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# Selectivities in Lewis Acid Promoted Reactions

edited by

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## FOREWORD

The ASI workshop on "**Selectivities in Lewis Acid Promoted Reactions**" held in the Emmantina-Hotel in Athens-Glyfada, Greece, October 2-7, 1988 was held to bring some light into the darkness of Lewis acid induced processes.

As such the workshop reflects some current trends in organic synthesis, where Lewis acids are becoming a powerful tool in many different modern reactions, e.g. Diels-Alder reactions, Ene reactions, Sakurai reactions, and in general silicon and tin chemistry.

The objective of this meeting was to bring together most of the world experts in the field to discuss the major reactions promoted by Lewis acids.

Organic synthesis will play a major role in this book connected with some fundamental mechanistic work on allylsilane and -tin chemistry. Both natural product synthesis and unnatural molecules are presented in the chapters.

The book presents all the 15 invited lectures and the contributions of 15 posters. I am confident that the material presented in this book will stimulate the chemistry, which has been discussed on our meeting, around the world.

The meeting and the book were only possible through a grant of the NATO Scientific Affairs Division and financial support by the following companies:

Kali Chemie (Hannover, W-Germany), E. Merck (Darmstadt, W-Germany), Sandoz (Basel, Switzerland), Schering (Berlin, W-Germany).

I gratefully acknowledge the help of the Organizing Committee Dr. Jürgen Graefe and Prof. Horst Kunz. In addition, many thanks are due to the graduate students of my group in Hannover, especially to Dr. Christos Allagiannis, who has done an excellent job in organizing most of the things on his home ground in Athens to make this meeting a success.

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## CONTROL OF ELECTROPHILICITY IN ALIPHATIC FRIEDEL CRAFTS REACTIONS

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ABSTRACT. Lewis acid promoted additions of alkyl halides, acetals and related compounds to aliphatic  $\pi$  systems (e.g.  $R-X + \text{C}=\text{C} \longrightarrow P-X$ ) represent a straightforward method for the formation of  $\text{CC}$ -bonds, if the consecutive addition of the 1:1 adduct to another alkene molecule can be inhibited. This article describes how the relative electrophilicities of reactants  $RX$  and products  $PX$  may be controlled by nature and quantity of the Lewis acid. Model studies on electrophilic additions of diarylmethyl chlorides to alkenes reveal that a catalytic amount of a (weak) Lewis acid has to be used if the reactant  $RX$  ionizes to a greater extent than  $PX$ , whereas an equimolar amount of a strong Lewis acid is needed if  $PX$  ionizes more readily than  $RX$ . Examples demonstrating the application range and limitations of these rules are presented.

### 1. CHEMOSELECTIVITY IN AROMATIC AND ALIPHATIC FRIEDEL CRAFTS REACTIONS

#### 1.1. Reaction Control by Relative Nucleophilicities of Reactants and Products

The problem of reactivity control in aromatic Friedel Crafts reactions is treated in almost any undergraduate textbook. It is well known that Lewis acid promoted reactions of acyl chlorides with arenes yield monoacylation products predominantly, since the complex **1** is less

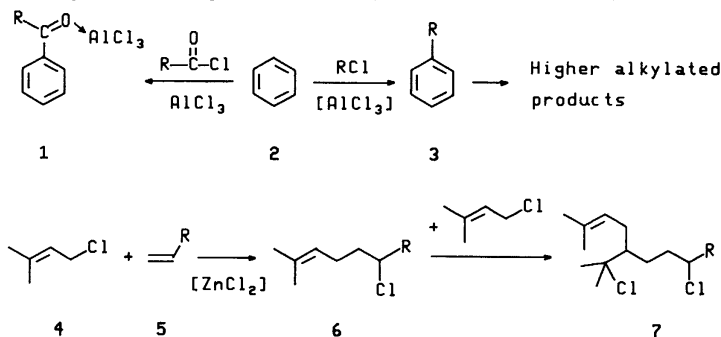


Figure 1. Chemoselectivity Control in Reactions with Nucleophilic Products.



nucleophilic than the nonacylated precursor 2. On the other hand, Friedel Crafts alkylations of arenes usually give rise to the formation of polyalkylated compounds, since 3 is more nucleophilic than 2. The rationalization of these results on the basis of the relative nucleophilicities of reactants and products appears straightforward to us, as we are familiar with the electronic effects of different substituents on aromatic rings.

A related selectivity problem arises in addition reactions of unsaturated alkyl derivatives. The example shown on the bottom of Figure 1 illustrates that the 1:1 product 6 can only be generated in reasonable yield, if the nucleophilicity of 5 is higher than that of 4 and 6.<sup>1</sup> An estimate for the relative nucleophilicities of olefinic  $\pi$  systems in such reactions can be derived from the recently determined reactivity ratios of alkenes and alkynes towards arylcarbenium ions.<sup>2</sup> An additional selectivity problem encountered in the reaction of 4 with 5 - compound 6 does not only incorporate a nucleophilic but also an electrophilic center - will be discussed in the next section.

## 1.2. Reaction Control by Relative Electrophilicities of Reactants and Products

In aliphatic Friedel Crafts reactions of type (1), we generally face the situation that one of the reactants as well as the product possesses electrophilic properties. As in the reactions discussed before - and in any other reaction - only those products can accumulate in the reaction mixture, which are less reactive than the starting materials. Now, it is the relative electrophilicity of R-X and R-C-C-X, which controls the course of the reaction. If bifunctional electrophiles are produced (eq.2), the reactivities at both positions of the 1:1 product have to be compared with the reactivity of the reactant R-CHX<sub>2</sub>. The competition situation encountered in both reactions 1 and 2 is illustrated on the bottom of Figure 2: The reactant, which may be predominantly covalent (RX) or ionic (R<sup>+</sup>), and the product (PX or P<sup>+</sup>) compete for the  $\pi$  nucleophile, and since we intend to produce the 1:1 products PX/P<sup>+</sup>, we have to search for conditions under which RX/R<sup>+</sup> is more reactive than PX/P<sup>+</sup>.

