

Catalytic Asymmetric Ring Openings of Meso and Terminal Aziridines with Halides Mediated by Chiral 1,2,3-Triazolium Silicates

Kohsuke Ohmatsu, Yuta Hamajima, and Takashi Ooi*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya, 464-8603, Japan

Supporting Information

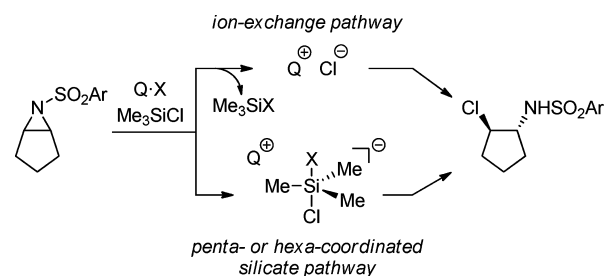
ABSTRACT: Catalytic asymmetric chloride and bromide ring openings of meso aziridines with trimethylsilyl halides have been developed using modular chiral 1,2,3-triazolium chlorides as catalysts. Control experiments suggest the reaction pathway involving hypervalent silicate ions as reactive intermediates. The application of this system to the efficient kinetic resolution of terminal aziridines is also reported.

Extra-coordinated silicon species, called hypervalent silicates, play important roles as reagents and intermediates in synthetic organic chemistry.¹ Owing to their enhanced reactivity, significant progress has been made in the development of catalytic asymmetric reactions that proceed through the intermediacy of penta- or hexacoordinated silicates.² One of the attractive features of the silicate-based methodologies is the allowance of asymmetric transformations with otherwise difficult-to-use nucleophiles, such as halide ions,^{3,4} under mild conditions, making it feasible to rapidly construct optically active halogen-containing organic molecules.⁵ For instance, the combined use of chlorosilanes and chiral Lewis base catalysts offers the fruitful opportunity of employing chloride ions as nucleophiles for asymmetric bond-forming processes.^{6,7} In fact, since the pioneering work by Denmark and co-workers,^{6a} several elegant studies have been reported on the design of chiral catalysts for chlorosilicate-mediated stereoselective reactions. However, despite the potential synthetic utility of halosilicates, their successful applications have been limited to the asymmetric ring openings of meso epoxides using the highly reactive silicon tetrachloride (SiCl_4). Herein, we describe the highly enantioselective chloride and bromide ring openings of aziridines based on the use of trimethylsilyl halides as a stoichiometric halide source in combination with chiral 1,2,3-triazolium chlorides as catalysts.⁸ This new catalytic system is effective not only for the desymmetrization of meso aziridines^{4,9} but also for the kinetic resolution of terminal aziridines,^{10,11} including the hitherto unknown kinetic resolution of differently 2,2-disubstituted aziridines. In addition, this study shows the importance of chiral triazolium halosilicates as a reactive intermediate, thereby providing mechanistic insight into ion-pair catalysis with silicon-based nucleophiles.

Ring opening of *N*-protected aziridines with trimethylsilyl chloride can be promoted by tetrabutylammonium fluoride (TBAF), affording *trans*- β -chloroamine derivatives in nearly quantitative yields.¹² In the reactions of silicon-based nucleophiles catalyzed by onium salts possessing relatively

hard, basic anions such as fluoride or phenoxide ions, there are two possible mechanistic scenarios (Scheme 1). One is the ion-

Scheme 1. Two Possible Reaction Pathways for Chloride Ring Opening of Aziridines Catalyzed by Onium Salts (Q^+X^-)



exchange reaction pathway, where the interaction of the silyl compound with Lewis basic anions (X^-) leads to the exclusion of Me_3SiX , generating requisite yet reactive ion pairs. The other mechanism involves the formation of onium silicate as a key intermediate.^{1,13} Although the latter, silicate-mediated pathway is conceivable, reactions of this type are often believed to proceed through the ion-exchange pathway.¹⁴ If this ion-exchange mechanism is operative in the chloride ring opening of aziridines, onium chloride itself should be reactive enough to effect C–N bond cleavage by the chloride ion transfer. To examine this possibility, we attempted the reaction of *N*-*p*-*tert*-butylbenzenesulfonyl aziridine **2a** with *L*-phenylalanine-derived, chiral 1,2,3-triazolium chloride **1a**·Cl (see the scheme for Table 1).⁸ As shown in Scheme 2, treatment of **2a** with 1 equiv of **1a**·Cl in toluene at -40°C for 12 h did not result in the formation of a detectable amount of the desired ring-opening product **3a**. The exposure of **2a** to a stoichiometric quantity of trimethylsilyl chloride (Me_3SiCl) led to an essentially quantitative recovery of the starting material. In contrast, the ring-opening reaction of **2a** was promoted by the combined use of a catalytic amount of **1a**·Cl and Me_3SiCl (1.2 equiv), giving **3a** in 35% isolated yield even with an appreciable level of enantioselectivity (65% ee). These results indicate that the hypervalent chlorosilicate acts as a reactive intermediate in this desymmetrization reaction. The intervention of the chlorosilicate was also supported by the ^{29}Si NMR spectroscopic analysis of a 1:1 mixture of **1a**·Cl and Me_3SiCl in toluene- d_6 ; this showed a single peak at $\delta = 6.6$ ppm, which is considerably shifted upfield from the original signal of Me_3SiCl (29.5

