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# Highly Enantioselective Sulfenylation of β-Ketoesters: H-Bond Acceptor Catalysis

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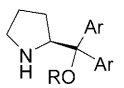
Asymmetric organocatalysis[1] has been experiencing a revival since MacMillan[2] and List,[3] independently, disclosed its potential in 2000, although the L-proline-catalyzed intramolecular aldol reaction[4] dated back to the 1970s. For the past decade, chiral secondary amino compounds have emerged as one of the most significant and versatile catalysts in the enantioselective construction of C–C[5] and various C–hetero[6–11] bonds through covalent activation modes involving enamines,[12] iminium ion,[13] and even SOMO[14] mechanisms. Despite this impressive progress, the reaction substrates activated by secondary amines are mainly restricted to aldehydes and ketones; therefore, it is desirable to extend the scope of the involved substrates for the further application of these catalysts. A quaternary stereocenter is an essential structural motif in many biologically active molecules and pharmaceuticals, and the construction of this framework in an asymmetric catalytic manner is a challenge in organic synthesis. Although functionalization of α-substituted β-ketoesters is a simple method for the generation of chiral quaternary carbon centers due to the α-acidic hydrogen, to the best of our knowledge, this transformation is traditionally catalyzed by a Lewis acid[15,16] or a tertiary amine.[17,18] Given the inherent basicity of secondary amines, we questioned whether they might be exploited as an alternative H-bond acceptor[19] to activate β-ketoesters.

Optically active sulfur-containing compounds constitute an important class of chiral ligands, auxiliaries, and synthetic intermediates in organic chemistry.[20] Moreover, many chiral sulfur-containing molecules exhibit pharmaceutical activities, such as β-lactam antibiotics. However, reports related to the direct asymmetric introduction of sulfur were limited to nucleophilic processes.[21] Recently, electrophilic sulfenylation as a complementary procedure was developed by several groups.[9,22] Jørgensen and co-workers[17f] described the first enantioselective cinchona-alkaloid derivative catalyzed α-sulfenylation of β-ketoesters, which gave the products in up to 91% *ee*. Further success in this area was achieved by Togni and co-workers,[15d,e] who developed chiral Ti (TADDOLato) complexes for this transformation. The sterically demanding ester moiety plays a crucial role in the reaction stereoselectivity in their catalytic system. In addition, an inert atmosphere is a prerequisite due to the use of moisture-sensitive sulfur reagents. Accordingly, we were interested in finding a facile and practical protocol for this sulfenylation reaction.

Herein, we report the asymmetric sulfenylation of β-ketoesters catalyzed by α,α-diaryl prolinols (Scheme 1). Initially, the air-stable and commercially available *N*-(phenylthio)phthalimide (**3a**) was chosen as the sulfur source for




**1a**, Ar = Ph, R = H
**1b**, Ar = 3, 5-$(CH_3)_2C_6H_3$, R = H
**1c**, Ar = 4-$CH_3OC_6H_4$, R = H
**1d**, Ar = 3, 5-$(CF_3)_2C_6H_3$, R = H
**1e**, Ar = Ph, R = TMS

Scheme 1. Prolinol derivative catalysts.

the investigations,[9b,22a] and this protocol was examined in $CH_2Cl_2$ with different β-ketoesters using diphenylprolinol (**1a**; 20 mol%) as the catalyst. However, preliminary studies revealed that the reaction activity and enantioselectivity were strongly dependent on the nature and structure of the substrates. The acyclic β-ketoester, ethyl 2-methyl-3-oxobutanoate only afforded the sulfenylation products in 35% *ee* and poor yield compared with cyclic ones, such as ethyl ester **2a** derived from 1-tetralone (Table 1, entry 1).

