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Geometrical Aspects of the Activation of Ketones by Lewis Acids

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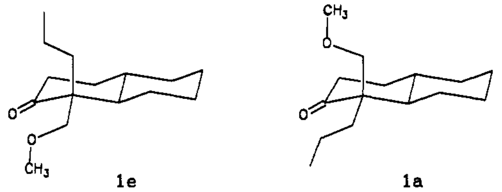
Abstract: The rates of reaction of the $TiCl_4$ complexes of two diastereomeric 1-(methoxymethyl)-1-propyldecahydronaphthalen-2-ones (**1a** and **1e**) with trimethylsilyl cyanide have been measured for the purpose of determining the preferred complexation geometry for the activation of carbonyls toward nucleophilic addition. Compound **1a** incorporates an axial methoxymethyl group which is designed to steer complexation of $TiCl_4$ to the π-system of the carbonyl, while an equatorial methoxymethyl group in **1e** directs complexation into the plane. Chemical shift changes in the ^1H and ^{13}C NMR spectra of **1a** and **1e** as $TiCl_4$ is added are indicative of the formation of 1:1 complexes. In the case of **1a**, complex formation involves a conformational change of the cyclohexanone portion of the naphthalenone from a chair to a twist-boat; no such conformational change is observed for **1e**. At −45 °C in CH_2Cl_2, 0.042 M **1e**·$TiCl_4$ and **1a**·$TiCl_4$ react with 0.38 M Me_3SiCN to give cyanohydrin products with pseudo-first-order rate constants of 0.028 and 0.0069 min^{-1}, respectively. These results exclude the possibility that the reaction of ketone–$TiCl_4$ complexes proceeds through a small concentration of a highly reactive π-complexed intermediate.

The rate of addition of nucleophiles to carbonyl carbons is dramatically accelerated by complexation of Lewis acids to the carbonyl oxygen.[1] The three-dimensional structure of a Lewis acid should, in principle, influence the stereoselectivity of the addition of nucleophiles to carbonyls; such effects have been successfully applied to the synthesis of optically active alcohols.[2] In order to rationally design Lewis acids for accomplishing stereoselective addition reactions, it is necessary to know the reactive geometry of the ketone–Lewis acid complex; these geometries may be broadly separated into those in which the acid is in the plane of the carbonyl and those in which it is perpendicular to this plane, in a position to interact with the π-system.[3] In the context of nucleophilic additions to ketone–Lewis acid complexes, it has generally been assumed that the reactive geometry is of an in-plane type.[4] The reasons for this assumption are numerous experimental[5,6] and theoretical studies[7] which indicate that this is the thermodynamically preferred geometry for Lewis acids commonly employed in organic synthesis (e.g., H^+, Li^+, BF_3). However, the reactive conformation of a molecule is not necessarily the same as the thermodynamically favored conformation (cf. the Curtin–Hammett principle[8]). It is *possible* that nucleophilic addition to a Lewis acid activated carbonyl could proceed largely through a small equilibrium concentration of a highly reactive π-complexed intermediate, rather than the thermodynamically favored in-plane intermediate. For this possibility to receive serious consideration it should meet two criteria: that a π-complexation geometry is not energetically unreasonable, and that an interaction of this type would lead to the activation of the carbonyl toward nucleophilic addition.

Scheme I



1e **1a**

Many examples are known in which a transition metal is bonded to a carbonyl in a π-type geometry (i.e., an η^2 fashion).[9,10] While the majority of these examples involve electron-rich metals which can engage in back-bonding to the carbonyl carbon, a number of cases are known in which a hard Lewis acid is complexed in this geometry.[11,12] Of particular interest in this regard is the report

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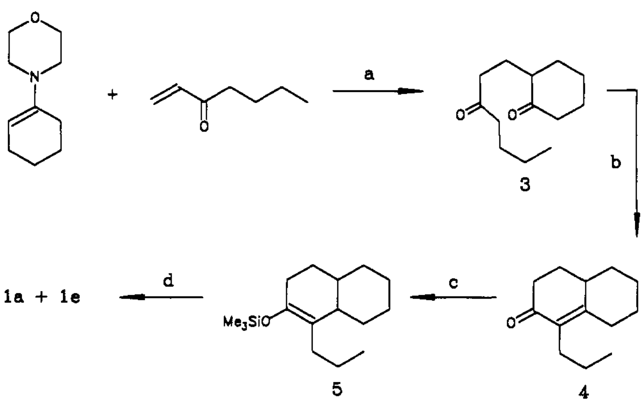
Scheme II[a]



[a] Conditions: (a) dioxane, reflux, 4 h; then H_2O/dioxane, reflux, 14 h, 52%; (b) *t*-BuOK, THF, room temperature, 12 h, 83%; (c) Li/NH_3; then remove NH_3; then Me_3SiCl/Et_3N, THF, −15 °C, 90%; (d) CH_3OCH_2Cl, catalytic $ZnBr_2$, CH_2Cl_2, 0 °C to room temperature, 86%.

by Helmchen and co-workers of the crystal structure of the complex formed between $TiCl_4$ and the ethyl lactate ester of acrylic acid.[11a] In the solid state this complex adopts a geometry in which the titanium is at a 63.6° angle with respect to the plane defined by the two oxygens and carbonyl carbon of the acrylate, suggesting a significant interaction with the π-system. The stereochemical results of the Diels–Alder reactions of this complex are consistent with a similar geometry in solution.

A simple resonance representation of the interaction of a Lewis acid with the π-system of a carbonyl provides a convincing argument for activation toward nucleophilic addition.

To the extent that there is a bond between the carbonyl oxygen and the Lewis acid, there *is not* a bond between the oxygen and the carbon; a large increase in electrophilicity should result. In fact, placing the Lewis acid above the carbonyl π-system is not a new idea. The additions of a number of organometallic species have been suggested to occur via four-center transition states with a Lewis acid in the π-system.[13,14] In addition, there have been a number of recent reports of reactions of aldehyde–transition-metal complexes which are believed to occur through this geometry.[15]

We have investigated the question of the *reactive* geometry of ketone–Lewis acid complexes by studying the reaction kinetics of the $TiCl_4$ complexes of the diastereomeric 1-propyl-1-(methoxymethyl)decahydronaphthalen-2-ones **1e** and **1a** with trimethylsilyl cyanide (Scheme I). Compounds **1e** and **1a** incorporate methoxymethyl groups to direct $TiCl_4$ toward an in-plane or π-type geometry, respectively. An *n*-propyl group is included in each compound as an isostere of the methoxymethyl group to minimize conformational differences between the two complexes. $TiCl_4$ was chosen as the activating Lewis acid because of its wide use in organic synthesis, and because previous work in our group suggested that $TiCl_4$ complexation could be directed with a high degree of fidelity by a nearby methoxymethyl group.[16]

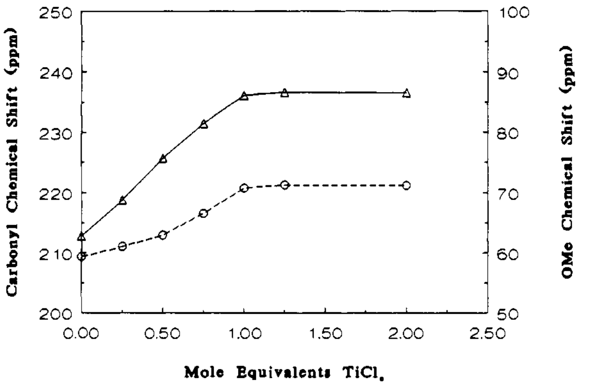


Figure 1. ^{13}C chemical shifts for the carbonyl (△) and methoxy (○) carbons as a function of added $TiCl_4$ for compound **1a**. [1a] = 0.21 M in CD_2Cl_2.

