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Enantioselective Reaction of 2*H*-Azirines with Phosphite Using Chiral Bis(imidazoline)-Zn(II) Catalysts**

Shuichi Nakamura,*[a,b] Daiki Hayama[a]

Dedication ((optional))

Abstract: The first highly enantioselective nucleophilic addition reaction of phosphites with 2*H*-azirines has been developed. The reaction was applied to various 3-substituted 2*H*-azirines using novel chiral bis(imidazoline)/Zn(II) catalysts to afford products in good yield with high enantioselectivity. The Transformation of the optically active aziridines obtained showed that 2*H*-azirines act as α,β- or β,β-dicarbocationic amine synthons.

Chiral aziridines can react with some nucleophiles to give chiral amines, therefore aziridines act as valuable building blocks in organic chemistry.[1] Futheromore, aziridines are an important class of synthetic targets, because they often exhibit a broad range of biological activities,[2] such as Mitomycin C,[3] Azicemicin A,B,[4] and Miraziridine A[5] (Figure 1).

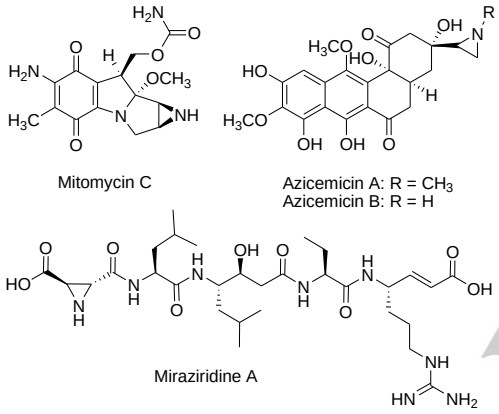

Figure 1. Biologically active compounds containing aziridine

Therefore, an intense research effort has been made to the develop an efficient asymmetric synthesis of chiral aziridines. Until now, three types of enantioselective syntheses of aziridines were developed; 1) enantioselective methylene insertion reaction to imines, 2) enantioselective aziridination reaction to olefins and 3) enantioselective cyclization of β-substituted amines (Figure 2a).[6] On the other hand, one of the efficient methods for the synthesis of optically active aziridines would be the catalytic enantioselective nucleophilic addition of some nucleophiles with 2*H*-azirines (Figure 2b).[7]

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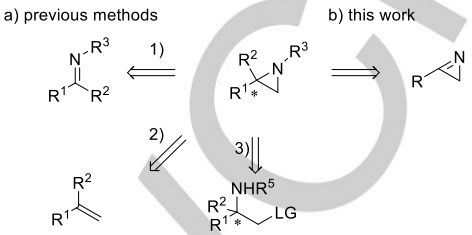


Figure 2. Synthetic methods for chiral aziridines

However, enantioselective reactions of nucleophiles with 2*H*-azirines have been far less explored due to the lower reactivity of 2*H*-azirines. Somfai and co-workers first reported the enantioselective reaction of 2*H*-azirines with Grignard reagents using a stoichiometric amount of (−)-sparteine as chiral additives to give products (up to 17% ee).[8] Recently, Zhang and co-workers reported the one example of the enantioselective reaction of azirine with pyrazole using chiral organocatalyst with moderate enantioselectivity (77% ee).[9] Although there are pioneering studies, there are no other reports on the highly enantioselective nucleophilic addition reaction to 2*H*-azirines.[10] In addition, obtained aziridines also accept reactions with other nucleophiles, allowing 2*H*-azirines to act as α,β- or β,β-dicarbocationic amine synthons (Figure 3).

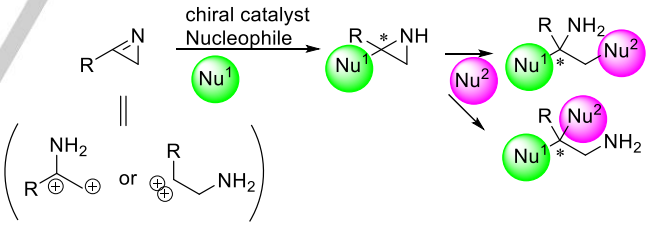
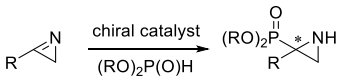


Figure 3. Enantioselective reaction with 2*H*-azirines and the synthetic utility of aziridines

On the other hand, optically active α- or β-amino phosphonic acids and their derivatives are also useful chiral building blocks for the preparation of pharmaceutical targets.[11] From this point of view, we recently reported the enantioselective reactions of ketimines with phosphites[12] and the enantioselective reaction of aziridines with phosphites.[13] We herein report the first highly enantioselective reaction of phosphites with 2*H*-azirines using our original chiral catalysts (Scheme 1).



