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Counterion-Induced Asymmetric Control on Azetidiniums: A Facile Access to Chiral Amines**

*Deyun Qian, Min Chen, Alex C. Bissember and Jianwei Sun**

Abstract: *Counterion-induced stereocontrol is a powerful tool in organic synthesis. However, such enantiocontrol on tetrahedral ammonium cations remains challenging. Herein we demonstrate the first example of using chiral anion phase-transfer catalysis to achieve intermolecular ring-opening of azetidiniums with excellent enantioselectivity (up to 97% ee). Precise control over the formation and reaction of the chiral ion pair as well as inhibition of the background reaction by the biphasic system is key to success.*

Quaternary ammonium salts have attracted considerable attention and found many applications in organic synthesis, including asymmetric catalysis. However, these species have been employed mainly as catalysts (e.g., cinchona alkaloid-derived phase-transfer catalysts)[1] or reagents (e.g., Selectfluor as an electrophilic fluorine source).[2] In contrast, the direct use of quaternary ammonium salts as substrates for catalytic asymmetric synthesis is rare.[3]

Azetidiniums are versatile synthons for the preparation of bioactive and organic targets.[4,5] They are susceptible to ring opening by nucleophiles due to inherent ring strain. Compared to neutral azetidines and oxetanes, their reactivity is much higher and may allow more mild conditions and more compatible nucleophiles. Enantioenriched azetidiniums are typically employed to furnish β-chiral amines by ring-opening, but unfortunately, the synthesis of these substrates is not straightforward.[4,5] Consequently, catalytic strategies that permit easy conversion of the readily available azetidinium species to enantioenriched amine products are particularly desirable. Indeed, enantioselective desymmetrization of the prochiral 3-substituted azetidiniums has not been developed. Such transformations would provide expedient access to *β*-chiral amines, a family of privileged structures present in a range of bioactive molecules, including various notable drug molecules.[6] Although several metal-catalyzed strategies have been devised to directly access *β*-chiral amines in an enantioselective manner,[7] few examples by organocatalytic methods have been developed.[8]

The cationic nature of azetidinium substrates suggests that the most straightforward tool for asymmetric induction would be the use of a chiral ion pair.[9,10] However, ion pair interaction is weaker than hydrogen bonding and thus expected to be more challenging in asymmetric induction relative to neutral azetidine opening.[11] Moreover, previous examples of chiral counter anion-directed asymmetric catalysis on prochiral electrophiles have mainly featured iminium and oxocarbenium cations with planar configuration in the reactive center, in which facial differentiation is relatively defined.[9,10] In contrast, the cationic center of azetidiniums is tetrahedral and the position of the counter anion is elusive. Furthermore, the clean exchange of the substrate counter anion by the catalytic chiral anion is required for exclusive asymmetric control, and background reaction should be inhibited (Fig. 1B). Finally, precise cooperation between the chiral ion pair and the nucleophile is required to achieve excellent enantioselectivity. Therefore, synergistic control on every stage of the process is needed.

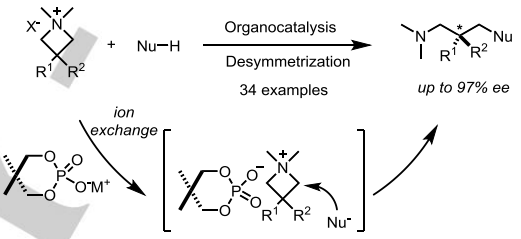

Figure 1. Counterion-induced asymmetric opening of azetidiniums.

With the above analysis, we envisioned chiral anion phase-transfer (CAPT) catalysis.[3,9,10] With this approach, a non-polar solvent should be employed so that the azetidinium salt substrate should be essentially insoluble. The catalyst would then provide a chiral organic counter anion, such as chiral phosphate, to pair with the azetidinium, and in the meanwhile increase the solubility of the chiral ion pair. In this scenario, the organic nucleophile then reacts in the solution phase to achieve both reactivity and asymmetric control. The background reaction of the insoluble substrate is thus inhibited due to ineffective contact with nucleophile.

