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Kinetic Resolution of Aziridines via Catalytic Asymmetric Ring-Opening Reaction with Mercaptobenzothiazoles

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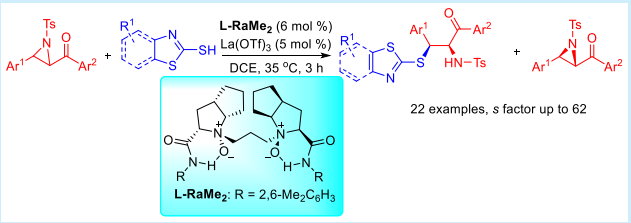
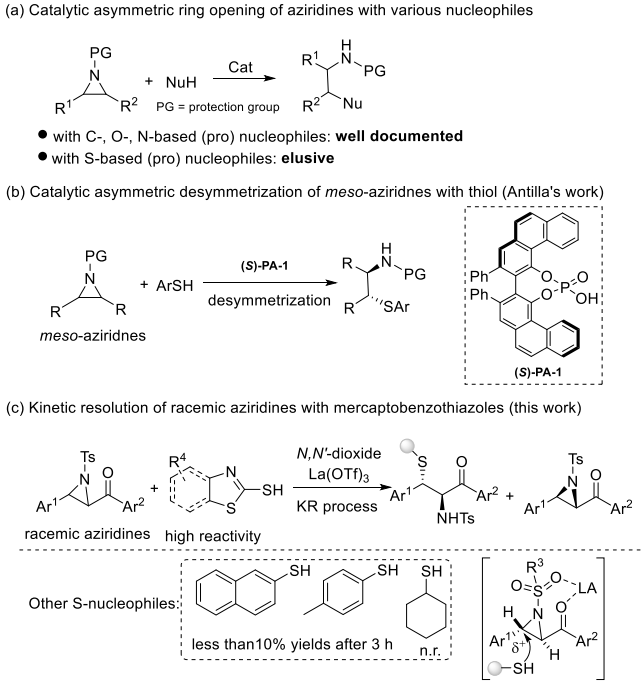
Supporting Information

ABSTRACT: A highly efficient kinetic resolution of racemic 2-acyl-3-aryl-*N*-tosylaziridines is achieved through a chiral Lewis acid promoted ring-opening reaction with 2-mercaptobenzothiazoles as the nucleophiles. The chiral *N*,*N*′-dioxide−lanthanum complex as catalyst and the 2-mercaptobenzothiazoles as active sulfur nucleophiles are the keys to the success of the reaction. A variety of enantioenriched *β*-amino thioethers and aziridines are obtained in good yields with good ee values.



The ring-opening of three-membered cyclic compounds with nucleophiles occupies an important position in organic synthesis.[1] Aziridines are attractive synthons due to their convenient construction of useful *N*-containing compounds. The carbon-,[2] oxygen-,[3] and nitrogen-based[4] nucleophiles have been well applied in the ring-opening reaction of aziridines (Scheme 1a). Comparatively, the ring-opening reaction with sulfur-based nucleophiles is challenging, especially when the Lewis acid is used as the catalyst, because sulfur nucleophiles might poison the catalyst for their strong coordination ability to the central metal.[5] However, it allows for construction of *β*-amino thioethers,[6] which are important synthetic blocks and widely present in ligands as well as in bioactive compounds,[7] such as L-cysteine, *β*-MeLan,[8] and mersacidin.[9] To the best of our knowledge, only one catalytic asymmetric report emerged in 2009, where Antilla's group realized the desymmetrization of *meso*-aziridines with functionalized thiols using the chiral phosphoric acid catalyst (Scheme 1b).[10]

Scheme 1. Asymmetric Ring-Opening Reactions of Aziridines



The ring-opening of racemic aziridines via kinetic resolution[11] with sulfur nucleophiles could entail both enantiomerically enriched *β*-amino thioethers and aziridines at the same time. The obtained chiral aziridines are also meaningful since this block exists in some compounds featuring fascinating anticancer activity.[12] Therefore, it is significant to develop efficient methods for the kinetic resolution of aziridines with sulfur nucleophiles.[13]

In addition, chiral *N*,*N*′-dioxide−metal complexes have been proved to be efficient Lewis acid catalysts in series of asymmetric reactions.[14] They might be promising in promoting the kinetic resolution of aziridines with sulfur nucleophiles. We selected racemic *trans*-2-acyl-3-aryl-*N*-tosylaziridines[15] as the substrates to undergo the ring-opening reaction since the carbonyl substituent and *N*-protection group in aziridines could cooperate with the catalyst in a bidentate manner, which will facilitate the enantiodiscrimination of the reaction.[16] As for the sulfur nucleophiles, cyclohexyl mercaptan, thiophenol, and naphthol did not or very weakly undergo the reaction. After considerable effort, 2-mercapto-