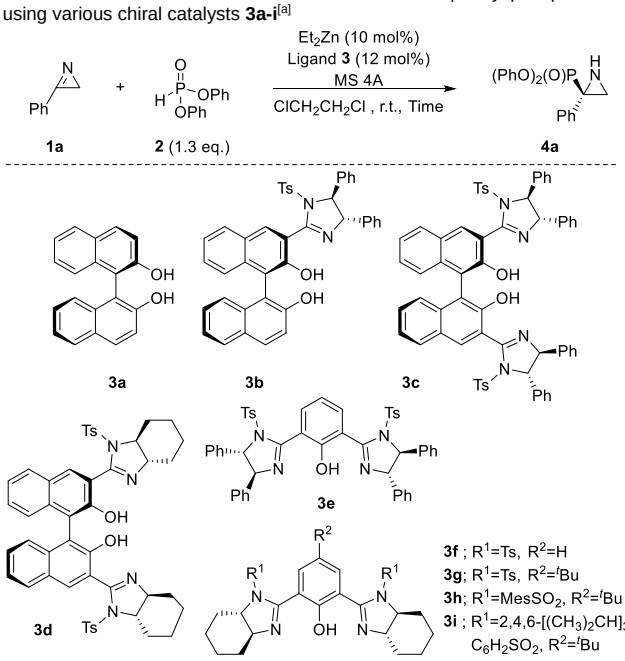
Scheme 1. Asymmetric synthesis of aziridines having a phosphonyl group via the reaction of 2*H*-azirines with phosphites

The reaction of 2*H*-azirine **1a** with diphenyl phosphite **2** (1.3 equiv.) was carried out in the presence of 12 mol% of various

10.1002/anie.201704133

ligands **3** and 10 mol% of Et_2Zn. The results are shown in Table 1.

Table 1. Enantioselective reaction of azirine **1a** with diphenyl phosphite **2** using various chiral catalysts **3a-i**[a]



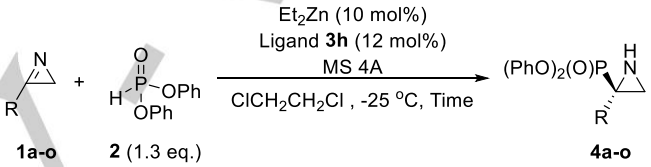
Entry	3	Time [h]	Yield [%]	Enantiomeric ratio[b]
1	**3a**	1	78	50:50
2	**3b**	1	80	64:36
3	**3c**	0.25	85	75:25
4	**3d**	1	81	66:34
5	**3e**	12	87	52:48
6	**3f**	4	78	82:18
7	**3g**	3	90	86:14
8	**3h**	4	89	88:12
9	**3i**	5	95	79:21
10[c]	**3h**	24	94	95: 5
11[c,d]	**3h**	48	93	97: 3
12[c,d,e]	**3h**	48	-	-

[a] Reaction conditions; 2*H*-azirine **1a** (0.1 mmol), **2** (1.3 equiv.), Et_2Zn (10 mol%), **3** (12 mol%), and MS 4A (50 mg) were used. The reaction was carried out in CH_2ClCH_2Cl (0.2 M). [b] Enantiomeric ratio was determined by HPLC analysis using a chiral column. [c] The reaction was carried out at −25 °C. [d] The reaction was carried out in CH_2ClCH_2Cl (0.1 M) and MS 4A (100 mg) was used. [e] $TBSOP(OPh)_2$ was used as a phosphite.

