JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 642–654 (1998)

Review Commentary

Linear free enthalpy relationships: a powerful tool for the design of organic and organometallic synthesis†

Herbert Mayr,* Oliver Kuhn, Matthias F. Gotta and Matthias Patz

Institut für Organische Chemie der Ludwig-Maximilians-Universität München, Karlstrasse 23, D-80333 Munich, Germany

Received 29 September 1997; revised 9 February 1998; accepted 12 February 1998

ABSTRACT: Structure–reactivity relationships are usually investigated within relatively narrow classes of compounds, where structural variation can unequivocally be assigned to certain electronic and steric effects. We present a novel, semiquantitative approach to predict possible reactions of cationic electrophiles (carbenium ions, metal π-complexes, diazonium ions) with neutral nucleophiles (alkenes, alkynes, arenes, hydrides, organometallics and n-nucleophiles). It is shown that the rate constants for these reactions are given with a precision better than a factor of 10–100 by the linear free enthalpy relationship $\log k_{(20\,^\circ\mathrm{C})} = s\,(E + N)$, where E characterizes the strengths of the electrophiles, N characterizes the strengths of the nucleophiles and s is a nucleophile-dependent slope parameter, usually close to 1. This deviation appears tolerable in view of the reactivity range extending over more than 30 orders of magnitude, the large structural variety of compounds included and the neglect of solvent and steric effects. The simultaneous treatment of aliphatic, aromatic and organometallic compounds, which becomes possible in this way, provides new qualitative insights, and it is shown how the rule of thumb that reactions proceed at 20 °C if $E + N > -5$ can be used for rationalizing and designing organic reactions. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: linear free energy relationships; organic synthesis; organometallic synthesis

INTRODUCTION

Linear free enthalpy relationships (LFERs) are not considered a popular topic nowadays. Thirty years ago, when I (H.M.) was an undergraduate student, the situation was quite different. I was fascinated when I was taught the Hammett equation.[1] The possibility of calculating relative rate and equilibrium constants on the basis of σ and ρ greatly intrigued me. It gave me the feeling of understanding organic reactions which before had appeared to be a relatively unrelated bundle of facts.

Nowadays, as our students grow up with mechanistic thinking from the very beginning, everybody seems to be familiar with inductive and mesomeric effects, and the excitement about the Hammett treatment has gone. LFERs are often considered as a playground for pedants who are elaborating exact numbers for facts which in principle everybody already knows.

As a consequence, most contemporary general textbooks on organic chemistry, e.g. those by Vollhardt, Streitwieser–Heathcock–Kosower, Solomon and Ege, do not even mention the Hammett equation. Mechanistically oriented texts such as the Lowry–Richardson, the Carey–Sundberg and the March, do discuss the Hammett approach, but even these do not treat $\sigma^{+}_{\mathrm{arene}}$ constants, in our view the most efficient way of comparing reactivities of benzenoid and non-benzenoid arenes.[2]

With this background, it is not surprising that many synthetic chemists are not familiar with LFER concepts and are reluctant to accept approaches to organic reactivity of that type, e.g. our Eqn (1), which calculates the rates of reactions of carbocations and related electrophiles with non-charged nucleophiles on the basis of the electrophilicity parameter E, the nucleophilicity parameter N and the nucleophile-specific slope parameter s:[3]

$$\log k_{(20\,^\circ\mathrm{C})} = s(E + N) \tag{1}$$

While synthetic chemists prefer qualitative concepts of reactivity, physical organic chemists strive for exact numbers. They search for structure–reactivity correlations within well-defined, usually rather narrow, classes of compounds, where the consequences of structural variation can clearly be assigned to a single factor, electronic or steric. In this community, the three-parameter Eqn (1) is often met with scepticism, because it includes

---

*Correspondence to: Herbert Mayr, Institut für Organische Chemie der Ludwig-Maximilians-Universität München, Karlstrasse 23, D-80333 Munich, Germany.
E-mail: hmy@org.chemie.uni-muenchen.de

†Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 65th birthday. Revised version of a Plenary Lecture presented at ESOR VI, Louvain la Neuve, July 1997.

Contract/grant sponsor: Deutsche Forschungsgemeinschaft.
Contract/grant sponsor: Fonds der Chemischen Industrie.
Contract/grant sponsor: Volkswagen-Stiftung.

CCC 0894–3230/98/080642–13 $17.50

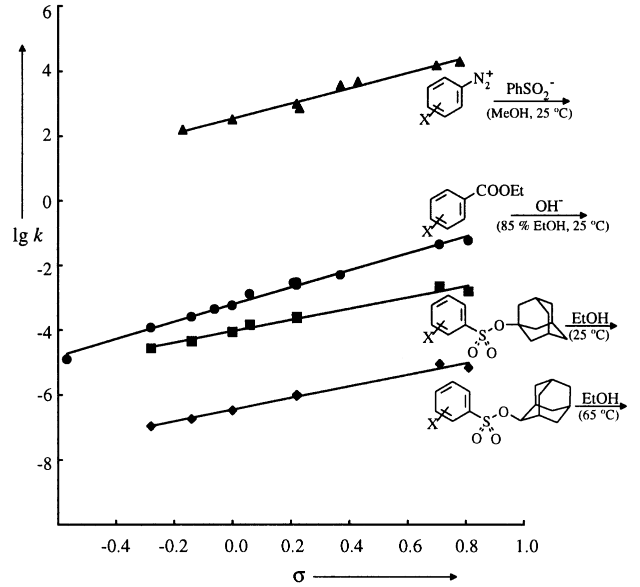
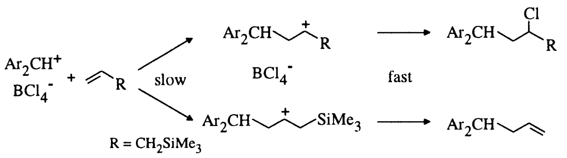


Figure 1. Hammett correlations hold because the variation of substituents occurs remote from the reaction center ▲, *Ref.* 4a; ●, *Refs* 4b and 4c; ■, ◆, *Ref.* 4d



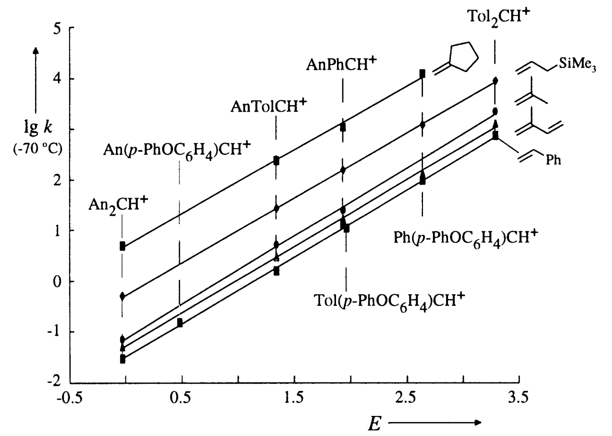


Figure 2. Constant selectivity relationships of the reactions of benzhydryl cations with π-nucleophiles. An = p-MeOC$_6$H$_4$; Tol = p-MeC$_6$H$_4$; for definition of E, see text

reactants of large structural variety, furthermore neglects solvent and steric effects and thus obviously ignores well known facts of organic reactivity. We realize these deficits, but think that owing to the simplicity and large variety of reactions covered by Eqn (1), this semiquantitative treatment of electrophile–nucleophile combinations opens up a new and valuable approach to organic reactivity. In view of the more than 30 orders of magnitude currently covered by Eqn (1), deviations of factors of 10–100 in the predicted rate constants appear tolerable to us, and justify the simultaneous treatment of aliphatic and aromatic, of organic and organometallic compounds as well as of n-, π-, and σ-nucleophiles with a single equation. Advantages and deficiencies of this concept compared with previous approaches to electrophilicity and nucleophilicity have been discussed in detail.[3]

LINEAR FREE ENTHALPY RELATIONSHIPS AND REACTIVITY SCALES

Let us first reflect why the Hammett equation has been so successful. In the reaction series considered in Fig. 1 substituents are varied in *meta*- and *para*-positions of the aromatic ring, while the vicinity of the reaction center is kept constant. As a consequence, only the electron density at the reaction center is modified within each reaction series, while the different steric requirements of the substituents do not affect the transition structures: linear correlations result.

