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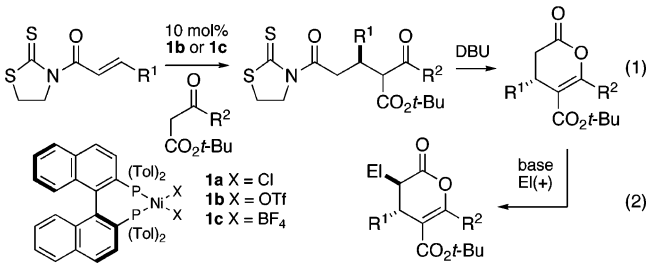
Ni(II) Tol-BINAP-Catalyzed Enantioselective Michael Reactions of β-Ketoesters and Unsaturated *N*-Acylthiazolidinethiones

David A. Evans,* Regan J. Thomson, and Francisco Franco
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received June 10, 2005; E-mail: evans@chemistry.harvard.edu

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.[1] Previously, our research group has reported selective Mukaiyama−Michael reactions of silylketene acetals to alkylidene malonates and unsaturated *N*-acyloxazolidinones, catalyzed by Cu(II) bisoxazoline complexes.[2] More recently, we reported a Ni(II)-catalyzed direct addition of malonates and β-ketoesters to nitroalkenes.[3] 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**.[4] The products are readily converted into dihydropyrone derivatives (eq 1), which are useful substrates for further stereoselective bond constructions (eq 2).

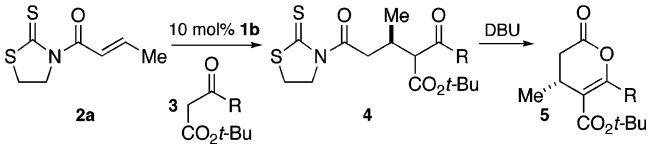


Kanemasa has reported the enantioselective Michael addition of 1,3-diketones and related nucleophiles to unsaturated acylpyrazoles and oxazolidinones, using a combination of a chiral Ni-based Lewis acid and an appropriate amine base.[5] Similar experiments by us, utilizing the readily available complex **1b**,[6] afforded little or no desired product. However, we have found that **1b** (10 mol %) catalyzes the addition of *tert*-butyl acetoacetate (**3a**) to crotonyl thiazolidinethione **2a**,[7] *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 dihydropyrone **5a**.[8] 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 *t*-butyl acetoacetate[9] reaction in hand, additions of other β-ketoester nucleophiles were evaluated.[10] 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**−**2c** generated the desired Michael adducts in good yield and with high enantioselectivity (Table 2, entries 1−3). 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

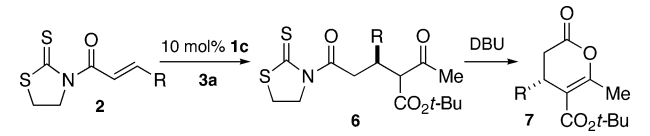
Table 1. Scope of the β-Ketoester Addition to Crotonyl Thione **2a**[a]



entry	**3** (R)	time (h)	yield **4** (%)[b]	yield **5** (%)[b]	ee (%)[c]
1	Me (a)	12	89	84	93
2	Et (b)	14	92	80	94
3	*n*-Pr (c)	14	86	85	93
4	*i*-Bu (d)	24	78	72	91
5	C_6H_{11} (e)	24	97	94	90
6	Ph (f)	12	85	94	83
7[d]	Ph (f)	12	95	94	91

[a] 0.25 mmol **2a**, 1.5 equiv of **3**, 0.2 M in EtOAc, 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 10 mol % catalyst **1c**.

