# Why Do Catalytic Quantities of Lewis Acid Generally Yield More Product Than 1.1 equiv in the Intramolecular Diels−Alder Reaction with a Furan Diene? Competitive Complexation NMR Studies Provide an Answer

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**Abstract:** The results presented here provide experimental support for a hypothesis made by us to rationalize literature observations on intramolecular Diels−Alder reactions (IMDA) and our own observations on IMDA with a furan diene (IMDAF) regarding the quantity (catalytic or stoichiometric) of Lewis acid required to facilitate reaction. Evidence suggests that the reactions can be divided into two classes: those that proceed with catalytic quantities of Lewis acid (herein defined as type A) and those that require a stoichiometric quantity of Lewis acid (type B). We believe that the relative basicity of the controlling functional groups in addend and adduct can be critical in determining the quantity of Lewis acid required. The relative Lewis basicity has been studied using competitive complexation studies using low-temperature NMR experiments to study the coordination of methylaluminum dichloride (MAC) and $BF_3{\cdot}Et_2O$ with model oxygen Lewis bases and IMDAF addends and adducts.

The Diels−Alder (DA) reaction[1] is a fundamental tool for synthetic organic chemists[2] by virtue of the high stereo- and regiocontrol that can be achieved in the construction of highly functionalized cyclic systems. In particular, intramolecular DA (IMDA) reactions have been widely applied in synthesis.[2e,f] Besides the exceptional synthetic utility of the DA reaction, the reaction has also provided many experimental features that are of interest to physical organic[3] and theoretical chemists[4] and has become a testing ground for chiral Lewis acids.[5]

The ability of Lewis acids (LA) to promote both inter- and intramolecular DA reactions in general is well-known.[6] Despite the sensitivity of the furan nucleus to acidic conditions,[7] successful *intermolecular* DA reactions involving furan dienes have been known since 1984.[8] Our interest in the *intramolecular* DA reaction of a furan diene (IMDAF)[9,10] with a ketone internally activated dienophile on the tether led to the discovery in 1991 that LA could be employed to promote this class of IMDA (Scheme 1).[10a] In particular, we found that methylaluminum dichloride (MAC) employed under truly catalytic conditions produced better conversion to products (P) than with 1.1 equiv of MAC (for examples see Scheme 1 and Table 1), giving good to excellent yields after 2 h at −65 °C.[10b,c] In contrast, we have found that related systems possessing acetylenic dienophiles (Scheme 2) give higher conversion to P with 1.1 equiv of dimethylaluminum chloride (DMAC)[10c] compared to the catalytic reaction (Table 1). These were intriguing observations that warranted further investigation.

Literature precedence for the above findings was difficult to find; however, similar observations have been made by Snider for the LA-catalyzed ene reaction.[11] For the most part, LA-promoted IMDA reactions have generally used at least 0.95 equiv of the LA when the dienophiles have been activated by esters or aldehydes.[12] Only a few examples of truly catalytic IMDA reactions, involving unsaturated aldehydes, could be

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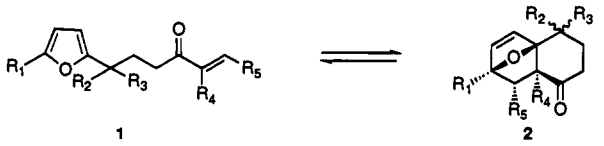
**Scheme 1**



1 2

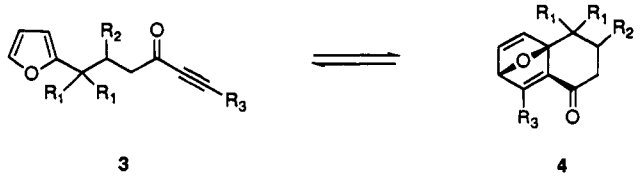
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| a | H | H | H | H | H |
| b | H | H | H | H | Me |
| c | H | H | H | Me | Me |
| d | Me | H | H | H | Me |
| e | H | Me | Me | H | Me |
| f | H | Me | Me | Me | Me |
| g | Me | Me | H | H | Me |

**Table 1.** Isolated SM:P Ratios for the Example Reactions of Schemes 1 and 2

| SM | 0.1 equiv of MAC[a] | 1.1 equiv of MAC[a] |
|---|---|---|
| **1a** | 0:100 | 0:100 |
| **1b** | 31:69 | 78:22 |
| **1c** | 95:5 | 100:0 |
| **1d** | 24:76 | 82:18 |
| **1e** | 27:73 | 73:27 |
| **1f** | 100:0 | 100:0 |
| **1g** | 17:83[b] | 79:21[b] |
| **3a** | | 0:100[c] |
| **3b** | 99:1 | 13:87[c] |

[a] Conditions are 1.1 equiv of MAC, $CH_2Cl_2$, 8 h, −78 °C and 0.1 equiv of MAC, $CH_2Cl_2$, 2 h, −65 °C,[9b,10] unless indicated otherwise. Isolated yields are generally good, and no decomposition products are detected. [b] In this example two products are formed in the ratios 79:4 (0.1 equiv of MAC) and 16:5 (1.1 equiv of MAC). [c] 1.1 or 0.1 equiv of DMAC, −50 °C, 2.5 h. Note that DMAC was used to reduce aromatization of adducts that was seen with MAC.

**Scheme 2**

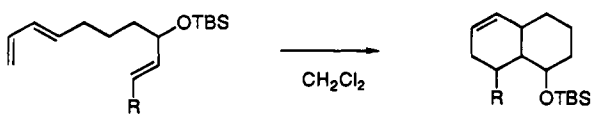


3 4

a $R_1 = R_3 = Me$, $R_2 = H$

b $R_1 = H$, $R_2 = Me$, $R_3 = TMS$

**Scheme 3**



5 6

a. R = CHO, 0.2 $EtAlCl_2$, -78°C, 62%

b. R = $CO_2iPr$, 1.0 $EtAlCl_2$, 8°C, 60%

found (for example, see Scheme 3).[13] An inspection of the available examples of IMDA suggests that there is a fundamental difference depending on the type of group activating the dienophile. Olefinic dienophiles activated by ketones or aldehydes can be used with catalytic quantities of LA and are herein defined as type A. Stoichiometric conditions are used for olefins

**Scheme 4**

$$SM + LA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SM...LA \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P...LA \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} P + LA$$

$$K_1 = k_1 / k_{-1} \qquad K_2 = k_2 / k_{-2} \qquad K_3 = k_3 / k_3$$

$$K_{eq} = [P] / [SM] = K_1 K_2 / K_3$$

$$K_{obs} = \frac{[P] + [P...LA]}{[SM] + [SM...LA]}$$

activated by esters and are herein defined as type B. Accordingly, our IMDAF reactions **3** → **4**, Scheme 2, with acetylenic dienophiles activated by ketones, are also classed as type B since they require stoichiometric amounts of LA for efficient conversion to P. Similar observations of some functional groups requiring stoichiometric LA and others requiring only catalytic LA have been made for intermolecular DA reactions.[14] Since there appears to be some uncertainty with respect to the amount of LA required for successful DA reactions (or indeed other types of reactions), we sought to provide or locate experimental and theoretical support for a rationale which would not only explain our results with the IMDAF reaction with both olefinic and acetylenic dienophiles, but also encompass the literature observations involving aldehyde- and ester-activated dienophiles.

