# Primary amine-metal Lewis acid bifunctional catalysts: the application to asymmetric direct aldol reactions†

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**The first example of metal Lewis acid-primary amine bifunctional cooperative catalyst derived from primary amino acids was developed, and it was found to catalyze aldol reactions of cyclic ketones highly efficiently with very good to excellent stereoselectivities.**

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions.[1] In nature, it is catalyzed by aldolases with excellent stereocontrol.[2] Type I aldolase activates the aldol donor by a primary amino group of lysine located at the active site through an enamine mechanism, based on which the enamine-based aminocatalysis was developed;[3] in type II aldolase a zinc cofactor is involved as a Lewis acid; several research groups have mimicked this process by using metal complexes.[4] We want to take advantage of both types of aldolases and develop a novel class of enamine (Lewis base)-metal Lewis acid bifunctional catalysts with the intention to bridge the more traditional fruitful transition metal catalysis with the newly established prosperous aminocatalysis.

As compared with their secondary amine counterpart (proline), which has been playing a major role in organocatalysis and has been intensively investigated in the past few years,[3] primary amino acids have received much less attention.[5] However, primary amino acids and their derivatives have shown unique selectivity and activity in organocatalysis as demonstrated by recent studies on aldol and Mannich reactions.[6] Although they are currently of much narrower substrate scope and lower activity than proline-based catalysts, primary amino acids have shown to offer better results for many reactions.[5,6] Herein, we wish to report the first example of primary amine-metal Lewis acid bifunctional catalysts derived from primary amino acids, and their successful application to asymmetric direct aldol reactions.

The major challenge in developing Lewis acid–Lewis base bifunctional catalysts lies in the acid–base self-quenching reaction leading to catalyst-inactivation.[7] To solve this problem, we tether the primary amino acid to a tridentate ligand (Fig. 1), so that the tridentate ligand will "trap" the incoming metal and prevent the metal from coordinating to the amine. In this way, the metal and the primary amine are brought in close proximity without interacting with each other. This design principle has been demonstrated in our proline-based enamine-metal Lewis acid catalysts.[8] The metal introduced into the chiral tridentate scaffold will act as a Lewis acid, and at the same time it will also serve to assemble the molecule into a relatively rigid structure, a desired property for bifunctional catalysts. Furthermore, the Lewis acidity and the secondary structure for substrate interaction can be easily tuned by introducing different metals.

Six tridentate ligands were prepared (Fig. 1). These ligands can be readily obtained through coupling reactions of 2,6-diaminopyridine with natural amino acids (see ESI† for synthetic details). We initially conducted metal screening with ligand **1a** in the aldol reaction of cyclohexanone with 4-nitrobenzaldehye in THF. While all metal salts examined displayed activity (Table 1, entries 1–4), $Cu(SbF_6)_2$ showed exceptionally good activity and high stereoselectivity. The aldol reaction was complete in only 12 h, and the aldol product **5a** was generated in 92% yield, 15:1 *dr* (*anti*/*syn*), and 90% *ee* (*anti*). The different activities and selectivities observed for different metals may arise from different Lewis acidities and coordination geometries of the metals. Counter anion effect was also observed: $Cu(OTf)_2$ displayed lower activity and stereoselectivity relative to $Cu(SbF_6)_2$ (entries 1 and 2). Slightly better results were obtained when neat conditions were applied (entry 5). We then screened the ligands in conjunction with $Cu(SbF_6)_2$ under neat conditions (entries 6–10). Excellent stereoselectivity (up to >99:1 *dr* and 95% *ee*) and activity were observed for L-valine derived catalysts (entries 5–8). As compared with L-valine-based catalysts, catalysts derived from L-phenylalanine showed lower stereoselectivity (entries 9 and 10). Among all the catalysts, **1c**/$Cu(SbF_6)_2$ offered the best results (entry 10). In comparison with the aldol reactions catalyzed by other metal Lewis acids

