Synthesis of Novel $C_2$-Symmetric Sulfur-Based Catalysts: Asymmetric Formation of Halo- and Seleno-Functionalized Normal- and Medium-Sized Rings

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Abstract The synthesis of novel, highly functionalized, $C_2$-symmetric sulfur-based catalysts is developed and their catalytic applications are explored in asymmetric bromo-, iodo- and seleno-functionalizations of alkenoic acids. This protocol provides the corresponding normal- and medium-sized bromo, iodo and selenolactones in up to 98% yield and 83% stereoselectivity.

Key words alkenoic acids, organosulfur catalysts, asymmetric catalysis, halolactones, selenolactones

The group 16 donor atoms sulfur (S), selenium (Se) and tellurium (Te) act as Lewis bases. The Lewis base catalyzed halogenation of organic substrates, in which an n−σ* interaction between a Lewis base chalcogenide and a Lewis acidic halogen source leads to an electrophilic halogenation between a Lewis base chalcogenide and a Lewis base, has been well documented in the literature.1 Denmark et al. established a variety of chiral and achiral Lewis bases, such as selenides and sulfides, for the activation of halogenation reactions by utilizing chalcogenide-based catalysts.2 In 2012, Yeung and co-workers reported the synthesis of medium-sized seven-membered bromolactones using a sulfur-based organocatalyst.3 However, catalytic asymmetric halogenation of medium-sized rings has not yet been explored. In contrast to the enantioselective halogenation of five- and six-membered rings,4 enantioenriched medium-sized halo- lactones are rare, despite their potential applications in the synthesis of biologically relevant molecules.5

Sulfide-catalyzed electrophilic bromination of various substrates has been achieved. Yeung and co-worker reported the triphenylphosphine sulfide catalyzed bromocyclization of amides to afford oxazolidines and oxazines.6 Similarly, Mukherjee and Tripathi described selective oxidation of secondary alcohols with NBS using a thiourea derivative as the catalyst.7 Moreover, Denmark and Burk accomplished the iodolactonization of alkenoic acids with N-iodosuccinimide catalyzed by the Lewis base, $n$-Bu$_3$P=S.3c

Numerous methodologies have been reported for the catalytic, enantioselective bromofunctionalization of alkenes.8d,9,10 In 2010, Yeung et al. developed a thiocarbamate which acts as a Lewis base for the enantioselective bromofunctionalization of alkenes. This sulfur-based catalyst has been employed in the cyclization of various disubstituted alkenes to obtain enantioenriched halolactones, 3-bromopyrrolidines, and 3,4-dihydroisocoumarins,10h,11

Our group has also been actively involved in selenium-catalyzed halocyclizations of alkenoic acids, where selenium plays a vital role in the transformation.12 Inspired by our recent development of the regioselective synthesis of medium-sized bromoiodolactones and bromooxepanes using a catalytic amount of a monoselenide (Scheme 1a),12b herein we present our results on the stereoinduction of normal- and medium-size rings (Scheme 1b). Studies on catalytic, enantioselective, chalcogenide-catalyzed medium-sized halogenation reactions are still lacking. Furthermore, the cyclization of linear-chain alkenoic acids is not a favorable process due to enthalpic and entropic factors.12d Substrates with an alkyl chain possess a high degree of flexibility that brings a negative entropy change during intramolecular cyclization reactions.13 Therefore, significant research is still required for the preparation of new chiral Lewis bases and diverse structural analogues.
In continuation of our studies on organochalcogen chemistry,\textsuperscript{12,14} we rationalized that the Lewis base sulfur would be able to activate a halogen for the synthesis of highly strained, medium-sized rings. Thus, we have designed a range of novel C\textsubscript{2}-symmetric sulfur-based chiral catalysts for the synthesis of enantioenriched bromolactones. Initially, the bromolactonization of 4-phenyl-4-pentenoic acid (1a) was carried out using 1.2 equivalents of NBS and 5 mol\text% of the chiral catalyst in dichloromethane at –78 °C. We screened thiophene dicarboxylates such as (–)-menthol-based cat 1 and found that it catalyzed the bromolactonization reaction, however, no enantioselectivity was observed (Scheme 2).