The reactions of **1** → **2** (Scheme 1) and **5a** → **6a** (Scheme 3)[12a] are examples of type A, while **3** → **4** (Scheme 2) and **5b** → **6b** (Scheme 3)[12a] are type B, normal DA reactions (*i.e.*, diene HOMO/dienophile LUMO controlled).[15] The accepted method for activation of any carbonyl system by a LA is coordination at the carbonyl oxygen,[16] which lowers the LUMO of the dienophile, reducing the controlling HOMO−LUMO gap. Understanding the activation process is therefore not sufficient to rationalize the difference in the number of equivalents of Lewis acid required for the two different types of IMDA reactions, as the mode of activation is the same for both type A and type B systems.

In order to explain the observed differences between catalytic and equivalent quantities of MAC on the IMDAF of compounds like **1** (Scheme 1), we have previously postulated[9b,10b] that the results can be rationalized using the equilibrium illustrated in Scheme 4 and the higher basicity of conjugated ketones compared to nonconjugated ketones[17,18] (*i.e.*, $K_1 > K_3$). With catalytic quantities of LA, the position of the equilibrium is governed by the relative free energies of the *uncomplexed* SM (starting material) and P, with the LA preferentially coordinating to the enone in SM. The DA reaction then proceeds, and once the P···LA complex is formed, the LA dissociates from P and is then able to recoordinate with SM. This ultimately shifts the equilibrium toward P. With an excess of LA, the observed equilibrium tends to reflect SM···LA ⇌ P···LA, which for the IMDAF reaction lies toward SM···LA, and workup then yields predominantly SM, Table 1. This postulate also encompasses dienophiles activated by an aldehyde group (Scheme 3), since

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(14) (a) Inukai, T.; Kasai, M. *J. Org. Chem.* **1965**, *30*, 3567. (b) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta.* **1987**, *70*, 436. (c) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(15) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.

(16) Houk, K. N.; Strozier, R. W. *Ibid.* **1973**, *95*, 4094. (b) Fleming, I. In *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; p 162.

(17) (a) March, J. In *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 221. (b) Stewart, R. In *The Proton: Applications to Organic Chemistry, Organic Chemistry, 46*; Wasserman, H. H., Ed.; Academic Press: New York, 1985. (c) Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223.

(18) Maria, P. C.; Gal, J. F. *J. Phys. Chem.* **1985**, *89*, 1296.

the Lewis basicity of enals is reported to be greater than that of saturated aldehydes.[19,20] A catalyst normally does not alter the position of an equilibrium. In our situation the observed P:SM corresponds to isolated yields after workup, and $K_{obs}$ is as defined in Scheme 4.

It is also possible to extend the above hypothesis to include the dienophiles found in the type B systems. The proton basicity for a saturated ester is reported to be greater than that of an unsaturated ester.[17,18] Limited experimental evidence for the same trend with LA is also available. Roush and co-workers have explained their observed requirements for >0.95 equiv of LA with unsaturated ester dienophiles by stating that "these reagents ($EtAlCl_2$ and $Et_2AlCl$) are relatively tame Lewis acids and stoichiometric quantities generally are required for the reactions to go to completion. The cycloadducts (saturated esters) are stronger Lewis bases than the trienes (unsaturated esters) and apparently form more stable complexes with the reagents. Thus, in order to maximise yield and minimise triene polymerisation we generally use 0.95 equivalents of the alkylaluminium species." [12a] No reference to experimental or theoretical evidence for the basicity of esters was provided.

Snider *et al.*[11] have investigated the Lewis basicity of ester systems toward $AlCl_3$ and found that the order of basicity is the following: saturated ester ≅ α,β-unsaturated ester > α,β-acetylenic ester. Inukai[21] has studied the kinetics of the $AlCl_3$-promoted DA reaction of butadiene and methyl acrylate and found that the adduct can compete with the acrylate for the catalyst.

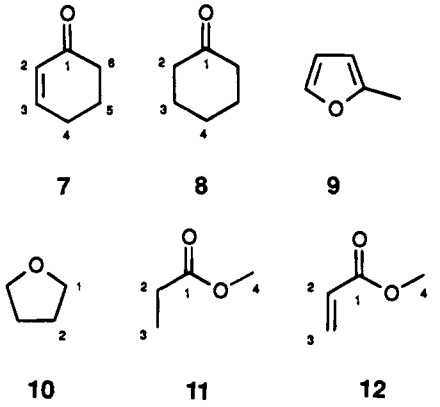
In our hypothesis, the higher basicity of the saturated ester over the unsaturated ester ($K_3 > K_1$) implies that P will complex in preference to SM. This will cause P to inhibit the catalyst, preventing the LA from promoting the forward reaction. Hence, an equivalent (or >95%) of catalyst is required to ensure that sufficient Lewis acid is present to complex SM. A similar rationale has been used by Snider for observations on the ene reactions of esters with alkenes.[11] With the acetylenic dienophiles, the P carbonyl is still conjugated, *i.e.*, it is an enone. Denmark has reported the basicity order as the following: 2-heptenal > 2-heptynal > heptanal toward $SnCl_4$.[19c] This indicates that P is more basic than SM and hence prevents catalytic LA from promoting these reactions.

It is, however, important to realize that the relative basicities of the reaction-controlling functional groups is only *part* of the whole reaction profile, as the *overall energetics* of the DA reaction itself (*i.e.*, $K_2$) could be a controlling factor.