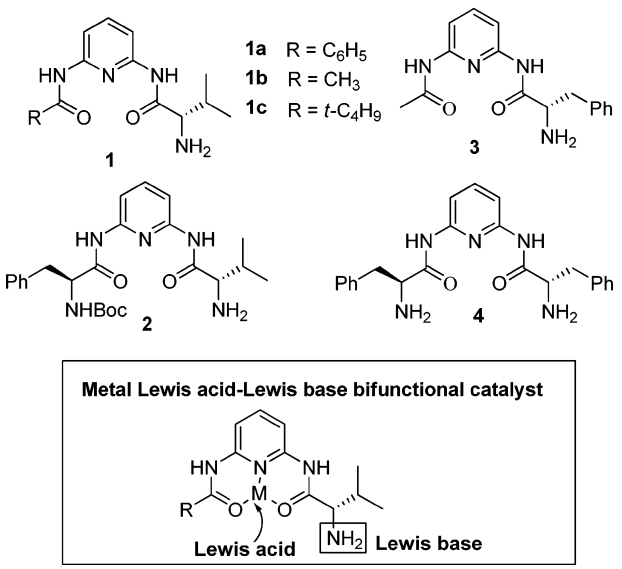


**Fig. 1** Structure of ligands and illustration of bifunctional catalyst.

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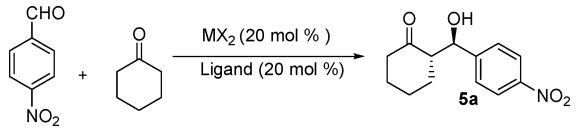
**Table 1** Metal and ligand screening[a]




| Entry | Ligand | Metal | Solvent | *T*/h | Yield (%)[e] | *Anti*/*syn*[f] | *ee* (%)[g] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $Cu(SbF_6)_2$ | THF | 12 | 92 | 15/1 | 91 |
| 2 | **1a** | $Cu(OTf)_2$ | THF | 24 | 56 | 8/1 | 87 |
| 3 | **1a** | $Zn(OAc)_2$ | THF | 48 | 36 | 1/1.3 | 25/12 |
| 4 | **1a** | $Co(ClO_4)_2$ | THF | 24 | 70 | 5/1 | 79 |
| 5 | **1a** | $Cu(SbF_6)_2$ | neat | 12 | 90 | 15/1 | 93 |
| 6 | **1b** | $Cu(SbF_6)_2$ | neat | 12 | 92 | 22/1 | 95 |
| **7** | **1c** | **$Cu(SbF_6)_2$** | **neat** | **12** | **90** | **>99/1[h]** | **95** |
| 8 | **2** | $Cu(SbF_6)_2$ | neat | 12 | 93 | >99/1[h] | 92 |
| 9 | **3** | $Cu(SbF_6)_2$ | neat | 12 | 95 | 8/1 | 81 |
| 10 | **4** | $Cu(SbF_6)_2$ | neat | 12 | 64 | 5/1 | 57 |
| 11[b] | **1c** | $Cu(SbF_6)_2$ | neat | 16 | 84 | 16/1 | 95 |
| 12[c] | **1c** | $Cu(SbF_6)_2$ | neat | 20 | 80 | 20/1 | 94 |
| 13[d] | **1c** | $Cu(SbF_6)_2$ | neat | 36 | 90 | 20/1 | 92 |

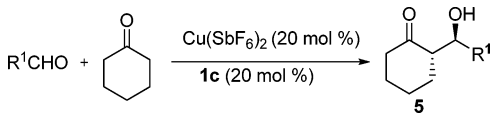
[a] The reactions were performed with 0.2 mmol of 4-nitrobenzaldehyde and 0.3 mL of cyclohexanone at room temperature in 0.6 mL THF; or 0.2 mmol of 4-nitrobenzaldehyde with 1 mL of cyclohexanone (neat). [b] 5 Equiv. of $H_2O$ was added. [c] 10 Equiv. of $H_2O$ was added. [d] 10 Mol% catalyst. [e] Combined yield. [f] Determined by $^1H$ NMR. [g] Determined by chiral HPLC. [h] The *syn* diastereomer was not observed on $^1H$ NMR.

requiring moist and air free,[4] this reaction system is water and air tolerant. The aldol reaction proceeded smoothly in the presence of water and air with slightly lower diastereoselectivities (entries 11 and 12). When lower catalyst loading was applied, longer reaction time was required for the completion of the reaction (entry 13).