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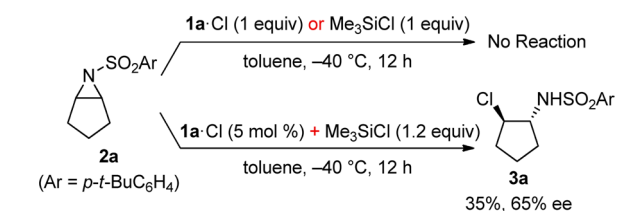
Table 1. Screening of the Structure of Triazolium Ions and Reaction Conditions for Enantioselective Chloride Ring Opening of Meso Aziridine 2a^a

entry	1	additive	% yield ^b	% ee ^c
1	1a	none	35	65
2	1b	none	24	81
3	1c	none	26	84
4	1d	none	42	87
5	1e	none	35	92
6	1f	none	49	93
7	1g	none	31	95
8	1g	MeOH	44	89
9	1g	PhOH	41	94
10	1g	Me ₃ SiOH	49	95
11 ^d	1g	Me ₃ SiOH	85	95
12 ^e	1g	Me ₃ SiOH	55	90
13 ^f	1g	Me ₃ SiOH	NA	NA

^aReactions were carried out with 0.10 mmol of **2a**, 0.12 mmol of Me₃SiCl, and 5 mol % of 1-Cl in 1 mL of toluene. ^bIsolated yield.

^cDetermined by chiral HPLC analysis. ^dReaction was performed with 1 equiv of Me₃SiOH. ^eWith 1.2 equiv of Et₃SiCl instead of Me₃SiCl.

^fWith 1.2 equiv of *t*-BuMe₂SiCl instead of Me₃SiCl. NA, not available.

Scheme 2. Control Experiments for Chloride Ring Opening of Meso Aziridine 2a

ppm).¹⁵ When tetrabutylammonium chloride was mixed with an equimolar amount of Me₃SiCl, a single peak was also detected at $\delta = 6.7$ ppm, thereby suggesting the generation of a silicate species through the interaction of chloride ions with Me₃SiCl.¹⁶

Based on this preliminary information, we next focused on improving the reaction efficiency and stereoselectivity of the asymmetric chloride ring opening reaction of the meso aziridine. For this purpose, we undertook a systematic