Initial catalyst screening revealed that BINOL **3a** was an active catalysts, but exhibited no enantioselectivity (entry 1). Although the reaction using chiral BINOL catalyst **3b** having one chiral imidazoline group at the 3-position gave product **4a** with low enantioselectivity, chiral bis(imidazoline)-BINOL catalyst **3c** afforded **4a** with moderate enantioselectivity (entries 2 and 3). The reaction using chiral BINOL-bis(imidazoline) catalyst **3d** derived from chiral cyclohexanediamine gave product **4a** with slightly lower enantioselectivity (entry 4). On the other hand, the reaction using chiral phenol-bis(imidazoline) catalyst **3f** derived from cyclohexanediamine showed good enantioselectivity (entry 6),[14] although the reaction using a similar catalyst **3e** derived from 1,2-diphenylethylene-1,2-diamine gave product **4a** as an almost racemic form (entry 5). To improve enantioselectivity, the substituent on the chiral ligand was examined (entries 7-9). As a result, the reaction using catalyst **3h** having a 2,4,6-trimethylbenzenesulfonyl group on nitrogen in imidazoline and a *tert*-butyl group on the phenol group afforded product **4a** in high yield with high enantioselectivity (89%, er = 88:12, entry 8). The reaction at a lower reaction temperature and lower concentration of reaction solution improved the yield and enantioselectivity slightly (entries 10 and 11). The reaction of **1a** with diphenyl *tert*-butyldimethylsilyl phosphite [$TBSOP(OPh)_2$] instead of diphenyl phosphite did not afford any product (entry 12).

Having established the suitable reaction conditions, the nucleophilic reaction of various azirines **1a**-**o** with diphenyl phosphite **2** using **3h**/Et_2Zn was examined (Table 2).

Table 2. Enantioselective reaction of various azirines **1a-o** with phosphite using **3h**/Et_2Zn[a]



Entry	1	R	Time [h]	Yield [%]	Er[b]
1	**1a**	Ph	48	93	97: 3
2	**1b**	4-$CH_3C_6H_4$	72	83	96: 4
3	**1c**	3-$CH_3C_6H_4$	24	97	96: 4
4	**1d**	3,5-$(CH_3)_2C_6H_3$	24	91	97: 3
5	**1e**	3-Ph-C_6H_4	72	99	95: 5
6	**1f**	4-$CH_3OC_6H_4$	72	95	94: 6
7[c]	**1g**	3-$CH_3OC_6H_4$	24	99	96: 4
8	**1h**	4-FC_6H_4	120	87	93: 7
9	**1i**	3-FC_6H_4	96	91	94: 6
10	**1j**	2-FC_6H_4	120	92	94: 6
11[c]	**1k**	1-naphthyl	120	81	94: 6
12	**1l**	2-naphthyl	36	96	96: 4
13	**1m**	2-thienyl	24	83	98: 2
14	**1n**	3-thienyl	96	91	96: 4
15[c]	**1o**	PhCH=CH	48	78	90:10

[a] Reaction conditions; 2*H*-azirine **1a** (0.1 mmol), **2** (1.3 equiv.), Et_2Zn (10 mol%), **3** (12 mol%), and MS 4A (100 mg) were used. The reaction was carried out in CH_2ClCH_2Cl (0.1 M) at -25 °C. [b] Enantiomeric ratio was determined by HPLC analysis using a chiral column. [c] The reaction was carried out in CH_2ClCH_2Cl (0.2 M) and MS 4A (50 mg) was used.

The reaction of azirines **1b-g** having electron-donating groups such as methyl, methoxy, or phenyl groups in the meta or para position gave corresponding products **4b-g** in good to moderate yield with high enantioselectivity (yield 83-99%, er=93:7-97:3, entries 2-7). The reaction of electron-deficient azirines **1h-j** having fluoro groups were tolerable in this reaction condition to give products **4h-j** with good enantioselectivity (entries 8-10).

