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Chiral Tertiary Sulfonium Salts as Effective Catalysts for Asymmetric Base-Free Neutral Phase-Transfer Reactions

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Dedicated to Professor Shoichi Shimizu on the occasion of his 60th birthday

Abstract: Although chiral quaternary ammonium and phosphonium salts are commonly used for asymmetric organocatalysis, the catalytic ability of chiral tertiary sulfonium salts has yet to be demonstrated in asymmetric synthesis. Herein, we show that chiral bifunctional trialkylsulfonium salts catalyze highly enantioselective conjugate additions of 3-substituted oxindoles to maleimides under base-free neutral phase-transfer conditions.

Chiral onium salts are recognized as some of the most reliable compounds in asymmetric synthesis (Figure 1).^[1–5] Various types of chiral quaternary ammonium and phosphonium salts have been synthesized, particularly over the past two decades.^[1,2] These compounds have been employed as chiral phase-transfer catalysts, and have enabled a wide variety of efficient enantioselective transformations.^[3] On the other hand, the catalytic ability of chiral tertiary sulfonium salts has yet to be demonstrated in asymmetric synthesis, despite the utility of these chiral compounds as reagents in stereoselective reactions.^[4,5] The limitations of chiral sulfonium salt catalysts have been attributed mainly to the high reactivity and instability of the compounds with acidic α -hydrogen atoms.^[6] The corresponding sulfonium ylides are thought to be formed from alkylsulfonium salts under ordinary basic phase-transfer conditions, and as a result, the catalytic activity of the sulfonium salts is lost. To avoid this problem and realize efficient asymmetric reactions with chiral sulfonium salt catalysts, we became interested in a base-free neutral phase-transfer reaction system.^[7] The formation of sulfonium ylides from sulfonium salts can be suppressed under base-free, neutral conditions. Under such conditions, chiral sulfonium salt catalysts could efficiently promote asymmetric neutral phase-transfer reactions with a high level of enantioselectivity. Herein, we report the development

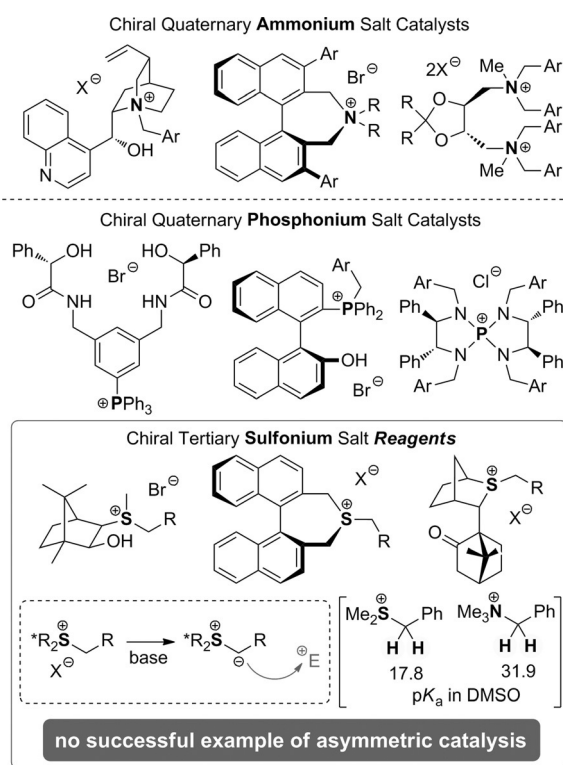
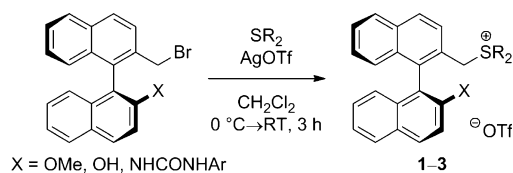


Figure 1. Chiral onium salts in organic synthesis.

of chiral tertiary sulfonium salt catalysts for highly enantioselective conjugate additions under base-free neutral phase-transfer conditions.^[8]

To achieve highly enantioselective phase-transfer reactions with chiral sulfonium salt catalysts, we employed a binaphthyl backbone as the chiral scaffold for the synthesis of the catalysts. The target chiral tertiary sulfonium triflates **1–3** (Scheme 1 and Table 1) were readily prepared in a similar manner, which involved a reaction of the corresponding binaphthol-derived arylmethyl bromide and dialkyl sulfide in



Scheme 1. Synthesis of chiral sulfonium salt catalysts. Tf = trifluoromethanesulfonyl.

