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An Organocatalytic Kinetic Resolution of Aziridines by Thiol Nucleophiles

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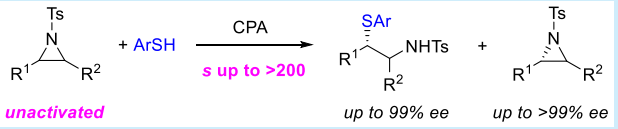
ABSTRACT: We report the first organocatalytic kinetic resolution of unactivated aziridines by sulfur nucleophiles with excellent enantioselectivity. A suitable chiral phosphoric acid was found to catalyze the intermolecular ring opening under mild conditions, furnishing a range of highly enantioenriched *β*-amino thioethers and aziridines, both of which are useful synthetic building blocks.

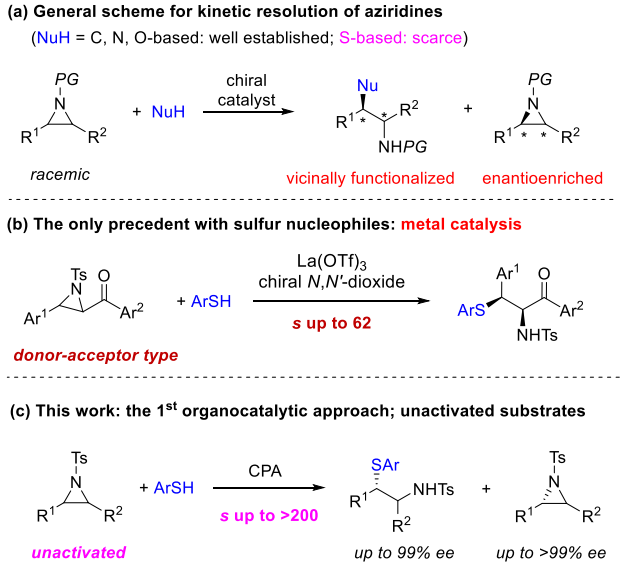


Kinetic resolution represents a powerful tool in asymmetric synthesis.[1] It is particularly useful when implemented on enantioselective opening of strained rings. For example, catalytic asymmetric ring-opening of racemic aziridines by kinetic resolution has been demonstrated as an important strategy to provide expedient access to chiral amine derivatives with various vicinal functionalities (Scheme 1a).[2−4] This process also leads to enantioenriched aziridines that are themselves important precursors to other useful chiral building blocks via stereospecific transformations. Owing to these exceptional utilities, various catalytic systems, particularly based on metal catalysts, have been developed for this process in the past two decades.[2,3] While a range of nucleophiles, including carbon-, nitrogen-, and oxygen-based ones, have been demonstrated as versatile reaction partners, it is worth noting that the use of sulfur-based nucleophiles have remained challenging and scarce. Sometimes these nucleophiles may deactivate metal catalysts due to their strong coordination ability.[5] However, if successful, this process could lead to useful enantioenriched chiral sulfur molecules with *β*-amino functionality, an important family of molecules with wide applications in medicinal chemistry and asymmetric synthesis.[6] In this context, the development of an efficient protocol to address this limitation remains in high demand.

Recently, Feng and co-workers reported the first and only example catalyzed by the metal complex lanthanum(III)/*N*,*N*′-dioxide (Scheme 1b).[4a] While this elegant reaction was achieved with good to excellent stereocontrol, it is worth noting that all the aziridines used in this work are activated donor−acceptor type. Thus, kinetic resolution of regular unactivated aziridines by sulfur nucleophiles still remains unknown. In 2009, Antilla and co-workers reported an organocatalytic enantioselectivie desymmetrization of aziridines by thiols with chiral phosphoric acid (CPA) catalysis.[4b] In this context, we report herein the first organocatalytic kinetic resolution of this type (Scheme 1c).