In order to provide evidence for the above expanded hypothesis for the difference in catalysis of the type A and type B systems and to explain the ability of catalytic MAC to provide more P than when 1.1 equiv is used in the IMDAF reactions **1** → **2**, and why $BF_3$·$Et_2O$ does not, we have performed a series of competitive complexation experiments using MAC and $BF_3$·$Et_2O$ with a variety of Lewis bases and carried out a direct low-temperature NMR study of IMDAF reactions promoted by MAC. The results from these studies are reported herein. In addition, the competitive binding studies provide direct experimental evidence for the relative basicities of saturated and unsaturated esters and ketones toward MAC and $BF_3$·$Et_2O$. The $BF_3$·$Et_2O$ studies, can be compared with similar complexation studies reported with $BF_3$ (in $CH_2Cl_2$ or $CDCl_3$).[22] The MAC studies also show the basicity of important functional groups toward alkylaluminum LA which are widely used in synthesis.[23]

## Results and Discussion

**1. Model Complexation Studies with MAC and $BF_3$·$Et_2O$.** 2-Cyclohexenone (**7**), cyclohexanone (**8**), 2-methylfuran (**9**), and THF (**10**) were chosen as model compounds to represent the various basic portions of addends **1** and adducts **2** (Scheme 1) both sterically and electronically. The two ketones were also



**7** **8** **9**

**10** **11** **12**

used to investigate the basicity of an enone compared to a ketone. Methyl propionate (**11**) and methyl acrylate (**12**) were chosen to investigate the relative basicity of saturated and unsaturated esters. In each case, the effect of addition of 1 equiv of MAC and $BF_3$·$Et_2O$ to each of the model compounds has been determined using low-temperature NMR. MAC is a hard Lewis acid with high oxygenophilic character[24] and is expected to form 1:1 complexes with carbonyl bases.[25] It should also be noted that, in the presence of excess LA, disproportionation of alkylaluminum halides is known to occur.[26] The results of these studies were later used to identify the complexed species in the competitive complexation studies (see below). The results of the NMR studies are shown (Tables 2 and 3) as the relative shifts, Δδ, where Δδ = δ(complex) − δ(free base). Hence a downfield shift has a positive Δδ.[27] Control studies (addition of aliquots of hexanes) have confirmed that the shifts observed

(19) (a) There is some disagreement on the proton basicity of aliphatic aldehyde. Compare the following: Levy, G. C.; Cargioli, J. D.; Racela, W. *J. Am. Chem. Soc.* **1970**, *92*, 6238. Brouwer, D. M.; van Doorn, J. A. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1010. (b) Denmark, S. E. Private communication, 1993. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133. (d) The Lewis basicity of acetaldehyde and benzaldehyde are indicated in ref 18. (e) It has been reported that saturated aldehydes are about 2.5−3 times more basic than unsaturated aldehydes in catalysis studies (see ref 20).

(20) (a) Odekirk, W.; Rheingold, A. L.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 6392. (b) Hollis, T. K.; Robinson, N. P.; Bosnich, B. *Ibid.* **1992**, *114*, 5464. (c) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *Ibid.* **1989**, *111*, 6070.

(21) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 872.

(22) (a) Fratiello, A.; Schuster, R. E. *J. Org. Chem.* **1972**, *37*, 2237. (b) Fratiello, A.; Vidulich, G. A.; Chow, Y. *Ibid.* **1973**, *38*, 2309. (c) Schuster, R. E.; Bennett, R. D. *Ibid.* **1973**, *38*, 2904. (d) Frateillo, A.; Stover, C. S. *Ibid.* **1975**, *40*, 1244.

(23) (a) Snider, B. B.; Rodini, D. J.; Karra, M., Kirk T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927. (b) Corey, E. J.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 7938. (c) Ward, D. E.; Gai, Y. *Tetrahedron Lett.* **1992**, *33*, 1851; *Can. J. Chem.* **1992**, *17*, 2627. (d) Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Synth. Commun.* **1988**, 1453.

(24) Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001.

(25) An extensive search of the literature and the Cambridge Crystallographic Database has revealed 1:1 complexes except (i) in the case where one ligand has been formally substituted and (ii) with strong bases such as amines (see ref 26a).

(26) (a) Mole, T.; Jeffery, E. A. In *Organoaluminum Compounds*; Elsevier: Amsterdam, 1972; Chapter 2. (b) The equilibrium $2Et_2AlCl \rightleftharpoons [Et_2Al]^+ + [Et_2AlCl_2]^-$ has also been suggested to rationalize the high selectivity seen when 1.4 equiv of $Et_2AlCl$ is used to promote the intermolecular DA reactions of α,β-unsaturated *N*-acyloxazolidinones with cyclopentadiene (see ref 14c).

(27) The results for the carbonyl-containing systems are consistent with the shifts reported for the complexes formed by $EtAlCl_2$ with analogous bases; see: Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.

**Table 2.** Change in the Chemical Shift, $\Delta\delta$, for Nucleus $i$ of Each of the Model Compounds Complexed in the Presence of 1 Equiv of MAC, Relative to the Uncomplexed Base, in $CDCl_3$ at − 60 °C[a]

| | | $\Delta\delta_i$/ppm[b] | | | | | |
|---|---|---|---|---|---|---|---|
| base | $i$ | 1 | 2 | 3 | 4 | 5 | 6 |
| cyclohexenone | $^1$H | | 0.60 | 0.76 | 0.27 | 0.14 | 0.45 |
| | $^{13}$C | 13.5 | −0.9 | 19.3 | −0.9 | −1.2 | 0.9 |
| cyclohexanone | $^1$H | | 0.52 | 0.25 | 0.13 | | |
| | $^{13}$C | 2.7 | 1.3 | 0.9 | −1.2 | | |
| methyl propionate | $^1$H | | 0.41 | 0.32 | 0.22 | | |
| | $^{13}$C | 8.3 | 0.7 | 5.4 | −0.5 | | |
| methyl acrylate | $^1$H | | 0.39 | 0.43 | 0.29 | | |
| | $^{13}$C | 7.4 | −3.1 | 10.2 | 5.7 | | |
| THF | $^1$H | 0.63 | 0.36 | | | | |
| | $^{13}$C | 5.5 | −0.1 | | | | |

[a] 2-Methylfuran polymerized under the experimental conditions and has been omitted from the table. [b] Column headings refer to the positions defined in the structural diagrams.