Synthesis

The similarity of **1a** and **1e** to the A/B ring system of many steroids provided a ready guide to their synthesis (Scheme II). Reaction of the morpholine enamine of cyclohexanone[17] with 1-hepten-3-one, followed by treatment of the resulting diketone **3** with potassium *tert*-butoxide in THF gave the annulation product **4** in 40% overall yield. Quenching the Li/NH_3 reduction product of **4** with Me_3SiCl/Et_3N afforded the enol silane **5** in 90% yield.[18] Finally, treatment of the enol silane with chloromethyl methyl ether and catalytic $ZnBr_2$ in dichloromethane[19] afforded an 86% yield of a 6:1 mixture of the desired target systems **1a** and **1e**, respectively. That the major diastereomer formed in this reaction was, indeed, the expected axial methoxymethylated compound **1a** was confirmed by $^1H-^1H$ NOE experiments. Irradiation of the axial methine proton α to the carbonyl produced a 6.9% enhancement of one of the two diastereotopic methylene proton resonances of the methoxymethyl group of **1a**; no such enhancement was observed for **1e**. Conversely, irradiation of the methylene protons of the methoxymethyl group gave an enhancement of the axial proton α to the carbonyl in the case of **1a**, but not in the case of **1e**.

Complexation Studies

The ^{13}C NMR spectra of mixtures of $TiCl_4$ with either **1a** or **1e** indicate the formation of highly associated 1:1 complexes. In particular, addition of increasing amounts of $TiCl_4$ to CD_2Cl_2 solutions of **1a** results in progressive downfield shifts of the ^{13}C NMR resonances associated with the carbonyl and methoxy carbons from 212.8 and 59.4 ppm to 236.6 and 71.2 ppm, respectively (Figure 1). The increases in the chemical shifts of the two carbons simultaneously stop when 1 equiv of $TiCl_4$ has been added, and they remain unchanged at 2 equiv. Thus, a 1:1 complex is present in which both oxygens are involved in coordination to the Lewis acid. From the data so obtained for the carbonyl carbon we estimate[20] an association constant for the **1a**·$TiCl_4$ complex of >5000 M^{-1}. Similar titration experiments with **1e** were complicated by severe exchange broadening at less than 1 equiv of $TiCl_4$. However, in the range of 1–2 equiv of $TiCl_4$ all ^{13}C resonances were sharp and constant, suggesting the formation of a strongly associated 1:1 complex involving both oxygens of the substrate. The changes in chemical shifts of the carbonyl and methoxymethyl group carbons of **1e** upon complex formation were similar to those seen with **1a** (from δ 212.9 to 234.6 ppm for the carbonyl carbon, and from δ 59.2 to 70.5 ppm for the methyl), and are comparable in magnitude to those found with other complexes of ketones and ethers with hard Lewis acids.[4a,5,21]

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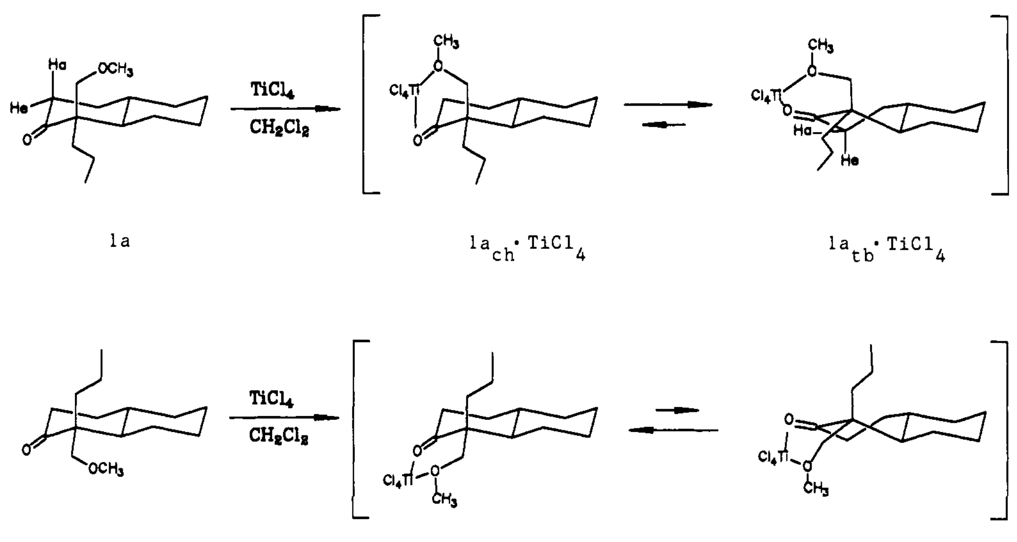
Scheme III



1a $1a_{ch}\cdot TiCl_4$ $1a_{tb}\cdot TiCl_4$

1e $1e_{ch}\cdot TiCl_4$ $1e_{tb}\cdot TiCl_4$

It is known that boat–twist-boat conformations are energetically more accessible to cyclohexanones than to cyclohexanes.[22] As a consequence, two limiting conformations must be considered for *each* of the complexes **1a**·$TiCl_4$ and **1e**·$TiCl_4$: a chair–chair form and a twist-boat–chair form (Scheme III). Assuming a Ti–O bond length of 2.1 Å for both in-plane and π-complex geometries,[11a] an examination of molecular models of the chair–chair conformer of **1a**·$TiCl_4$ suggests that from a purely geometrical standpoint π-coordination of the titanium is quite reasonable, but that it is not possible for the metal to be chelated in an in-plane geometry. However, a conformational change to a twist-boat–chair conformer ($\mathbf{1a}_{tb}\cdot TiCl_4$) would readily accommodate such a coordination geometry. Similar considerations lead to the conclusion that the chair–chair form of **1e**·$TiCl_4$ is expected to have an in-plane, rather than a π-type complexation geometry, but that the latter geometry is expected in the twist-boat–chair conformer ($\mathbf{1e}_{tb}\cdot TiCl_4$).