We employed azetidinium **1a** as the model substrate and mercaptobenzothiazole **2a** as the nucleophile (Table 1). A chiral phosphoric acid catalyst was employed in conjunction with a suitable base to provide chiral anion.[12] In the presence of Na_2HPO_4 and a catalytic amount of (*R*)-TRIP (**A1**), the reaction in toluene proceeded smoothly *at room temperature* to give the desired product with good conversion, albeit with low enantioselectivity (24% ee, entry 1). Other SPINOL-derived chiral phosphoric acid (*S*)-**B4** provided the highest but still moderate selectivity (43% ee, entry 7). Next, using $PhCF_3$ as solvent led to slight improvement (58% ee, entry 8). Finally, evaluation of other nucleophiles identified thiol **2d** as the best reaction partner (90% ee, entry 12). Notably, other bases proved inferior (entries 12–14).

Table 1: Reaction optimization.

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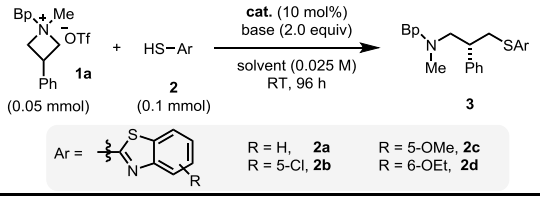
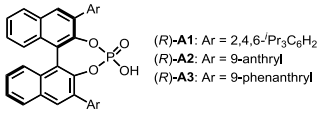
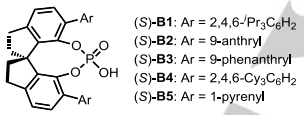


entry	cat.	2	base	solvent	conv [%][a]	ee [%][b]
1	**A1**	**2a**	Na_2HPO_4	toluene	76	24
2	**A2**	**2a**	Na_2HPO_4	toluene	>95	9
3	**A3**	**2a**	Na_2HPO_4	toluene	>95	6
4	**B1**	**2a**	Na_2HPO_4	toluene	>95	38
5	**B2**	**2a**	Na_2HPO_4	toluene	>95	26
6	**B3**	**2a**	Na_2HPO_4	toluene	>95	22
7	**B4**	**2a**	Na_2HPO_4	toluene	>95	43
8	**B4**	**2a**	Na_2HPO_4	$PhCF_3$	>95	58
9	**B4**	**2b**	Na_2HPO_4	$PhCF_3$	>95	47
10	**B4**	**2c**	Na_2HPO_4	$PhCF_3$	>95	42
11	**B4**	**2d**	Na_2HPO_4	$PhCF_3$	>95	90
12	**B4**	**2d**	Na_3PO_4	$PhCF_3$	>95	31
13	**B4**	**2d**	K_2HPO_4	$PhCF_3$	>95	16
14	**B4**	**2d**	Na_2CO_3	$PhCF_3$	>95	12