On the basis of these studies, **2a** was selected as a model substrate for the optimization of the catalyst and reaction

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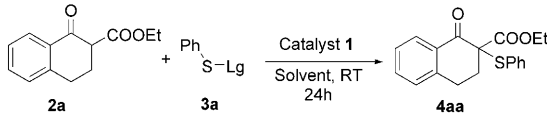
Table 1. Optimization of the catalyst and reaction conditions for the enantioselective sulfenylation of β-ketoester **2a**.[a]




**2a** **3a** **4aa**

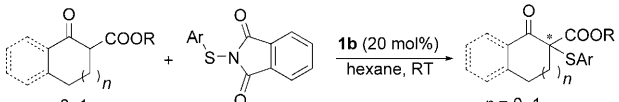
| Entry | Solvent | Catalyst | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | **1a** | 78 | 77 |
| 2 | $CH_2Cl_2$ | **1b** | 83 | 90 |
| 3 | $CH_2Cl_2$ | **1c** | 90 | 81 |
| 4 | $CH_2Cl_2$ | **1d** | 61 | 15 |
| 5 | $CH_2Cl_2$ | **1e** | 48 | 9 |
| 6 | toluene | **1b** | 80 | 89 |
| 7 | hexane | **1b** | 76 | 97 |
| 8[d] | hexane | **1b** | 56 | 97 |
| 9 | $Et_2O$ | **1b** | 92 | 95 |
| 10[d] | $Et_2O$ | **1b** | 60 | 91 |
| 11 | MTBE[e] | **1b** | 89 | 92 |
| 12 | cyclohexane | **1b** | 83 | 96 |
| 13[f] | hexane | **1b** | 70 | 97 |
| 14[g] | hexane | **1b** | 63 | 96 |

[a] Reaction conditions: compound **3a** (0.22 mmol) was added to the solution of β-ketoester **2a** (0.2 mmol) and catalyst (0.04 mmol, 20 mol%) in solvent (2 mL) at room temperature, and stirred for 24 h (Lg = phthalimide). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction ran at 0 °C. [e] MTBE = methyl *tert*-butyl ether. [f] 10 mol% of catalyst **1b** was used. [g] 5 mol% of catalyst **1b** was used.

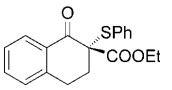
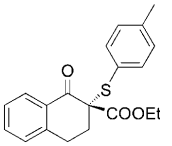
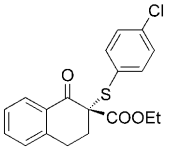
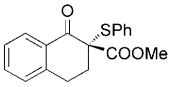
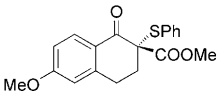
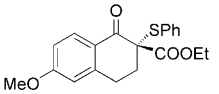
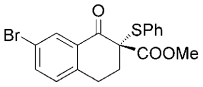
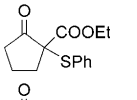
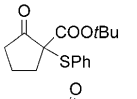
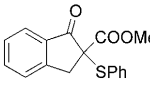
conditions. The results are summarized in Table 1. Investigations into the diaryl prolinols **1a**–**1d** revealed that the electronic properties of the aromatic ring of the catalyst had an impact on its performance (Table 1, entries 1–4). The sulfenylation product **4aa** was isolated in 83% yield with 90% *ee* in the presence of catalyst **1b** (Table 1entry 2). A minor decrease in enantioselectivity (81% *ee*) was observed albeit with a higher yield (90%) when **1c**, bearing an electron-donating group on the aromatic ring, was tested (Table 1, entry 3). Interestingly, the trimethylsilyl ether **1e** resulted in a sharp drop in both the reactivity and enantioselectivity (Table 1, entry 5), whereas it is thought to be one of the most highly effective and versatile catalysts in organocatalytic transformations. It is suggested that the free OH moiety of the catalyst is necessary in this process. Solvent screening demonstrated that hexane is the best choice (up to 97% *ee*, Table 1, entries 2 and 6–12). Some polar solvents, such as acetonitrile, had a deleterious effect on the enantioselectivity. Use of lower temperature (0 °C) led to some loss of catalytic efficiency (from 76% to 56% yield) but without any increase in the *ee* value (Table 1, entries 7 and 8). The same was true when diethyl ether was used as the solvent (Table 1, entries 9 and 10). Furthermore, a decrease in the catalyst loading (from 20 mol% to 5 mol%) has a negative effect on the reaction conversion (Table 1, entries 13 and 14).