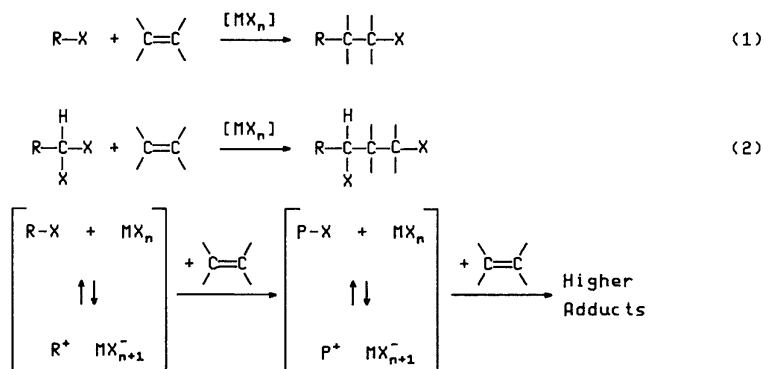


Figure 2. Chemoselectivity Control in Reactions with Electrophilic Products.

## 2. MODEL STUDIES ON THE CONTROL OF RELATIVE ELECTROPHILICITIES OF ALKYLATING AGENTS BY LEWIS ACIDS

Lewis acid initiated reactions of diarylmethyl chlorides with alkenes are suited for model studies, since many of these reactions give 1:1 adducts in quantitative yield. Kinetic<sup>3</sup> as well as thermochemical<sup>4</sup> investigations of these reactions have been reported. Competition experiments (Figure 3) have now been used to determine the influence of Lewis acids on the relative electrophilicities of diarylmethyl derivatives.<sup>5</sup> When a small amount of an alkene is added to a mixture of two diarylmethyl chlorides in presence of  $\text{BCl}_3$ , the relative reactivity of the two competitors can be derived from the ratio of the two 1:1 products.

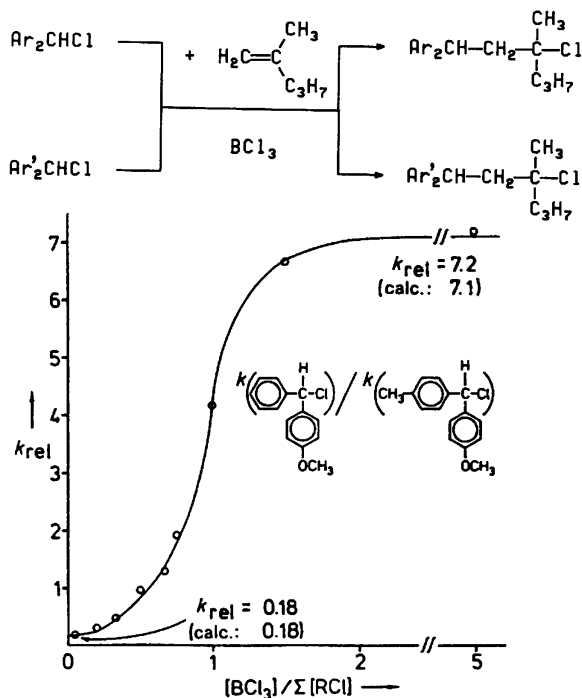


Figure 3. Relative Reactivity of two Diarylmethyl Chlorides towards 2-Methyl-1-pentene in  $\text{CH}_2\text{Cl}_2$  at  $-70^\circ\text{C}$  as a Function of the Lewis Acid Concentration.<sup>5</sup>

Figure 3 shows that in presence of excess  $\text{BCl}_3$ , the methoxy substituted compound is 7.2 times more reactive than the methoxy methyl substituted benzhydryl derivative. Under these conditions, both compounds are fully ionized, and we observe the higher reactivity of the less substituted carbenium ion. When the concentration of  $\text{BCl}_3$  is reduced, the reactivity ratio is reversed, and when only catalytic amounts of  $\text{BCl}_3$  are present, the reactivity ratio becomes 0.18. Now, a low concentration of the less stabilized carbenium ion ( $\text{CH}_3\text{O}$ -substituted) competes with a high concentration of the better stabilized carbenium ion ( $\text{CH}_3\text{O}$ ,

CH<sub>3</sub>-substituted), and as shown by Figure 3 (left), the product ratio reflects the relative concentrations of the carbenium ions, not their intrinsic addition rates.

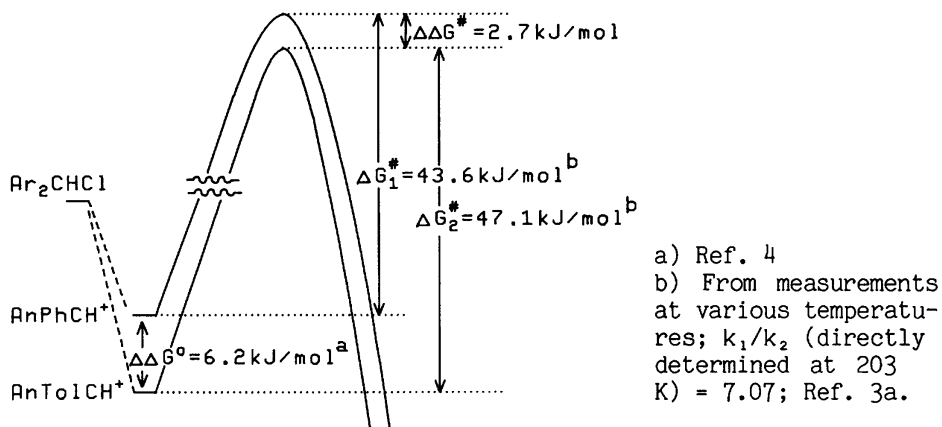


Figure 4. Energy Profiles for the Additions of p-Methoxy and of p-Methoxy-p'-methyl-benzhydryl Chloride towards 2-Methyl-1-pentene (-70°C).

