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Ni(II) Tol-BINAP-Catalyzed Enantioselective Orthoester Alkylations of *N*-Acylthiazolidinethiones

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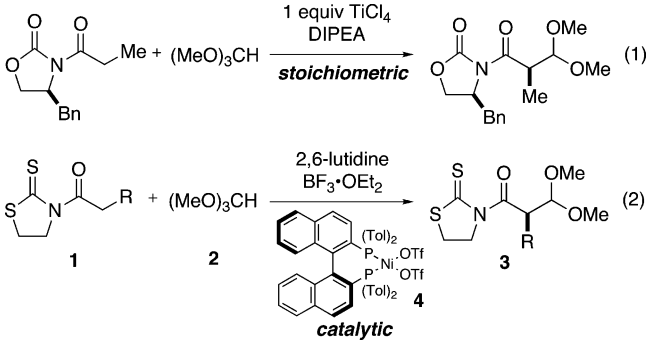
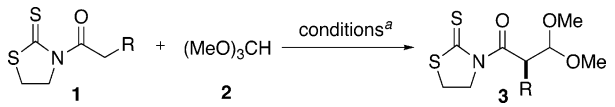
Chiral metal enolates are an extremely valuable family of nucleophiles that are employed widely in organic synthesis.[1] As such, the development of catalytic processes involving the in situ generation of chiral metal enolates is an area of considerable importance. Our interest in this area has focused predominantly on the utilization of *N*-acylthiazolidinethiones as useful substrates for catalytic aldol reactions.[2] The catalytic enantioselective direct alkylation of enolates, however, is a much less developed field.[3] Previous research from this laboratory has demonstrated that preformed titanium enolates derived from chiral *N*-acyloxazolidinones react with orthoesters to provide the alkylated adduct with high levels of diastereocontrol (eq 1).[4,5] We now report the development of Ni(II) (*S*)-Tol-BINAP-catalyzed orthoester alkylations of *N*-acylthiazolidinethiones that display useful substrate scope and enantioselectivity (eq 2).



While *N*-acyloxazolidinone-derived titanium enolates are sufficiently Lewis acidic to effectively ionize trimethyl orthoformate, nickel enolate derivatives of complex **4** are not. Accordingly, the use of an external activating agent is necessary. On the basis of observations made during development of our previously disclosed catalytic aldol reaction,[2] TMSOTf was considered because it should not adversely affect the Lewis acidic complex **4**. Initial experiments were conducted on propionyl thiazolidinethione **1a**[6] using 10 mol % of complex **4**, trimethyl orthoformate (1.5 equiv), 2,6-lutidine (2.5 equiv), and TMSOTf (1.5 equiv). Under these conditions, adduct **3a** was formed in excellent enantiomeric excess (97% ee) but with moderate conversion (66%). The replacement of TMSOTf with $BF_3{\cdot}OEt_2$ led to an increase in conversion (75%) with no detrimental effect on enantioselectivity. While the use of only 1 equiv each of trimethyl orthoformate, $BF_3{\cdot}OEt_2$, and 2,6-lutidine afforded low conversion, it was found that excellent conversion and selectivity could be obtained when using 3 equiv of these reagents. Catalyst loading could be decreased to 5 mol % of **4**, providing **3a** in good yield and with excellent enantioselectivity.

With optimized conditions in hand, the scope of the reaction was investigated for a range of substrates (Table 1). In general, saturated alkyl-substituted thiazolidinethiones (entries 1−5) provide the desired adducts in slightly lower yields than the corresponding allyl and benzyl derivatives (entries 6 and 7). Phenylacetyl derivatives provide the adducts in both excellent yield and enantiomeric excess (entries 8−10). Heteroatom substitution is also well tolerated, with glycolate derivative **1k** providing the corresponding dimethyl acetal in 89% yield and 90% ee (entry 11). The use of other orthoesters was investigated, and while triethyl orthoformate was competent under the developed conditions (68% yield, 98% ee), the use of trimethyl orthoacetate and trimethyl orthopropionate afforded no product. This lack of reactivity is ascribed to formation of the corresponding ketene dimethyl acetals under the reaction conditions.[7]

