DOI: 10.1002/ejoc.200900095

Desymmetrization of *meso*-*N*-Acylaziridines with Benzenethiols Promoted by α,α-Diaryl-L-prolinols

Alessandra Lattanzi*[a] and Giorgio Della Sala[a]

Keywords: Desymmetrization / Aziridines / Organocatalysis / Amino alcohols / Asymmetric catalysis

α,α-Diaryl-L-prolinols were disclosed to promote the desymmetrization of *meso*-*N*-acylaziridines with benzenethiols to afford the products in good yields and moderate enantioselectivities (up to 61 % *ee*), which can be greatly improved to >90 % *ee* after a single recrystallization.

Introduction

The elaboration of novel methodologies relying on the use of chiral organocatalysts is an area of intensive investigation in organic synthesis.[1] The simplicity of the reaction conditions as well as the accessibility to a great variety of organic compounds, to use as the promoters, constitute the most attracting features of the organocatalysis methodologies. Simultaneous generation of two contiguous chiral centres in a molecule is a powerful process, which serves to estabilish a high degree of functionalization. Ring opening of small heterocyclic compounds, like optically pure epoxides and aziridines, represents one of the possible routes to achieve such a goal in an enantioselective manner.[2] In this regard, although being rather challenging to differentiate two enantiotopic centres, the opening of *meso* compounds is an appealing process thanks to the use of achiral starting materials. Several methologies have been reported for the desymmetrization of *meso*-epoxides with various nucleophiles by either using metal-catalyzed asymmetric systems[3] or enzymes,[4] but, quite surprisingly, the enantioselective ring opening of *meso*-aziridines has received much less attention. The first examples of asymmetric metal-catalyzed desymmetrization of aziridines with carbon and heteroatom nucleophiles were reported by Oguni,[5] Müller[6] and Jacobsen.[7] Recently, highly enantioselective desymmetrization of *N*-acylaziridines has been developed by Shibasaki[8] employing TMSCN and $TMSN_3$ with chiral Gd or Y complexes and by Kobayashi treating *N*-arylaziridines with anilines as nucleophiles in the presence of Nb-BINOL complexes.[9] In the field of organocatalysis, cinchona alkaloid based promoters proved to catalyze the opening of *N*-sulfonylaziridines with thiols achieving moderate levels of asymmetric induction.[10] Notably, the desymmetrization of *N*-acylaziridines with $TMSN_3$ catalyzed by chiral phosphoric acids afforded the products in high enantioselectivity.[11] Very recently, 1,3-dicarbonyl compounds were employed as nucleophiles in the highly diastereo- and enantioselective opening of *N*-tosyl-protected aziridines under phase-transfer catalysis.[12] Thus, the development of catalytic systems for the desymmetrization of *meso*-aziridines, which are of general scope with respect to structure of aziridine, nitrogen protective group and nature of the nucleophile, turns out to be problematic. Indeed, it seems that catalytic ad hoc systems can be synthetically useful for the desymmetrization of specific aziridines.

Recently, we disclosed that α,α-diaryl-L-prolinols promote asymmetric Michael additions, such as the epoxidation of α,β-enones,[13] the β-peroxidation of nitroalkenes[14] and the malonate ester addition to nitroalkenes[15] with high to moderate levels of enantioselectivity. We proposed a dual mode of activation of the nucleophile and the electrophile provided by the amine and the hydroxy groups of these organocatalysts, respectively. We were intrigued to check the effectiveness of α,α-diaryl-L-prolinols as promoters in a mechanistically different process such as the ring opening of *meso*-aziridines with thiols (Figure 1).

We reasoned that the amine group would deprotonate the thiol, thus generating the reactive nucleophile, while the aziridine might be activated and preferentially orientated by hydrogen bonding between the catalyst OH group and an appropriate protecting group on the nitrogen atom (e.g. the carbonyl oxygen atom in case of an *N*-acylaziridine). This simultaneous activation of the reacting partners provided by the chiral promoter would likely result in an enantioselective desymmetrization process.

