Reactive Geometries in Lewis Acid-Mediated Diels−Alder Reactions: Insights from Covalently Attached Acids[1]

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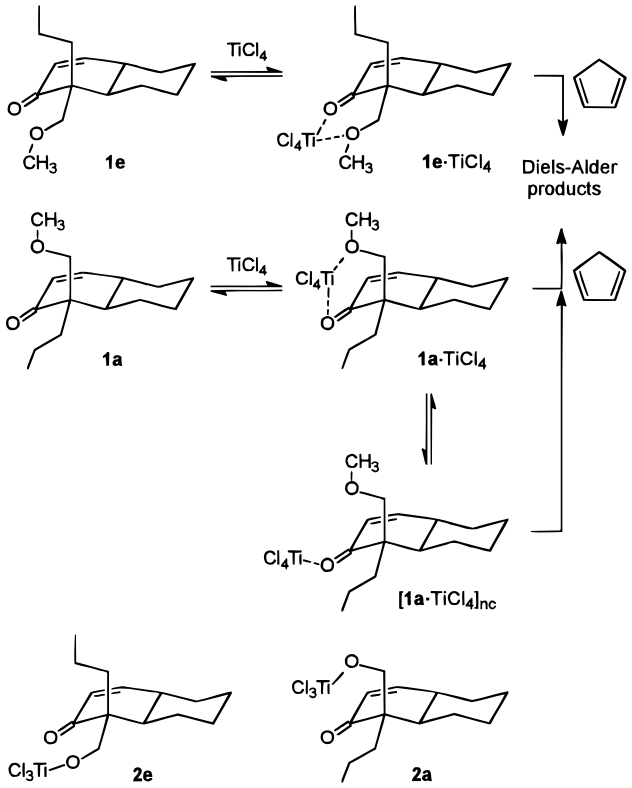
Reaction of diastereomeric β-benzyloxy enones with $TiCl_4$ results in the cleavage of the benzyl ethers and yields substrates for Diels−Alder reactions which incorporate covalently attached Lewis acids. The axial CH_2OTiCl_3 group of **2a** unambiguously directs complexation of the Lewis acidic titanium to the carbonyl oxygen *anti* to the enone carbon−carbon double bond in an out-of-plane coordination geometry, while the equatorial CH_2OTiCl_3 of **2e** directs complexation to an *anti* in-plane coordination geometry. The mono-THF adduct of the out-of-plane complex, **2a**·THF, is found to undergo cycloaddition reactions with cyclopentadiene 2.1−2.4 times more rapidly than the corresponding in-plane complex **2e**·THF. These results suggest that out-of-plane coordination geometries may play a significant role in titanium-derived Lewis acid-mediated Diels−Alder reactions and provide confirmation of our previous rate studies with substrates in which $TiCl_4$ coordination is directed by simple chelation effects.

The rational design of chiral Lewis acids which will mediate the formation of optically pure Diels−Alder adducts from achiral precursors requires a detailed knowledge of the structures of the reactive dienophile−Lewis acid complexes.[2] On the basis of what are essentially *thermodynamic* arguments it has generally been assumed that these *reactive* geometries involve coordination of the Lewis acid in the plane of the carbonyl.[3] The fact that for some reactions the thermodynamically preferred and reactive geometries are not identical (i.e., the Curtin−Hammett principle[4,5]) has led us to examine the *possibility* that the kinetically important species in Lewis acid-mediated reactions of carbonyl compounds are complexes in which the Lewis acid adopts out-of-plane coordination geometries.[6,7] When the reactivities of compounds **1a** and **1e** with cyclopentadiene were examined in the presence of titanium tetrachloride it was found that it was the putative out-of-plane complex **1a**·$TiCl_4$ which was the more reactive (15-fold), in spite of the 6-fold greater thermodynamic stability of the in-plane complex **1e**·$TiCl_4$ (Scheme 1).[6] These results were startling due to the implication that out-of-plane coordination geometries may indeed play a significant role in Lewis acid-mediated cycloaddition reactions. However, the force of this conclusion was somewhat weakened by two possible ambiguities.

Scheme 1



While the methoxymethyl groups in **1a** and **1e** had been *designed* to direct complexation of $TiCl_4$ to out-of-plane and in-plane coordination geometries, respectively, there was the possibility that **1a**·$TiCl_4$, in particular, might not have the desired structure.[8] This possibility may now be discounted on the basis of recent crystallographic and spectroscopic investigations which confirm that **1a**·$TiCl_4$ does indeed have the intended out-of-plane coordination geometry in both solid and solution states.[9] The other ambiguity of the kinetic study lies with the possibility that the reactive species in the case of **1a**·$TiCl_4$

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(1) Portions of this work were presented at the 210th National Meeting of the American Chemical Society, Chicago, Illinois, August, 1995.

(2) Two recent related studies of chiral Lewis acids which also provide leading references to the literature in this field: (a) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777. (b) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.

(3) The extensive literature on this subject has been cogently summarized and discussed by Denmark and Almstead as a part of their work on the spectroscopic characterization of enone−Lewis acid complexes: Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133.

(4) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(5) The extensive studies of Gladysz and coworkers on the reactions of complexes of carbonyl compounds with chiral rhenium Lewis acids provide a particularly apt example. For leading references to this work, see: (a) Wang, Y.; Gladysz, J. A. *J. Org. Chem.* **1995**, *60*, 903. (b) Klein, D. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 8710.

