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Guanidine-catalyzed enantioselective desymmetrization of *meso*-aziridines†

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An amino-indanol derived chiral guanidine was developed as an efficient Brønsted base catalyst for the desymmetrization of *meso*-aziridines with both thiols and carbamodithioic acids as nucleophiles, which provided 1,2-difunctionalized ring-opened products in high yields and enantioselectivities.

Aziridines and their ring-opened products are important intermediates in synthetic organic chemistry.[1] Asymmetric desymmetrization of *meso*-aziridines has attracted much attention as it can generate enantiomerically pure 1,2-difunctionalized products in a single step. Although some highly enantioselective desymmetrizations of *meso*-aziridines catalyzed by chiral metal complexes have been developed,[2] there are fewer organocatalytic examples. Chiral phosphoric acids were reported to be effective catalysts for the asymmetric ring opening of *meso*-aziridines with $TMSN_3$,[3] TMS–SPh[4] and thiols.[5] Brønsted base strategies using *Cinchona* alkaloid derivatives[6,7] and prolinols[8] have been recently exploited but with less success.

Our group has demonstrated the use of chiral bicyclic guanidines as Brønsted base catalysts in several enantioselective reactions.[9] Recently, we are trying to design guanidines that can be more easily accessible.[9c] In this communication, we reported an amino-indanol derived guanidine **1b** (Fig. 1), which can be synthesized in two simple steps (see ESI†). This catalyst was shown to be an excellent catalyst for the desymmetrization of *meso*-aziridines with sulfur nucleophiles.

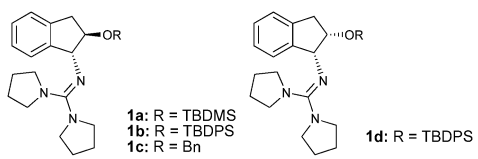

Fig. 1 Amino-indanol derived chiral guanidines.

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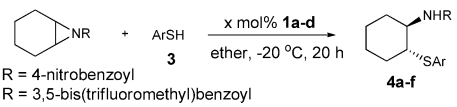
† Electronic supplementary information (ESI) available. CCDC 806368–806369. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc05840h

Preliminary studies showed that the ring opening of aziridine **2a** with thiophenol can be catalyzed with 10 mol% of guanidines **1a–d** (Table 1, entries 1–4). The *trans*-product **4a** was isolated in 33% ee in the presence of **1b** as a catalyst when the reaction was conducted in ether at −20 °C. Different *N*-protected aziridines were investigated with catalyst **1b** (entries 5 and 6). The enantioselectivity was slightly improved when a 3,5-dinitrobenzoyl group was used and amongst arylthiols that were tested, 2,6-dichlorobenzenethiol provided the desired product in 84% ee (entries 7–9). This result was further improved by decreasing the catalyst loading. When 2 mol% of catalyst was used in the desymmetrization, product **4f** was obtained in 92% ee with 92% yield (entry 11). A loading of 1 mol% catalyst gave the same enantioselectivity, but at the expense of longer reaction time.

Density functional theory (DFT) calculations[10] were performed to elucidate the origin of enantioselectivity for the reaction between aziridine **2c** and thiol (Ar = $2,6\text{-}Cl_2C_6H_3$). Two plausible mechanisms can be envisaged (Fig. 2a).

By comparing the lowest energy conformation located for the relevant transition state (TS) structures, the absolute

Table 1 Desymmetrization of *meso*-aziridines **2a–c** catalyzed by guanidines **1a–d**



2a R = 4-nitrobenzoyl
2b R = 3,5-bis(trifluoromethyl)benzoyl
2c R = 3,5-dinitrobenzoyl

Entry	Catalyst	2	Ar	*x* mol%	4	Yield[a] (%)	ee[b] (%)
1	**1a**	**2a**	Ph	10	**4a**	94	4
2	**1b**	**2a**	Ph	10	**4a**	94	33
3	**1c**	**2a**	Ph	10	**4a**	92	2
4	**1d**	**2a**	Ph	10	**4a**	89	2
5	**1b**	**2b**	Ph	10	**4b**	78	34
6	**1b**	**2c**	Ph	10	**4c**	95	44
7	**1b**	**2c**	$2,6\text{-}Me_2C_6H_3$	10	**4d**	92	67
8	**1b**	**2c**	$4\text{-}BrC_6H_4$	10	**4e**	92	59
9[c]	**1b**	**2c**	$2,6\text{-}Cl_2C_6H_3$	10	**4f**	93	84
10	**1b**	**2c**	$2,6\text{-}Cl_2C_6H_3$	5	**4f**	93	89
11	**1b**	**2c**	$2,6\text{-}Cl_2C_6H_3$	2	**4f**	92	92
12[d]	**1b**	**2c**	$2,6\text{-}Cl_2C_6H_3$	1	**4f**	92	92

[a] Isolated yield. [b] Determined by chiral HPLC analysis on a chiral phase. [c] The absolute configuration of **4f** was determined by X-ray analysis (see the ESI† for details). [d] The reaction was complete after 40 hours.

