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Highly effective and enantioselective α-amination of aldehydes promoted by chiral proline amide–thiourea bifunctional catalysts

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ABSTRACT

A series of secondary amine–thiourea catalysts derived from L-proline and chiral diamine were prepared and successfully applied to the highly effective and enantioselective α-amination of unmodified aldehydes with various azodicarboxylates in excellent yields (up to 99%) and enantioselectivities (up to 99% ee) within a few minutes.

The formation of carbon–nitrogen bond is a straightforward method to access optically active nitrogen-containing compounds, which has been widely applied to the preparation of natural products and pharmaceuticals of biological activities.[1] α-Amination of aldehydes is one of the most powerful and efficient methods for carbon–nitrogen bond formation and can afford α-amino aldehydes which are potentially important building blocks for a variety of valuable synthetic intermediates such as α-amino alcohols, α-amino acids.[2]

Over the past years, great progresses have been made on asymmetric α-amination of aldehydes. In 2002, Jørgensen and co-workers[3] and List[4] almost simultaneously reported the first example of α-amination of aldehydes catalyzed by L-proline in high yields and excellent enantioselectivities. Since then, α-amination of aldehydes with azodicarboxylates has received considerable attention in recent years. After that, Adolfsson reported the same amination catalyzed by chiral mono-sulfonyl-2-aminopyrrolidines in moderate yields and enantioselectivities.[5] Except L-proline[3,4,6] and its structural analogs,[5,7,8] Chen and co-workers recently developed a series of mono-sulfonyl-2-aminopyrrolidines with camphor scaffold for the direct α-amination of simple aldehydes in excellent yields and high enantioselectivities.[9] For a broader range of this reaction, asymmetric amination of ketones,[10,11] cyanoacetates,[12,13] alkylidene cyanoacetates,[14] and 2-oxindoles[15–17] have also been reported. Up to the present, a considerable amount of effort has been made on the discovery of chiral organocatalysts for this direct asymmetric conversion, however, to the best of our knowledge, there have been only a limited number of chiral catalysts available[3–8] for excellent enantioselectivities. It is still highly challenging and desirable to develop new, efficient catalytic systems for this reaction.

Recently, bifunctional activations, which simultaneously activate both acceptors and donors, have been regarded as an important strategy in asymmetric small molecular catalysis.[18] As a typical and effective activation model, chiral thiourea catalysts have been widely used due to their effective activation of carbonyl and nitro groups through double hydrogen-bonding interactions,[19] and secondary amines, especially L-proline and L-prolic amides, have been well identified as powerful catalysts to activate aldehydes or ketones via enamine or imine transition state.[20] Holding the concept of bifunctional activations, we expected that the kind

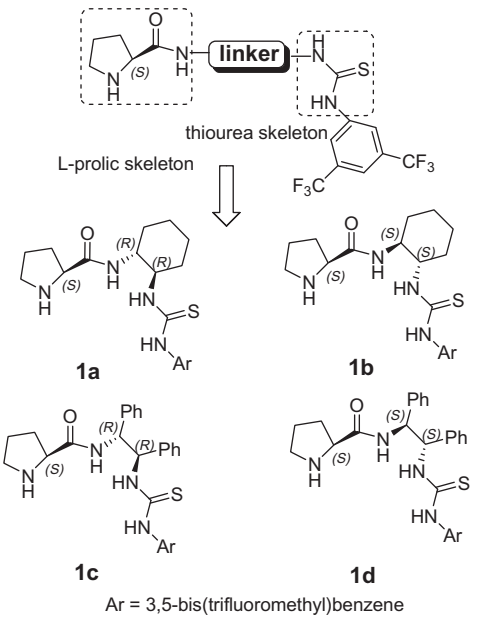

Figure 1. Secondary amine–thiourea catalysts.

