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Chiral Phosphoric Acid-Catalyzed Desymmetrization of *meso*-Aziridines with Functionalized Mercaptans

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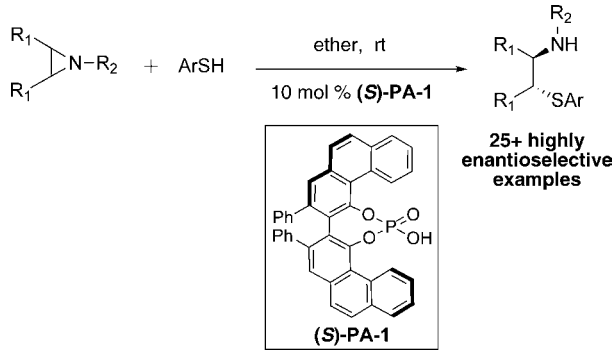
ABSTRACT



Conditions for the phosphoric acid-catalyzed highly enantioselective ring-opening of *meso*-aziridines with a series of functionalized aromatic thiol nucleophiles are described. The procedure utilizes commercially available aromatic thiols, a series of *meso*-aziridines, and a catalytic amount of VAPOL phosphoric acid to explore the substrate scope of this highly enantioselective reaction.

Aziridines are considered by many to be useful precursors for the production of advanced targets of interest primarily because of unique ring-opening chemistry that can allow for direct access to a variety of chiral amines.[1] In the case of nucleophilic ring-opening of aziridines, a judicious choice of the nucleophile can allow for the preparation of a variety of functionalized products.[1a]

We believe many have the opinion that stereocontrolled chemistry would be vital for achieving a high degree of synthetic utility for such ring-opening strategies. This control can be realized in cases where chiral catalysts allow for ring-opening desymmetrization reactions of *meso*-aziridines.[2] Examples include the implementation of catalytic chiral metal complexes that can allow for a high enantioselectivity of the resulting ring-opened product using primarily azide- or cyanide-based nucleophiles.[3] As part of a recent study that has focused on chiral Brønsted acid-catalyzed additions using heteroatom nucleophiles,[4] we discovered unique reactivity whereby chiral phosphoric acids[5] could activate aziridines

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(2) For a review on the desymmetrization of *meso*-aziridines, see: Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082.

(3) (a) Li, Z.; Fernandez, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611. (b) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252. (c) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (d) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Saro, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (e) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126.

(4) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (c) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

(5) For reviews with considerable chiral phosphoric acid coverage, 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. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Chem. Commun.* **2008**, 4097. (e) Adair, G.; Mukherjee, S.; List, B. *Aldrichchim. Acta* **2008**, *41*, 31.

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for enantioselective ring-opening chemistry with trimethylsilyl azide (TMS-N_3).[6]

Our discovery prompted us to expand the scope of this chemistry by investigating the ring opening with sulfur-based nucleophiles. This expansion of substrate scope would allow for the preparation of interesting chiral β-amino thioethers.[7] At the start of our study the previous methodology reporting catalytic asymmetric ring-opening desymmetrization reactions utilizing thiols were rare, with low enantiomeric excesses being found.[8] Late in our investigation using thiols, a publication by Della Sala[9] described an enantioselective ring-opening of *meso*-aziridines using (phenylthio)trimethylsilane (TMS-SPh) and the catalyst system we reported[6] in our above azide chemistry. Interestingly, this report implied that silylated nucleophiles were required, and the authors explained their chemistry by invoking our previously postulated mechanism involving the importance of silicon being present on the nucleophile. However, in this paper we reveal that *silylated thiols are not necessary* as simple unsubstituted thiols can be used to obtain the same ring-opened product with excellent yield and enantioselectivity using the same chiral VAPOL phosphoric acid catalyst **PA-1** (Figure 1).

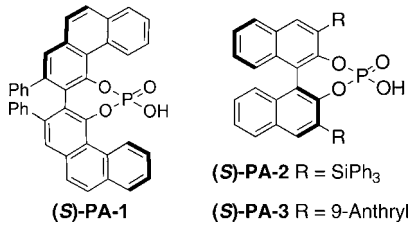
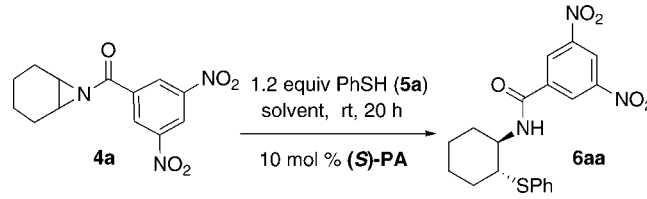


Figure 1. Chiral phosphoric acids.