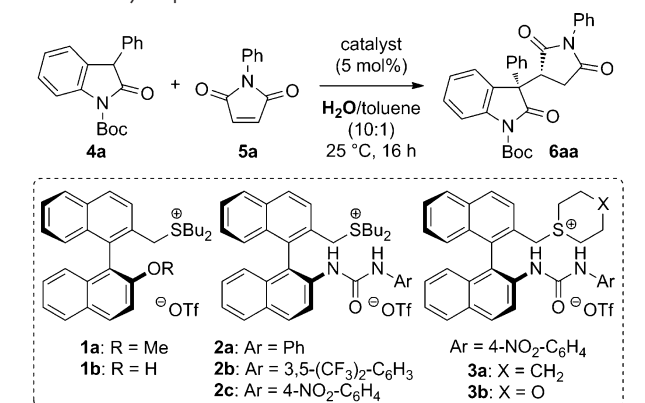
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the presence of silver triflate (see the Supporting Information for details).

As a model reaction to examine the ability of chiral sulfonium salts **1–3**, asymmetric conjugate additions of 3-substituted oxindoles **4** to maleimides **5** under base-free conditions were selected (Table 1).^[9] The reaction between 3-phenyloxindole **4a** and *N*-phenylmaleimide (**5a**) in H₂O/

Table 1: Catalyst optimization.^[a]



Entry	Catalyst	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	1a	< 5	—	—
2	1b	24	70:30	4
3	2a	31	86:14	74
4	2b	77	88:12	83
5 ^[e]	2c	64	92:8	91
6	3a	53	88:12	81
7	3b	15	74:26	76

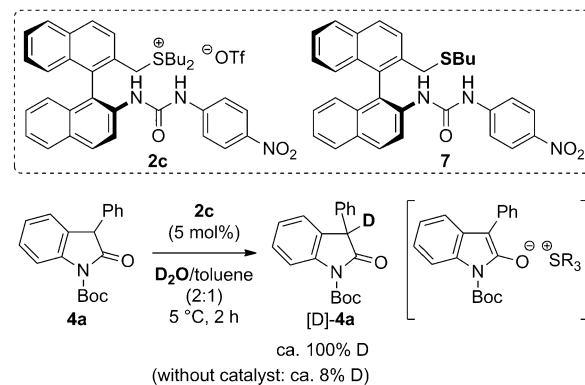
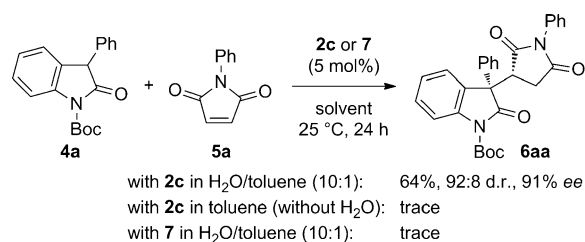
[a] Reaction conditions: **4a** (0.070 mmol), **5a** (0.084 mmol), catalyst (5 mol%, 0.0035 mmol), H₂O (2.0 mL)/toluene (0.2 mL), 25 °C, 16 h.

[b] Yield of isolated product **6aa**. [c] Determined by ¹H NMR and HPLC analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

[e] Reaction time: 24 h. Boc = *tert*-butoxycarbonyl.

