with a second HOOH to give a dioxygenase reactive intermediate [$(bpy)_2^{2+}Co^{III}OOCo^{III}(bpy)_2^{2+}$, **3**] (Scheme I).

In pure MeCN, species **1** appears to activate HOOH and *t*-BuOOH via formation of 1:1 adducts [$(bpy)_2^{2+}Co^{II}$(HOOH) (**4**) and $(bpy)_2^{2+}Co^{II}$(*t*-BuOOH) (**5**)], which, when formed in the presence of substrates, act as monooxygenases (c-C_6H_{12} → c-$C_6H_{11}OH$). As such, they are closely similar to the reactive intermediate from the combination of $[Fe^{II}(MeCN)_4](ClO_4)_2$ and HOOH in MeCN.[4,5] The formation of two reactive intermediates [**4**, favored in MeCN, and **3**, favored in MeCN/py] in combination with the product profiles of Table I is the basis for the proposed reaction pathways of Scheme I. Species **3** transforms methylenic carbons (>CH_2) to ketones (>C=O) and dioxygenates aryl olefins and acetylenes, and its precursor (species **2**) epoxidizes aliphatic olefins. Combination of *t*-BuOOH and $Co^{II}(bpy)_2^{2+}$ appears to form intermediates **5** and **6**; species **5** has reactivity similar to that of species **4**, but species **6** is unique and necessary to account for the observed ROOBu-*t* products (Table I).

In summary, the $Co^{II}(bpy)_2^{2+}$/HOOH/(4:1 MeCN/py) system forms a reactive intermediate (**3**) that selectively ketonizes methylenic carbon and, as such, is closely similar to the intermediate of the $Fe^{II}(PA)_2$/HOOH/(2:1 py/HOAc) system[1] and of related systems.[2,3] We believe that the common feature is a stabilized-dioxygen intermediate rather than a hypervalent metal-centered carbon oxidant.[2] The ability of $Fe^{II}(DPAH)_2$ to active O_2 to an intermediate that has the same unique selectivity for hydrocarbon ketonization[6] is further support for a common stabilized-dioxygen reactive complex. Several cobalt-dioxygen complexes exhibit oxygenase reactivity with organic substrates,[7,8] which is consistent with the dioxygen formulation for species **3**.

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(4) Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4283.
(5) Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1985**, *107*, 5712.
(6) Sheu, C.; Sobkowiak, A.; Jeon, S.; Sawyer, D. T. *J. Am. Chem. Soc.* **1990**, *112*, 879.
(7) Nishinaga, A.; Tomita, H. H. *J. Mol. Catal.* **1980**, *7*, 179.
(8) Matsuura, T. *Tetrahedron* **1977**, *33*, 2869.

New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Constructions with Representative Electrophiles

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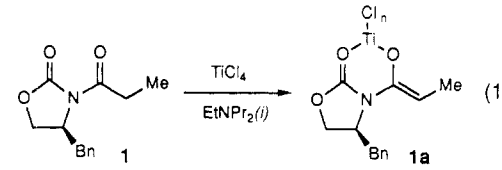
Metal enolates are one of the most valuable families of nucleophiles employed in organic synthesis, and those advances that provide more practical and more selective methods for the enolization of carbonyl compounds continue to be of considerable value to the field. The purpose of this communication is to describe a straightforward procedure for the formation of titanium enolates from the corresponding carbonyl precursors with titanium tetrachloride and a tertiary amine base under mild conditions (CH_2Cl_2, −78 → 0 °C). This method for titanium enolate formation complements related procedures based on transmetalation from alkali-metal enolates[1] or silyl enol ethers[2] while offering the advantage of operational simplicity.

