a**	48	trace	–
2	**3b**	48	36	54
3	**3c**	48	99	73
4	**3d**	48	98	74
5	**3e**	24	80	78
6	**4**	24	63	78
7[d]	**3e**	30	96	79
8[e]	**3e**	36	81	79
9[f]	**3e**	48	88	76

[a] Reactions conditions: aldehyde (1 mmol), nitrostyrene (0.25 mmol), [BMIM]BF_4 (200L).
[b] Catalyst structures are shown in Figure 1.
[c] Determined by HPLC analysis.
[d] The second reuse of the catalyst.
[e] The third reuse of the catalyst.
[f] The fourth reuse of the catalyst.

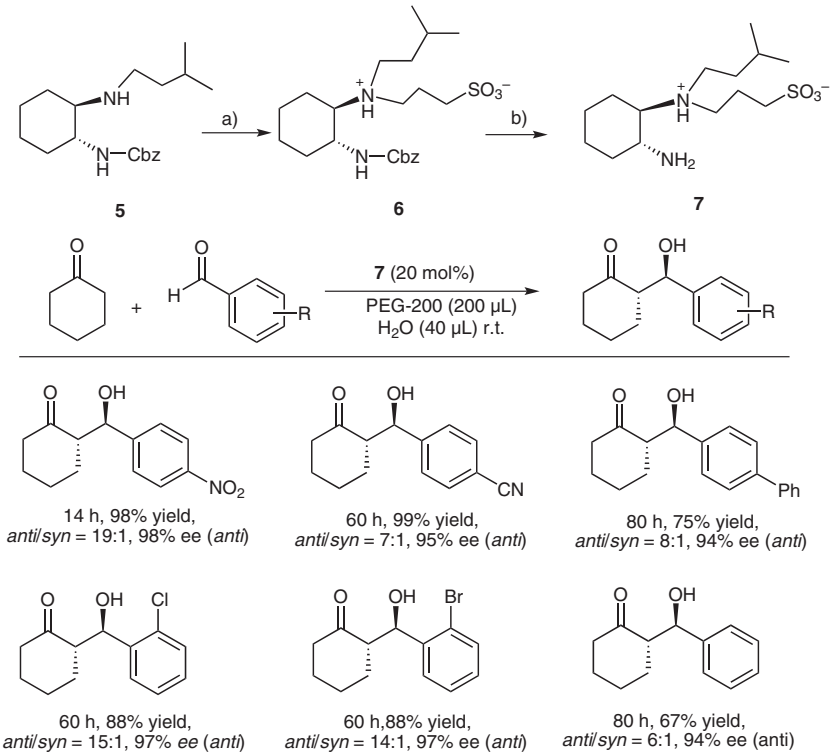


Scheme 3 Substrate scope of direct Michael reactions catalyzed by chiral zwitterions

To further demonstrate the potentials of our catalysts, the direct aldol reaction was also tested (Scheme 4). Under the catalysis of zwitterions **3e**, the aldol product could be obtained in excellent yield and high ee when using isobutyraldehyde as the donor. However, the reactions of ketone donors demonstrated only moderate enantioselectivities and diastereoselectivities, results that can be ascribed to the insufficient acidity of the zwitterionic moiety.[8]



Scheme 4 Aldol reaction catalyzed by zwitterion **3e**



Scheme 5 Synthesis of zwitterion **7** and its catalytic application. *Reagents and conditions*: a) 1,3-propanesultone, toluene, reflux; b) Pd/C, H_2, MeOH–H_2O (1:1).

We further expanded the utility of this zwitterions strategy to the chiral primary amine catalyst. Primary-tertiary diamine zwitterions **7** was synthesized following a similar route. The obtained zwitterionic catalyst **7** was then tested in the direct aldol reaction (Scheme 5). To our delight, the reactions between cyclohexanone and aryl aldehydes worked very well with up to 98% yield, 98% ee and 19:1 dr. These results are comparable to that obtained with chiral amine–Brønsted acid conjugate catalysts.[8b] In addition, the zwitterions catalyst **7** can also be recycled and reused with similar activity and stereoselectivity.

In conclusion, we have developed a new and facile approach for the synthesis of chiral zwitterionic ammonium sulfonates catalysts. These bifunctional zwitterionic catalysts demonstrate good activity and enantioselectivity in enamine-based transformations such as Michael and aldol reactions and can be utilized as a novel and practical alternative to the typical chiral amine–brønsted acid conjugate catalysts. Further applications of the catalysts to other types of reactions are currently under way in our laboratory.