The ^1H NMR spectra obtained during the titration studies of **1a** with $TiCl_4$ provided insights as to the conformation of the complex. The ^1H resonances of the methylene and methyl protons of the methoxymethyl group exhibited the expected smooth increase in chemical shift with added $TiCl_4$ up to 1 equiv and then remained sharp and constant (Table I). Though *qualitatively* similar, there are striking *quantitative* differences in the behavior of the axial and equatorial protons α to the carbonyl which strongly suggest a change in the conformation of the cyclohexanone portion of the substrate from chairlike in the free ketone to a boat or twist-boat conformation in the complex ($\mathbf{1a}_{tb}\cdot TiCl_4$). As $TiCl_4$ is added, the chemical shift of the equatorial proton (H_e) moves downfield much more rapidly than that of the axial proton, H_a (crossing it at ca. 0.25 equiv of $TiCl_4$). The relatively small change in chemical shift of H_a is explained on the basis of the opposing influences of increased carbonyl polarization (downfield shift) and the change from a deshielded to a relatively shielded environment (upfield shift).[23] For H_e, the two effects (polarization and change in environment) work in concert to give a considerably larger downfield shift upon complexation.

The changes in the splitting patterns of the two protons upon complex formation also support the suggested conformational change. The 14- and 6-Hz vicinal coupling constants of H_a in **1a** change to 7 and 4 Hz upon complex formation, while those of H_e change from 3 and 3 Hz to 10 and 10 Hz. Quantitative applications of the Karplus relationship to the prediction of conformations from vicinal coupling constants may be fraught with difficulties due to the effects which substituent electronegativity and orientation may have on the magnitudes of coupling constants.[24] The system under consideration here is particularly complicated, since a substituent (the carbonyl carbon) undergoes a change in electronegativity upon complex formation with $TiCl_4$. However, on a qualitative basis, vicinal coupling constants have been quite useful for assigning the general conformation of six-membered rings. The vicinal coupling constants of the α protons of **1a** are typical of those found in chair cyclohexanones;[25] their large changes upon addition of $TiCl_4$ are not consistent with the retention of a chair conformation in the complex. Comparison of the vicinal coupling constants of **1a**·$TiCl_4$ with those observed for the A-ring of a number of steroid derivatives[26] suggests the twist-boat form shown ($\mathbf{1a}_{tb}\cdot TiCl_4$), rather than an alternate twist-boat form (with the carbonyl at the prow[27]) or a half-chair.[28]

Table I. ^1H Chemical Shifts of Free and Complexed Substrates

	chemical shift (multiplicity)[a]	
proton	**1a**	**1a**·$TiCl_4$
$-CH_2OCH_3$ (methyl H)	3.24 (s)	4.10 (s)
$-CH_2OCH_3$ (methylene H)	3.69 (d, 9) 3.20 (d, 9)	4.98 (d, 12) 3.61 (d, 12)
$-CH_2C(O)-$		
H_{ax}	2.51 (ddd, 14, 14, 6)	2.67 (ddd, 14, 7, 4)
H_{eq}	2.32 (ddd, 14, 3, 3)	3.04 (ddd, 14, 10, 10)

	chemical shift (multiplicity)[a]	
proton	**1e**	**1e**·$TiCl_4$
$-CH_2OCH_3$ (methyl H)	3.32 (s)	4.10 (s)
$-CH_2OCH_3$ (methylene H)	3.78 (d, 9) 3.18 (d, 9)	5.16 (d, 13) 3.77 (d, 13)
$-CH_2C(O)-$		
H_{ax}	2.40 (ddd, 14, 14, 6)	3.0 (11, 12, 6)
H_{eq}	2.28 (ddd, 14, 5, 3)	2.7 (11, 3, 3)

[a] Numbers in parentheses are coupling constants (Hz).

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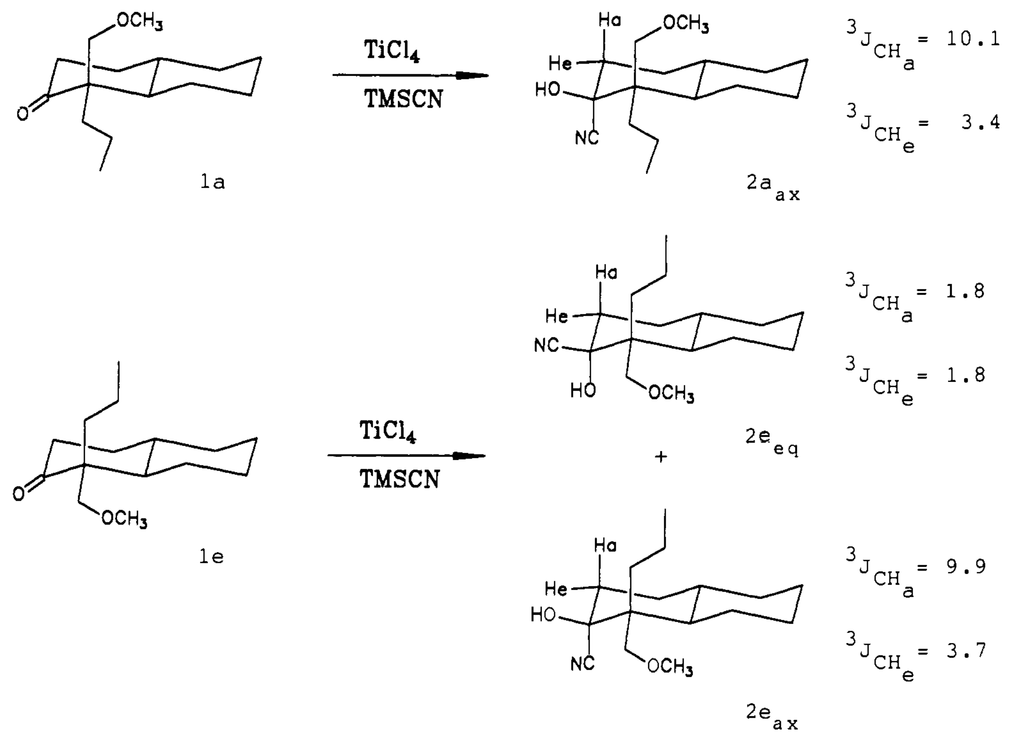
Scheme IV



In the titration studies with **1e** there was no evidence for a crossing in the chemical shifts of the axial and equatorial protons α to the carbonyl, nor were there significant changes in the coupling constants of the protons α to the carbonyl, although the signals of these protons are significantly broadened. Thus, it seems likely that the predominant conformer of **1e**·$TiCl_4$ is that in which the cyclohexanone unit remains a chair ($\mathbf{1e}_{ch}\cdot TiCl_4$). The signal broadening of the α protons may indicate a small contribution of another, fairly similar conformer (e.g., a half-chair).