(6) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 8973.

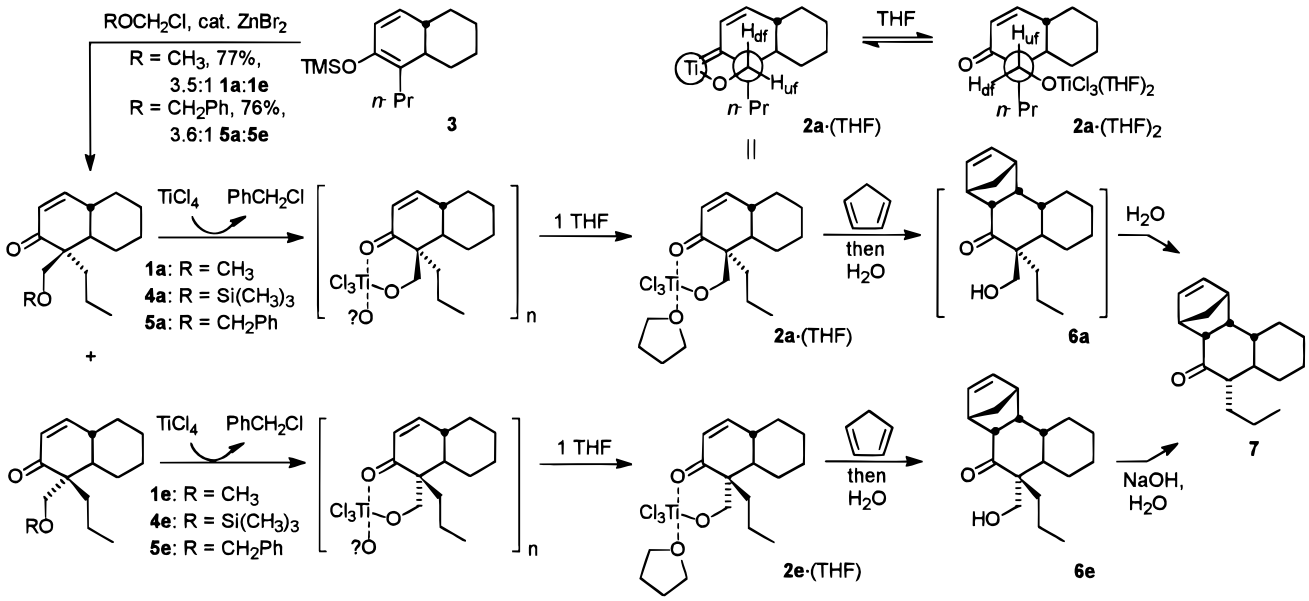
(7) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536.

(8) An example of a problem of this type may be found in ref 7.

(9) Singh, D. K.; Springer, J. B.; Goodson, P. A.; Corcoran, R. C. *J. Org. Chem.* **1996**, *61*, 1436−1442.

0022-3263/96/1961-1443$12.00/0

Scheme 2



was not the intended 1:1 chelated complex, but rather a 1:1 nonchelated complex such as [**1a**·$TiCl_4$]$_{nc}$ (Scheme 1). While the large association constant for the formation of the chelated complex meant that the concentration of such a species would be quite small, we expected that it would enjoy a much greater reactivity than either of the two chelated complexes, since the true Lewis acid in the latter species is $TiCl_4$·ORR′, as opposed to the "naked" $TiCl_4$ in [**1a**·$TiCl_4$]$_{nc}$. In order to rule out the possibility that the reactivity differences we had seen in our original studies were due to the intervention of nonchelated complexes we decided to examine the Diels−Alder reactivities of compounds **2a** and **2e**, in which a Lewis acid is *covalently attached* to the substrates, removing any ambiguities as to the site of complexation and activating Lewis acid.[10]

We had hoped to synthesize **2a**/**e** by a pathway involving demethylation of **1a**/**e** with iodotrimethylsilane[11] and subsequent cleavage of the trimethylsilylethers **4a**/**e** with $TiCl_4$.[10,12] In fact, treatment of **1a** with iodotrimethylsilane led to extensive decomposition of the substrate with no apparent formation of the desired silyl ether. Since it has been established[11] that benzyl ethers undergo cleavage reactions with TMSI with substantially greater facility than methyl ethers we prepared compounds 5**a**/**e** by a route similar to that which had been used to prepare **1a**/**e** (Scheme 2).[9] However, as for **1a**, only decomposition products were produced upon treatment of **5a** with iodotrimethylsilane. The key to our syntheses of compounds **2a**/**e** lies with our recognition of the similarity of **5a**/**e** to α- and β-benzyloxy aldehydes, which have been observed by us[13] and others[14] to undergo decomposition in the presence of $TiCl_4$. Indeed, when $TiCl_4$ was added to a CD_2Cl_2 or $CDCl_3$ solution of **5a** and the reaction was monitored by ^{1}H NMR, the initially formed complex was observed to disappear over a period of about 6 h to give the spectrum of benzyl chloride superimposed on a spectrum suggestive of extensive exchange broadening. While cooling the sample to −80 °C did not result in coalescence, addition of even a single equivalent of tetrahydrofuran caused the breakup of the presumed dimeric or oligomeric complexes to give distinct, though slightly broadened peaks. Further addition of THF led to increasingly sharp resonances accompanied by progressive upfield shifts of the olefinic and THF resonances. These results are readily accommodated by the supposition of an equilibrium between a "chelated" complex **2a**·THF, in which the $OTiCl_3$ is coordinated to the carbonyl oxygen and a single THF molecule, and an "open" complex **2a**·$(THF)_2$, in which the titanium is coordinated to two molecules of THF, but not to the carbonyl. Support for this interpretation comes from the behavior of the more upfield of the two diastereotopic CH_2OTiCl_3 protons, H_{uf}, in the ^{1}H NMR spectrum; of all of the protons in the spectrum, this is the only one which moves *downfield* upon addition of THF.[15] This behavior is to be expected; rotation of the bulky CH_2OTiCl_3·$(THF)_2$ away from the carbonyl should move H_{uf} into the deshielding region of the enone, resulting in a downfield shift of its ^{1}H NMR resonance (Scheme 2).