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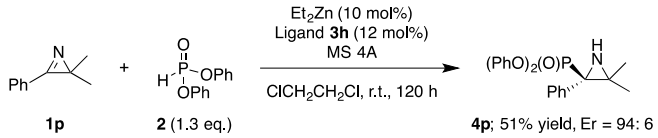
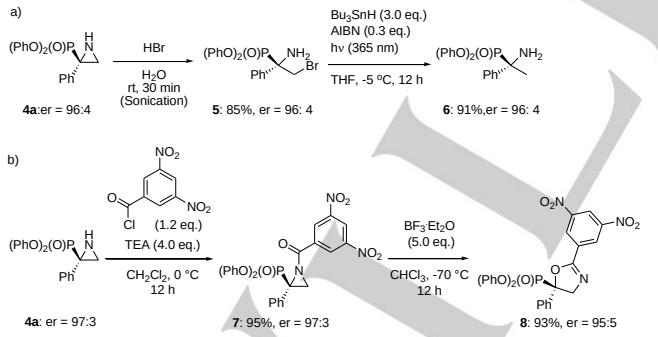
Azirines **1k-n** having 1- or 2-naphthyl or a heteroaryl group, such as 2 or 3-thienyl groups, also afforded products **4k-n** in 81-96% yield with 94:6-98:2 er (entries 11-14). The reaction of conjugated ketimine **1o** gave product **4o** with good enantioselectivity without generating any conjugation addition product (entry 15). After the reaction, most of catalyst **3h** could be recovered by column chromatography, and recovered catalyst could be used in the reaction to afford product **4a** in 94% yield with 97:3 e.r. We also examined the reaction of dimethylazirine **1p** with **2** using catalyst **3h**.[15] The reaction proceed slowly to give the product **4p** in moderate yield with high enantioselectivity (Scheme 2). These results are the first example of a highly enantioselective reaction of azirines with nucleophiles.



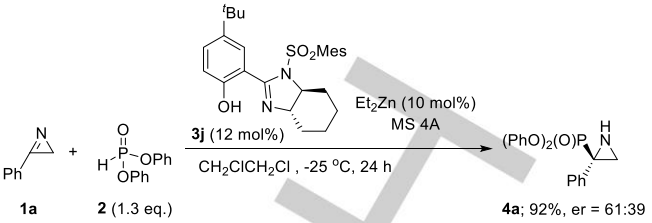
Scheme 2. Enantioselective reaction of dimethylazirine **1p** with **2** using bis-imidazoline catalyst **3h**

We next examined the ring-opening reaction of obtained aziridine **4a** (Scheme 3a). The reaction of **4a** with hydrogen bromide in water under sonication gave β-bromo-α-aminophosphonate **5** in high yield (85%). The bromo group in **5** can be removed by using Bu_3SnH and AIBN[16] to give α-aminophosphonate **6** without the loss of enantiopurity. The absolute configuration of **6** was assigned as (*S*), based on the value of the specific rotation for **6** reported in the literature.[12a] On the other hand, the transformation of 3,5-dinitrobenzoylated aziridine **7** prepared from **4a** using $BF_3{\cdot}OEt_2$ afforded oxazoline compound **8**, which could be converted to chiral aminoalcohols (Scheme 3b).[17] These reactions implied that azirines act as α,β- or β,β-dicarbocationic amine synthons.



Scheme 3. Ring-opening reaction of chiral aziridine **4a** using HBr and removal of bromide from **6**, and oxazoline formation reaction of **4a**

In order to clarify the reaction mechanism, the reaction using mono-imidazoline catalyst **3j** was carried out (Scheme 4). The reaction gave product **4a** in high yield but with low enantioselectivity (92%, 61:39 er). This result clearly showed the superiority of the bis-imidazoline catalyst **3h** over the mono-imidazoline catalyst (Table 1, entry 11).



Scheme 4. Enantioselective reaction of azirine **1a** with **2** using mono-imidazoline catalyst **3j**.

In addition, the reaction of **1a** with diphenyl phosphite gave products in good yield with good enantioselectivity, although the reaction with $TBSOP(OPh)_2$ did not afford any product (Table 1, entry 12). Based on these results, the proposed catalytic cycle for the hydrophosphinylation of azirine **1a** with diphenyl phosphite is shown in Figure 4. Diethylzinc reacts with a hydroxy group of chiral ligand **3h** to afford complex **A**. Then the azirine coordinates to the zinc cation of complex **A** to afford complex **B**, which coordinates and activates diphenyl phosphite **2**.[18] The activated phosphite attacks the imino carbon of azirine. Subsequently, the adduct-complex undergoes protonation and decomplexation to give the product and regenerated complex **A**. In order to clarify the assumed reaction mechanism, we conducted a spectroscopic analysis. The ESI-Mass spectroscopic analysis for the reaction mixture of **1a**, **3h**, Et_2Zn showed a dimer of complex **A** (cation mode, calcd for $C_{92}H_{126}N_{11}O_{10}S_4Zn_2^+$ as dimer complex **A**+2CH_3CN+NH_4^+: 1800.7, found: 1800.7). This signal supports our proposed reaction mechanism.

