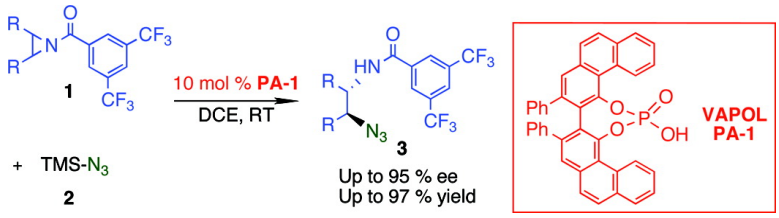
Communication

Brønsted Acid-Catalyzed Desymmetrization of *meso*-Aziridines

Emily B. Rowland, Gerald B. Rowland, Edwin Rivera-Otero, and Jon C. Antilla

J. Am. Chem. Soc., **2007**, 129 (40), 12084-12085• DOI: 10.1021/ja0751779 • Publication Date (Web): 18 September 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 37 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/18/2007

Brønsted Acid-Catalyzed Desymmetrization of *meso*-Aziridines

Emily B. Rowland, Gerald B. Rowland, Edwin Rivera-Otero,§ and Jon C. Antilla*

Department of Chemistry, University of South Florida, 4202 East Fowler Avenue CHE 205A, Tampa, Florida 33620

Received July 11, 2007; E-mail: jantilla@cas.usf.edu

The vicinal diamine structural moiety is a privileged framework in organic chemistry.[1] Vicinal diamines have been used extensively as chiral auxiliaries and chiral ligands. Chiral vicinal diamines can also be found in anticancer agents and anti-influenza drugs, as well as many other biologically active compounds. Researchers have developed many methods for the synthesis of these diamines.[1] One of the most direct methods for their synthesis is the ring-opening of aziridines with nitrogen nucleophiles.[2] While many of these existing strategies have been successful, the development of catalytic, enantioselective methods for the opening of *meso*-aziridines has been much less studied. In 1999, Jacobsen and co-workers reported the first enantioselective ring-opening of *meso*-aziridines with azidotrimethylsilane using a chiral chromium complex.[3] Recently, Shibasaki and co-workers have reported the use of chiral yttrium complexes for the desymmetrization of *meso*-azirdines in route to the synthesis of Tamiflu.[4] In this communication, we report the first example of a Brønsted acid-catalyzed enantioselective ring-opening of *meso*-aziridines as well as preliminary investigations into the mechanism of such reactions.

Organocatalysis, the use of small, chiral organic molecules as enantioselective catalysts, has been a fruitful area of research for the past decade.[5] In 2004, the research groups of Akiyama[6] and Terada[7] independently reported that phosphoric acids derived from BINOL could be used as enantioselective catalysts. Since the first report, our group, as well as other groups, has shown that chiral phosphoric acids are versatile catalysts for the addition of various nucleophiles to imines.[8] List and co-workers have demonstrated that amine salts of chiral phosphoric acids could be used for the asymmetric reduction of enones[10] and the dynamic kinetic resolution of racemic aldehydes.[11] Chiral phosphoric acids as mediators for the enantioselective desymmetrization of *meso*-aziridines would represent a new and powerful utilization of such catalysts as the potential activation involves a non-imine-based electrophile.Our initial investigation into the desymmetrization of *meso*- aziridines involved studying the effect of substitution on the nitrogen atom of the aziridine with **PA-1** as the catalyst (Table 1). The screening of both Cbz and BOC protecting groups on the nitrogen resulted in the formation of the product as the racemate in moderate yield (entries 1, 2). However, to our delight a 4-nitrobenzoyl-substituted imine resulted in the formation of the product in good yield and moderate enantioselectivity (entry 3). Corresponding substitution with a 3,5-dinitrobenzoyl group on the nitrogen (entries 6−8) provided for the desired product in an excellent yield and moderate ee. Our ideal conditions in terms of yield and enantioselectivity required the use of a bis-(3,5-trifluoromethyl)benzoyl group as a substituent (entries 9−10). However, the use of this substituent generally resulted in longer reaction times. Solvent studies revealed that the use of 1,2-dichloroethane resulted in the formation of the product in the highest yield and enantioselectivity.