**Table 3.** Change in the Proton Chemical Shift, $\Delta\delta$, and Percent Complex for Each of the Model Compounds Complexed in the Presence of 1 equiv of $BF_3$·$Et_2O$ in $CDCl_3$ at −60 °C[a]

| | | $\Delta\delta_H$/ppm[b] | | | | | |
|---|---|---|---|---|---|---|---|
| base | % complex | 1 | 2 | 3 | 4 | 5 | 6 |
| cyclohexenone | 72 | | brd[c] | 0.94 | 0.34 | 0.14 | 0.58 |
| cyclohexanone | 26 | | 0.55 | 0.25 | nd[d] | | |
| methyl propionate | 9 | | 0.64 | nd[e] | 0.51 | | |
| methyl acrylate | 0[f] | | | | | | |
| THF | 79 | 0.61 | 0.37 | | | | |

[a] 2-Methylfuran was not included in this study. [b] Column headings refer to the positions defined in the structural diagrams. [c] The H2 peak for the complex is broad due to exchange between *syn* and *anti* forms at −60 °C. At −90 °C, both the H2 and H3 peaks are resolved into two signals of approximately equal intensity, with $\Delta\delta_{H2}$ = 0.84, 0.47 ppm and $\Delta\delta_{H3}$ = 0.97, 0.88 ppm for the *syn* and *anti* forms. [d] The shift of this peak could not be accurately determined due to overlap with H2 of the free base. [e] The shift of this peak could not be accurately determined due to overlap with peaks from $Et_2O$. [f] No evidence of complexation (even in the presence of 5 equiv of $BF_3$·$Et_2O$).

for MAC are due to LA coordination and are not merely a solvent effect.

At −60 °C the MAC complexes are under fast exchange conditions, so the average shift of free and complexed base is observed (Table 2). Slow exchange conditions are obtained on cooling to −90 °C using $CD_2Cl_2$ solutions, but at this temperature the solubility of the complexes is reduced. The studies on cyclohexenone, methyl propionate, and methyl acrylate suggested the presence of more than one type of complex, presumably due to *syn* and *anti* arrangements of the LA.[28] We do not believe that *syn* ⇌ *anti* equilibration is the cause of the phenomena under investigation here. The experimental conditions, which were selected to represent typical MAC promoted IMDAF reaction conditions, caused 2-methylfuran to polymerize. This demonstrates the well-known instability of the furan nucleus under acidic conditions.[9] Complexation of THF produced shifts that are consistent with complexation at the ethereal oxygen,[29] and in contrast to the carbonyl-containing model compounds, no yellow color was observed.[30] For the esters, the observed shifts are consistent with complexation at the carbonyl rather than the alcoholic oxygen, in agreement with calculated[31] and observed structures.[28]

In contrast to the MAC complexes, the $BF_3$ complexes are under slow exchange conditions at −60 °C, so separate signals for the free and complexed base are observed. Hence, a measure of the amount of base complexed can be obtained by peak integration (Table 3). This data gives the relative basicity order as THF > cyclohexenone > cyclohexanone > methyl propionate > methyl acrylate.

The α-H2 signal of cyclohexenone−$BF_3$ complex was broadened at −60 °C, indicating that a second exchange process was occurring. Variable temperature studies have shown that coalescence of free and complexed signals occurs at approximately 0 °C, and that the second process (coalescence temperature of −60 °C), the equilibration of the *syn* and *anti* complexes[32] (1:1 ratio), freezes out at −90 °C. The signals for the free base were not involved in this second coalescence process, indicating that the isomerization of *syn*/*anti* complexes can occur without dissociation to the free base.[33]

The observation of free and complexed peaks in the NMR spectra at −60 °C of the $BF_3$ complexes provides a simple method for determination of the equilibrium constant for the complexation by recording the integrals of free and complexed peaks in the presence of different concentrations of $BF_3$·$Et_2O$. The results of these NMR titration experiments for cyclohexenone ($K$ = 3.5 ± 1.5) and cyclohexanone ($K$ = 0.09 ± 0.02) indicate that the enone is an order of magnitude more basic than the ketone[34] toward $BF_3$·$Et_2O$. These values compare favorably with a $K \cong 0.14$ for methacrolein.[35]

**2. Competitive Complexation Studies with Two Lewis Bases.** NMR intermolecular competitive complexation experiments using a 1:1:1 ratio of base X/base Y/Lewis acid have been performed to determine the relative Lewis basicities of all the sites in the IMDAF systems of Scheme 1 for both MAC and $BF_3$·$Et_2O$.

A typical example of the type of results obtained for MAC is shown (Figure 1) for experiment 1 (Table 4). In most cases one base exhibited preferential complexation (as judged by peak shifts and peak shapes) compared to the other, but minor shifts were often seen in the weaker base. Since these studies were carried out in the presence of only 1 equiv of MAC and under rapid exchange conditions, the shifts are reduced compared to those seen in the model studies. The results (Table 4) for each of the bases, in each of the experiments, are presented as the shifts observed in the competitive complexation studies for the $^1$H peak that was shifted the most in the model studies (Table 2).

Experiments 1 and 2 demonstrate the difference between the ketone and ester systems. The preferential complexation of MAC to the conjugated rather than the nonconjugated ketone

(28) (a) See: Shambayati, S.; Schreiber, S. L. In ref 2c, Vol. 1, pp 283−324. (b) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(29) The basicity of THF is commonly exploited to influence the structure of organolithium reagents in solution (see: Wakefield, B. J. In *Best Synthetic Methods: Organolithium Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: New York, 1988; p 5. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448) and the basicity of ethers to moderate the strength of Lewis acids (for an example: Guidon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912).

(30) The observation of a yellow coloration for aluminum complexes has been discussed previously by Ward and Gai (ref 23c). Our observations suggest that the yellow color is due to complexation at carbonyl systems and is reduced in the presence of competing ether complexation.

(31) Rauk, A.; Hunt, I. R.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6808.

(32) Paris, C.; Torri, G.; Elegant, L.; Azzaro, M. *Bull. Chim. Soc. Fr.* **1974**, 1449. Torri, J.; Azzaro, M. *Bull. Chim. Soc. Fr.* **1978**, II-283.

(33) We have verified our conclusions by performing a simulation of the spin system for the observed shifts of cyclohexenone H2. The limiting chemical shifts are 6.04 for the free base, and 6.51, 6.87 for the *syn*/*anti* complexed base. The experimentally observed coalescence behavior was best represented by a process involving a faster exchange of *syn* ⇌ *anti* than with free base and was incompatible with a process which interchanges *syn* and *anti* through the intermediacy of the free base.

(34) $K$ is defined in eq 1. Hence, it is the relative basicity of the substrate compared to $Et_2O$.

