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Catalytic Enantioselective Intermolecular Desymmetrization of Azetidines

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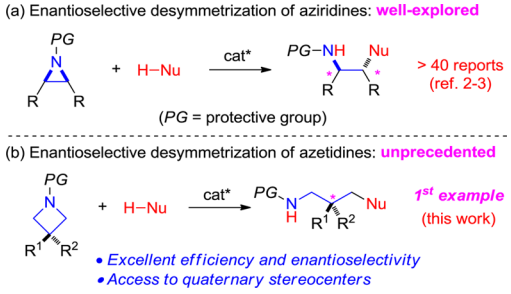
Supporting Information

ABSTRACT: The first catalytic asymmetric desymmetrization of azetidines is disclosed. Despite the low propensity of azetidine ring opening and challenging stereocontrol, smooth intermolecular reactions were realized with excellent efficiency and enantioselectivity. These were enabled by the suitable combination of catalyst, nucleophile, protective group, and reaction conditions. The highly enantioenriched densely functionalized products are versatile precursors to other useful chiral molecules. Mechanistic studies, including DFT calculations, revealed that only one catalyst molecule is involved in the key transition state, though both reactants can be activated. Also, the Curtin−Hammett principle dictates the reaction proceeds via amide nitrogen activation.

Enantioselective desymmetrization is a powerful strategy to access enantioenriched chiral molecules.[1] For example, asymmetric nucleophilic ring opening of *meso*-aziridines provides a rapid synthesis of highly useful chiral amine derivatives with vicinal stereocenters (Scheme 1a). As a result, various catalyst systems have been developed to achieve excellent efficiency and stereoselectivity for these processes, including those with chiral Brønsted acids, Lewis acids/bases, and phase-transfer catalysts.[2,3] However, in contrast to these well-established reactions of aziridines, their four-membered ring homologues— azetidines— have been much less-studied regarding their catalytic asymmetric opening reactions, although their synthesis, racemic reactions, and applications in medicinal chemistry have received increasing attention over the past few decades.[4,5] Indeed, enantioselective desymmetrization of the prochiral 3-substituted azetidines *remains unknown* (Scheme 1b).

Scheme 1. Enantioselective Desymmetrization of Aziridines and Azetidines



The challenge is partly due to the significantly lower ring-opening propensity of azetidines relative to aziridines.[4−6] Thus, to increase the nucleofugacity of the amine unit, an electron-withdrawing group is typically introduced (e.g., carbonyl for PG, Scheme 1). However, it may increase the difficulty in asymmetric induction due to the increased distance between the newly established stereogenic center and the catalyst activation site (e.g., the carbonyl oxygen upon LUMO-lowering activation).

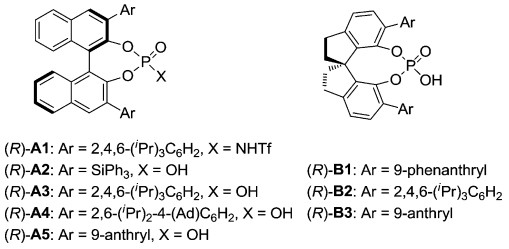
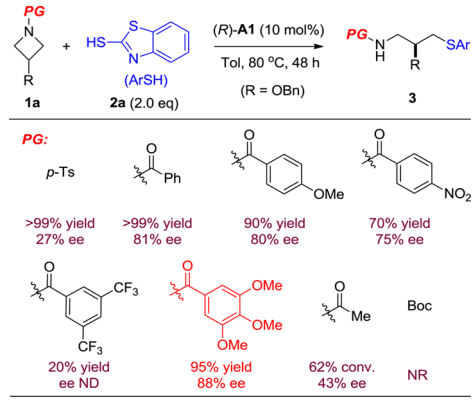


Figure 1. Chiral catalyst structures.

Scheme 2. Evaluation of Different Protective Groups[a]



[a]Yield based on ^{1}H NMR of the crude product with CH_2Br_2 as an internal standard. Ee value based on HPLC. ND = not determined.

