has been suggested to account for the dependence of product configuration on Lewis acid stoichiometry in the reactions of aldehydes with allylmetals.[19] Because Et_2AlCl is not capable of forming a pentacoordinated 2:1 complex, it shows no change in selectivity as a function of equivalents of Lewis acid.

Regardless of the mechanism, the results in Table I clearly demonstrated that it is possible to synthesize **4**, **5**, or **6** from the same enolate by simply changing the reaction conditions. It was not difficult to generalize the method to other aldehydes. With all aldehydes studied method A (slow addition of the aldehyde) gave the non-Evans syn aldol **6**, with stereoselectivities in the range 6:1–15:1 (Table II). Method C is a generally useful anti-selective method, especially with Et_2AlCl; all aldehydes gave a predominance of **5** by this method (Table III). With the aliphatic aldehydes, the anti–syn ratios range from 6:1 to 20:1. However, with benzaldehyde, the ratio is only 3:1, similar to the selectivity we had previously observed in the dibutylboron triflate mediated reaction.[9]

One final point deserves comment. In our optimization studies, we investigated three different chiral imides (**2**, R_c = *i*-Pr, $PhCH_2$,[20] and *t*-Bu[21]). Although space does not permit us to present all of the data here, it was found that the valine-derived reagent is most effective under the anti-selective conditions (Table III), whereas the *t*-leucine-derived reagent is most effective under the syn-selective conditions (Table II).

In conclusion, these results demonstrate that the Lewis acid mediated reaction of boron enolate **2** provides easy access to either the anti aldols **5a–f** or the non-Evans syn aldols **6a–f** with 80–95% diastereoselectivity. This, coupled with the original Evans methodology, provides access to three of the four possible aldol products of imide **1** with an aldehyde. Although the stereoselectivities in these Lewis acid mediated versions of the Evans reaction are not perfect, the products are usually crystalline and are easily purified by chromatography, thus providing easy access to multigram quantities of synthetically useful β-hydroxy acids of very high enantiomeric purity. Finally, these results further demonstrate that subtle changes in reaction conditions can have significant effects on the stereoselectivity of Lewis acid mediated processes.

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Supplementary Material Available: Experimental procedures and analytical data for aldols and their derived β-hydroxy acids (8 pages). Ordering information is given on any current masthead page.

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Enantioselective Michael Reactions. Diastereoselective Reactions of Chlorotitanium Enolates of Chiral *N*-Acyloxazolidinones with Representative Electrophilic Olefins

David A. Evans,*[†] Mark T. Bilodeau,[†] Todd C. Somers,[†] Jon Clardy,[‡] David Cherry,[‡] and Yoko Kato[‡]

Departments of Chemistry, Harvard University, Cambridge, Massachusetts 02138, and Cornell University, Ithaca, New York 14853

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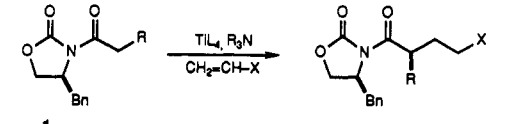
Summary: In the present study we wish to report the details of the diastereoselective reactions of titanium enolates derived from *N*-propionyloxazolidone **1** in inter- and intramolecular Michael reactions with ethyl vinyl ketone, methyl acrylate, and acrylonitrile (eq 1).

Several recent publications from this laboratory have illustrated the general utility of imide-derived titanium enolates[1,2] derived from *N*-propionyloxazolidone **1**[3] in a range of diastereoselective bond constructions. The purpose of this paper is to disclose our results on the application of these and related chiral enolates to the Michael reaction. Only a few previous studies have addressed the development of enantioselective Michael reactions of chiral auxiliary based, carboxylic acid derived enolates with α,β-unsaturated Michael acceptors.[4] Noteworthy examples include the use of Corey's phenmenthyl-derived ester enolate,[5] a selection of chiral amide enolates surveyed by Yamaguchi,[6] and the chiral Sn(II)–amine-complexed imide enolates reported by Mukaiyama.[7] The purpose of this Communication is to present our results on the diastereoselective reactions of chiral imides such as **1**,[3] through their derived titanium enolates,[1,2,8] with α,β-unsaturated ketones, esters, and nitriles.



