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Enantioselective Addition of Thiols to Imines Catalyzed by Thiourea–Quaternary Ammonium Salts

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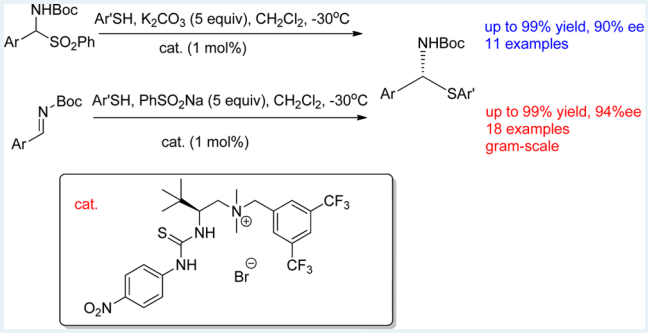
Supporting Information

ABSTRACT: Asymmetric phase-transfer catalysis was first applied to the synthesis of chiral N,S-acetals by using amino acid-based bifunctional thiourea-ammonium salt catalysts. The reaction could be performed on the gram scale to give up to 93% ee and 99% yield with a catalyst loading as low as 0.1 mol % within 5 min.



KEYWORDS: *N,S-acetal, organocatalysis, ion-pairs catalysis, phase-transfer catalysis, bifunctional catalyst*

N,S-acetals are important structural motifs present in numerous biologically active natural products. For example, the penicillium fungi derivative penicillin (**I**),[1,2] a family of *β*-lactam antibiotics for bacterial infections; fusaperazine A (**II**),[3] a bioactive natural product; the fungal metabolites *epi*-dithiodioxopiperazines (**III**),[4−6] unique natural products against parasites, viruses, bacteria and cancer cells; and the *epi*-dithioketopiperzine alkaloid (+)-11,11′-dideoxyverticillin A (**IV**)[7] all contain chiral N,S-acetal subunits (Figure 1). Therefore, the development of efficient synthetic methods for accessing these useful N,S-acetal compounds has been an attractive field for organic chemists.[8−12]

Among the various methods developed, the addition of thiols to imines stands out as an efficient direct strategy for the synthesis of N,S-acetals, especially for the development of enantioselective versions. To the best of our knowledge, until now, the only two asymmetric methods for this were based on this strategy. Antilla and co-workers reported their seminal work in 2011,[13] in which chiral phosphoric acids were found to be efficient in catalyzing the addition of thiols to N-acyl imines derived from aromatic aldehydes. Later, Wang and co-workers used cinchona-derived squaramides to catalyze the asymmetric addition of thiols to fluorinated aldimines (Scheme 1).[14] These two catalytic systems were all mainly based on similar acid–base bifunctional strategy through H-bond interactions. The potential of ion-pairs catalysis,[15−28] as an important and challenging catalytic strategy in organic chemistry, for this particular transformation has been unexplored until now. Phase-transfer catalysis as the outstanding ion-pairs catalysis has shown remarkable success in other relevant reactions, such as asymmetric Mannich reactions.[29−36] The "S" atom in

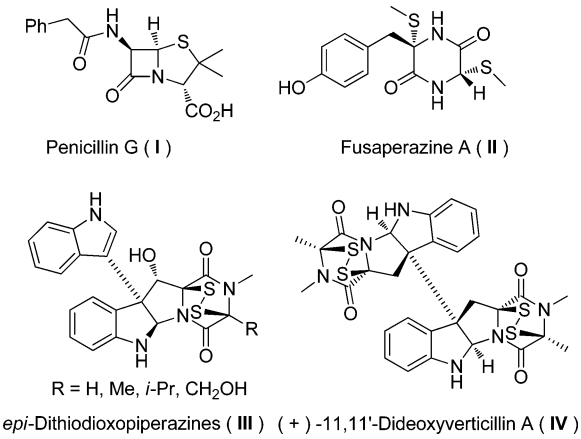


Figure 1. Representative biological molecules containing chiral N,S-acetal motifs.

nucleophile-mediated synthetic reactions catalyzed by chiral phase-transfer catalysts has been rare investigated. To the best of our knowledge, only two examples have been reported, by Dai[37] and Wang,[38] about the desymmetrization of aziridines with thiols catalyzed by cinchonine-derived chiral phase-transfer catalysts. Therefore, the asymmetric synthesis of N,S-acetals is a challenging project for the addition of thiols to imines catalyzed by phase-transfer catalysts. Moreover, the extension of the