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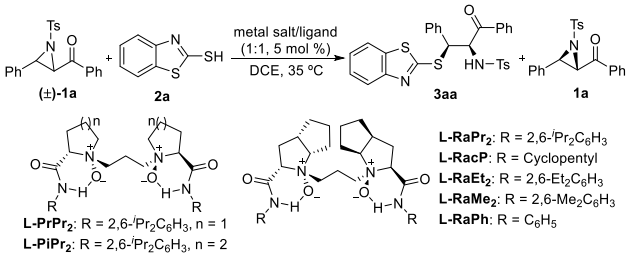
benzothiazoles were applied as excellent nucleophiles (Scheme 1c).[17]

Initially, various metal salts coordinating with *N,N′*-dioxide **L-PiPr$_2$** were tested (for details, see the Supporting Information). The complex of Sc(OTf)$_3$ could afford the desired product in 41% yield but 0% ee value; meanwhile, aziridine **1a** decomposed under the strong Lewis acid conditions (Table 1, entry 1). Further investigation showed

Table 1. Optimization of the Reaction Conditions[a]



entry	metal salt	ligand	yield[b] (%) 1a	yield[b] (%) 3aa	ee[c] (%) 1a	ee[c] (%) 3aa	*s*
1	Sc(OTf)$_3$	**L-PiPr$_2$**		41		0	
2	La(OTf)$_3$	**L-PiPr$_2$**	41	44	60	67	9
3	La(OTf)$_3$	**L-PrPr$_2$**	47	44	65	69	11
4	La(OTf)$_3$	**L-RaPr$_2$**	44	49	69	72	13
5	La(OTf)$_3$	**L-RaEt$_2$**	37	49	97	83	45
6	La(OTf)$_3$	**L-RaMe$_2$**	50	49	90	90	58
7	La(OTf)$_3$	**L-RaPh**	49	49	37	36	3
8[d]	La(OTf)$_3$	**L-RaMe$_2$**	49	49	92	90	62

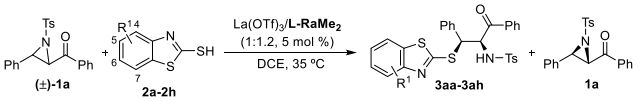
[a]Unless otherwise noted, all reactions were carried out with metal salt/ligand (1:1, 5 mol %), (±)-**1a** (0.10 mmol) and **2a** (0.05 mmol) in DCE (0.5 mL) at 35 °C for 2.5 h, DCE = CH_2ClCH_2Cl. [b]Yield of isolated product. [c]Determined by SFC analysis. The absolute configuration of **3aa** was determined by X-ray crystallographic analysis. [d]Metal salt/ligand (1:1.2, 5 mol %), (±)-**1a** (0.20 mmol) and **2a** (0.10 mmol), 2 mL DCE. $s = \ln[(1 - \text{conv})(1 - \text{ee}^1)]/\ln[(1 - \text{conv})(1 + \text{ee}^1)]$; conv = $\text{ee}^1/(\text{ee}^1 + \text{ee}^3)$.

that the **L-PiPr$_2$**/La(OTf)$_3$ complex could give the desired product **3aa** in 44% yield, 67% ee, and recovered **1a** in 41% yield with 60% ee (s = 9). Next, the chiral backbone in ligand was investigated. It was found that L-ramipril-derived **L-RaPr$_2$** was more competent than L-proline-derived **L-PrPr$_2$** and (*S*)-pipecolic acid derived **L-PiPr$_2$** in terms of enantiocontrol (Table 1, entries 2−4).

By reducing the steric hindrance on the amide benzene ring (**L-RaPr$_2$** to **L-RaMe$_2$**), the selectivity factor would rise from 13 to 58 (Table 1, entries 4−6). However, with no substituent on the phenyl ring (**L-RaPh**) the enantioselectivity dropped sharply (Table 1, entry 7). Finally, when the proportion of metal salt and ligand adjusted to 1:1.2, the enantioselectivity of recovered **1a** improved slightly, and the yields as well as the ee value of ring-opening product **3aa** were maintained (Table 1, entry 8).

