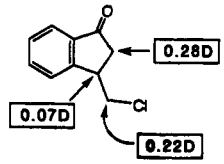
during the reaction ($AlCl_3$ (5 equiv) and CH_3OD (1 equiv) in CH_2Cl_2) and the reaction was quenched with H_2O, the mass spectrum of the product **4a** indicated that it contained 40% monodeuterated and 10% dideuterated compounds. ^1H NMR showed that deuterium was incorporated at the methylene adjacent to the carbonyl (28%), the chloromethyl group (22%), and the benzyl methine (7%).[12] These results indicate clearly that the hydrogen was derived from hydrogen halides already present in the reaction mixture during irradiation but not from H_2O added after irradiation for workup.



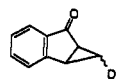
These experimental results led us to propose the reaction mechanism shown in Scheme II, though the detail is still ambiguous. Thus irradiation of C4-protonated species **2** leads to migration of the fused phenyl group to give an intermediate such as **6**. Addition of HX to **6** gives indanone **4** or **5** (path a). Formation of benzobicyclohexenone **3** (path b), if any, is less likely since cycloreversion of **3** to the starting material takes place readily. Thus interception of **6** by a halide ion (X^-) seems to play a crucial role in this ring contraction. In the case of 4-methyl derivative **1f**, migration of R group predominates over that of phenyl to yield 3-methyl-1-naphthol (**1e**).[13] Lack of reactivity in **1e** can be readily understood from the tertiary character of the cationic center of **2** derived from **1e**.

Finally, treatment of (chloromethyl)indanones **1a–d** with LDA gave benzobicyclo[3.1.0]hex-3-en-2-ones **3a–d**[14] in 74–91% yields.[15] Thus, although the mechanism of this photochemical ring contraction of **1a–d** is yet to be clarified, an overall lumiketone-type transformation (from keto tautomers) of **1a–d** was accomplished in two steps.

Acknowledgment. We are grateful to the Ministry of Education, Science and Culture for the support of the NMR and Mass Spectral facilities used in this work at the Instrumental Analysis Center of the Faculty of Engineering, Osaka University, and for partial support of this work through a Grant-in-Aid.

Supplementary Material Available: Experimental procedures and spectral data for **3a–d**, **4a–d**, **5a**, **5b**, and **5d** (6 pages). Ordering information is given on any current masthead page.

(12) The fact that a small amount of deuterium was found in the benzyl methine indicates that H3 of 1-naphthol (**1a**) was exchanged with deuterium during the photoreaction (see supplementary material). However, since this can be achieved by either 1,2-migration of a deuterium in the complex **2** (R = D in Scheme II) or cycloreversion of **3a** with a deuterium on the cyclopropyl methylene, i.e., **i**, the mechanism for this H/D exchange remains ambiguous.



i

(13) Similar 1,2-migration has been invoked in photoisomerization of 4,4-disubstituted benzocyclohexa-2,5-dienones.[5]

(14) **3a** has been known: House, H. O.; McDaniel, W. C.; Sieloff, R. F.; Vanderveer, D. *J. Org. Chem.* **1978**, *43*, 4316.

(15) For the related cyclopropane formation, see: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; p 542.

Extending the Scope of the Evans Asymmetric Aldol Reaction: Preparation of Anti and "Non-Evans" Syn Aldols[1]

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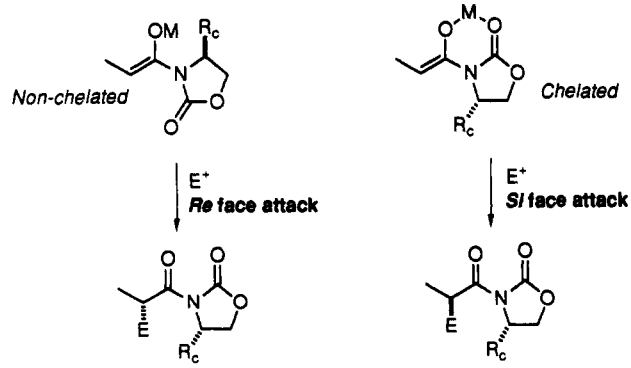
Summary: The Evans reagent, imide **1**, reacts with aldehydes under Lewis acid catalysis to give anti or "non-Evans" syn aldols **5** or **6**, depending on the reaction conditions. This discovery considerably amplifies the synthetic utility of these important reagents for asymmetric synthesis.