(35) Based on the report that a 1:1 mixture of methacrolein and $BF_3$·$Et_2O$ exists as a 73:27 ratio of uncomplexed:complexed. See: Corey, E. J.; Loh, T. P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

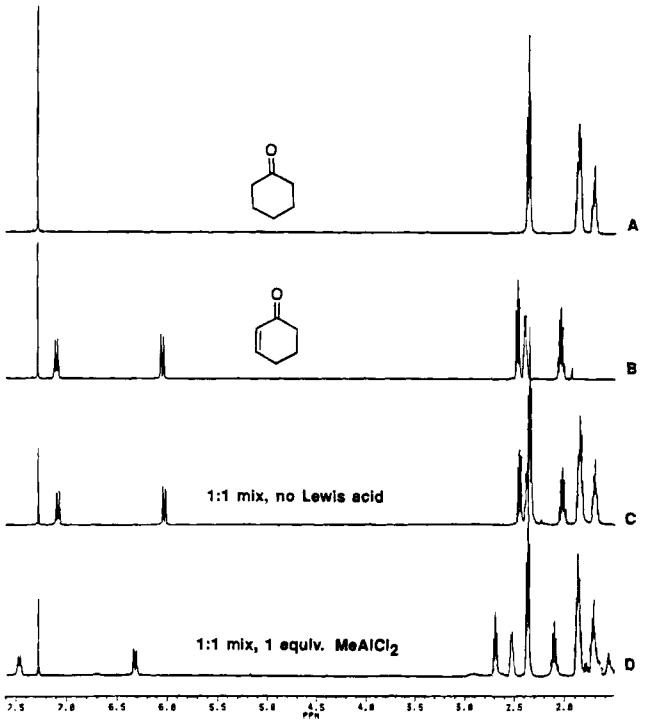



**Figure 1.** $^1$H NMR spectra (−60 °C in $CDCl_3$) of competitive complexation experiment 1, Table 3, between cyclohexenone (**7**) and cyclohexanone (**8**). A = **7**; B = **8**; C = 1:1 mixture of **7**:**8**; D = 1:1:1 mixture of **7**:**8**:MAC.

**Table 4.** Shifts Observed for Each of the Bases in the Competitive Complexation Experiments with 1 equiv of MAC, in $CDCl_3$ at −60 °C

| expt | base X | H | Δδ/ppm[a] | base Y | H | Δδ/ppm[a] |
|---|---|---|---|---|---|---|
| 1 | cyclohexenone | 3 | 0.36 | cyclohexanone | 2 | 0.00 |
| 2 | methyl propionate | 2 | 0.38 | methyl acrylate | 3 | 0.04 |
| 3 | cyclohexenone | 3 | 0.66 | 2-methylfuran | | *b* |
| 4 | cyclohexenone | 3 | 0.01 | THF | 1 | 0.16 |
| 5 | cyclohexanone | 2 | 0.01 | THF | 1 | 0.36 |

[a] Values are for the shift of the $^1$H peak that exhibited the largest shift on complexation in the model studies. [b] No figure is available for 2-methylfuran because of the polymerization observed during the model studies.

is observed in experiment 1. This is in support of the hypothesis for type A systems. Further evidence from the IMDAF systems will be discussed below. In experiment 2, MAC complexes to the ester rather than to the conjugated ester. The implication here is that, for ester type B systems, P will complex instead of SM as predicted in the hypothesis.

The remaining competitive complexation experiments were selected to examine the possibility of complexation by the ethereal oxygen sites of the IMDAF reactions. In experiment 3, the enone, the reactive site, is complexed and not the furan oxygen. It is of note that the furan did not polymerize and that no intermolecular DA reaction was observed during this experiment. The results of experiments 4 and 5 show that MAC is complexed by THF and not the ketone or the enone. These results do not support our hypotheses on the IMDAF reactions since coordination at the P ether bridge would produce inhibition of the catalyst by the adduct. These results, however, are in agreement with the general basicity trend. The reduced basicity of the ethereal oxygen in the oxatricyclic system of P is discussed below on the basis of the NMR studies of IMDAF reactions. The results for experiments 3−5 also demonstrate the reduced basicity of the aromatic furan ethereal oxygen

**Table 5.** Percentage of Each Base Complexed in the Competitive Complexation Experiments with 1 equiv of $BF_3$·$Et_2O$, in $CDCl_3$ at −60 °C

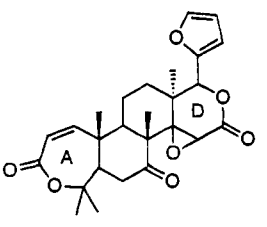
| expt | base X | % complex[a] | base Y | % complex |
|---|---|---|---|---|
| 6 | cyclohexenone | 65 | cyclohexanone | 5 |
| 7 | methyl propionate | 9 | methyl acrylate | 0 |
| 8 | cyclohexenone | 70 | 2-methylfuran | 0 |
| 9 | cyclohexenone | 6 | THF | 83 |
| 10 | cyclohexanone | 1 | THF | 87 |

[a] Values are based on peak integrals of free and complexed species.

compared to that of simple ethers, which are usually more basic than enones.

Experiments 6−10 (Table 5) are the $BF_3$·$Et_2O$ analogues of experiments 1−5 (Table 4) with MAC. These $BF_3$·$Et_2O$ studies show preferential complexation based on the comparison of the free and complexed peak areas (slow exchange) for each of the bases. Since we chose to use $BF_3$·$Et_2O$, the results actually indicate the basicity relative to $Et_2O$. An examination of these results leads to the same conclusions as obtained with MAC. Note that, in experiment 8, there was no polymerization of 2-methylfuran nor any evidence of any intermolecular DA reaction.