With the optimized conditions in hand, the substrate scope was then examined. At first, a series of 2-mercaptobenzothiazole derivatives were probed by reacting them with (±)-**1a** (Table 2). Both electron-withdrawing and electron-donating substituents on the phenyl ring had little effect on the reaction, and the corresponding benzenesulfonamides **3aa**−**3ah** together with recovered **1a** were obtained in excellent yields with good ee values, except for the recovered **2d** (65% ee), which

Table 2. Substrate Scope of the Benzothiazole-2-thiol Derivatives[a]



entry	2	R^1	yield[b] (%) 1a	yield[b] (%) 3	ee[c] (%) 1a	ee[c] (%) 3	s
1	**2a**	H	49	49 (**3aa**)	92	90 (1*S*,2*R*)	62
2	**2b**	5-Cl	45	49 (**3ab**)	83	90 (1*S*,2*R*)	49
3	**2c**	5-OMe	51	48 (**3ac**)	89	90 (1*S*,2*R*)	57
4	**2d**	6-Cl	50	49 (**3ad**)	65	91 (1*S*,2*R*)	41
5	**2e**	6-OMe	50	45 (**3ae**)	82	90 (1*S*,2*R*)	48
6	**2f**	4-Me	43	49 (**3af**)	94	88 (1*S*,2*R*)	55
7	**2g**	7-Me	48	49 (**3ag**)	93	88 (1*S*,2*R*)	53
8	**2h**		50	49 (**3ah**)	77	82 (1*S*,2*R*)	23

[a]Unless otherwise noted, all reactions were carried out with La(OTf)$_3$/**L-RaMe$_2$** (1:1.2, 5 mol %), (±)-**1a** (0.2 mmol) and **2a**−**2h** (0.1 mmol) in DCE (2 mL) at 35 °C for 3 h. [b]Yield of isolated product. [c]Determined by SFC analysis. The absolute configuration of **3aa** was determined by X-ray crystallographic analysis and other products **3** were determined by comparing their CD spectra with that of **3aa**. $s = \ln[(1 - \text{conv})(1 - \text{ee}^1)]/\ln[(1 - \text{conv})(1 + \text{ee}^1)]$; conv = $\text{ee}^1/(\text{ee}^1 + \text{ee}^3)$.

might be caused by its insoluble nature. It is worth mentioning that 4,5-dihydrothiazole-2-thiol **2h** without a phenyl ring could also undergo the kinetic resolution process smoothly, giving good results.

Next, a variety of racemic aziridines were assessed (Table 3). The electronic nature and position of substituents on the phenyl group of aryl aziridines also had little effect on the enantiocontrol of the kinetic resolution, and the selectivity factors varied from 28 to 55 (Table 3, entries 1−9). The naphthyl-substituted **1k** and **1l** performed well to give **3** in excellent ee values and **1a** in good ee values (Table 3, entries 10 and 11). Simultaneously, racemic aziridines with methyl-substituted benzoyl part were tested. *Meta* and *para* compounds gave good results, but the *ortho* compound resulted in a moderate outcome (Table 3, entries 12−14), which might be caused by the larger steric resistance. The absolute configuration of **3aa** was determined to be (1*S*,2*R*) by X-ray crystallographic analysis, and the other products **3** were also determined to be (1*S*,2*R*) by comparing their CD spectra with that of **3aa**.

To illustrate the potential utility of the methodology, a gram-scale synthesis was conducted. To our surprise, only 27% ee for the product **3aa** and 32% ee for the recovered **1a** were obtained under standard conditions. We surmised that polymeric La(III) species might exist in the catalytic system, especially in the case of amplification. This possibility was confirmed by the investigation of the nonlinear effect of the reaction, where a clear positive nonlinear effect was observed when varying the ee value of the chiral ligand and then recording the corresponding ee of **3aa** and **1a**. In addition, the

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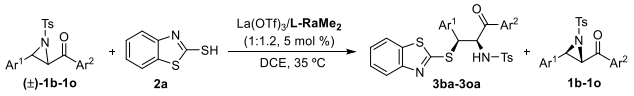
Table 3. Substrate Scope of the Aziridines[a]