(1)

[†] Harvard University.
[‡] Cornell University.

(1) Evans, D. A., Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
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(4) For an excellent review of the stereochemical attributes to the Michael reaction, see: Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227–407.
(5) Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025–5028.
(6) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959–962.
(7) Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1988**, 1021–1024.
(8) For the leading references to $TiCl_4$–R_3N enolization, see: (a) Lehnert, W. *Tetrahedron Lett.* **1970**, *54*, 4723–4724. (b) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135–4138. (c) Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211–5212.

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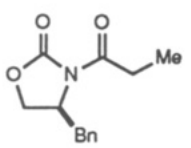
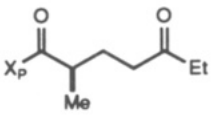
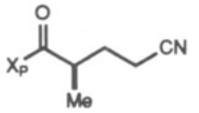
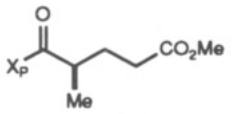
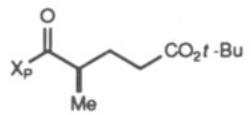
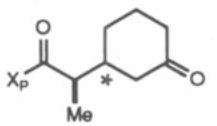
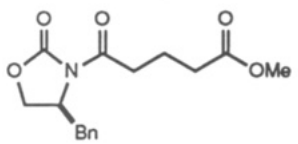
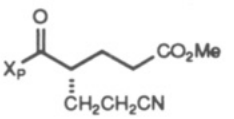
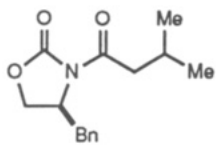
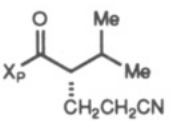
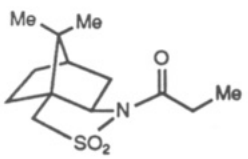
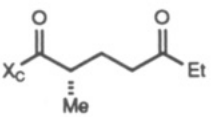
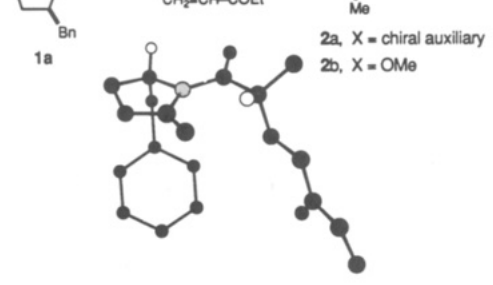
Table I. Diastereoselective Reactions of Chlorotitanium Enolates with Michael Acceptors

Entry	Substrate	Enolization[a]	Electrophile	Product	Yield, %[b]	Stereoselection[c]
A		$TiCl_4$ (1.05 equiv) 0 °C, 1.0 h	$EtCOCH{=}CH_2$[d] (1.1 equiv) -25 °C, 0.75 h		88 %	>99 : 1
B		$TiCl_3(Oi\text{-}Pr)$ (1.05 equiv) 0 °C, 1.0 h	$NCCH{=}CH_2$ (1.5 equiv) 0 °C, 6.5 h		93%	98:2
C		$TiCl_3(Oi\text{-}Pr)$ (1.05 equiv) 0 °C, 1.0 h	$MeO_2CCH{=}CH_2$ (1.5 equiv) 0 °C, 5 h		78%	99:1
D		$TiCl_3(Oi\text{-}Pr)$ (1.05 equiv) 0 °C, 1.0 h	$t\text{-}BuO_2CCH{=}CH_2$ (1.5 equiv) 0 °C, 4 h		79%	>95:5[e]
E		$TiCl_4$ (1.05 equiv) 0 °C, 1.0 h	cyclohexenone[d] (1.1 equiv) -45 °C, 1 h		80%[f]	56:44
F		$TiCl_3(Oi\text{-}Pr)$ (1.05 equiv) 0 °C, 1.0 h	$NCCH{=}CH_2$ (1.5 equiv) 25 °C, 5.5 h		70 %	>200 : 1
G		$TiCl_3(Oi\text{-}Pr)$ (1.05 equiv) 0 °C, 1.0 h	$NCCH{=}CH_2$ (1.5 equiv) 25 °C, 7 h		84%	>200:1
H		$TiCl_4$ (1.05 equiv) 0 °C, 0.5 h	$EtCOCH{=}CH_2$[d] (1.1 equiv) -25 °C, 0.75 h		33%	94:6