A quantitative description of this behavior is given in Figure 4. Whereas the competition constant observed in presence of excess  $\text{BCl}_3$  can be derived from the known addition rate constants of the two carbenium ions ( $\Delta\Delta G^\ddagger = \Delta G_1^\ddagger - \Delta G_2^\ddagger$ ), a Curtin Hammett situation is encountered in presence of catalytic amounts of Lewis acid. Now, the ratio of the two individual rate constants has to be multiplied with the equilibrium constant for the ionization ( $\Delta\Delta G^\ddagger = \Delta G_1^\ddagger - \Delta G_2^\ddagger + \Delta\Delta G^\circ$ ).

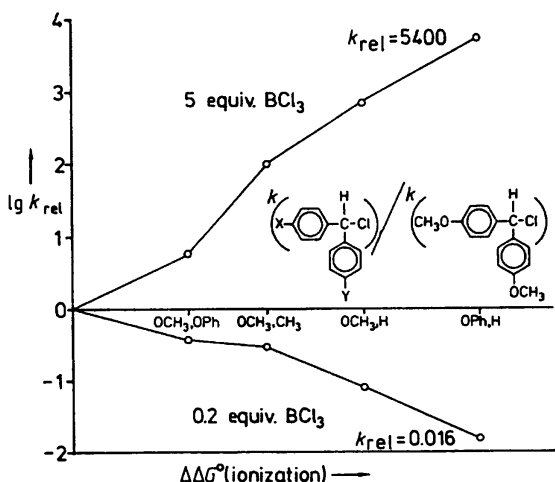


Figure 5. Relative Reactivities of para-Substituted Diarylmethyl Chlorides towards 2-Methyl-1-pentene in Presence of Catalytic Amounts of Lewis Acid (bottom) and under Conditions of Complete Ionization (top) ( $\text{CH}_2\text{Cl}_2/-70^\circ\text{C}$ ).<sup>5</sup>

This example illustrates that the relative electrophilicities of two alkylating agents can be influenced by varying the amount of Lewis acid. Figure 5 shows that the reactivity differences become quite remarkable, when the difference of stabilization of the carbenium ions increases. The phenoxy substituted benzhydryl compound, for example, is 5400 times more reactive than the dimethoxy substituted compound, when an excess of  $\text{BCl}_3$  is used, whereas a reactivity ratio of 0.016 is observed with catalytic amounts of  $\text{BCl}_3$ .

Of course, the relative reactivities do not only depend on the quantity but also on the nature of the Lewis acid. Figure 6 shows that different selectivity graphs are obtained for different ionizing media. The abscissa of Figure 6, which represents the ionization free enthalpy of diarylmethyl chlorides with  $\text{BCl}_3$ ,<sup>6</sup> can simply be viewed as a carbenium ion stability scale<sup>6</sup> with the highly stabilized carbenium ions on the left and the less stabilized ions on the right. The left part of the  $\text{BCl}_3$  graph corresponds to the upper line in Figure 5: The reactivity increases, when we go from the highly stabilized dimethoxy substituted carbenium ion to the less stabilized dimethyl substituted ion. Though the reactivity of the diarylcarbenium ions will further increase when the p-methyl substituents are replaced by hydrogen or chlorine, the gross reactivity of the system is decreasing. The reason is that the compounds with weaker donors are not fully ionized so that only low concentrations of carbenium ions are present.

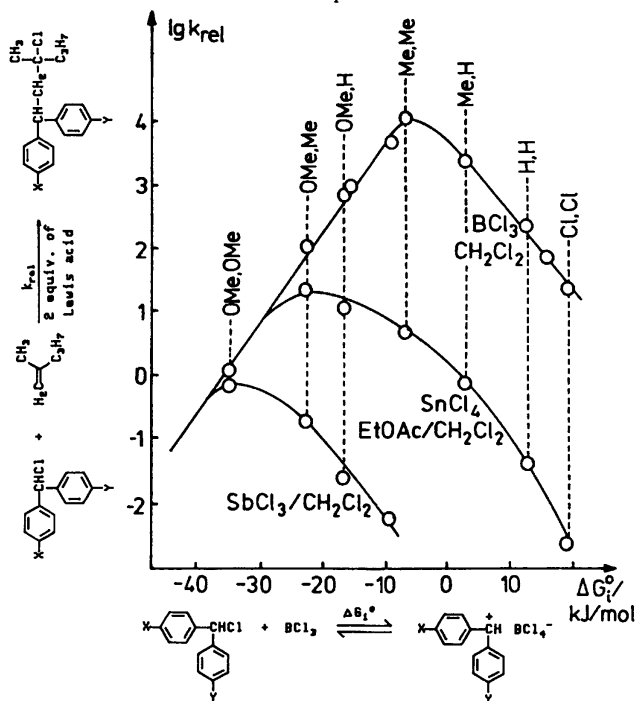


Figure 6. Relative Reactivities of Diarylmethyl Chlorides in Presence of an Excess of Lewis Acid.<sup>7</sup>