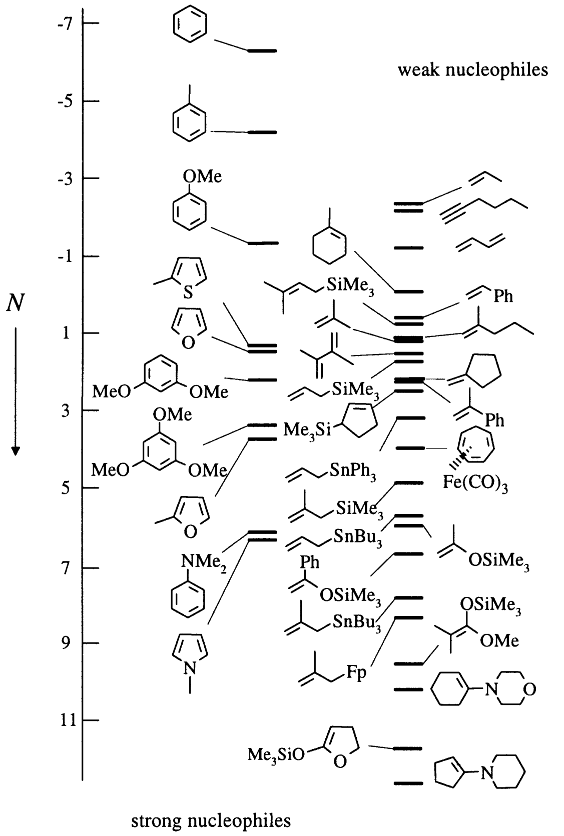
A closely related procedure was used for developing a reactivity scale for π-nucleophiles. When the rates of the reactions of benzhydryl cations with alkenes, allylsilanes and arenes were measured, only the *para* substituents of the benzhydryl cations were altered. As the surroundings of the reaction center remain constant within each reaction series, linear correlations are also obtained, which are by no means worse than most typical Hammett correlations.[5,6]

By accident, all correlation lines in Fig. 2 are parallel, implying that the relative reactivities of these π-systems are independent of the electrophile. Methylenecyclopentane appears to be 12 times more nucleophilic than allyltrimethylsilane, which is generally followed by isobutylene, isopropene and styrene.[6]

In analogy with Ritchie's N_+ scale,[7] an electrophile-independent nucleophilicity scale for π-systems appears feasible (Scheme 1). Benzhydryl cations can be used as reference electrophiles to determine nucleophilicities of π-systems (alkenes,[6,8–11] dienes,[11–13] alkynes,[14] arenes,[15] organometallics[16]), n-nucleophiles[17,18] (amines,[19] alcohols[20]) and hydrides (silanes,[21,22] stannanes,[23] hydrocarbons,[24] amine boranes[25]).

Although the slopes of the correlation lines for all these nucleophiles are similar, they are not always identical (as in Fig. 2), and the relative reactivities of the nucleophiles listed in Scheme 1 vary slightly when the reactivity of the electrophile is altered. A change of the solvent influences the rates of the reactions of carbocations with uncharged nucleophiles only slightly (less than a factor of 5),[8,9,16,21] and the nature of the counterion usually does not affect the rates of these reactions. A rationalization for these phenomena has been given.[9,26]

Before the 1970s, most information on nucleophile and



Scheme 1. Relative reactivities of π-nucleophiles towards carbocations and related electrophiles. Definition of N see text.

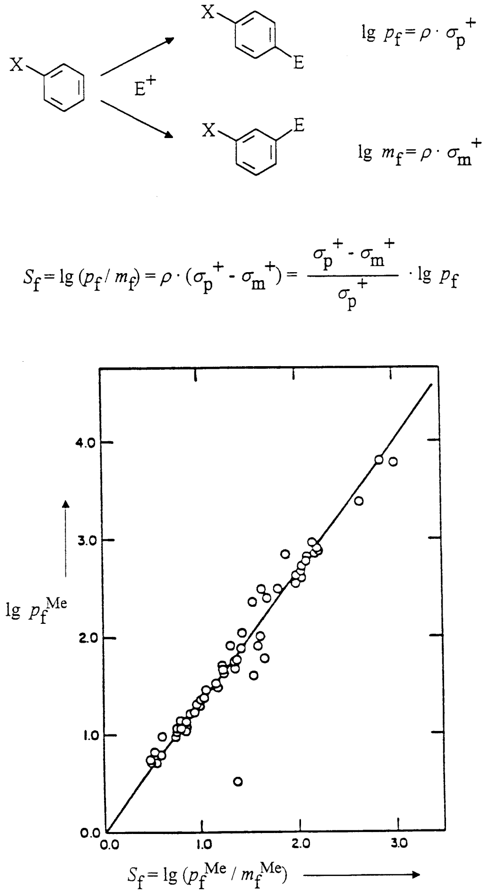


Figure 3. The Stock–Brown selectivity relationship: log $p_f = bS_f$.[28a]

electrophile reactivities had been derived from competition experiments. While this method has been employed successfully for determining relative arene reactivities,[27] the determination of the relative reactivities of the short-lived electrophilic intermediates in electrophilic aromatic substitutions is less straightforward.

Figure 3 illustrates the Stock–Brown relationship,[28a] the best known approach to relative electrophile reactivities. It is based on competitive studies of the relative reactivities of toluene and benzene in electrophilic aromatic substitutions. As shown in Fig. 3 there is a linear correlation between intermolecular selectivities (partial rate factor of the *para* position of toluene, log p_f^{Me}) and intramolecular selectivities [relative reactivities of the *para* and *meta* positions of toluene; $S_f = \log (p_f^{Me}/m_f^{Me})$], although the high quality of this correlation has been shown to be due to a statistical error.[28b]

On the basis of the reactivity–selectivity principle[29,30] it was then concluded that those electrophiles which were highly selective were the less reactive ones, and the unselective electrophiles were the highly reactive ones. Although obvious contradictions had been noted,[30d] the validity of this approach had generally been accepted until the early 1970s.

Even if the linear correlation between inter- and intramolecular selectivities illustrated in Fig. 3 is accepted as real, it only reflects that the electrophilic substitutions in *meta* and *para* positions of toluene obey the same LFER, as outlined at the top of Fig. 3. It is not possible, however, to conclude that selective electrophiles possess low reactivity and vice versa, since numerous violations of the reactivity–selectivity principle have been published since the early 1970s.[7,30,31] Figure 4 illustrates how contradictory results concerning relative reactivities might be derived if selectivities were the only experimental basis.

Imagine that we have no idea about substituent effects and their influence on the electrophilic reactivities of benzhydryl cations. Let us now assume that someone has determined the relative reactivities of (2-methylallyl)trimethylsilane and prenyltrimethylsilane [$(CH_3)_2C{=}CHCH_2SiMe_3$] towards benzhydryl cations by competition experiments. He or she would find that the carbenium ions on the left differentiate better between these two silanes than the carbenium ions on the right, i.e. he or she would observe a decrease in selectivity ($S = \log k_a - \log k_c$) from left to right. Employing the reactivity–selectivity principle, he or she would have come to the (correct) conclusion that the

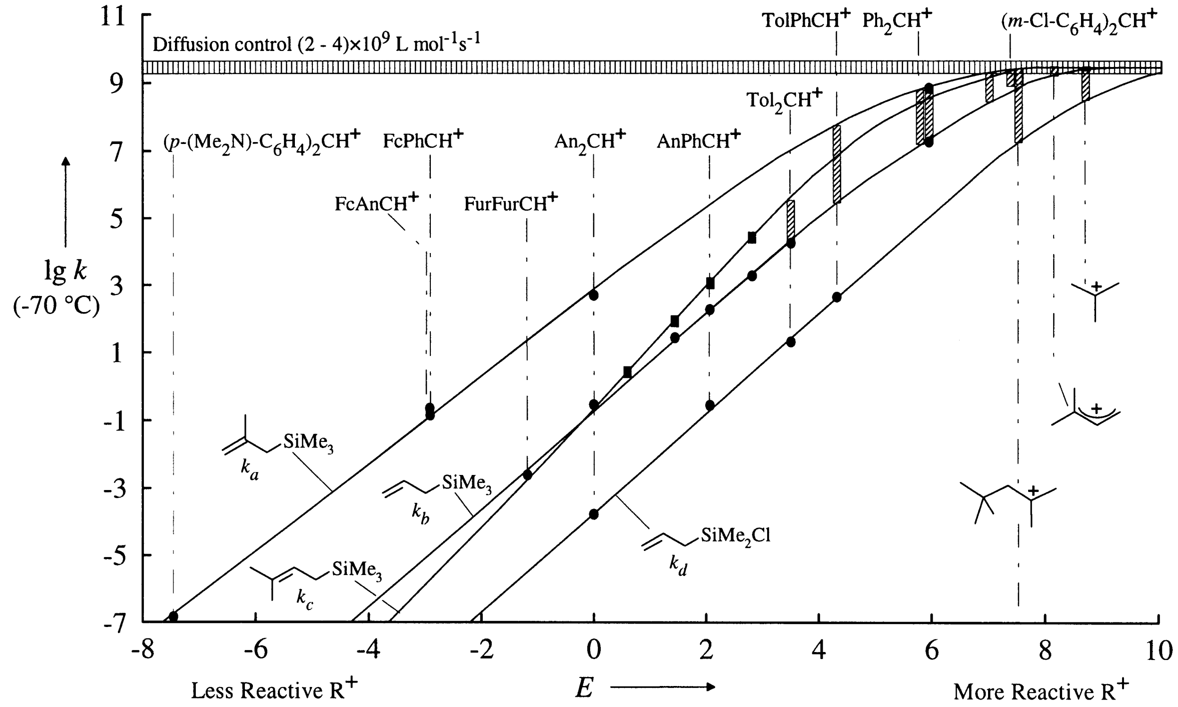


Figure 4. Rate constants for the reactions of carbenium ions with allylsilanes. Dots correspond to directly measured rate constants and shaded bars to the results of competition experiments. In part from *Ref.* 32

reactivities of the carbenium ions increase from left to right.

However, if this worker had selected the pair prenyltrimethylsilane–allylchlorodimethylsilane for the competition experiments, he or she would have observed an increase in selectivity ($S = \log k_c - \log k_d$) from left to right (until k_c approaches the diffusion limit). Applying the reactivity–selectivity principle he or she would now have come to the opposite (wrong) conclusion, namely that the reactivities of the carbenium ions in Fig. 4 decrease from left to right.

