TADDOL-Based Titanium Catalysts and Their Adducts: Understanding Asymmetric Catalysis of Diels–Alder Reactions

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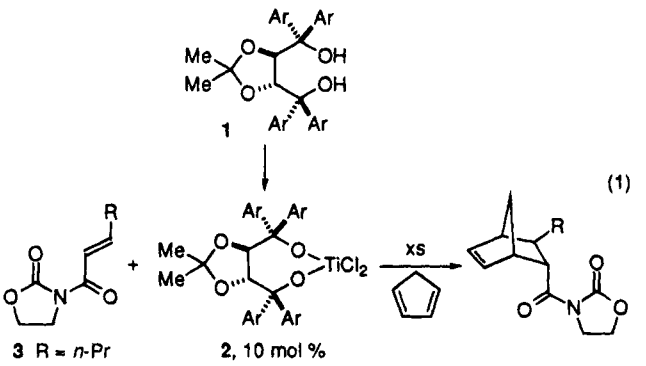
The parent TADDOL auxiliary **1a** and newly synthesized variants **1b–f** have been converted to TADDOLTiCl$_2$ catalysts **2a–f**, which are effective catalysts for asymmetric Diels–Alder reactions of cyclopentadiene and unsaturated *N*-acyloxazolidinones like **3**. As MW determination and VT-NMR demonstrated catalysts **2a–f** to be well-defined, a series of VT-NMR experiments were conducted on the adducts of these catalysts and (*i*-PrO)$_2$TiCl$_2$ with Lewis bases like **3**, diethyl dimethylmalonate, diethyl oxalate, and diisopropyl oxalate. These experiments led to the following conclusions: (1) the Lewis bases examined are bidentate ligands for **2a–f** and (*i*-PrO)$_2$TiCl$_2$; (2) of the five possible adducts between **3** and **2a–f**, only three are observed; (3) the most abundant adduct of **3** and **2a–f** has all four oxygen ligands in the equatorial plane of octahedral titanium and binds **3** remote to the TADDOL aryl residues; (4) the second most abundant adduct of **3** and **2a–f** has only three of the four oxygen ligands in the equatorial plane and binds **3** proximal to one of the pseudoaxial TADDOL aryl residues; (5) the exchange of catalyst **2a–f** bound **3** for free **3** is rapid relative to the rate of Diels–Alder addition.

Introduction

Recently there has been a great deal of activity in the area of asymmetric catalytic reactions,[1] particularly enantioselective, catalytic Diels–Alder reactions.[2,3] Relatively little effort, however, has been devoted to understanding the mechanistic aspects of these reactions.[4] An interesting example is the highly enantioselective Diels–Alder reaction of unsaturated *N*-acyloxazolidinones and cyclopentadiene catalyzed by chiral titanium complexes derived from widely applied α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols[5] (TADDOLs, e.g., **1**) as reported by Narasaka and co-workers (eq 1),[6] for which only two



(1)

mechanistic studies[7] have been reported to date.[8] The importance of understanding the origins of enantioselectivity for such reactions has prompted us to examine the ^{1}H and ^{13}C VT-NMR spectra of *trans*-3-hex-2-enoyl-1,3-oxazolidin-2-one (**3**), diisopropyl oxalate, and diethyl dimethylmalonate adducts with (*i*-PrO)$_2$TiCl$_2$ and several newly synthesized and characterized TADDOLTiCl$_2$ catalysts (**2**). The results of these experiments when accompanied by molecular modeling provide new insights into this enantioselective, catalytic process.

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(4) For example, see: (a) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325–6328. (b) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218–2229. (c) Ishihara, K.; Gao, Q. Z.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412–10413. (d) Togni, A.; Rist, G.; Rihs, G.; Schweiger, A. *J. Am. Chem. Soc.* **1993**, *115*, 1908–1915. (e) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938–7939. (f) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290–8292.

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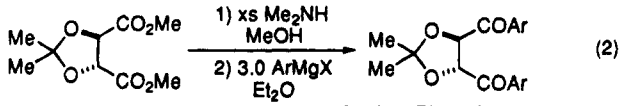
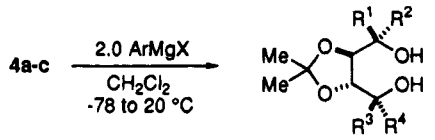
Results and Discussion

TADDOL Synthesis. TADDOL **1a** was synthesized as reported[9] and its analogue **1b** with 3,5-xylyl instead of phenyl substituents by similar means. Access to TADDOLs with two different aryl groups while maintaining C_2 symmetry (**1c–f**) required another approach relying on chelation-controlled addition of Grignard reagents to α-alkoxy ketones,[10] which has also been used by Seebach and co-workers (eqs 2 and 3).[11] Reaction of



(2)

4a Ar = Ph (ref 11)
4b Ar = *p*-fluorophenyl 66%
4c Ar = 3,5-xylyl 49%



(3)

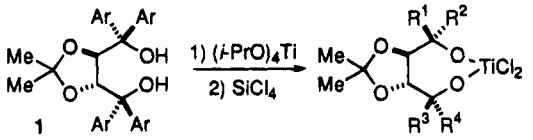
1a $R^1 = R^2 = R^3 = R^4 =$ Ph
1b $R^1 = R^2 = R^3 = R^4 =$ 3,5-xylyl
1c $R^1 = R^4 =$ Ph, $R^2 = R^3 =$ *p*-fluorophenyl
1d $R^1 = R^4 =$ *p*-fluorophenyl, $R^2 = R^3 =$ Ph
1e $R^1 = R^4 =$ Ph, $R^2 = R^3 =$ 3,5-xylyl
1f $R^1 = R^4 =$ 3,5-xylyl, $R^2 = R^3 =$ Ph

dimethylamine with the isopropylidene acetal of dimethyl L-tartrate[12] afforded an amide,[13] which upon treatment with the appropriate arylmagnesium halide gave ketones **4a–c**.[14] Addition of the appropriate arylmagnesium halide to ketones **4a–c** typically gave four products: two C_2-symmetric bisaddition products, a C_1-symmetric bisaddition product, and a monoaddition product. These were readily differentiated by ^{1}H NMR and chromatographically separable. The expected[10] C_2-symmetric product was greatly preferred relative to the other (≥20:1) and modestly preferred relative to the C_1-symmetric product (≥8:1). The monoaddition product constituted ca. 15% of the reaction mixture.[15] The major C_2-symmetric product was assigned the indicated configuration based on analogy to the results of Still and Seebach (see above).[16]

The substitution pattern at the 2-position of the 1,3-dioxolane ring of a TADDOL is recognized to influence dramatically the enantioselectivity of Diels–Alder reactions.[6] In the catalysts synthesized and characterized in this study, however, the substitution of the 2-position was kept constant with geminal methyl groups. This provided a clear spectroscopic marker and decreased the complexity of spectra in the NMR examinations of the adducts derived from these TADDOL$TiCl_2$ catalysts.

Catalyst Synthesis and Characterization. Several methods were evaluated for the preparation of TADDOL-$TiCl_2$ catalysts **2a–f**. Narasaka's method,[6] the metathesis reaction of TADDOLs and $(i\text{-PrO})_2TiCl_2$, did not provide pure catalysts in our hands. While the reaction could be driven to completion, the 2-propanol released associated strongly with the catalyst and could not be removed azeotropically or under high vacuum. Treatment of $TiCl_4$ directly with 1 equiv of a TADDOL in the presence or absence of acid scavenging agents gave complex mixtures. With the hope of effecting a milder metathesis reaction, $TiCl_4$ was treated with the bis(trimethylsilyl) ether of TADDOL **1a**. After extended periods at 20 °C or with heating, material with only one Ti–O bond was obtained as suggested by ^{1}H NMR.

Other procedures proved more profitable. The metathesis reaction of $TiCl_4$ and "spirotitanate" esters, derived from 2 equiv of TADDOL and $(i\text{-PrO})_4Ti$ with removal of 2-propanol, was effective; catalysts **2** afforded by this method gave a single set of sharp ^{1}H NMR signals at 20 °C and were free of contaminants.[5f] The protocol to obtain the necessary TADDOL "spirotitanate" esters, however, was time consuming and sometimes difficult to drive to completion. The protocol of Corey, sequential treatment of a TADDOL with $(i\text{-PrO})_4Ti$ and then $SiCl_4$, proved more effective (eq 4). The catalysts obtained



(4)

2a $R^1 = R^2 = R^3 = R^4 =$ Ph
2b $R^1 = R^2 = R^3 = R^4 =$ 3,5-xylyl
2c $R^1 = R^4 =$ Ph, $R^2 = R^3 =$ *p*-fluorophenyl
2d $R^1 = R^4 =$ *p*-fluorophenyl, $R^2 = R^3 =$ Ph
2e $R^1 = R^4 =$ Ph, $R^2 = R^3 =$ 3,5-xylyl
2f $R^1 = R^4 =$ 3,5-xylyl, $R^2 = R^3 =$ Ph

directly from TADDOLs were only contaminated by traces of mesitylene[17] and traces of a silicon-containing impurity. This protocol was used to generate the catalysts **2a–f** used in this study. When stored at 20 °C as solids under an inert atmosphere, significant decomposition of catalysts **2a-f** was observed within several days. When stored in the same manner except at −30 °C, they were stable for weeks.

That catalysts **2** were obtained cleanly with one set of NMR signals does not mean that they are well-behaved compounds. Transition metal alkoxides and mixed halide alkoxides are notorious for aggregation and fluxional behavior,[18] while bisalkoxides have an additional pathway available to them (eq 5).[19] MW determination and

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(13) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301–325.

(14) Briggs, M. A.; Haines, A. H.; Jones, H. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 795–798.