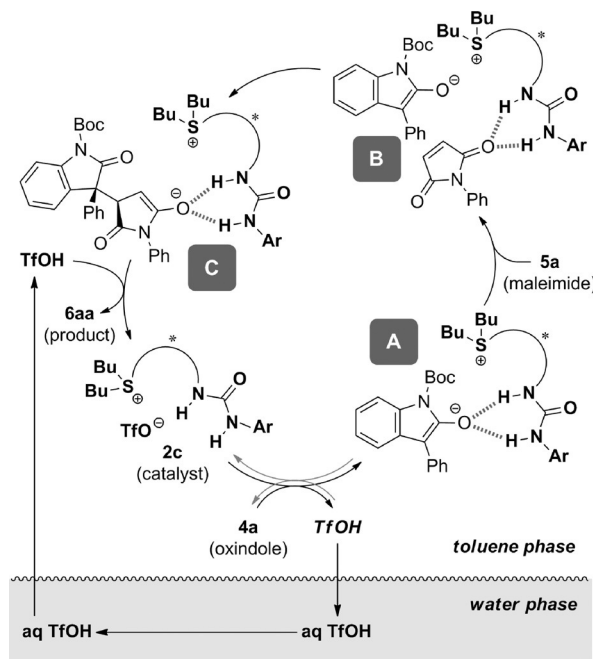
toluene (10:1) was run in the presence of catalyst **1a** or **1b** (5 mol%) at 25 °C for 16 h. Whereas methoxy-substituted catalyst **1a** afforded only a trace amount of product **6aa** (entry 1), the bifunctional catalyst **1b** with a hydroxy group promoted the reaction to give **6aa** in moderate yield, albeit with low enantioselectivity (4% *ee*; entry 2). These results suggested that a bifunctional catalyst design was beneficial to the reaction. Encouraged by this result, we next examined bifunctional sulfonium salts **2**, which also possess a urea group (entries 3–5).^[10] To our delight, phenylurea-substituted catalyst **2a** gave the product **6aa** in good diastereo- and enantioselectivity (74% *ee*; entry 3). Further tuning of the urea moiety on catalyst **2** improved both the yield and the stereoselectivity (entries 4 and 5), and the highest levels of diastereo- and enantioselectivity were achieved with catalyst **2c** (91% *ee*; entry 5).^[11,12] Changes in the alkyl groups on the sulfonium moiety (catalysts **3**) did not improve the results (entries 6 and 7).

Several control experiments were performed to clarify the mechanism of the present reaction (Scheme 2). We first examined the effect of H₂O on the base-free neutral phase-transfer reaction. Whereas this reaction was efficiently



Scheme 2. Control experiments.

promoted by catalyst **2c** in a H₂O/toluene biphasic solvent mixture, the reaction did not take place in a homogeneous toluene system.^[13] To clarify the importance of the sulfonium salt moiety on catalyst **2c**, the reaction with sulfide catalyst **7** was also examined in a H₂O/toluene biphasic system. Compound **7** was not able to catalyze the present base-free neutral phase-transfer reaction, that is, the tertiary sulfonium salt moiety of catalyst **2c** was essential in promoting the reaction. Furthermore, deuteration experiments were performed with 3-phenyloxindole **4a**. Treatment of **4a** with catalyst **2c** in



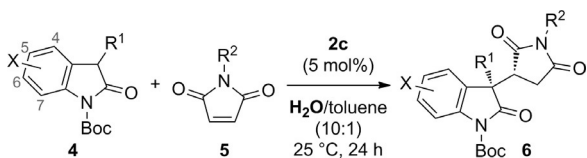
Scheme 3. Proposed catalytic cycle.

a D₂O/toluene biphasic system at 5 °C for 2 h returned deuterated 3-phenyloxindole, [D]-**4a**, in quantitative yield. However, in the absence of a catalyst, [D]-**4a** was obtained in only 8 % yield. These results completely agree with previous observations for base-free neutral phase-transfer reactions with quaternary ammonium and phosphonium salt catalysts, and indicate that the reaction proceeds via a sulfonium enolate intermediate.^[7h,i]

Based on these observations, a catalytic cycle for the present reaction was proposed (Scheme 3). For the reaction to proceed, the H₂O/toluene biphasic solvent mixture was indispensable. When the reaction was carried out in toluene without H₂O, the reversible reaction with oxindole **4a** and sulfonium salt **2c** to form sulfonium enolate **A** was not favored owing to the facile protonation of sulfonium enolate **A** with in situ generated TfOH. On the other hand, when the reaction was performed in the H₂O/toluene biphasic solvent system, the generated TfOH was moved into the aqueous phase. Consequently, contact between sulfonium enolate **A** and TfOH was suppressed, and the formation of sulfonium enolate **A** was promoted. The urea moiety of catalyst **2c** interacted with maleimide **5a** via hydrogen bonds, thus returning a well-organized complex **B**. It is noteworthy that hydrogen-bonding interactions between the α -hydrogen atoms of the trialkylsulfonium salt moiety^[14] on catalyst **2c** and the substrates may also be important in organizing the transition-state structure.^[15] A highly stereoselective conjugate addition then occurred to give intermediate **C**. Protonation of intermediate **C** by TfOH, which was generated during the reaction of sulfonium triflate **2c** with oxindole **4a**, afforded product **6aa** with regeneration of sulfonium salt catalyst **2c**.