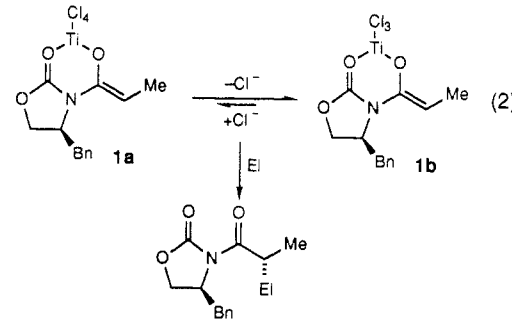
This enolization procedure, which was initially studied in detail for the *N*-propionyloxazolidone **1**,[3] has subsequently been generalized to other substrates. The following discussion reflects this order of development. Successive treatment of a 0.2–0.5 M solution of **1** in CH_2Cl_2 with 1.0 equiv of $TiCl_4$ and then 1.0 equiv of diisopropylethylamine (DIPEA) for 1 h at 0 °C results in the quantitative formation of the characteristic dark-red titanium enolate, as determined by a DCl/D_2O quench (eq 1). It is critical



(1)

that this order of reagent addition is followed so that substrate–$TiCl_4$ complexation (ca. 5 min) precedes the introduction of base. The reaction of uncomplexed $TiCl_4$ with DIPEA leads to irreversible complexation and, as a consequence, no enolization. Other titanium reagents may also effect substrate enolization. Quantitative enolate formation under the above conditions using isopropoxytitanium trichloride (*i*-PrOTiCl_3) in place of $TiCl_4$ may also be achieved. Increasing the number of alkoxy substituents on the titanium reagent decreases its enolization potential. For example, $(i\text{-PrO})_2TiCl_2$ and $(i\text{-PrO})_3TiCl$ afforded 70 and 10% enolization of **1**, respectively, with DIPEA under otherwise identical conditions. *A valuable attribute of these alkoxytitanium halides is that both DIPEA and triethylamine (TEA) complex reversibly with all three oxygenated titanium species; as a consequence, the order of reagent addition no longer has to be strictly followed.* For most of the substrates evaluated during the course of this study, DIPEA or TEA may be used interchangeably as the enolization base.

We have not yet unequivocally established the number of halogens associated with the metal center (eq 2); however, we have circumstantial evidence in this and related systems for the ate-complexed enolate **1a** rather than the expected trichlorotitanium enolate **1b**. Nonetheless, in reactions with most electrophiles, the stereochemical outcome is consistent with the presence of a chelated (*Z*) enolate and is the same as that observed with the analogous alkali-metal enolates previously described by us.[4]



(2)

Representative reactions of the titanium enolates derived from five carbonyl substrates and a selection of electrophiles are provided in Table I. The enolate derived from *N*-propionyloxazolidone **1** undergoes reaction with alkyl halides with a predisposition toward S_N1 reactivity (entry A).[5] Orthoesters and acetals (entries B and C) are also exceptionally good substrates. These enolates

(1) (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691–4694. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722–5728. (c) Riediker, M.; Duthaler, R. O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 494–495. Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Ibid.* **1989**, *28*, 495–497.
(2) (a) Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341–3342. (b) The $TiCl_4$-promoted condensation of silyl enol ethers with aldehydes and acetals (Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043–1054) could proceed through titanium enolates in certain instances.
(3) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–91.
(4) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
(5) For a review of Lewis acid promoted enolate alkylations, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96–108.

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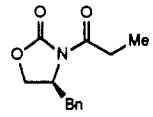
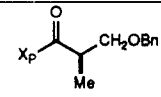
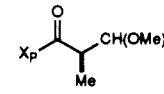
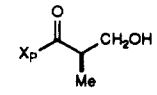
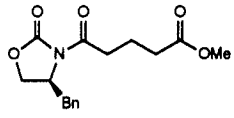
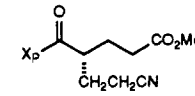
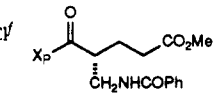
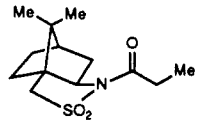
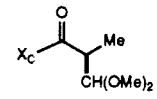
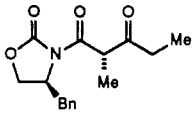
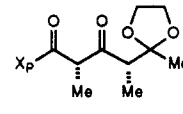
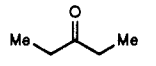
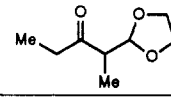
Table I. Diastereoselective Reactions of Chlorotitanium Enolates with Representative Electrophiles

