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Enantioselective Aza-Darzens Reaction Catalyzed by A Chiral Phosphoric Acid

Takahiko Akiyama,* Tohru Suzuki, and Keiji Mori

Department of Chemistry, Gakushuin University, 1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588, Japan

takahiko.akiyama@gakushuin.ac.jp

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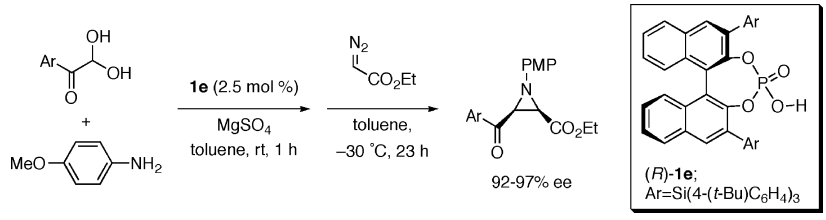
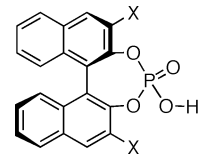
ABSTRACT



Aza-Darzens reaction of ethyl diazoacetate with aldimines, derived from phenyl glyoxal, furnished *cis*-aziridine carboxylates with excellent enantioselectivities by means of a chiral phosphoric acid.

Chiral aziridines are versatile intermediates for the preparation of optically active amines, which are employed as chiral building blocks, intermediates, auxiliaries, and ligands.[1] The structure is also found in antitumor and antibiotic compounds such as mitomycin and mitiromycin.[2] Most of the methods for the preparation of the chiral aziridines rely on starting from chiral compounds.[3] The development of a catalyzed reaction is highly desired. Reactions involving asymmetric nitrogen transfer reactions to alkene by means of transition-metal catalysts[4] as well as organocatalysts[5] have been extensively explored. The aza-Darzens reaction of α-diazoacetate with aldimine is a useful method for the preparation of aziridine carboxylates.[6] Wulff and co-workers developed a chiral Lewis acid catalyst.[7,8] Quite recently, Maruoka and co-workers reported that a chiral dicarboxylic acid also proved to be an efficient catalyst for the aza-Darzens reaction.[9]

Recently, chiral phosphoric acids have emerged as efficient green chiral catalysts.[10−12] As part of our ongoing program on the development of chiral Brønsted acid catalyzed reactions, we have investigated the reaction of aldimine with α-diazoacetate catalyzed by a chiral phosphoric acid (Figure 1). Terada and co-workers already have reported the chiral phosphoric acid catalyzed alkylation reaction of α-diazoacetate with aldimines bearing an *N*-acyl moiety (Scheme 1,



1a: X=4-$NO_2C_6H_4$
1b: X=9-anthryl
1c: X= 2,4,6-(i-Pr)$_3C_6H_2$
1d: X=$SiPh_3$
1e: X=Si(4-(t-Bu)C_6H_4)$_3$

Figure 1. Chiral phosphoric acid catalysts.

(1) Sweeney, J. B. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; p 117.

(2) Fürmeier, S.; Metzger, J. O. *Eur. J. Org. Chem.* **2001**, 649–659.

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(4) For the transition-metal-catalyzed addition of nitrenes to olefins, see: (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194–206. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329. (c) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676–678.

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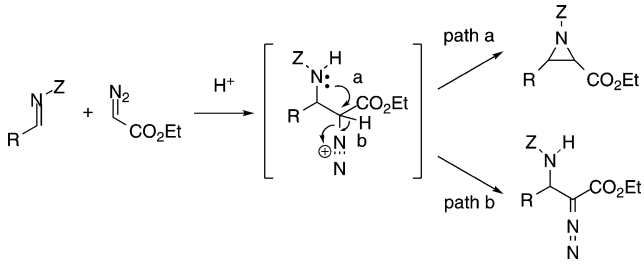
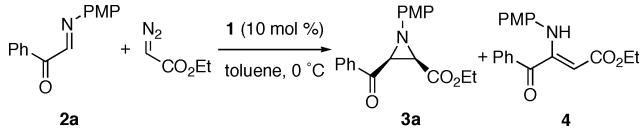
Scheme 1. Aza-Darzens Reaction versus Addition Reaction



path b).[13] We wish to report herein chiral phosphoric acid catalyzed aza-Darzens reaction leading to aziridines (Scheme 1, path a).

