

# Enantioselective conjugate addition of thiols to enones and enals catalyzed by chiral *N*-oxide–cadmium complex

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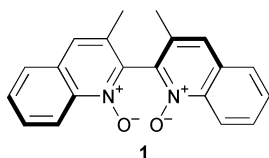
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A novel method of enantioselective conjugate addition of thiols to enones and enals produces sulfides with enantioselectivities up to 78% ee, employing a cadmium complex of (*S*)-3,3'-dimethyl-2,2'-biquinoline *N,N'*-dioxide **1** as a catalyst.

The development of enantioselective reactions requires the design of chiral ligands. Many recent studies have focused on the development of novel chiral ligands for use in metal-catalyzed reactions. Although *N*-oxide is a functional group possessing a unique electron-donating property, allowing it to form complexes with a variety of metals,<sup>1</sup> few attempts have been made to employ *N*-oxides as chiral ligands.<sup>2,3</sup> We recently reported an enantioselective allylation of aldehydes with allyltrichlorosilanes utilizing a chiral *N,N'*-dioxide **1** as a



catalyst, exploiting the electron-donating property of the *N*-oxide.<sup>3c</sup> Here, we describe an enantioselective conjugate addition of thiols to enones and enals catalyzed by a chiral *N*-oxide–cadmium complex.

Several chiral amine-catalyzed reactions have received considerable attention<sup>4</sup> since the first report on the enantioselective conjugate addition of thiols catalyzed by cinchona alkaloid.<sup>4a</sup> Due to their high efficacy, catalysis of enantioselective conjugate addition by lithium thiolate complexes of amino bisether,<sup>5</sup> heterobimetallic complexes,<sup>6</sup> and nickel oxazoline complexes<sup>7</sup> are of particular interest.

Recently, we described the optical resolution of **1** through the hydrogen-bonding of **1** and optically active binaphthol.<sup>3a</sup> We then hypothesized that thiophenol forms a hydrogen-bonding complex with **1**, controlling the nucleophilicity and steric accessibility of thiophenol to electron-deficient olefins in its enantioselective conjugate addition. We initially tested this hypothesis using 10 mol% of **1** as a catalyst in the conjugate addition of thiophenol to cyclohex-2-en-1-one in DCM. The reaction produced a significant yield of the corresponding sulfide, although the enantioselectivity was quite low (35%, 12% ee).

To enhance the reactivity and enantioselectivity, we used 10 mol% metal salt as an additive expected to coordinate with carbonyl oxygen. Among the various metal salts surveyed, addition of CdI<sub>2</sub> yielded the corresponding sulfide in high chemical quantity with moderate enantioselectivity (93%, 57% ee). Enantioselectivity increased up to 78% when the reaction was performed in toluene, whereas polar solvents decreased enantioselectivity substantially (THF: 99%, 0% ee; acetonitrile: 97%, 33% ee). Stoichiometric studies revealed that equimolar amounts of **1** and CdI<sub>2</sub> are sufficient for optimum enantioselectivity. The reaction was promoted by CdI<sub>2</sub> in the absence of *N*-oxide to produce the sulfide in 96% yield. These results

suggest that a 1:1 complex of **1** and CdI<sub>2</sub><sup>8</sup> functions catalytically in this enantioselective addition. This is the first example of an enantioselective reaction utilizing a cadmium compound,<sup>9</sup> exhibiting a distinctive binding to *N*-oxide.

Table 1 summarizes the conjugate addition of various thiols to cyclic enones under optimized conditions.† Slight modifications of the substrate strongly influenced enantioselectivity. Cyclohex-2-en-1-one (entry 2) gave an enantioselectivity comparable to that of cyclohex-2-en-1-one (entry 3), while cyclopent-2-en-1-one (entry 1) demonstrated low selectivity. It is surprising that the reaction of 4-methylthiophenol (entry 5) gave low selectivity compared to that of thiophenol (entry 3).

Although acyclic conjugate ketones were unsuccessful (chalcone: 30%, 10% ee), the reaction of acyclic conjugate aldehydes gives the corresponding sulfides in high chemical yields with enantioselectivities up to 70% ee after conversion to the corresponding alcohol (Table 2). The mildness of the reaction conditions allows the enantioselective conjugate addition of thiols to enals, a reaction never previously reported due to the lability of aldehydes.

