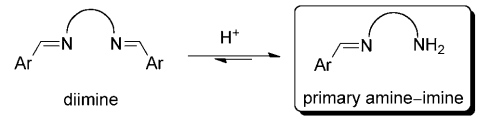
DOI: 10.1002/chem.201100200

In Situ Formed Bifunctional Primary Amine–Imine Catalyst for Asymmetric Aldol Reactions of α-Keto Esters

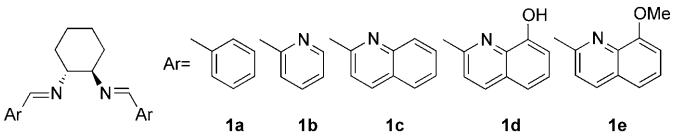
Xi Zhu,[a] Aijun Lin,[a] Ling Fang,[a] Wei Li,[b] Chengjian Zhu,*[a] and Yixiang Cheng*[a]

Asymmetric organocatalysis has become the main focus of research in asymmetric synthesis since the independent pioneering work of List, Barbas, and MacMillan.[1] Among the different kinds of organocatalysts, chiral secondary amines have been extensively used as amino catalysts in the past several years.[2] Recently, there has been growing interest in chiral primary amine catalysts because they are effective promoters for aldol reactions,[3] Michael additions,[4] α-aminations,[5] and cycloaddition reactions.[6] In asymmetric synthesis catalyzed by primary amines, the amido moiety is normally employed to form the enamine intermediates, which activate the nucleophile and facilitates the reaction.[7] Furthermore, the electronic effect and steric shielding are commonly utilized to afford a mutifunctional environment and improve the stereoselectivity. Chemists have succeeded in developing several mutifunctional primary amine catalysts for asymmetric synthesis. Jacobsen and Tsogoeva independently reported chiral primary amine–thiourea organocatalysts in 2006.[8] Luo and Cheng successfully developed a new chiral primary–tertiary diamine for aldol reactions in 2007.[9] Despite these significant advancements,[10] the chiral primary aminocatalysts can only be obtained by complex synthesis procedures, which limited their further applications. Therefore, it is of significance to develop more facile syntheses of chiral primary aminocatalysts.

Although the C_2-symmetric chiral salens are among the most widely studied ligands in asymmetric catalysis,[11] the non-C_2-symmetric chiral primary amine–imine has never been employed in chemistry. To the best of our knowledge, a reliable strategy to prepare a stable non-C_2-symmetric primary amine–imine has not been reported.[12] Due to the thermal instability, the primary amine–imine was inevitably converted to a C_2-symmetric diimine (Scheme 1); therefore, methods to isolate and take advantage of the primary amine–imine were challenging. In our study, we found that the diimine (such as the salen ligand) was easy to hydrolyze in acidic conditions and convert to the primary amine–imine. In the preliminary investigation, chiral diimine **1d** was prepared and acidified by AcOH in CH_2Cl_2 (Scheme 2).



Scheme 1. Hydrolysis equilibrium conversion of diimine and primary amine–imine.



Scheme 2. Structure of diimines.

Delightfully, the non-C_2-symmetric primary amine–imine could be detected by analysis of the mixture by using ESI-MS (Figure 1a). Other diimines (**1a–1c** and **1e**) also gave the similar results, and the data remained unchanged even after the mixtures had been stirred for five days. This showed that the primary amine–imine could be prepared from the diimine and was well-tolerated in acidic conditions.

Inspired by this finding, we herein report the in situ preparation of a series of novel bifunctional primary amine–imine catalysts from chiral diimine precusors. The bifunctional primary amine–imine catalysts can exhibit excellent enantioselectivities for the direct asymmetric aldol reactions of ketones with α-keto esters in high yields.

The aldol reaction of methyl phenylglyoxylate and acetone was selected as model reaction with diimine **1a** as pre-catalyst. The results are summarized in Table 1. Initially, the reaction failed to proceed without any additive (Table 1, entry 1). Surprisingly, when compound **1a** (10 mol%) was added with AcOH (0.1 mL), the desired product was afforded in 79% yield with 65% enantiomeric excess (*ee*) under solvent-free conditions at 0°C (Table 1, entry 2). Chiral diimines **1b–1e** were also tested and **1d** showed the best enantioselectivity of 83% *ee* (Table 1, entries 3–6). The

[a] X. Zhu, A. Lin, L. Fang, Prof. Dr. C. Zhu, Prof. Dr. Y. Cheng
School of Chemistry and Chemical Engineering
State Key Laboratory of Coordination Chemistry
Nanjing University, Nanjing, 210093 (China)
Fax: (+86) 25-83594886
E-mail: cjzhu@nju.edu.cn
yxcheng@nju.edu.cn

[b] Dr. W. Li
National Standard Laboratory of Pharmacology
for Chinese Medicine
Research Institute of Chinese Medicine
Nanjing University of Chinese Medicine, Nanjing, 210029 (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201100200.

