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Guanidines as a Nitrogen Source for Direct Conversion of Epoxides to Aziridines

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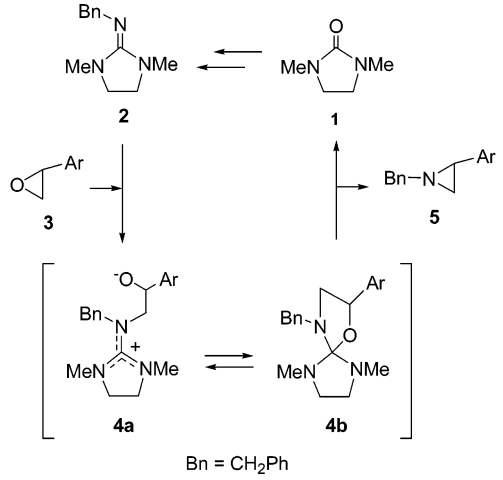
Abstract: Direct conversion of epoxides to aziridines was achieved with guanidines as a nitrogen source. Stereochemical inversion at the chiral centers of epoxides was observed without loss of optical purity.

Aziridines are some of the most versatile synthetic intermediates for the synthesis of biologically active *N*-containing compounds.[1] Normally, aziridines are synthesized via reactions of nitrenes and olefins or carbenes and imines, and intramolecular cyclization of β-amino alcohol derivatives.[2] We have reported a unique method for the synthesis of aziridines from guanidinium salts derived from ureas such as 1,3-dimethylimidazolidin-2-one (DMI; **1**) and aromatic aldehydes, and its application to asymmetric synthesis by using the corresponding chiral template.[3] The proposed reaction mechanism may involve the formation of spiro intermediates (like **4b** in Scheme 1) from guanidinium ylides and aromatic aldehydes via betains (like **4a** in Scheme 1), which undergo acid catalysis fragmentation to yield aziridines and **1**. We would expect the reaction of guanidines **2**, derived from **1**, with epoxides **3** to afford analogous betain species **4a**, which would then produce the corresponding aziridines **5** and **1** via spiro intermediates **4b** (Scheme 1). Until now, a few examples of direct conversion of epoxides to aziridines with iminophosphorane as a nitrogen source have been reported;[4] however, problems still remain in partial racemization of the product.[4c] Now we describe herein our preliminary approaches to direct conversion of epoxides to aziridines using guanidine as a nitrogen source.

Guanidines **2** were prepared from 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and primary amines according to the reported procedure.[5] Several epoxides were purchased or prepared by either simple epoxidation of the corresponding olefins or methylenation of aldehydes with trimethylsulfonium ylide.[6] Heating guanidine **2a** and racemic styrene oxide [(±)-**3a**] at 70 °C without a solvent for 24 h afforded the expected aziridine (±)-**5a** in 16% yield together with urea **1** (15%) (entry 1, Table 1). Reactions in several solvents showed that the yields depended on the solvent. When the reaction was carried out in DMF or THF, the yield was not improved compared with the solvent-free conditions (entries 2 and 3). A higher yield was observed in CH_3CN (entry 4). The use of EtOH resulted in the formation of a complex mixture that was formed because of the instability of **5a** in EtOH (entry 5). Chloroform gave the best result, in which **5a** was produced in 65% yield despite a long reaction time (entry 6). The use of toluene resulted in low yield (entry 7).

SCHEME 1. A Strategy for Direct Conversion of Epoxides to Aziridines



The ^{1}H NMR spectrum of the crude product obtained with chloroform as a solvent showed lower field-shifted signals assignable to the salt[7] of **2a** compared to the original ones. Thus, reactions in the presence of a basic additive were examined (Table 2); however, no improvement was found (entries 1−4). On the other hand, reaction in the presence of 10 mol % of *p*-toluenesulfonic acid hydrate ($TsOH\cdot H_2O$) in toluene afforded (±)-**5a** in 77% yield (entry 5). Although a similar result was obtained in replacement of the solvent from toluene to benzene (entry 6), the yield was lowered when the reaction was carried out under azeotropic conditions, suggesting that a small amount of water is necessary for this reaction (entry 7). Low yield was also observed in chloroform under the acidic condition (entry 8). In the previous paper[3] it was noted that SiO_2 played a crucial role for the formation of aziridine products. However,

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(7) A trace of acid may generate from the chloroform used as solvent.

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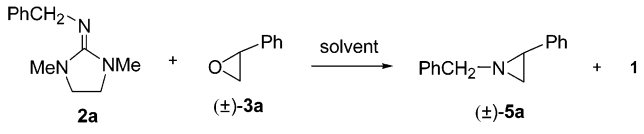
TABLE 1. Synthesis of Aziridine (±)-5a from Guanidine 2a and Racemic Styrene Oxide [(±)-3a]



			yield (%)[a]	
entry	solvent	conditions	(±)-**5a**	**1**
1	none	70 °C, 24 h	16	15
2	DMF	75 °C, 41 h	9	15
3	THF	reflux, 7 d	10	7
4	CH_3CN	reflux, 40 h	48	23
5	EtOH	rt, 2 d	*b*	*b*
6	$CHCl_3$	reflux, 7 d	65	72
7	toluene	75 °C, 41 h	2	8

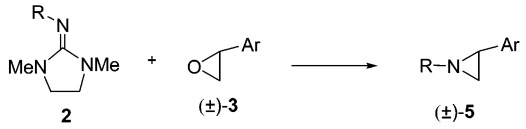
[a] Calculated yields by ^{1}H NMR, but not optimized. [b] Complex mixture.