Table 2. Scope of the Thiazolidinethione Michael Acceptor **2**[a]



entry	**2** (R)	time (h)	yield **6** (%)[b]	yield **7** (%)[b]	ee (%)[c]
1	Me (a)	12	95	84	93
2	Et (b)	14	88	89	95
3	*n*-Pr (c)	14	91	75	95
4[d]	*i*-Bu (d)	24	67	72	84
5	*i*-Pr (e)	72	−	10[e]	70
6	CO2Et (f)	12	87	97	97
7	Ph (g)	24	nr[f]	−	−

[a] 0.25 mmol **2**, 1.5 equiv of **3a**, 0.2 M in EtOAc, 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 0.8 M in EtOAc. [e] From unpurified **6e**. [f] No reaction.

γ-branched substrate **2e** (R = *i*-Pr), the reaction is prohibitively slow (Table 2, entry 5). Alternatively, the fumarate derivative **2f** (R = CO_2Et) 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 K_2CO_3 in methanol followed by acidic decarboxylation. Representative examples are illustrated in eq 3.[11]

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 recently reported addition of β-ketoesters to conjugated nitroalkenes.[3] However, the failure of complexes **1a**−**1c** to catalyze such a reaction provides some circumstantial evidence against such a 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).[12] Both of these results are consistent with addition of the

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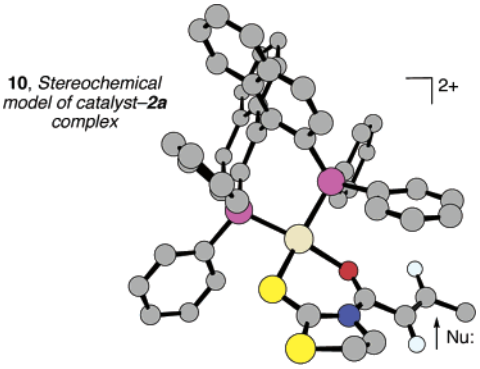
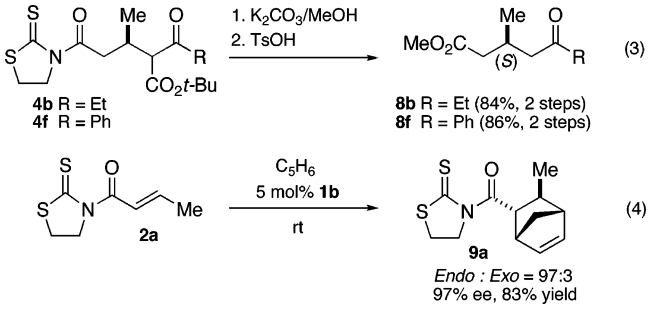


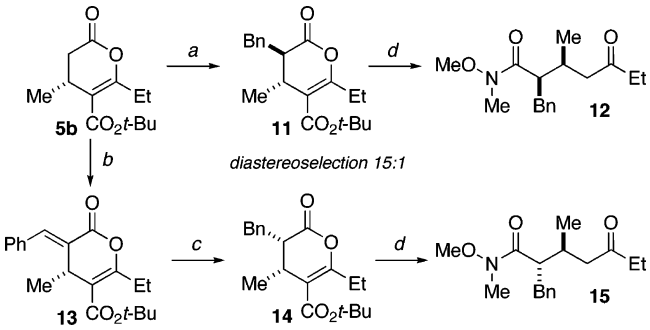
Figure 1. Stereochemical model for Michael reaction.

nucleophile/diene to the thiazolidinethione bound to a distorted square planar Ni center, as represented by structure **10** (Figure 1).[13] We suggest that the nucleophile is most likely a reactive enol tautomer of the β-ketoester, formed at equilibrium concentrations under the reaction conditions.