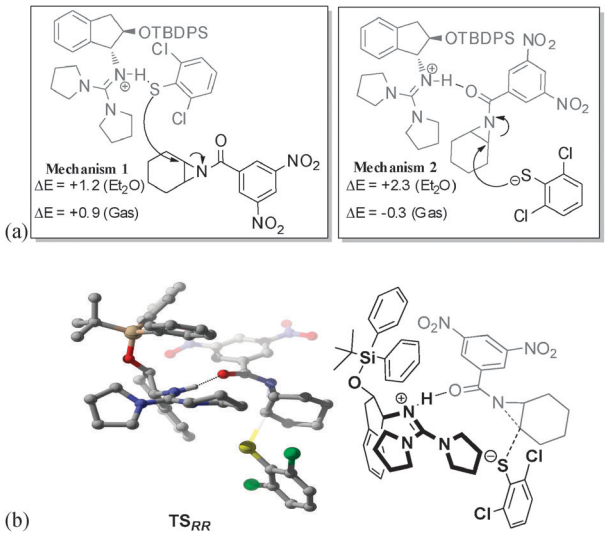


Fig. 2 (a) Possible mechanisms for aziridine-opening reaction. $\Delta E = E_{SS} - E_{RR}$ (kcal mol^{-1}), where E is the electronic energy at M06-2X/6-311+G(2df,2p)//B3LYP/6-31G(d,p). (b) Lowest energy TS structure for (*R*,*R*) product for mechanism 2 optimized at RB3LYP/6-31G(d,p). On the right is the ChemDraw representation of $\mathbf{TS_{RR}}$.

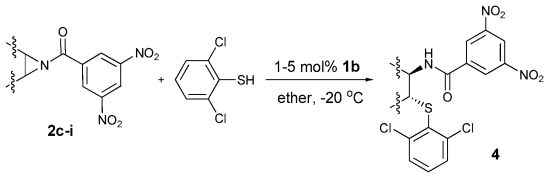
configuration of **4f**, that was determined by single-crystal diffraction, could be predicted correctly with both models. The (*R*,*R*) TS structure is lower in energy relative to the (*S*,*S*) one in both mechanisms: 1.2 kcal mol^{-1} for mechanism 1 and 2.3 kcal mol^{-1} for mechanism 2.

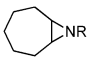
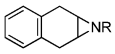
Both mechanisms were further tested in the prediction of the trend in enantioselectivity observed in Table 1 by using different thiols (Ar = Ph and Ar = 4-BrC_6H_4). Mechanism 1 predicted an increase in enantioselectivity relative to Ar = 2,6-$Cl_2C_6H_3$ for both cases ($\Delta E_{Ar=Ph}$ = 2.4 kcal mol^{-1}; $\Delta E_{Ar=4\text{-}BrC6H4}$ = 2.6 kcal mol^{-1}) which contradicts experimental results. Mechanism 2 is able to predict qualitatively the observed decrease in enantioselectivity for both substituted thiols ($\Delta E_{Ar=Ph}$ = 0 kcal mol^{-1}; $\Delta E_{Ar=4\text{-}BrC6H4}$ = 0.7 kcal mol^{-1}).

The TS structure of mechanism 2 in Fig. 2b provides a basis for rationalizing the enantioselectivity observed. Despite the much shorter hydrogen bond in $\mathbf{TS_{SS}}$, it is less stable than $\mathbf{TS_{RR}}$. This is ascribed to larger steric repulsion which arises from bringing the aziridine and thiol closer to the catalyst. The large increase in enantioselectivity when the phenyl group of the thiol is substituted with chlorine at the 2- and 6-positions can be attributed to an increase in steric repulsion between the two chloro-substituents and neighbour atoms of the catalyst–aziridine complex. The number of neighbouring atoms within 5 Å to both chloro-substituents is 29 in $\mathbf{TS_{SS}}$ (average: 4.1 Å) and 25 in $\mathbf{TS_{RR}}$ (average: 4.3 Å).[11] As chlorine (1.75 Å) has a larger van der Waals radius relative to hydrogen (1.20 Å),[12] destabilization of $\mathbf{TS_{SS}}$ relative to $\mathbf{TS_{RR}}$ will be more significant in Ar = 2,6-$Cl_2C_6H_3$ than Ar = Ph and contributes to the observed increase in ees.