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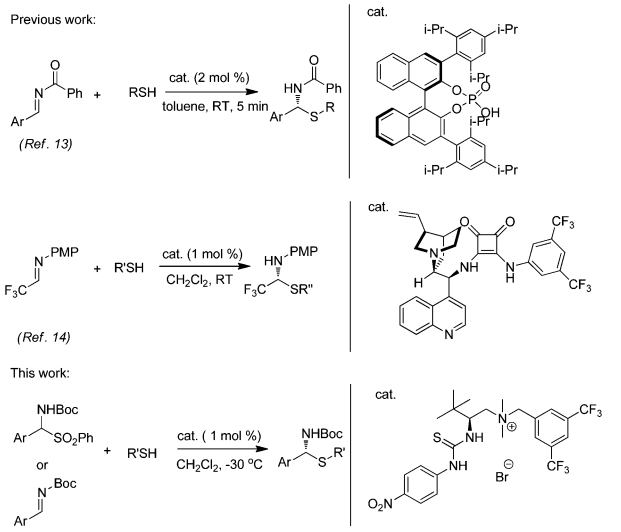
Scheme 1. Asymmetric Addition of Thiols to Imines



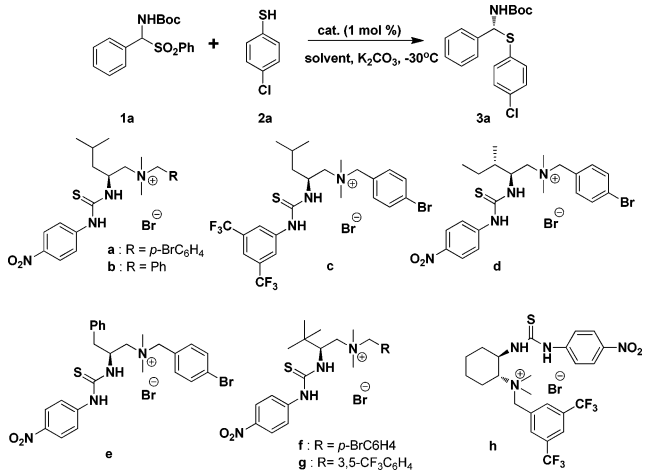
asymmetric version of this reaction to common N-Boc imines also is of current interest.

Inspired by the works from Deng,[39] Dixon[40] and Maruoka,[41,42] our group has first imported thiourea groups into phase-transfer catalysts based on acyclic natural amino acids, building bifunctional catalysts for highly enantioselective aza-Henry reactions.[43,44] The easy availability as well as highly modular structures of these novel bifunctional phase-transfer catalysts enable fine-tuning of catalytic activities for different specific reactions. As part of our ongoing project on extending the application scope of these catalysts, we herein describe the highly enantioselective addition of thiols to N-Boc-protected amidosulfones or imines to provide N,S-acetals catalyzed by bifunctional thiourea-ammonium salt catalysts.

Initially, we selected the reaction between thiol **2a** and amidosulfone **1a** as a model reaction for optimization of reaction conditions in the presence of catalyst **a**, an efficient catalyst for the aza-Henry reaction in our previous report[43] (Table 1). In toluene at −30 °C, the reaction proceeded efficiently to provide the desired product **3a** in 99% yield and 35% ee (Table 1, entry 1). The screen of several different solvents revealed that CH_2Cl_2 was more suitable for this reaction, with 55% ee (Table 1, entry 4). Next, we systematically examined the influence of the structures of these bifunctional phase-transfer catalysts on their catalytic efficiency in this transformation (Table 1, entries 7−11). Catalysts **a**−**g** derived from L-amino acid with different substituents at the thiourea moiety, chiral backbone, and the ammonium center were examined, and catalyst **g** bearing the 3,5-bistrifluoromethylbenzyl group derived from *tert*-butyl leucine was found to be more suitable for this reaction (Table 1, entry 12), with which 90% ee was obtained. We also prepared a novel catalyst derived from cyclohexanediamine; however, no better ee value was obtained (−35% ee, Table 1, entry 13).

Under the optimized conditions, we then surveyed the substrate scope of this reaction with different thiols and amidosulfones, and the results are summarized in Table 2. It is worth mentioning that all the examined reactions gave the desired products in almost quantitative yields. For different thiophenols, electron-poor and electron-rich aromatic thiophenols gave good and moderate enantioselectivities (Table 2,

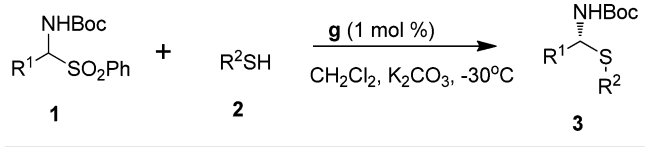
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	ee (%)[b]
1	**a**	Toluene	35
2	**a**	TBME	20
3	**a**	$PhCF_3$	45
4	**a**	CH_2Cl_2	55
5	**a**	$Cl(CH_2)_2Cl$	50
6	**a**	$CHCl_3$	54
7	**b**	CH_2Cl_2	40
8	**c**	CH_2Cl_2	50
9	**d**	CH_2Cl_2	70
10	**e**	CH_2Cl_2	52
11	**f**	CH_2Cl_2	79
12	**g**	CH_2Cl_2	90
13	**h**	CH_2Cl_2	−35

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), and K_2CO_3 (0.5 mmol) in solvent (4 mL) in the presence of a catalyst (1 mol %) to give **3a** in 99% yield. Reaction time, 5 h. [b]Determined by HPLC analysis.