At the outset, aza-Darzens reaction of an aldimine **2**, derived from phenylglyoxal and *p*-anisidine, with α-diazoacetate was examined using phosphoric acid **1**.[14] Treatment of **2** with ethyl diazoacetate in the presence of 10 mol % of phosphoric acid **1** in toluene at 0 °C furnished *cis*-aziridine **3** accompanied by **4**.[15] The effects of the 3,3′-substituents were studied, and the results are shown in Table 1. The

Table 1. Effect of the 3,3′-Substituents of Chiral Phosphoric Acid **1**[a]



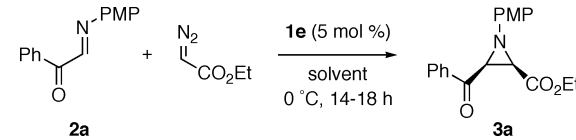
2a **3a** **4**

entry	X	**3**[b] (yield, %)	**3**[c] (ee, %)	**4**[b] (yield, %)
1	4-$NO_2C_6H_4$	69	−17	13
2	9-anthryl	63	−64	18
3	2,4,6-(*i*-Pr)$_3C_6H_2$	53	−88	34
4	$SiPh_3$	80	−22	20
5	Si(4-(*t*-Bu)$C_6H_4)_3$	81	90	17

[a] 2.0 equiv of ethyl diazoacetate was employed. [b] Yield of isolated product. [c] Enantiomeric excess was determined by chiral HPLC analysis.

enantioselectivities were determined by chiral HPLC analysis. TRIP (**1c**) exhibited high enantioselectivity (entry 3).

Table 2. Effect of Solvent[a]



2a **3a**

entry	solvent	**3a**[b] (yield, %)	**3a**[c] (ee, %)
1	Et_2O	69	89
2[b]	CH_2Cl_2	72	87
3[b]	CH_3CN	71	81
4[b]	mesitylene	76	87
5	benzene	64	89
6	toluene	78	90
7	toluene (−30 °C)	72	94

[a] 2.0 equiv of ethyl diazoacetate was employed. [b] Yield of isolated product. [c] Enantiomeric excess was determined by chiral HPLC analysis.

Interestingly, although **1d**, bearing triphenylsilyl groups, was not effective (entry 4), use of **1e** having a tris(*p*-*tert*-butylphenyl)silyl group proved to be highly effective (entry 5), and the corresponding aziridine **3** was obtained in 90% ee. It was found that the introduction of a bulky substituent to the terminal position on the phenyl group significantly improved the enantioselectivity. Recently, both Yamamoto[16] and List[17] demonstrated the beneficial effect of introducing a bulky group to the terminal position of the 3,3′-positions.

We then studied the effect of solvent in the presence of 5 mol % of **1e**, and the results are shown in Table 2. Aromatic

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(11) For our reports, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583–2585. (c) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523–1526. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (e) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071. (f) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141–143. (g) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764. (h) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402. (i) Itoh, J.; Fuchibe, K.; Akiyama, T. *Synthesis* **2008**, 1319–1322. (l) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016–4018.

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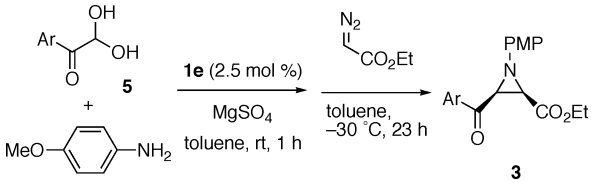
solvents gave better results, and among the solvents examined, toluene exhibited the highest enantioselectivity at 0 °C (90% ee, entry 6). Lowering the temperature to −30 °C improved the ee to 94% without reducing the chemical yield (entry 7).