Titration of **2a** with THF allows a rough estimate of the equilibrium constant K_{a2THF} associated with the formation of **2a**·$(THF)_2$ from **2a**·THF. If one assumes[16] that there is essentially no free **2a** in the presence of 1 equiv of THF (i.e., that one has only **2a**·THF with 1 equiv THF), then one may use the method of Macomber[17] to calculate a value of 2.7 M^{-1} for K_{a2THF} from the chemical shifts of the β-enone proton observed upon addition of further amounts of THF to the solution of **2a**·THF

(10) Other examples of carbonyl activation by covalently attached Lewis acids: (a) Wuest, J. D.; Bachand, B. *Organometallics* **1991**, *10*, 2015. (b) Bachand, B.; Belanger-Gariepy, G.; Wuest, J. D. *Organometallics* **1990**, *9*, 2860. (c) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510.

(11) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(12) Denmark, S. E.; Almstead, N. G. *Tetrahedron* **1992**, *44*, 5565.

(13) Springer, J. B.; DeBoard, J.; Corcoran, R. C. *Tetrahedron Lett.* **1995**, *36*, 8733.

(14) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

(15) When 1−3 equiv of THF is added, the chemical shift of this proton is obscured by other resonances. The peak moves from δ 4.72 at 4 equiv of THF to δ 4.88 at 7 equiv.

(16) We recognize that this assumption is not fully justified. An accurate estimate of K_{a2THF} would require a knowledge of K_{aTHF}, the equilibrium constant for the formation of **2a**·THF from **2a** and THF. We are unable to calculate this equilibrium constant due to gross uncertainties in the chemical shift value of the β-enone proton of **2a** which are a consequence of both exchange broadening and overlapping resonances associated with the phenyl protons of benzyl chloride.

(17) Macomber, R. S. *J. Chem. Ed.* **1992**, *69*, 375.

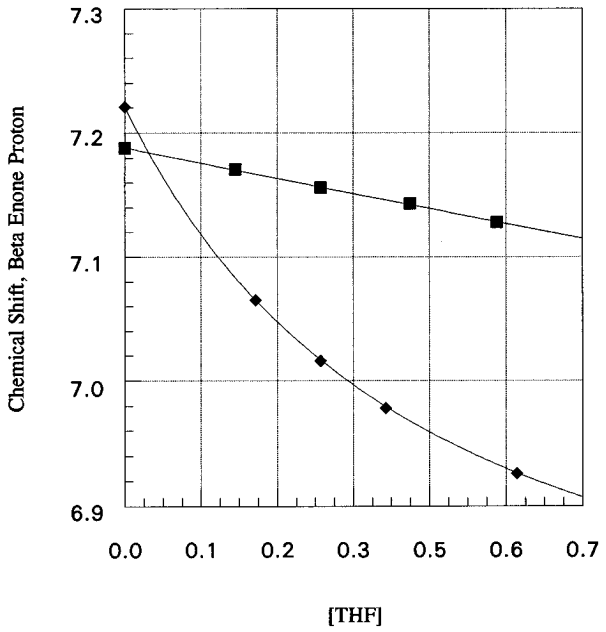
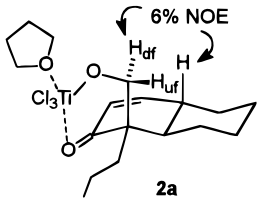


Figure 1. Effect of added THF on the chemical shifts of the β-enone protons of **2a**·THF and **2e**·THF. The solid lines represent chemical shifts calculated using equation 14 of ref 17 using the calculated values of $K_{a/e2THF}$ and $\delta_{\beta H}$ for **2a**/**e**·$(THF)_2$. (◆) **2a**·THF, with calculated $K_{a2THF} = 2.7\ M^{-1}$ and $\delta_{\beta H} = 6.726$ ppm for **2a**·$(THF)_2$. (■) **2e**·THF, with calculated $K_{e2THF} = 0.02\ M^{-1}$ and $\delta_{\beta H} = 1.536$ ppm for **2e**·$(THF)_2$.

(Figure 1).[18] Evidence that **2a**·THF has the intended out-of-plane coordination geometry comes from difference NOE experiments. Irradiation of the allylic bridgehead proton results in a 6% enhancement of the more downfield of the CH_2OTiCl_3 resonances, H_{df}, indicating the axial orientation of this group; this, in turn, indicates the desired coordination geometry for the titanium.[19] .