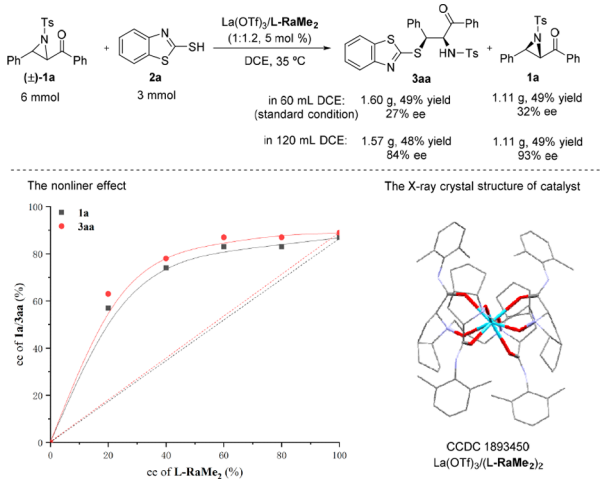


				yield[b] (%)		ee[c] (%)		
entry	1	Ar^1	Ar^2	1	3	1	3	*s*
1	**1b**	2-MeC_6H_4	Ph	48	48 (**3ba**)	88	90 (1*S*,2*R*)	55
2	**1c**	3-MeC_6H_4	Ph	47	48 (**3ca**)	93	87 (1*S*,2*R*)	49
3	**1d**	4-MeC_6H_4	Ph	45	48 (**3da**)	86	90 (1*S*,2*R*)	53
4	**1e**	2-ClC_6H_4	Ph	42	43 (**3ea**)	90	85 (1*S*,2*R*)	38
5	**1f**	3-ClC_6H_4	Ph	47	49 (**3fa**)	85	90 (1*S*,2*R*)	51
6	**1g**	4-ClC_6H_4	Ph	48	49 (**3ga**)	84	80 (1*S*,2*R*)	24
7	**1h**	4-$O_2NC_6H_4$	Ph	34	48 (**3ha**)	60	80 (1*S*,2*R*)	16
8	**1i**	4-$F_3CC_6H_4$	Ph	50	49 (**3ia**)	79	89 (1*S*,2*R*)	41
9	**1j**	4-BrC_6H_4	4-MeC_6H_4	40	44 (**3ja**)	74	90 (1*S*,2*R*)	42
10	**1k**	Ph	2-naphthyl	44	49 (**3ka**)	96	88 (1*S*,2*R*)	61
11	**1l**	2-naphthyl	Ph	40	49 (**3la**)	96	81 (1*S*,2*R*)	37
12	**1m**	Ph	2-MeC_6H_4	50	49 (**3ma**)	62	65 (1*S*,2*R*)	9
13	**1n**	Ph	3-MeC_6H_4	47	49 (**3na**)	87	90 (1*S*,2*R*)	54
14	**1o**	Ph	4-MeC_6H_4	44	49 (**3oa**)	94	85 (1*S*,2*R*)	43

[a]Unless otherwise noted, all reactions were carried out with La(OTf)$_3$/**L-RaMe$_2$** (1:1.2, 5 mol %), (±)-**1** (0.20 mmol), and **2a** (0.10 mmol) in DCE (2 mL) at 35 °C for 3 h. [b]Yield of isolated product. [c]Determined by SFC analysis. The absolute configuration of **3aa** was determined by X-ray crystallographic analysis, and other products **3** were determined by comparing their CD spectra with that of **3aa**. $s = \ln[(1 - \text{conv})(1 - \text{ee}^1)]/\ln[(1 - \text{conv})(1 + \text{ee}^1)]$; $\text{conv} = \text{ee}^1/(\text{ee}^1 + \text{ee}^3)$.

X-ray crystal structure of the catalyst showed that two molecules of **L-RaMe$_2$** could cooperate with La(III) complex (Scheme 2). Thus, we performed the reaction at decreased concentration. Just as expected, 1.57 g (48% yield) of **3aa** with 84% ee and 1.11 g (49% yield) of recovered aziridine **1a** with 93% ee were obtained when 6 mmol of **1a** and 3 mmol of **2a** reacted in a double amount of DCE (Scheme 2).

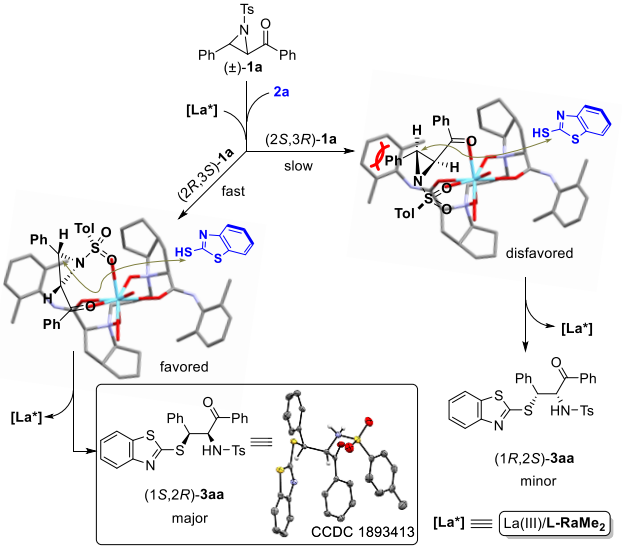
Scheme 2. Gram-Scale Synthesis, Nonlinear Effect, and X-ray Crystal Structure