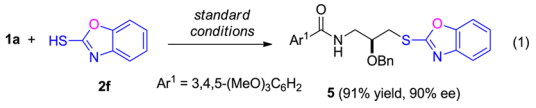


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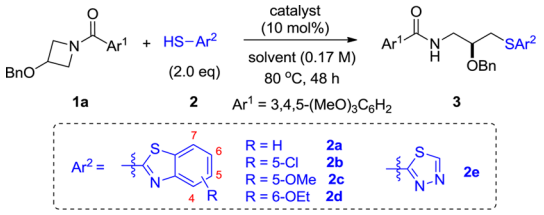
Table 1. Condition Optimization[a]



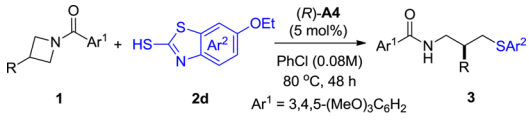
entry	catalyst	2	solvent	yield (%)[a]	ee (%)
1	(*R*)-**A2**	**2a**	toluene	53	53
2	(*R*)-**A3**	**2a**	toluene	99	88
3	(*R*)-**A4**	**2a**	toluene	99	91
4	(*R*)-**A5**	**2a**	toluene	99	48
5	(*R*)-**B1**	**2a**	toluene	89	−19
6	(*R*)-**B2**	**2a**	toluene	40	−65
7	(*R*)-**B3**	**2a**	toluene	53	−23
8	(*R*)-**A3**	**2b**	toluene	99	83
9	(*R*)-**A3**	**2c**	toluene	91	63
10	(*R*)-**A3**	**2d**	toluene	99	89
11	(*R*)-**A3**	**2e**	toluene	46	75
12	(*R*)-**A4**	**2a**	CPME	91	91
13	(*R*)-**A4**	**2a**	DCE	79	84
14	(*R*)-**A4**	**2a**	benzene	98	91
15	(*R*)-**A4**	**2a**	PhCl	94	92
16[b]	(*R*)-**A4**	**2d**	PhCl	97	93
17[b,c]	*(R)-**A4***	***2d***	*PhCl*	*94*	*94.5*
18[c,d]	(*R*)-**A4**	**2d**	PhCl	53	94
19[e]	(*R*)-**A4**	**2e**	PhCl	39	79

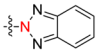
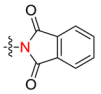
[a]Yield based on ^{1}HNMR of the crude product with CH_2Br_2 as an internal standard. Ee value based on HPLC. [b]Run with 5 mol % of **A4**. [c]Concentration = 0.08 M. [d]Run with 2.5 mol % of **A4** and 1.5 equiv of **2d**. [e]Run with 10 mol % of **A4** at 90 °C.

Therefore, it is a formidable challenge to balance reactivity and stereocontrol. In this context, herein we report the *first catalytic asymmetric intermolecular desymmetrization of azetidines* with excellent efficiency and enantioselectivity providing rapid access to highly functionalized chiral amine derivatives, including those with quaternary stereocenters.

Representative 3-monosubstituted azetidine substrates **1a** with various electron-withdrawing groups, including *p*-Ts and acyl groups, were employed for the study (Scheme 2). Inspired by the excellent catalytic ability of chiral phosphoric acids in a range of efficient enantioselective desymmetrization reactions,[7,8] we randomly chose a chiral phosphoric acid for the initial test of azetidine opening. However, to our disappointment, the exhaustive combination of these azetidines and various nucleophiles (including typical amines, alcohols, thiols, etc.) resulted in essentially no reaction at room temperature. This observation confirmed the low reactivity of azetidines. Next, we re-evaluated these reactions at 80 °C employing the relatively more acidic chiral catalyst *N*-triflyl phosphoramide **A1** (Figure 1).[9] While the majority of the nucleophiles were still unreactive, 2-mercaptobenzothiazole **2a** was found to be superior providing the desired ring-opening product **3**.[10] Quantitative yield was obtained with *p*-Ts protection, albeit with low enantioselectivity (27% ee). Subsequent evaluation of various *N*-acyl groups showed that the enantioselectivity could be significantly improved. Among them, the 3,4,5-trimethoxybenzoyl group proved best (95% yield, 88% ee). Its superior performance might

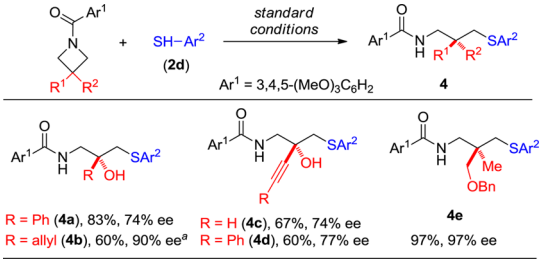
Table 2. Substrate Scope



entry	R	product	yield (%)[a]	ee
1	OBn	**3a**	96	95
2	OTBS	**3b**	93	97
3	O(allyl)	**3c**	98	85
4	O(propargyl)	**3d**	98	76
5	O(4-MeOC$_6$H$_4$)	**3e**	82	87
6	S(4-MeOC6H4)	**3f**	95	94
7[b]		**3g**	91	90
8		**3h**	98	99
9		**3i**	90	99
10	CH_2CN	**3j**	96	97
11	$CH_2{}^iPr$	**3k**	98	95
12	CH_2Ph	**3l**	95	97
13	Ph	**3m**	97	99
14	(*p*-F)C$_6$H$_4$	**3n**	96	97
15	(*p*-Cl)C$_6$H$_4$	**3o**	92	98
16	(*p*-CN)C$_6$H$_4$	**3p**	97	95
17	(*p*-OCF$_3$)C$_6$H$_4$	**3q**	83	97
18	(*p*-Ac)C$_6$H$_4$	**3r**	87	>99
19	(*m*-CF$_3$)C$_6$H$_4$	**3s**	96	>99
20		**3t**	77	98
21	2-Naphthyl	**3u**	73	98