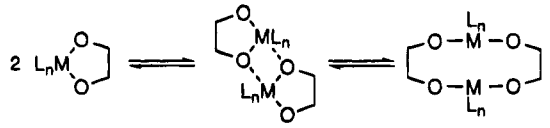
(15) Interestingly, the hydroxy ketone resulting from monoaddition was obtained as essentially a single stereoisomer, suggesting that the second Grignard addition is much less selective than the first.

(16) No effort was made to determine if racemization had occurred during the addition process. Seebach observes little or no racemization under these conditions (ref 11).

(17) Mesitylene was used to drive off volatile silicon-containing byproducts during its evaporation. See the Experimental Section.

(18) Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic Press: New York, 1978.

(19) For example, see the following and references therein: (a) Boyle, T. J.; Barnes, D. L.; Heppert, J. A.; Morales, L.; Takusagawa, F.; Connolly, J. W. *Organometallics* **1992**, *11*, 1112–1126. (b) Huffman, J. C.; Moloy, K. G.; Caulton, K. G. *Inorg. Chem.* **1988**, *27*, 2190–2192. (c) Erker, G.; Rump, M.; Krüger, C.; Nolte, M. *Inorg. Chim. Acta* **1992**, *200*, 679–687.



(5)

VT-NMR experiments suggest, however, that TADDOL-$TiCl_2$ catalysts are well-behaved, monomeric species. Application of the Signer method[20] to benzene solutions of **2a** and **2b** indicated that they were mononuclear: **2a**, calcd MW = 583, found = 572; **2b**, calcd MW = 696, found = 654. VT-NMR experiments spanning a temperature range of −80 to 35 °C gave no hint of any dynamic behavior to suggest aggregates or bridging dimers.

Bidentate Adducts of Compounds $(RO)_2TiCl_2$. Before describing the VT-NMR experiments performed, it is worthwhile to discuss the number and types of possible adducts between oxazolidinone **3** and $(i\text{-PrO})_2TiCl_2$ or catalysts **2a−f**. Given that **3** and the other Lewis bases used (vide infra) are bidentate ligands and given the proclivity of titanium to obtain a hexacoordinate state,[21] octahedral complexes should result. Then with $(i\text{-PrO})_2TiCl_2$ and **3**, four different adducts are possible (**A−D**, Chart 1). Of these, **D** can be ruled out because the two strongest π-donors, the alkoxy groups, are trans to each other, preventing maximization of oxygen-p titanium-d π-bonding.[22] Generally, the weakest bonded ligands like **3** are located opposite the strongest π-bonding ligands. With catalysts **2a−f** and **3**, five different adducts are predicted (**E−I**). The bisalkoxide nature of TADDOLs constrains the strongest π-donor alkoxy ligands to be cis to each other.

Adducts of 2a and $(i\text{-PrO})_2TiCl_2$ with 3. Combining oxazolidinone **3** and $(i\text{-PrO})_2TiCl_2$ in a 1.25:1 ratio in CD_2Cl_2, the NMR solvent used in all VT experiments described, led to broad signals in the ^1H NMR spectrum at 20 °C. Chilling this mixture to −30 °C or colder gave spectra at the slow exchange limit, where the formation of *one* adduct involving all the $(i\text{-PrO})_2TiCl_2$ was observed as indicated by chemical shift changes for several protons of oxazolidinone **3**.[23] In uncomplexed **3**, the C5 and C6 protons (see Table 1 for numbering) appear as a multiplet centered at 7.10 ppm. In the adduct, they were observed as a doublet at 6.13 ppm (C5-H) and a doublet of triplets at 7.57 ppm (C6-H). This is the same pattern of shielding and deshielding observed by Castellino in studies of *N*-acyloxazolidinones complexed to Lewis acids.[24]

Warming of the sample suggested that the dynamic process in question was the exchange of bound **3** for unbound **3**. In ^1H NMR spectra, signals for bound and unbound **3** began broadening at the same temperature. At higher temperatures, broad absorptions could be observed at chemical shifts that were the weighted average of chemical shifts for the corresponding protons

Chart 1

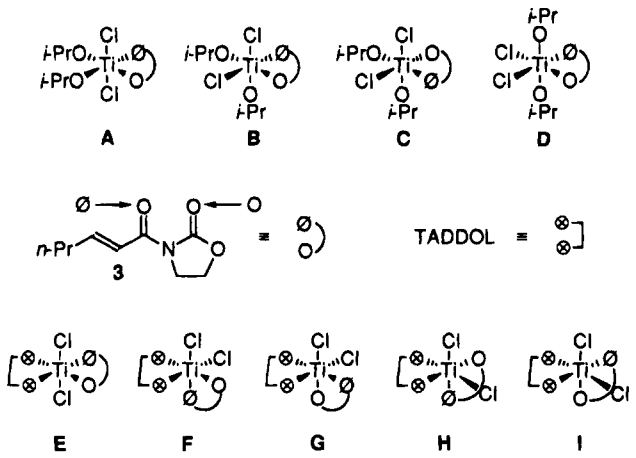
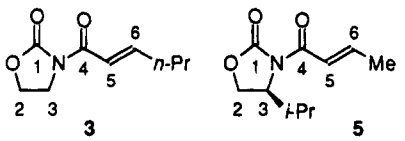


Table 1. ^{13}C NMR Chemical Shift Difference Data for Oxazolidinones 3 and 5 and Their Adducts with $SnCl_4$, $(i\text{-PrO})_2TiCl_2$, and Catalyst 2a



C no.	$SnCl_4$·**5**[a]	catalyst **2a**·**3**[b]	$(i\text{-PrO})_2Cl_2Ti$·**3**
1	+5.3	+3.0	+4.0
2	+3.1	+2.8	+2.9
3	+3.2	+1.6	+1.8
4	+4.0	+2.1	+1.6
5	−4.2	−1.6	−2.0
6	+18.4	+10.4	+10.8

[a] Data from ref 24a. [b] Chemical shift difference with most abundant adduct.

of bound and unbound **3**. This behavior held true for all the adducts discussed herein. Complete band shape analysis[25] allowed the free energy of activation for this process to be determined as 11.6 kcal/mol at 298 K. Further manipulation afforded $\Delta H^{\ddagger} = 17.2$ kcal/mol and $\Delta S^{\ddagger} = +19$ eu. The large and positive entropy of activation is consistent with a dissociative process. Binding of **3** to $(i\text{-PrO})_2TiCl_2$, the microscopic reverse of the observed process, can be assumed to have a small free energy of activation. Thus, the thermodynamic quantities obtained may be used as a measure of the affinity of $(i\text{-PrO})_2TiCl_2$ for **3** (vide infra).

At 30 °C, ^1H NMR spectra of oxazolidinone **3** and a slight excess of catalyst **2a** were broadened (see Figure 1). Chilling to ca. −10 °C gave spectra indicative of having reached the slow exchange limit and revealed the presence of *three* adducts in a 70:24:6 ratio. This was evident from the observation of three doublets each with coupling constants of ca. 15 Hz at 6.04, 5.45, and 5.95, in order of decreasing abundance, assignable to the C5-H of bound **3**. No free **3** was observed.

With the second most abundant adduct, two observations suggested that bound **3** was in proximity to a TADDOL phenyl residue. At −11 °C the doublet at 5.45 ppm, assignable to the C5-H of bound **3** in the second most abundant adduct, was observed ca. 0.60 ppm upfield of the corresponding peak for the most abundant adduct (6.05 ppm) and the $(i\text{-PrO})_2TiCl_2$ adduct (6.13 ppm), where no aryl shielding or deshielding effects are pos-

(20) This technique gives MW values with an accuracy of ±10%. See: Burger, B. J.; Bercaw, J. E. In *Experimental Organometallic Chemistry: A Practicum in Synthesis and Characterization*; Wayda, A. L., Darensbourg, M. Y., Eds.; ACS Symposium Series 357; American Chemical Society: Washington, D.C., 1987; Chapter 4, pp 94−96.

(21) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis, Vol. 1, Additions to C−X π Bonds*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Part 1, pp 283−324.

(22) Chisholm, M. H.; Rothwell, I. P. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: New York, 1987; Vol. 2, Chapter 15.3.

(23) With time, samples containing **3** and $(i\text{-PrO})_2TiCl_2$ formed two new species. The ^1H NMR signals for one of the two were consistent with the formation of isopropyl 2-hexenoate.

(24) (a) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197−5200. (b) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987.

(25) Sandström, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982.

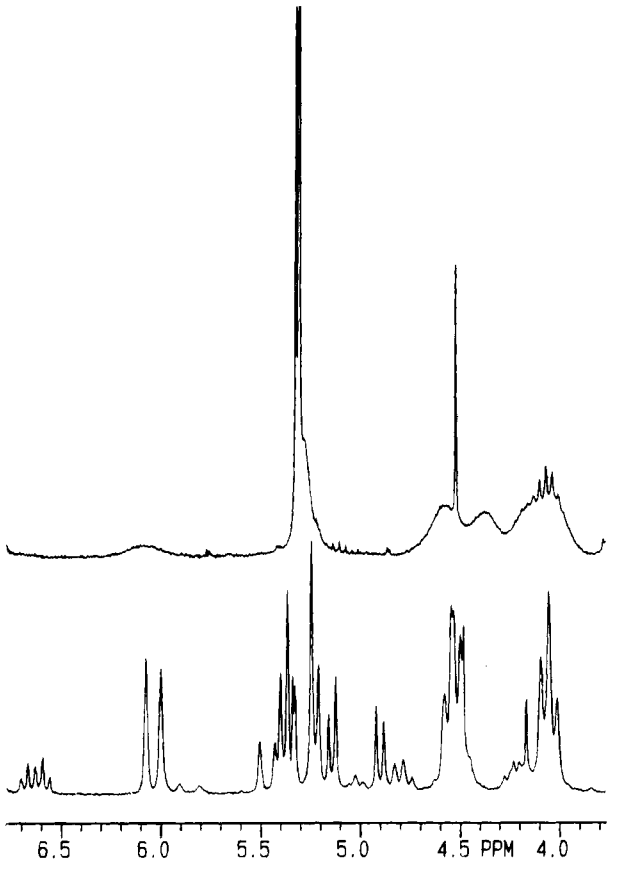


Figure 1. ^{1}H NMR data (200 MHz) for a selected region of a CD_2Cl_2 solution of catalyst **2a** and *N*-acyloxazolidinone **3** at 30 °C (top trace) and −11 °C (bottom trace).