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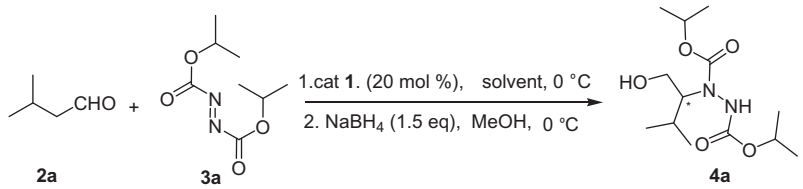
Table 1
Screening of catalysts **1a–d** and solvents[a]

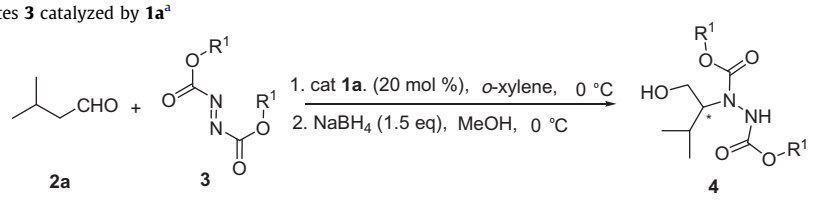


2a 3a 4a

Entry	Cat.	Solvent	Time[b] (min)	Yield[c] (%)	ee[d] (%)
1_f	**1a** (**1c**)	CH_3CN	40 (20)	71 (98)	89 (94)(R)
2_f	**1b** (**1d**)	CH_3CN	35 (240)	70 (70)	81 (76)(R)
3	**1a** (**1c**)	*n*-Hexane	25 (25)	76 (99)	91 (81)
4	**1a** (**1c**)	Cyclohexane	25 (25)	79 (64)	96 (83)
5	**1a** (**1c**)	*o*-Xylene	40 (50)	89 (91)	99 (94)
6	**1a** (**1c**)	Toluene	30 (270)	80 (82)	95 (87)
7	**1a** (**1c**)	DCE	23 (20)	92 (85)	95 (94)
8	**1a** (**1c**)	DCM	25 (144)	88 (89)	96 (91)
9	**1a** (**1c**)	$CHCl_3$	40 (180)	90 (97)	90 (92)
10	**1a** (**1c**)	Et_2O	35 (35)	75 (86)	97 (95)
11	**1a** (**1c**)	THF	660 (540)	45 (53)	97 (79)
12	**1a** (**1c**)	CH_3CN	18 (20)	93 (95)	92 (89)
13	**1a** (**1c**)	MeOH	330 (600)	18 (48)	54 (16)
14[e]	**1a**	*o*-Xylene	10	89	93

[a] Adding sequence: catalyst **1** (20 mol %), solvent (0.8 mL), isovaleral (0.3 mmol) and azodicarboxylate (0.2 mmol).
[b] Time of amination.
[c] Isolated yield.
[d] The ee value was determined by GC and the absolute configuration of **4a** was assigned as R (see Supplementary data).
[e] The reaction was carried out at 25 °C.

Table 2
Reaction of **2a** with azodicarboxylates **3** catalyzed by **1a**[a]



2a 3 4

Entry	R^1	**2a**:**3** (mol:mol)	Cat. loading (×mol %)	Time[b](min)	Yield[c] (%)	ee[d] (%)
1	*i*-Pr (**3a**)	1.5:1.0	20	40	**4a** 89	99
2	Bn (**3b**)	1.5:1.0	20	10	**4b** 70	98[e]
3	Et (**3c**)	1.5:1.0	20	5	**4c** 97	>99
4	*i*-Pr (**3a**)	1.0:1.0	20	80	**4a** 87	96
5	*i*-Pr (**3a**)	1.0:1.5	20	80	**4a** 93	90
6	Et (**3c**)	1.5:1.0	15	5	**4c** 93	>99
7	Et (**3c**)	1.5:1.0	10	50	**4c** 94	>99
8	Et (**3c**)	1.5:1.0	5	320	**4c** 92	>99
9	Et (**3c**)	1.5:1.0	2	1800	**4c** 90	>99