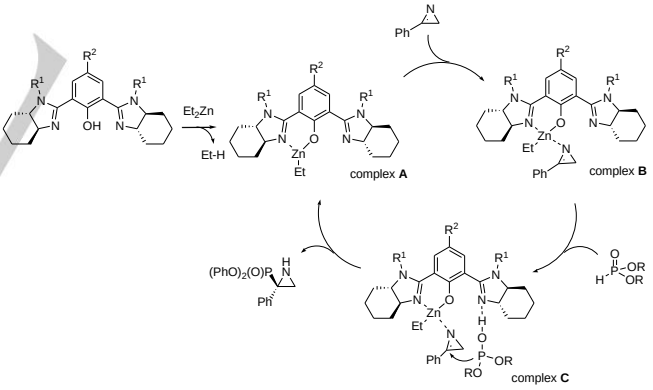


Figure 4. Assumed reaction mechanism for the enantioselective reaction of azirine **1a** with diphenyl phosphite **2** using **3h**

From the above consideration and absolute stereochemistry of the product, the assumed transition state for the reaction of azirine **1a** with **2** is shown in Figure 5. A nitrogen from imidazoline and an oxygen on the phenol group in **3h** coordinates to zinc(II) in a tetrahedral manner, and another imidazoline moiety makes a hydrogen bond with the hydroxyl group in phosphite. The phosphite approaches the *Re*-face of azirine, thereby avoiding steric repulsion, to give the (*R*)-isomer of **4a**.

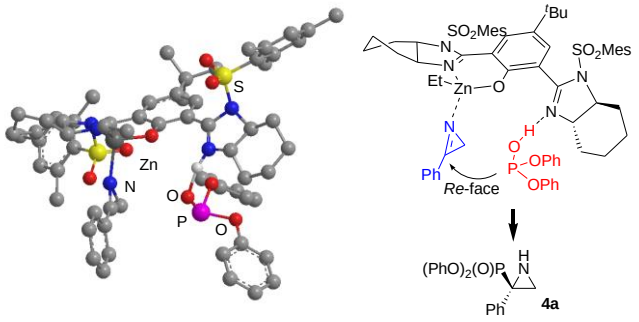


Figure 5. Proposed transition state of the reaction of azirine **1a** with **2** using **3h**. H atoms have been omitted for clarity.

In conclusion, we developed a highly enantioselective reaction of azirines with phosphite. The reaction was screened for a broad range of azirines. This approach is the first example of a highly enantioselective reaction of azirines with nucleophiles. The obtained aziridines can be converted to chiral tetra-substituted amines and oxazolines. We believe that the concept described here will open doors to the asymmetric reaction of azirines. Further studies are in progress to study the potential of these catalytic systems for other processes and enantioselective reaction of azirines.

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Keywords: asymmetric synthesis · azirine · imidazoline · aziridine

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Layout 2:

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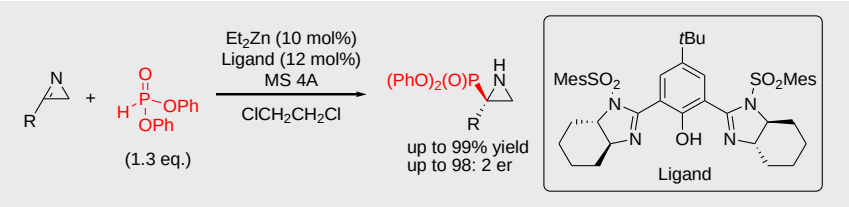

The first highly enantioselective nucleophilic addition reaction of phosphites with 2*H*-azirines has been developed. The reaction was applied to various 3-substituted 2*H*-azirines using novel chiral bis(imidazoline)/Zn(II) catalysts to afford products in good yield with high enantioselectivity. The Transformation of the optically active aziridines obtained showed that 2*H*-azirines act as α,β- or β,β-dicarbocationic amine synthons.

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Page No. – Page No.

Enantioselective Reaction of 2*H*-Azirines with Phosphite Using Chiral Bis(imidazoline)-Zn(II) Catalysts