In continuation of our interest in chiral Brønsted acid catalyzed asymmetric opening of strained rings,[7] we envisioned that the use of such an organocatalytic approach should be able to provide an alternative solution to the metal catalyzed system. To test this hypothesis, we employed phenyl aziridine **1a** as the model substrate. 2-Mercaptobenzothiazole (**2a**) was initially used as the nucleophile in view of its wide utility in organic synthesis and medicinal

Scheme 1. Kinetic Resolution of Aziridines with Sulfur Nucleophiles[a]



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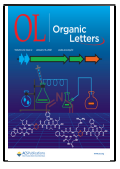

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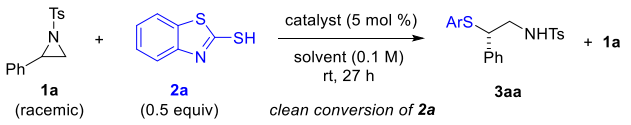
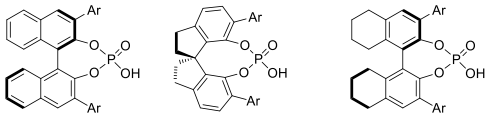
chemistry (Table 1).[8] Various chiral phosphoric acids (CPAs) were examined as potential catalysts.[9,10] Gratifyingly,

Table 1. Condition Optimization[a]



entry	catalyst	solvent	ee of **1a** (%)	ee of **3aa** (%)	s factor
1	(*R*)-**A1**	CH_2Cl_2	-21	-23	2
2	(*R*)-**A3**	CH_2Cl_2	-37	-40	4
3	(*R*)-**B1**	CH_2Cl_2	55	49	5
4	(*R*)-**B2**	CH_2Cl_2	68	87	29
5	(*R*)-**B3**	CH_2Cl_2	99	79	43
6	(*R*)-**C1**	CH_2Cl_2	-3	-45	1
7	(*R*)-**B3**	toluene	88	87	42
8	(*R*)-**B3**	THF	75	76	16
9	(*R*)-**B3**	EtOAc	91	84	36
10	(*R*)-**B3**	$CHCl_3$	99	90	99
11[b]	(*R*)-**B3**	$CHCl_3$	97	95	164
12[bc]	(*R*)-**B3**	$CHCl_3$	92	97	>200

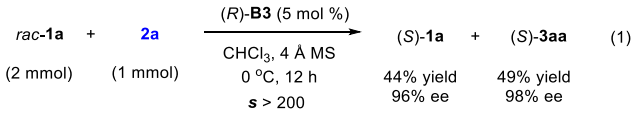


[a]Reaction scale: *rac*-**1a** (0.1 mmol), **2a** (0.05 mmol), solvent (1.0 mL). Conversion was determined by analysis of the ^{1}H NMR spectrum of the crude mixture using CH_2Br_2 as an internal standard. Ee was determined by HPLC with a chiral stationary phase. $s = \ln[(1 - \text{conv})(1 - \text{ee}^{1a})]/\ln[(1 - \text{conv})(1 + \text{ee}^{1a})]$; $\text{conv} = \text{ee}^{1a}/(\text{ee}^{1a} + \text{ee}^{3aa})$. [b]Run with 4 Å molecular sieves (20 mg). [c]Run at 0 °C.

the reaction of racemic **1a** and **2a** (0.5 equiv) in DCM at room temperature proceeded smoothly and cleanly to form the desired *β*-amino thioether **3aa** with complete conversion. Among these catalysts, the BINOL- and [H_8]BINOL-derived phosphoric acids resulted in poor enantiocontrol (s = 1−4). However, those with the spirocyclic backbone led to improved selectivity (entries 3−5). Specifically, catalyst **B3** provided the highest enantioselectivity (s = 43, entry 5). Further solvent screening identified anhydrous chloroform to be superior (entry 10). The use of molecular sieves as additive could further improve the outcome (entry 11). Furthermore, decreasing the reaction temperature to 0 °C enhanced the selectivity factor to an excellent level (s > 200). With this set of conditions, the product and the remained substrate were both obtained with excellent enantiopurity (entry 12).