To determine the reaction mechanism, we investigated several additives to the reaction of cyclohex-2-en-1-one and thiophenol in toluene. Addition of cyclohexanone (1.0 eq.) influenced neither chemical yield nor enantioselectivity (92%, 74% ee) of the reaction. The addition of cyclohexene (1.0 eq.), however, dramatically reduced enantioselectivity (92%, 45% ee). These results suggest the importance of the coordination of the cadmium complex to the carbon–carbon double bond, though the detail is not clear.

We have demonstrated the effectiveness of a chiral *N*-oxide–cadmium iodide complex as a catalyst for enantioselective conjugate addition of thiols to cyclic enones and enals. The present reaction provides the first example of utilizing a cadmium complex in an enantioselective reaction. Mechanistic studies and the design of chiral *N*-oxides, currently in progress, will further enhance enantioselectivity.

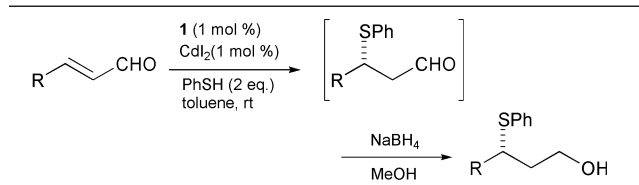
**Table 1** Enantioselective conjugate addition of thiols to enones catalyzed by CdI<sub>2</sub>–**1** complex

Entry	<i>n</i>	Thiol	Time/h	Yield (%)	Ee (%) <sup>a</sup>	Confgn <sup>b</sup>	[α] <sub>D</sub> <sup>24c</sup>
1	1	PhSH	4	94	21	—	+1.8
2	3	PhSH	24	68	61	—	–27.2
3	2	PhSH	6	96	78	<i>S</i>	–68.7
4	2	4-MeOC <sub>6</sub> H <sub>4</sub> SH	6	88	58	<i>S</i>	–43.2
5	2	4-MeC <sub>6</sub> H <sub>4</sub> SH	12	40	29	<i>S</i>	–23.7
6	2	PhCH <sub>2</sub> SH	12	48	40	<i>S</i>	–43.1

<sup>a</sup> Determined by HPLC analysis employing Daicel Chiralpak AD or AS.

<sup>b</sup> Configuration assignment by comparison to literature<sup>4b</sup> values of optical rotations. <sup>c</sup> *c* 1, CHCl<sub>3</sub>.

**Table 2** Enantioselective conjugate addition of thiophenol to enals catalyzed by  $\text{CdI}_2$ -**1** complex



Entry	R	Time/h	Yield (%)	Ee (%) <sup>a</sup>	Confgn	$[\alpha]_D^{25}$ <sup>b</sup>
1	Me	12	89	69	<i>S</i> <sup>c</sup>	+24.9
2	Et	12	91	70	<i>S</i> <sup>d</sup>	+14.0
3	<sup>i</sup> Pr	24	80	63	<i>S</i> <sup>d</sup>	+24.8
4	PhCH <sub>2</sub>	24	76	52	<i>S</i> <sup>d</sup>	+5.2 <sup>e</sup>

<sup>a</sup> Determined by HPLC analysis employing a Daicel Chiralcel OD. <sup>b</sup> *c* 1,  $\text{CHCl}_3$ . <sup>c</sup> Configuration assignment by comparison to literature<sup>5a</sup> values of optical rotations. <sup>d</sup> Configuration assignment by analogy. <sup>e</sup> *c* 1, benzene.

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## Notes and references

† The conjugate addition of thiol to enone was performed as follows: Thiophenol (220 mg, 2.0 mmol) in toluene (1 mL) was added to a stirred solution of cyclohex-2-en-1-one (96 mg, 1.0 mmol), *N*-oxide **1** (3.2 mg, 10  $\mu\text{mol}$ ) and  $\text{CdI}_2$  (3.6 mg, 10  $\mu\text{mol}$ ) in toluene (7 mL) and stirred for 6 h at rt. The reaction mixture was diluted in toluene and successively washed with aq. NaOH and brine. The solvent was evaporated and the residue was chromatographed on a silica gel column (eluent, toluene–AcOEt, 100:1) to afford 3-phenylthiocyclohexanone (198 mg, 96%) as an oil. *N*-Oxide **1** was recovered by elution with 10% EtOH in DCM without a loss of optical purity. The ee of the product was determined by chiral HPLC (Daicel

Chiralpak AD, hexane–Pr<sup>i</sup>OH, 9:1, 1.0 mL min<sup>-1</sup>,  $t_R$  (*S*), 8.5 min; (*R*), 10.0 min).

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