Table 1. Substrate Scope of Orthoester Alkylation



entry	R	yield (%)[b]	ee (%)[c]
1	Me (**1a**)	73 (**3a**)	97
2	Et (**1b**)	76 (**3b**)	95
3	*n*-Pr (**1c**)	61 (**3c**)	94
4	*i*-Bu (**1d**)	62 (**3d**)	93
5[d]	*i*-Pr (**1e**)	51 (**3e**)	91
6	allyl (**1f**)	92 (**3f**)	94
7	Bn (**1g**)	91 (**3g**)	92
8	Ph (**1h**)	91 (**3h**)	98
9	4-OMe-Ph (**1i**)	91 (**3i**)	98
10	4-Cl-Ph (**1j**)	63 (**3j**)	99
11	OBn (**1k**)	89 (**3k**)	90

[a] With 5 mol % of **4**, 0.5 mmol of **1**, 3 equiv of **2**, 3 equiv of 2,6-lutidine, 3 equiv of $BF_3{\cdot}OEt_2$, 0.8 M in CH_2Cl_2, −78 °C, 0.5 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Carried out using 10 mol % of **4** and a further 3 equiv of **2**, 2,6-lutidine, and $BF_3{\cdot}OEt_2$ added after 1 h.

The absolute sense of stereoinduction[8] observed for these reactions is consistent with a chelated *Z*-enolate bound to a distorted square planar Ni(II) complex, reacting with the derived oxocarbenium ion. The reaction of chiral thiazolidinethiones **5** and *ent*-**5** provides further support for this hypothesis. For the matched case, both the ligand and auxiliary screen the same face of the enolate, whereas for the mismatched case, both faces are blocked, leading to lower diastereoselectivity and conversion.[9] The sense of diastereoselection observed for *ent*-**5** indicates that the chiral catalyst is subordinate to the auxiliary in dictating the facial selectivity of the reaction. On the basis of these results and X-ray crystallographic data of related BINAP complexes,[10] the stereochemical model **6** is proposed.[11,12] The two depictions clearly show that extension of one of the phosphine aryl groups over the top of one face of the enolate provides the high enantioselectivity observed for this reaction. A plausible catalytic cycle is outlined in Scheme 1. Substrate coordination to the complex **I** gives rise to **II**, resulting in an increased acidity of the coordinated thiazolidinethione.[13] Enolization by 2,6-lutidine then proceeds to form the nickel-bound *Z*-enolate **III**, which reacts with the oxocarbenium ion formed in

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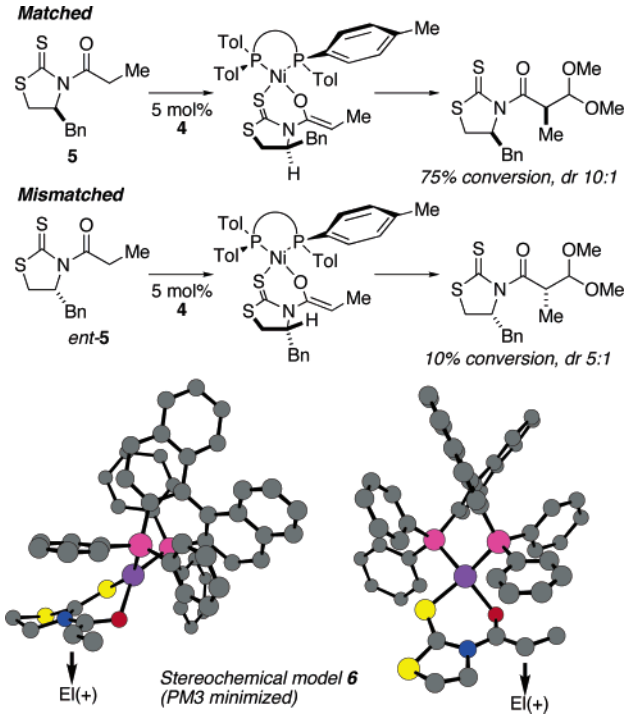
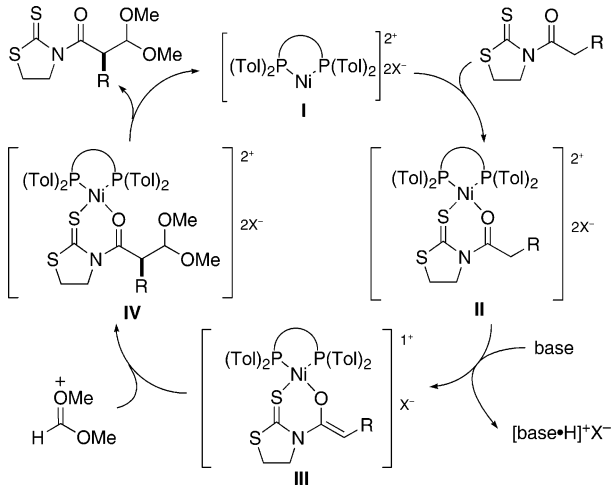