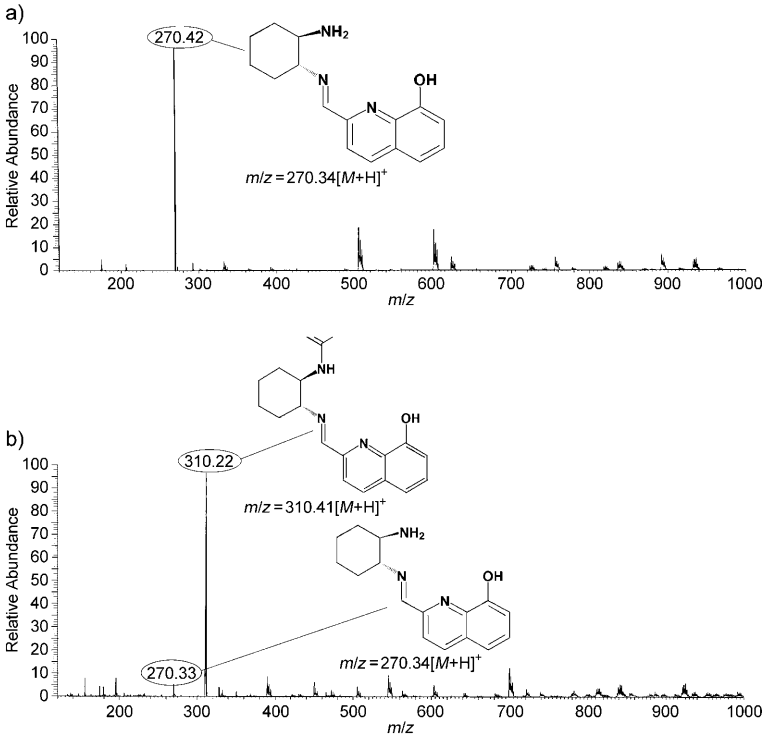
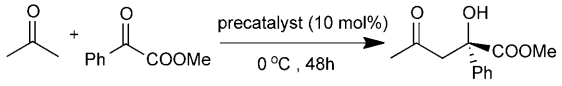


Figure 1. Mass spectra (ESI-MS) of mixture of **1d** with AcOH.[13] a) In CH_2Cl_2 b) In acetone.

Table 1. Direct aldol reaction of acetone and methyl phenylglyoxylate.



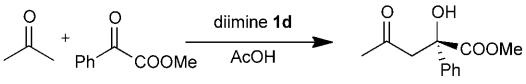
Entry[a]	Precatalyst	Additive	Yield [%][b]	*ee* [%][c]
1	**1a**	–	–	–
2	**1a**	AcOH	79	65
3	**1b**	AcOH	84	70
4	**1c**	AcOH	82	72
5	**1d**	AcOH	86	83
6	**1e**	AcOH	84	77
7	**1d**	HCOOH	60	73
8	**1d**	TFA	64	70
9	**1d**	TfOH	trace	n.d.[d]
10	**1d**	PhCOOH	trace	n.d.[d]
11	(*R*, *R*)-diaminocyclohexane	–/AcOH	87/86	41/43

[a] Carried out with methyl phenylglyoxylate (0.1 mmol), Brønsted acid (18 equiv to methyl phenylglyoxylate) and 10 mol% loading of diimine in acetone (0.3 mL) at 0°C for 48 h. TFA = trifluoroacetic acid. TfOH = trifluoromethanesulfonic acid. [b] Yield of isolated product. [c] Determined by chiral HPLC. The absolute configuration was established as *S* by comparison to the literature.[14] [d] n.d. = Not determined.

effect of the additive was also investigated. Among the Brønsted acids probed (Table 1, entries 5 and 7–10), it appeared that AcOH was the most effective, achieving the highest enantioselectivity. In addition, (*R*, *R*)-diaminocyclohexane was also investigated as the catalyst but poor enantioselectivity was obtained (41% *ee*), even with the addition of AcOH (43% *ee*, Table 1, entry 11). The results indicated that steric hindrance and the hydrophilic group were crucial for high enantioselectivity.

