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Highly Enantioselective Synthesis of β-Amidophenylthioethers by Organocatalytic Desymmetrization of *meso*-Aziridines

Giorgio Della Sala* and Alessandra Lattanzi

Department of Chemistry, University of Salerno, Via Ponte Don Melillo 8, 84024 Fisciano (SA), Italy

gdsala@unisa.it

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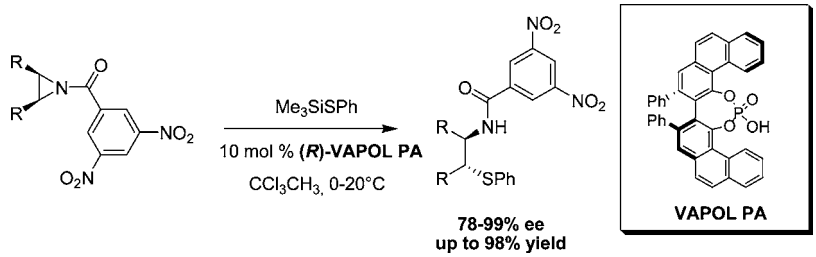
ABSTRACT



The desymmetrization of *N*-acylaziridines with Me_3SiSPh, catalyzed by commercially available (*R*) and (*S*)-VAPOL hydrogen phosphate, produced β-(*N*-acylamino)phenylthioethers in a highly enantioselective and efficient manner (78−99% ee). The selection of the suitable aziridine/nucleophile/catalyst molar ratio is crucial to obtain high ee's.

Chiral β-aminosulfur compounds found various applications both in pharmacology and in stereoselective synthesis. Particularly worthy of interest are β-aminothioethers featuring two contiguous stereogenic centers on carbons linked to nitrogen and sulfur. Some of them are described to be apoptosis promoters.[1] Moreover, thanks to their chelating ability, they are widely employed as chiral ligands in asymmetric catalysis.[2]

They are generally synthesized starting from natural or commercially available enantiopure precursors, mostly derived from the chiral pool, such as β-aminoalcohols from *ephedra* alkaloids, with two pre-existing adjacent stereogenic carbons.[3] Clearly, this approach seriously limits the variety of accessible final structures. Alternatively, the second stereogenic center may be formed in a diastereoselective step, for example by sulfenylation,[4] or the products can be eventually obtained in racemic form and then the enantiomers would separate.[5]

A process in which the two stereogenic centers are formed simultaneously starting from achiral material and with high enantioselectivity would be desirable. In this light, an intriguing approach is represented by the desymmetrization of *meso*-aziridines with thiols promoted by chiral catalysts.

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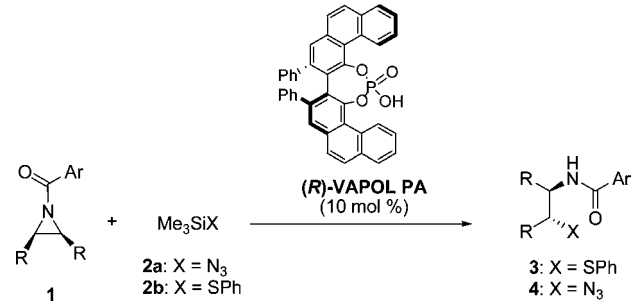
Although some highly enantioselective metal-catalyzed[6−9] and organocatalyzed desymmetrization[10] of activated aziridines have been described,[11] very few are examples employing thiols or their synthetic analogs as nucleophiles, and the methods reported are of limited scope or moderate enantioselectivity.[12]

The first desymmetrization of activated *meso*-aziridines with arenethiols was reported by Oguni et al.[12a] The reaction of three 4-nitrobenzoyl aziridines with 4-*t*-butylbenzenethiol, promoted by an equimolecular amount of zinc-dicyclohexyltartrate complex, gave the opening products with 84−93% ee and 89−98% yield. Anyway, the enantioselectivity decreased drammatically when differently substituted arenethiols were used.