For some time an objective to this group has been to understand the factors that govern stereoselectivity in the aldol reaction and to apply this reaction to the stereocontrolled synthesis of chiral acyclic compounds.[2] The present research was undertaken with two goals in mind: (1) to find a convenient asymmetric, "anti aldol" method and (2) to develop methodology whereby several of the possible aldol stereoisomers can be synthesized from the same carbonyl precursor by simply changing reaction conditions.[3] This communication describes our discovery

Scheme I



(1) Part 54 in a series of papers on Acyclic Stereoselection. For part 53, see: Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.

(2) For general reviews on aldol stereoselectivity, see: (a) Heathcock, C. H. *Science* **1981**, *214*, 395. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Organic Reactions*; Wiley: New York, 1982; Vol. 28. (d) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*, Buncel E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Part B, Chapter 4. (e) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (f) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (g) Braun, M. *Ibid.* **1987**, *26*, 24.

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Table I. Lewis Acid Mediated Aldol Reactions of Boron Enolate 2[a] with Isobutyraldehyde (3c)

entry	method	Lewis acid	equiv[b]	4c:5c:6c[c]	% yield[c]
1	C	$TiCl_4$	0.5	0:20:80	*d*
2	C	$TiCl_4$	1.0	0:17:83	71
3	C	$TiCl_4$	2.0	0:16:84	83
4	A	$TiCl_4$	1.0	0:11:89	77
5	C	$SnCl_4$	0.5	0:95:5	51
6	C	$SnCl_4$	1.0	0:71:29	65
7	C	$SnCl_4$	2.0	0:13:87	60
8	B	$SnCl_4$[e]	1.0	0:92:8	76
9	C	Et_2AlCl	0.5	68:28:4	91
10	C	Et_2AlCl	1.0	4:88:8	71
11	C	Et_2AlCl	2.0	0:95:5	63

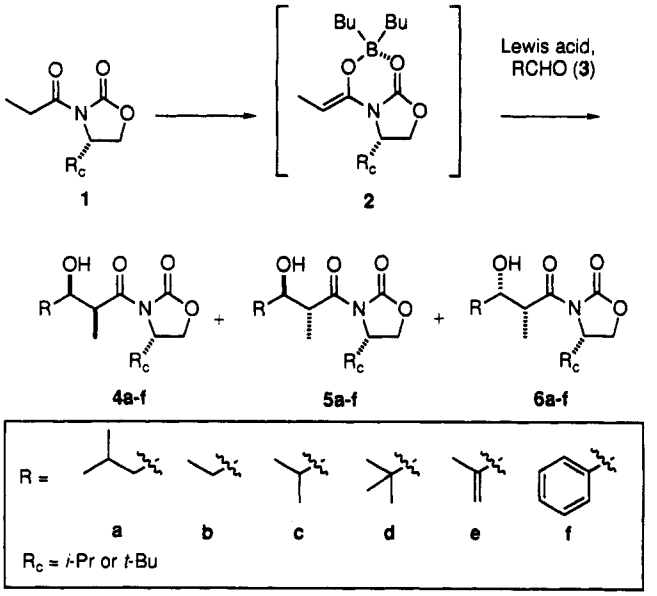
[a] R_c = *i*-Pr. [b] Equivalents of Lewis acid per equivalent of aldehyde. [c] Product ratios and yields were determined by integration of the ^1H NMR spectra of the product mixtures using an internal standard. The yield given is the total yield of aldol mixture. [d] The yield in this run was not determined. [e] In this run the enolate was formed with dicyclohexylboron triflate and Hunig's base; 1.5 equivalents of aldehyde were used.

that the boron enolate of the Evans reagent, imide 1, reacts with aldehydes that are complexed to Lewis acids to provide anti-aldols 5 or "non-Evans" syn aldols 6, depending upon reaction conditions. This finding greatly extends the utility of the Evans asymmetric aldol reaction,[4] a method of asymmetric synthesis that is already one of the most powerful in the armory of the organic chemist.