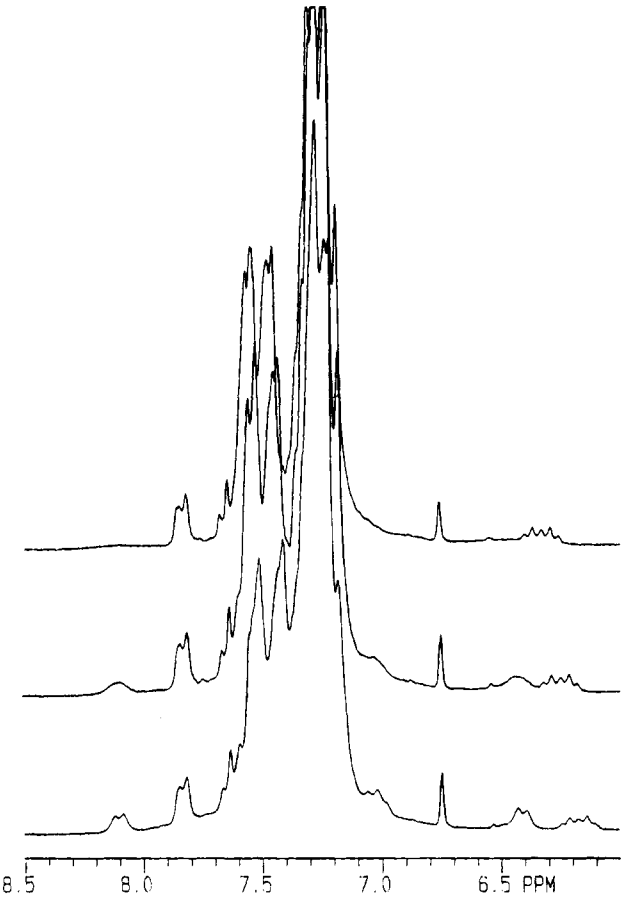


Figure 2. ^{1}H NMR data (200 MHz) for the aromatic region of a CD_2Cl_2 solution of catalyst **2a** and *N*-acyloxazolidinone **3** at −66, −77, and −88 °C (top to bottom).

sible. The doublet of triplets at 6.63 ppm, assignable to the C6-H of bound **3** in the second most abundant adduct, was ca. 1.0 ppm upfield of the corresponding peak for the most abundant adduct (ca. 7.60 ppm)[26] and the $(i\text{-PrO})_2TiCl_2$ adduct (7.57 ppm). Further, three of the four protons (the fourth is obscured) assignable to the C2 and C3 hydrogens of the second most abundant adduct were observed at 4.81, 4.22, and 3.50 ppm, suggesting significant differences between the two faces of the oxazolidinone. These protons were observed at 4.55 and 4.05 ppm for the most abundant adduct and at 4.76 and 4.41 ppm for the $(i\text{-PrO})_2TiCl_2$ adduct. The simplest explanation for this systematic shielding of bound **3** is its proximity to a TADDOL phenyl residue of **2a**.

The second observation concerned the simultaneous appearance of two broadened peaks at 8.11 and 6.43 ppm at −77 °C, which sharpened to two doublets with a coupling constant of 7.2 Hz at or below −86 °C (see Figure 2). These signals can be assigned to the two ortho protons of a TADDOL phenyl residue of the second most abundant adduct based on integration. Line shape analysis using a coupled two-site exchange model for their coalescence yielded a free energy of activation 9.9 kcal/mol at −77 °C. Again, this high rotational barrier can be explained by the proximity of bound **3** to a TADDOL phenyl residue.

The exchange of **2a** bound **3** in the most abundant adduct for unbound **3** was also analyzed by line shape analysis.[27] A free energy of activation of 15.3 kcal/mol at 298 K was determined for what is assumed to be the dissociation of bound **3**. This is significantly larger than the 11.6 kcal/mol observed for the adduct of $(i\text{-PrO})_2TiCl_2$ and **3** (vide supra). A similar analysis for the second most abundant adduct of **2a** bound **3** was not possible with the variable temperature NMR data collected to date. The free energy of activation appears comparable, though, given that the initiation of signal broadening for bound **3** of the second most abundant adduct occurs at roughly the same temperature as the most abundant adduct.

The phrase "ligand acceleration effect" was coined by Sharpless to describe the observation that titanium tartrate catalysts are more effective than $(i\text{-PrO})_4Ti$ for catalyzing epoxidation reactions.[28] Although there is no direct evidence for such an effect in $TADDOLTiCl_2$-catalyzed Diels–Alder reactions,[29] the related TADDOL-$Ti(O\text{-}i\text{-Pr})_2$ systems do display a "ligand acceleration effect" for dialkylzinc addition to aldehydes.[5f] If the free energies of activation for dissociation determined herein are a measure of catalyst binding affinity, the large difference in dissociation energy observed above offers

(26) The uncertainty of the chemical shift for this proton is because it is partially obscured by the broad aromatic envelope.

(27) Adduct interconversion via 5-coordinate titanium intermediates does not seem likely because adduct interconversion only occurred when exchange of free for bound **3** was observed, indicating a completely dissociative pathway.

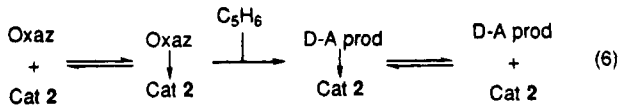
(28) See the following and references cited therein: Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.

(29) Under Narasaka's asymmetric Diels–Alder reaction conditions, an 87:13 ratio of $TADDOLTiCl_2$ to $(i\text{-PrO})_2TiCl_2$ exists (ref 7a). Despite this, high enantioselectivity was still observed, suggesting that the $TADDOLTiCl_2$ catalyst is more effective than its achiral variant.

an explanation for this effect. Simply, the more tightly bound adducts of TADDOLTiCl$_2$ and presumably TADDOLTi(O-*i*-Pr)$_2$ catalysts experience a higher degree of Lewis acid activation, leading to greater acceleration, than the more weakly bound and less activated adducts of (*i*-PrO)$_2$TiCl$_2$ and presumably (*i*-PrO)$_4$Ti. Given that the electron differences between a given TADDOL and achiral titanium catalyst pair are not obvious, the increased binding affinity observed with TADDOLTi catalysts is possibly the result of decreased steric interactions with bound substrates relative to achiral titanium catalysts.

The low-temperature ^{13}C NMR spectral data collected for the adducts of **3** with (*i*-PrO)$_2$TiCl$_2$ and **2a** allow the mode of association of **3** to be determined. In 1990, Castellino reported ^{1}H, ^{13}C, and ^{119}Sn VT-NMR data on the SnCl$_4$ adduct of (*S*,*trans*)-3-(but-2-enoyl)-4-(1-methylethyl)-1,3-oxazolidin-2-one (**5**).[24a] The ^{119}Sn chemical shift of this adduct was such that a six-coordinate tin species was assigned, indicating bidentate association of the oxazolidinone. As a similar experiment exploiting ^{47}Ti or ^{49}Ti NMR did not seem feasible,[30] a comparison was made of the ^{13}C NMR chemical shift differences between free and bound unsaturated *N*-acyloxazolidinone for these three adducts (see Table 1). Since the pattern of chemical shift differences is similar, albeit of reduced size, oxazolidinone **3** is coordinating in a bidentate manner, and titanium is six-coordinate and presumably octahedral. The smaller chemical shift differences seen with the two (RO)$_2$TiCl$_2$ compounds is expected given their decreased Lewis acidity relative to SnCl$_4$.

A plausible series of steps describing a Lewis acid catalyzed Diels–Alder reaction is shown in eq 6: (1)



(6)

binding and activation of the dienophile by Lewis acid catalyst, (2) Diels–Alder addition, and (3) release of Diels–Alder adduct from catalyst. The free energies of activation obtained for dissociation of **3** from (*i*-PrO)$_2$TiCl$_2$ and catalyst **2a** were extrapolated to provide rate constants at room temperature: 2980 and 17 s^{-1} at 290 K for (*i*-PrO)$_2$TiCl$_2$ and **2a**, respectively. Since the Diels–Alder additions catalyzed by **2a** require hours at 0 °C, the first step of the reaction is not rate determining. Also, if the Diels–Alder adduct is comparable to **3** as a ligand, a reasonable assumption, the third step is not rate determining either. With this, the Diels–Alder addition of the second step becomes both the rate- and stereochemistry-determining step, and Curtin-Hammett[31] reaction conditions prevail. Therefore, conclusions concerning the relative contributions of each of the adducts observed must be qualified.

Adducts of 2b–f with 3. ^{1}H NMR spectra of **3** and a slight excess of catalyst **2b** were broadened at 20 °C. Chilling to ca. −10 °C gave spectra at the slow exchange limit. At −50 °C, the presence of three adducts in a 59:34:7 ratio was indicated by AB spin systems at 5.30 and 4.91 ppm, 5.02 and 4.65 ppm, and 5.10 and 4.75 ppm, in order of decreasing abundance, assignable to the dioxolane methine signals of bound **2b**.

Shielded nuclei and hindered aryl rotation were observed again for the second most abundant adduct. At −50 °C, the multiplet at 5.91 ppm,[32] assignable to the C6-H of bound **3** in the second most abundant adduct, was observed 1.80 and 1.66 ppm upfield, respectively, of the corresponding peak for the major adduct (7.71 ppm) and the (*i*-PrO)$_2$TiCl$_2$ adduct (7.57 ppm). Further, a peak began to appear at 6.01 ppm at ca. −66 °C, which sharpened with decreasing temperature. Given the preceding and following examples, this signal can again be assigned to an ortho hydrogen of a 3,5-xylyl residue that has a significant barrier to rotation.