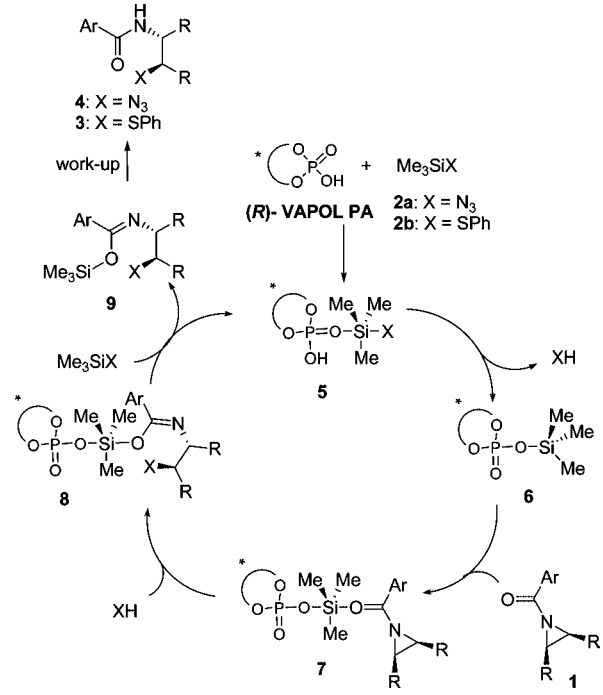
Asymmetric organocatalysis is an ever growing area of investigation in organic synthesis, thanks to the advantages arising from the simplicity of the procedures, mild conditions, and use of inexpensive and readily avalaible materials.[13] Organocatalytic desymmetrizations of sulfonylaziridines with arenethiols involving the use of chiral Brønsted base catalysts under homogeneous[12b] and phase transfer conditions have been recently reported.[12c] The resulting β-aminothioether derivatives were obtained with ee not exceeding 73%. We recently used α,α-diaryl-prolinols as bifunctional organocatalysts,[14] obtaining β-acylamino-arylthioethers in good yield and moderate enantioselectivities (up to 61% ee).[15]

A different organocatalytic approach for an enantioselective aziridine opening is based on the employment of silylated nucleophiles in the presence of a chiral Lewis base. The hypervalent adduct between the silane and the basic catalyst is characterized by increased Lewis acidity of the silicon atom and increased nucleophilicity of the peripherical electronegative group.[16] This principle was successfully applied to the desymmetrization of *meso*-epoxides.[17] Recently Antilla et al. reported an excellent asymmetric synthesis of β-acylamino-azides (49−97% yield, 70−95% ee) by desymmetrization of acylaziridines with trimethylsilyl azide, catalyzed by phosphoric acid **VAPOL PA** (VAPOL hydrogen phosphate; Scheme 1, X = N_3, Ar = 3,5-bis-(trifluoromethyl)benzoyl).[10] Some experimental proofs supported the mechanism depicted in Scheme 2, with **VAPOL PA** acting as a Lewis base promoter rather than a proton catalyst. Notably, an excess of aziridine compared to silyl nucleophile (molar ratio 1.5/1) was required in most cases to afford satisfactory enantioselectivities.

Scheme 1. *meso*-Acylaziridine Desymmetrization with Me_3SiN_3 and Me_3SiSPh Catalyzed by **(*R*)-VAPOL PA**



Scheme 2. Proposed Mechanism of *meso*-Acylaziridine Desymmetrization (X = N_3, SPh)



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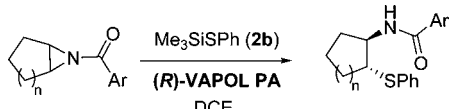
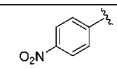
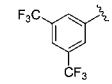
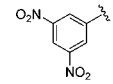
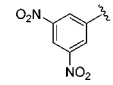
(15) Lattanzi, A.; Della Sala, G. *Eur. J. Org. Chem.* **2009**, 1845–1848.