[a] All reactions were carried out in methylene chloride (0.1–0.4 M) in the presence of 1.05–1.1 equiv of diisopropylethylamine. [b] Yields refer to diastereomerically pure product unless noted otherwise. [c] Diastereomer ratios determined by GLC unless noted otherwise. [d] This electrophile was precomplexed with 1.1 equiv of $TiCl_4$ (–25 °C) and added via cannula into enolate solution. [e] The minor diastereomer could not be detected by ^1H NMR. [f] Yield refers to combined yield of the mixture of diastereomers.

In the initial study, the chiral propionimide **1a**, upon enolization by successive treatment with $TiCl_4$ (1.05 equiv) and diisopropylethylamine, DIPEA (1.05 equiv) (0.3 M in CH_2Cl_2, 0 °C, 1 h) was found to react with the ethyl vinyl ketone–$TiCl_4$ complex (1.1 equiv, –25 °C, 45 min) to afford the adduct **2a**, mp 82–3 °C, in 88% yield after chromatographic purification (eq 2, Table I, entry A).[9] The



(2)

reaction diastereoselectivity was found to be >100:1. The stereochemical assignment of this adduct, determined by X-ray crystallography, is in accord with the precedent established for related titanium enolate–electrophile reactions.[1] Subsequent hydrolysis of **2a** with basic hydrogen peroxide[10] and esterification with diazomethane afforded the enantiomerically pure keto ester **2b** (93%), $[\alpha]_D$ –25.0° (*c* 1.05, $CHCl_3$). This reaction is complementary to the related transformation reported by Gennari[11] and is one of the few such documented transformations of a chiral

(9) All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, and optical rotation data as well as satisfactory combustion analyses for carbon and hydrogen. See supplementary materials for details.

(10) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

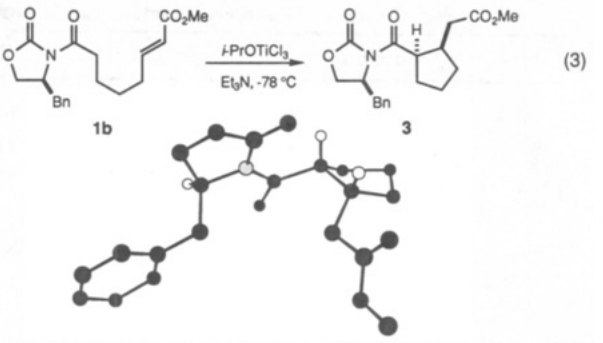
(11) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754–2760. The analogous transformation reported in this paper proceeded in 45% yield and 72% ee. The authors assigned the stereochemical course of their reaction by analogy. For a complementary enantioselective Michael reaction, see: Taber, D. F.; Mack, J. F.; Rheingold, A. L.; Geib, S. J. *J. Org. Chem.* **1989**, *54*, 3831–3836.

carboxylic acid derivative with unsaturated ketones.

The reactions of the *N*-propionyloxazolidone **1a** with methyl acrylate and acrylonitrile were also found to be highly diastereoselective (entries B–D).[12] Reaction optimization with these Michael acceptors leads to a slight modification of the preceding conditions with the adoption of *i*-PrOTiCl$_3$ as the enolizing Lewis acid, which, in concert with DIPEA[13] (0 °C, 1 h), is also known to quantitatively transform these substrates into their derived alkoxytitanium enolates.[1] In contrast to the reactions of these enolates with unsaturated ketones (entries A and E), acrylate and acrylonitrile electrophiles react at convenient temperatures (0–25 °C) without the necessity of utilizing a second equivalent of Lewis acid. Under these conditions, acid-labile *tert*-butyl esters survive intact (entry D).[14] These conjugate additions were also shown to be applicable to the other substrates shown in entries F and G. In both cases the reactions with acrylonitrile proceeded in good yield with the formation of only one detectable product diastereomer.

