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Enantioselective Addition of a Chiral Thiazolidinethione-Derived Titanium Enolate to Acetals

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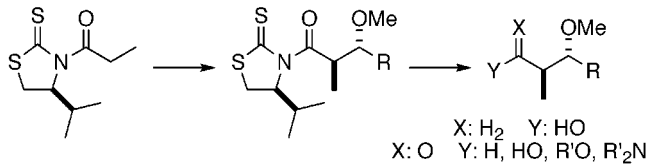
ABSTRACT



High stereoselectivities (up to 98% de) have been achieved for the Lewis acid-mediated cross-coupling reaction of dimethyl acetals to a chiral 1,3-thiazolidine-2-thione-derived titanium enolate. The reaction affords enantiopure *anti* α-methyl-β-alkoxy carbonyl compounds in a wide range of acetals.

Over the past 15 years, the Lewis acid-mediated reaction of acetals with silicon-containing nucleophiles has proven to be a powerful method for carbon−carbon bond formation.[1] Methods employing either chiral acetals[2] or crotylsilanes[3] are well-known and provide nonracemic adducts that, in turn, can be transformed into enantiopure *syn* α-alkyl-β-alkoxy carbonyl compounds.[3f,4] Despite the success of these approaches, most of the strategies addressing the synthesis of enantiomerically pure α-alkyl-β-alkoxy carbonyl compounds rely on a two-steps process: (i) enantioselective aldol reaction and (ii) alkylation of the aldol adduct.[5] Taking into account that the second step is often troublesome,[6] and that the integration of a multistep sequence in a single transformation increases the efficiency of a process, we envisioned that an enantioselective reaction of metal enolates with acetals might afford the aforementioned systems in a straightforward manner.[7] Inspired by the stereoselective addition of chiral titanium enolates to ortho esters reported by Evans,[7b] and taking advantage of our own experience,[8]

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(2) For a review on chiral acetals, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477−511. For examples using chiral acetals, see: (b) Ishihara, K.; Nakamura, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 7720−7721. (c) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709−1712. (d) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706−6707. (e) Andrus, M. B.; Lepore, S. D. *Tetrahedron Lett.* **1995**, *36*, 9149−9152. (f) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695−10704.

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(5) For methylation procedures, see: (a) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955−968. (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171−7172.

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(7) Stereoselective addition of metal enolates to acetals are scarce: (a) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53−56 (cyclic hemiacetals). (b) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216 (ortho esters and chloromethyl ethers).

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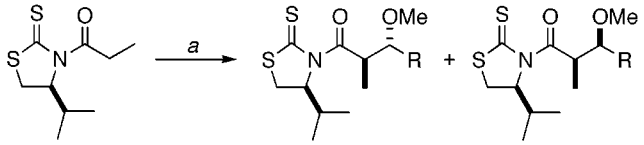
we have developed a general and efficient methodology to gain access to *anti* α-methyl-*β*-alkoxy carbonyl structures on the basis of the reaction of the titanium enolate arising from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1**)[9] with dimethyl acetals.

In preliminary studies, we observed that the titanium enolate of **1** underwent addition to benzaldehyde dimethyl acetal at −50 °C in moderate yield. Given that the presence of a Lewis acid in the reaction medium might enhance the electrophilicity of the acetal and promote the formation of the desired adduct, we decided to evaluate the effect of several Lewis acids. We were then pleased to find that treatment of a solution of titanium enolate of **1** with 1 equiv each of $BF_3{\cdot}OEt_2$[10] and benzaldehyde dimethyl acetal in CH_2Cl_2 at −78 °C smoothly furnished the corresponding *anti* adduct **2a** in diastereomeric ratio of 86:14; enantiopure **2a** was subsequently isolated by means of chromatographical purification in 75% yield (see Scheme 1 and Table 1).[11]

Scheme 1[a]



[a] See ref 12.

The above-mentioned mild conditions also afford good yields and diastereoselectivities in the case of aromatic (**a**−**d**) and α,*β*-unsaturated acetals (**e**−**f**), as shown in Table 1. However, lower yields were obtained in the case of aromatic acetal **g** and acetals **h**−**j**, derived from aliphatic aldehydes, even at higher temperatures. These less reactive substrates require a more powerful Lewis acid such as $SnCl_4$ in order to attain similar yields and diastereoselectivities up to 93:7 (Table 1).[12]