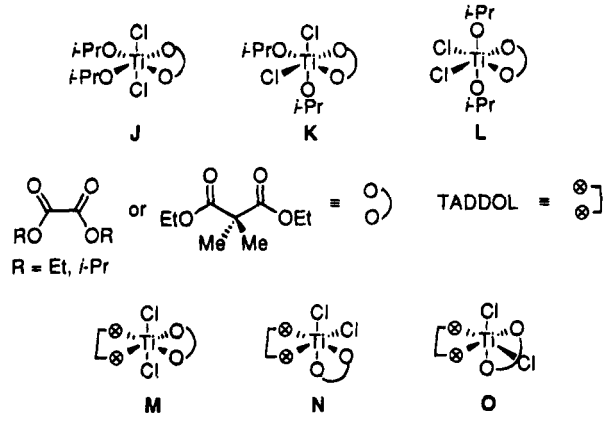
The structural features of TADDOLs are quite regular whether as the free alcohol or bound to titanium as revealed by a number of crystal structures.[5f,8,9,33] These structural studies revealed that the four aryl groups are not equivalent and can be broken into two sets of pseudoaxial and pseudoequatorial. The pseudoaxial aryl groups always point in the direction opposite to the nearest dioxolane oxygen-bearing methine C–H.

In light of this, the C_2-symmetric but differentially *para*-fluorinated TADDOL catalysts **2c** and **2d** were synthesized with the hope of performing heteronuclear NOE experiments on their adducts with **3**. While the planned NOE experiments proved inconclusive, the patterns observed with other adducts of **3** and TADDOLTiCl$_2$ catalysts were maintained. The ^{19}F NMR spectrum of catalyst **2d** combined with excess **3** at 20 °C showed a broad singlet. Chilling this sample to −75 °C gave four signals, which could be grouped into two sets based on their 6:1 relative areas. That two sets of two peaks were observed is not unexpected. The two C_2-related fluorinated aryl groups of catalysts **2c** and **2d** became different upon coordination of **3**, and the 6:1 ratio reflected the presence of two different adducts. The ^{19}F NMR spectrum of catalyst **2c** and **3** showed the same dynamic behavior at 20 °C. Unlike the mixture of **2d** and **3**, only a single pair of signals was observed by ^{19}F NMR at −75 °C for the solution of **2c** and **3**. ^{1}H NMR suggested, however, that two adducts were present for this mixture and that their ratio was comparable to that of **2d** and **3**.[34]

Homonuclear NOE experiments involving catalysts **2e** and **2f** also proved inconclusive. However, the hindered aryl rotations observed with other TADDOLTiCl$_2$ adducts of **3** suggested a means of differentiating the roles of the pseudoaxial and pseudoequatorial aryl groups. The ^{1}H NMR spectra resulting from combining catalysts **2e** or **2f** with **3** matched the previously described patterns: dynamic behavior and three adducts upon chilling to less than −10 °C (see the Experimental Section). Upon further chilling, the slowed rotation of one aryl group of the second most abundant adduct was again observed for both systems. With the adduct of **3** and catalyst **2e** starting at −65 °C, two *doublets* grew into the spectra at 8.02 and 6.35 ppm, indicating that an unsubstituted phenyl group had slowed its rotation. With the adduct of **3** and catalyst **2f** starting at −65 °C, two *singlets* grew into the spectra at 7.71 and 5.93 ppm, indicating that a substituted phenyl group had slowed its rotation. In

(30) *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983.
(31) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.
(32) The absorbance should appear as a doublet of triplets, but it overlaps with another signal at this temperature to afford a complex pattern.
(33) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336.
(34) The uncertainty is because ^{1}H NMR spectra were acquired through the decoupler channel of a fluorine probe, although of poor resolution, confirmed the reported ^{19}F NMR ratios.

Chart 2



addition, starting at −65 °C two singlets appeared at 2.26 and 1.93 ppm to either side of the envelope for the xylyl methyl groups. Since catalyst **2e** has a pseudoaxial phenyl group and catalyst **2f** has a pseudoaxial 3,5-xylyl group, it is the pseudoaxial aromatic group that rotates more slowly in these adducts and, by extension, in the other TADDOLTiCl$_2$ adducts of **3**.

Oxalate and Malonate Adducts. To differentiate between the observed adducts of (*i*-PrO)$_2$TiCl$_2$ and catalysts **2** with **3**, the adducts of bidentate, symmetric ligands like diethyl and diisopropyl oxalate and diethyl dimethylmalonate were examined. With (*i*-PrO)$_2$TiCl$_2$ and the preceding ligands, two adduct types can reasonably be expected (vide supra): adducts **J**, which should display symmetry in their NMR spectra, and adducts **K**, which should not (Chart 2). Similarly with catalysts **2**, adducts **M** should display symmetry in their NMR spectra, and adducts **N** and **O** should not. When constrained to a conformation suitable for bidentate association, the oxalates, the malonate derivative, and **3** all have carbonyl oxygen to carbonyl oxygen distances of 3.7−3.8 Å.[35]

The ^{1}H NMR spectrum of **2a** and diisopropyl oxalate at 20 °C gave no indication of a dynamic process. Two sharp singlets can be assigned to the dioxolane methine (5.24 ppm) and the acetonide methyl groups (0.68 ppm) of **2a**, while a heptet (5.29 ppm) can be assigned to diisopropyl oxalate. Significant line broadening, however, was observed in the temperature range of −20 to −88 °C, where the slow exchange limit was reached. The process was reversible and involved the exchange of bound oxalate for free oxalate in a dissociative manner.[36]

^{1}H NMR spectra obtained at −88 °C revealed that three species were present: free oxalate and a 1:1 ratio of C_2- and C_1-symmetric adducts of oxalate and **2a** as suggested by the observed downfield shifts. At −88 °C, uncomplexed diisopropyl oxalate displayed a methyl doublet at 1.27 ppm. In the adducts, most of the oxalate methyl groups were observed as a broad singlet centered at 1.43 ppm. The C_2 symmetry of one adduct was indicated by the observation of a single oxalate methine signal (5.50 ppm) and a single acetonide methyl signal (0.83 ppm), while the C_1 symmetry of the other was indicated by the presence of two oxalate methine signals (5.55 and 4.57 ppm) and two acetonide methyl signals (0.83 and 0.40 ppm).

The C_1-symmetric adduct appears to bind diisopropyl oxalate in proximity to a TADDOL phenyl residue. First, one of the two oxalate isopropyl methine signals for the unsymmetric adduct was 0.49 ppm upfield of the corresponding signal for uncomplexed oxalate at −88 °C. Second, two broad doublets integrating to one proton each appeared simultaneously at 8.07 and 6.48 ppm as the sample temperature was reduced. Irradiation of one of these signals led to the disappearance of the other. These two peaks can be assigned to the two ortho protons of a TADDOL phenyl residue in the C_1-symmetric adduct,[37] while the dynamic behavior and spin-saturation transfer indicate that they are undergoing a two-site exchange process caused by phenyl rotation. Line shape analysis[38] yielded a free energy of activation 9.6 kcal/mol at −77 °C.

Between −86 and 20 °C, ^{1}H NMR spectra of **2a** and excess diethyl oxalate closely parallel those of **2a** and diisopropyl oxalate. At −86 °C, two isomeric adducts were observed in a 1.5:1 ratio along with uncomplexed oxalate. The major adduct showed a single acetonide methyl signal at 0.54 ppm, while the minor adduct showed two acetonide methyl signals at 0.75 and 0.43 ppm. These and other signals indicated that the major isomer possesses C_2 symmetry and the minor C_1 symmetry.

Two observations again suggest that the minor C_1-symmetric adduct binds diethyl oxalate in proximity to a TADDOL phenyl residue. First, one of the two ethoxy methylene signals for the unsymmetric adduct was 0.33 ppm upfield of the corresponding signal for uncomplexed oxalate at −86 °C. Second, two broad doublets, assignable to a phenyl residue of the minor unsymmetric adduct, appeared simultaneously at 8.00 and 6.43 ppm at low probe temperatures.

At 20 °C, ^{1}H NMR spectra of diethyl dimethylmalonate and catalyst **2a** were at the fast exchange limit. Decreasing the sample temperature led to broadening beginning at ca. 0 °C and ending at ca. −55 °C. Spectra acquired in the slow exchange limit showed a *single* adduct possessing C_2 symmetry as suggested by a new set of downfield shifted diethyl dimethylmalonate resonances (unbound values in parentheses): 4.40 (4.05), 1.62 (1.29), and 1.30 (1.14) ppm. No loss of symmetry was found for the signals of the bound oxalate or the TADDOL of **2a** at −88 °C.[39] The methylene protons (4.40 ppm) of the bound diethyl dimethylmalonate were observed to be diastereotopic, but this is expected in a chiral, C_2-symmetric environment.

The dynamic behavior observed with diethyl dimethylmalonate and **2a** is consistent with the free and bound diethyl dimethylmalonate interconverting. For example, the observed ethoxy methylene quartet at 4.34 ppm (−11 °C) is in good agreement with the 4.35 ppm temperature corrected and population weighted average[40] of the free

(35) Oxygen−oxygen distances determined with suitably constrained structures using PCMODEL Version 4.51. Available from Serena Software, Box 3076, Bloomington, IN 47402-3076.

(36) Increasing the concentration of diisopropyl oxalate 2.7-fold does not change the onset or cessation temperatures for the dynamic process.

(37) With only one phenyl residue effected, it is difficult to link this behavior to the symmetric adduct.

(38) Sandström, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982.

(39) The dioxolane geminal methyl (0.56 ppm) and methine (5.14 ppm) protons of the adduct appear as singlets. The geminal methyl (1.62 ppm) and ethoxy methyl (1.30 ppm) protons of the bound diethyl dimethylmalonate remain homotopic.