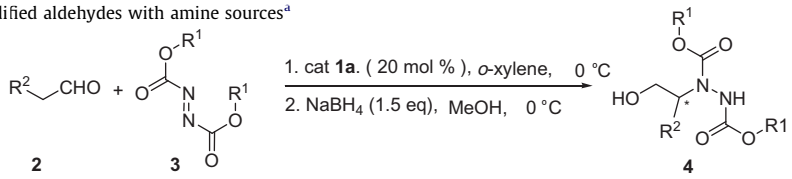
[a] Reactions performed with isovaleral, catalyst **1a** (20 mol %), and azodicarboxylate in *o*-xylene (0.8 mL).
[b] Time of amination.
[c] Isolated yield.
[d] The ee value was determined by GC.
[e] The ee value was determined by HPLC.

of catalysts bearing both L-proline and thiourea functional moieties linked by a suitable chiral linker might simultaneously activate both a nucleophile and an electrophile in the same asymmetric reaction. Typically, the secondary amine–thiourea catalysts **1a–d** (Fig. 1) in our hands, synergistically combining two catalytic sites of chiral thiourea and L-prolic amide skeleton haven't drawn enough attentions.[21] We regarded that these bifunctional organocatalysts may catalyze the asymmetric α-amination of aldehydes and the reactivity and enantioselectivity may be enhanced by double activation, mutual stereo-compatibility and chiral recognition.

As a part of our continuing interests in asymmetric synthesis,[22] herein, we wish to report the example of these chiral proline amide–thiourea bifunctional catalysts promoted enantioselective α-amination of aldehydes with azodicarboxylates in excellent yields and enantioselectivities. The whole scheme and strategies for these catalysts are illustrated in Figure 1.

Chiral catalysts **1a–d** may be similarly prepared as in the reported procedures.[21] To determine the optimal asymmetric reaction conditions, α-amination of isovaleral (**2a**) with diisopropyl azadicarboxylate (DIAD) (**3a**) was used as a model reaction and chiral catalysts **1a–d** were initially screened, and the results were summarized in Table 1. As expected, each reaction was successfully carried out in CH_3CN at 0 °C in the presence of 20 mol % catalysts (**1a–d**) and gave the corresponding primary alcohol **4a** after reduction with sodium borohydride in excellent overall yields (70–98%) and enantioselectivities (76–99% ee). Comparatively, catalysts

Table 3
Direct α-amination of various unmodified aldehydes with amine sources[a]



Entry	R^1	R^2	Time[b] (min)	Yield[c] (%)	ee[d] (%)
1	*i*-Pr (**3a**)	*i*-Pr (**2a**)	40	**4a** 89	99[e]
2	Bn (**3b**)	*i*-Pr (**2a**)	10	**4b** 70	98
3	Bn (**3b**)	Me (**2b**)	540	**4d** 82	91
4	Bn (**3b**)	Et (**2c**)	540	**4e** 73	97
5	Bn (**3b**)	*n*-Pr (**2d**)	540	**4f** 88	85
6	Bn (**3b**)	*n*-C_5H_{11} (**2e**)	660	**4g** 68	88
7	Et (**3c**)	Me (**2b**)	2	**4h** 89	96[e]
8[f]	Et (**3c**)	*i*-Pr (**2a**)	570	**4c** 96	99[e]
9	Et (**3c**)	*i*-Pr (**2a**)	1	**4c** 97	99[e]
10	Et (**3c**)	Bn (**2f**)	7	**4i** 65	77

[a] Reactions performed with aldehyde (0.3 mmol), catalyst **1a** (20 mol %), and azodicarboxylate (0.2 mmol) in *o*-xylene (0.8 mL).
[b] Time of amination reaction.
[c] Isolated yield.
[d] The ee value was determined by HPLC.
[e] The ee value was determined by GC.
[f] Reactions performed with isovaleral (0.3 mmol), catalyst **1a** (20 mol %), and diethyl azodicarboxylate (0.2 mmol) in *o*-xylene (2.0 mL)