Table 2. Scope Study with Different Amidosulfones and Thiophenols[a]



entry	**1**, R^1	**2**, R^2	**3**	ee (%)[b]
1	**1a**, Ph	**2a**, *p*-ClC_6H_4	**3a**	90
2	**1a**, Ph	**2b**, *p*-FC_6H_4	**3b**	82
3	**1a**, Ph	**2c**, *p*-BrC_6H_4	**3c**	74
4	**1a**, Ph	**2d**, Ph	**3d**	75
5	**1a**, Ph	**2e**, 2-naphthyl	**3e**	80
6	**1a**, Ph	**2f**, *p*-MeC_6H_4	**3f**	75
7	**1b**, *p*-FC_6H_4	**2g**, *p*-ClC_6H_4	**3g**	79
8	**1c**, *p*-MeC_6H_4	**2a**, *p*-ClC_6H_4	**3h**	83
9	**1d**, *p*-$MeOC_6H_4$	**2a**, *p*-ClC_6H_4	**3i**	75
10	**1e**, *p*-$NO_2C_6H_4$	**2a**, *p*-ClC_6H_4	**3j**	47
11	**1f**, 1-naphthyl	**2a**, *p*-ClC_6H_4	**3k**	70
12	**1g**, 2-thienyl	**2a**, *p*-ClC_6H_4	**3l**	84

[a]Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), and K_2CO_3 (0.5 mmol) in CH_2Cl_2 (4 mL) in the presence of **g** (1 mol %) to give 99% yield in 5 h. [b]Determined by HPLC analysis.

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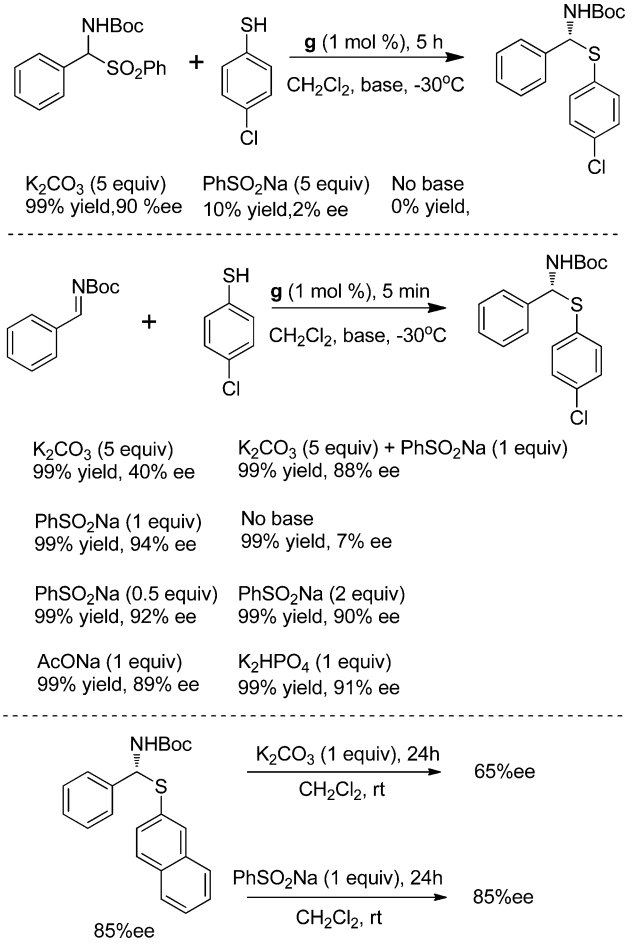
entries 1−6). Different amidosulfones bearing moderate electron-withdrawing/donating substituents also gave better enantioselectivities than strong electron-withdrawing substituents in this reaction (Table 2, entries 7−11). In addition, we surveyed aliphatic thiol; for example, benzyl mercaptan gave only a racemic product. Notably, the heteroaromatic substrate **1g** also participated in the reaction well to give a good ee value (Table 2, entry 12).