(40) The two ethoxy methylene absorptions shift downfield at the rate of +0.0011 ppm/°C, and the relative populations of complexed to uncomplexed diethyl dimethylmalonate are 0.546−0.454.

Figure 3. Molecular mechanics minimized stereoview of a symmetric adduct between catalyst **2a** and an α,β-unsaturated *N*-acyloxazolidinone.

and bound ethoxy methylene signals of diethyl dimethylmalonate observed at −55 °C. Band shape analysis yielded the following values: $\Delta G_{239}^{\ddagger} = 12.28$ kcal/mol; $\Delta G_{250}^{\ddagger} = 12.07$ kcal/mol; $\Delta G_{261}^{\ddagger} = 11.99$ kcal/mol (±0.10). The entropy of activation for this dynamic process can be estimated as +13 ± 5 eu from the preceding free energy of activation values but is of limited accuracy due to the small temperature range. This entropy of activation is consistent with a dissociative exchange process.

Although the oxalates and diethyl dimethylmalonate associate less strongly to catalyst **2a** than **3**, there are many parallels that allow assignments to be made with some degree of confidence. With diethyl oxalate and catalyst **2a**, the major symmetric adduct did not show the shielding effects and hindered aryl rotation that the minor unsymmetric adduct did. This parallels the behavior of the two most abundant adducts of catalyst **2a** and oxazolidinone **3**, suggesting that the most abundant adduct was **E**. That only one unsymmetric adduct was observed may be taken as information regarding the relationship of the two unsymmetric adducts seen with oxazolidinone **3** and TADDOLTiCl$_2$ catalysts; however, the small quantities of the least abundant unsymmetric adduct made its detection problematic in all cases studied.

At 20 °C, the ^{1}H NMR of spectrum of diethyl dimethylmalonate and a slight excess of (i-PrO)$_2$TiCl$_2$ were sharp. With cooling, broadening began at ca. 0 °C and ended at ca. −55 °C. Spectra acquired below −55 °C showed the appearance of new malonate peaks at 4.56 and 1.72 ppm, which were shifted downfield by 0.18 and 0.09 ppm, respectively, from diethyl dimethylmalonate at the same temperature. Additional signals at 5.28 and 1.51 ppm can be assigned to a new type of isopropoxide group. Interestingly, these new peaks constituted only 18% of the sample. While the preceding can be explained by partial formation of a C_2-symmetric adduct, a rapid and partial transesterification process catalyzed by titanium alkoxides[41] can also explain the observed ^{1}H NMR spectra.[42] Further, a low enough temperature may not have been reached to observe the slow or intermediate exchange regions for exchange of bound for free diethyl dimethylmalonate. Regardless of the explanation, **2a** binds diethyl dimethylmalonate more strongly than (i-PrO)$_2$TiCl$_2$.

The dynamic behavior that coalesced the two observed sets of isopropoxy, ethoxy, and *gem*-dimethyl signals upon warming can be modeled. Band shape analysis of the two sets of *gem*-dimethyl signals yielded a free energy of activation of 11.76 ± 0.10 kcal/mol at 213 K. This is comparable to the free energy of activation for the dynamic process observed with catalyst **2a** and diethyl dimethylmalonate, but is not inconsistent with a rapid transesterification process.

The preceding data do not allow differentiation of the three possible adducts (**J**-**L**) of bidentate Lewis bases and (i-PrO)$_2$TiCl$_2$, yet an argument based on ligand π-donor abilities can be made to differentiate among these possibilities. While a weaker π-donor than an alkoxy group, chloro groups are significantly stronger π-donors than the carbonyl oxygens of bound **3**. Using the argument of maximized π-bonding made earlier, the isopropoxy groups are expected to be cis to themselves and the chloro groups cis to the isopropoxy groups if possible. For example, such an arrangement is found with (i-PrO)TiCl$_3$(acetone)$_2$.[43] In this case, only **J** fits the constraints dictated.

Molecular Modeling. Through the use of molecular mechanics calculations,[35] the data acquired herein are reinforced and a foundation provided from which to make mechanistic extrapolations. Figure 3 is a minimized representation of a symmetric adduct (**E**) between an unsaturated *N*-acyloxazolidinone and catalyst **2a** as viewed perpendicular to the equatorial plane of the octahedral complex. The backbone of the TADDOL ligand is in the conformation found in almost every crystal structure known for it (vide supra), and the *N*-acyloxazolidinone is associated in a bidentate manner and in the s-cis conformation expected[44] and observed[45] for it. The lack of close contacts between the TADDOL aryl groups and the oxazolidinone might explain why this

(41) See ref 23 and the following: (a) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138−141. (b) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495−503. (c) Schnurrenberger, P.; Züger, M. F. *Helv. Chim. Acta* **1982**, *65*, 1197−1201. (d) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Salle + Sauerländer: Aarau, Switzerland, 1983; Vol. 3, pp 217−353. (e) Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.* **1987**, *65*, 230−235.

(42) Three sets of isopropoxy and ethoxy peaks are expected if transesterification occurred. Only two sets, however, were observed. The similarity of the compounds examined and the relatively low field strength used could explain the unobserved signals. This argument also makes the symmetry assignment of the adduct unreliable.

(43) Bachand, B.; Wuest, J. D. *Organometallics* **1991**, *10*, 2015−2025.

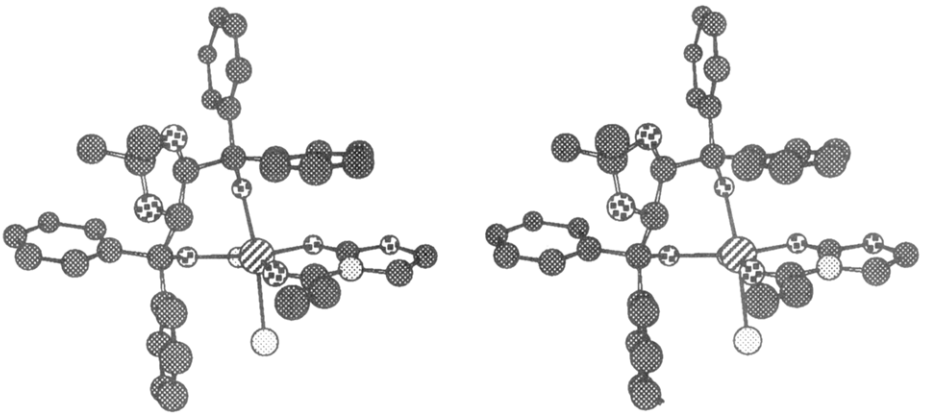


Figure 4. Molecular mechanics minimized stereoview of an unsymmetric adduct between catalyst **2a** and an α,β-unsaturated *N*-acyloxazolidinone.

configuration is favored at equilibrium and why it would not be expected to show strong shielding effects.

Although no kinetic data are available, two observations suggest that the adduct geometry depicted in Figure 3 is *not* responsible for the observed enantioselective Diels–Alder reaction. First, there is no obvious biasing of the dienophile faces necessary to achieve enantioselective addition. Second, the carbonyl oxygens of the *N*-acyloxazolidinone are trans to the strongly electron-releasing TADDOL oxygens. This suggests that the degree of Lewis acid activation experienced by the dienophile is relatively low even though it maximizes the oxygen-p titanium-d π-bonding.[22]

Figure 4 is a minimized representation of an unsymmetric adduct (**F** or **H**) between an unsaturated *N*-acyloxazolidinone and catalyst **2a**. The TADDOL backbone and the oxazolidinone conformation are the same as in Figure 3. The "stacked" arrangement between one of the aryl residues of the TADDOL ligand and the oxazolidinone explains two of the key observations made about the less abundant adducts: (1) the strong shielding seen for several oxazolidinone protons and (2) the high barrier to rotation for the pseudoaxial aryl residue of the TADDOL ligand. Note that *all* the unsymmetric adducts (**F-I**) can achieve this "stacked" arrangement of either a pseudoaxial or pseudoequatorial phenyl group and an oxazolidinone. Also, this arrangement explains the inability of diethyl dimethylmalonate to form unsymmetric adducts—the *gem*-dimethyls would impinge on the proximal TADDOL aryl group.

Again, in the absence of supporting kinetic data, three observations suggest that unsymmetric adducts like the one depicted in Figure 4 *are* responsible for the observed enantioselective Diels–Alder reaction. First, there is obvious biasing of the dienophile faces. Second, one carbonyl oxygen of the oxazolidinone is trans to a TADDOL oxygen, while the other is trans to a chloride. Since chloride is a weaker π-donor ligand than an alkoxy group, unsymmetric adducts may experience a higher degree of Lewis acid activation than the symmetric adduct, compensating for their lower concentrations. Third, the importance of aryl groups in asymmetric Diels–Alder reactions has been pointed out by several groups,[46] with the consensus that it is advantageous to have the dienophile proximal to an electron-rich or highly polarizable aromatic residue. That the "stacking" present in these unsymmetric adducts is responsible for high enantioselectivity agrees with the transition state assembly proposed by Corey for this reaction;[7b] however, Corey's proposed involvement of a pseudoequatorial TADDOL aryl group cannot be evaluated because of the unknown characteristics of the least abundant adducts of catalysts **2** and the uncertainties that follow.