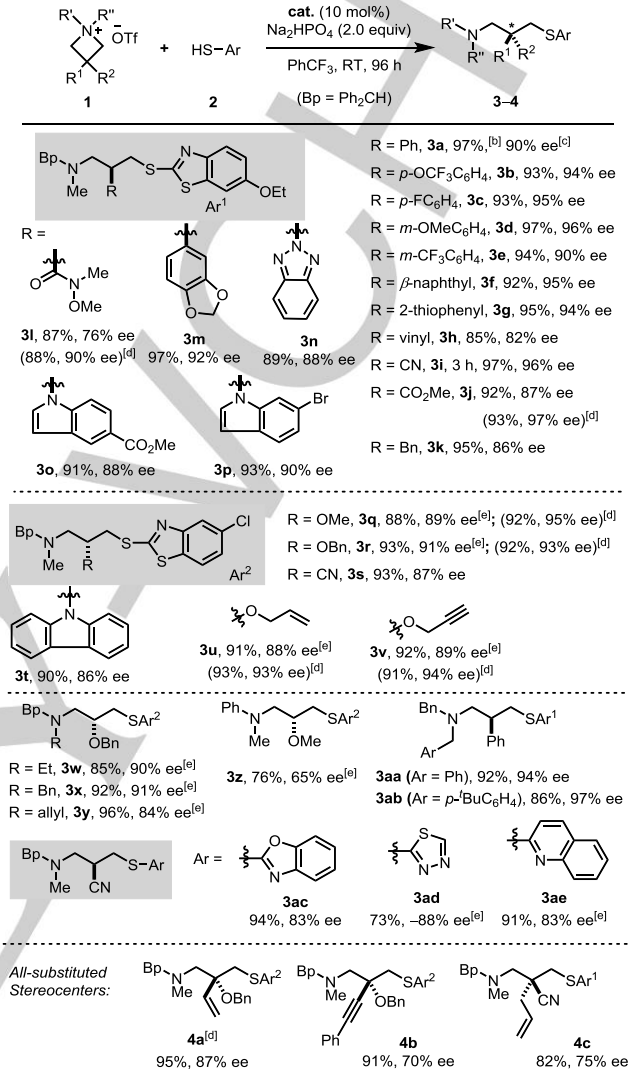




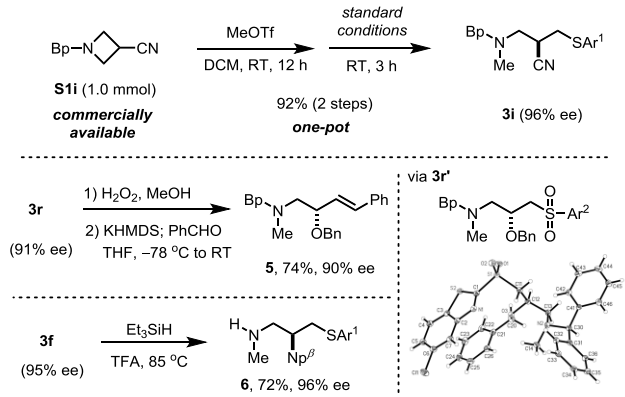
[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Determined by HPLC on chiral stationary phase. Bp = Ph_2CH.

A wide range of 3-azetidiniums smoothly participated in the mild desymmetrization process, directly providing a diverse set of densely functionalized *β*-chiral amines with good to excellent enantioselectivity (Scheme 1). Aryl-, alkenyl-, alkyl-, and hetero-substituents at the 3-position all worked well. Notably, nucleophile **2b** was also excellent, provided that catalyst **B2** is used for this nucleophile (**3q-3z**). 3,3-Disubstituted azetidiniums successfully lead to the formation of quaternary stereocenters (**4a-c**). The reaction conditions could tolerate a range of functional groups, including acetals, nitriles, esters, Weinreb amide, ethers, etc. Substrates featuring various *N*-alkyl and *N*-aryl substituents provided access to a range of chiral amine products (**3w–3ab**) that can be readily functionalized or derivatized. Other thiols, such as benzoxazole-2-thiol, 1,3,4-thiadiazole-2-thiol, and quinolone-2-thiol, are all useful nucleophiles. Although some of the substrates were used as mixtures of two diastereoisomers (**3g–j**, **3l–n**, **3q–s**, **3u–z**, **3ab–ae**, and **4b–c**), excellent stereocontrol could still be achieved, demonstrating extraordinary robustness of our process.[8–11]

The reaction products could be readily derivatized (Scheme 2). A one-pot reaction from the commercially available azetidine **S1i** efficiently furnished product **3i**. Furthermore, oxidation of thioether **3r** by H_2O_2 generated Julia olefination reagent **3r'**, which was used to synthesize alkene **5**. The absolute configuration of **3r'** was confirmed by X-ray crystallography. Finally, the benzydryl (Bp) group could be easily cleaved.



Scheme 1. Reaction scope. [a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), catalyst (0.02 mmol); (*S*)-**B2** for **3q–3z**, **3ad**, and **4a;** (*S*)-**B5** for **4b**; (*R*)-**B4** for all others, $PhCF_3$ (8.0 mL), RT, 96 h. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase. [d] Run with *cis*-**1** at RT, 6–24 h. [e] Run at 5 °C, 96 h.