Further, we attempted to incorporate a nitrogen-based chiral scaffold to make an effective chiral catalyst and chose various cinchona alkaloid as skeletons. However, the resulting catalysts, quinine cat 2 and cinchonine cat 3 (Scheme 2), had no effect on the enantioselectivity and only racemic mixtures were obtained. Surprisingly, changing the skeleton to dihydroquinine (DHQN) cat 4 (Scheme 2) resulted in an enantioselectivity (ee) of 31%. To further improve the enantioselectivity, we explored the impact of the ligand on the structure of the catalyst. Two sites in the catalyst were tuned: (i) the ester and amide units, and (ii) the O-alkoxy substituents on the hydroquinine unit, which was accomplished by demethylation followed by alkylation. The C\textsubscript{2}-symmetry of the scaffold also simplified the catalyst design and modification. Moreover, different substituents have been introduced to tune the steric hindrance. The catalyst was modified by demethylation using sodium ethylthiolate followed by incorporation of different alkyl chains such as n-butyl, n-hexyl, tert-butyl, iso-butyl, 2-butane and 2-methylpropane\textsuperscript{15} (Scheme 3). Similarly, the azide formed from the O-mesylated derivative of DHQN followed by azide reduction and hydrolysis provided 9-amino-(9-deoxy)-epi-cinchona alkaloids (DHQN-NH\textsubscript{2})\textsuperscript{16} Thus, the alkoxy or amine derivative of the cinchona alkaloid was treated with...
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2,5-thiophenedicarbonyl dichloride under basic conditions to afford catalysts cat 5–9 and cat 10–12, respectively. These bifunctional sulfur-based catalysts were then subjected to the asymmetric bromocyclization reaction.

When the reaction of 1a and NBS was conducted with C2-symmetric sulfur-based cat 5 (5 mol%) in dichloromethane (CH2Cl2), the desired bromolactone 2a was obtained in 88% yield with poor enantioselectivity (36% ee) within 16 hours (Table 1, entry 1). Next, various solvent systems were explored to improve the selectivity of the reaction. We observed that among several solvents, including dichloromethane, chloroform and toluene, the reaction in the less polar solvent hexane proceeded with modest enantioselectivity (45% ee) (entries 2–4). On varying the polarity with mixed solvent systems, CHCl3/hexane (1:2) showed the highest efficiency with an optimum 83% ee being obtained (entries 5–9). The nonpolar solvent mixture reduced the noncatalyzed reaction and strengthened the polar interaction among the alkenoic acid, NBS, and the catalyst, resulting in enhancement of the enantioselectivity. The hexyl substitution on the quinolone moiety of thiophene dicarboxylate cat 6, under the same conditions, gave a lower enantioselectivity (entry 10). Similarly, reactions with cat 7, cat 8 and cat 9 occurred with low enantioselectivity (entries 11–13). Furthermore, screening the efficient isopinocampheylamine/cinchonine framework, endeavoring to increase the acidity of the carboxylate in cat 10–12 by replacement with an amide functional group, however, resulted in a racemic mixture for cat 10, moderate 52% ee for cat 11 (entry 14), and 43% ee for cat 12, respectively. Also, the use of additives failed to improve the stereoselectivity.

Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cat 5</td>
<td>CH2Cl2</td>
<td>16</td>
<td>88</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>cat 5</td>
<td>toluene</td>
<td>20</td>
<td>75</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>cat 5</td>
<td>CHCl3</td>
<td>28</td>
<td>85</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>cat 5</td>
<td>hexane</td>
<td>30</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>cat 5</td>
<td>toluene/CH2Cl2 (1:1)</td>
<td>35</td>
<td>87</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>cat 5</td>
<td>CHCl3/toluene (1:1)</td>
<td>32</td>
<td>85</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>cat 5</td>
<td>CHCl3/toluene (1:2)</td>
<td>10</td>
<td>81</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>cat 5</td>
<td>CHCl3/hexane (1:1)</td>
<td>24</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>cat 5</td>
<td>CHCl3/hexane (1:2)</td>
<td>31</td>
<td>97</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>cat 6</td>
<td>CHCl3/hexane (1:2)</td>
<td>88</td>
<td>92</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>cat 7</td>
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<td>68</td>
<td>87</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>cat 8</td>
<td>CHCl3/hexane (1:2)</td>
<td>80</td>
<td>89</td>
<td>66</td>
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<td>13</td>
<td>cat 9</td>
<td>CHCl3/hexane (1:2)</td>
<td>50</td>
<td>92</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>cat 11</td>
<td>CHCl3/hexane (1:2)</td>
<td>40</td>
<td>85</td>
<td>52</td>
</tr>
</tbody>
</table>

* All reactions were carried out with 1a (0.1 mmol), NBS (0.12 mmol) and the chiral catalyst (5 mol%) in 2 mL of solvent at –78 °C in a 10 mL Schlenk tube under nitrogen. The reaction progress was monitored by TLC.

b Yield of isolated 2a.

c Enantiopurity was determined by HPLC analysis using a ChiralPak IC-3 column.
Having optimized the catalyst and reaction conditions, we next investigated the substrate scope. A broad range of 4-phenyl-4-pentenoic acids containing aromatic substituents on the olefin was converted into the corresponding bromolactones with high yields and good to moderate enantioselectivities (Figure 1). In particular, better results were obtained with the substrates 1b and 1c having electron-rich methyl and methoxy groups at the para positions of the aromatic rings, with the lactones 2b and 2c being obtained with 82% and 66% ee, respectively. Electron-deficient fluoro-, chloro-, and difluoro-substituted substrates 1d–f provided bromolactones 2d–f with good enantioselectivities (43–66%). The X-ray crystal structure of 4-fluorophenyl γ-lactone 2d is shown in Figure 1. Biphenyl-substituted alkenoic acid 1g provided bromolactone 2g with moderate selectivity (27% ee).

