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

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

Shiyao Liu,[a] Keiji Maruoka,[b] and Seiji Shirakawa*[a]

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

Abstract: Although chiral quaternary ammonium and phosphonium salts are recognized as representative asymmetric organocatalysts, the catalytic ability of chiral tertiary sulfonium salts has yet to be aptly demonstrated in an asymmetric synthesis. Herein, we demonstrate the catalytic ability of chiral bifunctional trialkylsulfonium salts in 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 developed, particularly in the past two decades.[1,2] These compounds have been employed as chiral phase-transfer catalysts, and have achieved 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 well in an 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. Given that scenario, chiral sulfonium salt catalysts could efficiently promote asymmetric neutral phase-transfer reactions with a high level of enantioselectivity. Herein, we report the development 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 catalysts. The target chiral tertiary sulfonium triflates 1–3 (Scheme 1; see also, Table 1) were readily prepared in a similar manner, which involved a reaction with the corresponding binaphthol-derived arylmethyl bromides and dialkyl sulfides in the presence of silver triflate (For details, see the Supporting Information).

Scheme 1. Synthesis of chiral sulfonium salt catalysts.
As a model reaction to examine the ability of chiral sulfonium salts 1–3, the 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 H$_2$O/toluene (10:1) took place in the presence of catalysts 1a or 1b (5 mol %) at 25 °C for 16 h. Although methoxy-substituted catalyst 1a afforded only a trace amount of product 6aa (entry 1), a hydroxy group possessing bifunctional catalyst 1b promoted the reaction to give 6aa in a moderate yield, albeit with low enantioselectivity (4% ee, entry 2). These results suggested that the bifunctional design of the catalysts was beneficial to the reaction. Encouraged by this result, we next examined bifunctional sulfonium salts 2, which 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 stereoselectivity (entries 4 and 5), and the highest levels of diastereo- and enantioselectivity were obtained with catalyst 2c (91% ee, entry 5).[11,12] The change in the alkyl groups on a sulfonium moiety (catalysts 3) did not improve the results (entries 6 and 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield [b]</th>
<th>d.r. [c]</th>
<th>ee [%] [d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>&lt;5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>24</td>
<td>70:30</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>31</td>
<td>86:14</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>77</td>
<td>88:12</td>
<td>83</td>
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<tr>
<td>5[c]</td>
<td>2b</td>
<td>64</td>
<td>92:8</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>53</td>
<td>88:12</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>15</td>
<td>74:26</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 1. Effect of catalysts.

[a] Reaction conditions: 3-phenyloxindole 4a (0.070 mmol), N-phenylmaleimide 5a (0.084 mmol), catalyst (5 mol %, 0.0035 mmol), H$_2$O (2.0 mL)/toluene (0.2 mL), 25 °C, 16 h. [b] Yield of the isolated product 6aa. [c] Determined by 'H NMR and HPLC analyses. [d] Determined by HPLC analysis. [e] Reaction time = 24 h.

Several control experiments were performed to clarify the mechanism for the present reaction (Scheme 2). We first examined the effect of H$_2$O for the base-free neutral phase-transfer reaction. Although this reaction was efficiently promoted by catalyst 2c in the H$_2$O/toluene biphasic solvent, the homogeneous reaction in toluene was completely shut off.[15] To clarify the importance of the sulfonium salt moiety on catalyst 2c, the reaction with sulfide catalyst 7 was also examined in H$_2$O/toluene biphasic solvent. The catalyst 7 showed no catalytic ability in the present base-free neutral phase-transfer reaction, that is, the tertiary sulfonium salt moiety of catalyst 2c was essential in promoting the reaction. Additionally, deuterium experiments of 3-phenyloxindole 4a were performed. Treatment of 4a with catalyst 2c in D$_2$O/toluene biphasic solvent at 5 °C for 2 h returned a deuterated 3-phenyloxindole 4a-D in a quantitative yield. However, in the absence of a catalyst, the 4a-D was obtained in only an 8% yield. These results completely agreed with the previous observations for base-free neutral phase-transfer reactions with quaternary ammonium and phosphonium salt catalysts, and indicated that the reaction proceeds via the sulfonium enolate intermediate.[17,18]

Scheme 2. Control experiments.