Next, the three-component reaction starting from phenylglyoxal monohydrate, *p*-anisidine, and diazo acetate was examined. Treatment of phenylglyoxal monohydrate and *p*-anisidine in the presence of 2.5 mol % of **1e** and $MgSO_4$ in toluene at room temperature for 1 h, followed by the addition of α-diazoacetate at −30 °C for 1 day gave rise to aziridines **3a** exclusively as the *cis* isomer[18] in 95% yield with 97% ee (entry 1). The three-component reaction gave better results than the reaction of aldimine with diazoacetate in terms of both chemical yield and enantioselectivity. It should be noted that the use of 1 mol % of **1e** as a catalyst gave aziridine in 84% yield with 96% ee (entry 2). The results with other phenylglyoxal derivatives are shown in Table 3. A range of aldimines derived from phenyl glyoxal

Table 3. Results of the Aza-Darzens Reaction[a]



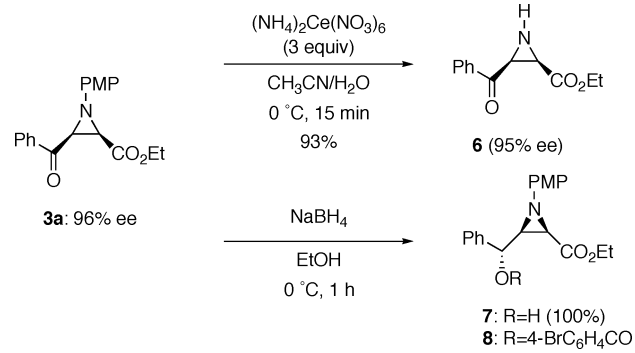
entry	Ar	**3**[b] (yield, %)	**3**[c] (ee, %)
1	Ph (**3a**)	95	97
2	Ph (**3a**)[d]	84	96
3	4-BrC_6H_4 (**3b**)	93	93
4	4-ClC_6H_4 (**3c**)	100	94
5	4-FC_6H_4 (**3d**)	100	94
6	4-$CF_3C_6H_4$ (**3e**)	91	97
7	4-MeC_6H_4 (**3f**)	94	92
8	4-$MeOC_6H_4$ (**3g**)	98	95
9	4-biphenyl (**3h**)	96	94
10	1-naphthyl (**3i**)	100	96
11	2-thienyl (**3j**)	100	92

[a] 2.0 equiv of ethyl diazoacetate was employed. [b] Yield of isolated product. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] 1.0 mol % of **1e** was employed.

derivatives underwent the aza-Darzens reaction to furnish corresponding aziridines with excellent ee's. The absolute stereochemistry of an aziridine **3b**, derived from **5b** (Ar = *p*-BrC_6H_4), was unambiguously determined to be (2*R*,3*S*) by X-ray analysis, and those of the other aziridines were surmised by the analogy.[19]

Cleavage of the PMP protecting group on the nitrogen of **3a** was effected by means of CAN to give the corresponding aziridine **6** in 93% yield (Scheme 2). On exposure of **3a** to

Scheme 2. Transformation of Aziridine **3a**



$NaBH_4$, reduction of the ketone proceeded to give an alcohol **7** with high diastereoselectivity (>98:<2), whose relative stereochemistry was determined by X-ray analysis of its *p*-bromobenzoate **8**.[19]

Terada's group employed aldimines with the *N*-acyl moiety for the formation of the alkylation product.[13] In that study, the electron density of the nitrogen atom was decreased by the presence of the electron-withdrawing group on the nitrogen, and therefore, nucleophilic addition was suppressed. In our case, the PMP group on nitrogen increased the nucleophilicity, and aziridination was promoted.

In summary, chiral phosphoric acid catalyzed aza-Darzens reaction of in situ generated aldimine with diazo acetate proceeded smoothly to furnish aziridines with excellent chemical yields and enantioselectivities.

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Note Added after ASAP Publication. A corrected Supporting Information file was posted on May 6, 2009.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900674T

(13) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360–9361.

(14) An aldimine derived from benzaldehyde and *p*-anisidine did not give the corresponding aziridine.

(15) α-Diazo compounds were decomposed during the purification by thin-layer chromatography to afford **4**.

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(17) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079–5081.

(18) Aziridines were obtained exclusively as the *cis* isomer, and the *trans* isomer was not observed by 400 MHz ^{1}H NMR in all cases examined.

(19) Crystallographic data for the structures of **3b** and **8** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-719446 and CCDC-722770. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).