When N-iodosuccinimide (NIS) was used as the halogen source, γ-iodolactone 2h was formed with 31% enantiomeric excess. By utilizing this protocol, five-membered selenolactone 2i was also prepared with 13% enantioselectivity and 62% yield. Furthermore, when 5-phenyl-5-hexanoic acid was subjected to the bromocyclization with NBS in the presence of 5 mol% of chiral catalyst 5 in CHCl3/hexane (1:1) at −60 °C, the desired product 2aa was obtained with 34% ee.

Next, the synthesis of various seven-membered bromo- and iodolactones was explored starting from the corresponding alkenoic acids (Figure 2). Bromolactone 3a with a phenyl ring attached was obtained as a racemic mixture using the developed protocol. Lactones 3b–i having an additional heteroatom in the chain were obtained in good to excellent yields (22–82%) and moderate to low enantiomeric excesses, which can be attributed to the reduction of transannular strain in the presence of the heteroatom. Electron-withdrawing Cl and NO2 substituents on the aromatic rings yielded products 3d,e with low enantioselectivities (<20%). Interestingly, electron-donating Me and OMe substituents induced slightly higher enantioselectivities (>30%) in products 3f,g. Polyaromatic bromolactone 3h containing a naphthyl ring was obtained with 14% ee.

We speculate that the halocyclization reaction proceeds through a rigid transition state model, in which the olefin–heteroatom in the chain was deprotonated by the quinine nitrogen of 5 to form an ion pair (Scheme 4). Cat 5 serves as a bifunctional catalyst by interacting with both the carboxylate nucleophile and the NBS electrophile, facilitating 5-exo cyclization to form desired five- to seven-membered halolactones.

In conclusion, we have developed a novel C2-symmetric sulfur-based chiral catalyst for the enantioselective bromolactonization of alkenoic acids. This protocol allows for the asymmetric synthesis of γ-, δ-, and ω-lactones and selenolactones. Further mechanistic studies and investigations of this class of catalysts in another asymmetric electrophilic cyclization reactions are underway.

Figure 1 Scope of catalytic enantioselective halo/seleno lactonization

Figure 2 Scope of the enantioselective formation of seven-membered bromo/iodolactones
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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610715.

References and Notes


Scheme 4 Proposed working model

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(19) Catalyst Preparation

To a stirred solution of 2,5-thiophenedicarbonyl dichloride (1.0 equiv, 0.1 mmol) in CH2Cl2 (20 mL) at 0 °C were added dropwise the alkyl derivative of the cinchona alkaloid (2.1 equiv, 1.0 mmol, 209 mg) in CH2Cl2 (20 mL) at 0 °C. The resulting solution was added dropwise to the mixture. The resulting solution was extracted with CH2Cl2 (3 × 20 mL) and the combined organic layer washed with brine (20 mL), dried over Na2SO4 and concentrated on a rotary evaporator under vacuum. The resulting solid was purified by column chromatography with CH2Cl2/MeOH (10:1).

2-[(15)-(6-Butoxyquinolin-4-yl)][(2S)-5-ethylquinuclidin-2-yl][methyl] 5-[(15)-(6-Butoxyquinolin-4-yl)][(2S,4S,5R)-5-ethylquinuclidin-2-yl][methyl] Thioephene-2,5-dicarboxylate (Cat 5)

White solid; yield: 576 mg (66%); mp 147–150 °C; [α]D 8.7 +24.9 (c 0.33, CHCl3). IR (plate): 1722, 1715, 1620, 1596, 1530, 1507, 1462, 1448, 1362, 1320, 1241 cm–1. 1H NMR (400 MHz, CDCl3): δ = 8.69 (d, J = 4.49 Hz, 2 H), 8.00 (d, J = 9.15 Hz, 2 H), 7.79 (s, 2 H), 7.41–7.35 (m, 6 H), 6.67 (d, J = 1.48 Hz, 2 H), 4.17–4.08 (m, 4 H), 3.43–3.38 (m, 2 H), 3.06 (q, J = 12.64 Hz, 2 H), 2.69–2.64 (m, 4 H). The reaction was quenched with saturated Na2SO3 (2 mL) –78 °C and the reaction progress monitored by TLC. After completion, the reaction was quenched with saturated Na2SO4 (2 mL) –78 °C and then warmed to room temperature. The solution was diluted with H2O (3 mL) and extracted with CH2Cl2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over Na2SO4 and concentrated in vacuo.

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