[a] Dipartimento di Chimica, Università di Salerno,
Via Ponte don Melillo, 84084 Fisciano, Italy
Fax: +39-089-969603
E-mail: lattanzi@unisa.it

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

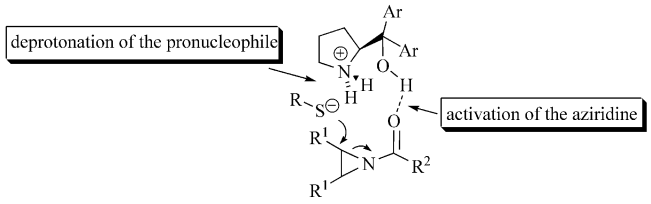
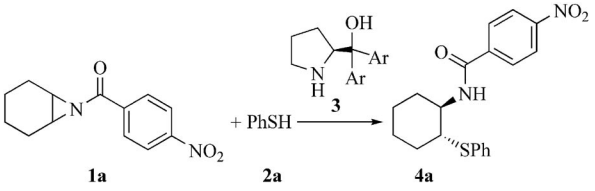


Figure 1. Proposed bifunctional mode of action of α,α-diaryl-L-prolinol as promoter for the desymmetrization of *meso*-*N*-acylaziridines.

Results and Discussion

Initially, we studied the desymmetrization of model *N*-acylaziridine **1a** with thiophenol (**2a**) using 20 mol-% loading of commercially available α,α-diphenyl-L-prolinol (**3a**) [Equation (1)].



(1)

Table 1 illustrates the results of the optimization process. To our delight, compound **3a** was able to catalyze the ring opening of *N*-acylaziridine **1a** when carrying out the reaction at room temperature in toluene as the solvent (Entry 1). The *trans* product **4a** was isolated in good yield and 40% *ee*. The absolute configuration of **4a** was estabilished to be (1*R*,2*R*) by comparison of the optical rotation reported in the literature.[5b] Different aromatic and halogenated solvents were then checked, and a slight improvement of the enantioselectivity was realized when chloroform was used (Entry 7).

The efficiency of various α,α-diaryl-L-prolinols in $CHCl_3$ at room temperature was then examined (Figure 2). Substitution on the phenyl rings in organocatalysts **3b**–**3d** did not affect the level of asymmetric induction (Entries 8–10), although a better conversion was achieved when alkyl-substituted promoters were employed (Entries 8 and 10). The reaction performed with the *O*-methylated compound **3e** confirmed the key role played by the free OH group in the catalysis (Entry 11).

Indeed, the conversion decreased, and an unselective desymmetrization process occurred. L-Prolinol proved to be highly active, although the reaction proceeded with poor stereocontrol (Entry 12). Finally, L-proline was found completely inactive (Entry 13). Reactions performed at lower temperatures and in different solvents, using the most active compound **3d**, unexpectedly afforded the product with slightly decreased *ee* (Entries 14–16). Catalyst **3d** could be successfully employed at 10 mol-% loading (Entry 17). Some experiments were then carried out at different molar concentrations by using catalyst **3d** to see the effect on the enantioselectivity (Figure 3).

Table 1. Desymmetrization of *meso*-aziridine **1a** with thiophenol (**2a**) promoted by compounds **3**.[a]

Entry	3	Solvent	*T* [°C]	*t* [h]	Yield of **4a** [%][b]	*ee* of **4a** [%][c]
1	**3a**	toluene	25	24	65	40
2	**3a**	*p*-xylene	25	22	67	25
3	**3a**	*m*-xylene	25	16	34	43
4	**3a**	hexane	25	22	17	9
5	**3a**	CH_2Cl_2	25	21	48	47
6	**3a**	$ClCH_2CH_2Cl$	25	22	66	42
7	**3a**	$CHCl_3$	25	23	55	49
8	**3b**	$CHCl_3$	25	24	67	52
9	**3c**	$CHCl_3$	25	24	61	52
10	**3d**	$CHCl_3$	25	22	69	53
11	**3e**	$CHCl_3$	25	24	33	–6
12	**3f**	$CHCl_3$	25	21	88	18
13	**3g**	$CHCl_3$	25	24	<5	n.d.
14	**3d**	$CHCl_3$	–6	48	87	51
15	**3d**	toluene	–6	72	88	50
16	**3d**	*m*-xylene	4	73	84	47
17[d]	**3d**	$CHCl_3$	25	30	62	51

[a] Reaction performed at 0.2 mmol scale of **1a**, 1.1 equiv. of **2a**, 20 mol-% of **3** at *c* = 0.2 M. [b] Yields after flash chromatography. [c] Determined by chiral HPLC analysis. Absolute configuration (1*R*,2*R*) was determined by comparison with the optical rotation reported in the literature. [d] Using 10 mol-% of **3d**.