Finally, if the worker had selected allyltrimethylsilane and prenyltrimethylsilane in the competition experiments he or she would have encountered the crossing of the correlation lines, i.e. he or she would first have observed a decrease in the selectivities ($S = \log k_b - \log k_c$) when moving from left to right, a selectivity of zero for An_2CH^+, and then an increase in the selectivities ($S = \log k_c - \log k_b$; selectivities are always positive) when turning to the carbenium ions further right. Application of the reactivity-selectivity principle would have led him or her to a third (wrong) order of carbocation reactivities.

These examples clearly show that changes in selectivity alone do not give any indication of relative electrophilicities of the carbenium ions. Reactivity orders can only be derived from competition experiments, when one of the competition partners is known to react with diffusion control.[32] Measurements of absolute rate constants are, therefore, needed to determine reactivities of electrophiles.

Figure 5 compares the rate constants for the reactions of some α-methoxybenzyl cations (carboxonium ions) and aldehyde–Lewis acid complexes with allylsilanes and alkenes with the corresponding rate constants for benzhydryl cations.[33] It can be seen that the relative reactivities of these π-systems determined towards

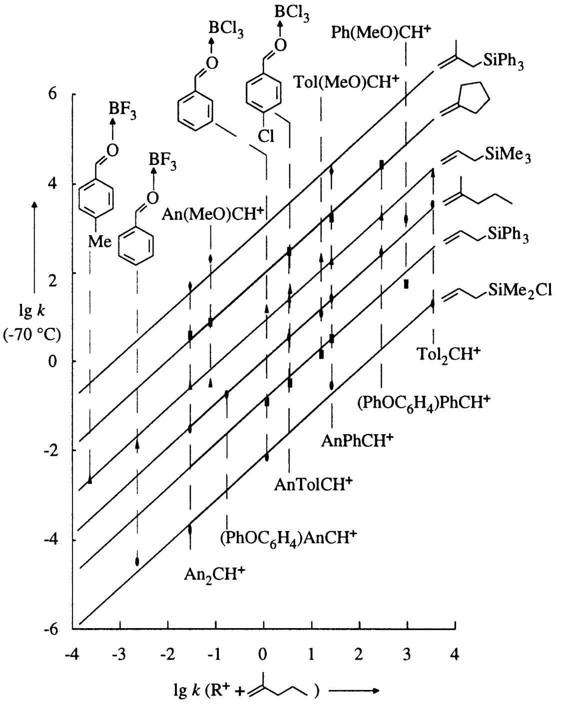
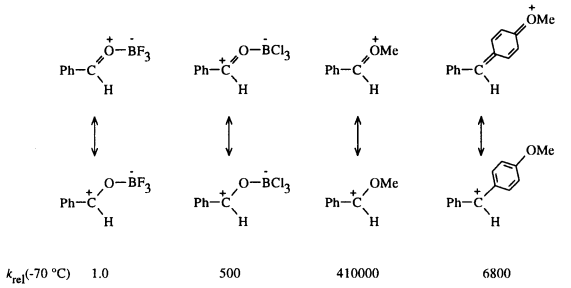


Figure 5. Rate constants for the reactions of benzhydryl cations, carboxonium ions and aldehyde–Lewis acid complexes toward allylsilanes and alkenes



Scheme 2. Comparison of the electrophilicities of carboxonium ions and aldehyde-BX_3-complexes.

carboxonium ions and aldehyde complexes are the same as those previously determined towards benzhydryl cations.[34] It is thus proved that the nucleophilicity scale in Scheme 1 is not restricted to reactions with benzhydryl cations. Furthermore, it is now possible to compare the electrophilic reactivities of carboxonium ions and aldehyde–BX_3 complexes with those of benzhydryl cations. Figure 5 shows that the electrophilicity of $Ph(MeO)CH^+$ is between those of $(PhOC_6H_4)PhCH^+$ and Tol_2CH^+, whereas the electrophilic reactivity of $Tol(MeO)CH^+$ is similar to that of $AnPhCH^+$.

Quantitative evaluation of Fig. 5 gives the numbers in Scheme 2 which show that the α-methoxybenzyl cation is 100 times more reactive than its phenylogue on the right. The relative electrophilic reactivities of the benzaldehyde–BX_3 complexes and of the α-methoxybenzyl cation can be interpreted in terms of increasing cation stabilizing effects of the substituents MeO < Cl_3BO^- < F_3BO^- on the carbenium center. It is remarkable that the genuine carbocation on the right of Scheme 2 and the uncharged benzaldehyde–BCl_3 complex differ only by a factor of 14 in reactivity.

In order to obtain a consistent set of averaged reactivity parameters for electrophiles and nucleophiles, reaction series as depicted in Figs 2 and 5 were subjected to a correlation analysis. Equation (2) is a typical analytical expression for the LFERs shown in these figures:

$$\log k_{(20\,°\mathrm{C})} = Nu + sE \tag{2}$$

In the plot of log *k* against the electrophilicity parameter *E*, the slopes of the correlation lines for the different nucleophiles are given by *s*, and the nucleophilicity parameters *Nu* are given by the intercepts of these lines on the ordinate ($E = 0$).

It is a disadvantage of this treatment that the *Nu* parameters thus defined often do not have any direct significance. Imagine the comparison of two very strong nucleophiles, e.g. phosphanes and enamines. One would need very weak electrophiles for their characterization in order to obtain rate constants which can conveniently be measured (10^{-2} to 10^3 L mol^{-1} s^{-1}), and the *Nu* parameters would be obtained by extrapolation from the experimental range (e.g. $E = -15$ to -9) to the point of intersection with the ordinate ($E = 0$). Since not all correlation lines are parallel, the probability of crossing will be high if a wide-ranging extrapolation is needed. As a consequence, the relative magnitudes of *Nu* do not necessarily represent the relative strengths of these nucleophiles in the experimentally relevant range. An

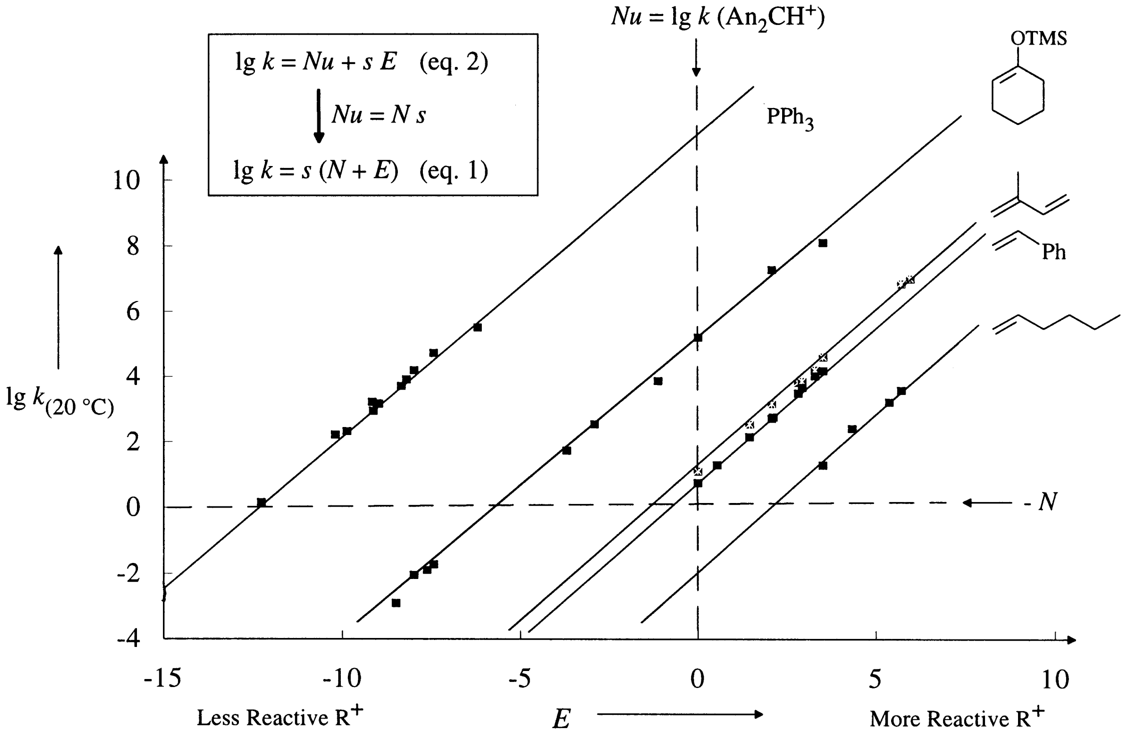
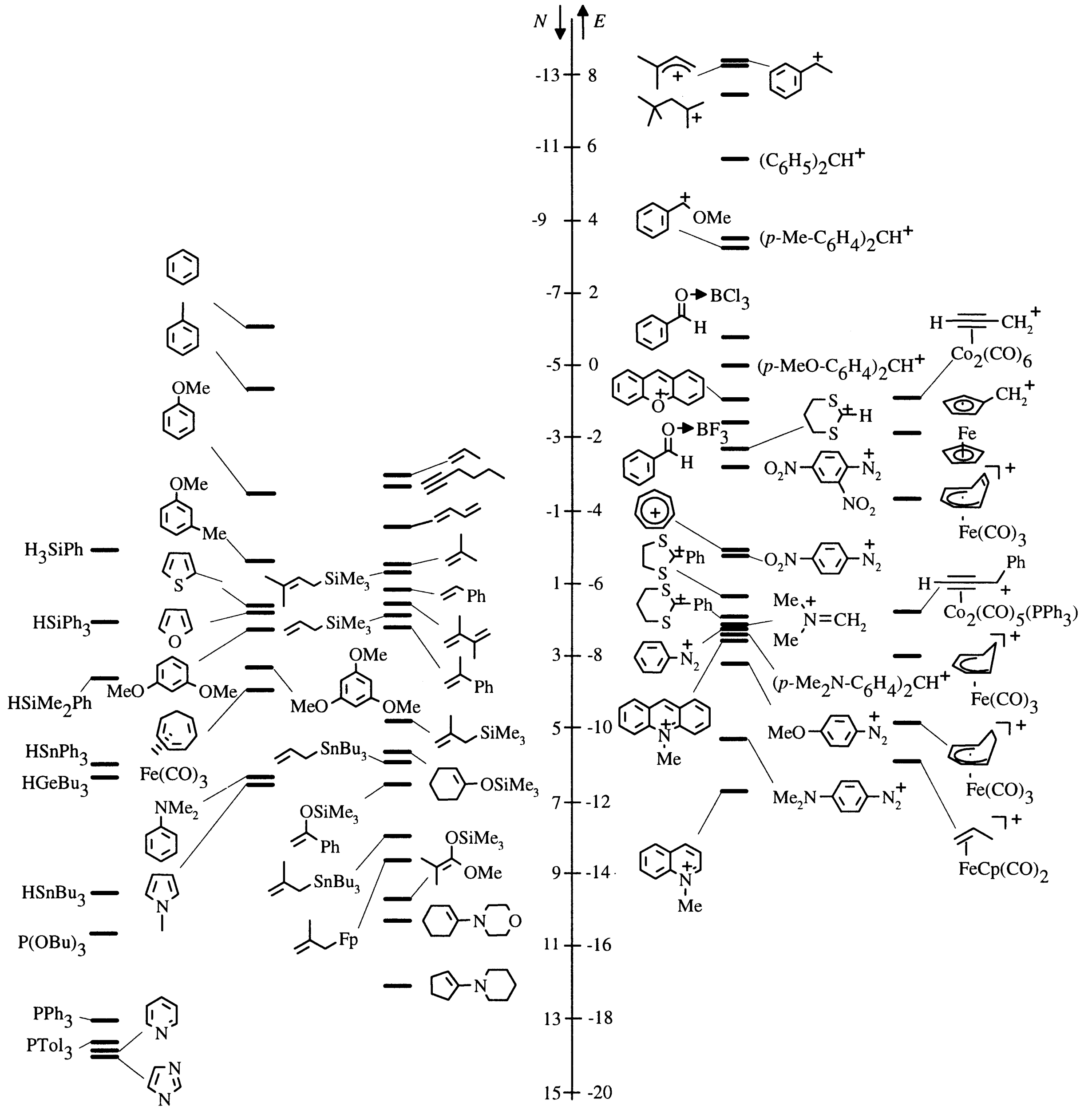