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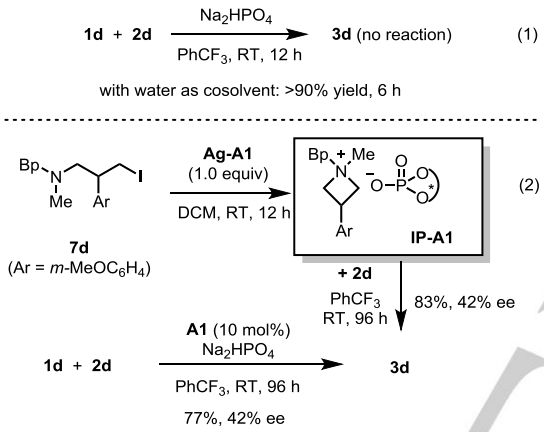
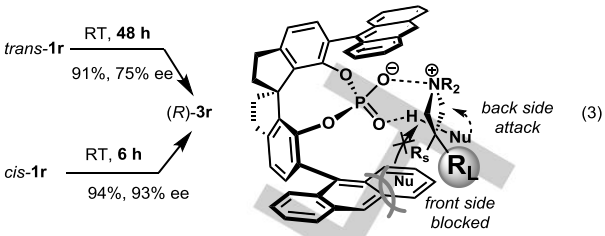
Scheme 2. Product transformations.

We carried out control experiments to understand the reaction mechanism. The background reaction of **1d** and **2d** did not proceed in the absence of catalyst (Eq. 1). In contrast, an aqueous-organic biphasic system smoothly promoted the background reaction. The results indicate the standard liquid-solid biphasic system is effective and critically important for clean ion exchange to ensure exclusive enantiocontrol via the chiral ion pair intermediate. Mixing iodide **7d** with silver phosphate salt **Ag-A1** provided chiral azetidinium phosphate salt **IP-A1**.[13] Treating this salt with nucleophile **2d** in $PhCF_3$ directly led to the formation of the ring-opening product (83% yield, 42% ee, Eq. 2). For direct comparison, the standard protocol from azetidinium **1d** with catalyst **A1** provided essentially the same level of enantiocontrol. These results agree well with the mechanistic proposal involving chiral ion pair.



Furthermore, the *cis* and *trans* isomers of **1r** were separately subjected to the reaction conditions. Interestingly, both led to **3r** favoring the same (*R*)-enantiomer, but the *cis* isomer reacted with higher enantioselectivity and much faster rate (Eq. 3).[14a] To explain this stereoconvergence, we proposed a transition state model, in which the ammonium motif provides ion-pairing interaction. The azetidinium ring is oriented with the larger substituent (R_L) pointing against the catalyst pocket to minimize steric clash. An additional hydrogen bond between the nucleophile and the phosphoryl oxygen increases its nucleophilicity and also helps achieve a pseudo bifunctional scenario.[14b] The nucleophile then approaches the back side, as the front side is blocked by the catalyst substituent. Thus, the product stereochemical outcome has little dependence on the relative *cis/trans* configuration of substrates or the size difference between the two substituents on the nitrogen, which is consistent with the experimental results (e.g., **3aa**). The higher reactivity of the *cis* isomer could be explained by the higher energy (*vs. trans* isomer) due to steric repulsion between the two large groups on the same face of the four-membered ring. It may also benefit from a better fit into the tight transition state. The lower enantioselectivity observed with the slower *trans* isomer might also be partly due to the relatively faster background reaction.



In conclusion, we have developed the first catalytic enantioselective desymmetrization of azetidiniums. The reaction provides rapid access to a wide range of *β*-chiral amine derivatives with high enantioselectivity under mild conditions. These highly enantioenriched and densely functionalized products can be easily transformed to other useful chiral building blocks. Mechanistically, a suitable chiral anion phase transfer (CAPT) catalytic system is critically important for precise control over each stage of the process. It also represents a rare example of excellent asymmetric induction by chiral counter anions on tetrahedral cations.

Keywords: asymmetric catalysis • phase-transfer catalysis • small ring systems • chirality • organocatalysis

[1] a) T. Hashimoto, K. Maruoka, *Chem. Rev*. **2007**, *107*, 5656-5682; b) S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348; *Angew. Chem.* **2013**, *125*, 4408-4445; For selected examples, see: c) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc*. **1999**, *121*, 6519-6520; d) Y. Wu, L. Hu, Z. Li, L. Deng, *Nature* **2015**, *523*, 445-450.

[2] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212; *Angew. Chem*. **2005**, *117*, 196-217.