modification of the structure of chiral triazolium ion **1** by taking advantage of its modularity (Table 1).¹⁷ Initial screening of the amide substituent (Ar¹) revealed that the introduction of a strongly electron-withdrawing *p*-nitrophenyl group (**1b**) delivered a notable enhancement in enantioselectivity (entry 2). The property of the benzylic appendage at the triazolium N(3) (Ar²) was also important for stereocontrol, and the *p*-trifluoromethylphenyl group was optimal (**1c**, entry 3). This set of aromatic substituents would impart an increased anion-binding ability to the triazolium ion **1** rendering its ion pairing with the silicate ion tight, which might be beneficial in terms of attaining a higher asymmetric induction. On the basis of this assumption, the electronic attribute of **1** was further tuned by installing a *p*-chlorophenyl group as Ar³ (**1d**), leading to a slight increase in the enantiomeric excess (entry 4). Furthermore, the incorporation of a trifluoromethyl group into the *para* position of the C(4) phenyl ring (**1e**) brought critical improvement in the selectivity (entry 5). We then turned our attention to the effect of the substituent attached to the stereogenic carbon of the amino acid origin (R¹) on the reaction profile. Interestingly, the appropriate choice of parent α -amino acid appeared to be crucial for eliciting the full potential of the catalyst, and **1g**-Cl prepared from L-cyclohexylalanine exerted excellent stereocontrolling ability (entries 6 and 7). Throughout these fruitful investigations, however, the conversion of aziridine **2a** into the product **3a** remains insufficient; this seems to be associated with the difficulty in facile regeneration of the active triazolium chlorosilicate, probably because of the relatively weak Lewis basicity of the *p*-*tert*-butylbenzenesulfonamide ion formed after the ring opening. Therefore, we considered the use of alcoholic additives to possibly facilitate this process by the generation of alkoxide ions through a proton transfer. Fortunately, among the several candidates examined, trimethylsilanol (Me₃SiOH) was identified to be suitable for increasing the catalyst turnover without loss of enantioselectivity (entry 10).¹⁸ Eventually, the addition of 1 equiv of Me₃SiOH allowed the reaction to proceed smoothly in the presence of **1g**-Cl as a catalyst, affording **3a** in 85% yield with 95% ee (entry 11). It should be added that the attempted reaction with triethylsilyl chloride (Et₃SiCl) instead of Me₃SiCl proceeded slowly to give **3a** in moderate yield with slightly lower enantioselectivity (entry 12). Use of *tert*-butyldimethylsilyl chloride (*t*-BuMe₂SiCl) resulted in no detectable formation of **3a** (entry 13). The observed dependence of the reactivity and selectivity on the structure of silyl substituents was consistent with the intermediacy of the silicate in the chloride ring-opening event.

The optimized conditions thus established were used for reactions with a variety of meso aziridines (Table 2). A near-quantitative yield was obtained in the chlorination of **2a** simply by extending the reaction time (entry 1). A cyclohexene-derived substrate **2b** was also employable for this desymmetrization, in which the chiral triazolium salt **1f**-Cl was found to be more effective than **1g**-Cl (entries 2 and 3). Other bicyclic and simple aziridines were well accommodated, and high stereoselectivities were uniformly observed (entries 4–6).¹⁹ It is noteworthy that the present system was successfully applied to the bromide ring opening of the aziridines using trimethylsilyl bromide, providing the corresponding β -bromoamine derivatives in high chemical yields with excellent enantiomeric excesses (entries 7 and 8).²⁰

The potential utility of the chiral 1,2,3-triazolium chloride **1**-Cl-catalyzed, asymmetric halide ring-opening protocol was further demonstrated by its successful application to the kinetic

Table 2. Enantioselective Chloride and Bromide Ring Openings of Meso Aziridines^a

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- (17) The reactions with aziridine bearing *p*-toluenesulfonyl group (Ts) exhibited a similar level of reaction efficiency and slightly lower enantioselectivity. For details, see Table S1 in the Supporting Information.
- (18) To interrogate the possibility of concomitant generation of hydrogen chloride (HCl) and its participation as a reactive promoter, the reaction of **2a** was conducted with 10 mol% of a proton scavenger, 2,6-di-*tert*-butylpyridine, under otherwise identical conditions with those of entry 7 in Table 1; this revealed that the differences in chemical yield and ee were marginal and thus HCl was irrelevant to the present catalytic system, even if it was generated.
- (19) The present system seems to be ineffective for aziridines having aromatic substituents. For instance, the reaction of *cis*-stilbene-derived aziridine proceeded sluggishly even at 0 °C, resulting in the formation of the desired product in 14% yield with 48% ee after 24 h.
- (20) The chlorinated product was not obtained even in the reaction with 30 mol% of **1f**Cl.
- (21) $S = k_{\text{fast}}/k_{\text{slow}} = \ln[(1 - C/100)(1 - ee/100)]/\ln[(1 - C/100)(1 + ee/100)]$ (C = conversion, ee = enantiomeric excess of recovered **4** or **6**).
- (22) The ring opening of styrene-derived aziridine showed an opposite regioselectivity and diminished stereoselectivity. For details, see the Supporting Information.
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- (24) The absolute configuration of **7a** was determined to be *R* by X-ray diffraction analysis. The minor regioisomers **8** were also obtained in enantioenriched form (**8a**: 64% ee, **8b**: 62% ee, **8c**: 80% ee). These products would arise from the stereo-invertive ring opening of (*R*)-aziridines, and the stereochemistry of **8** shown in Scheme 4 is based on this assumption. For stereo-invertive nucleophilic substitution at the disubstituted carbon of aziridine, see: Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullie, M. M. *J. Am. Chem. Soc.* **2007**, 129, 14463.