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Asymmetric Imino Aza-enamine Reaction Catalyzed by Axially Chiral Dicarboxylic Acid: Use of Arylaldehyde *N,N*-Dialkylhydrazones as Acyl Anion Equivalent

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The use of an acyl anion equivalent generated by the reactivity umpolung[1] of aldehydes provides a distinctive opportunity for the expedient C−C bond formation, as represented by well-established dithiane chemistry.[2] Aldehyde *N,N*-dialkylhydrazone, which can be easily prepared by the condensation of the corresponding aldehyde and *N,N*-dialkylhydrazine, is also known as a class of acyl anion equivalent due to its aza-enamine structure.[3] The synthetic utility of such hydrazones has been explored in the past four decades, taking advantage of their ready availability and ease of removal after the reaction (Scheme 1).[4] However, their application in the field of asymmetric synthesis has been limited only to the use of formaldehyde *N,N*-dialkylhydrazone bearing no substituent at the azomethine carbon atom of the hydrazone (R = H, Scheme 1). This limitation has long been considered a result of the poor nucleophilicity of aryl or aliphatic aldehyde *N,N*-dialkylhydrazones, thereby requiring a highly electrophilic reaction partner, such as sulfonyl isocyanates,[5] Vilsmeier reagent,[6] or trifluoroacetic anhydride.[7]

We here wish to report that axially chiral dicarboxylic acid (*R*)-**1**, which has been recently developed in our laboratory as a new class of chiral Brønsted acid,[8,9] has a unique ability to catalyze the unprecedented asymmetric addition of arylaldehyde *N,N*-dialkylhydrazones to *N*-Boc imines. This novel transformation provides a facile access to enantiomerically enriched α-amino ketones.[10,11]

Concerning the catalytic asymmetric reaction of formaldehyde *N,N*-dialkylhydrazone to *N*-Boc imines, there have been two reports to date, wherein the reaction was accomplished by chiral Brønsted acid using binaphthol[12] or phosphoric acid[13] as the hydrogen-bond donor.[14] However, the enantiomeric excesses of the products remained at moderate to good levels. Moreover, the use of aryl or aliphatic aldehyde *N,N*-dialkylhydrazones was completely unexplored. We initiated our study on the renovation of this reaction by resorting to the distinctive acidity and chiral efficiency of dicarboxylic acid catalyst (*R*)-**1**.

In the early stage of this investigation, we were pleased to find the unexpectedly high catalytic activity of (*R*)-**1** compared to that of previously utilized chiral Brønsted acids.[12,13] The reaction of benzaldehyde *N*-Boc imine **2** (R^1 = Ph) and formaldehyde *N,N*-tetramethylenehydrazone **3** (R' = $(CH_2)_4$) catalyzed by 5 mol % of (*R*)-**1** in CH_2Cl_2 was complete within 4 h at −20 °C (Table 1, entry 1). After a brief screening of the solvent, the use of chloroform was found to be optimal to attain high asymmetric induction, giving the adduct in 89% yield with 96% ee. Use of *N,N*-dimethylhydrazone **3** (R' = CH_3) was found to deteriorate both the yield and enantioselectivity (entry 4). In all experiments, molecular sieves were added to scavenge the adventitious water, which would cause the undesired hydrolysis of *N*-Boc imine. The scope of the reaction with various arylaldehyde *N*-Boc imines was then surveyed (entries 5−9). Irrespective of the substituent pattern and the electronic property of the aryl moiety, the products could be obtained in good yields with excellent enantioselectivities. The reaction with heteroarylaldehyde *N*-Boc imine was also feasible, although the enantioselectivity decreased slightly (entry 10). The catalyst loading could be further reduced to 2 mol % uneventfully, although the longer reaction time was required (entry 11).

Encouraged by the remarkable efficiency realized by the use of chiral dicarboxylic acid (*R*)-**1**, our attention has been focused on a yet-unsolved task: use of arylaldehyde *N,N*-dialkylhydrazones in asymmetric synthesis. As a preliminary experiment, the reaction of benzaldehyde *N,N*-tetramethylenehydrazone **4** (R^2 = Ph) and benzaldehyde *N*-Boc imine was conducted under the identical reaction conditions described above to give the desired adduct in low yield with the promising asymmetric induction of 92% ee (Table 2, entry 1).[15]

After slight modification of the reaction parameters, including the use of lower temperature, prolonged reaction time, and 3 equiv

