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Diastereoselective Addition of Chlorotitanium Enolate of *N*-Acyl Thiazolidinethione to *O*-Methyl Oximes: A Novel, Stereoselective Synthesis of α,*β*-Disubstituted *β*-Amino Carbonyl Compounds via Chiral Auxiliary Mediated Azetine Formation

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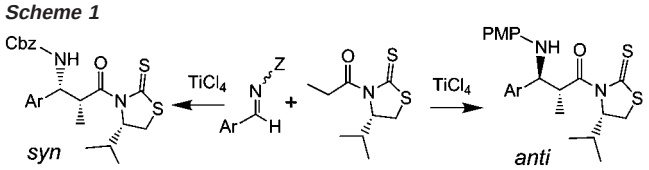
Carbon−carbon bond-forming reactions involving asymmetric aldol additions have emerged as powerful tools in organic synthesis. As demonstrated by the pioneering work of Evans,[1] Heathcock,[2] and others,[3,4] additions of enolates of acyl oxazolidinones, oxazolidinethiones, and thiazolidinethiones to aldehydes can be highly effective at selectively generating enantiomerically pure syn and anti aldol products. While, in principle, additions of these enolates to the C=N bond could be employed to generate *β*-amino carbonyl compounds,[5] in practice, the approach has only been used in a handful of cases, most of which involve nonenolizable imines.[6,7]

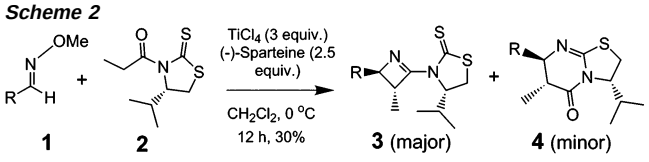
Scheme 1



Recently, we have reported that additions of *N*-acyl thiazolidinethione enolates to nonenolizable aldimines can be used to produce either the syn or the anti addition products by appropriate selection of the group (*Z*) on the nitrogen (Scheme 1).[7] Herein, we report the first details of a novel reaction of *N*-acyl thiazolidinethione enolates with enolizable aldoxime ethers to produce thiazolidinethione azetines with excellent diastereoselectivity. Subsequent addition of an acyl chloride to these azacyclobutene derivatives leads to the formation of the corresponding *N*-acyl-α,*β*-disubstituted *β*-amino acid derivatives.

Aldimines, although widely used in organic synthesis, exhibit lower reactivity than their parent aldehydes and, if enolizable, are often quite unstable chemically.[8−11] We speculated that this latter issue might be circumvented by employing "imines" that are less prone to deprotonation, tautomerization, and oligomerization. In this regard, *O*-alkyl oximes[12−14] seemed well suited for exploring additions to enolates despite their moderate electrophilicity, because this deficiency could be overcome by activation with a suitable Lewis acid. Because of previous successes with combinations of *N*-acyl thiazolidine-2-thione **2**,[15] titanium tetrachloride, and (−)-sparteine,[4,7] we initiated our studies using this approach.

Scheme 2



Although *O*-methyl benzaldoxime (**1**, R = phenyl) failed to react at lower temperatures (e.g., −70 to −20 °C), product formation was observed when the reaction was carried out for 12−14 h at 0 °C in the presence of 3 equiv of titanium tetrachloride. While we were able to elucidate the backbone structure of the product using normal spectroscopic techniques (^{1}H and ^{13}C NMR, IR, and MS), the absence of both methoxy and carbonyl groups in the product suggested that the reaction was more complex than a simple addition process. Surprisingly, X-ray crystallographic analysis indicated the major product to be azetine **3a** (R = Ph) (Scheme 2, Figure 1a).

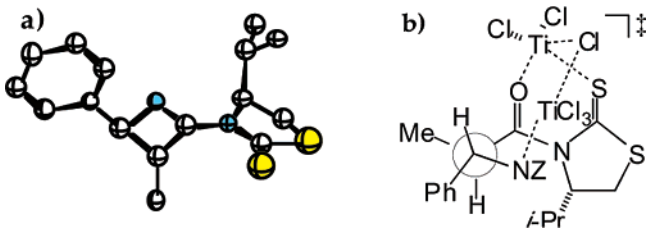


Figure 1. (a) X-ray structure of **3a** (R = Ph). (b) Transition state model for enolate addition to **1**; new bond hidden by Newman projection.

With the structure of the product firmly established, we focused our attention on improving the efficiency and exploring the scope and limitations of this novel transformation. By using 4 equiv of titanium tetrachloride and 2.5 equiv of (−)-sparteine, we obtained **3a** (R = Ph) as a single diastereoisomer in double the originally observed yield (Table 1). The reaction was also examined using other aromatic and heteroaromatic oximes with similar outcomes. It is particularly noteworthy that enolizable *O*-methyl oximes also gave the corresponding azetine product. For example, the *O*-methyl oxime ethers derived from hydrocinnamaldehyde and cyclohexane carboxaldehyde produced single "anti" isomers as the major product, albeit only in moderate yields.

