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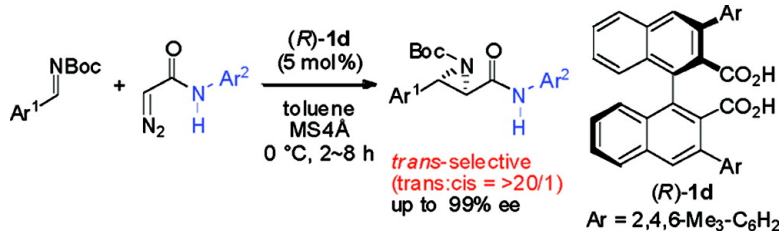

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Trans-Selective Asymmetric Aziridination of Diazoacetamides and *N*-Boc Imines Catalyzed by Axially Chiral Dicarboxylic Acid

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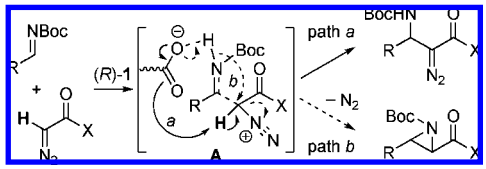
Enantiomerically pure aziridines constitute an important class of chiral synthons, since they can be easily converted to various types of important building blocks, such as functionalized α- or β-amino acid derivatives.[1] Hence, catalytic asymmetric aziridinations have drawn attention as a means to access these valuable compounds in a straightforward manner. One prevailing strategy for this purpose is the asymmetric nitrogen transfer to alkene by transition-metal catalysis[2] or organocatalysis.[3] Another attractive but less-studied approach to this end is the use of chiral Lewis acid-catalyzed asymmetric aziridination using imine and diazoacetate pioneered by Wulff et al.[4−6] It is well-known that this sort of aziridination including achiral acid catalysis[7,8] almost has always dominantly provided cis aziridine. In this context, we report herein that axially chiral dicarboxylic acid-catalyzed reaction of *N*-Boc imines and diazoacetamides offers a novel organocatalytic way for the asymmetric aziridination with remarkably high enantioselectivity and unique trans selectivity, hitherto unattainable using this strategy.



Chiral Brønsted acid catalysis recently introduced a new paradigm into the acid-catalyzed reaction of imine and diazoacetate. Terada and co-workers reported that chiral phosphoric acid facilitated the reaction of N-acyl imines and *tert*-butyl diazoacetate to furnish the Friedel−Craft-type adduct with an excellent level of enantioselectivity (path a).[9] We revealed the catalytic activity of axially chiral dicarboxylic acid (*R*)-**1e** in the similar reaction using *N*-Boc imines and diazo compounds.[10] The mode of these reactions is considered to involve the hydrogen abstraction of the putative intermediate **A** by the basic site of the catalyst as suggested by Terada. Here, we envisaged that the course of the reaction might be switched in favor of the formation of aziridine by lowering the acidity of the α-proton of diazo carbonyls (path b), thereby realizing unprecedented Brønsted-acid-catalyzed asymmetric aziridination.[8]

As diazo carbonyl derivatives capable of resisting the hydrogen abstraction, we chose diazoacetamides in consideration of the lower acidity of α-proton of amides compared to that of esters. Accordingly, dicarboxylic acid (*rac*)-**1**-catalyzed reaction of several diazoacetamides having different N,N-substituents and benzaldehyde *N*-Boc imine was initially investigated (Scheme 1). Although the use of N,N-disubstituted diazoacetamides was not found fruitful, we were encouraged by the result of the reaction using N-monosubstituted diazoacetamides. Thus, the reaction of *N*-phenyldiazoacetamide with benzaldehyde *N*-Boc imine provided the desired aziridine as a major product. Surprisingly, the trans isomer was formed exclusively, in sharp contrast to the previous acid-catalyzed aziridination which gives cis aziridine dominantly starting from diazoacetates and N-aryl or N-alkyl imines.[11] The stereochemical relationship was unambiguously established by X-ray crystallographic analysis (vide infra). Scrutiny of the byproduct led to confirmation of the major component as the 1,2-aryl shift product **3**, whereas a trace amount of 1,2-hydride shift product was also observed (not shown). The aziridination also proceeded with *N*-benzyldiazoacetamide, albeit in diminished yield.

