The Michael reaction ranks as one of the most useful C=C bond constructions, and the development of catalytic enantioselective variants has become an important endeavor. Previously, our research group has reported selective Mukaiyama−Michael reactions of silylketene acetics to alkydene malonates and unsaturated N-acyloxyazolidinones, catalyzed by Cu(II) bisoxazoline complexes. More recently, we reported a Ni(II)-catalyzed direct addition of malonates and β-ketoesters to nitroalkenes. Here we wish to report an operationally simple, direct addition of β-ketoesters to unsaturated N-acylthiazolidinethiones, catalyzed by Ni(II) p-Tol-BINAP Lewis acid complexes 1b and 1c. The products are readily converted into dihydropyrones (eq 1), which are useful substrates for further stereoselective bond constructions (eq 2).

Kanemasa has reported the enantioselective Michael addition of 1,3-diketones and related nucleophiles to unsaturated acylpyrazoles and oxazolidinones, using a combination of a chiral Ni-based Lewis acid and an appropriate amine base. Similar experiments by us, utilizing the readily available complex 1b, afforded little or no desired product. However, we have found that 1b (10 mol %) catalyzes the addition of tert-buty1 acetocatc (3a) to crotonyl thiazolidinethione 2a, in the absence of an amine base, to afford 4a as a 1:1 mixture of diastereomers. Treatment of 4a with DBU (20 mol %) resulted in the formation of enantioenriched dihydropyronse 5a. A solvent survey indicated that ethyl acetate is the preferred reaction medium in terms of reaction rate and enantioselectivity (Table 1, entry 1).

With effective conditions for the tert-buty1 acetocatco reaction in hand, additions of other β-ketoester nucleophiles were evaluated. Generally, unbranched and branched ketoester substrates afford good yields (78−97%) and enantioselectivities (Table 1, entries 1−5). The use of the tetrafluoroborate catalyst 1c affords slightly better enantioselectivity for 3f (Table 1, entry 7); however, this trend has not yet been evaluated for all cases.

The scope of the thione Michael acceptor is summarized in Table 2. While the triflate complex was an excellent catalyst for Michael acceptor 2a (R = Me), the tetrafluoroborate complex 1c is superior as its derived substrate complexes are generally more soluble, while maintaining similar reactivity to 1b. Thiones 2a−2e generated the desired Michael adducts in good yield and with high enantioselectivity (Table 2, entries 1−5). Substitution at the δ-position results in a marked decrease in reactivity and selectivity (Table 2, entry 4), a common attribute for this and related reactions. For γ-branched substrate 2e (R = i-Pr), the reaction is prohibitively slow (Table 2, entry 5). Alternatively, the fumarate derivative 2f (R = CO2Et) afforded the desired Michael adduct in high yield and 97% enantiomeric excess (Table 2, entry 6).

The Michael adducts are readily converted to the corresponding acyclic ketoester derivatives by treatment with K2CO3 in methanol followed by acidic decarboxylation. Representative examples are illustrated in eq 3. There are two plausible roles that the Ni catalyst could play in promoting this reaction: (a) generation of a Ni-bound ketoester enolate and (b) Lewis acid activation of the thiazolidinethione Michael acceptor. The first mechanism would be analogous to our proposal. The absolute sense of asymmetric induction observed in these reactions is the same as that observed for the 1b-catalyzed enantioselective Diels−Alder reaction of 2a with cyclopentadiene (eq 4). Both of these results are consistent with addition of the
nucleophile/diene to the thiazolidinethione bound to a distorted square planar Ni center, as represented by structure 10 (Figure 1).

We suggest that the nucleophile is most likely a reactive enol tautomer of the β-ketoester, formed at equilibrium concentrations under the reaction conditions.


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Supporting Information Available: Experimental procedures, spectral data for all compounds, crystallographic data, and stereochemical proofs (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References


(4) Complex 1b has been shown to catalyze an enantioselective alkylation, see: Evans, D. A.; Thomson, R. J. J. Am. Chem. Soc. 2005, 127, 10474–10475.


(6) Prepared in situ from 1a and 2.0 equiv of AgOTf. 1e was prepared in an analogous fashion using AgBF4.


(12) See Supporting Information for full details.

(13) Model generated from the X-ray structure of [Ni(Si)-BINAP]Cl, by docking the thiazolidinethione to the Ni center, followed by PM3 minimization. See Supporting Information for X-ray structure.