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Direct Asymmetric Iodination of Aldehydes Using an Axially Chiral Bifunctional Amino Alcohol Catalyst

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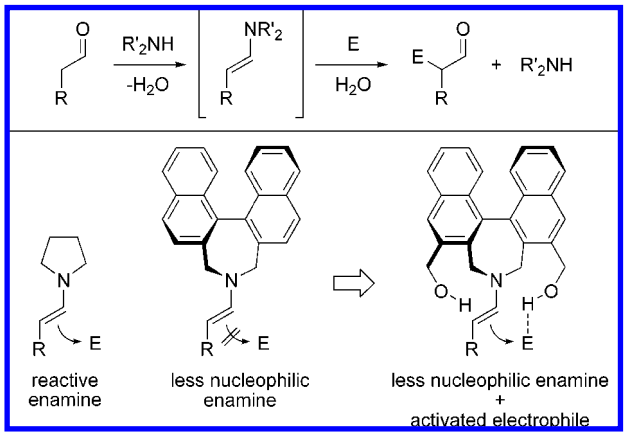
Development of organocatalytic reactions is one of the most exciting topics in practical organic synthesis because of its operational simplicity, mild reaction conditions, and environmental consciousness.[1] In this area, various asymmetric α-functionalization reactions of aldehydes and ketones were found to be successfully catalyzed by chiral pyrrolidines (e.g., proline) and their equivalents through their enamine intermediates.[2] Such highly nucleophilic and basic pyrrolidine-type catalysts, however, might not be appropriate for some specific asymmetric α-functionalizaion reactions such as iodination of aldehydes due to the undesired side reactions including self-aldol reaction and racemization of the product.[3] On the other hand, while a less nucleophilic and less basic binaphthyl-based amine is supposed to suppress such side reactions, its enamine is occasionally not reactive enough to undergo the α-functionalizaion reactions (Scheme 1). We have therefore been interested in the activation of certain electrophiles by introducing hydroxyl groups on such an amine catalyst to promote the desired α-functionalization with suppressing side reactions. An asymmetric iodination of aldehydes was chosen to exemplify this concept. Although some organocatalytic asymmetric α-halogenation reactions of aldehydes have been reported,[4−6] examples of asymmetric synthesis of α-iodoaldehydes as a member of synthetically valuable α-haloaldehydes are especially scarce despite their characteristic features including the high leaving group ability and the steric bulk of the iodo group.[6,7] Herein we wish to report a direct asymmetric α-iodination of aldehydes using a novel axially chiral bifunctional amino alcohol catalyst.

Scheme 1



We first investigated α-iodination of 3-methylbutanal with *N*-iodosuccinimide (NIS) in THF in the presence of 5 mol % of an amine catalyst of type **1** at 0 °C, and the results are shown in Table 1. The use of pyrrolidine as a catalyst[6] afforded the α-iodoaldehyde in moderate yield along with the self-aldol byproducts (entry 1), and chiral pyrrolidines, L-proline and (*S*)-diphenylprolinol gave poor

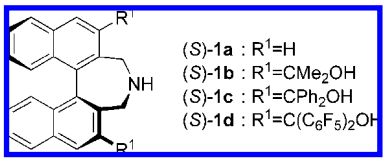
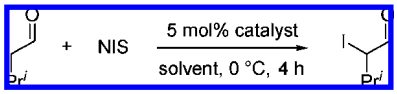


Table 1. Organocatalytic Direct Asymmetric Iodination of 3-Methylbutanal with NIS[a]



entry	catalyst	solvent	% conversion[b]	% ee[c]
1	pyrrolidine	THF	39	
2	L-proline	THF	32	−14
3	(*S*)-diphenylprolinol	THF	2	47
4	(*S*)-**1a**	THF	14	−10
5	(*S*)-**1b**	THF	23	−1
6	(*S*)-**1c**	THF	67	−26
7	(*S*)-**1d**	THF	28	80
8	(*S*)-**1d**	MeCN	46	12
9	(*S*)-**1d**	DMF	23	45
10	(*S*)-**1d**	CH_2Cl_2	73	32
11	(*S*)-**1d**	toluene	65	76
12	(*S*)-**1d**	Et_2O	48	94
13[d]	(*S*)-**1d**	Et_2O	94	99

[a] The reaction of 3-methylbutanal and NIS (1.1 equiv) was carried out in the presence of an amine catalyst (5 mol %) at 0 °C for 4 h. [b] Determined by GC analysis using decane as an internal standard. [c] Determined by GC analysis using chiral capillary column. Details are given in Supporting Information. [d] Benzoic acid (5 mol %) was added.

results (entries 2 and 3). The reaction using less nucleophilic binaphthyl-based amine (*S*)-**1a** gave only a small amount of the product as expected (entry 4). We then examined bifunctional catalysts (*S*)-**1b-d**, which would activate NIS through hydrogen bonding with hydroxylmethyl groups at 3,3′-positions. When (*S*)-**1b** is used,[8] the α-iodination was accelerated to give the α-iodoaldehyde in low yield with almost no enantioselectivity (entry 5). With (*S*)-**1c**,[8] the α-iodoaldehyde was obtained in moderate yield albeit with low enantioselectivity (entry 6). To our surprise, use of (*S*)-**1d**, which has sterically more congested and more acidic *tert*-alcohol moieties at 3,3′-positions, afforded the iodination product with the opposite enantiomer predominating (entry 7). We then examined the solvent effects using (*S*)-**1d** (entries 7−12), and ether was found to be the choice of solvent in terms of enantioselectivity (entry 12). When 5 mol % of benzoic acid was employed as an additive,[6] a further increase in both yield and enantioselectivity was observed (entry 13).