Scheme 1. Preliminary Investigation of Dicarboxylic-Acid-Catalyzed Aziridination of Diazoacetamides and *N*-Boc Imine

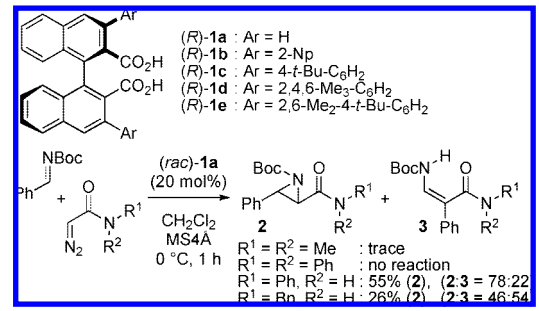
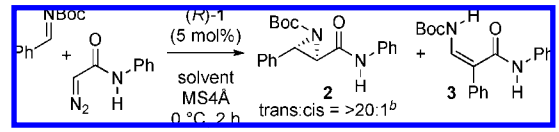


Table 1. Screening of Catalysts (*R*)-**1**[a]



entry	catalyst	solvent	**2**:**3**[c]	**2** yield[d] (%)	**2** ee[e] (%)
1	(*R*)-**1a**	CH_2Cl_2	66:34	15	−19
2	(*R*)-**1b**	CH_2Cl_2	79:21	54	68
3	(*R*)-**1c**	CH_2Cl_2	77:23	34	66
4	(*R*)-**1d**	CH_2Cl_2	79:21	70	92
5	(*R*)-**1e**	CH_2Cl_2	65:35	24	72
6	(*R*)-**1d**	$CHCl_3$	78:22	69	95
7	(*R*)-**1d**	toluene	90:10	61	97

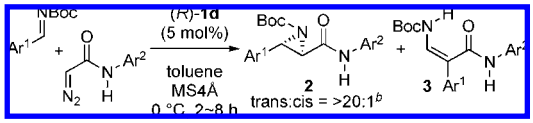
[a] Reactions were performed with benzaldehyde *N*-Boc imine (0.10 mmol) and *N*-phenyldiazoacetamide (0.12 mmol) in the presence of 5 mol % (*R*)-**1** (0.005 mmol). [b] Determined by ^{1}H NMR analysis of the crude material. [c] Determined by ^{1}H NMR analysis of the crude material. [d] Isolated yield. [e] Determined by chiral HPLC analysis.

We then set out to investigate the viability of enantiomerically pure dicarboxylic acid (*R*)-**1** in this novel trans-selective aziridination as summarized in Table 1. Screening of the reaction with benzaldehyde *N*-Boc imine and *N*-phenyldiazoacetamide in CH_2Cl_2 using 5 mol % of (*R*)-**1** having 3,3′-diaryl substitutents led to the identification of 3,3′-dimesityl substituted dicarboxylic acid (*R*)-**1d** as optimal catalyst, giving the trans aziridine exclusively in 70% yield with 92% ee (entry 4). Further optimization revealed the use of toluene as solvent of choice (entries 7 vs 6).

The scope of this trans-selective asymmetric aziridination was then examined using 5 mol % of (*R*)-**1d** as summarized in Table

10.1021/ja805635c CCC: $40.75

Table 2. Scope of Trans-Selective Asymmetric Aziridination[a]



entry	Ar^1	Ar^2	**2**:**3**[c]	**2** yield[d] (%)	**2** ee[e] (%)
1	Ph	Ph	90:10	61	97
2	4-tolyl	Ph	73:27	51	99
3	3-tolyl	Ph	81:19	52	98
4	2-Np	Ph	82:18	66	99
5	4-$MeOC_6H_4$	Ph	56:44	<20	N.D.
6	4-$PivOC_6H_4$	Ph	77:23	49	96
7	3-$MeOC_6H_4$	Ph	72:28	55	96
8	4-FC_6H_4	Ph	72:28	31	89
9	3-ClC_6H_4	Ph	77:23	50	91
10	Ph	4-$MeOC_6H_4$	87:13	61	97
11	2-Np	4-$MeOC_6H_4$	88:12	71	99
12	4-$PivOC_6H_4$	4-$MeOC_6H_4$	74:26	57	97
13	Ph	4-ClC_6H_4	85:15	60	97
14	2-Np	4-ClC_6H_4	81:19	70	99

