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Highly Efficient Asymmetric *Trans*-Selective Aziridination of Diazoacetamides and *N*-Boc-imines Catalyzed by Chiral Brønsted Acids

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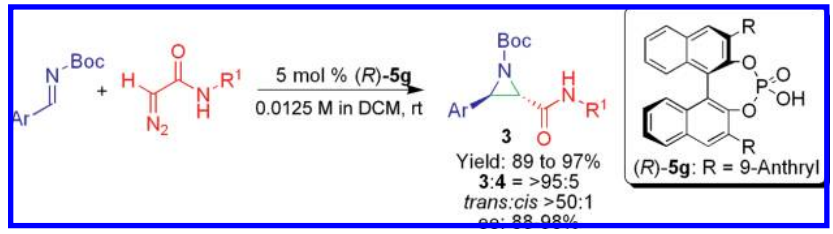
ABSTRACT



A clean and fast (10 min) aziridination of diazoacetamides with *N*-Boc-imines, as well as *N*-Cbz-imines, catalyzed by chiral phosphoric acid (*R*)-5g in DCM at room temperature was developed. The excellent yields (89−97%), diastereoselectivities (*trans/cis* > 50:1), chemoselectivities (3:4 = >95:5), and enantioselectivities (88−98% ee) were achieved in the reaction.

Chiral aziridines are important intermediates in organic synthesis as they may be easily converted to optically pure amines, α-amino acids, amino alcohols, diamines, and a variety of other amino compounds.[1] For instance, the enantiopure aziridines are the key intermediates in the synthesis of the cell adhesion inhibitor BIRT-377[2,8a] and some important optically pure amino acids (Figure 1).[3]

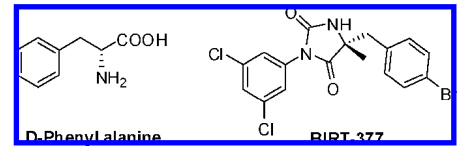


Figure 1. Some important compounds derived from chiral aziridines.

Previous research revealed that most of the optically pure aziridines were derived from other chiral materials,[4] and only a few methods are available for catalytic asymmetric aziridination.[5] The most reported strategy among them is the asymmetric nitrogen transfer to alkene catalyzed by transition-metal catalysis[6] or organocatalysis.[7] An alternative

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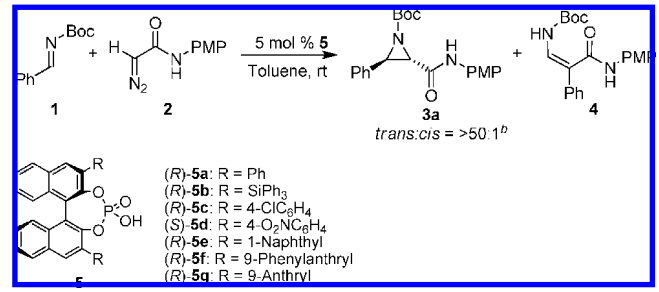
method is the chiral Lewis or Brønsted acid catalyzed asymmetric aziridinations of imines and diazoacetyl compounds, which were reported by Wulff et al.,[3,8] Maruoka et al.,[9] and Akiyama et al.[10] *trans*- or *cis*-aziridines can be obtained by these methodologies in high diastereo- and enantioselectivities, but the yields and chemoselectivities of the aziridination reactions of *N*-Boc-imines and diazoacetyl compounds still need to be improved. In this context, we report an (*R*)-BINOL-derived chiral phosphoric acid catalyzed reaction of *N*-Boc-imines and diazoacetamides, providing a highly efficient organocatalytic method for the asymmetric aziridination in excellent yields and remarkably high chemo-, enantio-, and *trans*-selectivities.

Recently, chiral Brønsted acid catalysis has become a rapidly growing area.[11] Chiral BINOL-derived chiral phosphoric acids, pioneered by Akiyama et al. and Terada et al., have received considerable attention and been applied in a wide range of asymmetric organic transformations.[12,13] In particular, Terada and co-workers demonstrated that chiral phosphoric acid is a highly efficient catalyst for the reaction of *N*-acylimines and *tert*-butyl diazoacetate to furnish the Friedel−Crafts-type adduct with excellent enantioselectivity.[14] We hypothecized that chiral phosphoric acids should be efficient catalysts for the reaction of *N*-Boc-imines and -diazoacetamides with the possibility of improvement in the yield and chemoselectivity of the aziridination reaction.