The scope of these reactions does not extend to include β-substituted, α,β-unsaturated esters or nitriles, which are unreactive, even as their Lewis acid conjugates; however, this restriction does not apply to α,β-unsaturated ketones. Unfortunately, this latter family of Michael acceptors shows no appreciable stereocontrol with regard to the additional prochiral center resident on the electrophilic olefin (entry E).

The application of this methodology to intramolecular reactions was also evaluated (eq 3). The reaction of substrate **1b** proved to proceed well when *i*-PrOTiCl$_3$ was employed as the enolizing Lewis acid. In contrast to the intermolecular cases, reaction diastereoselection was markedly better when triethylamine rather than DIPEA was used as the enolizing base. The optimized conditions involve addition of the substrate to a mixture of *i*-PrOTiCl$_3$ (2.0 equiv) and triethylamine (1.0 equiv) in CH_2Cl_2 (–78



(3)

°C, 5 h). Under these conditions, **1b** affords a 93:7 ratio of diastereomers from which the major adduct **3** (88%) was isolated as a crystalline solid, mp 136.6–137 °C, after chromatographic purification. The X-ray structure of **3** is fully consistent with the expected sense of asymmetric induction on the chelated *Z* enolate while the cis ring stereochemistry implicates the requirement for internal metal relocation during the Michael process.

We have also examined the Michael reactions of the Oppolzer *N*-propionylsultam[15] (entry H). The reaction with ethyl vinyl ketone proceeded with high stereoselectivity but in modest yield (33%), the principal side reaction being competing 1,2 addition (54%). These results are surprising in light of the analogous reaction with *N*-propionyloxazolidone **1a**, which affords no 1,2-addition products. Reaction of the sultam with either methyl acrylate or acrylonitrile could not be induced under a variety of conditions. The full scope of these and related reactions will be reported in due course.

Acknowledgment. Support has been provided by the NIH, the NSF, and Merck. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities. A postdoctoral fellowship for T.C.S. (NIH) is gratefully acknowledged.

Supplementary Material Available: Experimental procedures and spectral data for all new compounds (10 pages). Ordering information is given on any current masthead page.

(12) The sense of asymmetric induction in these reactions has been assigned by analogy.

(13) As a point of mechanistic interest, all of the bimolecular reactions employing DIPEA proceed with markedly better stereoselectivity than the analogous reactions using triethylamine as the enolizing base.

(14) This transformation was carried out by James R. Gage of this laboratory.

(15) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772.

Enantioselective Synthesis of β-Hydroxy δ-Lactones: A New Approach to the Synthetic Congeners of 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors

G. Bhaskar Reddy, Tatsuya Minami, Takeshi Hanamoto, and Tamejiro Hiyama*

Sagami Chemical Research Center, 4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

Received May 21, 1991

Summary: Chiral β,δ-diketo esters derived from Taber's chiral alcohol or its enantiomer were reduced either in one step (Et_2BOMe, $NaBH_4$, THF–MeOH) or in two steps (2 equiv $HAl(i\text{-}Bu)_2$, THF; Et_2BOMe, $NaBH_4$, THF–MeOH) to give *syn*-β,δ-dihydroxy esters with high diastereoselectivity. Hydrolysis of the esters followed by lactonization afforded the title lactones of high optical purity ranging from 49 to >97% ee.

The discovery of compactin (**1a**) and mevinolin (**1b**), highly potent inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG Co-A) reductase,[1] led to a number of publications concerning the synthesis and biological properties of their structural analogues (e.g., **2**), all of which

(1) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.

0022-3263/91/1956-5752$02.50/0