Figure 6. Linear free enthalpy relationships for the reactions of carbenium ions with nucleophiles



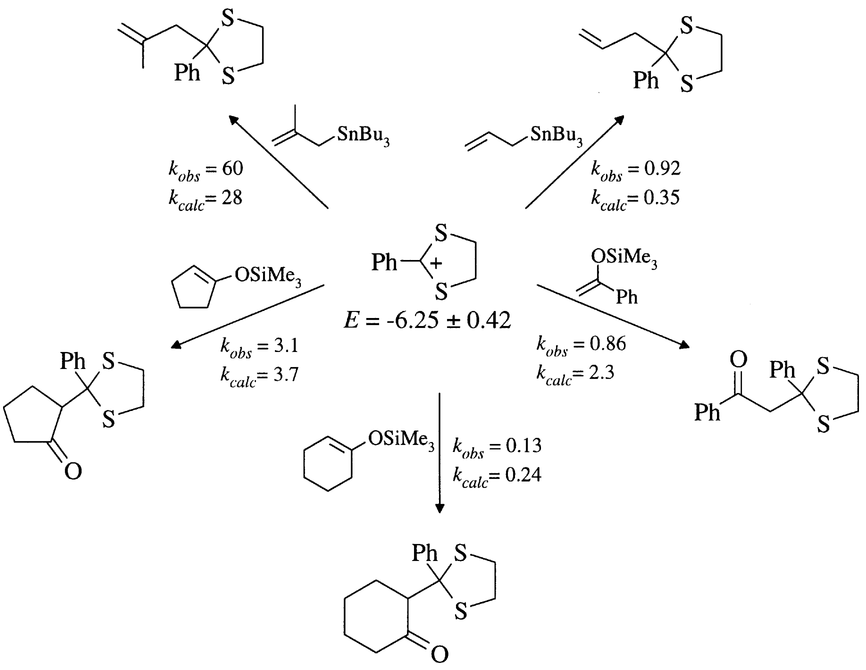
Scheme 3. Nucleophilicity and electrophilicity scales.

analogous situation is encountered when very weak nucleophiles are compared. We therefore substituted *Nu* by *sN* and thus obtained Eqn (1), where *N* equals the negative value of *E* at the intersection of the correlation lines with the abscissa (log $k = 0$, see Fig. 6).[3]

Although Eqns (1) and (2) are mathematically equivalent, i.e, application of either one would give log *k* with the same precision, Eqn (1) is preferable for qualitative discussions, because *N*, in contrast to *Nu*, gives direct information on the relative reactivities of nucleophiles in the reactivity range most relevant in practice ($k \approx 1$ L mol^{-1} s^{-1}). Whereas the *Nu* scale refers to An_2CH^+ as the standard electrophile, the *N* scale is based on a floating reference scale, i.e. weak nucleophiles are gauged with strong electrophiles, and strong nucleophiles are gauged with weak electrophiles.

With *E* and *N* thus defined, a simple semiquantitative treatment of electrophile–nucleophile reactions becomes possible.[3] For this purpose, nucleophiles and electrophiles are ordered according to increasing *N* and decreasing *E* parameters, respectively, as shown in Scheme 3.

One can see that the two scales are adjusted in such a way that at any place $E + N = -5$. This arrangement implies that for combinations of electrophiles and nucleophiles located at the same level a second-order rate constant of log $k = -5s$ is calculated by Eqn (1), corresponding to *k*-values between 10^{-6} and 10^{-3} L



Scheme 4. Rate constants (20°C, CH_2Cl_2, L mol^{-1} s^{-1}) of the 2-phenyl-1,3-dithiolan-2-ylium cation with various nucleophiles.[36]

mol^{-1} s^{-1} (20 °C), since for most nucleophiles *s* values between 0.6 and 1.2 have been found. Assuming 1 mol L^{-1} as a typical concentration for synthetic transformations, these rate constants imply half-times of reaction between 10 min and 200 h, the basis of our rule of thumb that at room temperature electrophiles will react only with those nucleophiles which are positioned at the same level or below themselves in Scheme 3.[3] Some recent examples demonstrating the applicability of this scheme will now be discussed.

HETEROSUBSTITUTED CARBOCATIONS

In order to define the synthetic potential of dithiosubstituted carbenium ions, we studied the kinetics of their reactions with suitable nucleophiles, i.e. allylsilanes, allylstannanes and silylated enol ethers.[35] For the 2-phenyl-1,3-dithiolan-2-ylium cation, for example, reactions with five nucleophiles were studied (Scheme 4).

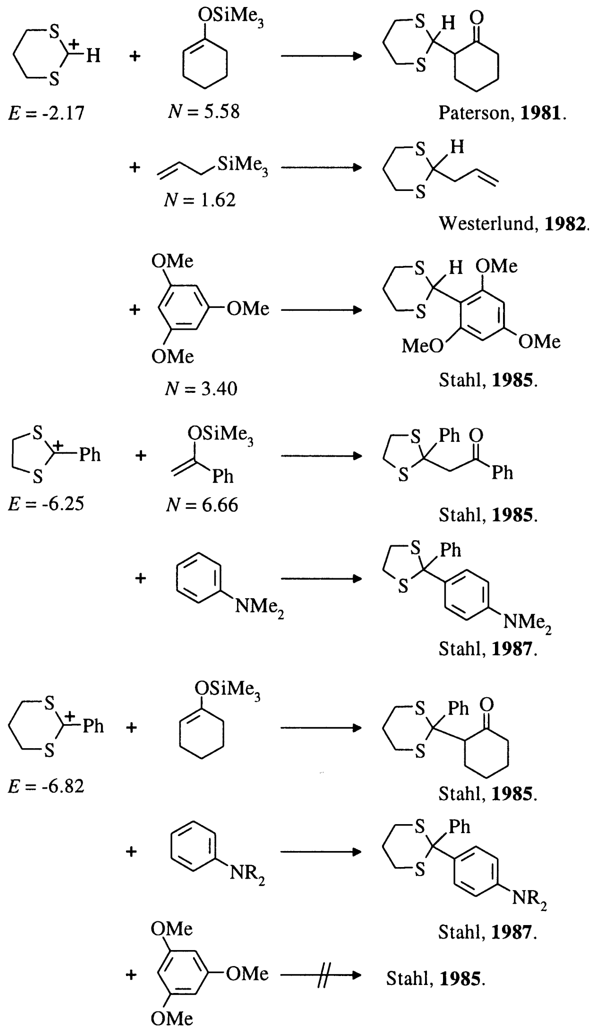
As *s* and *N* were known for these nucleophiles,[3] each of these rate constants could be used to calculate the *E* value of the 2-phenyl-1,3-dithiolan-2-ylium ion ($E = -6.25 \pm 0.42$) by substituting log *k*, *N* and *s* into Eqn (1). The coincidence of observed and calculated [by Eqn (1) using the averaged *E* parameter] rate constants within a factor of 2.5 (Scheme 4) indicates the validity of the LFER [Eqn (1)] for these reactions. In a similar way, *E* parameters for other dithiocarbenium ions were determined, which allow their positioning in Scheme 3. Published reactions of these electrophiles are collected in Scheme 5 and readers may convince themselves that all nucleophiles reported to react with these cations are located below the corresponding electrophiles in Scheme 3.