Reactions and Kinetics

Our choice of nucleophile for these studies was dictated by the desirability of avoiding the introduction of counterions which could make the identity of the activating Lewis acid ambiguous. While allylsilanes, enol silanes, and ketene silyl acetals seemed attractive candidates in this respect, they all failed to react with the sterically hindered substrate–$TiCl_4$ complexes. However, $TiCl_4$ complexes of both **1a** and **1e** react rapidly with (TMS)CN at room temperature to give quantitative yields of cyanohydrin products[29] (Scheme IV). The axial nitrile $\mathbf{2a}_{ax}$ is produced as the sole product in the reaction of **1a**. The reaction of **1e** leads to a 2.8:1 mixture of diastereomers $\mathbf{2e}_{eq}$ and $\mathbf{2e}_{ax}$, respectively. The stereochemical assignment of all of these products was readily made on the basis of three bond ^{13}C–^{1}H coupling constants between the nitrile carbon and the protons which were formerly α to the carbonyl; the magnitude of $^{3}J_{CH}$ as a function of the dihedral angle is known to follow a modified Karplus relationship.[30,31] The nitrile carbon of the major product in the reaction of **1e** appears as a triplet in the ^{13}C NMR spectrum, with $^{3}J_{CH}$ = 1.8 Hz, consistent with a gauche relationship between the nitrile carbon and both of the coupled protons ($\mathbf{2e}_{eq}$). For the minor product ($\mathbf{2e}_{ax}$), the nitrile carbon appears as a widely spaced doublet of doublets ($^{3}J_{CH}$ = 9.9 and 3.7 Hz), indicative of one gauche and one trans coupling. The product of the reaction of **1a** is assigned an axial nitrile geometry on a similar basis (dd, $^{3}J_{CH}$ = 10.1 and 3.4 Hz). The surprising[32] predominance of the equatorial nitrile product from **1e** may be rationalized on the basis of molecular models which show one of the chlorines of the complexed $TiCl_4$ blocking the bottom face of the cyclohexanone.

The kinetics of the reactions of $TiCl_4$ complexes of **1a** and **1e** were determined under pseudo-first order conditions by dividing a freshly prepared stock solution of the appropriate substrate-$TiCl_4$ complex amongst several vials, cooling to −45 °C, and adding 9 equivalents of (TMS)CN to each vial to give 0.042 M substrate·$TiCl_4$ and 0.38 M (TMS)CN.[42] At appropriate intervals aliquots were quenched and worked up. The relative amounts of starting material vs product(s) were determined by integration of the well-separated methoxy singlets in the ^{1}H NMR spectrum. Typically, 4–5 data points were obtained in each kinetics experiment, with good reproducibility of the rate constants obtained in separate runs. Plots of −ln [**1a**] and −ln [**1e**] vs time are shown in Figure 2; the data shown are those combined from nine separate kinetics experiments. Under these conditions we find that the pseudo-first-order rate constant for the reaction of **1a**·$TiCl_4$ with (TMS)CN is $(6.9 \pm 0.3) \times 10^{-3}$ min^{-1}, while that of **1e** is $28 \pm 2) \times 10^{-3}$ min^{-1}, corresponding to half-lives of 100 and 25 min, respectively.

Discussion

In-Plane vs Out-of-Plane Complexation: Thermodynamics. Complexing agents for carbonyls may be broadly classified as being electron-rich or electron-deficient. The majority of the out-of-plane (i.e., η^2, or π) carbonyl complexes which have been reported have involved electron-rich transition metals.[9] It was recognized early on that this geometry is probably a consequence of back-bonding from the metal to the carbonyl antibonding π^*-orbital.[32] Thus, an out-of-plane geometry is expected to be especially favored by an electron-rich metal with an electron-poor carbonyl. Until recently, there was little experimental evidence to support these predictions, due to the lack of systems in which both types of coordination geometry could be observed. However, a number of recent studies have confirmed those predictions having to do with the electronic nature of the carbonyl substrate, as well as determining the influence of solvent and temperature on the η^1 vs η^2 equilibrium.[34]

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(29) In the absence of $TiCl_4$ neither **1a** nor **1e** reacted with (TMS)CN over a 24-h time period, nor did they react with $TiCl_4$ in the absence of (TMS)CN.

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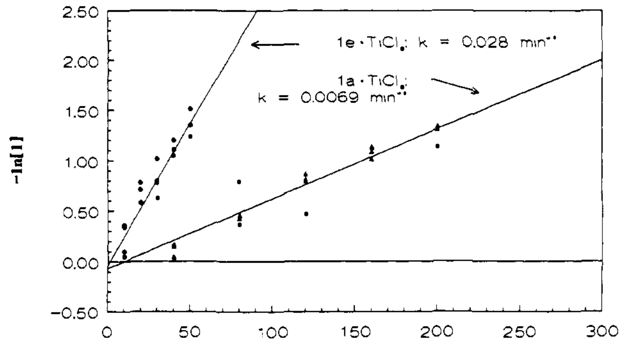

Figure 2. $-\ln[\mathbf{1a}]$ vs time (▲) and $-\ln[\mathbf{1e}]$ vs time (●) for the reactions of **1a**·$TiCl_4$ and **1e**·$TiCl_4$ with (TMS)CN in CH_2Cl_2 at −45 °C. [**1**·$TiCl_4$] = 0.042 M, [(TMS)CN] = 0.38 M. The solid lines are linear least-squares fits to the data: $-\ln[\mathbf{1a}] = 0.0069(t) - 0.066$ ($r^2 = 0.97$) and $-\ln[\mathbf{1e}] = 0.028(t) - 0.033$ ($r^2 = 0.96$).

Main-group Lewis acids and highly electron deficient transition metals (e.g., d^0 $TiCl_4$) are similar in the sense that no back-bonding can be expected to the carbonyl carbon in a complex. Little is known about the relative stabilities of in-plane vs out-of-plane complexes of these types of compounds. Calculations of minimum energy geometries of main-group Lewis acid–carbonyl complexes have consistently shown that an in-plane geometry is preferred.[7] Both geometries have been observed in crystal structures of $TiCl_4$–carbonyl complexes.[6a] However, we are aware of no instances of the spectroscopic characterization of a π-complex geometry between a carbonyl and a main-group Lewis acid or transition metal which is incapable of back-bonding to the carbonyl carbon. This lack of data might be interpreted to mean that out-of-plane complexes do not exist in solution. However, in at least one instance (Helmchen's $TiCl_4$–acrylate complex;[11a] see above) the results of solution chemistry are consistent with the out-of-plane geometry observed in the crystal structure. An alternative explanation for this lack of spectroscopic data is that the phenomenological basis for the characterization of π-complexes of transition metals lacks generality. Typical spectral changes which have been associated with a π-complex geometry are a very substantial (often greater than 100 ppm) upfield shift of the carbonyl carbon in the ^{13}C NMR spectrum, a small upfield shift of protons α to the carbonyl in the ^1H NMR spectrum, and complete loss of the C=O stretching frequency in the IR spectrum.[35] These changes are explained by the back-donation of electrons from the metal to the carbonyl carbon; in effect, a carbonyl is no longer present, and the structure is better described as an oxametallocyclopropane than as a carbonyl–transition-metal complex.[33d,35c]