With the optimized conditions, we examined the scope of this kinetic resolution protocol. A range of racemic aziridines with different substituent patterns smoothly participated in this ring-opening reaction under mild conditions. The corresponding *β*-amino thioether products and the remained aziridines were all obtained with good to high enantioselectivity. It is worth noting that excellent selectivity factors were observed for substituted phenylazridines (entries 1−14). These results meant that, in most cases, when one of the two enantiomers was consumed, the other enantiomer was remained essentially untouched, which highlighted the remarkable stereocontrol. Different substituted mercaptobenzothiazoles were also good nucleophiles (entries 2−4). Notably, 6-ethoxy-substituted one **2d** also led to excellent selectivity (s > 200, entry 4). However, other sulfur nucleophiles, such as thiophenol, aliphatic thiols, and thio acids, did not react under the standard conditions (see the Supporting Information for details). Furthermore, 1,2-disubstituted aziridine **1m** was also an excellent substrate, which afforded the highly enantioenriched product with two consecutive chiral centers. While indene-derived aziridine **1n** and alkyl-substituted aziridine **1o** also reacted with excellent chemical efficiency, their enantioselectivity was very low when **2a** was used as nucleophile. However, **2d** could result in a selectivity factor of about 12 (entries 17 and 18). Notably, no other regioisomer was observed in the case of **1o**. Finally, the product absolute stereochemistry was confirmed by X-ray crystallography in the case of **1d**.

This protocol could be applied to a 1 mmol scale reaction without modification (eq 1). The reaction efficiency and stereoselectivity at a larger scale (2 mmol of **1a**) were comparable to the results obtained in a smaller scale (Table 2, entry 1).



The highly enantioenriched products and recovered aziridines are useful building blocks in organic synthesis.[11] For example, the enantiopure aziridine **1a** was known as a versatile substrate for highly stereospecific transformations to diversely functionalized chiral amine derivatives (Scheme 2). Moreover, the benzothiazole unit in the enantioenriched *β*-amino thioether product **3aa** could also be converted or removed. In the presence of MeONa/MeOH, the reaction

Scheme 2. Product Transformations

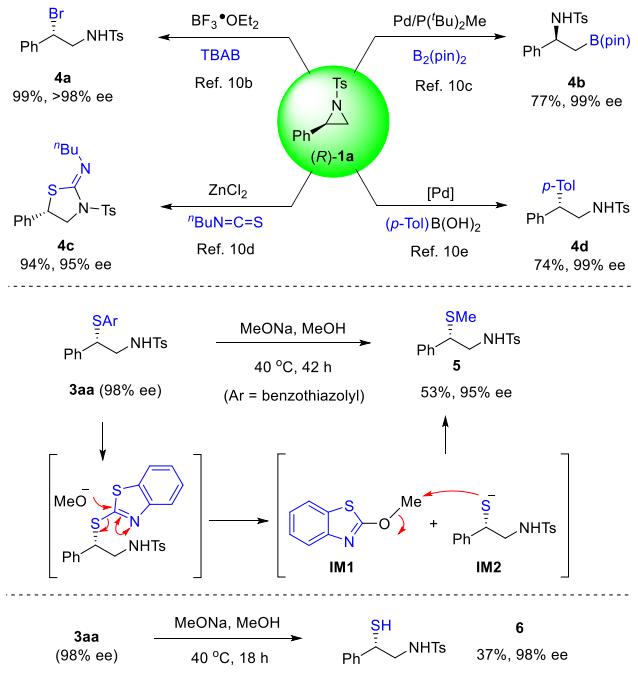


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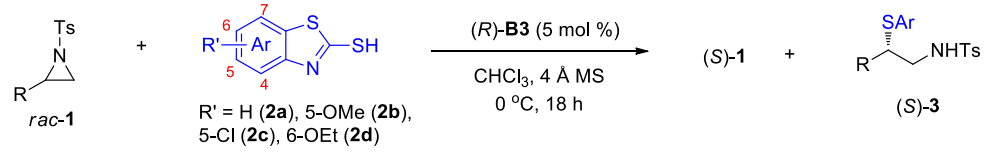
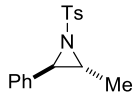
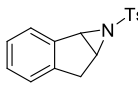
Table 2. Substrate Scope[a]