1a and **1c** gave better yields and enantioselectivities (Table 1, entries 1 versus 2). It is probably due to the compatibility of the two catalytic chiral centers. The less incompatible chiral centers in **1b** and **1d** probably exert no synergic or negative effects on the enantioselectivity. So, both catalysts **1a** and **1c**, bearing a *R*, *R*-linker, affording the desired products in almost the same enantioselectivity (Table 1, entry 1), were chosen for further optimization. After that, a range of solvents were screened for the model reaction catalyzed by **1a** or **1c** at 0 °C. As shown in Table 1, the enantioselectivities and yields are highly variable with different solvents. In all the aprotic solvents such as *n*-hexane, *o*-xylene, $CHCl_3$, both **1a** and **1c** delivered excellent yields (up to 99%) and enantioselectivities (up to 99% ee) (Table 1, entries 2–12). Comparatively, when the reaction was carried out in MeOH, only poor to moderate yields (18–48%) and disappointing enantioselectivities (16–54% ee) (Table 1, entry 13) were obtained. Particularly, the highest enantioselectivity (99% ee) was obtained in *o*-xylene in the presence of 20 mol % **1a** (Table 1, entry 5). To further optimize the results, the reaction temperature was raised to room temperature, while no significant improvement in yield was observed (Table 1, entry 14). Those results indicated that **1a** was the promising catalyst and *o*-xylene was the suitable candidate solvent for this reaction (Table 1, entry 5).

To obtain better results, various azodicarboxylates **3** and catalyst loadings were also screened and the results were listed in Table 2. The reaction was performed smoothly, catalyzed by 20 mol % **1a** in excellent results regardless of azodicarboxylate **3a**, **3b** or **3c** as acceptor. The molar ratio of **2a** to **3** was also studied, however, no significant improvement was observed (Table 2, entries 1, 4, 5). Further decrease of the catalyst loading of **1a** from 20 to 2 mol %, the conversion was still completed within a few hours in excellent enantioselectivities and yields (Table 2, entries 3 and 6–9). Through extensive screening, the optimized reaction conditions were found to be 20 mol % of catalyst **1a**, diethyl azodicarboxylate (DEAD) **3c** used as donor, and 1.5 equiv isovaleral in *o*-xylene at 0 °C (Table 2, entry 3).

Under the optimized conditions, the scopes of this amination of various aldehydes (**2a**–**f**) with azodicarboxylates (**3a**–**c**) were further studied and the results were summarized in Table 3. All the reactions were performed smoothly in *o*-xylene at 0 °C with 20 mol % **1a** and afforded moderate to excellent yields (65–97%) and enatioselecitvities (77–99% ee). All the aldehydes gave satisfying yields and excellent enantioselectivities (Table 3, entries 1–9), except that 3-phenylpropionaldehyde (**2f**) gave a relatively lower yield (65%) and moderate enantioselectivity (77% ee) (Table 3, entry 10). Particularly, when DEAD was used as an acceptor, **1a** showed excellent and extraordinary reactivity and enantioselectivity for propanal and isovaleral, and the reaction finished almost in no time (within only two minutes) after the addition of the reactants (Table 3, entries 7 and 9).

Based on the experimental results and the absolute configuration of the products, we suggested a plausible bifunctional catalytic mechanism involving hydrogen binding and enamine formation as shown in Figure 2. The azodicarboxylate might be directed and activated by hydrogen binding interaction with the thiourea moiety and thus enhances its electrophilicity, and the pyrrolidine group activated isovaleral by the formation of enamine intermediate. The excellent reactivity and enantioselectivity may be attributed to the double activation, mutual stereo-compatibility and chiral recognition.

In summary, we have successfully applied the newly developed secondary amine–thiourea bifunctional catalysts **1a**–**d** with two catalytic sites of chiral thiourea and L-prolic amide skeleton to promote the direct asymmetric α-amination of various aldehydes with azodicarboxylates in excellent yields (up to 99%) and enantioselectivities (up to 99% ee). Further applications of those catalysts in other reactions are currently underway in our laboratory.

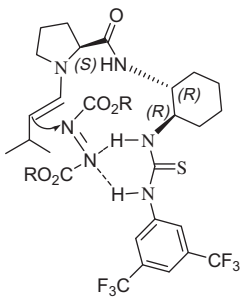


Figure 2. Proposed Transition State Model.

Acknowledgments

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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.2010.07.042.