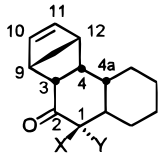
2a

The behavior of **5e** on treatment with $TiCl_4$ was qualitatively similar to that of **5a**, though the cleavage reaction was substantially slower (roughly 16 h to completion). As for **2a**, addition of a 1 equiv of THF to a CD_2Cl_2 solution of **2e** resulted in the transformation of the exchange broadened ^1H NMR spectrum into a well defined spectrum of the THF complex **2e**·THF. However, in contrast to the behavior of **2a**·THF, addition of further THF (up to 5 equiv) had only minor effects on the chemical shifts of the β-enone proton, suggesting that any equilibrium between chelated and open forms strongly favors the former for **2e**·THF. We were unable to calculate a believable value for K_{e2THF}. The observation of solvent-induced chemical shift changes (e.g., the effect of added THF on the chemical shift of residual $CHDCl_2$) began to become apparent at higher THF concentrations,

(18) Though the fit of the data to the calculated curve is clearly quite good ($\sigma^2 = 0.006$), we are nevertheless inclined to view these results with some caution for the reasons outlined in ref 16.

(19) As expected, irradiation of the allylic bridgehead proton of **2e**·THF gave no enhancement of either of the methylenes of the CH_2OTiCl_3.

Table 1. Spectral Characteristics of Diels−Alder Cycloadducts[a]



6e: X = Pr, Y = CH_2OH
7: X = H, Y = Pr
8a: X = CH_2OCH_3, Y = Pr
8e: X = Pr, Y = CH_2OCH_3

spectral feature	6e	7	8a	8e
δ H_{C3}	2.87	2.83	2.88	2.82
δ H_{C4}	2.75	2.63	2.64	2.64
$J_{H(C3)/H(C4)}$, Hz	9.6	9.6	9.6	9.6
$J_{H(C4)/H(C4a)}$, Hz	7.7	7.7	8.4	8.4
$J_{H(C4)/H(C12)}$, Hz	3.1	3.0	3.2	3.0
$J_{H(C3)/H(C9)}$, Hz	4.0	3.9	4.5	4.2

[a] Data for **8a**/**e** taken from ref 6.

leading us to question the reliability of the already small chemical shift changes; utilization of the data below 6 equiv THF in an attempt to extract the equilibrium constant gave an unrealistic estimate of the chemical shift of the β-enone proton, and we therefore have little faith in the calculated value of 0.02 M^{-1} for K_{e2THF}.[20] However, while we cannot thus compare K_{a2THF} with K_{e2THF} on a quantitative basis, *qualitatively* it is clear that at a given THF concentration that the amount of the "chelated" complex **2e**·THF is significantly greater than that of **2a**·THF, as would be expected on the basis of the known *thermodynamic* preference for an in-plane coordination geometry.

Both **2a** and **2e** undergo cycloaddition reactions upon addition of freshly cracked cyclopentadiene. In the case of **2a** the product isolated upon quenching the reaction with water is compound **7**, resulting from hydrolysis of the O−Ti bond and subsequent retroaldol reaction of **6a**; in no case was any of the simple hydrolysis product observed. As may be seen from Table 1, the ^1H NMR chemical shifts and coupling constants for diagnostic protons of **7** and the Diels−Alder products **8a**/**e** (obtained previously from **1a**/**e**[6]) are quite similar, allowing the assignment of stereochemistry in **7** as being that due to the expected cycloaddition from the α-face of the enone by way of an *endo* transition state. In contrast to **2a**, **2e** undergoes cycloaddition and subsequent hydrolysis to give the equatorial hydroxymethyl compound **6e**. While none of the retroaldol product **7** is observed (by capillary GC) in the course of simple aqueous hydrolysis, quenching the cycloaddition reaction with aqueous base leads to the production of small amounts of **7**, confirming the expectation that the stereochemistry of the cycloaddition reaction occurred in the same fashion as for **2a**. Though similar to **1a**/**e** in terms of the product stereochemistries, the cycloaddition reactions of **2a** and **2e** differed from those of the former in two important aspects, both of which appear to be related to the reduced Lewis acidity of the $OTiCl_3$ group relative to $TiCl_4$. While **1a** and **1e** reacted with cyclopentadiene in the presence of $TiCl_4$ over the course of hours at −45 °C, the reactions of **2a** and **2e** took place over a period of many days at room temperature. Furthermore, while polymerization of cyclopentadiene was a serious problem for the reactions of **1a**/**e**, this side reaction was quite slow for **2a**/**e**, being insignificant relative to the thermal dimerization to dicyclopentadiene.

(20) A measure of the unreliability of this number may be gathered from the calculated value of 1.536 for the chemical shift of the β-enone proton of **2e**·$(THF)_2$.