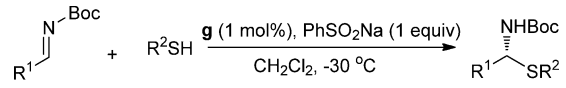
It has been reported that preformed imines might give better results in some asymmetric reaction than imines in situ generated from amidosulfone.[45,46] To further explore the reaction scope as well as to improve the enantioselectivities, we performed some control experiments to test the role of imines and amidosulfones (Scheme 2). Under weaker base and no base conditions, the amidosulfones gave poor yields and enantioselectivities because the imines could not be well formed during the transition state. To our delight, the preformed imines improved the ee value to 94% using only 1 equiv of $PhSO_2Na$; however, K_2CO_3 gave only 40% ee. A moderate result (88% ee) was obtained with mixed use of K_2CO_3 and $PhSO_2Na$, so we think a strong base could lead the products to racemization because of the instabilities of the N,S-acetals. Then we performed a control experiment to check the role of K_2CO_3 and $PhSO_2Na$ on the product. To a vial containing the base in CH_2Cl_2 was added **4e** at room temperature. The mixture was stirred for 24 h, and we found the enantioselectivity of **4e** was lowered to only 65% ee using the K_2CO_3; however, using the weak base $PhSO_2Na$, an 85% ee value was obtained, which was the same as the original enantioselectivity of **4e**.

Scheme 2. Control Experiments for Improving Enantioselectivities



Under the superior conditions, we explored the scope and limitation of the imines. As shown in Table 3, to our delight, generally higher enantioselectivities could be achieved when preformed N-Boc imines were used. Electron-donating and electron-withdrawing substituents on both the thiols and aromatic imines all gave good to excellent ee values and yields within a short reaction time of 5 min. Notably, the reaction could be performed on gram scale to give the desired product with high enantioselectivity and yield within the same short time with a catalyst loading of **g** as low as 0.1 mol % (Table 3, entry 18). The absolute configuration of the N,S-acetal **4e** was determined to be *R* by X-ray cratallographic analysis, and the others were assigned by analogy (see the Supporting Information for more details).

Table 3. Scope Study with Preformed Imines[a]



1′ 2′ 4

entry	1′, R^1	2′, R^2	4	ee (%)[b]
1	**1′a**, Ph	**2′a**, *p*-ClC_6H_4	**4a**	94
2	**1′a**, Ph	**2′b**, *p*-FC_6H_4	**4b**	87
3	**1′a**, Ph	**2′c**, *p*-BrC_6H_4	**4c**	91
4	**1′a**, Ph	**2d**, Ph	**4d**	80
5	**1′a**, Ph	**2′e**, 2-naphthyl	**4e**	85
6	**1′a**, Ph	**2′f**, *p*-MeC_6H_4	**4f**	79
7	**1′a**, Ph	**2′g**, *m*-ClC_6H_4	**4g**	90
8	**1′b**, *p*-FC_6H_4	**2′a**, *p*-ClC_6H_4	**4h**	95
9	**1′c**, *p*-MeC_6H_4	**2′a**, *p*-ClC_6H_4	**4i**	86
10	**1′d**, *p*-$MeOC_6H_4$	**2′a**, *p*-ClC_6H_4	**4j**	86
11	**1′e**, 1-naphthyl	**2′a**, *p*-ClC_6H_4	**4k**	78
12	**1′f**, 2-thienyl	**2′a**, *p*-ClC_6H_4	**4l**	89
13	**1′g**, *p*-ClC_6H_4	**2′a**, *p*-ClC_6H_4	**4m**	86
14	**1′h**, *p*-BrC_6H_4	**2′a**, *p*-ClC_6H_4	**4n**	79
15	**1′i**, *p*-$CF_3C_6H_4$	**2′a**, *p*-ClC_6H_4	**4o**	77
16	**1′j**, *m*-ClC_6H_4	**2′a**, *p*-ClC_6H_4	**4p**	85
17	**1′k**, *o*-FC_6H_4	**2′a**, *p*-ClC_6H_4	**4q**	75
18[c]	**1′a**, Ph	**2′a**, *p*-ClC_6H_4	**4a**	93

[a]Unless otherwise noted, all reactions were carried out with **1′** (0.1 mmol), **2′** (0.2 mmol), and $PhSO_2Na$ (0.1 mmol) in CH_2Cl_2 (4 mL) in the presence of **g** (1 mol %) to give 99% yield in 5 min. [b]Determined by HPLC analysis. [c]The reaction was carried out with **1′a** (10 mmol), **2′a** (20 mmol), and $PhSO_2Na$ (10 mmol) in CH_2Cl_2 (100 mL) catalyzed by **g** (0.1 mol %) in 5 min; 99% yield was received.

In summary, we have reported the first synthesis of novel chiral N-Boc-protected N,S-acetals by using asymmetric phase-transfer catalysis. These amino acid-based bifunctional thiourea−quaternary ammonium salts demonstrated high catalytic efficiency in the reaction, which could be carried out on gram scale with catalyst loading as low as 0.1 mol % to complete within 5 min. Further investigation of the "S" atom and related nucleophile-mediated reactions catalyzed by chiral thiourea−ammonium salt phase-transfer catalysts are under way in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Details of condition optimization, experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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