With the information available and the assumption that symmetric adducts (**E**) are not leading to enantioselective product formation, it is tempting to evaluate the unsymmetric adducts to determine which leads to the endo Diels–Alder adduct enantiomer favored by TADDOLs derived from L-tartaric acid.[6,8,47] The orientation of bound **3**, however, remains unaccounted for as a degree of freedom. Adduct pairs **F/G** and **H/I** are interconverted by 180° rotation of **3**, changing the face of **3** exposed to the diene and, hence, the endo Diels–Alder adduct enantiomer expected. With only two of the four unsymmetric adducts observed and one predominate, some organizing feature is at work. One possibility involves the differing Lewis basicities of the two carbonyl oxygens of *N*-acyloxazolidinones observed by Castellino.[24b] Presumably, the more Lewis basic external carbonyl coordinates opposite the weakest π-donor ligand (chloride). The adduct of Figure 4 displays this orientation mode and leads to the correct enantiomer of the endo Diels–Alder product. However, additional data on the binding mode of *N*-acyloxazolidinones, the nature of the least abundant unsymmetric adducts, and rate data are needed before a definitive explanation can be made.

Summary and Conclusion

TADDOLTiCl_2 catalysts appear to be well-defined and isolable entities when prepared using the method of Corey,[7b] allowing detailed ^1H and ^{13}C VT-NMR analysis of catalyst adducts with bidentate Lewis bases. These

(44) The s-trans conformer is strongly destabilized by an $A^{1,3}$-interaction. Modeling (ref 35) indicates that the s-cis conformer is favored over the s-trans by ca. 4.5 kcal/mol.

(45) NOE difference measurements (CD_2Cl_2, −60 °C) on the most abundant adduct formed between oxazolidinone **3** and a derivative of catalyst **2b** where ethyl groups have replaced the methyl groups of the dioxolane indicate an s-cis conformation of bound **3**. A 28% enhancement of the C5-H is observed upon irradiation of the two C3-H, while only a 1.3% enhancement of the the C6-H is observed upon irradiation of the two C3-H (refer to Table 1 for numbering).

(46) See refs 3o, 4, and 7b as well as the following and references therein: (a) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657–1660. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184–1186.

(47) This statement holds true for the phenyl-based TADDOLs described herein, but not with naphthyl-based TADDOLs. See ref 8.

NMR studies revealed that a limited subset of the possible adducts are observed, that there are two broad classes of adducts (symmetric and unsymmetric), and that TADDOL aryl groups play a role in one class of adducts (unsymmetric). The synthesis of catalysts with different pseudoaxial and pseudoequatorial TADDOL phenyl groups provided more information about one of the two unsymmetric adducts. Complete band shape analysis for a dynamic process assigned to the dissociation of bound *N*-acyloxazolidinone **3** from TADDOLTiCl$_2$ **2a** indicated that the Diels–Alder addition step is the rate- and stereochemistry-determining step. Comparison of TADDOLTiCl$_2$ catalysts to (*i*-PrO)$_2$TiCl$_2$ suggested that the latter binds bidentate Lewis bases more weakly than the former, which is a possible clue to understanding the "ligand acceleration effect" observed with TADDOL ligands.

While these studies have removed several of the degrees of freedom surrounding the catalytic asymmetric Diels–Alder additions catalyzed by TADDOLTiCl$_2$ catalysts, additional NMR experiments and kinetic studies will be necessary to clarify fully this interesting system. These are the focus of ongoing efforts.

Experimental Section

NMR spectra were measured at rt in $CDCl_3$ and are referenced to residual $CHCl_3$ at an operating frequency of 200 and 50.3 MHz for ^{1}H and ^{13}C NMR, respectively, unless otherwise noted. Spectra acquired in CD_2Cl_2 are referenced to residual $CHDCl_2$. ^{19}F NMR spectra were proton decoupled and referenced to 4 M trifluoroacetic acid in acetone-d_6 diluted with CD_2Cl_2. All reported coupling constants are in Hz. With all adduct NMR studies at or below the slow exchange limit, (*i*-PrO)$_2$TiCl$_2$ and the titanium catalysts were always completely complexed when excess ligand was present. When and where possible, peaks are assigned to the adducts based on symmetry (C_1 = unsym, C_2 = sym) or on relative areas.

Band shape analysis was performed using DNMR5 (QCPE program No. 569) by visually fitting calculated to experimental spectra. Chemical shifts that were not directly measurable were extrapolated linearly from data collected below the slow exchange limit. NMR probe temperatures were determined by the chemical shift difference of the two ^{1}H NMR absorptions of MeOH.[48] Combustion analyses were performed by the Microanalytical Laboratory of University of California at Berkeley.

N-Acyl-1,3-oxazolidinone **3** was prepared according to the procedure of Evans[49] and matched the reported characteristics reported by Narasaka.[6] The literature method was used to prepare (*i*-PrO)$_2$TiCl$_2$.[50] Diethyl oxalate and diethyl dimethylmalonate were purchased from Aldrich Chemical Co. and fractionally distilled. Diisopropyl oxalate was prepared by reaction of oxalyl chloride with 2-propanol and fractionally distilled. TADDOLs **1a** and **1b** were obtained using the procedure of Seebach[9] with dimethyl 2,3-*O*-isopropylidene-L-tartrate.[12] TADDOL-based catalysts were synthesized using the procedure of Corey[7b] with the substitution of mesitylene for toluene during the evaporative cycle to remove silicon-containing impurities and doubling the amount of $SiCl_4$ used. Except for **1e**, the hydroxyl protons of **1b–f** could not be observed due to broadening. For compounds **1c–f**, "diastereomeric ratio" refers to the ratio of desired C_2-symmetric to undesired C_1- and C_2-symmetric products, respectively. All reactions were conducted in oven-dried (150 °C) glassware in a nitrogen-filled glovebox or under a nitrogen atmosphere. Unless otherwise stated, reaction products were isolated extractively using either CH_2Cl_2 or Et_2O and the resulting organic extracts dried over anhyd Na_2SO_4 and concentrated *in vacuo*.

(2*R*,3*R*)-2,3-*O*-Isopropylidene-1,1,4,4-tetrakis(3′,5′-dimethylphenyl)-1,2,3,4-butanetetrol (1b). To a solution of (3,5-dimethylphenyl)magnesium bromide (100 mL, 1.3 M in Et_2O) was added dimethyl 2,2-dimethyl-4,5-dioxolanedicarboxylate (4.15 g, 16.9 mmol) in 50 mL of Et_2O at rt. The reaction was stirred for 4 h and then treated with saturated aqueous NH_4Cl. Chromatography (EtOAc/hexane 1:8) gave **1b** (3.5 g, 36%) as a foam: mp 90–91 °C (lit.[8] mp 92.0–93.2 °C); $[\alpha]^{20}_D$ −40.0° (*c* 1.12, $CHCl_3$) (lit.[8] $[\alpha]^{rt}_D$ −42.6 (*c* 1.0, $CHCl_3$)); IR (CH_2Cl_2) 3372, 2988, 2921, 2869, 1604, 1461, 1376, 1068; ^{1}H NMR δ 1.04 (s, 6H), 2.20 (s, 6H), 2.28 (s, 6H), 4.53 (s, 2H), 6.83 (s, 2H), 6.91 (s, 4H), 7.12 (s, 2H), 7.24 (s, 4H); ^{13}C NMR δ 21.46, 27.03, 77.85, 81.05, 109.17, 125.25, 126.30, 128.61, 129.05, 136.22, 137.20, 142.61, 145.88. Anal. Calcd for $C_{39}H_{46}O_4$: C, 80.93; H, 8.01. Found: C, 81.01; H, 8.15.

(1*S*,2*R*,3*R*,4*S*)-2,3-*O*-Isopropylidene-1,4-diphenyl-1,4-bis(4′-fluorophenyl)-1,2,3,4-butanetetrol (1c). Two aliquots of PhMgBr (1.4 mL, 2.5 M in Et_2O) were added 30 min apart to a solution of **4b** (1.0 g, 3.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The reaction mixture was stirred for 2 h and then treated with saturated aqueous NH_4Cl at −78 °C and warmed to rt. Chromatography (EtOAc/hexane 1:8) gave **1c** (873 mg, 60%) as a crystalline solid: diastereomeric ratio 88:11:1; mp 151–153 °C; $[\alpha]^{20}_D$ −63.3° (*c* 0.59, $CHCl_3$); IR (CH_2Cl_2) 3584, 3564, 3382, 3050, 2985, 2355, 1644, 1602, 1508, 1418, 1381, 1272, 1228, 1162, 1080, 1014, 885; ^{1}H NMR δ 1.06 (s, 6H), 4.50 (s, 2H), 6.93 (t, J = 8.7, 2H), 7.27–7.57 (m, 16H); ^{13}C NMR δ 27.08, 77.73, 81.00, 109.54, 114.95 (d, J = 21), 127.39, 128.35, 129.31, 129.48, 141.56, 142.31, 162.37 (d, J = 246); HRMS calcd for $C_{31}H_{28}F_2O_4$ (M^+) 502.1956, found 502.1955.

(1*R*,2*R*,3*R*,4*R*)-2,3-*O*-Isopropylidene-1,4-diphenyl-1,4-bis(4′-fluorophenyl)-1,2,3,4-butanetetrol (1d). Two aliquots of (4-fluorophenyl)magnesium bromide (1.6 mL, 2.5 M in Et_2O) were added 30 min apart to a solution of **4a** (1.0 g, 3.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The reaction mixture was stirred for 2 h and then treated with saturated aqueous NH_4Cl at −78 °C and allowed to warm to rt. Chromatography (EtOAc/hexane 1:8) gave **1d** (1.140 g, 71%) as a crystalline solid: diastereomeric ratio 94:5:1; mp 188–191 °C; $[\alpha]^{20}_D$ −59.3° (*c* 0.75, $CHCl_3$); IR (CH_2Cl_2) 3573, 3379, 3046, 2986, 2898, 1601, 1508, 1447, 1381, 1270, 1224, 1160, 1081, 1014, 888; ^{1}H NMR δ 1.09 (s, 6H), 4.55 (s, 2H), 7.03 (t, J = 8.5, 2H), 7.30–7.54 (m, 16H); ^{13}C NMR δ 26.86, 76.74, 80.47, 109.10, 113.76 (d, J = 19), 113.85, 127.24, 127.41, 127.94, 130.06, 138.12, 145.41, 162.84 (d, J = 248); HRMS calcd for $C_{31}H_{28}F_2O_4$ (M^+) 502.1956, found 502.1953.