It is not clear that an electron-deficient transition metal incapable of back-bonding should induce the same spectroscopic changes in a carbonyl compound as an electron-rich metal. Regardless of whether such a complex is considered to involve a symmetrical structure with a three-center two-electron bond, or an unsymmetrical structure in which the primary bonding interaction is between the metal and the oxygen, the carbonyl carbon will be more electron deficient in the complex than in the free state. As a result, the spectral changes expected in such a complex should not resemble those associated with π-complexes of electron-rich transition metals, but rather those found with in-plane complexes; i.e., *downfield* chemical shifts should be expected in the ^{13}C and ^1H NMR spectra of π-complexes.[5,21] Thus, gross changes (i.e., upfield vs downfield) of the carbonyl ^{13}C chemical shift or of the α ^1H chemical shifts may not provide a suitable criterion for distinguishing between in-plane vs π-complexes of carbonyls with main-group Lewis acids or highly electron deficient transition metals. More subtle shift effects should, in principle, allow this distinction to be made. In particular, a ketone with a plane of symmetry such as acetone would retain this symmetry in a π-complex, but would lose it in an in-plane complex, resulting in differing NMR signals for the groups syn and anti to the Lewis acid. Unfortunately, the interpretation of chemical shift differences of this type must also be subject to some ambiguity due to the time scale of the NMR measurement. Rapid isomerization may lead to signal averaging, resulting in an apparent equal change in chemical shifts for both positions α to the carbonyl. This has been observed by Gladysz in the case of $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}C(CH_3)_2)]^+BF_4^-$; only by the adoption of heroic means (utilization of the $^{13}CH_3COCH_3$ complex at −145 °C) was it possible to decoalesce the two methyl resonances.[36] Even if separate signals are seen for the positions flanking the carbonyl carbon of a symmetrical ketone, this does not rule out the possibility that a π-complex (uniform change in chemical shifts) is in rapid equilibrium with an in-plane complex (differential changes in chemical shift). In sum, even if π-complexes of carbonyls with main-group Lewis acids or highly electron deficient transition metals do exist in solution, it is not surprising that they have not been assigned as such on the basis of spectroscopic data; furthermore, the prospects for using spectroscopic methods for estimating the relative stability of such complexes seem poor, other than with exceptional cases.[37]

The conformational change of the cyclohexanone unit of **1a** upon complex formation to give $\mathbf{1a}_{tb}$·$TiCl_4$ allows a minimum estimate of the energy difference between in-plane and π-type carbonyl complex geometries for $TiCl_4$ to be inferred. Empirical calculations suggest an energy difference of ca. 2.7 kcal/mol between the chair and twist-boat conformations of cyclohexanone.[38] In accord with these results, we have found[39] a calculated difference in energy between the chair–chair and twist-boat–chair forms of **1a** of 3.1 kcal/mol. In addition to the inherent steric and torsional factors associated with the cyclohexanone ring which influence the chair vs twist-boat conformational preference, two additional effects must be considered in the case of the complex: an electronic preference for an in-plane coordination geometry by titanium and unfavorable steric interactions which might be associated with an out-of-plane geometry. The most obvious interaction of the latter type would arise from a van der Waals repulsion between one of the chlorines of the $TiCl_4$ and H_a of $\mathbf{1a}_{ch}$·$TiCl_4$. From examination of molecular models which were constructed assuming a covalent radius of 1.8 Å for chlorine,[40] and Ti–O and Ti–Cl bond lengths of 2.1 and 2.26 Å, respectively,[11a] it does not seem that the latter interaction should be very significant. Thus, the value of 3.1 kcal/mol due to conformational change in the cyclohexanone ring should be a fairly reasonable estimate of the "price" which titanium must pay in order to achieve an in-plane coordination geometry, and as such, represents a *minimum* value for the energy difference between in-plane geometries and π-geometries.

In-Plane vs Out-of-Plane Complexation: Activation. We believe that the studies presented here represent the first strong evidence that the preferred geometry for the activation of carbonyls toward nucleophilic attack involves in-plane complexation of the Lewis

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[36] Dalton, D. M.; Fernandez, J. M.; Emerson, R. D.; Larsen, R. D.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9198.

[37] Faller (ref 5a) has attributed the broadening of an aldehyde proton resonance in a complex with the relatively hard Lewis acid $[HC(pyr)_3W)(NO)_2]^{2+}$ to the presence of a small (<1%) concentration of an η^2 complex in equilibrium with the free aldehyde and an η^1 complex.

[38] Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1977**, *28*, 1173.

[39] Calculations were performed with the program PCMODEL, Version 3.0, Serena Software, Bloomington, IL. The molecular mechanics force field employed in this program is derived from the MM2 force field of N. L. Allinger (QCPE-395, 1977).

[40] Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960; Section 7.12.

acid. We have established that the major species present in the complexes of **1a** and **1e** with TiCl$_4$ are of an in-plane geometry. However, this by no means precludes the existence of other species in smaller concentrations which have different coordination geometries, nor does it necessarily follow that the predominant conformer is the most reactive conformer.[8] The complex **1a**·TiCl$_4$ may exist as an equilibrium mixture of **1a**$_{ch}$·TiCl$_4$, in which the titanium is π-complexed, and **1a**$_{tb}$·TiCl$_4$, in which it is coordinated in-plane. The same type of equilibrium is possible for **1e**·TiCl$_4$, between the in-plane complex **1e**$_{ch}$·TiCl$_4$ and the π-complex **1e**$_{tb}$·TiCl$_4$. It is reasonable to assume that there will be a higher concentration of the π-complex of **1a**·TiCl$_4$ than that of **1e**·TiCl$_4$ ([**1a**$_{ch}$·TiCl$_4$] $\gg$ [**1e**$_{tb}$·TiCl$_4$]). While the energetically unfavorable change in coordination geometry on going to **1a**$_{ch}$·TiCl$_4$ will be offset to some degree by the relaxation of the twist-boat cyclohexanone of **1a**$_{tb}$·TiCl$_4$ to a chair, *both* of these factors will disfavor the twist-boat π-complex **1e**$_{tb}$·TiCl$_4$. The overall rate of reaction of **1a**·TiCl$_4$ will be the sum of the rates of reaction from the in-plane complex and the π-complex (k_{ip}[**1a**$_{tb}$·TiCl$_4$] and k_π[**1a**$_{ch}$·TiCl$_4$], respectively, eq 1). Similarly, the overall rate of reaction of **1e**·TiCl$_4$ will be the sum of the individual rates of reaction of the two complexes (eq 2).