[3] a) G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc*. **2008**, *130*, 14984-14986; b) T. H. West, D. S. B. Daniels, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc*. **2014**, *136*, 4476-4479.

[4] a) F. Couty, G. Evano, *Synlett* **2009**, *19*, 3053-3064; b) T. M. Bott, F. J. West, *Heterocycles* **2012**, *84*, 223-264; c) F. Couty, B. Drouillat, G. Evano, O. David, *Eur. J. Org. Chem*. **2013**, 2045-2056.

[5] a) G. Kalaus, N. Malkieh, I. Katana, M. Kajtár-Peredy, T. Koritsánszky, A. KálmAn, L. Szabó, C. Szántay, *J. Org. Chem.* **1985**, *50*, 3760-3767; b) F. Couty, F. Durrat, G.; Evano, D. Prim, *Tetrahedron Lett*. **2004**, *43*, 7525-7528; c) F. Couty, O. David, F. Durrat, G. Evano, S. Lakhdar, J.; Marrot, M. Vargas-Sanchez, *Eur. J. Org. Chem*. **2006**, 3479-3490; d) D.-H. Leng, D.-X. Wang, J. Pan, Z.-T. Huang, M.-X. Wang, *J. Org. Chem*. **2009**, *74*, 6077-6082; e) M. Buchman, K. Csatayová, S. G. Davies, A. M. Fletcher, I. T. T. Houlsby, P. M. Roberts, S. M. Rowe, J. E. Thomson, *J. Org. Chem*. **2016**, *81*, 4907-4922.

[6] a) *Chiral Amine Synthesis*, (Eds.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; For selected examples, see: b) T. Huang, J. Sun, L. An, L. Zhang, C. Han, *Bioorg. Med. Chem. Lett*. **2016**, *26*, 1854-1859; c) M. Nettekoven, J.-M. Plancher, H. Richter, O. Roche, S. Taylor, PCT Int. Appl. WO US 2007/0135416 A1, **2007**; d) H. Shibata, K. Yonezawa, Y. Mori, K. Shimizu, JP09235278A, Japan, **1997**; e) P. R. Blakemore, *J. Chem. Soc. Perkin Trans.1* **2002**, 2563–2585.

[7] For selected recent reports, see: a) Z. Lu, A. Wilsily, G. C. Fu, *J. Am. Chem. Soc*. **2011**, *133*, 8154-8157; b) Y. Takeda, Y. Ikeda, A. Kuroda, S. Tanaka, S. Minakata, *J. Am. Chem. Soc*. **2014**, *136*, 8544-8547; c) S. Zhu, S. L. Buchwald, *J. Am. Chem. Soc*. **2014**, *136*, 15913-15916; d) B. P. Woods, M. Orlandi, C.-Y. Huang, M. S. Sigman, A. G. Doyle, *J. Am. Chem. Soc*. **2017**, *139*, 5688-5691; e) D. Wang, F. Wang, P. Chen, Z. Lin, G. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 2054-2058; *Angew. Chem.* **2017**, *129*, 2086-2090; f) D. Wang, L. Wu, F. Wang, X. Wan, P. Chen, Z. Lin, G. Liu, *J. Am. Chem. Soc*. **2017**, *139*, 6811-6814.

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[8] a) S. Hoffmann. M. Nicoletti, B. List, *J. Am. Chem. Soc*. **2006**, *128*, 13074-13075; b) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc*. **2008**, *130*, 13862-13863.

[9] a) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem*. **2012**, *4*, 603-614; b) M. Mahlau, B. List, *Angew. Chem. Int. Ed*. **2013**, *52*, 518-533; *Angew. Chem.* **2013**, *125*, 540-556; c) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed*. **2013**, *52*, 534-561; *Angew. Chem.* **2013**, *125*, 558-588; d) D. Parmar,E. Sugiono, S. Raja, M. Rueping, *Chem. Rev*. **2014**, *114*, 9047-9153.