During our optimization process, we quickly became aware that silylated nucleophiles were not necessary for the phosphoric acid-catalyzed thiophenol ring-opening reactions of substituted *N*-benzoylaziridine substrates. As in the chemistry by Della Sala, we found that the 3,5 dinitro substitution was necessary to achieve the best enantioslectvity.[9] Nonpolar solvents like toluene provided moderate enantioselectivity for the reaction (entry 1), while dichloromethane (DCM) gave improved ee (entry 2). Polar solvents like EtOAc (entry 3), MeCN (entry 4), or tetrahydrofuran (THF) gave much lower enantioselectivity (entry 5), following a trend found in many other reactions involving chiral phosphoric acid catalysis.[4a,6] Both methyl *tert*-butyl ether (entry 6) and diethyl ether (entry 7) were excellent solvents for the thiophenol ring-opening, with the product found in these conditions having excellent yield and ee. Several additional catalysts were screened, but those evaluated gave poor selectivity results. For example, with catalyst **PA-2** (entry 8) or **PA-3** (entry 9) we found the enantioselectivities dropped to low levels. Unfortunately, when the catalyst loading was decreased to 5 mol % a lower yield and ee for **6aa** was also found (entry 10) Table 1.

Table 1. Optimization of the Aziridine Ring-Opening with PhSH



entry	catalyst (*S*)	solvent	yield,[a] %	ee,[b] %
1	**PA-1**	toluene	74	70
2	**PA-1**	DCM	91	86
3	**PA-1**	EtOAc	89	31
4	**PA-1**	MeCN	82	40
5	**PA-1**	THF	95	12
6	**PA-1**	MTBE	99	96
7	**PA-1**[c]	ether	95	97
8	**PA-2**	ether	78	0
9	**PA-3**	ether	64	11
10	**PA-1**[d]	ether	65	89

[a] Isolated yields. [b] Ee values were determined by chiral-HPLC (see the Supporting Information). [c] With **(*R*)-PA-1** as the catalyst a 96% yield and 96% ee favoring the opposing enantiomer was found for product **6aa**. [d] Reaction with 5 mol % of catalyst **(*S*)-PA-1**.

Inspired by the high degree of catalytic activity and selectivity, we wanted to establish the generality of the reaction. In Table 2, we show the details of our investigations into varying the thiol substrate. We found that the reaction was very general for arene thiols. For example, we were able to perform the reaction with naphthyl-2-thiol (entry 2) and a variety of *ortho*-, *meta*-, or *para*-substituted thiophenols (entries 3−7). Electron-withdrawing substituents on the thiophenol were not detrimental to the reactivity and selectivity as chloro, fluoro, trifluoromethyl groups were all tolerated (entries 8−11). Likewise, electron-donating substituents on the arene were shown to be compatible with phenoxy, methoxy, and methyl sulfide groups in the *para* position (entries 12−14). Esters were shown to be compatible with the ring-opening chemistry (entry 15), as were 2-methylfuran-3-thiol (entry 16), benzo[*d*]thiazole-2-thiol (entry 17), and 1-phenyl-1*H*-tetrazole-5-thiol (entry 18), albeit in moderate yield and selectivity. Unfortunately, the use of alkyl thiols also leads to lower enantioselectivities. For example, while benzyl thiols were moderately good substrates (entries 19 and 20), longer chain thiols like 2-phenylethanethiol (entry 21) and *n*-hexanethiol (entry 22) were relatively poor reaction partners with these conditions.

We were also pleased to find that the aziridine substrate could be varied with little compromise in yield or enanti-

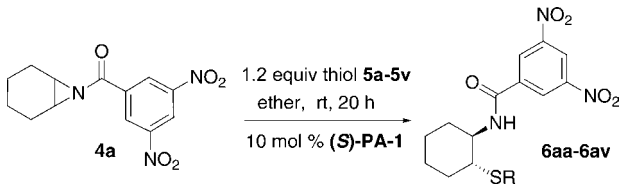
(6) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084.

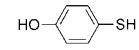
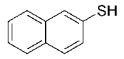
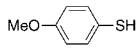
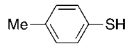
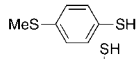
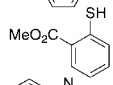
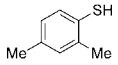
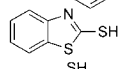
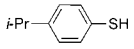
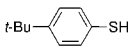
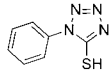
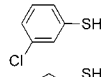
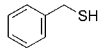
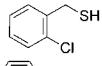
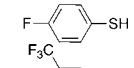
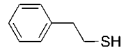
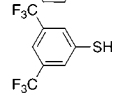
(7) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297.