$$d[\mathbf{1a}\cdot\mathrm{TiCl_4}]/dt = -[k_{ip}[\mathbf{1a}_{tb}\cdot\mathrm{TiCl_4}] + k_\pi[\mathbf{1a}_{ch}\cdot\mathrm{TiCl_4}]][\mathrm{TMSCN}] \quad (1)$$

$$d[\mathbf{1e}\cdot\mathrm{TiCl_4}]/dt = -[k_{ip}[\mathbf{1e}_{ch}\cdot\mathrm{TiCl_4}] + k_\pi[\mathbf{1e}_{tb}\cdot\mathrm{TiCl_4}]][\mathrm{TMSCN}] \quad (2)$$

If π-type reactive geometries of ketone–Lewis acid complexes were highly preferred (i.e., $k_\pi \gg k_{ip}$), then the rate of reaction of **1a**·TiCl$_4$ would be faster than that of **1e**·TiCl$_4$, since [**1a**$_{ch}$·TiCl$_4$] should be greater than [**1e**$_{tb}$·TiCl$_4$]; this is not what is observed. Hence, the fact that **1e**·TiCl$_4$ reacts faster than **1a**·TiCl$_4$ is *not* consistent with a highly reactive conformer having an out-of-plane complexation geometry. Insofar as the predominant coordination geometry present is of an in-plane type for both **1a**·TiCl$_4$ and **1e**·TiCl$_4$, the relatively small 4-fold difference in their rates of reactions with (TMS)CN is likely due to a slightly greater degree of steric hindrance to attack in the case of **1a**$_{tb}$·TiCl$_4$. Our finding that the preferred conformation of **1a**·TiCl$_4$ has a twist-boat cyclohexanone (**1a**$_{bt}$·TiCl$_4$) in which the Lewis acid has adopted an in-plane coordination geometry does not allow us to answer the question of whether the rate of reaction through an in-plane geometry is *much* faster than that through a π-type geometry ($k_{ip} \gg k_\pi$), or whether the rates are comparable ($k_{ip} \simeq k_\pi$). A determination of this question will require systems in which the concentration of in-plane complexes and π-complexes can be accurately measured. However, the possibility that the preferred reaction pathway proceeds by way of a small concentration of a highly reactive π-complex can be excluded.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR were obtained on General Electric QE-300 or GN-300 spectrometers; ^{1}H spectra were at 300 MHz, and ^{13}C spectra were at 75 MHz. Chemical shifts were referenced to the residual solvent peak. Infrared spectra were obtained with either a Perkin-Elmer Model 599 infrared spectrometer or a Perkin-Elmer Model 1800 Fourier transform infrared spectrometer. Mass spectra were obtained with a Hewlett-Packard 5970 mass selective detector attached to a Model 5890 gas chromatograph fitted with a 25-m × 0.22-mm HP-1 (methyl silicone) capillary column. Combustion analyses were performed by Oneida Research Services, Ltd. (Whitesboro, NY).

All reactions were performed under nitrogen atmosphere, and standard precautions against moisture were taken. THF was distilled under nitrogen from potassium/benzophenone; dioxane was obtained as "anyhydrous" from Aldrich Chemical Co. and used without further drying; dichloromethane was distilled under nitrogen from CaH$_2$; triethylamine was distilled from CaH$_2$ and stored over 3-Å molecular sieves. CD$_2$Cl$_2$ for the TiCl$_4$ titration studies was dried over 3-Å molecular sieves. TiCl$_4$ was fractionally distilled, taking a large forerun, and stored with all glass seals/stopcocks; it was stored no more than 4 days before redistillation.

2-(3-Oxoheptyl)cyclohexanone (3). A solution of 1-hepten-3-one (2.33 g, 20.8 mmol) dissolved in dry dioxane (25 mL) was added dropwise via syringe to a room temperature solution of the morpholine enamine of cyclohexanone (3.48 g, 20.8 mmol) in dry dioxane (55 mL). The solution was heated to reflux, and after 4 h, water (55 mL) was added. After an additional 14 h of reflux the mixture was cooled to room temperature, diluted with water (90 mL), and extracted with several portions of ether. The combined ether extracts were washed with 3 N HCl and saturated aqueous NaHCO$_3$ and then dried (MgSO$_4$) and filtered, and the ether was removed by rotary evaporator. Purification by flash chromatography (10% ethyl acetate/petroleum ether) gave **3** (2.29 g, 52%). ^{1}H NMR (CDCl3): δ 2.60–2.20 (m, 7 H), 2.19–1.79 (m, 4 H), 1.77–1.20 (m, 8 H), 0.89 (t, 7 Hz, 3 H). ^{13}C NMR (CDCl$_3$): δ 213.2, 211.4, 50.2, 42.8, 42.4, 40.6, 34.7, 28.4, 26.3, 25.3, 24.2, 22.7, 14.2. IR (CCl$_4$): 1708 cm^{-1}. MS, *m/e* (intensity): 210 (8, M$^+$), 181 (3, M – C$_2$H$_5$), 55 (100, C$_4$H$_7$). Anal. Calcd for C$_{13}$H$_{22}$O$_2$: C, 74.24; H, 10.54. Found: C, 73.97; H, 10.82.

4,4a,5,6,7,8-Hexahydro-1-propyl-2(3*H*)-naphthalenone (4). A solution of potassium *tert*-butoxide (1.07 g, 9.57 mmol) in dry THF (60 mL) was added to a 0 °C solution of **3** (2.01 g, 9.57 mmol) in dry THF (20 mL). The cooling bath was removed and the solution stirred overnight. After dilution with ether (400 mL) the organics were washed with water and brine and then dried (MgSO$_4$). Rotary evaporation gave an oil which was purified by flash chromatography (10% ethyl acetate/petroleum ether) to yield **4** (1.52 g, 83%). ^{1}H NMR (CDCl$_3$): δ 2.9–2.78 (m, 1 H), 2.47–2.20 (m, 5 H), 2.10–1.70 (m, 5 H), 1.65–1.15 (m, 6 H), 0.88 (t, 7 Hz, 3 H). ^{13}C NMR (CDCl$_3$): δ 199.4, 160.0, 133.2, 38.8, 36.4, 35.0, 31.2, 28.6, 27.2, 26.7, 25.5, 22.7, 14.0. IR (CCl$_4$): 1675 cm^{-1}. MS, *m/e* (intensity): 192 (38, M$^+$), 163 (11, M – C$_2$H$_5$), 149 (100, M – C$_3$H$_7$). Anal. Calcd for C$_{13}$H$_{20}$O: C, 81.20; H, 10.48. Found: C, 80.89; H, 10.72.