One problem is that Stahl[36a] reported the failure of the 2-phenyl-1,3-dithianylium ion to react with 1,3,5-trimethoxybenzene, although Scheme 3 predicts a slow reaction at room temperature. We repeated Stahl's experiment, and indeed did not find any reaction even upon warming. We therefore assume that in this case steric effects cannot be neglected.

REACTIONS OF METAL π-COMPLEXES

Already in 1984, Kane-Maguire and Sweigart[37] summarized their extensive kinetic studies on the reactions of electrophilic metal π-complexes with amines, phosphanes and other nucleophiles and demonstrated that Ritchie's constant-selectivity relationship[7] was applicable to these reactions. Their data represent an essential basis for our description of the reactions of electrophiles with nucleophiles. Therefore, it was to be expected that Eqn (1) and Scheme 3 should also be useful for the design of organic syntheses via organometallics. Let us turn to the question of which nucleophiles and electrophiles to use for realizing the reaction sequence illustrated in Scheme 6.

The systematic approach is described in Schemes 7, 8 and 9. According to Scheme 7 the tricarbonylirontropylium complex is too electrophilic to allow the kinetic determination of its reaction with the highly nucleophilic



Scheme 5. Reactions of dithiocarbenium ions with nucleophiles.[36]

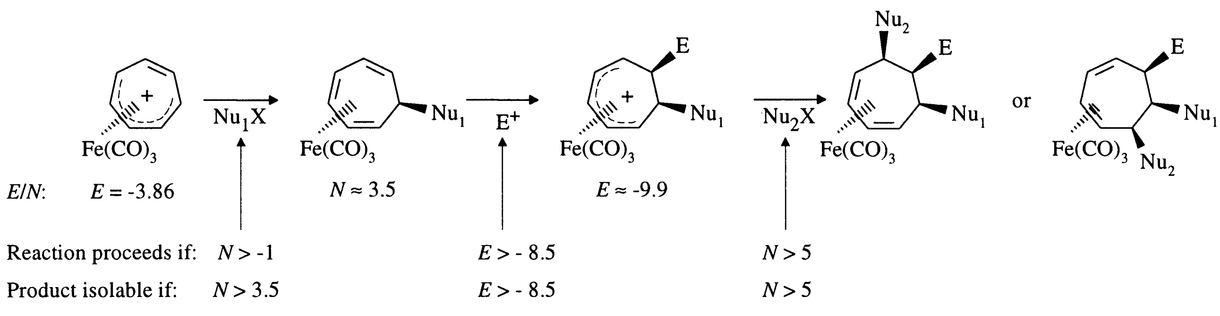
silylated ketene acetal (Scheme 7 left). The reactions with allylsilanes and allylstannanes could be followed, however, and the closely similar value of $E = -3.86 \pm 0.19$ derived from reactions with three different nucleophiles again indicates the applicability of Eqn (1). The magnitude of E suggests that the tropylium complex should react with all nucleophiles for which $N > -1$, i.e. with all nucleophiles stronger than anisole or 1,3-butadiene (Scheme 3).[38a]

Now turn to the second step of the reaction sequence in Scheme 6. Which electrophiles can attack at tricarbonyliron-coordinated cycloheptatriene complexes? In accord with Dauben's and Bertelli's report[39] on the reactions of tritylium ions with tricarbonylironcycloheptatriene, benzhydryl cations do not abstract hydride from this complex but add to its triene system (Scheme 8). Müller[38a] measured rate constants for its reactions with four different benzhydryl cations, and the linear correlation with a slope close to unity (Scheme 8) again demonstrates the validity of Eqn (1). The value $N = 3.58$ ($\Leftrightarrow$ $-E$ for $\log k = 0$) identifies the cycloheptatriene complex as a relatively strong nucleophile, comparable to allylsilanes or 1,3-dimethoxy- and 1,3,5-trimethoxybenzene. From $E + N \geq -5$ one derives that tricarbonyl(cycloheptatriene)iron should react with the large variety of electrophiles characterized by $E \geq -8.5$.

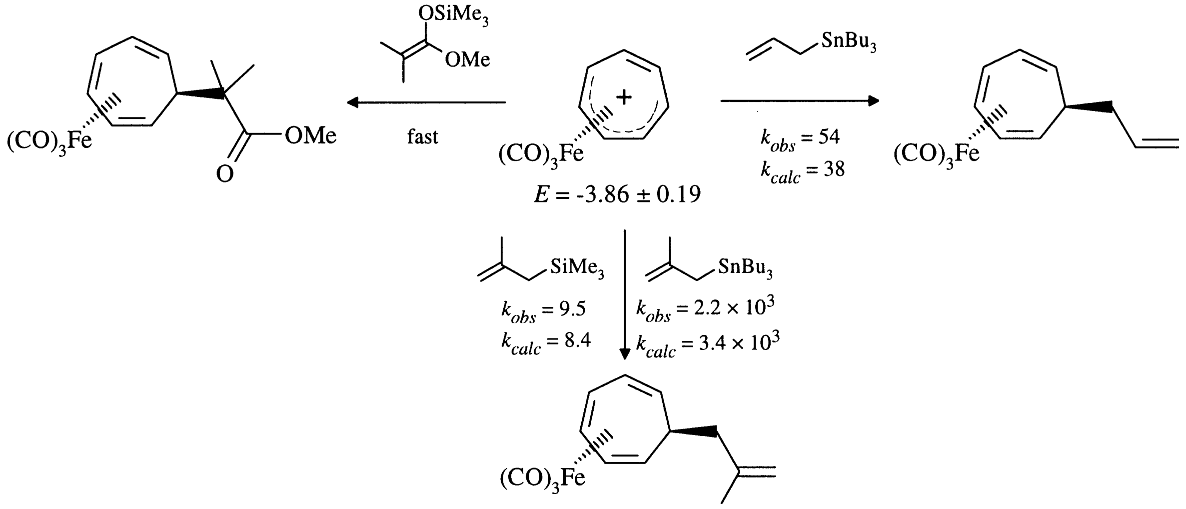
The final step of the reaction sequence in Scheme 6 is the reaction of a nucleophile with a tricarbonylironcycloheptadienylium cation. Scheme 9 shows that such complexes are considerably less electrophilic than the corresponding tropylium complex described in Scheme 7. While the silylated ketene acetal, derived from methyl isobutyrate, reacts too fast with the tropylium complex to be followed with our kinetic device (Scheme 7), the reaction of this ketene acetal with the cycloheptadienylium complex is relatively slow (Scheme 9 upper left[38b]). The rate constants for the reactions of the two complexes with (2-methylallyl) tributylstannane are directly comparable: the cycloheptatrienylium complex in Scheme 7 is 10^5 times more reactive than the cycloheptadienylium complex in Scheme 9.

From $E = -9.9$ it is obvious that tricarbonylironcycloheptadienylium cations are very weak electrophiles, which can only be attacked by strong nucleophiles ($N \geq 5$).

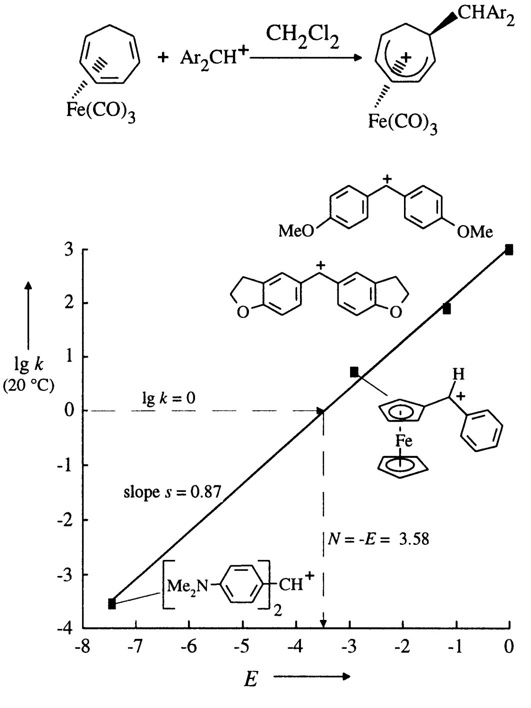
Until now, the discussion of Scheme 6 has only considered the question of whether the reaction of a certain electrophile with a certain nucleophile will be fast enough to be synthetically useful. A second question is of similar importance for the success of a synthesis: can the



Scheme 6. Design of synthetically useful reaction sequences.[38]



Scheme 7. Rate constants (20°C, CH_2Cl_2, L mol^{-1} s^{-1}) for the reactions of the tricarbonylirontropylium ion with various nucleophiles.[38a]



Scheme 8. Determination of the nucleophilicity parameters *N* and *s* for tricarbonylironcycloheptatriene.[38a]

products be isolated? Consider the first step of Scheme 6: the reaction of the tropylium complex with Nu_1X gives a tricarbonylironcycloheptatriene complex. This product is nucleophilic and may, therefore, react with its precursor, the electrophilic tropylium complex. This consecutive reaction can only be suppressed when Nu_1X is a stronger nucleophile than tricarbonyl(cycloheptatriene)iron. Since for the latter $N = 3.5$ has been derived, Nu_1X should be at least as nucleophilic, i.e. $N \geq 3.5$.