(1*S*,2*R*,3*R*,4*S*)-2,3-*O*-Isopropylidene-1,4-diphenyl-1,4-bis(3′,5′-dimethylphenyl)-1,2,3,4-butanetetrol (1e). Two aliquots of PhMgBr (1.6 mL, 2.5 M in Et_2O) were added 30 min apart to a solution of **4c** (1.17 g, 3.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The reaction mixture was stirred for 2 h and then treated with saturated aqueous NH_4Cl at −78 °C and allowed to warm to rt. Chromatography (EtOAc/hexane 1:7) gave **1e** (892 mg, 53%) as a crystalline solid: diastereomeric ratio 96:3:1; mp 78–80 °C; $[\alpha]^{20}_D$ −30.5° (*c* 0.19, $CHCl_3$); IR (CH_2Cl_2) 3561, 3380, 2989, 2919, 2867, 1598, 1444, 1370, 1160, 1054, 865; ^{1}H NMR δ 1.15 (s, 6H), 2.29 (s, 12H), 4.06 (s, 2H), 4.66 (s, 2H), 6.91 (s, 2H), 7.02 (s, 4H), 7.35–7.68 (m, 10H); ^{13}C NMR δ 21.48, 27.05, 77.99, 80.89, 109.29, 125.23, 126.31, 127.01, 127.15, 128.48, 137.36, 142.93, 145.73. Anal. Calcd for $C_{35}H_{38}O_4$: C, 80.43; H, 7.33. Found: C, 80.58; H, 7.88.

(1*R*,2*R*,3*R*,4*R*)-2,3-*O*-Isopropylidene-1,4-diphenyl-1,4-bis(3′,5′-dimethylphenyl)-1,2,3,4-butanetetrol (1f). Two aliquots of (3,5-dimethylphenyl)magnesium bromide (1.7 mL, 2.4 M in Et_2O) were added 30 min apart to a solution of **4a** (1.0 g, 3.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C. The reaction mixture was stirred for 2 h and then treated with saturated aqueous NH_4Cl at −78 °C and warmed to rt. Chromatography (EtOAc/hexane 1:7) gave **1f** (976 mg, 58%) as a crystalline solid: diastereomeric ratio 95:4:1; mp 82–85 °C; $[\alpha]^{20}_D$ −38.3° (*c* 0.41, $CHCl_3$); IR (CH_2Cl_2) 3565, 3382, 3044, 2985, 2921, 1598, 1496, 1450, 1168, 898; ^{1}H NMR δ 1.14 (s, 6H), 2.35 (s, 12H), 4.61 (s, 2H), 6.99 (s, 2H), 7.23 (s, 4H), 7.27–7.42 (m,

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10H); ^{13}C NMR δ 21.48, 27.07, 77.92, 81.14, 109.26, 126.28, 127.38, 127.60, 128.00, 128.79, 136.45, 142.34, 145.98. Anal. Calcd for $C_{35}H_{38}O_4$: C, 80.43; H, 7.33. Found: C, 77.99; H, 7.95.

Catalyst 2a. Compound **2a** was obtained as an off-white powder: ^{1}H NMR δ 7.58–7.51 (m, 4H), 7.41–7.26 (m, 16H), 5.18 (s, 2H), 0.75 (s, 6H); ^{13}C NMR δ 144.17, 139.52, 128.65, 128.36, 128.24, 128.03, 127.53, 126.89, 111.47, 103.38, 81.09, 26.99.

Catalyst 2b. Compound **2b** was obtained as an off-white powder: ^{1}H NMR δ 7.09 (s, 4H), 7.06 (s, 4H), 6.93 (s, 4H), 5.01 (s, 2H), 2.28 (s, 12H), 2.27 (s, 12H), 0.76 (s, 6H); ^{13}C NMR δ 143.92, 139.54, 137.33, 136.71, 129.88, 129.39, 126.60, 124.78, 110.93, 103.89, 81.38, 27.05, 21.54, 21.41.

Catalyst 2c. Compound **2c** was obtained as an off-white powder: ^{1}H NMR δ 7.56–7.22 (m, 14H), 7.05 (m, 4H), 5.08 (s, 2H), 0.73 (s, 6H); ^{13}C NMR δ 162.23 (d, J = 248), 140.63, 139.99, 128.97 (d, J = 9), 128.73, 127.96, 127.48, 114.96 (d, J = 22), 111.51, 101.14, 81.14, 27.01; ^{19}F NMR ($CDCl_3$, 20 °C) δ −36.0.

Catalyst 2d. Compound **2d** was obtained as an off-white powder: ^{1}H NMR δ 7.53 (br s, 4H), 7.47–7.28 (m, 10H), 7.00 (t, J = 8.6, 4H), 5.12 (s, 2H), 0.78 (s, 6H); ^{13}C NMR δ 162.34 (d, J = 248), 143.95, 135.82, 130.54 (d, J = 8), 128.43, 128.29, 126.86, 114.41 (d, J = 22), 111.42, 102.87, 80.81, 27.07; ^{19}F NMR ($CDCl_3$, 20 °C) δ −37.61.

Catalyst 2e. Compound **2e** was obtained as an off-white powder. Thirteen lines are expected for the ^{13}C NMR, but only 12 are observed: ^{1}H NMR δ 7.52 (m, 4H), 7.37 (m, 6H), 7.07 (s, 4H), 6.93 (s, 2H), 5.07 (s, 2H), 2.26 (s, 12H), 0.78 (s, 6H); ^{13}C NMR δ 144.25, 139.66, 136.83, 129.48, 128.08, 126.99, 126.52, 111.10, 103.38, 81.33, 27.05, 21.44.

Catalyst 2f. Compound **2f** was obtained as an off-white powder: ^{1}H NMR δ 7.42 (m, 4H), 7.29 (m, 6H), 7.08 (s, 4H), 6.94 (s, 2H), 5.04 (s, 2H), 2.28 (s, 12H), 0.71 (s, 6H); ^{13}C NMR δ 144.16, 139.76, 137.53, 130.03, 128.67, 127.86, 127.47, 124.62, 111.21, 103.49, 81.28, 26.97, 21.60.

3-((*E*)-2-Hexenoyl)-1,3-oxazolidin-2-one (3). The ^{13}C NMR spectrum of **3** was not reported by Narasaka:[6] ^{13}C NMR δ 164.95, 153.32, 151.02, 119.82, 61.85, 42.43, 34.33, 21.06, 13.40.

Adducts of 2a and Diisopropyl Oxalate. The ratio of oxalate to **2a** was 2:1. At −88 °C, the isomeric adducts were present in a 1:1 ratio: ^{1}H NMR (CD_2Cl_2, −88 °C) δ 8.07 (br d, 1H, unsym), 7.68–7.23 (m, arom), 7.07 (br t, 1H, unsym), 6.48 (br d, 1H, unsym), 5.55 (hept, J = 5.7, 1H, unsym), 5.50 (hept, J = 5.6, 2H, sym), 5.18 (s, 2H, sym), 5.15 (d, J = 7.3, 1H, unsym), 5.06 (hept, J = 6.2, oxalate), 4.78 (d, J = 7.3, 1H, unsym), 4.57 (hept, J = 5.8, 1H, unsym), 1.43 (br s, 21H), 1.27 (d, J = 6.2, oxalate), 1.17 (d, J = 5.6, 3H, unsym), 0.83 (s, 3H, unsym), 0.56 (s, 6H, sym), 0.40 (s, 3H, unsym).

Adducts of 2a and Diethyl Oxalate. The ratio of oxalate to **2a** was 2.3:1. At −86 °C, isomeric adducts were present with a 1.5:1 ratio of symmetric to unsymmetric: ^{1}H NMR (CD_2Cl_2, −86 °C) δ 8.00 (br d, 1H, unsym), 7.64–7.16 (m, arom), 7.03 (br t, 1H, unsym), 6.43 (br d, 1H, unsym), 5.19 (s, 2H, sym), 5.09 (d, J = 7.1, 1H, unsym), 4.77 (d, J = 7.1, 1H, unsym), 4.69 (q, J = 7.1, 4H, sym), 4.25 (q, J = 7.1, oxalate), 3.92 (br m, 2H, unsym), 1.43 (br t, J = 7.1, 6H), 1.27 (t, J = 7.1, oxalate), 0.75 (s, 3H, unsym), 0.54 (s, 6H, sym), 0.43 (s, 3H, unsym).

Adducts of 2a and Oxazolidinone 3. The ratio of catalyst **2a** to oxazolidinone **3** was 1.1:1 and 1:2 for the ^{1}H and ^{13}C NMR spectra, respectively. Three adducts were observed in the ^{1}H NMR spectrum at −11 °C in a ratio of 70:24:6 and are referred to as A, B, and C, respectively. Only the ^{13}C NMR signals of bound and free oxazolidinone **3** are reported: ^{1}H NMR (CD_2Cl_2, −11 °C) δ 7.89 (m, 1H, A), 7.71–7.52 (m), 7.37–7.25 (m), 6.63 (dt, J = 15.0, 6.9, 1H, B), 6.04 (d, J = 15.0, 1H, A), 5.95 (d, J = 15.0, 1H, C), 5.45 (d, J = 15.2, 1H, B), 5.39 (d, J = 7.0, 1H, A), 5.23 (d, J = 7.0, 1H, A), 5.14 (d, J = 7.3, 1H, B), 5.01 (d, J = 6.9, 1H, C), 4.90 (d, J = 7.3, 1H, B), 4.81 (m, 1H, B), 4.55 (m, 2H, A), 4.22 (m, 1H, B), 4.05 (m, 2H, A), 3.50 (m, 1H, B), 2.38 (q, J = 7.3, 2H, A), 2.16 (q, J = 7.1, 2H, B), 1.58 (m, 2H, A), 1.44 (m, 2H, B), 1.12 (s, 3H, B), 0.99 (t, J = 7.3, 3H, A), 0.93 (t, J = 7.4, 3H, B), 0.70 (s, 3H, A), 0.59 (s, 3H, A), 0.39 (s, 3H, B); ^{13}C NMR (CD_2Cl_2, −66 °C) 166.23, 164.13, 161.26, 155.90, 152.87, 150.90, 118.58, 117.02, 64.29, 61.44, 43.38, 41.73, 34.59, 33.86, 20.51 (br), 13.01.