The kinetics of the cycloaddition reactions of 0.10 M solutions of **2a**·THF and **2e**·THF with cyclopentadiene were examined at 20.0 °C under pseudo first-order conditions (10 equiv diene). The covalently attached acid substrates **2a** and **2e** were freshly prepared for each kinetic run by combining the precursor benzyloxymethyl compounds **5a** and **5e** with 1 equiv of $TiCl_4$. To ensure complete formation of the covalently linked enone−Lewis acid substrates the cleavage reactions were allowed to proceed for double the length of time which had been estimated to be necessary for complete reaction. Prior to addition of freshly cracked cyclopentadiene 5 equiv of THF were added to each sample. The addition of THF served two purposes. Control experiments had established that **5a** is essentially unreactive toward $TiCl_4$ in the presence of this amount of THF; thus, we could be assured that the product monitored (ultimately, **7**, in the case of **5a**) arose as a consequence of the desired cycloaddition reaction of **2a**·THF, rather than from a pathway involving $TiCl_4$-mediated cycloaddition to **5a**, followed by cleavage of the benzyloxymethyl group to give the *apparent* product of reaction of **2a**·THF. Addition of this large an excess of THF also ensures that any activation of the enone occurs by way of the *intra*molecular coordination of a $OTiCl_3$ group and not by an *inter*molecular (and possibly in-plane) interaction with another molecule of **2a**/**e**·THF. On the basis of the exchange broadened ^1H spectra observed on initial formation of **2a**/**e** we suspect that interactions of this type are indeed possible (see above). Tetrahydrofuran is a substantially stronger Lewis base than even unhindered ketones,[21] and it is thus unsurprising that only 1 equiv of THF was sufficient to give monomeric **2a**/**e**·THF. Though 1 equiv of THF appears sufficient to break up the undesired intermolecular interactions, the use of 5 equiv offered an even greater level of surety that the reactive species would be monomeric **2a**·THF and **2e**·THF. Product formation (**7** in the case of **2a**, **6e** in the case of **2e**) was monitored by periodic removal of aliquots which were then quenched in ice−water, and the products were extracted with ether and analyzed by HPLC after addition of an internal standard. To maintain the pseudo first-order approximation kinetic data was acquired at less than 10% conversion. Collection of data over this time period also ensured that dimerization of cyclopentadiene was negligible. Under these conditions it was found that the *apparent* second-order rate constants for the reactions of **2**a and **2e** were $(9.0 \pm 1.3) \times 10^{-2}$ M^{-1} h^{-1} and $(7.1 \pm 0.8) \times 10^{-2}$ M^{-1} h^{-1}, respectively.[22]

Discussion

It is well established that an in-plane coordination geometry is thermodynamically preferred in complexes of ketones and enones with electron deficient Lewis acids.[3] This geometry results from the greater Lewis basicity of the nonbonding electrons of the carbonyl oxygen as compared to the bonding π-electrons of the carbon−oxygen double bond. The results presented here affirm the greater donating ability of the nonbonding electrons, but suggest that an enhanced interaction with the out-of-plane electrons of the π-system of the carbonyl may result in an enhanced reactivity in Diels−Alder reactions.

Two aspects of the current work testify to the greater donor ability of the nonbonding electrons in the plane of the carbonyl relative to those in the π-system. A kinetic manifestation of this difference may be seen in the differences in rates in the benzyl cleavage reactions of **5a** and **5e**. If the extent of electron donation from oxygen to titanium is more effective in the in-plane complex **5e**·$TiCl_4$ than in the out-of-plane complex **5a**·$TiCl_4$, then the titanium of the latter complex will be relatively more electron deficient, and hence a stronger and more reactive Lewis acid; this is what is observed. A thermodynamic manifestation of the difference in electron-donating ability may be seen in the substantial differences in the stability of the complexes **2a**·THF and **2e**·THF with respect to added THF. Though the ether oxygen of THF is a stronger Lewis base than a carbonyl oxygen, it is unable to effectively compete with the intramolecular in-plane coordination available in **2e**·THF; in contrast, despite the entropic advantage of the carbonyl oxygen in **2a**·THF it is relatively easily displaced by THF.

At first glance, it may appear that the reactivities of **2a**·THF and **2e**·THF are nearly identical, with only a 1.3-fold rate advantage in favor of the out-of-plane complex. However, this direct comparison of rates is not appropriate, since the concentrations of reactive species differ in the two reactions. In the presence of the 0.5 M THF used in the cycloaddition reactions compound **2a** will exist as a 51:49 mixture of **2a**·THF and **2a**·$(THF)_2$. Lacking any activation of the enone carbonyl by a Lewis acid, the latter species is expected to be completely unreactive toward cyclopentadiene; as a consequence, the concentration of *reactive* species in these kinetic runs will be 0.051 M, and the second order rate constant for the reaction of **2a**·THF may be adjusted to $(18 \pm 3) \times 10^{-2}$ M^{-1} h^{-1}. Due to the unreliability of our calculated value for K_{e2THF}, it is difficult to estimate the concentration of the reactive species **2e**·THF; however, it is perhaps possible to define a plausible range for its value. As a lower limit for the value for K_{e2THF}, we take the 0.02 M^{-1} calculated from the chemical shift data of Figure 1. In order to estimate an upper limit for the value of K_{e2THF} we will assume that the relative stabilities of the in-plane and out-of-plane species **2a**·THF and **2e**·THF mirror the relative stabilities of their noncovalent counterparts **1a**·$TiCl_4$ and **1e**·$TiCl_4$,[6] leading to an estimate of $(0.167)(2.7\ M^{-1}) = 0.45\ M^{-1}$. On the basis of these estimates of K_{e2THF}, the range of concentrations of the reactive **2e**·THF is 0.099 to 0.085 M, and the range of adjusted rate constants $(7.2 \pm 0.8) \times 10^{-2}$ M^{-1} h^{-1} to $(8.3 \pm 0.9) \times 10^{-2}$ M^{-1} h^{-1}. The resulting 2.1 to 2.4-fold rate advantage of **2a**·THF over **2e**·THF in Diels−Alder reactions with cyclopentadiene thus represents an unambiguous indication that an out-of-plane coordination geometry results in a greater reactivity than the in-plane geometry. It is difficult to say with certainty why the observed rate difference between **2a**·THF and **2e**·THF is so much smaller than that observed for **1a**·$TiCl_4$ and **1e**·$TiCl_4$. However, it would not be surprising if the substantial difference in Ti−O bond lengths for titanium alkoxides vs titanium ate complexes[23] resulted in subtle changes in coordination