[a]Isolated yield. [b]Run at 70 °C for 96 h.

Scheme 3. Formation of Quaternary Stereocenters



[a]Run at 70 °C for 96 h.

be partly due to its suitable electron-withdrawing ability, which is sufficient but not too strong to ensure both good nucleofugacity (leaving ability) and nitrogen basicity for effective acid activation and stereocontrol.

Aiming to further improve the enantioselectivity, we next carried out parallel optimizations of different reaction parameters (Table 1). Evaluation of various chiral phosphoric acid catalysts indicated that the BINOL-derived catalyst **A4** gave the highest enantioselectivity (entry 3).[11] Different analogous nucleophiles were also compared (entries 8−11). Thiol **2d** gave slightly better results than **2a** (entry 10). Solvent screening identified chlorobenzene as the best solvent (entry 15). Further studies

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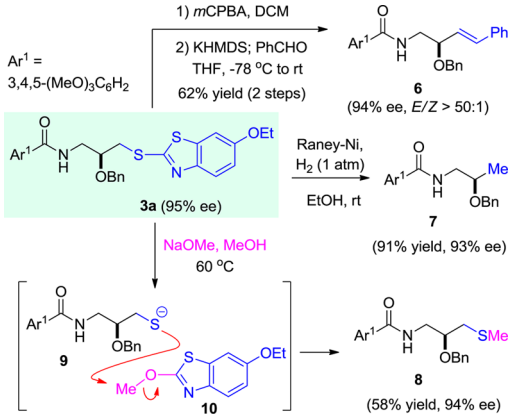
Scheme 4. Representative Product Transformations



on catalyst loading and concentration identified the optimal conditions with both excellent efficiency and remarkable enantioselectivity (entry 17). Thiol **2e** remained less reactive, even at a higher temperature (entry 19).

Under the standard conditions, a wide range of 3-azetidines smoothly participated in the intermolecular desymmetrization reactions (Table 2), providing a diverse set of densely functionalized three-carbon chiral building blocks **3** with excellent enantioselectivity. Alkyl-, aryl-, and heterosubstituents (e.g., O, S, N) at the 3-position all worked well. 3,3-Disubstituted azetidines are also suitable substrates generating the corresponding quaternary stereocenters with good to excellent enantioselectivity (Scheme 3). Particularly noteworthy is the formation of an all-carbon quaternary stereocenter in 97% ee (**4e**). The reaction conditions could tolerate a range of functional groups, including ethers (**3a**, **3c**–**e**, and **4e**), TBS-protected alcohols (**3b**), ketones (**3r**), acetals (**3t**), and free tertiary alcohols (**4a**–**d**). This is surprising considering the high temperature and acidic conditions. It is also worth noting that examples with excellent stereocontrol at such a high temperature are scarce in chiral phosphoric acid catalysis. All these results demonstrate the extraordinary robustness of our process.

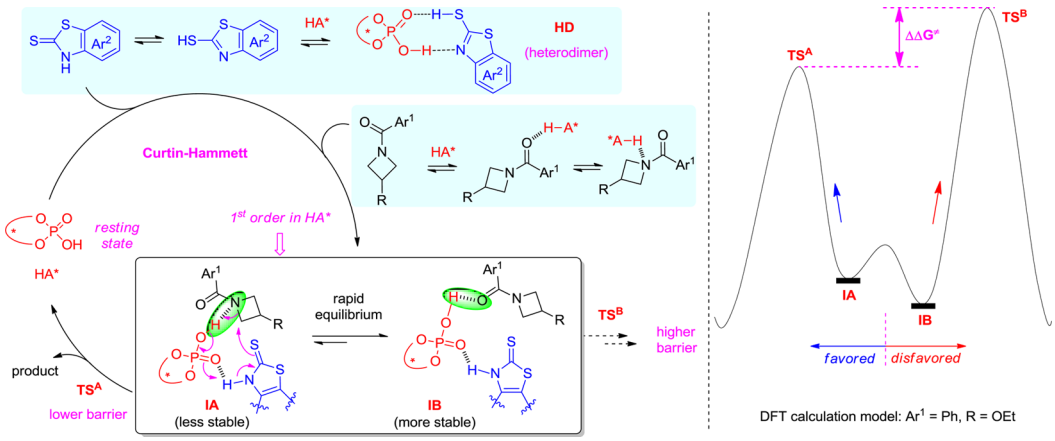
Benzoxazole-2-thiol (**2f**) could also serve as a nucleophile to form the ring-opening product **5** with excellent efficiency and high enantioselectivity (eq 1). It is worth noting that both benzothioazole and benzoxazole are important subunits in a wide range of natural products and biologically active molecules.[12]