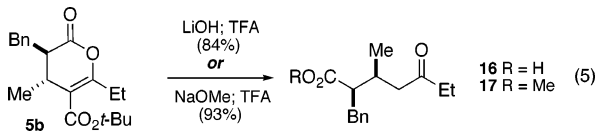


The product pyrones **5** are excellent substrates for further enolate-based stereoselective transformations (Scheme 1). For example, the lithium enolate derived from **5b** may be selectively alkylated with benzyl bromide to provide the anti lactone **11**. Alternatively, aldol condensation of **5b** with benzaldehyde provides α,β-unsaturated lactone **13**. Hydrogenation of **13** (10% Pd/C, toluene) afforded the syn-substituted product **14** with excellent diastereoselectivity. Both the anti and syn adducts may be transformed into their derived Weinreb amides **12** and **15**, respectively, without loss of stereochemistry after TFA-induced decarboxylation. Dihydropyrone **5b** may also be hydrolyzed to its derived carboxylic acid **16** (R = H) upon exposure to aqueous LiOH in THF and subsequent decarboxylation (eq 5). In a similar manner, treatment of **5b** with sodium methoxide affords the corresponding methyl ester **17** (R = Me) in high yield. No loss of stereochemical integrity was observed during any of these ring-opening processes.

Scheme 1. Stereoselective Elaboration of Dihydropyrone **5b**[a]



[a] Reagents and conditions: (a) LiHMDS (1 equiv), BnBr (5 equiv); (b) i. LiHMDS (1.5 equiv), PhCHO (1.5 equiv), −78 °C, THF; ii. MsCl (2 equiv), Et_3N (2.5 equiv), CH_2Cl_2, rt; iii. DBU (2 equiv), toluene, rt, 81% (three steps); (c) H_2, 10% Pd/C, toluene, 100%; (d) i. Me(OMe)NH·HCl (5 equiv), *i*-PrMgCl (9 equiv), THF, −20 °C; ii. TFA, CH_2Cl_2, rt, 80%.



The present study is complementary to a recent enantioselective addition−cyclization sequence reported by Kanemasa.[5a] The method detailed in this communication provides a practical approach to the enantioselective construction of monocyclic dihydropyrone derivatives.[14] These adducts afford useful options for the stereoselective construction of vicinal alkyl stereocenters in both diastereochemical variants (Scheme 1). These stereochemical options are complementary to the Claisen rearrangement for the construction of either syn or anti vicinal carbon substituents on bis-functionalized carbon chains.[15]

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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

(1) For reviews, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 3, Chapter 31.1. (b) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171−196. For recent examples, see: (c) Wang, E.; Wang, J.; Ji, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369−1371. (d) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *J. Chem. Soc., Chem. Commun.* **2004**, 1414−1415. (e) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148−11149. (f) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204−11205.

(2) (a) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480−4491. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

(3) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958−9959.

(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.

(5) (a) 1,3-Diketones: Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979−981. (b) Malononitrile: Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron: Asymmetry* **2003**, *14*, 635−639. (c) Nitromethane: Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (d) Thiols: Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675−8676.

(6) Prepared in situ from **1a** and 2.0 equiv of AgOTf. **1c** was prepared in an analogous fashion using $AgBF_4$.

(7) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.

(8) For the synthesis of related structures, see: Katritzky, A. R.; Deniski, O. V. *J. Org. Chem.* **2002**, *67*, 3104−3108. See also ref 5a.

(9) Other alkyl acetoacetates were also effective; Me: 86% ee, Et: 91% ee, Bn: 93% ee. See Supporting Information for full details.

(10) (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087−2088. (b) Hoffman, R. V.; Saenz, J. E. *Tetrahedron Lett.* **1997**, *38*, 8469−8472.

(11) **8b** and **8f** are known compounds and allowed the assignment of the absolute stereochemistry. See: (a) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *45*, 4967−4970. (b) Shi, Y.; Wulff, W. D.; Glenn, P. A.; Rheingold, A. L. *Chem. Commun.* **1996**, 2601−2602.

(12) See Supporting Information for full details.

(13) Model generated from the X-ray structure of [Ni((*S*)-BINAP)]Cl_2 by docking the thiazolidinethione to the Ni center, followed by PM3 minimization. See Supporting Information for X-ray structure.

(14) An enantioselective hydrogenation of pyrone derivatives to 5,6-dihydro-2-pyrones has been reported. See: Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *J. Org. Chem.* **1999**, *64*, 5678−5776 and references therein.

(15) For a review, see: Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2.

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