Studies on a wide variety of substrates complexed by $BF_3$ have been reported[22] using low-temperature $^1$H and $^{19}$F NMR. The magnitudes of the $^{19}$F shifts on complexation reflect the strength of interaction with the base and give the following trend of decreasing basicity (in $CH_2Cl_2$): ethers > alcohols > amides > esters > enones > ketones > aldehydes. The complexation seems, however, to be very sensitive to steric and electronic effects (particularly the presence of enolization and resonance effects). Complexation of trialkylaluminums has also been reported to be sensitive to steric effects.[36] The enthalpies of complex formation of 76 compounds (aromatic and saturated systems) with $BF_3$ (in $CH_2Cl_2$) provide another valuable source of information.[18] The same general trend is demonstrated, along with the importance of steric effects. *Ab initio* calculations[31] on the stability of $BF_3$ complexes produce a similar trend. The proton basicities, based on the $pK_a$ values of the conjugate acids (in $H_2O$), are as follows: $RCH_2OH$ > ROR > ArOR, ArCOR > RCOOR′ > RCOR, ArCHO > ArCOOR > RCHO.[17] This shows the same general trend as for $BF_3$. The proton scale data, experimental enthalpies of complexation, and theoretical stabilities[31] show that conjugated esters are less basic than nonconjugated esters, but that olefin conjugated ketones and aldehydes are more basic than the nonconjugated systems. Experimental evidence for the low basicity of furan oxygen is provided by the $BF_3$ complex of the steroid obacunone **13** (in $CDCl_3$), which complexes at the A-ring lactone and the D-ring lactone rather than the furan.[22c] The $BF_3$ studies report that complexation to an ethereal oxygen is gradually weakened along the series dimethyl ether > methyl *n*-butyl ether and di-*n*-butyl ether due to steric effects,[22a] so it is possible that the steric requirements about the bridgehead ether inhibit complexation at the P ether site.




**13**

**Table 6.** Isolated SM:P Ratios for **1d** → **2d** with 0.1 and 1.0 equiv of Various Lewis Acids, 2 h, −78 °C, $CH_2Cl_2$

| Lewis acid | 0.1 equiv of LA | 1.1 equiv of LA |
|---|---|---|
| $AlCl_3$ | 8:92 | 68:32 |
| $MeAlCl_2$ | 24:76 | 82:28 |
| $Me_3Al$ | 100:0 | |
| $BF_3{\cdot}Et_2O$ | 96:4 | 63:37 |
| $TiCl_4$ | 27:73 | 89:11 |
| $Ti(O\text{-}i\text{-}Pr)_4$ | 100:0 | 100:0 |

Bosnich *et al.* have recently reported studies with LA based on ruthenium and titanium.[20a,b] They established that methacrolein was 3 times more basic than the DA adduct derived from the reaction of methacrolein with isoprene, and that the adducts from aldehyde or ketone dienophiles did not inhibit their catalysts (0.01 equiv of catalyst employed). The ruthenium catalyst (0.01 equiv) was reported not to catalyze reactions of α,β-unsaturated esters. This can now be explained by the greater basicity of the product ester causing inhibition of the catalyst. A tungsten-based catalyst has been studied by Hersh *et al.*[20c] They report that acrolein is 2.5 times more basic than the acrolein−isoprene adduct toward their catalyst. Unlike Bosnich and co-workers' catalysts, the tungsten system promoted the reactions of methyl acrylate.

**3. LA Effects on IMDAF Addends and Adducts.** The following studies of IMDAF reactions were designed to investigate the curious dependence upon LA that they generally demonstrate (Table 1).[37]

In order to determine if the observed effect of increased adduct with less catalyst was unique to MAC, the reaction **1d** → **2d** has been investigated with 0.1 and 1.1 equiv of various LA. The results (Table 6) indicate that the effect is not specific to MAC; however, it is not general to all LA. For example, the LA $Me_3Al$ and $Ti(O\text{-}i\text{-}Pr)_4$ are too weak to promote the IMDAF reaction, while $BF_3{\cdot}Et_2O$ promotes the reaction but requires 1 equiv of LA for high adduct formation. We believe that the difference between $BF_3{\cdot}Et_2O$ and MAC arises from (1) the significantly longer lifetime of the $BF_3$ complexes as indicated by the higher coalescence temperatures (and therefore the difference in the rate constants for both the association and dissociation processes), (2) the presence of the strong Lewis base, $Et_2O$ (competitive inhibition), and (3) the ability of $BF_3$ to complex at the P ether oxygen of the bridge, *vide infra*, which causes P inhibition.

Addition of MAC to P gives isolated SM:P ratios that are identical to those produced by the forward reaction under the same conditions, indicating that the reaction is under thermodynamic control. Observation of the retro reaction is evidence for MAC complexation at the P ketone, at least to some extent, since the law of microscopic reversibility[38] requires that the reaction pathways of forward and reverse reactions be identical. It is possible that the reverse reaction (and indeed the forward reaction) can be promoted by the presence of just a fraction of the total MAC complexed at the ketone, *i.e.*, by a minor component of an equilibrating system or a preequilibrium for the reaction.

Further information on the IMDAF reactions **1** → **2** can be obtained by careful consideration of some of the experimental observations. The relative energies of SM and P are established by considering the position of the equilibrium SM:P in the presence of low concentrations of catalyst. With 0.1 equiv of MAC the ratio SM:P typically favors P,[10b,c] though there are exceptions (*e.g.*, **1c**,**f**, **3a**,**b**). This indicates that, in general, for the reaction **1** → **2**, P is the more stable species and that it is in fact a *favorable* equilibrium (*i.e.*, $K_{eq} > 1$, Scheme 4). The presence of a high activation energy for the forward reaction is consistent with the low yields and long reaction times of the thermal IMDAF.[39] Similarly, a high barrier can be inferred for the reverse reaction on the basis of the thermal stability of IMDAF adducts (which were distilled for the complexation studies without cycloreversion). The relative energies of the complexes of SM···LA and P···LA can be crudely estimated on the basis of the isolated SM:P obtained in the presence of 1.1 equiv of MAC (*e.g.*, 80:20 for **1d**−**2d**, Table 1) when both SM and P are complexed. Under this situation, the forward IMDAF has to compete with the retro DA reaction ($k_2$[SM···LA] = $k_{-2}$[P···LA]). This situation could be described as a Lewis acid stationary state.[40] The higher stability of SM···LA in LA-promoted DA reactions is generally unusual because of the highly favorable energetics of most DA reactions (*i.e.*, $K_{eq} \gg 1$).[41] However, the aromaticity of furan stabilizes the SM and strain in the bridged adducts destabilizes P to make the equilibrium of IMDAF reactions much closer to unity ($K_{eq} \cong 1$).

With catalytic LA, the SM enone complexes in preference to the ketone of P ($K_1 > K_3$), Scheme 4, and decomplexation of P must be more rapid than the retro reaction ($k_3 > k_{-2}$). This frees the LA to recomplex with SM and repeat the catalytic cycle. The decomplexation of P means that the reverse reaction, at least initially, essentially cannot occur via the catalytic pathway since $k_{-2}$[P···LA] is too low. Therefore, the reverse reaction can occur only via the uncatalyzed pathway, which has a prohibitively high activation barrier, until the quantity of SM decreases to the point at which MAC is available for complexation of P. The situation, at least initially, can be likened to a one-way valve or an electronic diode with complexation allowing the forward reaction to occur, but decomplexation preventing the reverse reaction.