To further improve the enantioselectivity, the effects of reaction temperature and the catalyst loading were investigated. As summarized in Table 2, lowering the temperature to −20°C led to an improvement of the enantioselectivity but a slight loss of yield (Table 2, entry 2). Further lowering of the temperature caused very poor reactivity (Table 2, entry 3). Decreasing catalyst loading from 20 to 2 mol% provided comparable enantioselectivities but had a considerable negative impact on the yield (Table 2, entries 2 and 4–6). The loading of AcOH was also studied; 24 equiv of AcOH to methyl phenylglyoxylate was found to be suitable for the reaction scale (Table 2, entry 8). It appeared that the amount of AcOH might affect the hydrolysis reaction equilibrium of the chiral diimine. Optimization of the reaction conditions revealed that a 10 mol% loading of **1d** and AcOH (24 equiv) added in acetone (0.3 mL) at −20°C afforded the best reactivity (85% yield) and enantioselectivity (96% *ee*) in 72 h. The absolute configuration of the product was determined to be *S* by comparison with the optical rotation of its known counterpart.[14]

Table 2. Optimization of the reaction conditions.



Entry[a]	*T* [°C]	**1d** [mol%]	*t* [h]	AcOH [equiv][b]	Yield [%][c]	*ee* [%][d]
1	0	10	48	18	86	83
2	−20	10	72	18	80	93
3	−30	10	120	18	33	93
4	−20	2	96	18	19	94
5	−20	5	96	18	45	92
6	−20	20	72	18	86	86
7	−20	10	72	21	81	92
8	−20	10	72	24	85	96
9	−20	10	72	27	80	93
10	−20	10	72	30	74	88

[a] Carried out with methyl phenylglyoxylate (0.1 mmol) in acetone (0.3 mL). [b] Equiv of AcOH to methyl phenylglyoxylate. [c] Yield of isolated product. [d] Determined by chiral HPLC.

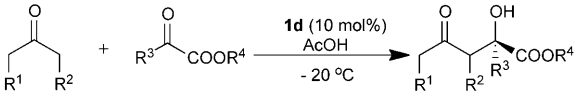
With the optimized conditions, the substrate generality was investigated. In general, the aldol reactions proceeded smoothly with a wide range of α-keto esters and ketones to

generate the corresponding products with high enantioselectivities (Table 3). The methyl, ethyl, isopropyl, and cyclohexyl phenylglyoxylate underwent the reaction with acetone in high yields and 91–96% *ee* (Table 3, entries 1–4). α-Keto esters that had electron-donating substituents (Table 3, entries 5–10) and electron-withdrawing substituents (Table 3, entries 11–14) on the aromatic rings were introduced and well-tolerated. The results revealed that the electronic nature of the aromatic ring has no effect on the enantioselectivity. Methyl 2-(2,5-dimethoxyphenyl)-2-oxoacetate was examined for the first time as a substrate and showed the best enantioselectivity of 99% *ee* (Table 3, entry 10). The α-keto ester with a naphthyl in the β position showed good enantioselectivity but the reactivity was inferior to other α-keto esters (Table 3, entry 16). The heteroaromatic compound methyl 2-oxo-2-(tetrahydrothiophen-2-yl) acetate was also a good aldol acceptor and gave the product with high enantioselectivity and only a small decrease in yield (Table 3, entry 16). Other ketones were tested and provided the products with a slight decrease in yield and enantioselectivity (Table 3, entries 17–19).

For further demonstration of the reaction process, diimine **1d** was acidified by AcOH in acetone and the ESI-MS analysis was used to study the reaction mixture. The enamine intermediates were detected significantly in the spectra (Figure 1b). Compared with the catalysts **1a**–**1c** (Table 1), **1d** showed an obviously higher enantioselectivity. On the other hand, catalyst **1e** with protection of the alcohol gave some loss of *ee* value, showing that the alcohol is a key moiety for high enantioselectivity. The structure of **1d** was considered to contribute to the enantio-induction not only due to steric hindrance, but also due to the electronic effect (hydrogen bonding with the α-keto ester). Based on this result, we proposed a mechanism of the aldol reaction as depicted in Scheme 3. The chiral diimine was hydrolyzed under acidic conditions and converted to primary amine–imine (A), which promotes the aldol reaction as a bifunctional organocatalyst through the enamine. The interaction between ketone and amine gives the active enamine (B), which activates the α-keto ester by hydrogen bonding (C). The aromatic moiety and the active enamine are bent upwards and downwards respectively. The active enamine is much more accessible to attack the methyl phenylglyoxylate from the *Re* face, affording the major stereoisomer.