Table 1. Enolate Additions Leading to Azetine **3** Formation[16]

oxime *O*-methyl ether, **1**(R)	isolated product yield (%)	major to minor product ratio (**3**/**4**)
phenyl	65	>95:5
1-naphthyl	78	6:1
2-thienyl	60	15:1
2-phenylethyl	45	>95:5
cyclohexyl	31	>95:5

The formation of a strained four-membered ring can be rationalized as being initiated by the combination of oxime and $TiCl_4$ to give a highly electrophilic trichlorotitanium iminium intermediate (**i** in Scheme 3), which undergoes addition by the enolate to form **ii** and subsequent reversible ring closure to form azacyclobutane **iii**. Irreversible elimination of bis-trichlorotitanium oxide, $O(TiCl_3)_2$, provides the ultimate driving force to produce the azetines listed in Table 1. Under similar conditions, the corresponding *N*-

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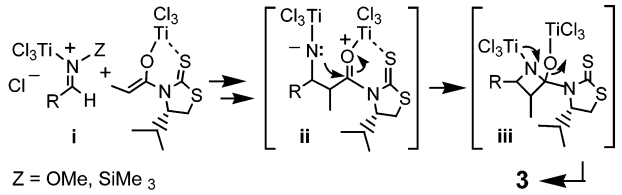
trimethylsilyl benzaldimine[17] delivers **3a** (R = Ph) in 85% yield, possibly through the intermediacy of a trichlorotitanium imine.[18,19] Finally, while we have no direct information regarding the transition state of these reactions, Figure 1b depicts a simple model for rationalizing the observed anti stereochemistry.

Scheme 3



"Hydrolytic" opening of azetinyl thiazolidine-2-thiones that produce the corresponding α,β-disubstituted β-amino carbonyl compounds is, to our knowledge, unprecedented. Initial attempts involving simple acid/base-catalyzed hydrolysis led to the formation of complex product mixtures. We speculated that a successful approach would proceed by selective generation of a reactive iminium salt[20] followed by subsequent hydrolysis. Preliminary attempts at *N*-alkylations involving the use of either MeI or Me_3OBF_4 failed apparently because of competition from the nucleophilic sulfur in the thiazolidine-2-thione. However, azetines **3** could be successfully converted to the corresponding *N*-acyl β-amino carbonyl compounds **5** by simple exposure to benzoyl chloride, followed by stirring at room temperature in air (Table 2 and Scheme 4). These reactions presumably involve the formation of an acyl iminium cation intermediate, followed by a subsequent hydrolysis. In our hands, benzoyl chloride was found to be superior to other commonly used acylating agents. The retained absolute stereochemistry of the "anti" β-amino carbonyl compound was confirmed by X-ray crystallographic analyses of **5a** (R = Ph, see Supporting Information).

Scheme 4

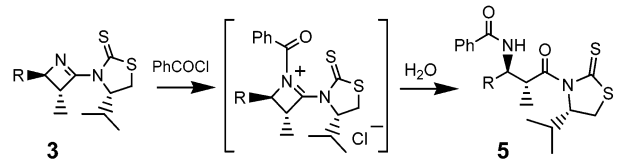


Table 2. Hydrolytic Opening of Azetines **3** To Give **5**[16]

R	yield (%)
phenyl	78
1-naphthyl	59[21]
2-thienyl	60[21]
2-phenylethyl	44
cyclohexyl	38

In summary, we have discovered a novel and highly diastereoselective synthesis of azetinyl thiazolidine-2-thiones that utilizes additions of the chlorotitanium enolates of *N*-acyl thiazolidin-2-thiones to *O*-methyl aldoximes. The "anti" azetines can be subsequently converted to the corresponding β-amino carbonyl compounds with retention of stereochemistry. While elucidating the full scope and limitations of these additions will require additional study, this approach has excellent potential for becoming a general method for synthesizing a wide variety of α,β-disubstituted β-amino carbonyl derivatives.

Acknowledgment. We are grateful to Dr. Kenneth Hardcastle (Emory University) for determining the X-ray structures of compounds **3** and **5**.

Supporting Information Available: Synthetic details, as well as the X-ray structures for **3** and **5**, R = Ph (CIF and PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (i) ^{1}H NMR was employed to determine the presence and the ratio of diastereoisomers. While none of the other diastereomer was detected in any of the reactions listed in Scheme 2, a minor byproduct, **4**, was detected, which provides interesting insight into the mechanistic pathway involved. (ii) In the reactions involving oxime ethers with R = phenyl, 2-phenylethyl, and cyclohexyl, none of the minor product **4** was observed after 12 h.
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(19) Conversion of **1** to a trichlorotitanium imine requires reduction of the N−O bond, presumably by titanium tetrachloride. Studies aimed at elucidating the mechanism of this conversion are underway.
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(21) On the basis of preliminary analyses of crude reaction mixtures, these reactions may result in low levels (<10%) of epimerization.

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