Scheme 1. Aza-enamine Property of *N,N*-Dialkylhydrazone

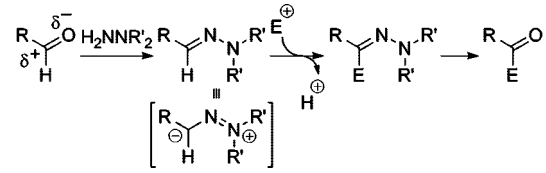
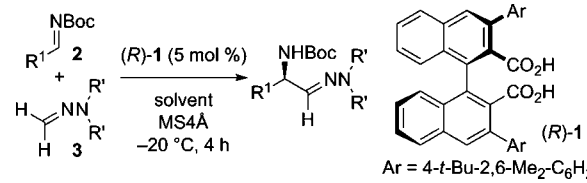


Table 1. (*R*)-**1**-Catalyzed Asymmetric Addition of Formaldehyde *N,N*-Dialkylhydrazone to *N*-Boc Imines[a]



entry	R^1	R'	solvent	% yield[b]	% ee[c]
1	Ph	$(CH_2)_4$	CH_2Cl_2	82	81
2	Ph	$(CH_2)_4$	toluene	53	93
3	Ph	$(CH_2)_4$	$CHCl_3$	89	96
4	Ph	CH_3	$CHCl_3$	23	87
5	3-MeC_6H_4	$(CH_2)_4$	$CHCl_3$	80	93
6	2-Np	$(CH_2)_4$	$CHCl_3$	76	99
7	4-$MeOC_6H_4$	$(CH_2)_4$	$CHCl_3$	83	93
8	4-ClC_6H_4	$(CH_2)_4$	$CHCl_3$	70	97
9	2-BrC_6H_4	$(CH_2)_4$	$CHCl_3$	76	97
10	2-furyl	$(CH_2)_4$	$CHCl_3$	86	89
11[d]	Ph	$(CH_2)_4$	$CHCl_3$	82	95

[a] Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and formaldehyde *N,N*-dialkylhydrazone (0.12 mmol) in the presence of 5 mol % of (*R*)-**1** (0.005 mmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed with 2 mol % of (*R*)-**1** for 24 h.

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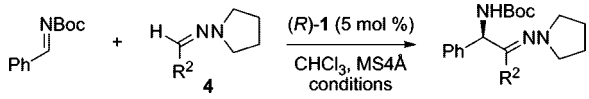
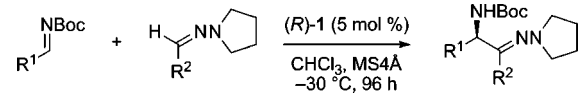
Table 2. (*R*)-**1**-Catalyzed Asymmetric Addition of Arylaldehyde *N*,*N*-Tetramethylenehydrazones to Benzaldehyde *N*-Boc Imine[a]



entry	R^2	conditions (°C, h)	% yield[b]	% ee[c]
1[d]	Ph	−20, 4	16	92
2	Ph	−30, 96	66	95
3	3-tolyl	−30, 96	51	92
4	2-Np	−30, 96	56	92
5	4-$MeOC_6H_4$	−30, 96	55	92
6	4-ClC_6H_4	−30, 96	60	91

[a] Reactions were performed with benzaldehyde *N*-Boc imine (0.10 mmol) and arylaldehyde *N*,*N*-tetramethylenehydrazone (0.30 mmol) in the presence of 5 mol % of (*R*)-**1** (0.005 mmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed with 0.12 mmol of benzaldehyde *N*,*N*-tetramethylenehydrazone.

Table 3. (*R*)-**1**-Catalyzed Asymmetric Addition of Arylaldehyde *N*,*N*-Tetramethylenehydrazones to *N*-Boc Imines[a]



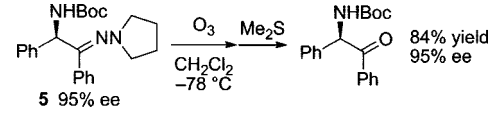
entry	R^1	R^2	% yield[b]	% ee[c]
1	3-tolyl	Ph	55	91
2	2-Np	Ph	51	92
3	4-$MeOC_6H_4$	Ph	35	84
4	3-$MeOC_6H_4$	Ph	54	91
5	4-ClC_6H_4	Ph	77	90
6	4-ClC_6H_4	4-ClC_6H_4	73	89
7	4-ClC_6H_4	4-$MeOC_6H_4$	67	91

[a] Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and arylaldehyde *N*,*N*-tetramethylenehydrazone (0.30 mmol) in the presence of 5 mol % of (*R*)-**1** (0.005 mmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

of hydrazone, the yield and enantioselectivity of this transformation reached a satisfactory level (entry 2). Using this optimized condition, the scope of this unprecedented transformation was investigated as summarized in Tables 2 and 3. The effect of the substituent at the aryl moiety of the hydrazone was first examined. Use of hydrazones having the 3-tolyl and 2-naphthyl groups provided the adducts in moderate yields with high enantioselectivities (entries 3 and 4). Hydrazones containing an electron-donating or electron-withdrawing aromatic group reacted equally well, giving products with high enantioselectivities (entries 5 and 6).