Having proposed a plausible catalytic cycle, we examined the generality of the asymmetric conjugate addition with various 3-substituted oxindoles **4** and maleimides **5** under base-free neutral phase-transfer conditions (Table 2). Not only *N*-aryl maleimides (**5a–5c**) but also *N*-alkyl maleimides (**5d**) were found to be suitable substrates for the reaction to give products **6** with high enantioselectivities (86–91 % *ee*; entries 1–4). Furthermore, a wide variety of 3-aryl oxindoles **4** with electron-withdrawing and -donating substituents on both the 3-aryl group and the oxindole core were also applicable, and uniformly gave high diastereo- and enantioselectivities (83–93 % *ee*; entries 5–18).^[16] Unfortunately, 3-alkyl oxindoles, such as a 3-butyloxindole **4e**, showed low reactivity in this reaction system (entry 9).

Table 2: Scope and limitation.^[a]



Entry	4	X	R ¹	5	R ²	Product	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1	4a	H	Ph	5a	Ph	6aa	64	92:8	91
2 ^[e]	4a	H	Ph	5b	4-MeO-C ₆ H ₄	6ab	42	86:14	86
3 ^[f]	4a	H	Ph	5c	4-CF ₃ -C ₆ H ₄	6ac	60	87:13	86
4 ^[e]	4a	H	Ph	5d	Me	6ad	17	89:11	86
5	4b	H	4-Me-C ₆ H ₄	5a	Ph	6ba	45	85:15	83
6 ^[f]	4b	H	4-Me-C ₆ H ₄	5c	4-CF ₃ -C ₆ H ₄	6bc	54	85:15	83
7	4c	H	3-Me-C ₆ H ₄	5a	Ph	6ca	28	83:17	88
8	4d	H	4-F-C ₆ H ₄	5a	Ph	6da	59	90:10	83
9	4e	H	Bu	5a	Ph	6ea	< 5	–	–
10	4f	5-Me	Ph	5a	Ph	6fa	46	87:13	83
11	4g	5-F	Ph	5a	Ph	6ga	81	88:12	90
12 ^[f]	4g	5-F	Ph	5c	4-CF ₃ -C ₆ H ₄	6gc	70	96:4	93
13	4h	6-Cl	Ph	5a	Ph	6ha	66	92:8	88
14	4i	7-F	Ph	5a	Ph	6ia	61	88:12	83
15 ^[f]	4i	7-F	Ph	5c	4-CF ₃ -C ₆ H ₄	6ic	73	89:11	84
16	4j	5-F	4-Me-C ₆ H ₄	5a	Ph	6ja	66	90:10	86
17	4k	5-F	4-F-C ₆ H ₄	5a	Ph	6ka	85	89:11	84
18 ^[f]	4k	5-F	4-F-C ₆ H ₄	5c	4-CF ₃ -C ₆ H ₄	6kc	56	92:8	85

[a] Reaction conditions: **4** (0.070 mmol), **5** (0.084 mmol), **2c** (5 mol%, 0.0035 mmol), H₂O (2.0 mL)/toluene (0.2 mL), 25 °C, 24 h. [b] Yield of isolated product **6**. [c] Determined by ¹H NMR and HPLC analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction time: 16 h. [f] At 0 °C.

In summary, we have successfully demonstrated that chiral tertiary sulfonium salt catalysts can promote asymmetric reactions with a high level of enantioselectivity. Binaphthyl-modified bifunctional sulfonium salts bearing a urea group were efficient catalysts for the asymmetric conjugate addition of 3-substituted oxindoles to maleimides under base-free neutral phase-transfer conditions. To the best of our knowledge, this is the first example of a highly enantioselective reaction catalyzed by a chiral tertiary sulfonium salt.

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Conflict of interest

The authors declare no conflict of interest.

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