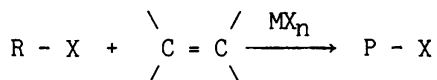
The dimethoxy substituted benzhydryl chloride is also fully ionized in a  $\text{SnCl}_4/\text{EtOAc}/\text{CH}_2\text{Cl}_2$  solution, and the reactivity towards 2-methyl-1-pentene is identical as in the  $\text{BCl}_3/\text{CH}_2\text{Cl}_2$  solution (Figure 6). The  $\text{SnCl}_4/\text{EtOAc}/\text{CH}_2\text{Cl}_2$  mixture does not fully ionize p-methoxy-p'-methyl benzhydryl chloride, however, and this compound is somewhat less reactive in  $\text{SnCl}_4/\text{EtOAc}/\text{CH}_2\text{Cl}_2$  than in the  $\text{BCl}_3/\text{CH}_2\text{Cl}_2$  solution. Further reduction of the electron releasing ability of X and Y causes a reactivity decrease in  $\text{SnCl}_4/\text{EtOAc}/\text{CH}_2\text{Cl}_2$  because of the diminishing carbenium ion concentration.

The weak Lewis acid  $\text{SbCl}_3$  does not even fully ionize the p,p'-dimethoxy substituted benzhydryl chloride, and only one branch of the  $\text{SbCl}_3/\text{CH}_2\text{Cl}_2$  graph can be seen in Figure 6.

We conclude that each Lewis acid/solvent system can be represented by a characteristic graph as shown in Figure 6. An increase of Lewis acidity is associated with an increase of the reactivity maximum, which is simultaneously shifted towards less stabilized carbenium ions. In order to design conditions for Lewis acid promoted addition reactions we have to locate reactants and products on the abscissa of Figure 6 and then select conditions characterized by a graph with  $k_{\text{rel}}$  (reactant)  $>$   $k_{\text{rel}}$  (product).

Qualitatively, this procedure can be summarized by two rules.

#### Rules for the choice of Lewis acids



##### A) Concentration Control

If the carbenium ion  $\text{R}^+$  is better stabilized than  $\text{P}^+$ , the selective formation of 1:1 products requires conditions, under which the electrophilic reactivities are controlled by the relative concentration of  $\text{R}^+$  and  $\text{P}^+$ :  
(Catalytic amounts of a) weak Lewis acid

##### B) Addition Rate Control

If the carbenium ion  $\text{R}^+$  is less stabilized than  $\text{P}^+$ , the selective formation of 1:1 products requires conditions, under which the electrophilic reactivities are controlled by the addition rates of  $\text{R}^+$  and  $\text{P}^+$ :  
> Equimolar amounts of a completely ionizing Lewis acid

### 3. SYNTHETIC APPLICATIONS

#### 3.1. Alkyl Chloride Additions

Several years ago, we have studied additions of alkyl chlorides to alkenes in presence of catalytic amounts of Lewis acids (conditions of Rule A) and found that 1:1 products are only isolable if the reactants ionize faster than the products (Figure 7).<sup>8</sup> We have suggested the

employment of solvolysis rate constants of model compounds to predict the outcome of such reactions: The selective formation of 1:1 products is only possible if the  $S_N1$  reactivities of the reactants are higher than the  $S_N1$  reactivities of the products. This statement, which was restricted to systems with a small degree of ionization,<sup>8,9</sup> is equivalent to rule A, since the solvolytic reactivities ( $\log k_{SOLV}$ ) are linearly correlated with the corresponding ionization enthalpies<sup>10</sup> or ionization free enthalpies.<sup>6</sup>

Solvolysis Rates of 1:1 Products

Solvolysis Rates of Reactants	→						
(CH <sub>3</sub> ) <sub>2</sub> CHCl	—	—	—	—	—	—	—
(CH <sub>3</sub> ) <sub>3</sub> CCl	41%	35%	—	—	—	—	—
	52%	50%	71%	72%	—	—	—
(CH <sub>3</sub> ) <sub>2</sub> C=CH-CH <sub>2</sub> Cl	32%	27%	65%	75%	10%	—	—
Ph-C≡C-C(CH <sub>3</sub> ) <sub>2</sub> Cl	67%	46%	93%	91%	67%	—	—
Ph-C(CH <sub>3</sub> ) <sub>2</sub> Cl	58%	65%	71%	71%	64%	58%	—
Ph <sub>2</sub> CHCl	92%	85%	97%	88%	82%	75%	—
CH <sub>3</sub> O-CH <sub>2</sub> Cl	47%	70%	60%	75%	64%	37%	—
	78%	65%	90%	57%	52%	84%	68%

Figure 7. Yields of 1:1 Products from Lewis Acid Catalyzed Reactions of Alkyl Halides with Alkenes ( $RX + \text{C}=\text{C} \rightarrow R-\dot{\text{C}}-\dot{\text{C}}-X$ ).<sup>8</sup>

Figure 8 shows an application of this reaction type in natural product synthesis. Under conditions of concentration control (rule A), the reaction of the cyclohexenyl chlorides **8** with isoprene terminates at the 1:1 product stage, since the terminally trialkylated allyl cations formed from **8** are better stabilized than the terminally dialkylated allyl cations, which arise from **9**. Cyclization of **9** and successive treatment with KOtBu yields a mixture of  $\beta$ - and  $\gamma_2$ -muurolene.<sup>11</sup>