Direct study of the complexation of IMDAF SM is, of course, complicated by the very facile nature of the DA reaction that MAC promotes. Important evidence for the site of complexation has, however, been obtained by the study of such systems.

Addition of 0.1 equiv of MAC to SM **1g** promotes the reaction but also shows a downfield shift in the olefinic protons of the enone fragment (Figure 2). The magnitude of the shift gradually increases as the reaction progresses due to the increase in the fraction of remaining SM that is complexed. Similar increases in the magnitude of the downfield shifts can be produced by the addition of increasing quantities of MAC. There is no evidence of a shift in the product olefinic protons due to coordination at the bridgehead ether.

For the IMDAF reactions of **1**, the presence of 1.1 equiv of MAC with respect to the initial amount of SM ensures that there

(36) See ref 26a, Chapter 4, pp 106−118.

(37) Although the IMDAF reaction seems to be a special case due to the delicate balance of the equilibrium, we still believe that the trend is general but often is experimentally unobservable. In order to establish that the general trend of increased adduct yields with reduced amounts of catalyst could be related to SM and P basicities, we have developed a computer model of the equilibria in Scheme 4 to calculate SM:P for various "reaction conditions". We found that the simulation successfully predicted the experimental observations both when $K_1 > K_3$ (type A) and when $K_3 > K_1$ (type B behavior) over a range of $K_2$ values. A more complete description of the analysis is being prepared for publication elsewhere.

(38) (a) Lowry, T. H.; Richardson, K. S. In *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 194. (b) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry: Part A, Structure and Mechanism*, 2nd ed.; Plenum:, New York, 1984; p 176.

(39) DeClerq, P. J.; Van Royen, L. A. *Synth. Commun.* **1979**, *9*, 771.

(40) This situation is analogous to the photochemical stationary state (see ref 38a, p 1011).

(41) For example, the non-furan analogue of **1** → **2** with a 1,3-butadiene system has a $t_{1/2}$(0 °C) = 4 h : Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002.

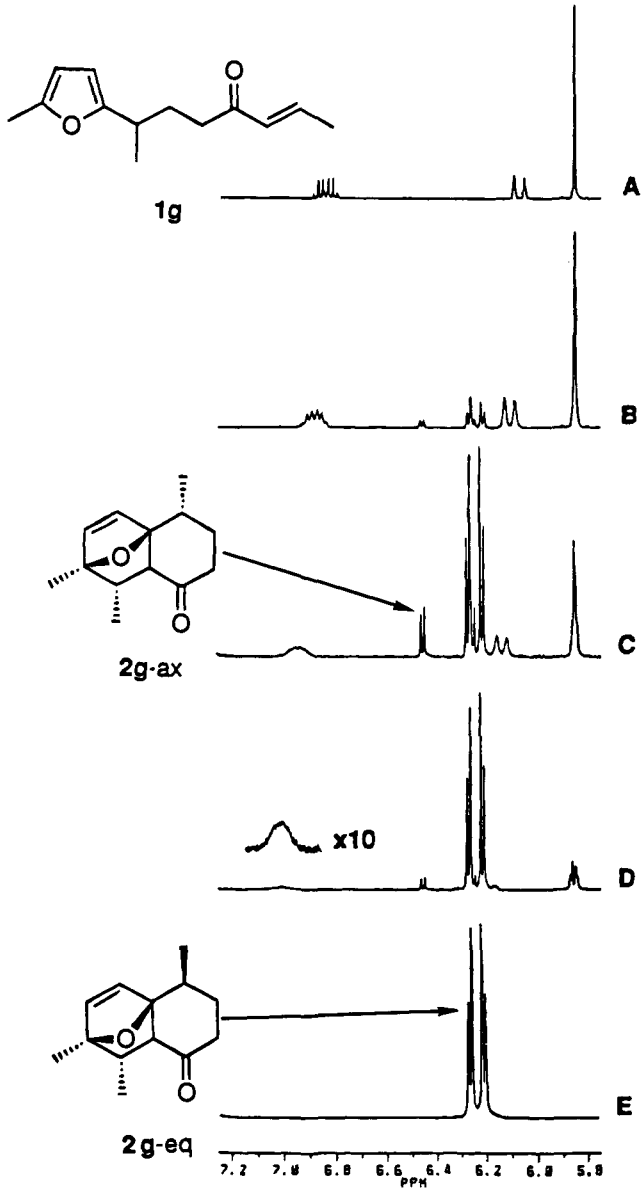



**Figure 2.** $^1$H NMR spectra (−60 °C in $CDCl_3$) obtained for the IMDAF reaction of **1g** to **2g** in the presence of 0.1 equiv of MAC. A = **1g**; B = **1g** + 0.1 MAC, 5 min; C = **1g** + 0.1 MAC, 15 min; D = **1g** + 0.1 MAC, 3 h; E = **2g**.

is sufficient MAC to complex the carbonyl groups of both SM and P. Under these conditions the $^1$H NMR shows SM enone complexation. The observation of shifts of the α-protons due to complexation at the P ketone is generally more difficult due to overlap with SM (which is generally the major species) peaks. Evidence for complexation at the P ketone has been obtained for the **1a** → **2a** system since adduct **2a** is more stable to MAC than most of the other systems as indicated by the yields of **1a**:**2a** in the presence of 1.1 equiv of MAC (Table 1). Complexation studies with **2a** and 1 equiv of MAC showed a downfield shift for the α-protons and upfield shifts for other protons in the cyclohexanone ring. These upfield shifts are presumably due to anisotropy effects caused by the ligands on the aluminum.[28] No evidence of any complexation to the bridgehead ethereal oxygen was observed. A similar study with $BF_3$·$Et_2O$ showed downfield shifts in the α-protons and small shifts in the olefin and bridgehead protons. An aromatic decomposition product, 1-tetralone, was also formed and observed as both free and complexed species. The possibility of bidentate coordination by aluminum LA has recently been suggested[42] for a sterically controlled substrate and to rationalize experimental observations.[14c] Molecular models of the IMDAF adduct indicate that these systems are not geometrically suitable for the complexation of a single aluminum atom between the ketone and the bridgehead ether. *Ab initio* calculations[31] show that 7-oxanorbornene is more basic toward $BF_3$ than either ketones or enones and should complex preferentially with $BF_3$ orientated *anti* to the double bond. In the IMDAF systems **2** this site is sterically hindered by the *exo*-cyclohexanone ring system. We[9c] and others[43] have reported aluminum LA catalyzed IMDA reactions of addends containing ether oxygens without the problem of complexation at these sites.

