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

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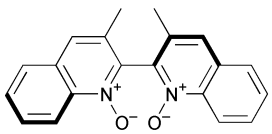
A novel method of enantioselective conjugate addition of thiols to enones and enals produces sulfides with enantioselectivities up to 78% ee, employing a cadmium complex of (*S*)-3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide 1 as a catalyst.

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,[1] few attempts have been made to employ *N*-oxides as chiral ligands.[2,3] We recently reported an enantioselective allylation of aldehydes with allyltrichlorosilanes utilizing a chiral *N*,*N*′-dioxide **1** as a



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catalyst, exploiting the electron-donating property of the *N*-oxide.[3c] 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[4] since the first report on the enantioselective conjugate addition of thiols catalyzed by cinchona alkaloid.[4a] Due to their high efficacy, catalysis of enantioselective conjugate addition by lithium thiolate complexes of amino bisether,[5] heterobimetallic complexes,[6] and nickel oxazoline complexes[7] are of particular interest.

Recently, we described the optical resolution of **1** through the hydrogen-bonding of **1** and optically active binaphthol.[3a] 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_2 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_2 are sufficient for optimum enantioselectivity. The reaction was promoted by CdI_2 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_2[8] functions catalytically in this enantioselective addition. This is the first example of an enantioselective reaction utilizing a cadmium compound,[9] exhibiting a distinctive binding to *N*-oxide.

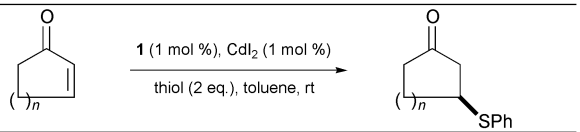
Table 1 summarizes the conjugate addition of various thiols to cyclic enones under optimized conditions.† Slight modifications of the substrate strongly influenced enantioselectivity. Cyclohept-2-en-1-one (entry 2) gave an enantioselectivity comparable to that of cyclohex-2-en-1-one (entry 3), while 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_2–**1** complex



Entry	*n*	Thiol	Time/h	Yield (%)	Ee (%)[a]	Confgn[b]	$[\alpha]_D^{24}$[c]
1	1	PhSH	4	94	21	—	+1.8
2	3	PhSH	24	68	61	—	−27.2
3	2	PhSH	6	96	78	*S*	−68.7
4	2	4-$MeOC_6H_4SH$	6	88	58	*S*	−43.2
5	2	4-MeC_6H_4SH	12	40	29	*S*	−23.7
6	2	$PhCH_2SH$	12	48	40	*S*	−43.1

[a] Determined by HPLC analysis employing Daicel Chiralpak AD or AS. [b] Configuration assignment by comparison to literature[4b] values of optical rotations. [c] *c* 1, $CHCl_3$.

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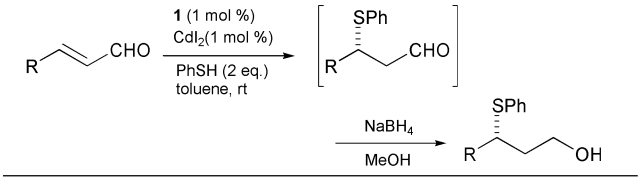
Table 2 Enantioselective conjugate addition of thiophenol to enals catalyzed by CdI_2–**1** complex



Entry	R	Time/h	Yield (%)	Ee (%)[a]	Confgn	$[\alpha]_D^{23}$[b]
1	Me	12	89	69	*S*[c]	+24.9
2	Et	12	91	70	*S*[d]	+14.0
3	^{i}Pr	24	80	63	*S*[d]	+24.8
4	$PhCH_2$	24	76	52	*S*[d]	+5.2[e]

[a] Determined by HPLC analysis employing a Daicel Chiralcel OD. [b] *c* 1, $CHCl_3$. [c] Configuration assignment by comparison to literature[5a] values of optical rotations. [d] Configuration assignment by analogy. [e] *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 μmol) and CdI_2 (3.6 mg, 10 μmol) 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^{i}OH, 9 : 1, 1.0 mL min^{-1}, t_R (*S*), 8.5 min; (*R*), 10.0 min).

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