TABLE 2. Effects of Additives on the Reaction of Guanidine 2a and Epoxide (±)-3a

entry	solvent	additive	conditions	yield (%)[a] of (±)-**5a**
1	$CHCl_3$	Et_3N[b]	reflux, 4 d	51
2	$CHCl_3$	pyridine[b]	reflux, 54 h	53
3	$CHCl_3$	TMG[b,c]	reflux, 7 d	53
4	$CHCl_3$	K_2CO_3[b]	reflux, 7 d	38
5	toluene	TsOH·H_2O[d]	reflux, 80 h	77
6	benzene	TsOH·H_2O[d]	reflux, 7 d	68
7[e]	benzene	TsOH·H_2O[d]	reflux, 7 d	22
8	$CHCl_3$	TsOH·H_2O[d]	reflux, 5 d	21
9	CH_3CN	SiO_2[f]	reflux, 35 h	<10

[a] Calculated yields by ^{1}H NMR, but not optimized. [b] 1 molar equiv. [c] 1,1,3,3-Tetramethylguanidine. [d] A catalytic amount (0.1 molar equiv). [e] Using Dean−Stark apparatus. [f] 1 g per 1 mM.

TABLE 3. Substituent Effects on the Aziridine Formation



entry	R in **2**	Ar in (±)-**3**	conditions[a]	yield (%)[b] of (±)-**5**
1	allyl	Ph	A	60
2	$CH_2CO_2{}^tBu$	Ph	A	54
3	^{i}Pr	Ph	A	29
4	Ph	Ph	B	no reaction
5	CH_2Ph	*o*-MeOPh	B	46
6	CH_2Ph	*p*-MeOPh	B	61[c]
7	CH_2Ph	*p*-MePh	B	40[c]
8	CH_2Ph	*p*-ClPh	B	55[c]

[a] A: reflux in toluene with TsOH·H_2O (0.1 molar equiv) for 3.5 d. B: reflux in $CHCl_3$ for 7 d. [b] Isolated yields, but not optimized. [c] Calculated yields by ^{1}H NMR, but not optimized.

utilization of SiO_2 resulted in a trace amount of production of **5a** due to the instability of **5a** against SiO_2 (entry 9).

We next examined the reaction using substrates with a different substituent (Table 3). Guanidines with a primary alkyl group on the imino nitrogen gave aziridine products (entries 1 and 2), but the reaction was suppressed in the case of a secondary alkyl-substituted guanidine (entry 3). The reaction was sluggish with *N*-phenylguanidine because of low nucleophilicity (entry 4). No acceleration was observed even when electron-rich styrene oxides were used (entries 5−8). Unfortunately, reactions were retarded with use of 1,1-disubstituted **3b**, 1,2-disubstituted epoxides **3c**−**e**, and aliphatic epoxides **3f** and **3g** shown in Figure 1.

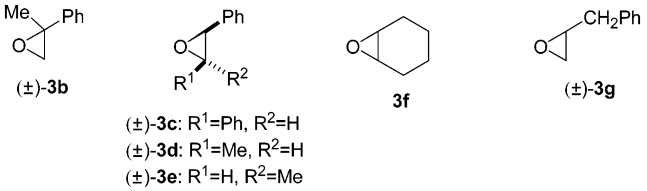
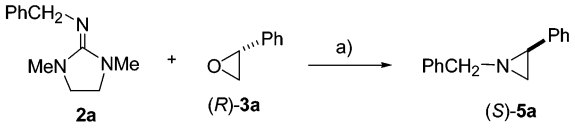


FIGURE 1. Epoxides examined for the conversion.

SCHEME 2. Reaction of Guanidine 2a and Chiral Styrene Oxide (*R*)-3a[a]



[a] Reagents and conditions: (a) TsOH·H_2O (1 molar equiv), toluene reflux, 90 h (41%).

A trial with chiral (*R*)-styrene oxide[8] (*R*)-**3a** afforded (*S*)-aziridine (*S*)-**5a** in 41% yield (Scheme 2). The absolute configuration of the product was determined by optical rotation {$[\alpha]^{24}_D$ +69.2 (c 2.0, EtOH)},[9] showing that inversion of configuration occurred during the reaction. Optical purity of the product was estimated as ca. 96% ee from chiral HPLC analysis (DAICEL CHIRALCEL OD-H, hexane only, 254 nm, 1.2 mL/min). Thus, high retention of chirality should be expected in this direct conversion of epoxides to aziridines.

In summary, we have established a direct conversion method of epoxides to aziridines with guanidine as a nitrogen source. This reaction proceeds via inversion of configuration at the asymmetric carbon on styrene oxides with high chirality control. Detailed mechanistic studies and the application of aziridines[10] to the synthesis of natural products are under way in our laboratory.

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Supporting Information Available: Experimental procedures for this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Purchased from Aldrich, 95% ee.

(9) Kawamoto et al. reported the optical rotation of (*R*)-**5a** with 98% ee to be $[\alpha]^{20}_D$ −49.4 (*c* 2.0, EtOH) [Kawamoto, A.; Wills, M. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3257−3261]. The lower value may be due to the lability of **5a** in EtOH.

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