(8) (a) Hayashi, M.; Ono, K.; Oshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817. (b) Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2007**, *18*, 443. (c) Wang, Z.; Sun, X.; Ye, S.; Wang, W.; Wang, B.; Wu, J. *Tetrahedron: Asymmetry* **2008**, *19*, 964. (d) Lattanzi, A.; Della Sala, G. *Eur. J. Org. Chem.* **2009**, 1845.

(9) Della Sala, G.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330.

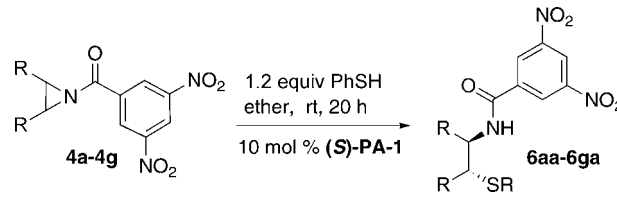
Table 2. Enantioselective Ring-Opening of **4a** with Thiols **5a**−**v**

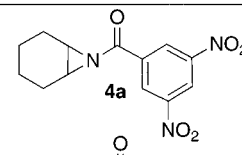
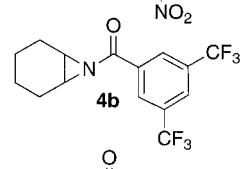
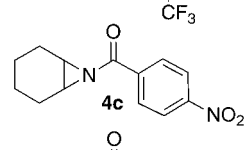
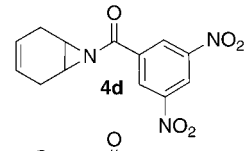
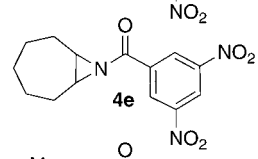
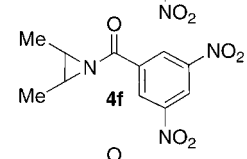
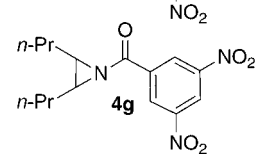


entry	thiol	yield, %[a]	ee, %[b]	entry	thiol	yield, %[a]	ee, %[b]
1		97	96	12		81	89
2		99	95	13		99	>99
3		94	93	14		78	90
4		88	94	15		72	74
5		85	93	16		75	55
6		99	93	17		71	82
7		96	93	18		78	61
8		87	96	19		86	59
9		89	98	20		42	62
10		85	91	21		40	32
11		70	84	22	HS−*n*-hexyl	15	18

[a] Isolated yields. [b] Ee values were determined by chiral-HPLC (see the Supporting Information).

Table 3. Enantioselective Ring-Opening of Aziridines **4a**−**g** with Thiophenol



entry	aziridine	yield, %[a]	ee, %[b]
1		95	97
2		97	43
3		63	6
4		99	95
5		95	96
6		97	95
7		94	87

[a] Isolated yields. [b] Ee values were determined by chiral-HPLC (see the Supporting Information).

oselectivity (Table 3). Our previous study with TMS-N_3 ring-openings utilized aziridines with nitrogen protected by a 3,5-trifluoromethyl-substituted benzoyl group.[6] However, in these thiol studies this substrate, while reactive, gave a much lower enantioselectivity for the ring-opened product (entry 2). Substitution in the *para* position of the benzoyl group on the aziridine proved to be detrimental to the selectivity, with the ring-opened product being obtained in a nearly racemic form (entry 3).

We continued the study by investigating the reaction with two additional *meso* aziridines with fused ring systems and two substrates with acyclic substituents. The fused cyclohexene-based substrate **4d** was shown to be an excellent reaction partner with thiophenol (entry 4). A fused cycloheptane **4e** was also a suitable substrate for the reaction (entry 5). Both methyl (entry 6) and *n*-propyl (entry 7) 1,2-disubstituted *meso* aziridines could be used in the ring-opening chemistry, providing high yield and enantioselectivity of the respective products using **PA-1** as the catalyst.

Our discovery that simple, nonsilylated aromatic thiols can be used for these chiral phosphoric acid-catalyzed additions strongly suggests that a more simple hydrogen-bond activation of the aziridine *N*-acyl moiety and the incoming thiol could be invoked to explain the mechanism.[10] This is in contrast to the previous phosphoric acid catalyzed methodology for aziridine ring-openings that may be following a mechanism based on silicon catalysis.[6,9]

In conclusion, we have discovered a catalytic enantioselective process for the ring-opening of *meso N*-acyl aziridines in a high yielding, enantioselective manner. In comparison to known methods,[8,9] we believe our procedure is attractive due to the reactions procedural simplicity. Finally, the

(10) For a description of this type of mechanism with regard to imine activations, see a "three point contact model" description in: Simon, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.

reaction is the first of its type to tolerate a wide range of aromatic and heteroaromatic thiols.

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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.

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