References and notes

1. Genet, J. P.; Greck, C.; Lavergne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000. Chapter 3.
2. (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395; (b) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399.
3. Bøgevig, A.; Kumaragurubaran, N.; Zhuang, W.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793.
4. (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657; (b) Luo, J.; Xu, L.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437–440.
5. Dahlin, N.; Bogevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101–1105.
6. (a) Kotrusz, P.; Alemayehu, S.; Toma, Š.; Schmalz, H. G.; Adler, A. *Eur. J. Org. Chem.* **2005**, 4904–4911; (b) Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, *19*, 2448–2449; (c) Baumann, T.; Bächle, M.; Hartmann, C.; Bräse, S. *Eur. J. Org. Chem.* **2008**, 2207–2212; (d) Chowdari, N. S.; Barbas, C. F., III *Org. Lett.* **2003**, *5*, 1685–1688; (e) Baumann, T.; Vogt, H.; Bräse, S. *Eur. J. Org. Chem.* **2007**, 266–282.
7. Chowdari, N. S.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 867–870.
8. Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
9. Liu, P.-M.; Chang, C.; Reddy, R. J.; Ting, Y.-F.; Kuan, H.-H.; Chen, K. *Eur. J. Org. Chem.* **2010**, 42–46.
10. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255.
11. Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117–1119.
12. Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.
13. Liu, X.-F.; Li, H.-M.; Deng, L. *Org. Lett.* **2005**, *7*, 167–169.
14. Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614–11615.
15. Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874–3877.
16. Bui, T.; Borregan, M.; Barbas, C. F. *J. Org. Chem.* **2009**, *74*, 8935–8938.
17. Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753.
18. (a) Tillman, A. L.; Ye, J. X.; Dixon, D. J. *Chem. Commun.* **2006**, 1191–1193; (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370.
19. (a) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896–5897. for inspiring discussions, see:; (b) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126; (c) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259–3262; (d) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647–6650; (e) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; (f) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279–1281; (g) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10013; (h) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (i) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem.* **2005**, *117*, 470–472. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
20. (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245–1248; (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (d) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199–201; (e) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177; (f) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579.
21. Mei, K.; Zhang, S. L.; He, S. T.; Li, P.; Jin, M.; Xue, F.; Luo, G. S.; Zhang, H. Y.; Song, L. R.; Duan, W. H.; Wang, W. *Tetrahedron Lett.* **2008**, *49*, 2681–2684.
22. (a) Wang, Q.-W.; Peng, L.; Fu, J.-Y.; Huang, Q.-C.; Wang, L.-X.; Xu, X.-Y. *ARKIVOC* **2010**, 340–351; (b) Bai, J.-F.; Xu, X.-Y.; Huang, Q.-C.; Peng, L.; Wang, L. X. *Tetrahedron Lett.* **2010**, *51*, 2803–2805; (c) Peng, L.; Xu, X.-Y.; Wang, L.-L.; Huang, J.; Bai, J.-F.; Huang, Q.-C.; Wang, L.-X. *Eur. J. Org. Chem.* **2010**, 1849–1853; (d) Wang, L.-L.; Xu, X.-Y.; Huang, J.; Peng, L.; Huang, Q.-C.; Wang, L.-X. *Lett. Org. Chem.* **2010**, *7*, 367–372; (e) Chen, Y. Z.; Lin, H.; Xu, X. Y.; Xia, S. W.; Wang, L. X. *Adv. Synth. Catal.* **2008**, *350*, 426–430; (f) Chen, Y. Z.; Xu, J. G.; Xu, X. Y.; Xia, Y.; Lin, H.; Xia, S. W.; Wang, L. X. *Tetrahedron: Asymmetry* **2007**, *18*, 2537–2540; (g) Wang, L. X.; Shen, J. F.; Tang, Y.; Chen, Y.; Wang, W.; Cai, Z. G.; Du, Z. J. *Org. Process Res. Dev.* **2007**, *11*, 487–489; (h) Lin, H.; Chen, Y. Z.; Xu, X. Y.; Xia, S. W.; Wang, L. X. *J. Mol. Catal. B: Enzym.* **2009**, *57*, 1–5.