***trans*-3,4,4a,5,6,7,8,8a-Octahydro-1-propyl-2-[(trimethylsilyl)oxy]-naphthalene (5).** Lithium wire (0.088 g, 12 mmol) was added to freshly distilled (from Na) liquid ammonia (130 mL) which had been cooled in dry ice/acetone. After 10 min, a solution of the enone **4** (0.77 g, 4 mmol) in THF (16 mL) was added dropwise via syringe to the stirred solution. After addition was complete the solution was stirred for an additional 10 min and then quenched by dropwise addition of isoprene until the blue color faded. After removal of the ammonia (first at room temperature and then under high vacuum) the residual solid was suspended in dry THF and cooled under N$_2$ in ice/methanol for 20 min. A mixture of Me$_3$SiCl (3.0 mL, 24 mmol) and dry Et$_3$N (3.36 mL, 24 mmol) was centrifuged, and 3.20 mL of the supernatant was added to the cold enolate solution. After 20 min the reaction was worked up by adding ice cold saturated aqueous NaHCO$_3$ and extracting rapidly with cold pentane (2 × 40 mL). Rotary evaporation of the combined organics gave an oil which was passed *rapidly* through a 3- × 15-cm column of silica gel with CH$_2$Cl$_2$ as eluant to afford the enol silane **5** as an oil (0.96 g, 90%). The enol silane was used for subsequent reactions as soon as possible. ^{1}H NMR (CDCl$_3$): δ 2.30–1.00 (m, 18 H), 0.88 (t, 7.0 Hz, 3 H), 0.16 (s, 9 H). ^{13}C NMR (CDCl$_3$): δ 144.5, 120.1, 43.7, 43.2, 34.9, 32.1, 31.8, 31.5, 29.0, 28.1, 27.6, 22.7, 15.3, 1.8. MS, *m/e* (intensity): 266 (19, M$^+$), 237 (48, M – C$_2$H$_5$), 223 (100, M – C$_3$H$_7$).

1α-(Methoxymethyl)-1β-propyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (1e) and 1β-(Methoxymethyl)-1α-propyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (1a). Chloromethyl methyl ether (0.31 mL, 4.13 mmol) was added to an ice cold solution of enol ether **5** (0.92 g, 3.44 mmol) in dry CH$_2$Cl$_2$ (10 mL). Freshly sublimed zinc bromide (ca. 20 mg) was added, the cooling bath removed, and the solution stirred for 1 h. After removal of the solvent by rotary evaporation the crude material was immediately purified by flash chromatography (10% ethyl acetate/petroleum ether) to yield a ca. 6:1 mixture of **1a** and **1e** (0.71 g, 86%). The diastereomers were separated by flash chromatography using a step gradient of equal volumes of 360:39:1, 360:38:2, and 360:36:4 CH$_2$Cl$_2$/petroleum ether/MeOH.

Data for 1a. ^{1}H NMR (CD$_2$Cl$_2$): δ 3.69 (d, 9.0 Hz, 1 H), 3.24 (s, 3 H), 3.20 (d, 9.0 Hz, 1 H), 2.51 (ddd, 14, 14, 6 Hz, 1 H), 2.32 (ddd, 14, 3, 3, Hz, 1 H), 2.0–1.0 (m, 16 H), 0.90 (t, 7.0 Hz, 3 H). ^{13}C NMR (CDCl$_3$): δ 212.8, 77.8, 59.4, 55.7, 47.2, 40.3, 37.2, 34.8, 34.0, 33.9, 27.1, 26.9, 26.5, 17.8, 15.1. IR (CCl$_4$): 1709 cm^{-1}. MS, *m/e* (intensity): 238 (4, M$^+$), 196 (100, M – C$_3$H$_6$). Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.32; H. 10.98.

Data for 1e. ^{1}H NMR (CD$_2$Cl$_2$): δ 3.78 (d, 9.0 Hz, 1 H), 3.32 (s, 3 H), 3.18 (d, 9.0 Hz, 1 H), 2.40 (ddd, 14, 14, 6 Hz, 1 H), 2.28 (ddd, 14, 5, 3 Hz, 1 H), 1.9–0.8 (m, 19 H). ^{13}C NMR (CDCl$_3$): δ 212.9, 72.5, 59.2, 55.8, 46.7, 39.6, 36.0, 34.6, 34.2, 32.8, 26.7, 26.5, 26.4, 17.6, 15.0. IR (CCl$_4$): 1715 cm^{-1}. MS, *m/e* (intensity): 238 (4, M$^+$), 196 (100, M – C$_3$H$_6$). Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.58; H, 11.09.

The ^{1}H and ^{13}C NMR spectra of mixtures of **1a** and **1e** (20 mg in 0.4 mL CD$_2$Cl$_2$) with 1 equiv of TiCl$_4$ are as follows.

Data for 1a·TiCl$_4$. ^{1}H NMR: δ 4.98 (d, 12.0 Hz, 1 H), 4.10 (s, 3 H), 3.61 (d, 12.0 Hz, 1 H), 3.04 (ddd, 14, 10, 10 Hz; 1 H), 2.67 (ddd, 14, 7, 4 Hz, 1 H); 2.30–1.05 (m, 16 H), 0.98 (t, 7 Hz, 3 H). ^{13}C NMR: δ 236.2, 78.0, 70.8, 55.2, 46.1, 39.2, 35.6, 35.1, 34.8, 30.0, 27.5, 26.3, 26.0, 18.2, 14.8.

Data for 1e·TiCl$_4$. ^{1}H NMR: δ 5.16 (d, 13 Hz, 1 H), 4.10 (s, 3 H), 3.77 (d, 13 Hz, 1 H), 3.00 (ddd, 12, 11, 6 Hz, 1 H), 2.7 (ddd, 11, 3, 3 Hz, 1 H), 2.4–1.0 (m, 16 H), 0.94 (t, 7 Hz, 3 H). ^{13}C NMR: δ 234.6, 76.1, 70.5, 58.1, 50.2, 41.4, 37.0, 36.2, 33.1, 33.0, 26.9, 26.0, 25.9, 18.3, 14.9.

2-Cyano-2-hydroxy-1α-(methoxymethyl)-1β-propyldecahydronaphthalene (2e). TiCl$_4$ (0.11 mL, 1 mmol) was added dropwise to a solution of ketone **1e** (0.24 g, 1 mmol) in dry CH$_2$Cl$_2$, followed by rapid addition of Me$_3$SiCN (0.66 mL, 5 mmol). After 5 min, the reaction was quenched by addition of saturated aqueous NaHCO$_3$, and the mixture extracted with ether. The organic extracts were dried (MgSO$_4$), the solvents were evaporated, and the residue was purified by flash chromatography (10% ethyl acetate/petroleum ether) to yield the cyanohydrin **2e** (0.25 g, 96%) as a ca. 2.8:1 mixture of diastereomers (based on integration of the OCH$_3$ peaks). IR (CCl$_4$): 3400, 2350, 2325 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.31; H, 10.44; N, 5.28. While separate ^{1}H and ^{13}C spectral data are given below for the two diastereomers, it should be understood that these data were obtained from spectra of a *mixture* of the two. The assignment of resonances to one compound or the other must be regarded as tentative in the case of the ^{13}C data; the basis for assignment of peaks to the major/minor diastereomer was relative peak height in "doubled" peaks.