In conclusion, we have developed a new bifunctional primary amine–imine catalyst, which is prepared in situ from a chiral diimine under acidic conditions. The catalyst promotes the direct aldol reactions between ketones and α-keto esters in high yields and with excellent enantioselectivity. Ef-

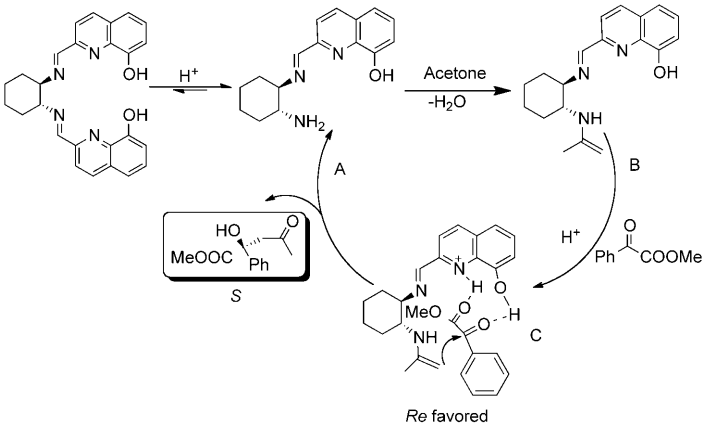
Table 3. Calalyst **1d**-promoted asymmetric aldol reaction of ketones with α-keto esters under optimum conditions.



2 **3** **4**

Entry[a]	**2**	**3** R^3	**3** R^4	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	acetone	Ph	Me	72	**4a**	85	96 (*S*)[d]
2	acetone	Ph	Et	72	**4b**	82	96
3	acetone	Ph	*i*Pr	72	**4c**	75	96
4	acetone	Ph	cyclohexyl	96	**4d**	81	91
5	acetone	2-$CH_3C_6H_4$	Me	96	**4e**	88	95
6	acetone	3-$CH_3C_6H_4$	Me	96	**4f**	86	97
7	acetone	4-$CH_3C_6H_4$	Me	96	**4g**	82	95
8	acetone	3,4-$(CH_3)_2C_6H_4$	Me	96	**4h**	79	96
9	acetone	4-$CH_3OC_6H_4$	Me	96	**4i**	76	87
10	acetone	2,5-$(CH_3O)_2C_6H_4$	Me	96	**4j**	82	99
11	acetone	3-ClC_6H_4	Me	72	**4k**	84	96
12	acetone	4-ClC_6H_4	Me	72	**4l**	86	96
13	acetone	4-BrC_6H_4	Me	72	**4m**	87	96
14	acetone	4-FC_6H_4	Me	72	**4n**	85	96
15	acetone	2-Naphthyl	Me	72	**4o**	71	94
16	acetone	2-Thiophenyl	Me	96	**4p**	65	95
17	2-butanone	Ph	Me	96	**4q**	81	87
18	cyclohexanone	Ph	Me	96	**4r**	82	89/93[e]
19	acetophenone	Ph	Me	96	**4s**	67	87[f]

[a] Unless otherwise noted, the reaction was carried out with methyl phenylglyoxylate (0.1 mmol), AcOH (24 equiv to methyl phenylglyoxylate), and 10 mol% loading of **1d** in ketone (0.3 mL) at −20°C. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] The absolute configurations were established as *S* by comparison to the literature.[14] [e] Diastereomeric ratio (d.r.)=2.6:1, for major product (89% *ee*) and for minor product (93% *ee*). The absolute configuration of the major diastereoisomer was established as (*S*, *R*) by comparison to the literature.[14] [f] The reaction was carried out at 0°C with CH_2Cl_2 (0.3 mL) to dissolve acetophenone.



Scheme 3. Proposed catalytic mechanism.

forts are focused on a more detailed mechanism and further application of the catalyst system in our laboratory.

Experimental Section

General procedure: To a stirred solution of diimine **1d** (4.2 mg, 0.01 mmol) in anhydrous acetone (0.3 mL) was added methyl phenylglyoxylate (15.0 μL, 0.1 mmol) and then AcOH (24 equiv to methyl phenylglyoxylate) at −20 °C. The resulting mixture was stirred at −20 °C for 72 h. The mixture was directly purified by flash column chromatography on silica gel (EtOAc/petroleum ether = 1:5) to afford the product as a white solid.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (20832001, 20972065, 21074054, 81072542) and the National Basic Research Program of China (2007CB925103, 2010CB92330) for their financial support.

Keywords: aldol reaction · asymmetric catalysis · ketones · organocatalyst · primary amine–imine

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Received: January 19, 2011
Published online: June 7, 2011