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

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(5) **Spectral Data for Catalyst 3a**
^{1}H NMR (300 MHz, D_2O): δ = 7.93–7.95 (m, 1 H), 7.63–7.66 (m, 2 H), 7.48–7.51 (m, 1 H), 3.78–3.91 (m, 2 H), 3.65–3.70 (m, 1 H), 3.33–3.48 (m, 2 H), 2.04–2.23 (m, 3 H), 1.82–1.89 (m, 1 H). ^{13}C NMR (75 MHz, D_2O): δ = 172.5, 139.5, 133.1, 131.6, 127.8, 127.2, 60.6, 45.4, 39.8, 26.8, 22.6. IR (neat): 3403, 3077, 2977, 2886, 1637, 1595, 1566, 1531, 1431, 1316, 1234, 1170, 1143, 1085, 1018, 833, 767, 731 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{16}N_2O_4S$ [M + H]$^+$: 285.0904; found: 285.0902. $[\alpha]_D^{20}$ +32.2 (*c* 0.5, MeOH).
Compound **3b**: ^{1}H NMR (300 MHz, D_2O): δ = 3.72 (br s, 1 H), 3.33 (br s, 2 H), 2.82–2.97 (br, 6 H), 2.22 (s, 1 H), 1.97–2.06 (m, 4 H), 1.73 (s, 1 H). ^{13}C NMR (75 MHz, D_2O): δ = 59.0, 49.3, 48.8, 47.1, 45.5, 28.1, 23.6, 23.1. IR (neat): 3422, 2964, 2866, 1644, 1461, 1419, 1186, 1042 cm^{-1}. HRMS: *m/z* calcd for $C_8H_{18}N_2O_3S$ [M + H]$^+$: 223.1111; found: 223.1109. $[\alpha]_D^{20}$ +32.2 (*c* 0.5, MeOH).
Compound **3c**: ^{1}H NMR (300 MHz, D_2O): δ = 3.80–3.84 (t, *J* = 6.6 Hz, 1 H), 3.37–3.41 (br, 2 H), 2.91–2.96 (br, 3 H), 2.62–2.75 (m, 4 H), 2.35 (br s, 2 H), 2.02–2.23 (m, 4 H), 1.94 (br s, 2 H), 1.75 (br, 7 H), 1.53 (br s, 1 H), 1.26–1.28 (br, 4 H), 0.91–0.94 (br, 2 H). ^{13}C NMR (75 MHz, D_2O): δ = 60.9, 57.9, 55.7, 52.5, 48.9, 45.2, 35.3, 31.6, 28.0, 26.6, 25.9, 25.8, 22.9, 21.3. IR (neat): 3444, 2923, 2850, 1644, 1453, 1203, 1042 cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{30}N_2O_3S$ [M + H]$^+$: 319.2050; found: 319.2049. $[\alpha]_D^{20}$ +33.8 (*c* 0.5, MeOH).
Compound **3d**: ^{1}H NMR (300 MHz, D_2O): δ = 3.80–3.82 (m, 1 H), 3.37–3.42 (t, *J* = 7.2 Hz, 2 H), 2.92–2.97 (m, 3 H), 2.71–2.78 (m, 4 H), 2.37 (s, 2 H), 2.04–2.25 (m, 3 H), 1.95–1.97 (m, 2 H), 1.76–1.82 (m, 1 H), 0.95 (s, 9 H). ^{13}C NMR (D_2O, 75 MHz): δ = 66.7, 58.1, 57.0, 54.7, 49.0, 45.1, 32.1, 28.0, 27.8, 22.8, 21.4. IR (neat): 3446, 2953, 2867, 2828, 1644, 1481, 1464, 1394, 1361, 1186, 1042 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{28}N_2O_3S$ [M + H]$^+$: 293.1893; found: 293.1891. $[\alpha]_D^{20}$ +16.8 (*c* 0.5, MeOH).
Compound **3e**: ^{1}H NMR (300 MHz, D_2O): δ = 3.84 (s, 1 H), 3.33–3.38 (t, *J* = 6.6 Hz, 2 H), 2.66–3.03 (m, 7 H), 1.96–2.26 (m, 5 H), 1.71–1.77 (m, 1 H), 1.57–1.61 (m, 1 H), 1.40–1.42 (m, 1 H), 0.92–0.94 (d, *J* = 6 Hz, 6 H). ^{13}C NMR (75 MHz, D_2O): δ = 57.5, 54.7, 51.6, 51.4, 48.7, 45.2, 33.8, 28.2, 26.0, 23.0, 22.0, 21.9, 20.8. IR (neat): 3460, 2957, 2871, 1651, 1467, 1384, 1368, 1196, 1042 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{28}N_2O_3S$ [M + H]$^+$: 293.1893; found: 293.1882. $[\alpha]_D^{20}$ +12.2 (*c* 0.5, MeOH).
Compound **7**: ^{1}H NMR (300 MHz, D_2O): δ = 3.09–3.14 (m, 1 H), 2.94–3.03 (br s, 2 H), 2.51–2.79 (m, 4 H), 2.16–2.20 (d, *J* = 11.4 Hz, 1 H), 1.80–2.00 (m, 5 H), 1.57–1.63 (m, 1 H), 1.33–1.44 (m, 6 H), 0.92–0.96 (q, *J* = 3.6, 6.3 Hz,). ^{13}C NMR (75 MHz, D_2O): δ = 62.7, 50.9, 48.8, 48.2, 47.8, 36.9, 30.2, 25.9, 24.6, 23.8, 23.2, 23.0, 22.3, 21.8. IR (neat): 3483, 3447, 2951, 2867, 1637, 1468, 1383, 1367, 1207, 1183, 1043 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{30}N_2NaO_3S$ [M + Na]$^+$: 329.1869; found: 329.1868. $[\alpha]_D^{20}$ +59.4 (*c* 0.5, MeOH).

(6) Upon long-term storage (>3 months), the solid becomes syrup due to the absorption of moisture. This syrup can be restored to solid power after dried under vaccum.

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