The scope of the aryl moieties of *N*-Boc imines was then investigated, wherein the dependence of the reactivity to the electronic nature of the imine was observed (Table 3). Thus, electronically unbiased 3-tolyl- and 2-naphthyl-substituted *N*-Boc imines could be converted to the products in moderate yields with 91 and 92% ee, respectively (entries 1 and 2). Use of electron-rich 4-methoxybenzaldehyde *N*-Boc imine decreased both the yield and enantioselectivity slightly (entry 3). On the other hand, 3-methoxybenzaldehyde *N*-Boc imine was found to be a suitable substrate, giving the product in 54% yield with 91% ee (entry 4). Subjection of *N*-Boc imine bearing the electron-withdrawing 4-chlorophenyl group gave the product in good yield (entry 5). Finally, the reactions combining 4-chlorobenzaldehyde *N*-Boc imine and other hydrazones were examined. Use of hydrazone derived from 4-chlorobenzaldehyde gave the adduct in 73% yield with 89% ee (entry 6). The reaction of hydrazone derived from 4-methoxybenzaldehyde proceeded as well, giving the product in 67% yield with 91% ee (entry 7). At this moment, the use of *N*-Boc imines and hydrazones derived from aryl aldehydes is considered to be inevitable.

Scheme 2. Transformation of α-Amino Hydrazone to the Corresponding α-Amino Ketone by Ozonolysis



Optically active α-amino hydrazones thus obtained can be easily transformed into the corresponding α-amino ketones as exemplified in Scheme 2. The removal of the hydrazone moiety of the α-amino hydrazone **5** could be facilitated by ozonolysis, giving the corresponding α-amino ketone in good yield without a deleterious effect on enantioselectivity. Absolute configuration of the adduct **5** was deduced from this α-amino ketone by comparison of the optical rotation of the same α-amino ketone derived from (*R*)-phenylglycine.

In summary, we have succeeded in the development of asymmetric imino aza-enamine reaction of aldehyde hydrazones to *N*-Boc imines catalyzed by axially chiral dicarboxylic acid (*R*)-**1**. To the best of our knowledge, this is the first example employing arylaldehyde *N*,*N*-dialkylhydrazones as practical acyl anion equivalent in asymmetric synthesis.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(2) (a) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (b) Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35.
(3) For an excellent review, see: Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629.
(4) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157.
(5) (a) Brehme, R.; Nikolajewski, H. E. *Tetrahedron* **1969**, *25*, 1159. (b) Brehme, R.; Nikolajewski, H. E. *Tetrahedron Lett.* **1982**, *23*, 1131.
(6) Brehme, R. *Chem. Ber.* **1990**, *123*, 2039.
(7) (a) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokoyama, T. *J. Org. Chem.* **1988**, *53*, 129. (b) Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T.; Ohara, S.; Yamada, K.; Yoshikawa, N. *J. Org. Chem.* **1988**, *53*, 519.
(8) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054.
(9) For a recent review on chiral Brønsted acid catalysis, see: Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
(10) For the use of NHC catalysis, see: (a) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Soc. Chem.* **2001**, *123*, 9696. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654. (c) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852.
(11) For the use of acylsilanes, see: (a) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363. (b) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715. (c) Garrett, M. R.; Tarr, J. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 12944.
(12) Dixon, D. J.; Tillman, A. L. *Synlett* **2005**, 2635.
(13) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Kockritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065.
(14) For the other examples using formaldehyde *N*,*N*-dialkylhydrazones in organocatalysis, see: (a) Pettersen, D.; Herrera, R. P.; Bernardi, L.; Fini, F.; Sgarzani, V.; Fernandez, R.; Lassaletta, J. M.; Ricci, A. *Synlett* **2006**, 239. (b) Herrera, R. P.; Monge, D.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Org. Lett.* **2007**, *9*, 3303.
(15) Isolated as an equilibrating mixture of two isomers (∼3:1 ratio). For details, see Supporting Information.

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