entry	R	NuH	(S)-1		(S)-3		s
			yield (%)[b]	ee (%)[b]	yield (%)[c]	ee (%)[c]	
1	Ph (**1a**)	**2a**	49	92	48	98	> 200
2	Ph (**1a**)	**2b**	48	91	40	92	76
3	Ph (**1a**)	**2c**	45	96	38	80	35
4	Ph (**1a**)	**2d**	45	90	40	97	> 200
5	X = F (**1b**)	**2a**	46	> 99	49	98	> 200
6	X = Cl (**1c**)	**2a**	46	> 99	46	96	> 200
7	X = Br (**1d**)	**2a**	45	97	48 (X-ray)	99	> 200
8	X = CF_3 (**1e**)	**2a**	54	88	45	99	> 200
9	X = CO_2Me (**1f**)	**2a**	50	95	49	94	120
10	X = OAc (**1g**)	**2a**	42	> 99	52	98	> 200
11	X = Me (**1h**)	**2a**	47	91	48	94	103
12	X = Ph (**1i**)	**2a**	50	99	49	96	> 200
13	X = Bpin (**1j**)	**2a**	46	99	42	96	> 200
14	(*o*-Br)C_6H_4 (**1k**)	**2a**	50	79	46	90	46
15	2-naphthyl (**1l**)	**2a**	47	90	52	90	58
16	 (**1m**)	**2a**	50	> 99	49	90	99
17	 (**1n**)	**2d**	46	74	50	71	13[d]
18	$PhCH_2CH_2$ (**1o**)	**2d**	44	80	49	66	12[e]

[a]Reaction scale: *rac*-**1** (0.4 mmol), **2** (0.2 mmol), (*R*)-**B3** (5 mol %), 4 Å MS (80 mg), $CHCl_3$ (4.0 mL), 0 °C. Isolated yield and ee are from the same single trial. The ee values were determined by chiral HPLC. $s = \ln[(1 - \text{conv})(1 - \text{ee}^1)]/\ln[(1 - \text{conv})(1 + \text{ee}^1)]$; $\text{conv} = \text{ee}^1/(\text{ee}^1 + \text{ee}^3)$. [b]Yield and ee are referred to the recovered substrate. [c]Yield and ee are referred to the product **3**. [d]Run at 0 °C for 48 h. [e]Run at 0 °C for 144 h followed by rt for 24 h.

proceeded at 40 °C to form the highly enantioenriched methyl thioether **5** as the major product. It is believed that this reaction initially forms the methyl aryl ether **IM1** and sulfide anion **IM2** followed by a nucleophilic substitution (S_N2) reaction between these two intermediates.[12] While it was difficult to control this process to stop at the free thiol stage, it is worth noting that the free thiol **6** could be isolated at partial conversion.[13] Notably, no obvious erosion in product enantiopurity was observed in these transformations.

To help understand the origin of the excellent stereocontrol, we also carried out DFT calculations of the enantiodetermining transition states. The results indicated that the (*S*)-enantiomer of the aziridine substrate experiences severe steric repulsion when the nucleophile approaches the reactive center, resulting in much higher barrier than that of the (*R*)-enantiomer (see the SI for more details).

In conclusion, we have developed the first organocatalytic kinetic resolution of aziridines by sulfur nucleophiles. With this new protocol, efficient kinetic resolution of unactivated aziridines by sulfur nucleophiles has been demonstrated. The proper choice of a suitable chiral phosphoric acid catalyst enabled these reactions to proceed under mild conditions with good to excellent enantiocontrol, achieving selectivity factors among the highest in aziridine kinetic resolutions. The

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β-amino thioether products and the remained aziridines were all obtained with good to high enantiopurity. These molecules are important precursors to other synthetically useful chiral building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04074.

Experimental procedures, kinetic analysis, and spectral data; crystal data and structural refinement, atomic coordinates and displacement parameters, and bond lengths and angles for compound **3da**; DFT calculations with energies, structures, and atomic coordinates; deermination of absolute stereochemistry (PDF)

Accession Codes

CCDC 2022350 contains 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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