To validate this, we started to investigate the reaction of *N*-Boc-imines and -diazoacetamides catalyzed by chiral phosphoric acid catalysts as the model reaction using *N*-(4-methoxyphenyl)diazoacetamide and benzaldehyde-derived *N*-Boc-imine. In the presence of 5 mol % of catalysts (*R*)-**5a**−**g** in toluene, a fast, clean, and complete reaction occurred at room temperature within 10 min, furnishing the aziridination product **3a** in good selectivities, as shown in Table 1. From this survey, we observed that the sterically more hindered phosphoric acids emerged as catalysts with better yields (81−90%) and diastereo- (*trans:cis* > 50:1) and enantioselectivities (from 56−80%) (Table 1, entries 3 and 5−7). The best result was obtained with (*R*)-**5g** as catalyst, which afforded the *trans*-selective aziridination product in excellent yield (90%) diastereoselectivity (*trans*:*cis* > 50:1) and slightly better enantioselectivity (80% ee). However, the chemoselectivity between **3** and **4** is still unsatisfied (**3**:**4** less than 90:10).

Table 1. Aziridination Reaction of Benzaldehyde *N*-Boc-imine and *N*-PMP-diazoactamide Catalyzed by Different Chiral Phosphoric Acids in Toluene[a]



entry	catalyst	time (min)	yield[b] (%)	**3**:**4**[c]	ee[d] (%)
1	(*R*)-**5a**	10	80	80:20	45
2	(*R*)-**5b**	10	71	69:31	30
3	(*R*)-**5c**	10	81	82:18	56
4	(*S*)-**5d**	10	85	85:15	−65
5	(*R*)-**5e**	10	89	89:11	70
6	(*R*)-**5f**	10	90	88:12	78
7	(*R*)-**5g**	10	90	90:10	80

[a] Reactions were performed with benzaldehyde *N*-Boc-imine (0.12 mmol) and *N*-(4-methoxyphenyl)diazoacetamide (0.05 mmol) in the presence of 5 mol % of (*R*)-**5** (0.005 mmol) in 1.0 mL of toluene at 23 °C (room temperature). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis.

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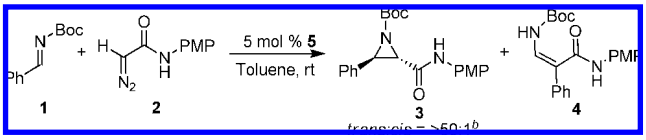
Further examination focused on the investigation of the solvent effect in the reaction. With 5 mol % of (*R*)-**5g** at room temperature, the reaction proceeded smoothly in all common solvents such as toluene (80% ee), DCM (86% ee), $CHCl_3$ (70% ee), and Et_2O (85% ee) except MeOH (no reaction). DCM was then chosen as the optimal solvent, and the reaction in DCM led to the highest yield (96%), chemoselectivity (>95:5), and enantioselectivity (86% ee, Table 2, entry 2). This tendency is in agreement with our

Table 2. Reaction of Benzaldehyde *N*-Boc-imine and *N*-PMP-diazoactamide Catalyzed by 5 mol % of (*R*)-**5g** in Different Solvents[a]



entry	solvent	concentration (M)	time (min)	**3** yield[c] (%)	**3**:**4**[d]	ee[e] (%)
1	toluene	0.1	10	93	90:10	80
2	DCM	0.1	10	96	>95:5	86
3	$CHCl_3$	0.1	30	81	85:15	70
4	Et_2O	0.1	60	85	89:11	85
5	MeOH	0.1	60	no reaction		
6	DCM	0.05	10	95	>95:5	87
7	DCM	0.025	10	96	>95:5	88
8	DCM	0.0175	10	95	>95:5	90
9	DCM	0.0125	10	97	>95:5	93
10	DCM	0.01	10	96	>95:5	89

[a] Reactions were performed with benzaldehyde *N*-Boc-imine (0.12 mmol) and *N*-(4-methoxyphenyl)diazoacetamide (0.05 mmol) in the presence of 5 mol % of (*R*)-**5g** (0.005 mmol) at rt. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the crude product. [e] Determined by chiral HPLC analysis.

earlier observations: halogenated and aromatic solvents often gave superior selectivities in the chiral phosphoric acid catalyzed organic reactions. Next, we tested the effect of reaction concentration in DCM (Table 2). It was observed that a decrease in reaction concentration in DCM from 0.1 to 0.0125 M caused the enantioselectivities to be increased from 86% to 93% (entries 6−9). Further reduction of the concentration to 0.01 M led to slightly lower ee (89%). Thus, the best result was achieved with 5 mol % of (*R*)-**5g** in 0.0125 M DCM solution at room temperature in 10 min.