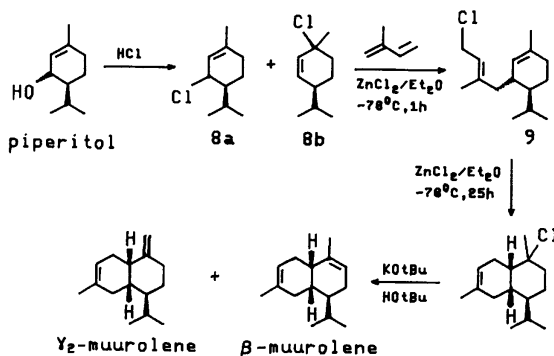


Figure 8. Synthesis of Muurolenes via  $ZnCl_2$  Catalyzed Reaction of Piperityl Chloride with Isoprene.<sup>11</sup>

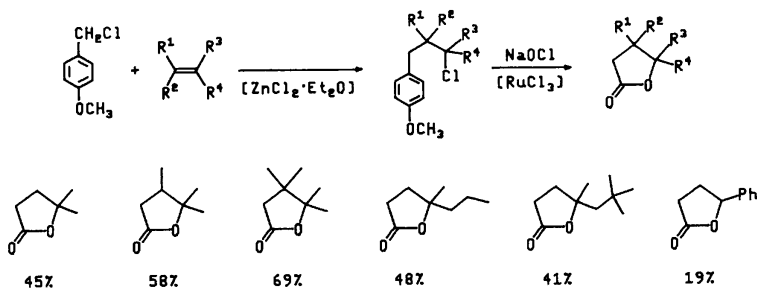


Figure 9. Synthesis of  $\gamma$ -Lactones Using p-Methoxybenzyl Chloride as  $^+\text{CH}_2\text{-CO}_2^-$  Equivalent.<sup>12</sup>

A novel  $\gamma$ -lactone synthesis (Figure 9) uses the high  $S_N1$  reactivity of p-methoxybenzyl chloride to give 1:1 addition products with a variety of alkenes. The oxidative degradation of the aromatic ring and lactonisation are achieved in a one-pot reaction, and preliminary experiments indicate that  $\alpha$ -substituted  $\gamma$ -lactones are also accessible by this method.<sup>12</sup>

All synthetic examples, discussed above, have been carried out under the conditions specified by rule A (concentration control). Reactions controlled by addition rates (rule B) require the handling of stable ion solutions, and their practical use will be restricted to highly stabilized carbenium ions. An example is given in Figure 10, which shows that the reaction of the trichlorocyclopropenylum tetrachloroaluminate with alkenes terminates at the 1:1 product stage, since the trichlorocyclopropenylum ion is more electrophilic than the better stabilized alkylidichloro substituted cyclopropenylum ion.<sup>13</sup> With weak Lewis acids (concentration control) the formation of 2:1 and 3:1 products would be preferred. Treatment of 10 with aqueous bicarbonate solution yields the chlorocyclopropenones 11, which readily undergo nucleophilic displacement reactions of the vinylic chloride or undergo thermal rearrangements with formation of the acetylenic acid chlorides 12.<sup>14</sup>

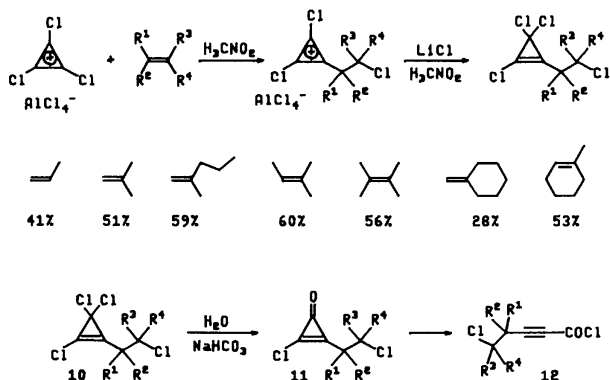
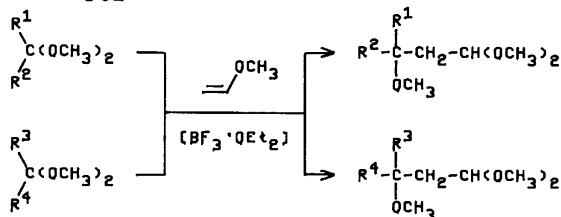


Figure 10. Formation of 1:1 Addition Products from Trichlorocyclopropenylum Tetrachloroaluminate and Alkenes.<sup>13</sup>

## 3.2 Addition Reactions of Acetals, Orthoesters and Related Compounds

Additions of acetals and orthoesters to enol ethers probably represent the most intensively studied class of Lewis acid promoted reactions in the chemistry of aliphatic compounds.<sup>15</sup> Since usually catalytic amounts of  $\text{BF}_3 \cdot \text{OEt}_2$  have been employed, concentration control (rule A) should predominate. Unlike the solvolyses of alkyl halides, the acid catalyzed hydrolyses of acetals and orthoesters do not follow a rate equilibrium relationship<sup>16</sup> so that the corresponding hydrolysis rates cannot be used for the analysis of electrophilic addition reactions. We have, therefore, carried out competition experiments to determine relative reactivities of acetals and orthoesters towards methyl vinyl ether in presence of catalytic amounts of  $\text{BF}_3 \cdot \text{OEt}_2$  (Figure 11).<sup>17</sup> As the reactivity order towards other  $\pi$  nucleophiles can be expected to be similar, the  $k_{\text{rel}}$  values of Figure 11 can be used to rationalize or predict the results of acetal and orthoester additions: 1:1 Adducts can only be generated selectively if the  $k_{\text{rel}}$  values of the designed products are smaller than the  $k_{\text{rel}}$  values of the reactants.