Having established the optimal protocol for the reaction, namely 20 mol% of catalyst **1b** in hexane at room temperature, we then explored the electronic properties of the sulfur source and the variation in β-ketoesters. As shown in Table 2, the sulfur reagents **3a**–**3c** with an electron-donating or an electron-withdrawing group on the aromatic ring were found to be tolerated in this transformation (Table 2, entries 1–3), of which **3c** displayed the higher reactivity. In general, the electronic properties of the aryl group and the steric factors associated with the ester moiety appeared to slightly influence the level of stereoselectivity achieved with the 1-tetralone derivatives **2a**–**2e**; all of them afforded the desired products in excellent enantioselectivities and satisfactory yields (92–97% *ee* with 70–82% yield, Table 2, en-

Table 2. Organocatalytic asymmetric sulfenylation of β-ketoesters.[a]




**2a-h** **3a**, Ar = Ph; **3b**, Ar = *p*Me-Ph; **3c**, Ar = *p*Cl-Ph **4**

| Entry | **3** | *t* [h] | Product **4** | | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | 36 |  | **4aa** | 78 | 97 (*R*) |
| 2 | **3b** | 48 |  | **4ab** | 68 | 95 (*R*) |
| 3[d] | **3c** | 36 |  | **4ac** | 88 | 96 (*R*) |
| 4 | **3a** | 36 |  | **4ba** | 72 | 96 (*R*) |
| 5[d] | **3a** | 36 |  | **4ca** | 70 | 94 (*R*) |
| 6[d] | **3a** | 36 |  | **4da** | 73 | 95 (*R*) |
| 7 | **3a** | 36 |  | **4ea** | 82 | 95 (*R*) (>99)[e] |
| 8 | **3a** | 4 |  | **4fa** | 88 | 86 |
| 9 | **3a** | 4 |  | **4ga** | 89 | 79 |
| 10 | **3a** | 1 |  | **4ha** | 98 | 30 |

[a] Reaction conditions: compound **3** (0.22 mmol) was added to the solution of β-ketoester (0.2 mmol) and catalyst **1b** in hexane (2 mL) at room temperature, and stirred for the given time. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis, and the absolute configuration of products **4aa**–**4da** were determined by the comparison of the characteristic CD spectra with that of **4ea**. [d] Hexane/$CH_2Cl_2$ (4:1) was used as the solvent. [e] After recrystallization.

tries 1 and 4–7). Optically pure **4ea** (>99% *ee*) was obtained upon recrystallization (Table 2, entry 7), and its absolute configuration was determined to be *R* by means of an X-ray crystallographic analysis (Figure 1).[23] Furthermore,

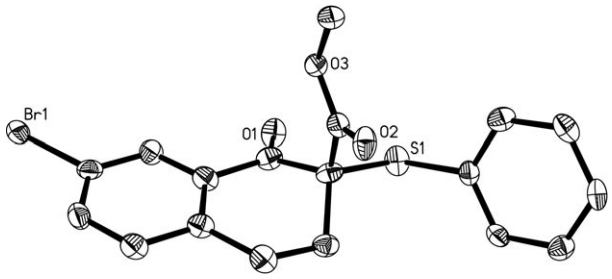



Figure 1. X-ray crystal structure of **4ea**. Thermal ellipsoids set at 30% probability level.

aliphatic five-membered ring β-ketoesters **2f** and **2g** can complete the reaction in 4 h, with up to 86% *ee* (Table 2, entries 8 and 9). These results revealed that the sterically demanding substrate was not the significant factor for the high *ee* values with diaryl prolinol as the catalyst. However, stereocontrol with methyl ester **2h**, derived from 1-indanone, failed, albeit that the reactivity was higher (Table 2, entry 10), and no acceptable improvement was achieved even at −25 °C.[24]

In effort to gain an insight into the reaction mechanism, **1a** with a 100 mol% catalyst loading was added to a solution of β-ketoester **2f** in $CDCl_3$ (0.5 M). After the mixture had been left to stir overnight, no enamine intermediate was detected in the NMR spectra, and no distinct changes were noted in these two components, which suggests that an enamine mechanism may be less acceptable.[25]

Instead, we suggest that hydrogen bonding plays a role in this mechanism. As depicted in Figure 2, the catalyst could effectively recognize the prochiral faces of the β-ketoester (probably enol form) by way of the H-bond donor OH group and the acceptor NH group.[26] This proposed activation model was partly supported by NMR spectroscopic experiments:[27] i) With the addition of catalyst **1b** to the solution of substrate **2e** in $CDCl_3$,[28] the previously stable intramolecular H-bond signal of **2e** at $\delta = 12.34$ ppm (99% enol form, Figure 3a) became rather wide (5 mol% **1b** in Figure 3b, and 10 mol% **1b** in Figure 3c).[29] This phenomenon