As shown in Scheme I, an *S* imide enolate reacts on its *Re* face if the metal is *not* coordinated to the oxazolidone carbonyl at the time of electrophilic attack (the normal situation in an uncatalyzed boron enolate aldol reaction)[4] and on its *Si* face if the metal *is* coordinated to the oxazolidone carbonyl (the normal situation in enolate alkylations[5] and Diels–Alder reactions of the corresponding acryloylimides[6]). This dual mode of reactivity can allow control of the configuration at the α carbon in an aldol reaction if one can control whether or not the metal is chelated at the time of the aldol reaction. One approach to this problem has recently been reported by Nerz-Stormes and Thornton, who used titanium enolates of the Evans imides to obtain non-Evans syn aldols.[7,8]

We have been following up our discovery that boron enolate 2 can under certain circumstances react with aldehydes that are complexed with a Lewis acid, presumably through an open transition state, to give anti aldols.[9] This original anti aldol method, which consisted simply of using 2 equiv of dibutylboron triflate and ethyldiisopropylamine (Hunig's base) when forming the boron enolate, was discovered in work with β-(arylthio)- and β-(alkyltho)acrolein

Scheme II



derivatives. These conditions turned out to be quite limited in scope; although they worked with benzaldehyde, they did not work for simple aliphatic aldehydes or other acrolein derivatives. Consequently, we have investigated the use of other Lewis acids, both precomplexed to the aldehyde and as additives to the aldehyde–enolate reaction mixture. Inital explorations were carried out with boron enolate 2 (R_c = *i*-Pr) and isobutyraldehyde (3c). Three different protocols were evaluated. In Method A,[10] the imide was first treated with 1 equiv each of dibutylboron triflate and Hunig's base in CH_2Cl_2 at 0 °C to form the boron enolate. After the solution was cooled to −78 °C, the Lewis acid was added in one portion followed by the aldehyde over a 30-min period. In Method B,[11] the boron enolate was prepared at 0 °C, cooled to −78 °C, and treated with the aldehyde followed by addition of the Lewis acid with a syringe pump over a period of 3–4 h. In Method C,[12] the aldehyde was precomplexed with the Lewis acid in CH_2Cl_2 at −78 °C and the boron enolate was added to the cold solution with a cannula. The results of this study are summarized in Scheme II and Table I.[13-15]

(3) For previous publications dealing with these problems, see, inter alia: (a) Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278. (b) Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897. (c) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (d) Evans, D. A.; Clark, S. J.; Rainer, M.; Novack, V. J.; Sheppard, G. S. *Ibid.* **1990**, *112*, 866. (e) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99. (f) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (g) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *Ibid.* **1990**, *112*, 6339.

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(6) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(7) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

(8) For another approach to controlling stereoselectivity in aldol reactions by making use of chelation, see ref 1.

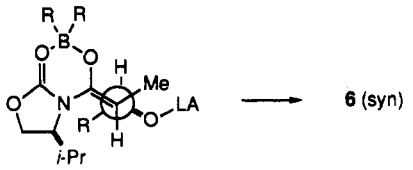
(9) Danda, H.; Hansen, M. N.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.

(10) **General Method A.** To a solution of 199 mg (1.00 mmol) of imide 1 (R_c = *t*-Bu) in 2.00 mL of CH_2Cl_2 at 0 °C were added 0.20 mL (148 mg, 1.15 mmol) of *i*-Pr_2NEt and 0.30 mL (330 mg, 1.20 mmol) of Bu_2BOTf. After 45 min at 0 °C the solution was cooled to −78 °C and 1.10 mL of $TiCl_4$ (0.92 M in CH_2Cl_2) was added. The aldehyde (1.00 mmol) was added dropwise over 30 min. After 3–5 h the reaction was quenched with a 5:1 mixture of MeOH/30% H_2O_2. Stirring was continued at −78 °C for another 10 min after which the solution was allowed to warm to 0 °C and stirred an additional 30 min. Water was added, and the layers were separated. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic layers were washed with dilute $NaHCO_3$ and brine then dried ($MgSO_4$). After filtration and evaporaton of the solvent the crude product was chromatographed on SiO_2 (230–400 mesh, 3:1–4:1 hexanes/EtOAc).