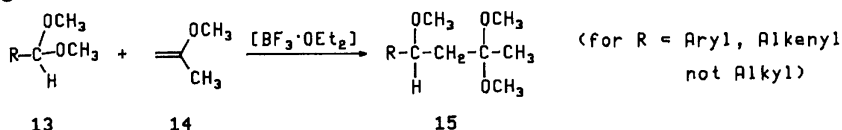
	$k_{\text{rel}}$		$k_{\text{rel}}$
$\text{CH}_2(\text{OCH}_3)_2, \text{CH}_3\text{C}(\text{OCH}_3)_2$	very slow	$p\text{-Br-C}_6\text{H}_4\text{-CH}(\text{OCH}_3)_2$	<b>13h</b> 132
$\text{CH}_3\text{-CH}(\text{OCH}_3)\text{-CH}_2\text{-CH}(\text{OCH}_3)_2$	<b>13a</b> 0.184	$p\text{-Cl-C}_6\text{H}_4\text{-CH}(\text{OCH}_3)_2$	<b>13i</b> 156
$\text{CH}_3\text{-CH}(\text{OCH}_3)_2$	<b>13b</b> 1.00	$p\text{-F-C}_6\text{H}_4\text{-CH}(\text{OCH}_3)_2$	<b>13j</b> 463
$\text{CH}_3\text{-CH}_2\text{-CH}(\text{OCH}_3)_2$	<b>13c</b> 2.28	$\text{C}_6\text{H}_5\text{-CH}(\text{OCH}_3)_2$	<b>13k</b> 818
$\text{CH}_3\text{-}(\text{CH}_2)_2\text{-CH}(\text{OCH}_3)_2$	<b>13d</b> 2.31	$p\text{-CH}_3\text{-C}_6\text{H}_4\text{-CH}(\text{OCH}_3)_2$	<b>13l</b> $6.55 \times 10^3$
$(\text{CH}_3)_2\text{CH-CH}(\text{OCH}_3)_2$	<b>13e</b> 2.38	$\text{C}_6\text{H}_5\text{-CH=CH-CH}(\text{OCH}_3)_2$	<b>13m</b> $3.16 \times 10^4$
$\text{HC}(\text{OCH}_3)_3$	<b>13f</b> 13.1	$p\text{-CH}_3\text{O-C}_6\text{H}_4\text{-CH}(\text{OCH}_3)_2$	<b>13n</b> $3.46 \times 10^4$
$(\text{CH}_3)_2\text{C}(\text{OCH}_3)_2$	<b>13g</b> 27.0	$\text{CH}_3\text{-CH=CH-CH}(\text{OCH}_3)_2$	<b>13o</b> $3.61 \times 10^4$

Figure 11. Relative Reactivities of Acetals and Orthoesters towards Methyl Vinyl Ether ( $\text{BF}_3 \cdot \text{OEt}_2, \text{CH}_2\text{Cl}_2, -70^\circ\text{C}$ ).<sup>17</sup>

The fivefold reactivity preference of **13b** over **13a** explains that additions of aliphatic acetals to alkyl vinyl ethers may be terminated at the 1:1 product stage, but because of the small reactivity difference an excess of acetal is required to obtain high yields of 1:1 adducts.<sup>18</sup> The aromatic and  $\alpha, \beta$ -unsaturated acetals shown in Figure 11 are considerably more reactive than **13a**, and 1:1 products with alkyl vinyl ethers are also formed in good yield, when the acetals and vinyl ethers are employed in equimolar amounts.<sup>19</sup>

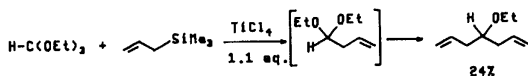


The failure to obtain 1:1 adducts from saturated aldehyde acetals and 2-propenyl ethers can be explained by the  $k_{rel}$  value of ketal **13g**, which is higher than that of aldehyde acetals.<sup>17</sup> As expected from the large reactivity difference between **13k** and **13g**, benzaldehyde dimethylacetal (**13k**) was found to give a high yield of 1:1 product with **14**,<sup>20</sup> and unsaturated acetals were reported to behave similarly.<sup>21</sup> Further literature data have been shown to be in accord with the data presented in Figure 11.<sup>17</sup>



A change of the reactivity order in Figure 11 takes place if conditions of addition rate control are employed. Hosomi, Endo and Sakurai studied the reaction of triethyl orthoformate with allyltrimethylsilane in presence of equimolar amounts of  $\text{TiCl}_4$ .<sup>22</sup> As expected for conditions of addition rate control, the homoallylic acetal was found to be more reactive than ethyl orthoformate, and only a 2:1 product was isolated. When we repeated this reaction with catalytic amounts of  $\text{SnCl}_4$ , the homoallylic acetal was obtained in 51% yield. In a similar way the other  $\beta,\gamma$ -unsaturated acetals shown in Figure 12 were synthesized under conditions of concentration control.<sup>23</sup>

#### Addition Rate Control



#### Concentration Control

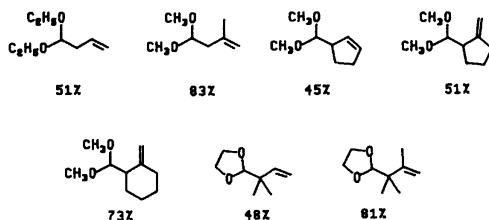
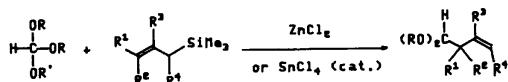


Figure 12. Lewis Acid Promoted Reactions of Orthoformates with Allylsilanes.