[10] a) A. D. Lackner, A. V. Samant, F. D. Toste, *J. Am. Chem. Soc*. **2013**, *135*, 14090-14093; b) F. Romanov-Michailidis, L. Guénée, A. Alexakis, *Angew. Chem. Int. Ed.* **2013**, *52*, 9266-9270; *Angew. Chem*. **2013**, *125*, 9436-9440; c) W. Q. Xie, G. D. Jiang, H. Liu, J. D. Hu, X. X. Pan, H. Zhang, X. L. Wan, Y. S. Lai, D. W. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12924-12927; *Angew. Chem*. **2013**, *125*, 13162-13165; d) H. M. Nelson, S. H. Reisberg, H. P. Shunatona, J. S. Patel, F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 5600-5603; *Angew. Chem*. **2014**, *126*, 5706-5709; e) Z. Shen, X. Pan, Y. Lai, J. Hu, X. Wan, X. Li, H. Zhang, W. Xie, *Chem. Sci*. **2015**, *6*, 6986-6990; f) Z. Yang, Y. He, F. D. Toste, *J. Am. Chem. Soc*. **2016**, *138*, 9775-9778.

[11] For neutral azetidine opening, the reaction requires high temperature: a) Z. Wang, F. K. Sheong, H. H. Y. Sung, I. D. Williams, Z. Lin, J. Sun, J., *J. Am. Chem. Soc.* **2015**, *137*, 5895−5898. For examples of related oxetane desymmetrization reactions, see: b) Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun, *Angew. Chem. Int. Ed.* **2013**, *52*, 2027−2031; c) Z. Wang, Z. Chen, J. Sun, *Angew. Chem. Int. Ed.* **2013**, *52*, 6685−6688; d) W. Yang, J. Sun, *Angew. Chem. Int. Ed.* **2016,** *55*, 1868−1871; e) W. Yang, Z. Wang, J. Sun, *Angew. Chem. Int. Ed.* **2016,** *55*, 6954−6958.

[12] For pioneering works of chiral phosphoric acid catalysis, see: a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357; b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568; *Angew. Chem*. **2004**, *116*, 1592-1594; For selected examples involving chiral phosphate anion catalysis, see: c) S. Mayer, B. List, *Angew. Chem. Int. Ed.* **2006**, *45*, 4193-4195; *Angew. Chem*. **2006**, *118*, 4299-4301; d) T. Liang, Z. Zhang, J. C. Antilla, *Angew. Chem. Int. Ed.* **2010**, *49*, 9734-9736; *Angew. Chem*. **2010**, *122*, 9928-9930; e) M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732-3735; f) H. Qian, H. W. Zhao, Z. Wang, J. Sun, J. *J. Am. Chem. Soc*. **2015**, *137*, 560-563; g) H. Wu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 15411-15414; *Angew. Chem.* **2016**, *128*, 15637-15640; h) J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu, B. Tan, *J. Am. Chem. Soc*. **2015**, *137*, 14039-14042; i) Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8883-8886; *Angew. Chem*. **2017**, *129*, 9009-9012.

[13] Unfortunately, the analogous silver phosphate salts from the optimal catalyst **B2** or **B4** were not successfully made. See SI for more details.

[14] a) When a 1:1 mixture of diastereomers was used, the product *ee* value decreased over the reaction progress due to the fact that the faster *cis* isomer provides higher *ee* at early conversion; b) The mercaptobenzothiazole nucleophiles have low solubility in $PhCF_3$ and low acidity (vs. chiral phosphoric acid), so complete deprotonation by the base in forming ion pair with azetidinium is unlikely.

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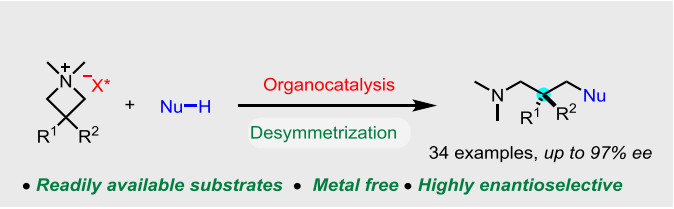

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Counterion-induced asymmetric induction over tetrahedral ammonium cations is useful but remains challenging. Herein we demonstrate the use of chiral anion phase transfer catalysis to achieve ring-opening reactions of tetrahedral azetidiniums with enantioselectivity (up to 97% ee). Precise control over the formation and reaction of the key chiral ion pair as well as inhibition of the background reaction by the biphasic system is key to success.

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