With the axially chiral bifunctional amino alcohol catalyst (*S*)-**1d** in hand, the direct asymmetric α-iodination reaction of several

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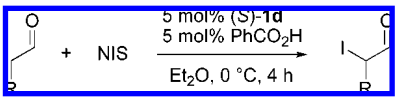
Table 2. Direct Asymmetric Iodination of Various Aldehydes with NIS Catalyzed by (*S*)-**1d**[a]



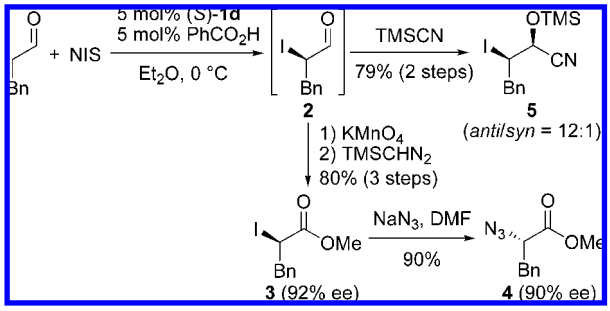
entry	R	% yield[b]	% ee[c]	entry	R	% yield[b]	% ee[c]
1	*i*-Pr	93 (36)	99	5	benzyl	81 (80)	92[f] (*R*)
2[d]	Cy	86 (34)	98	6	CH_2Cy	74 (64)	90[f]
3	Et	76 (32)	98	7	CH_2 OBn	97 (30)	93[f] (*R*)
4[d,e]	allyl	98 (31)	95				

[a] The reaction of an aldehyde and NIS (1.1 equiv) was carried out in Et_2O in the presence of (*S*)-**1d** (5 mol %) and benzoic acid (5 mol %) at 0 °C for 4 h. [b] Determined by GC analysis using an internal standard technique. The numbers in parentheses are isolated yields of the corresponding methyl esters. [c] Determined by GC analysis using chiral capillary column. Details are given in Supporting Information. [d] Use of 10 mol % of (*S*)-**1d**. [e] The reaction was carried out for 1 h. [f] Enantiomeric excess was determined by conversion to the corresponding methyl ester and GC or HPLC analysis.

other aldehydes with NIS was examined, and selected results are shown in Table 2. In general, these direct asymmetric α-iodination reactions proceeded smoothly to give the corresponding α-iodoaldehydes in good yields with excellent levels of enantioselectivities.

In order to assign the absolute configuration of the obtained α-iodoaldehyde and to extend the synthetic utility of this transformation, an optically enriched α-iodoaldehyde **2** was converted to the corresponding α-amino acid derivative (Scheme 2). Thus, treatment of the α-iodoaldehyde **2** with $KMnO_4$, followed by addition of $TMSCHN_2$, resulted in clean formation of the corresponding methyl ester **3**. By treatment with NaN_3, the resulting methyl ester **3** was transformed to the α-azido ester **4**, which can be readily reduced to the corresponding α-amino ester.[5b] By comparison of optical rotation of the α-azido ester **4** with the literature value the absolute configuration of the α-iodoaldehyde **2** was determined to be *R*.

Scheme 2. Transformation of α-Iodoaldehyde



Furthermore, since silylcyanation of aldehydes with TMSCN is known to be catalyzed by I_2,[9] we examined the one pot silylcyanation of the α-iodination product with TMSCN in the presence of I_2 generated from slightly excess NIS. The α-iodination product **2** was found to be smoothly converted to the corresponding silylcyanation product **5** with high diastereoselectivity, probably due to the steric bulk of the iodo group.[10]

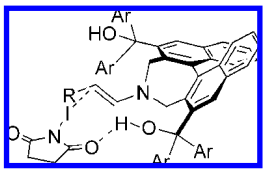


Figure 1. Transition state model for the direct asymmetric iodination reaction catalyzed by (*S*)-**1d**.

On the basis of the observed stereochemistry, a plausible transition state is proposed (Figure 1). The activated and directed NIS by hydroxyl group on (*S*)-**1d** approaches the Re face of the enamine. Hence, the reaction of an aldehyde with NIS catalyzed by (*S*)-**1d** provides *R* isomer predominantly.

In summary, we have developed a direct asymmetric iodination reaction of aldehydes catalyzed by the novel axially chiral bifunctional amino alcohol catalyst (*S*)-**1d**. This method represents a rare example of the catalytic and highly enantioselective synthesis of optically active α-iodoaldehydes. We are currently investigating further application of α-iodoaldehydes by taking advantage of the characteristic features of iodine containing compounds.

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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) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (d) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007.
(2) For reviews, see: Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001.
(3) For instance, an optically active α-iodoaldehyde in ether is partially racemized by a catalytic amount of pyrrolidine at 0 °C, while almost no racemization occurs under similar conditions in the absence of pyrrolidine; see Supporting Information for detail.
(4) Fluorination: (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706. (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826.
(5) Chlorination: (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
(6) Bromination and Iodination: Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.
(7) Asymmetric synthesis of α-iodoaldehydes using a chiral auxiliary: Jacoby, C.; Braekman, J.-C.; Daloze, D. *Tetrahedron* **1996**, *52*, 10473.
(8) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046.
(9) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703.
(10) Under similar conditions the corresponding α-chloroaldehyde was silylcyanated with low diastereoselectivity (9% de).

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