Based on these observations, a catalytic cycle for the present reaction is proposed in Scheme 3. For the reaction to proceed, the H$_2$O/toluene biphasic solvent was indispensable. When the reaction was carried out in toluene without H$_2$O, the reversible reaction with oxindole 4a and sulfonium salt 2c to form sulfonium enolate A was not favored due to the facile protonation of sulfonium enolate A with in situ-generated TfOH. On the other hand, when the reaction was performed in an H$_2$O/toluene biphasic solvent, the generated TfOH was moved into the aqueous phase. Consequently, the 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 transition state B. It was noteworthy that hydrogen-bonding interactions between the hydrogen atoms of the trialkylsulfonium salt moiety[19] on catalyst 2c and substrates may also be an important step in organizing the transition state structure.[20] A highly stereoselective conjugate addition occurred to give intermediate C. The protonation of intermediate C by TfOH, which was generated upon the reaction...
of sulfonium triflate 2c with oxindole 4a, afforded product 6aa with a regeneration of sulfonium salt catalyst 2c.

With the assumed catalytic cycle in hand, we examined the generality of the asymmetric conjugate additions of various 3-substituted oxindoles 4 to 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 employable for the reaction to give the products 6 with high enantioselectivities (86–91% ee, entries 1–4). Furthermore, a wide variety of 3-aryloxindoles 4 possessing electron-withdrawing and -donating substituents on both the 3-aryl group and the oxindole core were also applicable to this reaction, and uniformly gave high diastereome- and enantioselectivities (83–93% ee, entries 5–18).

Unfortunately, 3-alkyloxindoles, such as a 3-butyloxindole 4e, showed low reactivity in this reaction system (entry 9).

Table 2. Scope and limitation.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>4 (X)</th>
<th>4 (R¹)</th>
<th>5 (R²)</th>
<th>Yield [%]</th>
<th>d.r. [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>Ph</td>
<td>64</td>
<td>92:8</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Ph</td>
<td>4-MeO-C6H4</td>
<td>42</td>
<td>86:14</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>4-CF3-C6H4</td>
<td>60</td>
<td>87.13</td>
<td>86</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: oxindole 4 (0.070 mmol), maleimide 5 (0.084 mmol), catalyst 2c (5 mol %, 0.0035 mmol), H2O (2.0 mL)/toluene (0.2 mL), 25 °C, 24 h.
[b] Yield of the isolated product 6. [c] Determined by 1H NMR and HPLC analyses.
[d] Determined by HPLC analysis.
[e] Reaction time = 16 h. [f] Reaction temperature = 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 additions of 3-substituted oxindoles to maleimides under base-free neutral phase-transfer conditions. As far as could be ascertained, this is the first example of a highly enantioselective reaction catalyzed by chiral tertiary sulfonium salts.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • ion pairs • organocatalysis • phase-transfer catalysis • sulfur

Fan et al, examined a chiral tertiary sulfonium salt-catalyzed asymmetric conjugative addition under ordinary phase-transfer conditions using Ag2CO3 as a base, and the product was obtained in 0% ee, see: X.-Z. Zhang, Y.-H. Deng, X.-Y. Yu, F.-X. Wang, X.-Y. Ma, C.-A. Fan, J. Org. Chem. 2008, 81, 5655.


The remaining starting materials 4a and 5a were observed after the reaction.

The longer reaction time did not improve the yield.

The effect of water amount was also examined (Scheme S1 in Supporting Information).

The catalytic ability of chiral bifunctional trialkylsulfonium salts was demonstrated in highly enantioselective conjugate additions of 3-substituted oxindoles to maleimides under base-free neutral phase-transfer conditions.