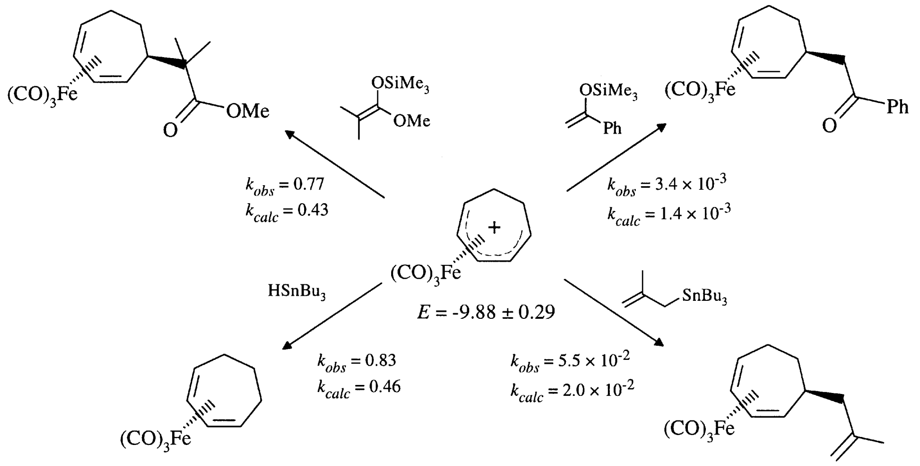
There are no problems with the following two reactions in Scheme 6! Cycloheptadienylium ions are very weak electrophiles ($E \approx -9.9$), and the subsequent reactions with their nucleophilic cycloheptatriene precursors ($N \approx 3.5$) will be very slow and can be neglected. Finally, the cycloheptadiene complexes produced in the last step of Scheme 6 are very weak nucleophiles, since electrophilic attack at the diene system would yield a 16-electron complex. Consecutive reactions therefore cannot take place. Since the electrophilic and the nucleophilic additions to the tricarbonyliron complexes in Scheme 6 generally take place at the site opposite to the tricarbonyliron group, the stereoselective formation of 5,6,7-trisubstituted cycloheptadienes can be expected if the criteria described at the bottom of Scheme 6 are fulfilled. Control of the regioselectivity in the final step still has to be solved, however.

The examples discussed in Schemes 6,7,8 and 9, as well as our recent studies on ferrocenylmethylium ions,[40] hexacarbonyldicobalt coordinated propargylium ions[41] and palladium-coordinated allyl cations[42] and the extensive work of Kane-Maguire and Sweigart[37] indicate that Eqn (1) is applicable not only to reactions of ordinary carbenium ions but also to reactions of electrophilic metal π-complexes.

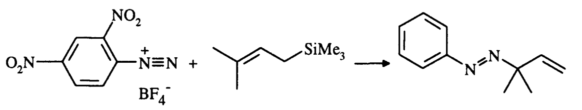
The question arises of whether hetero-electrophiles also follow this equation. In previous work[9,43] we had already shown that bridging electrophiles, such as halogens, sulfenyl and selenyl halides, or mercury ions show different selectivities than carbocations and therefore cannot be expected to follow the LFER [Eqn (1)]. The situation should be different for diazonium ions, however, which have previously been reported to follow Ritchie's constant selectivity relationships.[44]

DIAZONIUM IONS

Whereas azo couplings with arenes represent one of the



Scheme 9. Rate constants (20°C, CH_2Cl_2, L mol^{-1} s^{-1} for the reactions of the tricarbonylironcycloheptadienyl cation with various nucleophiles.[38]



Scheme 10. Reaction of the 2,4-dinitrobenzenediazonium ion with prenyltrimethylsilane.

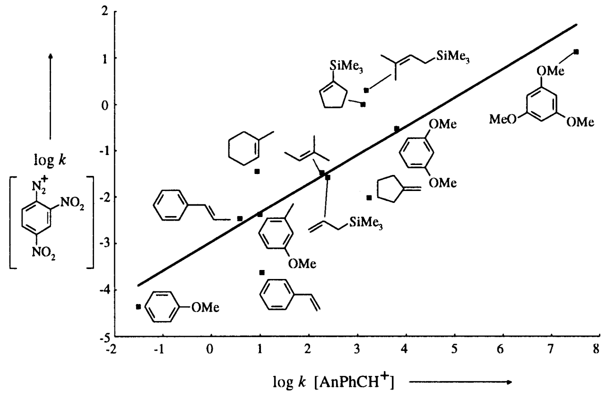
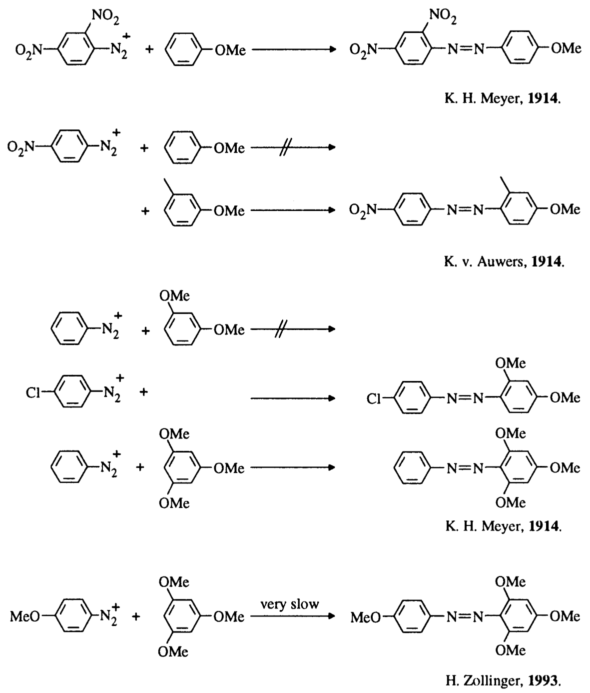


Figure 7. Correlation of the reactivities of various π-nucleophiles towards An_2CH^+ (CH_2Cl_2, −70 °C) and the 2,4-dinitrobenzenediazonium ion (CH_3CN, 20 °C)

most important processes in industrial organic chemistry,[45] reactions with non-aromatic π-systems have been much less investigated.[45,46] About 30 years ago, Marxmeier and Pfeil[47] reported the reactions of the 2,4-dinitrobenzenediazonium ion with alkenes, and we have recently reported on an efficient synthesis of allylazo compounds by reactions of diazonium ions with allylsilanes and allylstannanes (Scheme 10).[48]

Figure 7 shows a moderate correlation of the rate constants for the reactions of the 2,4-dinitrobenzenediazonium ion with arenes, alkenes and allylsilanes[49] with the rate constants of the corresponding reactions of the *p*-methoxybenzhydryl cation.[9,11,15,16,50] Although the quality of this correlation may be disappointing, the general information given by Fig. 7 is very relevant: *m*-methylanisole, allyltrimethylsilane and 2-methyl-2-butene, three arbitrarily selected representatives of three different classes of compounds, which have been found to show similar reactivities toward carbenium ions (the basis of the nucleophilicity scale in Scheme 1), also show similar reactivities towards diazonium ions, i.e. in a semiquantitative analysis of electrophile–nucleophile combination reactions diazonium ions can be treated simultaneously with carbenium ions.

Correlation analysis, as described in Ref. 49, gave *E*



Scheme 11. Azo-coupling of benzenediazonium ions.

parameters for 14 diazonium ions, covering a reactivity range of eight orders of magnitude from the highly electrophilic 2,4-dinitrobenzenediazonium ion ($E = -2.5$) to 4-(dimethylamino)benzenediazonium ion ($E = -10.4$), the weakest electrophile investigated in this series. The general textbook statement that diazonium ions are weak electrophiles and, therefore, only couple with phenolates and aromatic amines can now be specified.

Scheme 11 summarizes some azo couplings reported in the literature, which may be rationalized by inspection of Scheme 3. In accord with its position below the 2,4-dinitrobenzenediazonium ion, anisole was reported to react with this electrophile.[51] The less electrophilic 4-nitrobenzenediazonium ion, which is located below anisole in Scheme 3 was found not to couple with this arene, but with 1-methoxy-3-methylbenzene,[52] which sits at the same level as this electrophile.