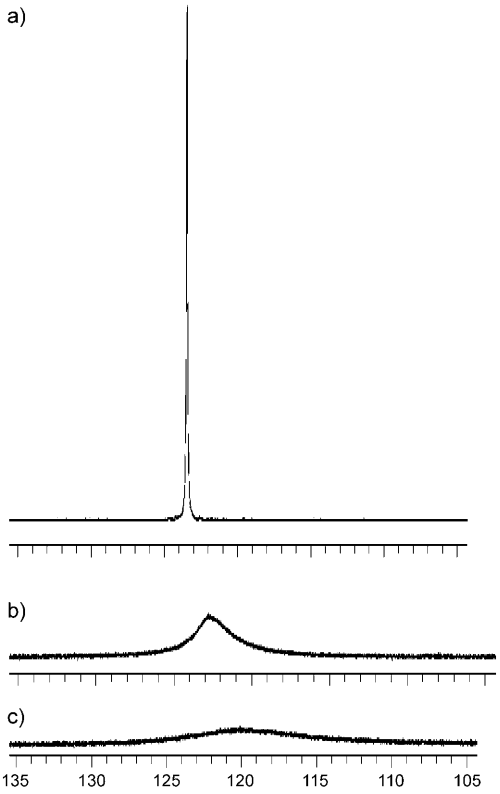



Figure 3. $^1$H NMR spectra of β-ketoester **2e** (enol form) and mixture of **2e** with different amount of catalyst **1b**: a) **2e** without catalyst; b) **2e** with 5 mol% catalyst; c) **2e** with 10 mol% catalyst.

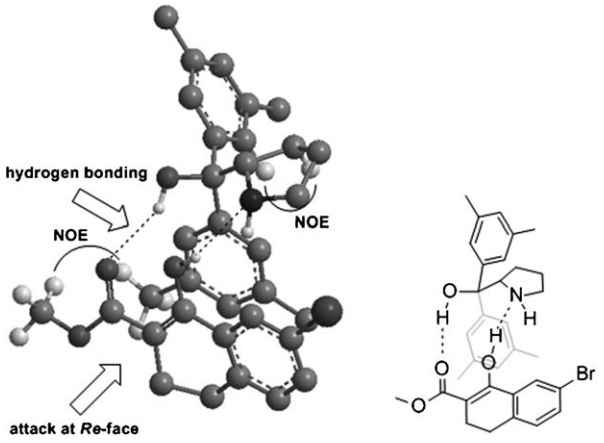



Figure 2. Proposed pre-TS assembly for *re*-side attack of electrophile on the β-ketoester **2e** promoted by catalyst **1b** (other hydrogen atoms are omitted for clarity).

indicates the probable existence of an intermolecular hydrogen bond. This is in accord with the solvent effects on the reaction enantioselectivity: an apolar solvent is superior to a polar one (vide supra). ii) When an equivalent of catalyst **1b** was added, a weak intermolecular NOE could be observed between the methyl-H group of substrate **2e** and the aromatic methyl-H group of the catalyst, as well as the intramolecular NOE of the catalyst (Figure 2). Thus, by virtue of the effective shielding of the aryl group on the catalyst, the electrophilic attack at the *Re*-face of the substrate–catalyst complex leads to the (*R*)-configured product **4ea**.

In summary, we have succeeded in developing the α,α-diaryl prolinol catalyzed sulfenylation of β-ketoesters for the construction of quaternary carbon centers with excellent enantioselectivity and good yields. Studies suggested that the activation mode involved a molecular interaction rather than a covalent bond. The proposed H-bond mode opens up the attractive prospect that chiral secondary amines might

serve as efficient catalysts for substrates other than aldehydes and ketones.

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[24] In fact, we discovered that there is a significant background reaction without any catalyst when **2h** was tested as the substrate. This could partly account for its poor enantioselectivity displayed under identical reaction conditions.

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[27] See the Supporting Information for details.

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[29] An amount of the keto form of **2e** was also observed in the NMR spectra. However, the stable intramolecular H-bond signal completely disappeared on increasing the catalyst loading to 20 mol%. In fact, the sharp $^1H$ NMR resonance is visible even in unpurified $CDCl_3$, in which the equilibrium between the enol and the keto forms exists.

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