§ University of South Florida Interdisciplinary Nuclear Magnetic Resonance Facility.

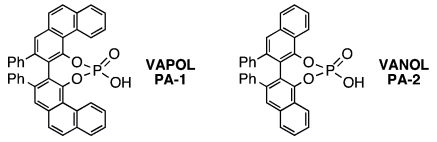
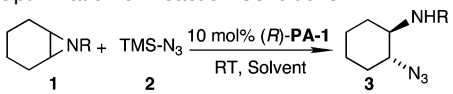
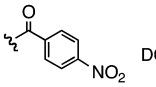
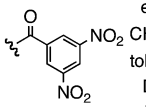
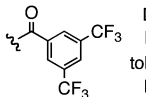


Figure 1. VAPOL and VANOL phosphoric acids.

Table 1. Optimization of Reaction Conditions[f]



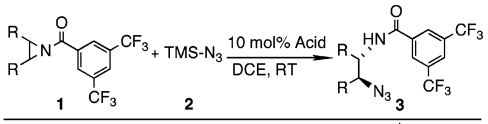
Entry[a]		R	Solv.	Time,h	% Yield[b]	% ee[c]
1[d]	**1a**	Cbz	DCE	22	49	0
2	**1b**	BOC	DCE	42	70	0
3	**1c**		DCM	26	72	35
4			ether	23	52	4
5			CH_3CN	46	85	43
6	**1d**		toluene	14	80	59
7			DCM	15	94	65
8			DCE	6	90	77
9[d]			DCM	22	96	90
10[d]	**1e**		DCE	21	97	95[e]
11[d]			toluene	22	89	65
12[d]			PhCl	22	69	68

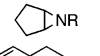
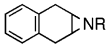
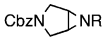
[a] General Procedure: molar ratio of **1**/**2** = 1:1.5 in 0.5 mL of solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction performed using a molar ratio of **1**/**2** = 1.5:1. [e] Catalyst derived from (*S*)-VAPOL resulted in a reversal of the retention time for the major enantiomer of **3** as judged by chiral HPLC (see SI). [f] DCM = dichloromethane, DCE = 1,2-dichloroethane.

We next turned our attention to the variation of the aziridine (Table 2). Using the optimized reaction conditions, **PA-2** derived from the VANOL framework proved to be a comparable catalyst for the desymmetrization of the *meso*-aziridine derived from cyclohexane as **PA-1** (entries 1, 2). However, the use of **PA-2** for ring-opening an aziridine derived from 1,4-cyclohexadiene resulted in the formation of the product in much lower yield than using **PA-1** but with similar enantioselectivity (entries 3, 4). Azide addition to a cycloheptane aziridine resulted in the formation of the ring-opened product in excellent enantioselectivity but with a decrease in the yield of the product (entry 5). Heating this reaction to 60 °C resulted in the formation of the product in excellent yield and moderate selectivity (entry 6). The reaction time for both reactions is much longer than the time required for the ring-opening of the cyclohexane aziridine. Various aziridines derived from cycloalkanes resulted in the formation of the ring-opened product in good yield and enantioselectivity. Aziridines containing acyclic aliphatic and aryl substituents resulted in the formation of the product in excellent yield and with good enantioselectivity (entries

10.1021/ja0751779 CCC: $37.00

Table 2. Variation of Aziridine Substrate



Entry	Aziridine[a]		Acid	Time,h	%Yield[b]	% ee[c]
1		**1e**	(*S*)**PA-1**	21	97	95
2			(*R*)**PA-2**	21	90	94
3		**1f**	(*S*)**PA-1**	21	84	92
4			(*R*)**PA-2**	21	55	91
5[d]		**1g**	(*S*)**PA-1**	91	64	91
6[d,e]			(*S*)**PA-1**	72	95	69
7		**1h**	(*S*)**PA-1**	55	68	84
8[d]		**1i**	(*S*)**PA-1**	48	90	70
9		**1j**	(*S*)**PA-1**	21	88	86
10		**1k**	(*S*)**PA-1**	48	95	83
11		**1l**	(*S*)**PA-1**	48	49	87
12		**1m**	(*S*)**PA-1**	24	94	71