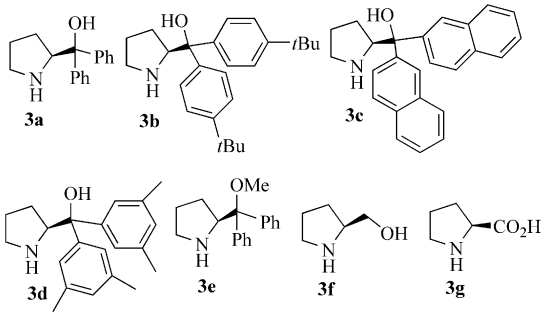


Figure 2. Catalysts tested in the model desymmetrization process.

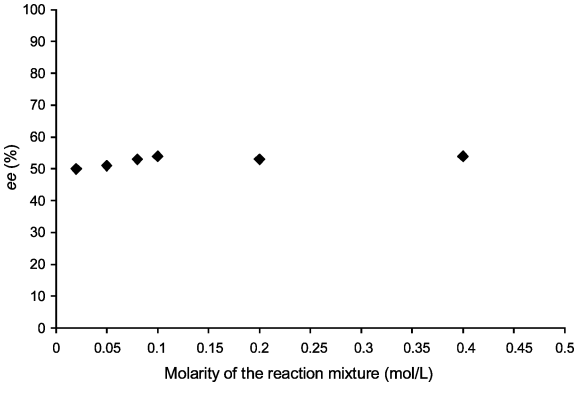


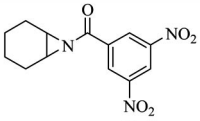
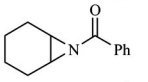
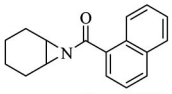
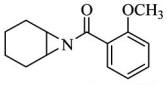
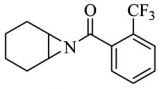
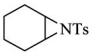
Figure 3. *ee* vs. molarity for the reaction of **1a** with **2a** catalyzed by 20 mol-% of **3d** at room temperature in $CHCl_3$.

An almost constant level of the enantioselectivity was observed for the reactions carried out from 0.4 to 0.02 M concentration. This indicates that the organocatalyst does not give rise to autoaggregation phenomena, which is in agreement with linear effects[16] previously observed in the

epoxidation of α,β-enones promoted by **3a** with *tert*-butyl hydroperoxide,[13a] thus suggesting that a single molecule of the catalyst should be involved in the ring-opening process.

Aziridines are versatile electrophiles, whose reactivity can be finely tuned by proper modification of the nitrogen protecting group. Hence, a variety of aziridines were treated with thiol **2a** under the optimized conditions employing catalysts **3a** and **3d** (Table 2). As expected, two nitro groups on the phenyl ring activated the aziridine **1b**, and, after few hours, the product was formed in satisfactory yield, but in racemic form (Entry 1). The unsubstituted less reactive aziridine **1c** furnished the product in 54% *ee* (Entry 2). When using catalyst **3d** as the promoter, a significant improvement in the yield and slightly better *ee* were observed (Entry 3). Aziridine **1d**, bearing the 1-naphthoyl-substitution on the nitrogen atom, gave the product in good yield and 61% *ee* (Entry 4).

Table 2. Desymmetrization of *meso*-aziridines **1** with thiophenol (**2a**) promoted by compounds **3a** and **3d** in $CHCl_3$ at 25 °C.[a]

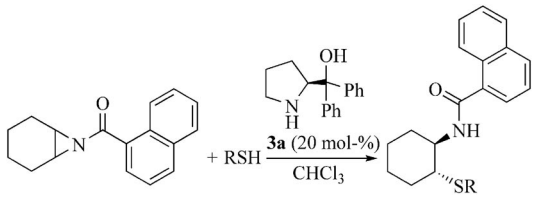
Entry	1	3	Time [h]	4	Yield [%][b]	*ee* [%][c]
1		**3a**	3.5	**4b**	45	3
2		**3a**	18	**4c**	23	54
3		**3d**	24	**4c**	39	57
4		**3a**	96	**4d**	71	61
5		**3d**	90	**4d**	69	54
6		**3a**	48	**4e**	74	57
7		**3d**	45	**4e**	79	55
8		**3a**	22	**4f**	48	36
9		**3a**	22	**4g**	6	13
10		**3a**	23	**4g**	8	6

[a] Reaction performed at 0.2 mmol scale of **1a**, 1.1 equiv. of **2a**, 20 mol-% of **3** at c = 0.2 M. [b] Yields after flash chromatography. [c] Determined by chiral HPLC analysis.

