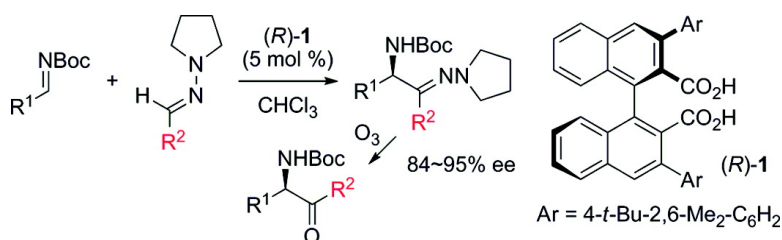


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Asymmetric Imino Aza-enamine Reaction Catalyzed by Axially Chiral Dicarboxylic Acid: Use of Arylaldehyde *N,N*-Dialkylhydrazones as Acyl Anion Equivalent

Takuya Hashimoto, Maya Hirose, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received April 13, 2008; E-mail: maruoka@kuchem.kyoto-u.ac.jp

The use of an acyl anion equivalent generated by the reactivity umpolung¹ 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 binaphthol¹² or phosphoric acid¹³ 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** (R¹ = Ph) and formaldehyde *N,N*-tetramethylenhydrazone **3** (R' = (CH₂)₄) catalyzed by 5 mol % of (*R*)-**1** in CH₂Cl₂ 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' = CH₃) 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

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

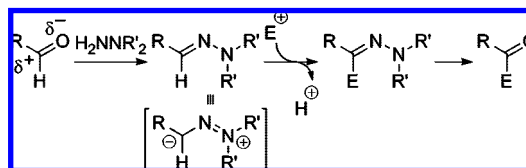
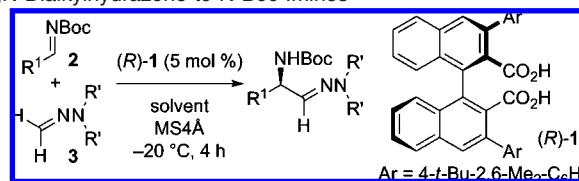


Table 1. (*R*)-**1**-Catalyzed Asymmetric Addition of Formaldehyde *N,N*-Dialkylhydrazone to *N*-Boc Imines^a



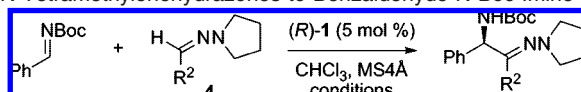
entry	R ¹	R'	solvent	% yield ^b	% ee ^c
1	Ph	(CH ₂) ₄	CH ₂ Cl ₂	82	81
2	Ph	(CH ₂) ₄	toluene	53	93
3	Ph	(CH ₂) ₄	CHCl ₃	89	96
4	Ph	CH ₃	CHCl ₃	23	87
5	3-MeC ₆ H ₄	(CH ₂) ₄	CHCl ₃	80	93
6	2-Np	(CH ₂) ₄	CHCl ₃	76	99
7	4-MeOC ₆ H ₄	(CH ₂) ₄	CHCl ₃	83	93
8	4-ClC ₆ H ₄	(CH ₂) ₄	CHCl ₃	70	97
9	2-BrC ₆ H ₄	(CH 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.

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).

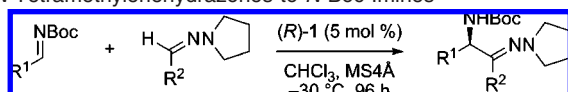
Encouraged by the remarkable efficiency realized by the use of chiral dicarboxylic acid (*R*)-**1**, our attention has been focused on a yet-unsolved task: use of arylaldehyde *N,N*-dialkylhydrazones in asymmetric synthesis. As a preliminary experiment, the reaction of benzaldehyde *N,N*-tetramethylenhydrazone **4** (R² = 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

Table 2. (*R*)-1-Catalyzed Asymmetric Addition of Arylaldehyde *N,N*-Tetramethylethylenhydrazones 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 ₆ H ₄	-30, 96	55	92
6	4-ClC ₆ H ₄	-30, 96	60	91

^a Reactions were performed with benzaldehyde *N*-Boc imine (0.10 mmol) and arylaldehyde *N,N*-tetramethylethylenhydrazone (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*-tetramethylethylenhydrazone.

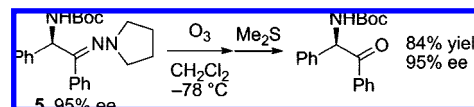
Table 3. (*R*)-1-Catalyzed Asymmetric Addition of Arylaldehyde *N,N*-Tetramethylethylenhydrazones to *N*-Boc Imines^a

entry	R ¹	R ²	% yield ^b	% ee ^c
1	3-tolyl	Ph	55	91
2	2-Np	Ph	51	92
3	4-MeOC ₆ H ₄	Ph	35	84
4	3-MeOC ₆ H ₄	Ph	54	91
5	4-ClC ₆ H ₄	Ph	77	90
6	4-ClC ₆ H ₄	4-ClC ₆ H ₄	73	89
7	4-ClC ₆ H ₄	4-MeOC ₆ H ₄	67	91

^a Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and arylaldehyde *N,N*-tetramethylethylenhydrazone (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 pro-

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

ceeded 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.

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>.

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