Ligand **1c**/$Cu(SbF_6)_2$ was then selected for further investigation. Under the optimal conditions, the aldehyde scope of the direct aldol reaction of cyclohexanone was evaluated (Table 2). Not only were the reactive electron-deficient aldehydes excellent substrates, giving 6/1 to >99/1 diastereoselectivity (*anti*/*syn*), and 88–95% enantioselectivity (Table 2, entries 1–8), but the unreactive electron-rich aldehydes also furnished the aldol products **5** in good yields with high stereoselectivities (8/1–12/1 *dr*, 83–90% *ee*) (entries 9–11).

Several other ketone donors were also investigated and the results are summarized in Table 3. The six-membered heterocyclic ketones reacted with both electron-rich and electron-poor aldehydes and generated aldol products (**6**) in high yields with excellent diastereoselectivities (10/1–46/1, *anti*/*syn*) and very good enantioselectivities (87–94%) (entries 2–7). It is noteworthy that only 2.5 eq. of heterocyclic ketones were used in these aldol reactions. However, the reactions of cyclopentanone and acetone with 4-nitrobenzaldehyde lead to the corresponding aldol products in lower diastereoselectivity and enantioselectivity, respectively (entries 1 and 8).

**Table 2** Aldehyde scope of direct aldol reaction of cyclohexanone[a]



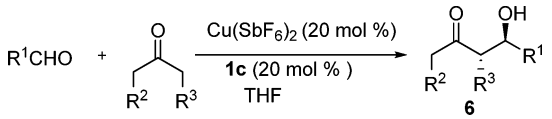

| Entry | $R^1$ | Product | Yield (%)[b] | *Anti*/*syn*[c] | *ee* (%)[d] |
|---|---|---|---|---|---|
| 1 | $4\text{-}NO_2C_6H_4$ | **5a** | 90 | >99/1[e] | 95 |
| 2 | $3\text{-}NO_2C_6H_4$ | **5b** | 90 | 20/1 | 95 |
| 3 | $2\text{-}NO_2C_6H_4$ | **5c** | 82 | >99/1[e] | 94 |
| 4 | $4\text{-}CNC_6H_4$ | **5d** | 93 | 12/1 | 92 |
| 5 | $4\text{-}COOMeC_6H_4$ | **5e** | 89 | 9/1 | 94 |
| 6 | $2,6\text{-}Cl_2C_6H_3$ | **5f** | 98 | 12/1 | 92 |
| 7 | $4\text{-}ClC_6H_4$ | **5g** | 73 | 6/1 | 88 |
| 8 | $4\text{-}BrC_6H_4$ | **5h** | 60 | 6/1 | 94 |
| 9 | $C_6H_5$ | **5i** | 76 | 10/1 | 86 |
| 10 | 2-Naphthyl | **5j** | 71 | 12/1 | 90 |
| 11 | $4\text{-}MeC_6H_4$ | **5k** | 75 | 8/1 | 83 |

[a] The reactions were performed with 0.2 mmol of aldehyde at room temperature in 1 mL of cyclohexanone for 12–48 h. [b] Combined yield. [c] Determined by $^1H$ NMR. [d] Determined by chiral HPLC. [e] The *syn* diastereomer was not observed on $^1H$ NMR.

In order to understand the nature of the catalysts, we have conducted a series of reactions (Scheme 1). When free ligand **1a** was solely used as the catalyst in the absence of a metal, no reaction was detected. Addition of benzoic acid (20 mol%) lead to less than only 5% of formation of the aldol product. $Cu(SbF_6)_2$ alone cannot catalyze the aldol reaction. These data are in striking contrast to the aldol reactions carried out with **1a**/metal indicating that both ligand **1a** and $Cu(SbF_6)_2$ are essential for the aldol reaction to occur. It has been well accepted that for primary amine catalyzed aldol reactions, the presence of water is necessary to facilitate the formation of enamine leading to the aldol product.[5a,9] It is noteworthy that the aldol reactions catalyzed by this bifunctional catalyst, even though water tolerant (Table 1, entries 11 and 12), proceeded highly efficiently in the absence of water. These data strongly support that this primary amine-metal Lewis acid bifunctional catalyst function cooperatively, and the aldol acceptors (aldehyde) are more activated in this bifunctional catalytic system relative to those in the primary amino acid-based (enamine-Brønsted acid) organocatalytic system,[5,6] showing the great potentials of these catalysts. All the aldol reactions predominately generated the *anti* aldol products with a (2*S*, 1′*R*) configuration. We speculate that the metal coordinates with the chelating ligand to form a rigid chiral structure and acts as a Lewis acid to activate the aldehyde; the primary amine reacts with cyclohexanone to form an enamine; the enamine attacks the activated aldehyde from the *re*-face to generate the products (Fig. 2).