Adduct of 2a and Diethyl Dimethylmalonate. Ratio of malonate to **2a** was 1.8:1. At −88 °C, only a single adduct was observed. The multiplet at 4.40 ppm is the AB component of an ABX_3 spin system, which is adequately simulated by $\nu_A - \nu_B$ = 15 Hz, J_{AB} = 10.0 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz: ^{1}H NMR (CD_2Cl_2, −88 °C) δ 7.60 (m, 4H), 7.48 (br s, 4H), 7.35–7.20 (m, 12H), 5.14 (s, 2H), 4.40 (m, 4H), 4.05 (q, J = 7.1, ester), 1.62 (s, 6H), 1.30 (t, J = 6.9, 6H), 1.29 (s, ester), 1.14 (t, J = 7.1, ester), 0.56 (s, 6H).

Adducts of 2b and Oxazolidinone 3. Catalyst **2b** was present in slight excess to oxazolidinone **3**. Three adducts were observed in the ^{1}H NMR spectrum at −50 °C in a ratio of 59:34:7 and are referred to as A, B, and C, respectively: ^{1}H NMR (CD_2Cl_2, −50 °C, 500 MHz) δ 7.82 (s, 1H, A), 7.71 (dt, J = 14.8, 6.9, 1H, A), 7.37–7.24 (m), 7.18–7.07 (m), 6.98–6.77 (m), 6.06 (d, J = 14.8, 1H, A), 5.91 (m, 1H, B, 1H, C), 5.40 (d, J = 15.0, 1H, B), 5.30 (d, J = 7.0, 1H, A), 5.10 (d, J = 7.0, 1H, C), 5.02 (d, J = 7.5, 1H, B), 4.91 (d, J = 7.0, 1H, A), 4.75 (d, J = 7.0, 1H, C), 4.67 (m), 4.65 (d, J = 7.5, 1H, B), 4.49 (m), 4.09 (m), 3.63 (m, 1H, B), 2.38–2.02 (m), 1.54 (m, 2H, A), 1.50 (s, 3H, B), 1.28 (m, 2H, B), 0.94 (t, J = 7.2, 3H, A), 0.90 (t, J = 7.2, 3H, B), 0.85 (s, 3H, A), 0.54 (s, 3H, A), 0.42 (s, 3H, C), 0.18 (s, 3H, B).

Adducts of 2c and Oxazolidinone 3. Only one adduct was observed: ^{19}F NMR (CD_2Cl_2, −75 °C) δ −38.76, −38.82.

Adducts of 2d and Oxazolidinone 3. Two adducts were observed in a ratio of 5:1: ^{19}F NMR (CD_2Cl_2, −75 °C) δ −39.01 (minor), −39.30 (minor), −39.61 (major), −39.71 (major).

Adducts of 2f and Oxazolidinone 3. Oxazolidinone **3** and catalyst **2f** were in a ratio of ca. 2:1. Three adducts were observed in the ^{1}H NMR spectrum at −50 °C in a ratio of 60:34:6 and are referred to as A, B, and C, respectively: ^{1}H NMR (CD_2Cl_2, −50 °C, 500 MHz) δ 7.74 (s, 1H, A), 7.68 (dt, J = 14.8, 6.9, 1H, A), 7.61 (d, J = 7.5, 2H, A) 7.51 (d, J = 7.5, 2H, B), 7.35–7.16 (m), 6.96 (s, 2H, B), 6.87 (s, 2H, A), 6.04 (d, J = 15.1, 1H, A), 5.92 (m, 1H, B, 1H, C), 5.35 (d, J = 15.0, 1H, B), 5.32 (d, J = 7.0, 1H, A), 5.08 (d, J = 7.0, 1H, A), 5.00 (d, J = 7.4, 1H, B), 4.87 (d, J = 7.0, 1H, C), 4.78 (d, J = 7.4, 1H, B), 4.66 (m), 4.53 (m), 4.07 (m), 3.66 (m, 1H, B), 2.37 (m, A, B), 2.28–2.08 (m), 1.55 (m, 2H), 1.47 (s, 3H, B), 1.31 (m, 2H, B), 0.97 (t, J = 7.0, 3H, A), 0.95 (t, J = 7.2, 3H, B), 0.76 (s, 3H, A), 0.58 (s, 3H, A), 0.52 (s, 3H, C), 0.22 (s, 3H, B).

Adduct of (i-PrO)$_2$TiCl$_2$ and Oxazolidinone 3. Oxazolidinone **3** and (i-PrO)$_2$TiCl$_2$ were present in a 1.26:1 ratio. Over the course of hours, a reaction took place between these two compounds to give isopropyl *trans*-2-hexenoate: ^{1}H NMR (CD_2Cl_2, −56 °C) δ 7.57 (dt, J = 15.0, 7.0, 1H), 6.13 (d, J = 15.2, 1H), 5.09 (hept, J = 6.2, 1H), 5.08 (hept, J = 6.2, 1H), 4.76 (br t, J = 8.1, 2H), 4.41 (br t, J = 7.6, 2H), 2.33 (br q, J = 7.4, 2H), 2.19 (m, 2H, oxaz), 1.46 (m, 2H), 1.30 (d, J = 6.2, 6H), 1.25 (d, J = 6.2, 6H), 0.89 (t, J = 7.2, 3H); ^{13}C NMR (CD_2Cl_2, −66 °C) δ 166.47, 161.81, 157.29, 117.80, 84.55, 84.14, 64.69, 44.24, 35.18, 23.82, 23.76, 20.58, 13.52.

Adduct of (i-PrO)$_2$TiCl$_2$ and Diethyl Dimethylmalonate. The malonate to (i-PrO)$_2$TiCl$_2$ ratio was 1.0:1.06. The ratio of unbound to bound malonate was 4.4:1 at −93 °C: ^{1}H NMR (CD_2Cl_2, 16 °C) δ 4.96 (br s, 2H), 4.30 (q, J = 7.2, 4H), 1.53 (s, 6H), 1.44 (t, J = 6.0, 12H), 1.32 (t, J = 7.2, 6H); ^{1}H NMR (CD_2Cl_2, −93 °C) δ 5.28 (hept, J = 6.2, 2H, adduct), 5.14 (hept, J = 6.2, 2H), 4.56 (q, J = 7.1, 4H, adduct), 4.38 (q, J = 7.2, 4H), 1.72 (s, 6H, adduct), 1.62 (s, 6H), 1.51 (d, J = 6.3, 12H, adduct), 1.34 (t, J = 7.2, 6H), 1.29 (d, J = 6.2, 12H).

(4*R*,5*R*)-4,5-Bis(4′-fluorobenzoyl)-2,2-dimethyl-1,3-dioxolane (4b). To a solution of (4*R*,5*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide[13] (3.0 g, 12 mmol) in Et_2O (200 mL) at rt was added (4-fluorophenyl)-magnesium bromide (16.4 mL, 2.2 M in Et_2O) in Et_2O. After being stirred for 4 h, the reaction mixture was treated with saturated aqueous NH_4Cl. Chromatography (EtOAc/hexane 1:6) gave **5b** (2.76 g, 66%) as a crystalline solid: mp 174–178 °C; $[\alpha]^{20}_D$ +28.7° (*c* 0.72, $CHCl_3$); IR (CH_2Cl_2) 3060, 2994, 2934, 1691, 1596, 1505, 1224, 1154, 1070, 857, 838; ^{1}H NMR δ 1.39 (s, 6H), 5.79 (s, 2H), 7.12 (dd, J = 6.8, 8.9, 2H), 8.16 (dd, J =

8.9, 10.9, 2H); ^{13}C NMR δ 26.44, 78.84, 113.69, 115.69 (d, J = 22), 132.32, 132.42, 165.78 (d, J = 251), 194.56; HRMS calcd for $C_{19}H_{17}F_2O_4$ (M + H^+) 347.1094, found 347.1081.

(4*R*,5*R*)-4,5-Bis(3′,5′-dimethylbenzoyl)-2,2-dimethyl-1,3-dioxolane (4c). To a solution of (4*R*,5*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide[13] (3.0 g, 12 mmol) in Et_2O (200 mL) at 25 °C was added 13 mL of a 2.4 M solution of (3,5-dimethylphenyl)magnesium bromide in Et_2O. After being stirred for 4 h, the reaction mixture was treated with saturated aqueous NH_4Cl. Chromatography (EtOAc/hexane 1:6) gave **5c** (2.15 g, 49%) as a yellow oil: $[\alpha]^{20}_D$ −11.1° (*c* 0.32, $CHCl_3$); IR (CH_2Cl_2) 2988, 2919, 2865, 1706, 1602, 1449, 1384, 1301, 1152, 1072, 853; ^1H NMR δ 1.46 (s, 6H), 2.37 (s, 12H), 5.83 (s, 2H), 7.22 (s, 2H), 7.70 (s, 4H); ^{13}C NMR δ 21.10, 26.66, 78.78, 113.10, 127.00, 134.84, 135.34, 138.15, 196.42; HRMS calcd for $C_{23}H_{26}O_4$ (M + H^+) 367.1909, found 367.1906.

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Supplementary Material Available: ^1H NMR spectra for the following: **1b−e**; **4b**; **4c**; adducts of **2a** with **3**, diisopropyl oxalate, diethyl oxalate, and diethyl dimethylmalonate; and adduct of **2b** and **3** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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