The unsubstituted benzenediazonium ion has been reported not to react with 1,3-dimethoxybenzene[51] although the reaction partners are located at the same level in Scheme 3. The borderline situation for this electrophile–nucleophile combination is illustrated by the fact that the *p*-chlorobenzenediazonium ion, only a slightly stronger electrophile than the unsubstituted benzenediazonium ion ($\Delta E = 0.5$)[49] was found to couple with this arene.[51]

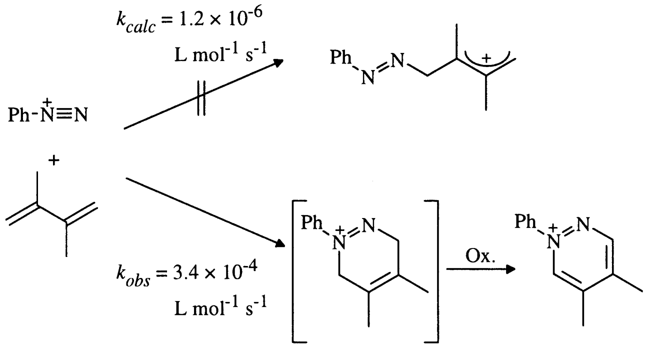
Because of its high nucleophilicity, 1,3,5-trimethoxybenzene not only reacts with the parent benzenediazonium ion[51] but also with the highly stabilized *p*-methoxybenzenediazonium ion. The latter reaction was reported to be very slow,[53] however, as expected from the position of the corresponding reactants at the same level in Scheme 3.

Reactions with non-aromatic π-nucleophiles have been analyzed analogously.[49] It should be considered, however, that diazonium ions can easily be reduced[54] with the consequence that the expected azo couplings are sometimes outstripped by SET processes and subsequent loss of nitrogen.

LIMITATIONS OF THE LINEAR FREE ENTHALPY RELATIONSHIP AND PERICYCLIC REACTIONS

The feasibility of fast alternative reactions is a general problem. Although one can generalize that electrophile–nucleophile combination reactions are reasonably fast at room temperature if the nucleophiles are located below the corresponding electrophiles in Scheme 3, one can never exclude the occurrence of faster competing reactions.

A related situation is encountered when a nucleophile is located above a certain electrophile. Scheme 3 only predicts that the ordinary electrophile–nucleophile combination with formation of one new σ-bond will be too slow to be observable at room temperature. One cannot exclude alternative reaction pathways, however.

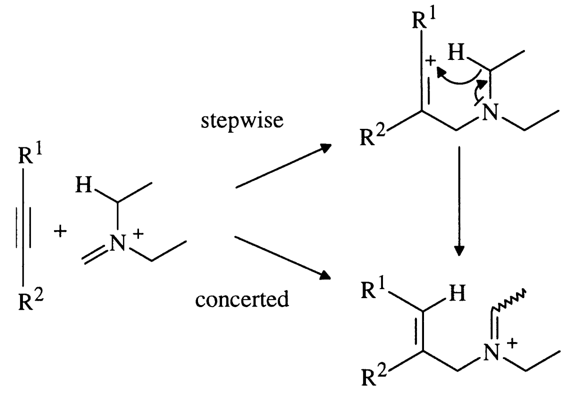


Scheme 12. (4+2)-Cycloaddition reaction of the benzenediazonium ion with 2,3-dimethylbutadiene.

Inspection of Scheme 3 indicates that the benzenediazonium ion should not react with 2,3-dimethyl-1,3-butadiene. Application of Eqn (1) predicts a rate constant of 10^{-6} L mol^{-1} s^{-1}, corresponding to a half-time of reaction of 200 days ($c = 1$ mol L^{-1}). However, the calculation refers only to the upper reaction in Scheme 12. This reaction indeed does not take place, but nature finds an alternative pathway, the concerted $(4+2)$-cycloaddition formulated at the bottom of Scheme 12,[55] the rate of which cannot be predicted by Eqn (1).

For *N,N*-dialkyliminium ions, *E* parameters between -7 and -8 have been determined.[56] If they reacted with π-systems in the same manner as other carbenium ions, Eqn (1) and Scheme 3 would predict that 1,3-dimethoxybenzene and α-methylstyrene are among the weakest nucleophiles to be attacked. It was observed, however, that iminium hexachloroantimonates also react with less nucleophilic alkynes.[57]

Although slowly, the *N,N*-diethyliminium ion even reacts with 2-methyl-1-buten-3-yne, a nucleophile which we could not combine with any of the benzhydryl cations used to characterize other π-nucleophiles.[9,58] An alternative reaction mechanism is again indicated.



Scheme 13. Stepwise and concerted ene reactions of alkynes with the diethylmethyleneammonium ion.

Whereas both the concerted and the stepwise ene reaction formulated in Scheme 13 may account for the stereoselective (with respect to the CC double bond) formation of the *N*-allyliminium ions, only the concerted mechanism is in accord with the fact that even weakly nucleophilic alkynes undergo this reaction. The deviation the between calculated and observed rate constants may be considered as a measure of the concertedness of these reactions.

CONCLUSIONS

The LFER [Eqn (1)] and the graphical approximation in Scheme 3 can be used for designing syntheses via reactions of cationic electrophiles with neutral nucleophiles. It is this combination which keeps the total charge constant (+1), from reactants through transition states to products, and thus eliminates significant solvent effects (a factor of <5 in reactions of carbocations). Only in reactions with diazonium ions, which undergo specific interactions with donor solvents, can the influence of solvents on reaction rates not be neglected.[49]

The wide reactivity range covered by Eqn (1) and by Scheme 3 permits steric effects to be ignored in most cases. While they can usually be considered as the noise of these correlations, specific consideration of steric effects is necessary when bulky reactants are involved.

It is obvious that these correlations can hold only when related mechanisms are involved. In all reactions considered, σ-bonds are not broken in the electrophile, and only one new bond is formed in the rate-determining step. S_N2-type and pericyclic reactions are therefore excluded, but it seems probable that the difference between calculated and observed rate constants of pericyclic reactions represents a measure of the concertedness of these reactions.

Acknowledgements

Generous support of this work by the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie* and the *Volkswagen-Stiftung* is gratefully acknowledged. We thank the members of our group whose contributions represent the basis of this concept.