Entry	Substrate	Enolization[a]	Electrophile	Product[b]	Yield, %[c]	Stereoselection[d]
A		$TiCl_4$ (1.05 equiv) 0 °C, 1.0 h	$BnOCH_2Cl$ (2.0 equiv) 0 °C, 6 h		99 %	>100 : 1 (GLC)
B		$TiCl_4$ (1.0 equiv) 0 °C, 1.0 h	$(MeO)_3CH$ (1.2 equiv) 0 °C, 0.5 h		95 %	99 : 1 (GLC)
C		$TiCl_4$ (1.05 equiv) 0 °C, 1.0 h	*s*-Trioxane[e] (1.1 equiv) 0 °C, 2 h		89 %	>98 : 2 (GLC)
D		$Me_2CHOTiCl_3$ (1.05 equiv) 0 °C, 1.0 h	CH_2=CHCN (1.5 equiv) 25 °C, 5.5 h		70 %	>100 : 1 (GLC)
E		$TiCl_4$ (1.0 equiv) 0 °C, 0.75 h	$PhCONHCH_2Cl$[f] (1.2 equiv) 0 °C, 0.5 h		87 %	96 : 4 (GLC)
F		$TiCl_4$ (1.0 equiv) 0 °C, 0.5 h	$(MeO)_3CH$ (1.5 equiv) -78 °C, 4 h		70 %	85 : 15 (GLC)
G		$TiCl_4$ (1.05 equiv) -50 °C, 0.5 h	$(CH_2O)_2C(OMe)Me$ (2.5 equiv) -20 °C, 1.5 h		86 %	93 : 7 (NMR)
H		$TiCl_4$[g] (1.0 equiv) -78 °C, 1.5 h	$(CH_2O)_2CHOMe$ (1.2 equiv) 0 °C, 0.5 h		83 %	—

[a] All reactions were carried out in methylene chloride (0.2–0.5 M) in the presence of 1.0–1.1 equiv of diisopropylethylamine unless otherwise specified. [b] Physical and spectroscopic properties for all compounds provided in the supplementary material. [c] Yields refer to diastereomerically pure product. [d] Diastereomer ratios determined by the indicated method (GLC, HPLC, or NMR spectroscopy). [e] After the addition of electrophile, an additional 1.1 equiv of $TiCl_4$ was added to the reaction mixture to catalyze in the process. [f] See ref 7 for the preparation of this reagent. [g] Enolization was carried out with 1.0 equiv of Et_3N.

are also well-suited for the Michael reaction with unsaturated nitriles (entry D), ketones, and esters (not illustrated).[6] Finally, amidoalkylation[7] reactions (entry E) may also be executed in good yield. Each of the transformations illustrated with the *N*-acyloxazolidones (entries A–E) represents either an improvement of a previously reported reaction[4] or an amplification in the range of electrophiles which may be employed with this chiral enolate system. The last three entries in Table I are included to illustrate that this enolization procedure may be generalized to other carbonyl substrates. The diastereoselective acylation of the sensitive β-ketoimide (entry G) is particularly noteworthy.[8] In this reaction, enolization may be directed away from the labile methyl-bearing stereocenter. The sense of asymmetric induction in the ensuing orthoacylation also appears to be controlled by chelate organization and is the same as that observed for the analogous titanium aldol reaction with the same enolate.[9]

There are some limitations. Self-condensation appears to be the principal side reaction with unhindered ketones. This reaction was observed with some methyl ketones (acetophenone) and cyclohexanone. Although alkyl esters (e.g., ethyl acetate) do not readily enolize, it is projected that the more activated carboxyl derivatives will be useful substrates.

The first indication that the $TiCl_4$/amine system might find utility in enolization is contained in the Knoevenagel study reported by Lehnert.[10] Harrison subsequently reported the aldol condensation of aromatic ketones and benzaldehyde where titanium enolization was transiently achieved in the presence of the nonenolizable aldehyde.[11] The present study provides added scope and understanding to the details of the enolization process.

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Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products are included as well as other related examples (8 pages). Ordering information is given on any current masthead page.

(6) *i*-PrOTiCl$_3$/DIPEA proved to be the general enolization system of choice for Michael reactions with methyl acrylate and acrylonitrile.

(7) For a preparation of *N*-(chloromethyl)benzamide, see: Bohme, H.; Broese, R.; Dick, A.; Eiden, F.; Schunemann, D. *Chem. Ber.* **1959**, *92*, 1599.

(8) This transformation was carried out by Dr. Bret Huff of this laboratory.

(9) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.

(10) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723–4724.

(11) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135–4138.