The use of **3d** led to a satisfactory conversion, but a lower *ee* was detected (Entry 5). The *ortho*-methoxyphenyl-substituted aziridine afforded the product in good yield and 57% *ee* when catalyst **3a** was used (Entry 6). Again, the use of promoter **3d** was detrimental for the stereocontrol (Entry 7). When the *ortho*-(trifluoromethyl)phenyl-substituted aziridine was employed, a good conversion was observed with catalyst **3a**, but the enantioselectivity dropped to 36% (Entry 8). Surprisingly, *N*-tosylaziridine **1g** reacted sluggishly either in chloroform or toluene as the solvents (Entries 9 and 10).

The scope of the reaction with respect to different benzenethiols using aziridine **1d** with 20 mol-% of **3a** in chloroform was investigated next (Table 3).

Table 3. Desymmetrization of aziridine **1d** with benzenethiols **2** promoted by **3a** in $CHCl_3$ at 25 °C.[a]



1d **2** **4**

Entry	2	4	Yield [%][b]	*ee* [%][c]
1[d]	PhSH	**4c**	71 (68)	61 (>99)
2[e]	4-*t*BuC$_6$H$_4$SH	**4h**	50	54
3	4-MeC$_6$H$_4$SH	**4i**	64 (65)	55 (93)
4[e]	2-MeC$_6$H$_4$SH	**4j**	61	50
5	4-MeOC$_6$H$_4$SH	**4k**	79	52
6[d]	4-BrC$_6$H$_4$SH	**4l**	82	56
7	2-naphthalenethiol	**4m**	77	37

[a] Reaction performed at 0.2 mmol scale of **1a**, 1.1 equiv. of **2**, 20 mol-% of **3a** at c = 0.4 M. [b] Yields after flash chromatography; yields after recrystallization are reported in parentheses. [c] *ee* determined by chiral HPLC; *ee*s after recrystallization are reported in parentheses. [d] Reaction performed at c = 0.2 M. [e] Using 30 mol-% of **3a**.

Good yields of the ring-opened products were generally observed. The nature of substituents seems to slightly affect the stereocontrol, as *para*- and *ortho*-substituted benzenethiols afforded compounds **4** in comparable *ee*s (Entries 2–6).[17] A lower *ee* was observed when sterically more demanding 2-naphthalenethiol was used (Entry 7). Compounds **4** were obtained as solids, and their optical purity could be efficiently enhanced to excellent *ee* values after only a single recrystallization, which makes the methodology synthetically more attractive (Entries 1 and 3).[18]

Conclusions

We have developed a novel catalytic desymmetrization methodology of *N*-acylaziridines with benzenethiols promoted by simple α,α-diaryl-L-prolinols. Among the catalysts tested, commercially available α,α-diphenyl-L-prolinol proved to be the most efficient. The products were isolated in good yields and moderate *ee*s, which can be improved to high levels by a single recrystallization. With this work we showed that α,α-diaryl-L-prolinols can act as promoters to be considered useful in mechanistically different processes. This contributes to enlarge their synthetic applications and find a place among well-known classes of bifunctional organocatalysts. Further investigations on the full scope of the desymmetrization of *meso*-aziridines are underway.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterizations of unknown aziridines and ring-opened products.

Acknowledgments

The Ministero Italiano dell'Università e Ricerca Scientifica (MIUR) is gratefully acknowledged for financial support. Dr. Patrizia Iannece is acknowledged for MS analyses.

[1] For recent general reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) K. H. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, issue 8; c) A. Berkessel, H. Gröger in *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; d) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; e) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.

[2] a) D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) T. Ibuka, *Chem. Soc. Rev.* **1998**, *27*, 145; c) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701; d) G. S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107*, 2080; for a recent review on enantioselective ring opening of aziridines, see: C. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48*, 2082.