The enantioenriched products from our reaction are both densely and diversely functionalized. They can be readily transformed to other useful chiral molecules (Scheme 4). Oxidation of the benzothiazole thioether **3a** by *m*CPBA generated the corresponding sulfone, which could serve as a Julia olefination reagent to synthesize alkene **6** with good overall efficiency. The thioether moiety in **3a** could be cleaved to form amide **7**.[13] Furthermore, in the presence of NaOMe/MeOH, substitution of the benzothiazole unit to form methylthioether **8** was observed. The reaction might proceed by initial methoxide substitution on the benzothiazole ring to form intermediates alkylsulfide **9** and 2-methoxybenzothiazole **10**, followed by an S_N2 reaction between them. Notably, no obvious erosion of optical purity was observed in any of these derivatizations.

To understand the reaction mechanism, we carried out a series of experimental and theoretical studies. First of all, we were interested to know whether the acid catalyst activates the azetidine, the nucleophile, or both species. Acid activation of the azetidine could enhance its electrophilicity by lowering its LUMO level (Scheme 5). On the other hand, the 2-mercaptobenzothiazole may also interact with the chiral phosphoric acid catalyst by forming a heterodimer (e.g., **HD**).[14] This interaction would raise its HOMO level, thereby increasing its nucleophilicity. Either activation mode could facilitate the reaction. Indeed, by mixing the acid catalyst with the azetidine or the nucleophile separately, we observed both activations by ^{31}P NMR (details in the SI). Thus, it may be envisioned that the two activated species approach each other to react in the rate- and stereo-determining transition state, in which two catalyst molecules would be involved. However, kinetic studies indicated that the reaction is first-order in catalyst (details in the SI), suggesting that only one catalyst molecule is involved (e.g., via **IA** or **IB**), which was also confirmed by DFT calculations.

Although acid activation on the amide carbonyl oxygen (i.e., **IB**) is generally accepted, nitrogen activation in geometrically constrained amides can also be possible. Our DFT calculations indicated that the oxygen-activated form **IB** is more stable than the nitrogen-activated form **IA**, which is consistent with the general belief.[15] However, further calculations suggested that it is the less stable nitrogen-activated **IA** that leads to a lower activation barrier. Thus, in view of the rapid equilibrium between **IA** and **IB**, the Curtin–Hammett principle applies.[16] Therefore, we propose that our reaction proceeds via nitrogen activation, in which the chiral catalyst is located closer to the reaction center for better asymmetric induction. This is also consistent with the

Scheme 5. Proposed Mechanism and Qualitative Reaction Diagram



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observed excellent stereocontrol even at high temperature. The corresponding catalytic cycle together with a qualitative energy diagram is depicted in Scheme 5.[17]

In conclusion, we developed the first catalytic enantioselective desymmetrization of azetidines. Despite the low propensity of azetidine ring opening and significant challenge in stereocontrol, the smooth intermolecular desymmetrization of a wide range of 3-substituted azetidines has been achieved with excellent efficiency and remarkable enantioselectivity, enabled by the optimal combination of catalyst, protective group, nucleophile, and reaction conditions. Both tertiary and quaternary stereocenters can be generated efficiently. The highly enantioenriched densely and diversely functionalized products can be easily transformed to other useful chiral building blocks. Mechanistically, although both reaction partners could be activated by the catalyst, only one catalyst molecule is involved in the bond-forming transition state according to kinetic studies and DFT calculations. Finally, although the carbonyl oxygen activation provides a more stable intermediate, the reaction proceeds with a lower overall barrier via nitrogen activation, which is consistent with the Curtin−Hammett principle and the observed excellent stereocontrol. Further studies on other asymmetric reactions of azetidines are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03083.

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Notes

The authors declare no competing financial interest.

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(13) The amide carbonyl group in **7** could also be cleaved (see the SI).

(14) Heterodimers of chiral phosphoric acids have been proposed by List and co-workers before. See refs 3c and 8b, c for examples.

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(17) The free catalyst was determined to be the catalyst resting state.

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