(11) **General Method B.** To a solution of 391 mg (1.00 mmol) of dicyclohexylboron triflate in 2.00 mL of CH_2Cl_2 were added 0.20 mL (148 mg, 1.15 mmol) of *i*-Pr_2NEt and 185 mg (1.00 mmol) of imide 1 (R_c = *i*-Pr). After 1 h at 0 °C the solution was cooled to −78 °C and a solution of the aldehyde (1.00 mmol) in 1.00 mL of CH_2Cl_2 cooled to −78 °C was added by cannula. After this, 0.54 mL of $SnCl_4$ (1.84 M in CH_2Cl_2) was added over 3 h by syringe pump. Stirring was continued overnight at −78 °C. The reaction was quenched and worked up as in Method A.

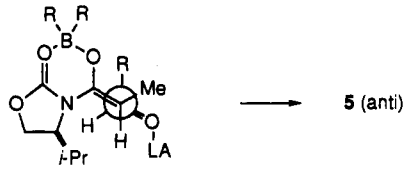
(12) **General Method C.** The boron enolate 2 (R_c = *i*-Pr) was generated as in method A and cooled to −78 °C. In a separate flask the aldehyde (1.5 mmol) was added to a solution of 3.00 mL of Et_2AlCl (1.0 M in hexanes) in 2.00 mL of CH_2Cl_2. After being stirred for 5 min the cooled enolate was added by cannula, using an additional 1.00 mL of CH_2Cl_2 to aid the transfer. After 3–5 h the reaction was quenched and the mixture worked up as in Method A.

Scheme III



6 (syn)

A: favored for small Lewis acids



5 (anti)

B: favored for large Lewis acids

Table I shows that in almost all of these Lewis acid mediated cases the normal Evans syn aldol **4** is formed in only trace amounts, if at all. The stereoselectivity, both in sense and in magnitude, is dependent on several factors—the nature of the Lewis acid, the number of equivalents of Lewis acid (with respect to aldehyde), and the order in which the reactants are combined. For example, utilizing method C with 1.0 equiv of Lewis acid (entries 2, 6, 10), $TiCl_4$ is syn selective, whereas $SnCl_4$ and Et_2AlCl are anti selective. With 2.0 equiv of Lewis acid (entries 3, 7, 11) $TiCl_4$ and $SnCl_4$ are both syn selective while Et_2AlCl gives the anti product. Finally, with 0.5 equiv of Lewis acid (entries 1, 5, 9) $SnCl_4$ is extremely anti selective, $TiCl_4$ is only moderately syn selective, and Et_2AlCl gives mostly the Evans syn product **4c** (the **5c:6c** ratio of 28:4 corresponds to 88:12, about the same as it is with either 1.0 or 2.0 equiv of Et_2AlCl). The unqiue behavior of the different Lewis acids is therefore summarized as follows: $TiCl_4$ is syn selective regardless of stoichiometry, Et_2AlCl is anti selective regardless of stoichiometry, and $SnCl_4$ is syn or anti selective, depending on whether an excess of aldehyde (entry 5) or Lewis acid (entries 7 and 11) is used. A large excess of one of the reactants can also be achieved by slowly adding either the aldehyde (Method A) or Lewis acid (Method B), and both of these experiments gave high selectivity (entries 4 and 8). This protocol works because the Lewis acid mediated aldol reaction of **2** is much faster than the uncatalyzed reaction; at −78 °C, the half-life for the uncatalyzed reaction is on the order of 5 h. Use of dicyclohexylboron triflate (entry 8) slows the uncatalyzed reaction even further.