However, as shown in the single crystal of the catalyst, the coordination sites of the metal are occupied, and it is difficult to activate the substrates. Thus, what was the active species in the solution? The HRMS analysis showed that in the spectra of the mixture of **L-RaMe$_2$**, La(OTf)$_3$, and **1a** in a 1.2:1:1 ratio in DCE an ion at *m*/*z* 1025.1782 ([**L-RaMe$_2$**+ La^{3+} + $2TfO^-$]$^+$ *m*/*z* calcd 1025.1774) was displayed, indicating that the ligand coordinated with the metal in a 1:1 ratio. The spectra in the mixture of **L-RaMe$_2$**, La(OTf)$_3$, **1a**, and **2a** (1.2:1:1:1) in DCE displayed an ion at *m*/*z* 1402.2852 ([**L-RaMe$_2$** + La^{3+} + $2TfO^-$ + **1a**]$^+$ *m*/*z* calcd 1402.2860), suggesting that the **1a** coordinated to the catalyst in a 1:1 molecular ratio. Meanwhile, the characteristic signal of **2a** coordinating with the catalyst was not observed. Hence, the single coordination of the ligand and metal was more likely the active one, and the catalyst activated the aziridine **1a** rather than the 2-mercaptobenzothiazole **2a**.

On the basis of the analysis above and the determination of the absolute configuration of product **3aa**, a possible catalytic mechanism is proposed. As shown in Scheme 3, the two polarized oxygen atoms of *N*-oxide and amide oxygens of **L-RaMe$_2$** combine with La(III) in a tetradentate manner. When

Scheme 3. Proposed Catalytic Mechanism



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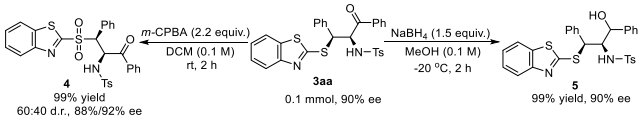
1a is added, (2*R*,3*S*)-**1a** coordinates to the catalyst with the oxygen atom of the carbonyl group and one oxygen atom of the Ts group, forming a distorted dodecahedral conformer. There are different activation modes in different catalytic systems.[18] The $\pi-\pi$ interactions between the two phenyl rings of **1a** and **L-RaMe$_2$** can decrease the energy of transition state, therefore making it favored. The inner side is blocked by the framework of ligand and **2a** attacks from the outer side, affording the (1*S*,2*R*)-**3aa**. Nevertheless, if the (2*S*,3*R*)-**1a** isomer coordinates to the catalyst, steric hindrance between the chiral backbone of catalyst and the phenyl ring in aziridine appear. Therefore, it is difficult for (2*S*,3*R*)-**1a** to undergo the subsequent ring-opening process, and it is recovered.

Transformations of **3aa** were also carried out. As shown in Scheme 4, the oxidation reaction with *m*-CPBA afforded the

Scheme 4. Transformations of Product 3aa



sulfone **4** in quantitative yield without any erosion of the enantioinduction. In addition, when **3aa** was treated with $NaBH_4$ in MeOH at −20 °C, the carbonyl group was reduced, affording the corresponding alcohol **5** in 99% yield with 90% ee.

In conclusion, we have developed an efficient *N*,*N*′-dioxide/$La(OTf)_3$ complex system for kinetic resolution of racemic aziridines. The synergistic strategy tolerates various sulfur-based nucleophilic 2-mercaptobenzothiazole derivatives and racemic *trans*-2-acyl-3-aryl-*N*-tosylaziridines derivatives. The corresponding β-amino thioethers were obtained in high activity together with high levels of stereocontrol (up to 92% ee). Besides, a possible catalytic mechanism was proposed to illustrate the stereoinduction. Further applications of the catalysts are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02058.

Experimental details; analytic data (NMR, SFC, HRMS, CD spectra) (PDF)

Accession Codes

CCDC 1893413 and 1893450 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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