(21) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 1049.

(22) The values given in each case are the weighted average of four five-point kinetic runs. Weighting factors were based on the variances of the slopes obtained from plots of -ln([substrate]/[substrate]$_o$) vs time plots: Young, H. D. *Statistical Treatment of Experimental Data*; McGraw-Hill: New York, 1962; section IV.14.

(23) The crystal structure of a complex of the type $ROTiCl_3$·O=C-(CH_3)(*t*-Bu) is reported in ref 10b. The RO−Ti bond length is 1.725 Å, as compared to 2.121 Å for the Ti−O=C bond length.

geometry which could influence effective Lewis acidity and thus rate of reaction. Indeed, it would be rather surprising if the rate differences seen in the two pairs of compounds were identical.

Conclusions

By covalently attaching Lewis acids to enone substrates and examining their Diels−Alder reactivity in the presence of the strongly coordinating ligand THF, we have been able to unambiguously define the nature of the reactive geometry in the complexes **2a**·THF and **2e**·THF. The exclusion of the possibility of reaction by way of nonchelated in-plane complexes for these systems, coupled with the finding that it is the out-of-plane complex which is the more reactive, strongly supports the conclusions we drew from our reactivity studies with the more synthetically relevant **1a**·$TiCl_4$ and **1e**·$TiCl_4$; that for titanium derived Lewis acids, the possibility that the kinetically competent complex in Lewis acid-mediated Diels−Alder reactions may possess an out-of-plane coordination geometry cannot be excluded.

Experimental Section

All glassware was oven-dried or flame-dried before use. THF was distilled from potassium/benzophenone under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere, while CD_2Cl_2 was dried over 3 Å molecular sieves. Benzyl chloromethyl ether was purchased from Aldrich Chemical Co. and distilled from $CaCl_2$ prior to use. $TiCl_4$ was purchased from Aldrich Chemical Co. and was distilled and stored under a nitrogen atmosphere for no more than two days before use. Flash column chromatography was carried out on 230−400 mesh silica gel; radial chromatography was performed on a Chromatotron (Harrison and Harrison) using Merck grade 60PF_{254} silica gel coated plates. Combustion analyses were performed by Atlantic Microlab, Inc.

(1*S,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-[(benzyloxy)-methyl]-1-propyl-2(1*H*)-naphthalenone (5a) and (1*R**,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-[(benzyloxy)-methyl]-1-propyl-2(1*H*)-naphthalenone (5e).** (4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-propyl-2-(trimethylsilyl)oxynaphthalene[9] (**3**, 807.3 mg, 3.052 mmol) was dissolved in CH_2Cl_2 (7.7 mL) under an argon atmosphere; the solution was cooled to 0 °C and benzyl chloromethyl ether [**CAUTION: Potent Carcinogen**] (0.61 mL, 4.58 mmol) was added in one portion. Freshly sublimed $ZnBr_2$ (102 mg, 0.45 mmol) was added in one portion, the mixture was stirred at 0 °C for 1 min, and the ice bath was removed, allowing the reaction mixture to warm to rt over 1.5 h. The CH_2Cl_2 was removed, and the residue was prepurified by rapidly passing it through a plug of silica using ether as eluent. The crude product thus obtained was purified by radial chromatography using 3% ether/petroleum ether to afford a 3.6:1 mixture of **3a** and **3e**, respectively (724.9 mg, 76%). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.52; H, 9.08.

The diastereomers were separated by radial chromatography using 3% ether in petroleum ether as eluent.

3a. ^{1}H-NMR ($CDCl_3$): δ 7.10−7.45 (m, 5H), 6.59 (d, 1H, J = 10.2 Hz), 5.97, (dd, 1H, J = 2.6 Hz, J = 10.2 Hz), 4.41 (d, 1H, J = 11.7 Hz), 4.35 (d, 1H, J = 11.7 Hz), 3.51 (d, 1H, J = 9.4 Hz), 3.43 (d, 1H, J = 9.4 Hz), 2.53 (m, 1H), 1.60−1.95 (m, 6H), 1.00−1.40 (m, 7H), 0.87 (t, 3H, J = 6.5 Hz). ^{13}C-NMR ($CDCl_3$): δ 203, 155, 138, 129, 128, 127.3, 127.2, 75, 73, 52, 44, 38, 33.0, 32.7, 26.43, 26.37, 25.8, 17, 15. IR (KBr, neat): 1669.3 (s, C=O).