With the understanding gained from our studies we can rationalize the divergent experimental observations for the IMDAF reactions of **5a** and **5b** (Scheme 3). The reaction of **5a** proceeds catalytically because an unsaturated aldehyde is more basic than a saturated aldehyde. On the other hand, **5b** requires 1 equiv of MAC because of product inhibition due to the greater basicity of the saturated ester compared to the unsaturated ester. Addends **5a**,**b** and adducts **6a**,**b** also contain silyl ether groups which are potential sites for complexation. It is known, however, that silyl ethers are less basic than dialkyl ethers.[44]

## Conclusions

In summary, the results of the studies support the expanded hypothesis for both type A and B systems by establishing experimental and theoretical evidence for the relative Lewis basicity of the functional group that activates the dienophile. The competitive complexation studies have provided direct evidence for the relative basicities of saturated and unsaturated ketones and esters. The results verify the statements made by Roush[12a] for ester systems and also explain observations made by Bosnich *et al.*[20a,b]

The experiments have shown that MAC in catalytic (*i.e.*, less than stoichiometric) amounts promotes the IMDAF reactions **1** → **2** because the most basic site in the system is the reactive site in SM so that P does not inhibit the catalyst. Increasing the number of equivalents of MAC decreases the conversion because SM···LA is the more stable of the complexed forms. Hence, catalytic MAC gives better overall conversion than 1 equiv of MAC.

The basicity studies show that the basicity order of the various Lewis bases toward MAC is the same as that observed and reported for $BF_3$. Understanding the relative basicities of all the functional groups in both SM and P enables one to determine whether the IMDA reaction (or other reactions) can be carried out catalytically (hopefully minimizing side reactions such as polymerization) or requiring 1 equiv of Lewis acid. It has been stated that "the choice of the appropriate Lewis acid and the amount in which it should be used continue to tax the ingenuity and intuition of the chemist. As a rule, trial and error remains the best way to answer these questions".[45] We feel that these studies go some way to removing some of the "trial and error".

We are currently using the results to develop chiral LA catalysts that can be applied to the IMDAF reaction under truly catalytic rather than equivalent conditions and investigating the

(42) Sharma, V.; Simard, M.; Wuest, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 7931.
(43) Taschner, M. J.; Cyr, P. T. *Tetrahedron Lett.* **1990**, *31*, 5297
(44) (a) Shepherd, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5581. (b) Kahn, S. D.: Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. Keck, G. E.; Castellino, S. *Ibid.* **1987**, *28*, 281. Keck, G. E.; Boden, E. P. *Ibid.* **1984**, *25*, 265. (c) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.
(45) Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750.

general Scheme 4 in the form of a computer model.[37] These topics will be the subjects of future publications.

## Experimental Section

The model Lewis bases and Lewis acids for the complexation studies were obtained from Aldrich with the exception of $AlCl_3$ (Janssen). The IMDAF SM and P **1**−**4** were prepared as previously described.[9b,c,10b,c] The Lewis acids were used as supplied. $^1H$ and $^{13}C$ NMR spectra were routinely recorded at −60 °C except for the variable temperature studies.

**Complexation Studies.** Samples of the bases were dried over $Na_2SO_4$ and distilled under $N_2$ immediately prior to use. Stock solutions (0.1 or 0.2 M) of each base were prepared using oven-dried glassware (overnight, 125 °C) under an $N_2$ atmosphere by adding the required amount of $CDCl_3$ (dried over $K_2CO_3$) or $CD_2Cl_2$ (for temperatures below −60 °C) to a preweighed sample. NMR tubes were oven-dried and evacuated and purged with $N_2$ at least 3 times before use. For the complexation studies with the model bases, 0.6 mL aliquots of the 0.1 M sample solutions were added via syringe under an $N_2$ atmosphere. For the competitive complexations, 0.3 mL aliquots of 0.2 M solutions of each base were used. Tubes were immediately capped and sealed, and the spectra of the uncomplexed bases were obtained. The required quantity of the Lewis acid was then added by microsyringe directly to the NMR tubes while cooling at −78 °C, and the spectra were recorded after equilibration to the acquisition temperature.

**NMR Titrations.** NMR samples were prepared as described above for the complexation studies. The association constant was determined with 0.1 M base in $CDCl_3$ at −60 °C in the presence of 0.5, 1.0, and 1.5 equiv of $BF_3{\cdot}Et_2O$ by integration of the signals of free and complexed base. The integrals were used to evaluate the relative concentration of each species and were used in eq 1 to determine the association constant. As defined, eq 1 indicates the relative basicity of the base to $Et_2O$.

$$K = [BF_3{\cdot}{\cdot}{\cdot}base][Et_2O]/[BF_3{\cdot}ET_2O][base] \quad (1)$$

**IMDAF NMR Complexations.** Studies using the IMDAF systems were performed on freshly distilled samples of SM **1** using solutions prepared in exactly the same manner as described above for the model bases. Where applicable the relative quantities of SM and P were determined by integration of the NMR signals.

**IMDAF 1d → 2d with Various Lewis Acids.** To a stirred solution of SM **1d** (20 mg, 0.1 mmol) in dry $CH_2Cl_2$ (5 mL) at −78 °C under an atmosphere of $N_2$ was added the required quantity (0.1 or 1.1 equiv) of the appropriate Lewis acid by microsyringe.[46] The solution was stirred for 2 h and then quenched at −78 °C by addition of aqueous $NaHCO_3$ (10%, 2.5 mL). After standing for 5 min, the cooling bath was removed and the reaction mixture allowed to warm to room temperature. The mixture was extracted with $Et_2O$ (3 × 5 mL) and $CH_2Cl_2$ (2 × 5 mL), and the combined organic phases were dried over $Na_2SO_4$. Removal of the solvent *in vacuo* gave the crude reaction mixture as an oil, which was analyzed by NMR without further purification. SM:P ratios were determined from appropriate integrals.

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(46) In the case of $AlCl_3$, a saturated solution in $CH_2Cl_2$ was prepared under $N_2$ prior to use. The concentration was estimated by taking a known volume and removing the solvent *in vacuo* to determine the weight of the residue.