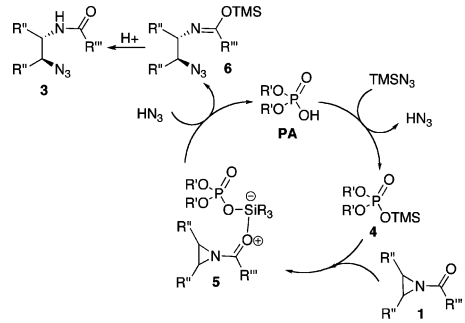
[a] General conditions: molar ratio of **1**/**2** = 1.5:1. [b] Isolated yield. [c] Enantioselectivity determined by HPLC analysis. [d] Molar ratio of **1**/**2** = 1:2. [e] Reaction performed at 60 °C.

9 and 10). Heterocyclic aziridines could also be employed in the ring-opening reaction. The use of an aziridine derived from 2,5-dihydrofuran resulted in a drastic decrease in yield of the product, with the balance of mass attributed primarily to unreacted starting material (entry 11).

Preliminary studies into the mechanism of the organocatalytic desymmetrization of *meso*-aziridines indicate that the presence of the trimethylsilyl group is required for the formation of the ring-opened product. It has long been known that compounds containing an amide, sulfoxide, or a P═O double bond can activate silane compounds into donating a nucleophile.[12] The reaction of the aziridine with tetrabutylammonium azide and NaN_3 in the presence of the phosphoric acid resulted in no reaction. Notable is the fact that the reaction does not occur with azidotrimethylsilane in the absence of the phosphoric acid. However, the use of NaN_3 in the presence of trimethylsilyl chloride resulted in the formation of the product in moderate yield. Preliminary ^{1}H NMR studies indicate the presence of a new compound containing proton signals indicative of the formation of the new TMS-containing compound **6**. This evidence leads us to speculate that the reaction occurs by the mechanism shown in Scheme 1. The first step of the reaction involves the formation of the active catalyst by displacement of the azide. The resulting chiral silane **4** then activates the aziridine by means of coordinating to the carbonyl functionality of the aziridine, resulting in the formation of **5**. Species **5** then undergoes attack by the azide nucleophiles, resulting in **6** and the reformation of **PA**. Compound **6** readily decomposes on silica gel to form product **3**.

In conclusion, we report the first organocatalytic desymmetrization of *meso*-aziridines using chiral phosphoric acids derived from VAPOL and VANOL. The active catalytic species appears to be a chiral silane that is generated in situ by the reaction of the chiral phosphoric acid with azidotrimethylsilane. Future work will include extension of the substrate scope and theoretical and experimental studies into the mechanism of this and related transformations.

Scheme 1. Proposed Mechanism of the Organocatalytic Desymmetrization of *meso*-Aziridines



Acknowledgment. We thank the Petroleum Research Fund for financial support (PRF 45899-G1). We are also grateful to Ted Gauthier (HRMS, NSF-CRIF:MU #0443611) of USF.

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

References

(1) For a review of the synthesis and utility of chiral 1,2-diamines, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
(2) For reviews, see: (a) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Masahiko, H.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817.
(3) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611.
(4) (a) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (b) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259. For the enantioselective desymmetrization of *meso*-aziridines with TMSCN, see: Miti, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.
(5) For reviews of enantioselective organocatalysis, 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) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
(6) Akiyama, T.; Itoh, J.; Yokota, D.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
(7) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
(8) For reviews of chiral phosphoric acid catalysis ,see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.
(9) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (c) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (e) Hoffmann, S.; Saeyad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (f) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (g) Rueping, M.; Antonchick, A. P.; Thiessmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (h) Rueping, M.; Antonchick, A. P.; Thiessmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (i) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (j) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (k) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (l) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (m) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (n) Kang, Q.; Zhao, Z. A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484.
(10) (a) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193. (b) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.
(11) Hoffman, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.
(12) For an excellent review on the activation of silanes, see: Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

JA0751779