Table 1. Stereoselective Synthesis of *anti* α-Methyl-*β*-alkoxy Carbonyl Compounds

acetal	R	Lewis acid	React. Cond. T, t	dr[a] **2**:**3**	yield[b] (%)
a	Ph	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	86:14	75
b	4-$MeOC_6H_4$	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	81:19	77
c	3-$MeOC_6H_4$	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	92:8	79
d	4-ClC_6H_4	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	91:9	81
e	(*E*)-PhCH=CHMe	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	96:4	94
f[c]	H−≡−≡ $Co_2(CO)_6$	$BF_3{\cdot}OEt_2$	−78 °C, 2.5 h	99:1	84
g	4-$NO_2C_6H_4$	$SnCl_4$	−78 °C, 2 h	86:14	70
h	$CH_3CH_2CH_2$	$SnCl_4$	−50 °C, 2 h[d]	93:7	64[e]
i	$(CH_3)_2CHCH_2$	$SnCl_4$	−20 °C, 2 h[d]	92:8	76
j	$(CH_3)_2CH$	$SnCl_4$	−20 °C, 2 h[d]	88:12	50

[a] dr by HPLC. [b] Isolated yield of **2**. [c] Diethyl acetal was used. [d] After 15 min at −78 °C. [e] Isolated yield of the corresponding ethyl ester.

The stereochemistry of the adducts **2a**, **2d**, and **3d** was established by X-ray diffraction analysis (Figure 1)[13] and, in the case of **2i**, it was confirmed by chemical correlation.

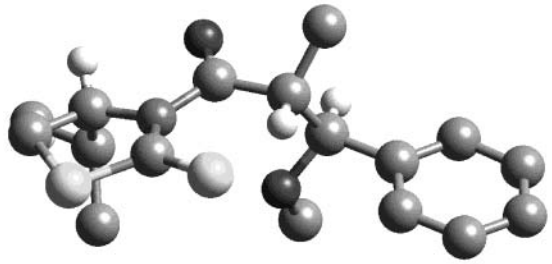


Figure 1. X-ray crystal structure of **2a**.

Although the mechanistic details are currently under scrutiny, it is likely that the reaction proceeds via an S_N1-like process.[14] Thus, the observed stereochemistry might be ruled by an open transition state which involves the approach of an intermediate oxocarbenium ion to the less hindered

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(9) (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777. (b) Zuev, D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 679−682. (c) Nagao, Y.; Nagase, Y.; Kumagai, T.; Matsunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem.* **1992**, *57*, 4243−4249. (d) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393.

(10) Other Lewis acid (BCl_3, $TiCl_4$, Et_2AlCl, $SnCl_4$, TMSOTf, $Ti(OiPr)_4$, $ZnCl_2$, $MgBr_2{\cdot}OEt_2$, $LaCl_3$) were also investigated but turned out to be less suitable.

(11) Flash silica gel chromatography can be easily visually monitored because all of the adducts prepared to date are bright yellow.

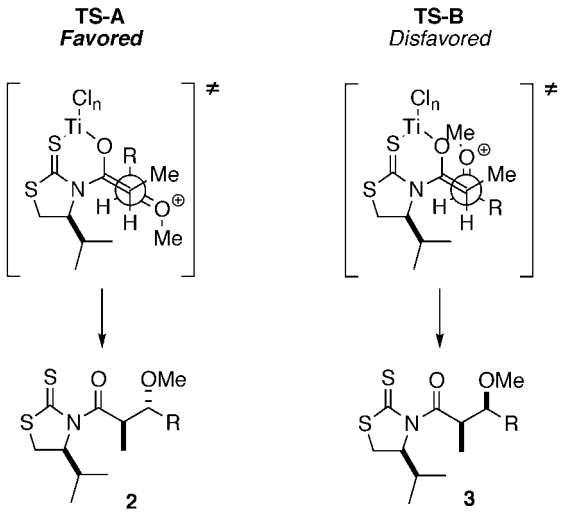
(12) **Typical experimental procedure.** Neat $TiCl_4$ (0.12 mL, 1.1 mmol) was added dropwise to a solution of **1** (218 mg, 1.0 mmol) in CH_2Cl_2 (8 mL), at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 °C and cooled at −78 °C, and a solution of diisopropylethylamine (0.19 mL, 1.1 mmol) in CH_2Cl_2 (1 mL) was added. The dark red enolate solution was stirred for 2 h at −40 °C, and 1 equiv each of Lewis acid and dimethyl acetal was successively added dropwise. The resulting mixture was stirred at the temperature and time shown in Table 1. The reaction was quenched by the addition of 6 mL of saturated ammonium chloride with vigorous stirring, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography on silica gel (hexanes/EtOAc) afforded the pure major diastereomer **2**.