Dichloromethyl methyl ether, a potential formylating agent with higher electrophilicity, had been reported to give only 2:1 products with alkenes.<sup>24</sup> This result can be explained by concentration control, since

17 ionizes to a greater extent than 16. All efforts to formylate alkenes with 16 under conditions of addition rate control (excess of strong Lewis acids) have been unsuccessful, but it has been reported that vinyl silanes can be formylated with 16, when 1.2 equivalents of  $TiCl_4$  were employed.<sup>25</sup> We interpreted this result by the low intrinsic reactivity of the intermediate alkoxyallyl cation 19 (addition rate control) and concluded that 16 should also give 1:1 products with other substrates if alkoxyallyl cations are formed as intermediates: The bottom line of Figure 13 shows that dialkylacetylenes can be chloroformylated in this way under conditions of addition rate control.<sup>26</sup>

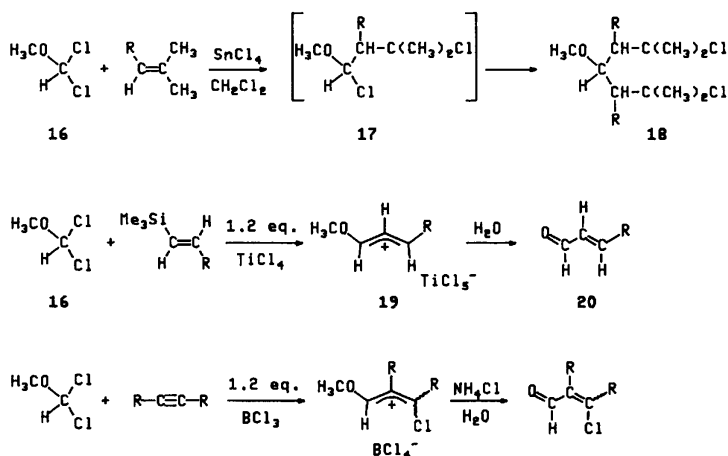
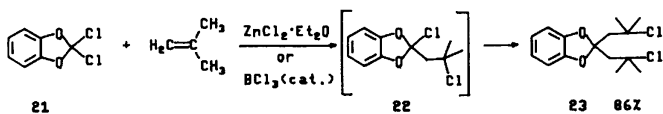


Figure 13. Electrophilic Reactions of Chloromethyl Methyl Ether

Because of the low electrophilicity of trialkoxycarbenium ions, ortho-carbonates cannot be used for the carboxylation of alkenes. This reaction can be achieved with dichloroacetals, however. Figure 14 shows that the formation of 1:1 products from 21 and ordinary alkenes requires addition rate control: When 21 and isobutene are treated with  $ZnCl_2$  or catalytic amounts of  $BCl_3$ , only the 2:1 products 23 are formed, since 22 ionizes to a greater extent than 21. With equimolar amounts of  $BCl_3$ , the relative reactivities of reactants and products become controlled by the addition

#### Concentration Control



#### Addition Rate Control

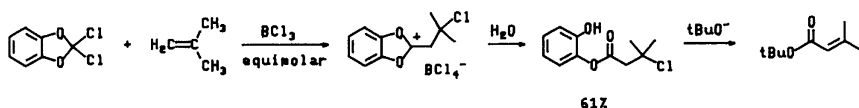


Figure 14. Electrophilic Carboxylation of Isobutene.<sup>27</sup>

rates of the corresponding carbenium ions, and the reactions terminate at the 1:1 product stage.<sup>27</sup> Though a series of alkenes has been carboxylated in this way,<sup>27</sup> we prefer to replace **21** by the acyclic chloroacetals **25**, which are readily accessible by radical initiated chlorination of the formaldehyde acetals **24**.<sup>28</sup> Because of the milder workup conditions, the yields of carboxylated alkenes are usually higher than those obtained with **21**. Figure 15 shows that the reaction of **25** with allylsilanes under conditions of addition rate control offers a simple access to  $\beta,\gamma$ -unsaturated carboxylates.

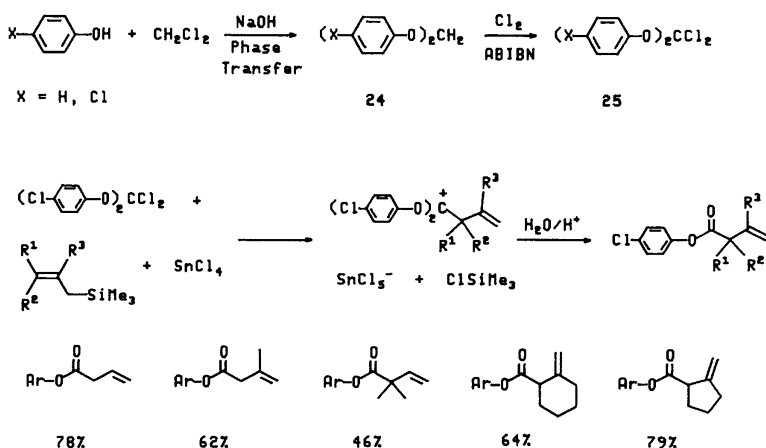


Figure 15.  $\beta,\gamma$ -Unsaturated Carboxylates from Dichloroacetals and Allylsilanes.

### 3.3 Addition Reactions with Consecutive Cyclizations

All examples discussed in Sections 3.1 and 3.2 follow the simple Scheme outlined on the bottom of Figure 2, and the results can be explained by considering the competition of  $\text{RX}/\text{R}^+$  and  $\text{PX}/\text{P}^+$  for the  $\pi$  nucleophile. This analysis may fail, however, if the addition reaction is part of a more complex reaction sequence. A well-known example is the tert. alkylation of siloxyalkenes with tert. alkyl chloride/Lewis acid mixtures.<sup>30</sup> The rapid desilylation of the initially generated siloxycarbenium ion prevents this ion to act as an electrophile towards other  $\pi$  systems.