(16) For an excellent review on Lewis base catalysis, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

Table 1. Desymmetrization of Aziridines **1a−d** in DCE[a]



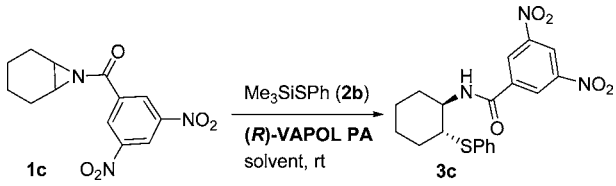
entry	1		t (°C)	time (h)	% yield[b]	% ee[c]
1		n: 2 (**1a**)	rt	24	62	61
2		n: 2 (**1b**)	rt	23	79	80
3		n: 2 (**1c**)	rt	1.5	98	85
4			0	2	94	94
5			0	70	26[d]	74
6		n: 1 (**1d**)	rt	48	63[e]	66
7[f]			rt	48	55[g]	3

[a] General reaction conditions: 1 equiv of **1** (0.08 mmol), 1.5 equiv of **2b** (0.12 mmol), 0.10 equiv of **(R)-VAPOL PA** (0.008 mmol), 0.4 mL of DCE. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Three percent of **10a**. [e] Six percent of **10a**. [f] **2b** (3.0 equiv) was used. [g] Twenty-six percent of **10a**.

be used as the nucleophile in the presence of **VAPOL PA** as catalyst (Scheme 1, X = SPh).

Initially, DCE (1,2-dichloroethane) was used, as previously optimized solvent for the azide nucleophile.[10] An excess of nucleophile **2b** compared to the aziridines **1a−d** was employed, since we regarded the latter as synthetically more valuable reagents (Table 1).

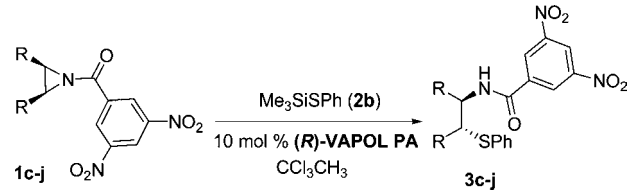
Table 2. Solvent Effect in the Desymmetrization of **1c**[a]

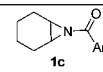
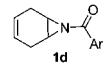
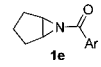
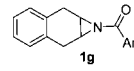
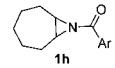
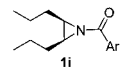
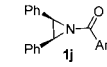


entry	solvent	time (h)	% yield[b]	% ee[c]
1	THF	3.5	92	6
2	CH_3CN	7	100	17
3	toluene	2	93	69
4	CH_2Cl_2	1.5	90	66
5	1,2-dichlorobenzene	1.5	94	66
6	$CHCl_2CHCl_2$	5	83[d]	69
7	PhCl	1	100	74
8	CCl_4	2	100	74
9	$CHCl_3$	7	93	81
10	CCl_3CH_3	1	94	89
11[e]	CCl_3CH_3	3	97	87
12[e,f]	CCl_3CH_3	3	97	93

[a] General reaction conditions: 1 equiv of **1** (0.08 mmol), 1.5 equiv of **2b** (0.12 mmol), 0.10 equiv of **(R)-VAPOL PA** (0.008 mmol), 0.4 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Eight percent of **10b**. [e] Reaction performed at 0 °C. [f] Solvent (0.8 mL) was used.

Table 3. Desymmetrization of Aziridines **1c−j**



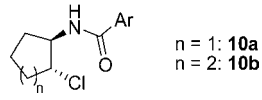
entry	1	method[a]	t (°C)	time (h)	% yield[b]	% ee[c]
1		A	0	3	97	93
2[d]		A	0	3	89	90[e]
3		A	0	23	90	83
4		A	0	23	85	96
5		A	0	6	88	94
6		A	0	48	68	99 (91)[f]
7		A	40	22	85	47
8		B	20	25	78	68
9		C	20	23	88	78
10		A	0	23	60	54
11		B	0	23	60	70
12		C	0	23	52	80
13		A	20	23	100	77
14		C	0	23	98	86

[a] Method A: 1 equiv of **1** (0.08 mmol), 1.5 equiv of **2b** (0.12 mmol), 0.10 equiv of **(R)-VAPOL PA** (0.008 mmol), 0.8 mL of CCl_3CH_3. Method B: 1 equiv of **1** (0.08 mmol), 1.5 equiv of **2b** (0.12 mmol), 0.20 equiv of **(R)-VAPOL PA** (0.016 mmol), 0.8 mL of CCl_3CH_3. Method C: 1.5 equiv of **1** (0.12 mmol), 1 equiv of **2b** (0.08 mmol), 0.10 equiv of **(R)-VAPOL PA** (0.008 mmol), 0.8 mL of CCl_3CH_3. [b] Isolated yields. [c] Determined by chiral HPLC. [d] **(S)-VAPOL PA** was used. [e] (1*S*,2*S*)-**3c** was obtained. [f] Product isolated by precipitation from the reaction mixture. The value in parentheses was measured by direct chiral HPLC injection of the crude mixture.