Having identified the optimized reaction conditions, we explored the reaction scope with different *N*-Boc-imines and -diazoacetamides under optimal conditions to furnish the aziridination products. Experimental results were summarized in Table 3. For the *N*-Boc-imines derived from different aldehydes, all of the reactions gave excellent yields (90−97%), diastereoselectivities (all with *trans*:*cis* > 50:1), and enantioselectivities (88−96% ee) (Table 3, entries 1, 2, and 4−8) except for the *N*-Boc-imine bearing the electron-donating

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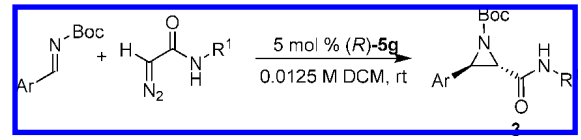
Table 3. Aziridination Reaction of Various *N*-Boc-imines and Diazoacetamides Catalyzed by 5 mol % of (*R*)-**5g** in DCM at rt[a]

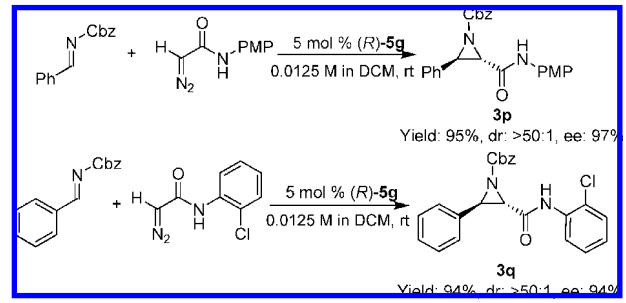


entry	Ar	R^1	**3**:**4**[b]	yield of **3**[c] (%)	ee[d]
1	Ph	4-$MeOC_6H_4$	>95:5	97 (**3a**)	93
2	4-FC_6H_4	4-$MeOC_6H_4$	>95:5	91 (**3b**)	94
3	4-$MeOC_6H_4$	4-$MeOC_6H_4$		messy	
4	3-$MeOC_6H_4$	4-$MeOC_6H_4$	>95:5	96 (**3c**)	96
5	4-MeC_6H_4	4-$MeOC_6H_4$	>95:5	90 (**3d**)	88
6	4-BrC_6H_4	4-$MeOC_6H_4$	>95:5	95 (**3e**)	90
7	3-MeC_6H_4	4-$MeOC_6H_4$	>95:5	96 (**3f**)	90
8	2-Np	4-$MeOC_6H_4$	>95:5	91 (**3g**)	88
9	4-BrC_6H_4	3,5-ClC_6H_3	>95:5	89 (**3h**)	98
10	Ph	Ph	>95:5	95 (**3i**)	92
11	Ph	2-ClC_6H_4	>95:5	95 (**3j**)	94
12	Ph	4-ClC_6H_4	>95:5	96 (**3k**)	88
13	Ph	2-$MeOC_6H_4$	>95:5	93 (**3l**)	92
14	Ph	3-$MeOC_6H_4$	>95:5	94 (**3m**)	96
15	Ph	3,5-ClC_6H_3	>95:5	81 (**3n**)	95
16[e]	Ph	3,5-ClC_6H_3	>95:5	92 (**3o**)	96

[a] Reactions were performed with *N*-Boc-imine (0.12 mmol) and diazoacetamide (0.05 mmol) in the presence of 5 mol % of (*R*)-**5g** (0.005 mmol) at rt, and all of the reactions finished in 10 min. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out on a 1.5 mmol scale.

4-methoxyphenyl moiety leading to poor conversion (Table 3, entry 3), which is similar to the result reported by Maruoka.[9] We also tried different diazoacetamides with benzaldehyde *N*-Boc-imine in the aziridination reaction (Table 3, entries 9−13). The reaction turned out to be highly tolerant to arene substitution on the diazoacetamides as all *ortho*-, *meso*-, and *para*-substituted diazoacetamides gave excellent results. However, slightly lower enantioselectivities were obtained for the diazoacetamides with electron-withdrawing groups (Table 3, entries 11 and 12), despite the excellent yields and diastereoselectivities that were achieved. The ee values were obtained by chiral-phase HPLC, and the absolute configuration of the aziridination products was

Scheme 1. Aziridination Reaction of *N*-Cbz-imine and Diazoacetamides Catalyzed by 5 mol % of (*R*)-**5g** in DCM at rt



confirmed to be 2*R*,3*S* by comparison with the data reported in the literature.[9]

Furthermore, the *N*-Cbz-protected imine was also tested in the aziridination reaction (Scheme 1). The reaction proceeded well and excellent yields and enantio- and diastereoselectivities were obtained for benzaldehyde-derived *N*-Cbz-imine with *N*-(4-methoxyphenyl)- and *N*-(2-chlorophenyl)diazoacetamides (for **3p**, yield 95%, dr >50:1, ee 97%; for **3q**, yield 94%, dr >50:1, ee 94%). The *N*-Cbz-protected imine is also thus a perfect substrate for this transformation.

In conclusion, a highly efficient, clean, and fast aziridination reaction of diazoacetamides and *N*-Boc-imines, as well as *N*-Cbz-imines, catalyzed by chiral phosphoric acid in DCM at room temperature, was developed. In all cases, excellent yields and chemoselectivities of the aziridination reactions were obtained while the diastereo- and enantioselectivities were kept at excellent levels. Further investigations to clarify the reaction mechanism and other types of imines in this reaction, and its application to synthesis of other important chiral compounds, are underway.

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

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