The ring opening of aziridine-2,3-dicaboxylates is a direct synthetic approach towards β-substituted aspartates.[13] Catalyst **1b** proved to be an efficient catalyst for the desymmetrization of the *N*-tosyl *meso*-aziridine **5** with thiols. Both 2,6-dichlorobenzenethiol and 2,6-dimethylbenzenethiol provided the

Table 2 Desymmetrization of *N*-3,5-dinitrobenzoyl aziridines **2c–i** catalyzed by guanidine **1b**



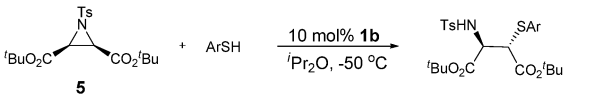
Entry	**2** (R = 3,5-dinitrobenzoyl)	**4**	*x* mol%	Yield[a] (%)	ee[b] (%)
1[c]	 **2c**	**4f**	1	92	94
2	 **2d**	**4g**	1	94	94
3	 **2e**	**4h**	2	93	90
4	 **2f**	**4i**	5	91	95
5	 **2g**	**4j**	5	90	90
6	 **2h**	**4k**	5	93	88
7	 **2i**	**4l**	2	91	93

[a] Isolated yield. [b] Determined by chiral HPLC analysis on a chiral phase. [c] The reaction was performed at −50 °C.

ring-opened products with good ees and yields (Scheme 1). Absolute configuration of **6a** is determined by X-ray crystallographic analysis (see ESI†).

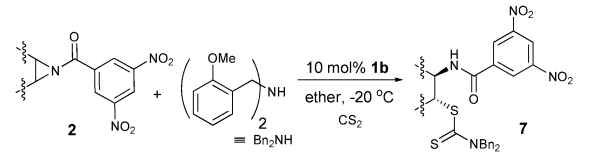
Dithiocarbamates with substitutions at the thiol chain are compounds with potential biological activity.[14a] One of the most convenient approaches to these compounds is the generation of the carbamodithioic acid from an amine and carbon disulfide, followed by the ring opening of an epoxide.[14] However, no variant with aziridines was reported. To further extend the scope of our methodology, we studied the desymmetrization of *N*-3,5-dinitrobenzoyl *meso*-aziridines with *in situ* generated carbamodithioic acid. This three component reaction was investigated with amines, and bis(2-methoxybenzyl)-amine was found to provide the best enantioselectivity. The results were less ideal when we used carbamodithioic acid that was prepared separately. The reactions of various aziridines with different ring-size and acyclic aziridine were investigated. Good enantioselectivities and yields were observed for bicyclic aziridines containing six- and five-membered rings (Table 3, entries 1–3). A lower ee and much lower yield were observed when aziridine **2f** with a seven-membered ring was used (entry 4). With 20 mol% **1b** as a catalyst, acyclic *meso*-aziridine **2h** provided the ring-opened product with high enantioselectivity and yield (entry 5). Excellent optical purity of the products could be easily obtained through a single recrystallization.

The enantiopure 1,2-difunctionalized products obtained can be readily transformed into valuable compounds (Scheme 2). For instance, the ring-opened product **4f** (95% ee) could be easily oxidized to a sulfoxide intermediate as a single diastereoisomer



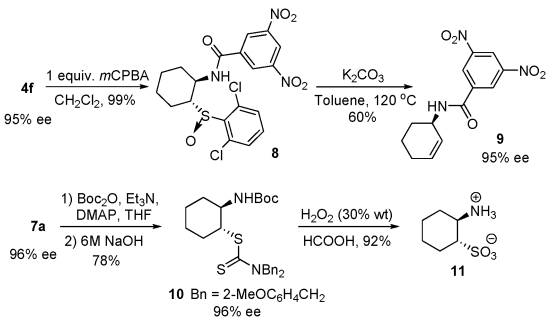
Scheme 1 Desymmetrization of *cis*-aziridine-2,3-dicaboxylate **5**.

Table 3 Desymmetrization of *N*-3,5-dinitrobenzoyl aziridines **2c–h** with amine and CS_2



Entry	**2** (R = 3,5-dinitrobenzoyl)		**7**	Yield[a] (%)	ee[b] (%)
1[c]		**2c**	**7a**	98	89 (96)
2		**2d**	**7b**	98	85 (91)
3		**2e**	**7c**	80	84 (95)
4		**2f**	**7d**	67	80 (90)
5[d]		**2h**	**7e**	91	90 (98)

[a] Isolated yield. [b] Determined by chiral HPLC analysis on a chiral phase; ees after recrystallization are reported in parentheses. [c] The reaction was performed at −50 °C. [d] The reaction was carried out with 20 mol% of catalyst **1b**.



Scheme 2 Preparation of allylic amide **9** and β-amino sulfonic acid **11**.

with high yield. Pyrolysis[15] then afforded the chiral allylic amide, which is difficult to synthesize *via* other means. In addition, oxidative cleavage of the C=C bond allows access to α-amino acid of high optical purity. The ring-opened product **7a** (96% ee) was subjected to Boc protection, followed by removal of the 3,5-dinitrobenzoyl group with 6 M aqueous NaOH and finally oxidized with performic acid to form the zwitterionic chiral β-amino sulfonic acid.

In summary, we have developed an easy, efficient catalyst **1b** for highly enantioselective desymmetrization of *meso*-aziridines. This is the first report on the use of carbamodithioic acid as a nucleophile for asymmetric ring opening of aziridines. Compounds that are useful in medicinal chemistry such as chiral allylic amides and β-amino sulfonic acids could be readily synthesized from the ring-opened products.

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