[3] For selected examples, see: a) W. M. Nugent, *J. Am. Chem. Soc.* **1992**, *114*, 2768; b) L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897; c) S. Sagawa, H. Abe, Y. Hase, T. Inaba, *J. Org. Chem.* **1999**, *64*, 4962; d) A. Sekine, T. Oshima, M. Shibasaki, *Tetrahedron* **2002**, *58*, 75; e) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, M. Massaccesi, P. Melchiorre, L. Sambri, *Org. Lett.* **2004**, *6*, 2173; f) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Org. Lett.* **2004**, *6*, 3973; g) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem. Int. Ed.* **2004**, *43*, 5691; h) E. Mai, C. Schneider, *Chem. Eur. J.* **2007**, *13*, 2729; i) H. Bao, J. Zhou, Z. Wang, Y. Guo, T. You, K. Ding, *J. Am. Chem. Soc.* **2008**, *130*, 10116; j) A. Tschöp, M. V. Nandakumar, O. Pavlyuk, C. Schneider, *Tetrahedron Lett.* **2008**, *49*, 1030; k) M. Tiecco, L. Testaferri, F. Marini, S. Sternativo, F. Del Verme, C. Santi, L. Bagnoli, A. Temperini, *Tetrahedron* **2008**, *64*, 3337; l) B. Gao, Y. Wen, Z. Yang, X. Huang, X. Liu, X. Feng, *Adv. Synth. Catal.* **2008**, *350*, 385.

[4] a) L. Zhao, B. Han, Z. Huang, M. Miller, H. Huang, D. S. Malashock, Z. Zhu, A. Milan, D. E. Robertson, D. P. Weiner, M. J. Burk, *J. Am. Chem. Soc.* **2004**, *126*, 11156; b) M. S. Smit, M. Labuschagne, *Curr. Org. Chem.* **2006**, *10*, 1145; c) C. Chiappe, E. Leandri, B. D. Hammock, C. Morisseau, *Green Chem.* **2007**, *9*, 162.

[5] a) M. Hayashi, K. Ono, H. Hoshimi, N. Oguni, *J. Chem. Soc., Chem. Commun.* **1994**, 2699; b) M. Hayashi, K. Ono, H. Hoshimi, N. Oguni, *Tetrahedron* **1996**, *52*, 7817.

[6] P. Müller, P. Nury, *Org. Lett.* **1999**, *1*, 439.

[7] Z. Li, M. Fernández, E. N. Jacobsen, *Org. Lett.* **1999**, *1*, 1611.

[8] a) T. Mita, I. Fijimori, R. Wada, J. Wen, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 11252; b) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312.

[9] K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 8103.

[10] a) Z.-B. Luo, X.-L. Hou, L.-X. Dai, *Tetrahedron: Asymmetry* **2007**, *18*, 443; b) Z. Wang, X. Sun, S. Ye, W. Wang, B. Wang, J. Wu, *Tetrahedron: Asymmetry* **2008**, *19*, 964.

[11] E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084.

[12] a) T. A. Moss, D. R. Fenwick, D. J. Dixon, *J. Am. Chem. Soc.* **2008**, *130*, 10076; b) M. W. Paixão, M. Nielsen, C. Borch Jacobsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2008**, *6*, 3467.

[13] a) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579; b) A. Lattanzi, *Adv. Synth. Catal.* **2006**, *348*, 339; c) A. Lattanzi, A. Russo, *Tetrahedron* **2006**, *62*, 12264; d) A. Russo, A. Lattanzi, *Eur. J. Org. Chem.* **2008**, 2767.

[14] A. Russo, A. Lattanzi, *Adv. Synth. Catal.* **2008**, *350*, 1991.

[15] A. Lattanzi, *Tetrahedron: Asymmetry* **2006**, *17*, 837.

[16] a) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 4000; b) H. B. Kagan, *Adv. Synth. Catal.* **2001**, *343*, 227; c) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402.

[17] This is a positive feature of the present organocatalytic system, as in previously reported methodologies, the type of substitution on the phenyl ring of benzenethiols significantly affected the level of enantioselectivity observed in the products; see refs.[5,10]

[18] Absolute configuration of adducts **4** was assigned as (*R*,*R*) by analogy assuming a uniform mechanistic pathway.

Received: January 28, 2009
Published Online: March 16, 2009