Data for 2e$_{eq}$, Major Diastereomer. ^{1}H NMR (CDCl$_3$): δ 5.68 (s, 1 H, exchanges with D$_2$O), 3.81 (d, 10 Hz, 1 H), 3.70 (d, 10 Hz, 1 H), 3.42 (s, 3 H), 2.0–0.98 (m, 18 H), 0.88 (t, 7 Hz, 3 H). ^{13}C NMR (CDCl$_3$): δ 122.8, 79.9, 75.2, 59.5, 44.0, 39.0, 34.7, 34.4, 33.3, 31.9, 27.0, 26.9, 26.2, 26.1, 18.0, 15.4.

Data for 2e$_{ax}$, Minor Diastereomer. ^{1}H NMR (CDCl$_3$): δ 5.41 (s, 1 H, exchanges with D$_2$O), 3.85 (d, 10 Hz, 1 H), 3.63 (d, 10 Hz, 1 H), 3.40 (s, 3 H), 2.0–0.98 (m, 17 H), 0.88 (t, 7 Hz, 3 H). ^{13}C NMR (CDCl$_3$): δ 121.8, 78.5, 77.2, 59.3, 47.5, 45.2, 35.1, 34.1, 31.7, 30.3, 28.2, 27.1, 26.5, 25.9, 19.7, 15.2.

In the undecoupled ^{13}C spectrum the δ 122.8 resonance appeared as a triplet (J = 1.8 Hz), while the δ 121.8 resonance was a doublet of doublets (J = 9.9 and 3.7 Hz). Assignment of the δ 122.8 and 121.8 resonances to the major and minor diastereomers, respectively, was based on their integrated ratio of 2.7:1 in the proton decoupled spectrum, which was nearly the same as the ratio of 2.8:1 seen for the OCH$_3$ resonances in the ^{1}H NMR. While integration of ^{13}C resonances must be approached with some caution,[41] the diastereomeric nature of the nitrile carbons makes it unlikely that they will differ substantially in relaxation time or NOE enhancement; thus, the integrated ratio should be a fairly reliable indication of their true ratio.

2-Cyano-2-hydroxy-1β-(methoxymethyl)-1α-propyldecahydronaphthalene (2a). This compound was prepared in 95% yield from **1a** in exactly the same manner as described for **2e**. Only a single diastereomer could be observed. ^{1}H NMR (CDCl$_3$): δ 5.14 (s, 1 H, exchanges with D$_2$O), 3.90 (d, 10 Hz, 1 H), 3.48 (d, 10 Hz, 1 H), 3.32 (s, 3 H), 2.14 (ddd, 4, 4, 3 Hz, 1 H), 2.0–1.0 (m, 17 H), 0.94 (t, 7 Hz, 3 H). ^{13}C (CDCl$_3$): δ 121.0, 78.4, 75.1, 59.4, 48.1, 45.2, 36.8, 36.0, 36.3, 34.4, 31.1, 26.8, 26.7, 25.8, 18.5, 15.2. In the undecoupled ^{13}C spectrum the δ 121.0 resonance was a doublet of doublets (J = 10.1 and 3.4 Hz). IR (CCl$_4$): 3417, 2290 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.59; H, 10.63; N, 5.26.

Titration of 1a with TiCl$_4$. Samples were prepared individually, as follows. An accurately weighed amount of **1a** (ca. 20 mg) in an oven-dried vial was dissolved in CD$_2$Cl$_2$, and 1.0 M TiCl$_4$ in CD$_2$Cl$_2$ was added; the amount of CD$_2$Cl$_2$ used was such as to give a 0.40-mL total volume in the final solution. The sample was then transferred to an NMR tube and the spectrum acquired.

Kinetic Studies. Oven-dried glassware was used for reaction vessels. Strict precautions were taken to avoid moisture contamination. TiCl$_4$ was fractionally distilled under N$_2$, taking a large forerun; 1.0 M solutions of TiCl$_4$ were prepared by removing the TiCl$_4$ directly from the distillation receiver via syringe and combining it with dry CH$_2$Cl$_2$. TiCl$_4$ solutions older than 4 days were not used. (TMS)CN was fractionally distilled. The following illustrates a typical kinetics experiment. To a solution of **1a** (12 mg, 0.055 mmol) in dry CH$_2$Cl$_2$ (1.145 mL) was added 1.0 M TiCl$_4$ (0.055 mL, 0.055 mmol). After stirring for 2–3 min, 0.20-mL portions were transferred to each of five 2-mL vials equipped with magnetic stir bars and septa. The vials were cooled for 20 min under N$_2$ by inserting them in individual wells in a drilled aluminum block submerged in a -45 ± 1 °C cooling bath. A solution of (TMS)CN in CH$_2$Cl$_2$ (20 μL of a 1:1 (v/v) mixture) was added to each vial. At appropriate intervals individual vials were quenched by addition of ice cold saturated aqueous NaHCO$_3$ (0.20 mL). The resulting mixture was extracted with ether (2 × 1 mL), and the organic extracts were dried (MgSO$_4$), filtered, and evaporated. The relative proportions of starting material and product were determined by integration of the –OCH$_3$ protons in the ^{1}H NMR.

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Registry No. 1a, 136764-01-7; **1a**·TiCl$_4$ complex, 139731-53-6; **1e**, 136764-02-8; **1e**·TiCl$_4$ complex, 139892-67-4; **2a**, 138382-63-5; **2e** (isomer 1), 138325-15-2; **2e** (isomer 2), 138382-62-4; **3**, 136764-03-9; **4**, 18943-04-9; **5**, 139731-52-5; 1-hepten-3-one, 2918-13-0; 4-(cyclohex-1-enyl)morpholine, 670-80-4; titanium chloride, 7550-45-0; trimethylsilyl cyanide, 7677-24-9.

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(41) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden & Sons: London, 1978; pp 264–7.

(42) The fact that the complexation and kinetics studies were performed at different temperatures should not affect the conclusions to be drawn from these studies. Even at room temperature, the formation of 1:1 complexes of **1a** and **1e** with TiCl$_4$ is so favorable that only a lower limit for the equilibrium constants can be measured. With the reasonable assumption of a negative entropy of complexation, the association constant for complex formation should be even greater at the lower temperatures of the kinetics studies.