[a] Reactions were performed with arylaldehyde *N*-Boc imine (0.10 mmol) and *N*-aryldiazoacetamide (0.12 mmol) in the presence of 5 mol % (*R*)-**1d** (0.005 mmol). [b] Determined by ^{1}H NMR analysis of the crude material. [c] Determined by ^{1}H NMR analysis of the crude material. [d] Isolated yield. [e] Determined by chiral HPLC analysis. N.D. = Not determined

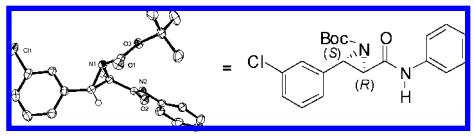


Figure 1. Ortep representation of **2** (Ar^1 = 3-ClC_6H_4, Ar^2 = Ph) with elipsoids shown at 50% probability level. Hydrogen atoms are omitted for clarity.

2. The reaction of 3- and 4-tolualdehyde *N*-Boc imine provided the trans aziridine in moderate yields with high enantioselectivities (entries 2 and 3). 2-Naphthaldehyde *N*-Boc imine was converted to the aziridine in 66% yield with 99% ee (entry 4). Although the use of *N*-Boc imine bearing the electron-donating 4-methoxyphenyl moiety led to poor conversion (entry 5), use of 4-pivaloyloxybenzaldehyde *N*-Boc imine as an alternative gave the aziridine having 4-oxygenated aryl group in 49% yield with 96% ee (entry 6). 3-Methoxybenzaldehyde *N*-Boc imine could be utilized uneventfully (entry 7). As for arylaldehyde *N*-Boc imines bearing electron-withdrawing group, subsititution at para position led to the diminished yield regardless of the prolonged reaction time of 8 h (entry 8). The reaction of 3-chlorobenzaldehyde *N*-Boc imine was completed within 5 h, giving the trans aziridine in 50% yield with 91% ee (entry 9). Both electron-donating and withdrawing groups were tolerated as N-aryl substituents of diazoacetamide in the reaction with a range of *N*-Boc imines (entries 10−14).

While (*R*)-**1d** catalyzed Friedel−Craft-type reaction proceeded via the attack of diazoacetate from the *si*-face of *N*-Boc imines,[10] this *trans*-selective aziridination furnished the compound stemming from the *re*-face selective nucleophilic addition of diazoacetamide as determined by X-ray crystallographic analysis of **2** (Ar^1 = 3-ClC_6H_4, Ar^2 = Ph) (Figure 1). This inverted enantiofacial selectivity is indicative of the intervention of a different mechanism as suggested (vide supra).

We speculated the trans selectivity arises from the preference of a rotamer wherein the carboxamide group and the aryl group of

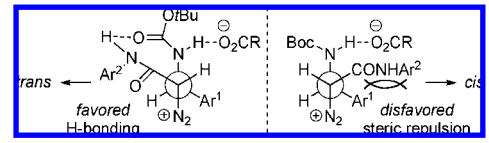


Figure 2. Possible explanation of the observed trans selectivity.

N-Boc imine adopt antiperiplanar orientation. Synclinal orientation would be destabilized by the steric repulsion (Figure 2).[12] The hydrogen-bonding between amide N−H bond and Boc group might act as a secondary factor.[13]

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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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(11) Trans/cis ratio was >20/1, as determined by ^{1}H NMR analysis of the crude material.
(12) Diazoacetates having a bulky ester moiety are known to give the trans aziridine favorably (see ref 7m).
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