Figure 1. Model for the observed sense of stereoinduction and double-stereodifferentiating experiments.

Scheme 1

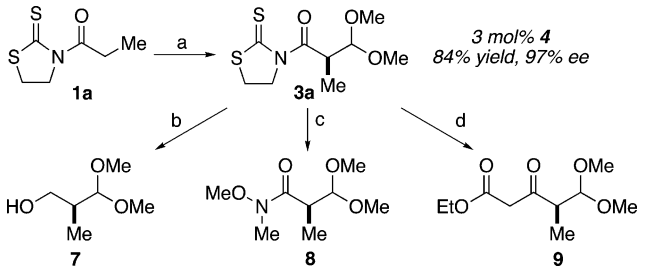


situ from trimethyl orthoformate and $BF_3{\cdot}OEt_2$. Product dissociation then regenerates catalyst **I**.[14]

On a larger scale (2.0 g, 11.4 mmol **1a**), the catalyst loading could be lowered to 3 mol % with no detrimental effect on yield or enantioselectivity (Scheme 2). As shown in Scheme 2, **3a** is readily converted into a variety of potentially useful substrates. Reduction of **3a** with $LiBH_4$[15] provides the corresponding alcohol **7** in moderate yield (58%).[16] Conversion to Weinreb amide **8** is achieved in a straightforward manner upon exposure of **3a** to Me(OMe)NH·HCl, Et_3N, and imidazole. Under the conditions described by Smith and co-workers, β-ketoester **9** can be prepared in good yield (73%).[17]

In conclusion, we have developed a Ni(II) (*S*)-Tol-BINAP-catalyzed orthoester alkylation of *N*-acylthiazolidinethiones that displays wide substrate scope for the nucleophile and excellent enantioselectivity. The ease with which the products may be

Scheme 2 [a]



[a] Reaction conditions: (a) 3 mol % of **4**, trimethyl orthoformate (3 equiv), 2,6-lutidine (3 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), CH_2Cl_2, −78 to 0 °C, 84%; (b) $LiBH_4$ (3 equiv), Et_2O, 0 °C, 58%; (c) Me(OMe)NH·HCl (5 equiv), imidazole (5 equiv), Et_3N (5 equiv), CH_2Cl_2, rt, 92%; (d) ethyl malonate, K-salt (2 equiv), $MgCl_2$ (1 equiv), imidazole (1 equiv), THF, rt, 73%.

converted into a broad range of functional groups means this chemistry should find application to the synthesis of a wide variety of molecules.

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

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(6) *N*-Propionyloxazolidinone gave no reaction under similar conditions.

(7) Treatment of acetals with TMSOTf and base affords the corresponding enol ethers. See: Gassman, P. G.; Burns, S. J. *J. Org. Chem.* **1988**, *53*, 5574−5578.

(8) See Supporting Information for details.

(9) The lower selectivity observed for **5** versus that for **1a** is presumably the result of a change about the metal due to the benzyl substituent.

(10) [Ni((*S*)-BINAP)]Br_2 is distorted square planar. See: Spielvogel, D. J.; Davis, W. M.; Buchwald, S. L. *Organometallics* **2002**, *21*, 3833−3836.

(11) [Ni((*S*)-BINAP)]OTf_2 is an effective catalyst for the alkylation of **1a**, but gives slightly lower enantiomeric excess (94%).

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

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(16) The moderate yield is due to volatility and water solubility of the product.

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