(13) Crystallographic data (excluding structure factors) for the structures **2a**, **2d**, and **3d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-150269, 150271, and 150270, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

(14) Reactions of acetals with carbon nucleophiles have been shown to proceed via carbocation intermediates. See, for example: (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169. (b) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541−4542. (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916. (d) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999. For earlier mechanistic discussions, see: (e) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.;

face (*Si* face) of a putative chelated[15] *Z*-enolate and determines the *R* configuration at the α-center.[16] Furthermore, transition states TS-A and TS-B shown in Scheme 2 can be

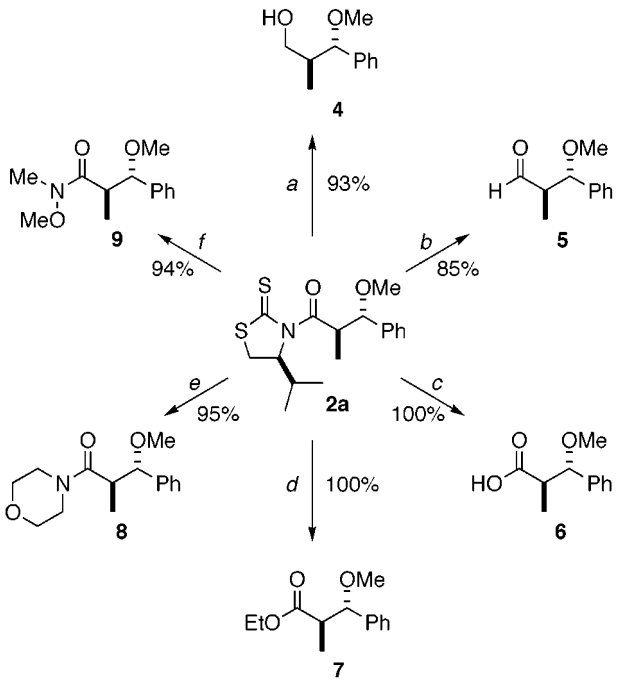
Scheme 2



invoked in order to explain the stereochemistry of **2** and **3**, assuming that interactions of the substituents of the oxocarbenium ion and the auxiliary must be minimized. Then, the preferential formation of the *anti* adduct can be rationalized through an antiperiplanar arrangement (TS-A) on the basis of stereoelectronic and steric considerations.[17]

The chiral thiazolidinethione auxiliary can easily be removed by using a variety of methods, which allows the adducts to be transformed into a wide range of derivatives.[8,9,18] As a model, **2a** was converted into the corresponding enantiopure alcohol **4**, aldehyde **5**, carboxylic acid **6**, ethyl ester **7**, morpholine amide **8**, and Weinreb amide **9** under very mild conditions and in excellent yields as shown in Scheme 3. In all cases, the end point is reached when the initial yellow solution becomes almost colorless.[19]

Scheme 3 [a]



[a] (a) $NaBH_4$ (4.5 equiv), THF−H_2O, rt, 4 h; (b) DIBAL-H (1.1 equiv), CH_2Cl_2, −78 °C, 3 h; (c) LiOH·H_2O (6 equiv), CH_3CN−H_2O, rt, 12 h; (d) EtOH, DMAP cat., rt, 24 h; (e) morpholine (4 equiv), THF, rt, 12 h; (f) NH(OMe)Me·HCl (1.5 equiv), Et_3N (1 equiv), DMAP cat., CH_2Cl_2, rt, 24 h.

In summary, we have described a simple and efficient methodology to obtain enantiopure *anti* α-methyl-*β*-alkoxy carbonyl compounds based on the stereoselective addition of a chiral titanium enolate to a wide range of acetals. The adducts can be, in turn, easily transformed into a large number of 1,3-dioxygenated compounds with a high interest in organic synthesis.

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Supporting Information Available: Spectroscopic data for adducts **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115 and references therein. Other reaction of acetals do not appear to involve free cations, see: (f) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110 and references therein.

(15) It deserves to be mentioned that the C=S bond of the auxiliary constitutes a key feature of the process. 1,3-Oxazolidine-2-thione derived auxiliary also displays an excellent performance, although its final removal has been proven less efficient. However, 1,3-oxazolidin-2-one and camphorsultam-derived auxiliaries afforded worse results.

(16) The stereochemical outcome of the reaction reveals complete facial control by the chiral titanium enolate (only products arising from the addition to the *Si* face of the enolate have been observed).

(17) For a similar discussion of related Lewis acid-mediated aldol addition transition states, see: Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120 and references therein.

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(19) The chiral auxiliary can be recovered by flash column chromatography in ≥90% yield or, in certain cases, by washing the reaction mixture using 1 M NaOH and acidification.