The following two examples from our recent work also illustrate the limitations of our systematic approach to Lewis acid promoted alkylations of aliphatic  $\pi$  systems. The reaction of cumyl chloride **26** with tetramethylethylene in presence of various Lewis acids gave complex mixtures of products, probably because of the strain generated during the formation of the regular addition product. Titanium tetrachloride, however, induces a rapid consecutive cyclization, and the  $\text{TiCl}_4$  catalyzed reaction of **26** with tetramethylethylene yields hexamethylindane in 72% yield.<sup>31</sup> Since the aromatic ring can be oxidized under  $\text{Ru(VIII)}$  catalysis, the reaction sequence shown in Figure 16 allows the construction of acyclic compounds with adjacent quaternary carbon atoms.<sup>31</sup>

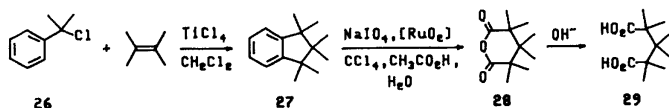


Figure 16. Construction of Compounds with Adjacent Quaternary Centers.<sup>31</sup>

While the  $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$  catalyzed reaction of the trimethylallyl chloride **30** with acetyl acetone yielded 60% of the cyclopentadiene **31**, attempts to synthesize **32-34** analogously gave complex mixtures of products. These cyclopentadienes became accessible, however, by the two step synthesis shown in Figure 17.<sup>32</sup> By trial and error we found that compound **33** can also be synthesized (55%) in one step from 3-methyl-3-penten-2-ol and 3-methyl-pentan-2,4-dione and  $\text{FSO}_3\text{H}$ . In all these cases, the sequence of elementary reactions is too complex to allow a simple rationalization of the reaction conditions.

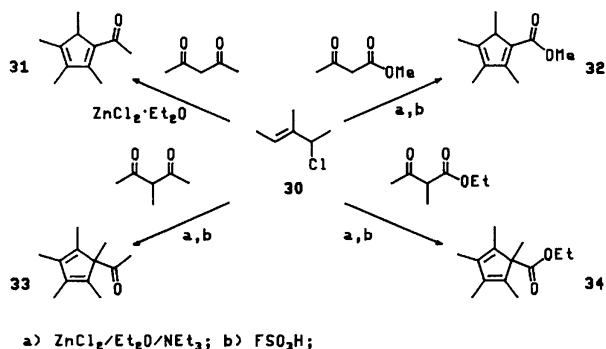


Figure 17. Synthesis of Polymethylated Functionalized Cyclopentadienes.<sup>32</sup>

#### 4. OUTLOOK

Though the limitations of a systematic approach to Lewis acid promoted reactions have been indicated in Section 3.3, conditions for simple addition reactions (Figure 2) can be derived from the model discussed in Section 2. It may be worth mentioning that the implications of the terms "concentration control" and "addition rate control", which we have used for our analysis, are well known to synthetic chemists carrying out base promoted reactions.

For Michael additions of  $\text{CH}$  acidic compounds (e.g. diethyl malonate with  $\alpha,\beta$ -unsaturated ketones) the following recommendations are given:<sup>33</sup> "When possible, relatively weak basic catalysts such as piperidine... should be selected. If stronger bases are required, it is normally appropriate to use only 0.1 to 0.3 equivalent of the base." The analogy of these conditions to those specified by our rule A is obvious (concentration control). On the other hand, preformed carbanions (organometallics) are usually employed when the addend is more basic than the enolate produced by attack at the unsaturated carbonyl compound. Though the nature of the metal ion plays a crucial rule in many "carbanionic" addition reactions, a first understanding of the principles involved can be

Lewis acid promoted Additions		Base promoted Additions	
Lewis acids	Bases	Bases	Acids
$MX_n$	$R-X$	$B$	$R-H$
	$\Downarrow \Delta G^\circ \sim \Delta LA$		$\Downarrow \Delta G^\circ \sim \Delta pK_a$
$R^+$	$MX_{n+1}^-$	$R^-$	$BH^+$
Electrophilic attack	$\downarrow$	Nucleophilic attack	$\downarrow$
	+ $\text{C}=\text{C} \begin{matrix} \text{D} \\ \text{O} \end{matrix}$		+ $\text{C}=\text{C} \begin{matrix} \text{R} \\ \text{C} \end{matrix}$
$P^+$	$MX_{n+1}^-$	$P^-$	$BH^+$
	$\Downarrow$		$\Downarrow$
$MX_n$	$P-X$	$B$	$P-H$

Figure 18. Analogy Between Acid and Base Promoted Addition Reactions.

based on the Brønsted  $pK_a$  scale, which provides a comparison of the basicities of  $R^-$ ,  $B$  and  $P^-$ . As basicity is known to be correlated with nucleophilicity, linear free energy relationships can be used to derive nucleophilic reactivities from  $pK_a$  values.<sup>34</sup> Figure 18 shows that the relationship between the thermodynamic quantity "acidity" (carbenium ions are Lewis acids!) and the kinetic term "electrophilicity" is of the same kind as the relationship between "basicity" and "nucleophilicity", and we are presently working on a quantification of this correlation, hoping that this will provide a deeper understanding of Lewis acid promoted additions.

**Acknowledgment.** This progress report is based on the work of a group of excellent coworkers, whose names are given in the references and to whom I would like to express my sincere thanks. Generous financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the A.v.Humboldt-Stiftung is gratefully acknowledged.

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