REFERENCES

1. (a) L. P. Hammett. *Physical Organic Chemistry*. McGraw-Hill, New York (1970); (b) O. Exner. *Correlation Analysis of Chemical Data*. Plenum Press, New York (1988); (c) C. Hansch, A. Leo and R. W. Taft. *Chem. Rev.* **91,** 165–195 (1991).
2. (a) R. Taylor. *Electrophilic Aromatic Substitution*. Wiley, Chichester (1990); (b) A. R. Katritzky and R. Taylor. *Adv. Hetrocycl. Chem.* **47,** 1–467 (1990).
3. H. Mayr and M. Patz. *Angew. Chem.* **106,** 990–1010 (1994); *Angew. Chem., Int. Ed. Engl.* **33,** 938–957 (1994).
4. (a) C. D. Ritchie, J. D. Saltiel and E. S. Lewis. *J. Am. Chem. Soc.* **83,** 4601–4605 (1961); (b) C. K. Ingold and W. S. Nathan. *J. Chem. Soc.* 222–225 (1936); (c) D. P. Evans, J. J. Gordan and H. B. Watson. *J. Chem. Soc.* 1430–1432 (1937); (d) D. N. Kevill, K. C. Kolwyck, D. M. Shold and C.-B. Kim. *J. Am. Chem. Soc.* **95,** 6022–6027 (1973).
5. H. Mayr, R. Schneider and U. Grabis. *Angew. Chem.* **98,** 1034–1036 (1986); *Angew. Chem., Int. Ed. Engl.* **25,** 1017–1019 (1986).
6. H. Mayr, R. Schneider and U. Grabis. *J. Am. Chem. Soc.* **112,** 4460–4467 (1990).
7. (a) C. D. Ritchie. *Acc. Chem. Res.* **5,** 348–354 (1972); (b) C. D. Ritchie. *Can. J. Chem.* **64,** 2239–2250 (1986).
8. H. Mayr, R. Schneider, C. Schade, J. Bartl and R. Bederke. *J. Am. Chem. Soc.* **112,** 4446–4454 (1990).
9. H. Mayr. *Angew. Chem.* **102,** 1415–1428 (1990); *Angew. Chem. Int. Ed. Engl.* **29,** 1371–1384 (1990).
10. M. Roth, C. Schade and H. Mayr. *J. Org. Chem.* **59,** 169–172 (1994).
11. H. Mayr, R. Schneider, B. Irrgang and C. Schade. *J. Am. Chem. Soc.* **112,** 4454–4459 (1990).
12. B. Irrgang and H. Mayr. *Tetrahedron* **47,** 219–228 (1991).
13. H. Mayr and M. Hartnagel. *Liebigs Ann. Chem.* 2015–2018 (1996).
14. H. Mayr, J. L. Gonzalez and K. Lüdtke. *Chem. Ber.* **127,** 525–531 (1994).
15. H. Mayr, J. Bartl and G. Hagen. *Angew. Chem.* **104,** 1689–1691 (1992); *Angew. Chem., Int. Ed. Engl.* **31,** 1613–1615 (1992).
16. G. Hagen and H. Mayr. *J. Am. Chem. Soc.* **113,** 4954–4961 (1991).
17. (a) R. A. McClelland. *Organic Reactivity: Physical and Biological Aspects,* pp. 301–319. The Royal Society of Chemistry, Cambridge (1995); (b) R. A. McClelland, V. M. Kanagasabapathy, N. Banait and S. Steenken. *J. Am. Chem. Soc.* **111,** 3966–3972 (1989).
18. J. Bartl, S. Steenken and H. Mayr. *J. Am. Chem. Soc.* **113,** 7710–7716 (1991).
19. R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait and S. Steenken. *J. Am. Chem. Soc.* **114,** 1816–1823 (1992).
20. R. A. McClelland, V. M. Kanagasabapathy and S. Steenken. *J. Am. Chem. Soc.* **110,** 6913–6914 (1988).
21. H. Mayr, N. Basso and G. Hagen. *J. Am. Chem. Soc.* **114,** 3060–3066 (1992).
22. N. Basso, S. Görs, E. Popowski and H. Mayr. *J. Am. Chem. Soc.* **115,** 6025–6028 (1993).
23. H. Mayr and N. Basso. *Angew. Chem.* **104,** 1103–1105 (1992); *Angew. Chem., Int. Ed. Engl.* **31,** 1046–1048 (1992).
24. H. Mayr, M. Roth and G. Lang. *Kinetics of Carbocationic Polymerizations: Initiation, Propagation, and Transfer Steps* in *Cationic Polymerization, Fundamentals and Applications,* edited by T. D. Shaffer and R. Faust, ACS Symposium Series, No. 665, pp. 25–40. American Chemical Society, Washington, DC (1997).
25. M. A. Funke and H. Mayr. *Chem. Eur. J.* **3,** 1214–1222 (1997).
26. H. Mayr, R. Schneider and C. Schade. *Makromol. Chem., Macromol. Symp.* **13/14,** 43–59 (1988).
27. H. C. Brown and Y. Okamoto. *J. Am. Chem. Soc.* **80,** 4979–4987 (1958).
28. (a) L. M. Stock and H. C. Brown. *Adv. Phys. Org. Chem.* **1,** 35–154 (1963); (b) O. Exner. *Org. React. (Tartu)* **21,** 3–26 (1984).
29. (a) S. J. Formosinho. *J. Chem. Soc., Perkin Trans. 2* 839–846 (1988); (b) B. Giese. *Acc. Chem. Res.* **17,** 438–442 (1984); (c) R. Ta-Shma and Z. Rappoport. *J. Am. Chem. Soc.* **105,** 6082–6095 (1983); (d) C. D. Johnson and B. Stratton. *J. Chem. Soc., Perkin Trans. 2* 1903–1907 (1988); (e) A. Pross. *Adv. Phys. Org. Chem.* **14,** 69–132 (1977); (f) R. Huisgen. *Angew. Chem.* **82,** 783–794 (1970); *Angew. Chem. Int. Ed. Engl.* **2,** 751–762 (1970); (g) J. E. Leffler and E. Grunwald. *Rates and Equilibria of Chemical Reactions*. Wiley, New York (1963); (h) W. P. Jencks. *Chem. Rev.* **85,** 511–527 (1985); (i) I. Lee. *Chem. Soc. Rev.* **19,** 317–333 (1990).
30. (a) O. Exner. *J. Chem. Soc., Perkin Trans. 2* 973–979 (1993); (b) E. Buncel and H. Wilson. *J. Chem. Educ.* **64,** 475–480 (1987); (c) B. Giese. *Angew. Chem.* **89,** 162–173 (1977); *Angew. Chem., Int. Ed. Engl.* **16,** 125–136 (1977); (d) R. Taylor. *Electrophilic Aromatic Substitution,* pp. 479–481. Wiley, Chichester (1990); (e) J. P. Richard. *Tetrahedron* **51,** 1535–1573 (1995).
31. (a) E. M. Arnett and K. Molter. *J. Phys. Chem.* **90,** 383–389 (1986); (b) E. M. Arnett and K. E. Molter. *Acc. Chem. Res.* **18,** 339–346 (1985); (c) J. P. Richard, T. L. Amyes and T. Vontor. *J.*

Am. Chem. Soc. **114,** 5626–5634 (1992); (d) P. Denton and C. D. Johnson. *J. Chem. Soc., Perkin Trans. 2* 477–481 (1995).
32. M. Roth and H. Mayr. *Angew. Chem.* **107,** 2428–2430 (1995); *Angew. Chem., Int. Ed. Engl.* **34,** 2250–2252 (1995).
33. H. Mayr and G. Gorath. *J. Am. Chem. Soc.* **117,** 7862–7868 (1995).
34. Further kinetic data on alkoxy-substituted carbenium ions: (a) S. Steenken, J. Buschek and R. A. McClelland. *J. Am. Chem. Soc.* **108,** 2808–2813 (1986); (b) S. Steenken and R. A. McClelland. *J. Am. Chem. Soc.* **110,** 5860–5866 (1988); (c) S. Steenken and R. A. McClelland. *J. Am. Chem. Soc.* **111,** 4967–4973 (1989); (d) T. L. Amyes and W. P. Jencks. *J. Am. Chem. Soc.* **111,** 7888–7900 (1989); (e) V. Jagannadham, T. L. Amyes and J. P. Richard. *J. Am. Chem. Soc.* **115,** 8465–8466 (1993); (f) R. A. McClelland, K. M. Engell, T. S. Larsen and P. E. Sørensen. *J. Chem. Soc., Perkin Trans. 2* 2199–2206 (1994).
35. H. Mayr, J. Henninger and T. Siegmund. *Res. Chem. Intermed.* **22,** 821–838 (1996).
36. (a) I. Stahl. *Chem. Ber.* **118,** 4857–4868 (1985); (b) I. Paterson and L. Price. *Tetrahedron Lett.* **22,** 2833–2836 (1981); (c) C. Westerlund. *Tetrahedron Lett.* **23,** 4835–4838 (1982); (d) I. Stahl. *Chem. Ber.* **118,** 1798–1808 (1985); (e) I. Stahl. *Chem. Ber.* **120,** 135–139 (1987).
37. L. A. P. Kane-Maguire, E. D. Honig and D. A. Sweigart. *Chem. Rev.* **84,** 525–543 (1984).
38. (a) K.-H. Müller. PhD Thesis, Technical University of Darmstadt (1997); (b) H. Mayr, K.-H. Müller and D. Rau. *Angew. Chem.* **105,** 1732–1734 (1993); *Angew. Chem., Int. Ed. Engl.* **32,** 1630–1632 (1993).
39. H. J. Dauben, Jr and D. J. Bertelli. *J. Am. Chem. Soc.* **83,** 497–498 (1961).
40. H. Mayr and D. Rau. *Chem. Ber.* **127,** 2493–2498 (1994).
41. O. Kuhn, D. Rau and H. Mayr. *J. Am. Chem. Soc.,* **120,** 900–907 (1998).
42. O. Kuhn. PhD thesis, Ludwig-Maximillians-Universität München (1998).
43. H. Mayr and R. Pock. *Chem. Ber.* **119,** 2473–2496 (1986).
44. (a) C. D. Ritchie and P. O. I. Virtanen. *J. Am. Chem. Soc.* **94,** 1589–1594 (1972); (b) C. D. Ritchie and D. J. Wright. *J. Am. Chem. Soc.* **93,** 2429–2432 (1971).
45. H. Zollinger. *Diazo Chemistry I.* VCH, Weinheim (1994).
46. S. M. Parmerter. *Org. React.* **10,** 1–142 (1959).
47. (a) H. Marxmeier and E. Pfeil. *Chem. Ber.* **97,** 815–826 (1964); (b) H. Marxmeier and E. Pfeil. *Liebigs Ann. Chem.* **678,** 28–38 (1964).
48. H. Mayr and K. Grimm. *J. Org. Chem.* **57,** 1057–1059 (1992).
49. H. Mayr, M. Hartnagel and K. Grimm. *Liebigs Ann. Chem.,* 55–69 (1997).
50. H. Mayr. *Fundamentals of the Reactions of Carbocations with Nucleophiles* in *Cationic Polymerizations: Mechanism, Synthesis, and Applications,* edited by K. Matyjaszewski, pp. 51–136. Marcel Dekker, New York (1996).
51. K. H. Meyer, A. Irschick and H. Schlösser. *Ber. Dtsch. Chem. Ges.* **47,** 1741–1755 (1914).
52. K. V. Auwers and F. Michaelis. *Ber. Dtsch. Chem. Ges.* **47,** 1275–1297 (1914).
53. H. Iwamoto, H. Kobayashi, P. Murer, T. Sonoda and H. Zollinger. *Bull. Chem. Soc. Jpn.* **66,** 2590–2602 (1993).
54. M. P. Doyle, J. K. Guy, K. C. Brown, S. N. Matrpatro, C. M. VanZyl and J. R. Pldziewicz. *J. Am. Chem. Soc.* **109,** 1536–1540 (1987).
55. M. Hartnagel, K. Grimm and H. Mayr. *Liebigs Ann. Chem.* 71–80 (1997).
56. H. Mayr and A. R. Ofial. *Tetrahedron Lett.* **38,** 3503–3506 (1997).
57. A. R. Ofial and H. Mayr. *Angew. Chem.* **109,** 145–147 (1997); *Angew. Chem., Int Ed. Engl.* **36,** 143–145 (1997).
58. H. Mayr and R. Pock. *Chem. Ber.* **119,** 2497–2509 (1986).