We believe that the configurational dependence on the Lewis acid to aldehyde ratio is related to the effective steric bulk of the Lewis acid. Our working hypothesis, illustrated in Scheme III, is that aldols **6** and **5** result from the open transition states **A** and **B**, respectively.[16] If the Lewis acid is small, transition sate **A** is preferred because it minimizes gauche interactions about the forming bond. However, if the Lewis acid is large, transition state **B** becomes competitive because of the methyl–Lewis acid interaction in **A**. We think that Et_2AlCl acts as a bulky Lewis acid and gives anti because the O–Al bond is short and the ligands are relatively bulky. On the other hand, $SnCl_4$ and $TiCl_4$ are effectively smaller than Et_2AlCl because of the longer Sn–O and Ti–O bond lengths. However, with $SnCl_4$ and $TiCl_4$ slow addition of the Lewis acid to the aldehyde gives a reactive 2:1 complex[17] in which the effective bulk of the Lewis acid is increased because of its octahedral coordination; hence, this protocol gives anti.[18] A similar effect

Table II. Syn-Selective, Lewis Acid Mediated Aldol Reactions of Boron Enolate 2[a] with Different Aldehydes

entry	method	aldehyde	Lewis acid[b]	5:6[c]	% yield[c]
1	A	**3a**	$SnCl_4$	7:93	64
2	A	**3a**	$TiCl_4$	13:87	68
3	A	**3b**	$SnCl_4$	10:90	66
4	A	**3b**	$TiCl_4$	12:88	72
5	A	**3c**	$TiCl_4$	6:94	70
6	A	**3d**	$TiCl_4$	11:89	50
7	A	**3e**	$TiCl_4$	13:87	65
8	A	**3f**	$TiCl_4$	8:92	65

[a] R_c = *t*-Bu. [b] Unless otherwise indicated, 2.0 equiv of Lewis acid were used. [c] Determined by ^1H NMR. The yield given is the total yield of aldol mixture.

Table III. Anti-Selective, Lewis Acid Mediated Aldol Reactions of Boron Enolate 2[a] with Different Aldehydes

entry	method	aldehyde[b]	Lewis acid[b]	5:6[c]	% yield[c]
1	C	**3a**	Et_2AlCl	86:14[d]	86
3	C	**3b**	Et_2AlCl	88:12	81
5	C	**3c**	Et_2AlCl	95:5	63
6	C	**ed**	Et_2AlCl	95:5	65
7	C	**3e**	Et_2AlCl	90:10	67
8	C	**3f**	Et_2AlCl	74:26	62

[a] R_c = *i*-Pr. [b] In all runs 1.5 equiv of aldehyde and 3.0 equiv of Et_2AlCl were used. [c] Determined by ^1H NMR. The yield given is the total yield of aldol mixture. [d] In this run, about 4% of aldol **4a** was also produced.

(13) In addition to the three Lewis acids shown, a number of others were evaluated: BF_3–Et_2O, $B(OTf)_3$, BCl_3, *n*-Bu_2BOTf, TMSOTf, $TiCl_2(O\text{-}i\text{-}Pr)_2$, $Zn(OTf)_2$, $ZnCl_2$, $ZnBr_2$, $TiCl_4$–PPh_3, $EtAlCl_2$, *i*-Bu_2AlCl, MAD, (BHT)MeAlOTf. Each was inferior because of low yields, poor selectivity, or irreproducible results.

(14) Appropriate control experiments were carried out to assure that the reactions were under kinetic control.

(15) The structures of **4c** and **5c** were assigned by (i) ^1H NMR and ^{13}C NMR correlations and (ii) removal of the chiral auxiliary with LiOH/H_2O_2 and characterization of the known β-hydroxy acids; details are given in the supplementary material.

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(17) (a) Satchell, D. P. N.; Satchell, R. S. *Chem. Rev.* **1969**, *69*, 251. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (c) Lazlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750. (d) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Hiedelberg, 1986.

(18) When using method B (slow addition of the Lewis acid), the uncatalyzed reaction leading to **4** tends to compete. For this reason, we found it best to use the dicyclohexylboron enolate in this case, since it is less reactive than the dibutylboron enolate under uncatalyzed conditions.

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

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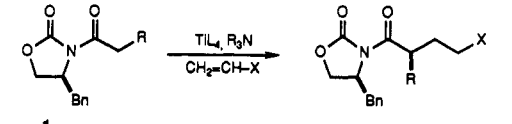
Summary: In the present study we wish to report the details of the diastereoselective reactions of titanium enolates derived from *N*-propionyloxazolidone **1** in inter- and intramolecular Michael reactions with ethyl vinyl ketone, methyl acrylate, and acrylonitrile (eq 1).

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.



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