3e. ^{1}H-NMR ($CDCl_3$): δ 7.10−7.40 (m, 5H), 6.55 (d, 1H, J = 10.2 Hz), 5.88, (dd, 1H, J = 2.6 Hz, J = 10.2 Hz), 4.58 (d, 1H, J = 11.8 Hz), 4.38 (d, 1H, J = 11.8 Hz), 4.04 (d, 1H, J = 7.8 Hz), 3.25 (d, 1H, J = 7.8 Hz), 2.14−2.23 (m, 2H), 1.61−1.92 (m, 4H), 1.02−1.45 (m, 8H), 0.79 (t, 3H, J = 6.5 Hz). ^{13}C-NMR ($CDCl_3$): δ 202, 153, 139, 128.0, 127.8, 127.4, 127.2, 73, 69, 52, 44, 38, 32, 31, 26.5, 26.0, 25, 17, 15. IR (KBr, neat): 1675.9 (s, C=O).

(1*S,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-propyl-1-[[(trichlorotitanio)oxy]methyl]-2(1*H*)-naphthalenone (2a) and (1*R**,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-propyl-1-[[(trichlorotitanio)oxy]methyl]-2(1*H*)-naphthalenone (2e).** In a typical procedure, a 0.233 M stock solution of **5a** (0.60 mL, 0.140 mmol) in CH_2Cl_2 was introduced to a flame-dried vial under a nitrogen atmosphere and dry CH_2Cl_2 (0.20 mL) was added. A 0.233 M stock solution of $TiCl_4$ (0.60 mL, 0.140 mmol) in CH_2Cl_2 was added, and the solution was stirred at rt. By ^{1}H NMR analysis of analogous CD_2Cl_2 or $CDCl_3$ solutions, the cleavage reaction appeared to be complete after 6 h; however, for kinetics runs, stirring was continued for an additional 11−14 h to be sure that no **5a** remained. THF (57 μL, 0.70 mmol) was added, and this 0.10 M solution of **2a** in 0.5 M THF/CH_2Cl_2 was used directly for the kinetics experiments. Solutions of **2e** were prepared in an analogous fashion, except that stirring of the **5e**/$TiCl_4$ solution was continued for a total of 32−36 h.

2a (with 5.0 equiv of THF). ^{1}H-NMR ($CDCl_3$): δ 6.98 (d, 1H, J = 9.6 Hz), 6.23, (d, 1H, J = 9.6 Hz), 5.51 (d, 1H, J = 11.7 Hz), 4.88 (d, 1H, J = 11.7 Hz), 2.40 (m, 1H), 1.10 - 2.25 (m, >13H), 0.90 (t, 3H, J = 6.8 Hz). ^{13}C-NMR ($CDCl_3$): δ 208, 161, 137, 91, 55, 46, 43, 38, 33, 23, 17, 14. (Because of the large amount of THF and $PhCH_2Cl$ present, it is difficult to say with certainty where *all* of the ^{13}C NMR signals are.)

2e (with 5.0 equiv of THF). ^{1}H-NMR ($CDCl_3$): δ 7.12 (d, 1H, J = 10.1 Hz), 6.15, (dd, 1H, J = 2.5 Hz, J = 10.1 Hz), 5.25 (d, 1H, J = 11.8 Hz), 4.38 (d, 1H, J = 11.8 Hz), 2.50 (m, 1H), 1.15−2.10 (m, >13H), 0.92 (t, 3H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 211, 164, 137, 86, 52, 48, 46, 40, 32, 19, 15 (because of the large amount of THF and $PhCH_2Cl$ present, it is difficult to say with certainty where *all* of the ^{13}C NMR signals are.).

Preparative Diels−Alder Reaction of 5a with Cyclopentadiene. To a vial containing a CH_2Cl_2 solution of **2a** (0.5063 mmol) prepared as described above, but without addition of THF, was added freshly cracked cyclopentadiene (0.42 mL, 5.1 mmol). The total volume was brought to 5.1 mL with the addition of dry CH_2Cl_2 and the mixture stirred at room temperature under N_2 for 7 days, occasionally adding aliquots of cyclopentadiene (4 × 0.42 mL, 4 × 5.1 mmol). The black, turbid reaction mixture was poured into a flask containing ice−water and was swirled vigorously for a few minutes. The mixture was extracted with ether (3 × 50 mL); the ether was dried (Na_2SO_4, and evaporated to give a crude oil. The oil was purified by flash chromatography on silica gel using gradient elution: hexane→2.5% ethyl acetate/hexane→100% ethyl acetate, followed by radial chromatography on a 2 mm silica plate using 2.5% ethyl acetate/hexane, followed by radial chromatography on a 1 mm silica plate using 2.5% ethyl acetate/hexane, to give **7** (57.3 mg, 44%) as a waxy, colorless solid. ^{1}H-NMR ($CDCl_3$): δ 6.04 (m, 2H), 3.35 (bs, 1H), 3.00 (bs, 1H), 2.83 (dd, 1H, J = 3.9 Hz, J = 9.6 Hz), 2.63 (ddd, 1H, J = 3.0 Hz, J = 7.7 Hz, J = 9.6 Hz), 1.50−1.90 (m, 8H), 1.00−1.42 (m, 9H), 0.85 (t, 3H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 214, 138, 135, 55, 52, 50, 48, 46, 43, 42, 36, 32.0, 31.6, 26.9, 26.5, 26.0, 19, 15. IR (CH_2Cl_2): 1689.8 (s, C=O). Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.53; H, 10.10.