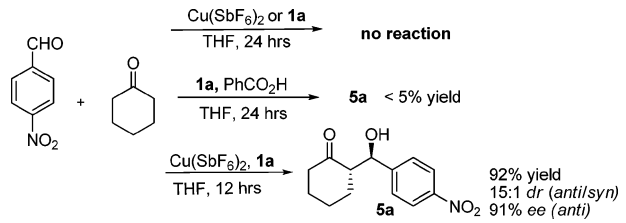
 

**Table 3** The aldol reaction of different ketone donors[a]




| Entry | $R^1$ | $R^2$, $R^3$ | Product | Yield (%)[c] | *Anti*/*syn*[b] | *ee* (%)[d] |
|---|---|---|---|---|---|---|
| 1[e] | 4-$NO_2C_6H_4$ | $-CH_2CH_2-$ | **6a** | 66 | 3/1 | 86 |
| 2 | 4-$NO_2C_6H_4$ | $-CH_2OCH_2-$ | **6b** | 97 | 10/1 | 87 |
| 3 | 4-$NO_2C_6H_4$ | $-CH_2SCH_2-$ | **6c** | 82 | 22/1 | 94 |
| 4 | 2-$NO_2C_6H_4$ | $-CH_2SCH_2-$ | **6d** | 76 | 25/1 | 94 |
| 5 | 4-$CNC_6H_4$ | $-CH_2SCH_2-$ | **6e** | 86 | 46/1 | 91 |
| 6 | 2-Naphthyl | $-CH_2SCH_2-$ | **6f** | 57 | 34/1 | 87 |
| 7 | $C_6H_5$ | $-CH_2SCH_2-$ | **6g** | 68 | 25/1 | 94 |
| 8[e] | 4-$NO_2C_6H_4$ | H, H | **6h** | 84 | — | 72 |

[a] The reactions were performed with 0.2 mmol of aldehyde and 0.5 mmol of ketone at room temperature in 1 mL of THF for 12–48 h. [b] Determined by $^1$H NMR. [c] Combined yield. [d] Determined by chiral HPLC. [e] The reaction was performed with 0.2 mmol of aldehyde with 1 mL of ketone (neat).




**Scheme 1** Cooperative nature of the bifunctional enamine-metal Lewis acid catalyst.

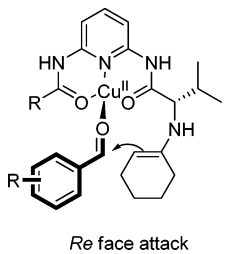



**Fig. 2** Proposed transition state.

In summary, we have developed a novel class of primary amine-based enamine-metal Lewis acid cooperative bifunctional catalysts, and successfully applied them to asymmetric direct aldol reactions. These catalysts are highly efficient in catalyzing the aldol reaction of cyclic ketones with both electron-rich and electron-poor aldehydes in very good to excellent stereoselectivity. It is found that the coexistence of the primary amine and metal Lewis acid is critical for the reaction to occur. This catalytic system has the following features: (1) it is the first example of bifunctional catalyst combining metal Lewis-acid catalysis and primary amine catalysis; (2) the catalysts' structure can be easily tuned by introducing different metals and/or different acyclic amino acids; (3) the ligands are very simple and can be readily prepared in large scales; (4) the reaction does not need an inert atmosphere as required by most metal catalysis. Application of these catalysts to Mannich reactions and Michael reactions is underway.

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