Under these conditions, opening of 4-nitrobenzoyl aziridine **1a** at room temperature afforded the product **3a** in moderate yield and enantioselectivity (entry 1, Table 1). The absolute configuration of **3a** was established to be (1*R*,2*R*) by comparison of the optical rotation reported in the literature.[12a,18] As expected, both the reactivity and the ee were improved with aziridine **1b** (entry 2, Table 1). Interestingly, faster and more enantioselective opening of aziridine **1c** occurred (entry 3, Table 1). The reaction was complete in a short time even at 0 °C, affording the product in high yield and with 94% ee (entry 4, Table 1).

Unfortunately, when the same conditions were applied to less reactive five-membered ring aziridine **1d**, the product **3d** was formed with a significantly lower ee and was accompanied by a small amount of chloride opening product **10a** (entries 5−6, Table 1). Apparently, nucleophilic substitution of **2b** on DCE, catalyzed by the phosphoric acid, afforded (2-chloroethylthio)benzene and Me_3SiCl, which

ultimately gave **10a**.[19] When 3.0 mol equiv of **2b** were used, the conversion was improved, but a great amount of **10a** was obtained and **3d** was recovered in an almost racemic form (entry 7, Table 1). The in situ formation of Me_3SiCl, and possibly HCl, playing as additional acid catalysts involved in the opening of aziridines, can be invoked, thus justifying the enantioselectivity drop. Unlike Me_3SiN_3, Me_3SiSPh is incompatible with DCE in the presence of a Lewis base. Hence, the performance of several different solvents, less prone to nucleophilic substitution was checked (Table 2).



n = 1: **10a**
n = 2: **10b**

In the desymmetrization reaction of **1c**, CCl_3CH_3 allowed the isolation of the product in high yield and enantioselectivity, when working at 0 °C (entry 12, Table 2).

This new protocol (method A) was applied to the opening of a wide range of 3,5-dinitro-benzoyl aziridines **1c**−**j** (Table 3). We were very pleased to observe that the corresponding acylaminothioethers **3** were generally obtained in high yield and enantioselectivity. No trace of product arising from chloride opening was observed. The opposite enantiomer of **3c** was isolated when using **(*S*)-VAPOL PA** as the catalyst (entry 2, Table 3). The presence of a carbon−carbon double bond is compatible with the above conditions (entry 3, Table 3).

Substrates **1h**−**j** showed to be more problematic (entries 7, 10, 13, Table 3). For the less reactive seven-membered ring aziridine **1h** and for compound **1i**, a slight increase of the enantioselectivity was obtained by using 20% mol of catalyst (method B; entries 8, 11, Table 3). Finally, the reverse ratio of the reagents **1h**−**j** and **2b** (method C) led to a remarkable enhancement of the ee's (entries 9, 12, 14, Table 3).

In conclusion, we developed a highly enantioselective and efficient method for the synthesis of enantioenriched β-aminothioethers, based on the organocatalytic desymmetrization of meso-*N*-acylaziridines. This easy procedure employs phosphoric acid **VAPOL PA**, commercially avalaible in both enantiomeric forms. The scope is fairly general, leading to opened products with the best ee's reported to date.

Further work will be devoted to extend the scope to different silylthioether as nucleophiles, including the synthetic elaboration of the products obtained.

Acknowledgment. We are grateful to the Ministero Italiano dell'Università e Ricerca Scientifica (MIUR) for financial support. Our thanks to Rosa Zarra, Department of Chemistry, University of Salerno, for ESI-MS and elemental analyses.

Supporting Information Available: Experimental procedures, synthesis of racemic products and characterization of unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) This assigment was consistent with the reported (1*R*,2*R*) configuration for the product of desymmetrization with trimethylsilyl azide promoted by (***R*)-VAPOL PA** (ref 10).

(19) In the opening of **1d** in DCE, (2-chloroethylthio)benzene was isolated from the reaction mixtures.