Some material tentatively identified by ^{1}H NMR as the hydroxymethyl compound resulting from the hydrolysis of **2a** was also obtained (**9**, 20.4 mg, 21%). ^{1}H-NMR ($CDCl_3$): δ 6.65 (d, 1H, J = 10.2 Hz), 5.97 (dd, 1H, J = 2.8 Hz, J = 10.2 Hz), 3.77 (d, 1H, J = 10.2 Hz), 3.60 (m, 1H), 0.95−2.15 (m, 14H), 0.90 (t, 3H, J = 7.2 Hz). This material underwent slow retroaldol reaction upon storage at room temperature to yield a compound with a ^{1}H NMR identical to that of (1*S**,4a*S**,8a*R**)-4a,5,6,7,8,8a-hexahydro-1-propyl-2(1*H*)-naphthalenone (**10**), the starting material for the preparation of **3**.[9]

Diels−Alder Reactions of 5e with Cyclopentadiene. Freshly cracked cyclopentadiene (52.8 μL, 0.64 mmol) was added to a CH_2Cl_2 solution of **5e** (0.064 mmol) prepared as above, but without addition of THF. After bringing the total volume to 0.64 mL with dry CH_2Cl_2 the reaction was allowed to stir at rt for three weeks, adding more cyclopentadiene (52.8

μL, 0.64 mmol) after one week. The black, turbid reaction mixture was poured into a flask containing a 1 M aqueous solution of NaOH (10 mL), and the flask was swirled vigorously for a few minutes. The mixture was extracted with ether (3 × 10 mL); the ether was dried (Na_2SO_4) and evaporated to give a crude oil. The oil was prepurified by passing the crude through a plug of silica gel using ether. The resulting material was purified by radial chromatography on a 1 mm silica plate using gradient elution 3% MTBE/hexane→20% MTBE/hexane to elute the Diels−Alder product **6e** (8.0 mg, 43%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$): δ 6.10 (m, 2H), 4.08 (dd, 1H, J = 4.9 Hz, J = 11.5 Hz), 3.35 (bs, 1H), 3.23 (dd, 1H, J = 11.5 Hz, J = 11.5 Hz), 3.00 (bs, 1H), 2.87 (dd, 1H, J = 4.0 Hz, J = 9.6 Hz), 2.75 (ddd, 1H, J = 3.1 Hz, J = 7.7 Hz, J = 9.6 Hz), 0.93−2.05 (m, 17H), 0.85 (t, 3H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 218, 139, 134, 62, 55, 51, 49, 46.2, 45.7, 43, 38, 35, 32, 31, 27, 26.1, 26.0, 18, 15. IR (CH_2Cl_2): 1685.0 (s, C=O).

Also isolated was the retroaldol Diels−Alder product **7**, spectroscopically identical to the material isolated from the reaction of **2a** with cyclopentadiene (0.5 mg, 3%), and the retroaldol product of hydrolyzed **2e** (**10**, 1.6 mg, 13%). Material tentatively identified by ^{1}H NMR as the simple hydrolysis product of **2e** (2.5 mg, 18%) was also obtained. ^{1}H-NMR ($CDCl_3$): δ 6.60 (d, 1H, J = 12.8 Hz), 5.87 (dd, 1H, J = 2.6 Hz, J = 12.8 Hz), 4.20 (dd, 1H, J = 3.8 Hz, J = 11.4 Hz), 3.42 (dd, 1H, J = 7.7 Hz, J = 11.4 Hz), 2.43 (m, 1H), 0.95−2.10 (m, 14H), 0.83 (t, 3H, J = 7.2 Hz). It is of note that when the Diels−Alder reaction of **2e** is worked up by pouring the reaction mixture into ice−water instead of aqueous base, *no retroaldol product **7** or retroaldol starting material **10** can be detected by capillary GC analysis.*

General Procedure for Kinetics Experiments. To a flame-dried vial containing a CH_2Cl_2 solution of **2a** or **2e** (0.140 mmol) and THF (0.70 mmol), under a nitrogen atmosphere at 20.0 °C, was added freshly cracked cyclopentadiene (116 μL, 1.406 mmol) while simultaneously starting a stop watch, and the total volume was brought to 1.40 mL with the addition of dry CH_2Cl_2. Carefully measured aliquots (0.20 mL) were removed at timed intervals and quenched by injecting them into ice−water (10 mL). The aqueous mixture was extracted with ether (3 × 15 mL), and the ether was dried (Na_2SO_4) and evaporated. The residue was taken into solvent[24] (0.80 mL) and a 0.042 M stock solution of cyclohexanone (100 μL, as an internal standard) in the same solvent was added. This entire solution was transferred to a vial and was analyzed by HPLC on a Microsorb Si 80-125 C5 column equipped with guard column. Product concentrations were determined on the basis of relative response factors derived from calibration curves obtained the same day as the analysis. Reactions were quenched at low overall conversions (<10%) to avoid significant change in reactant concentration.

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(24) The solvents used were the same as the eluents used for their HPLC analysis: 5% ethyl acetate/hexane in the case of **2a** and 20% ethyl acetate/hexane in the case of **2e**.