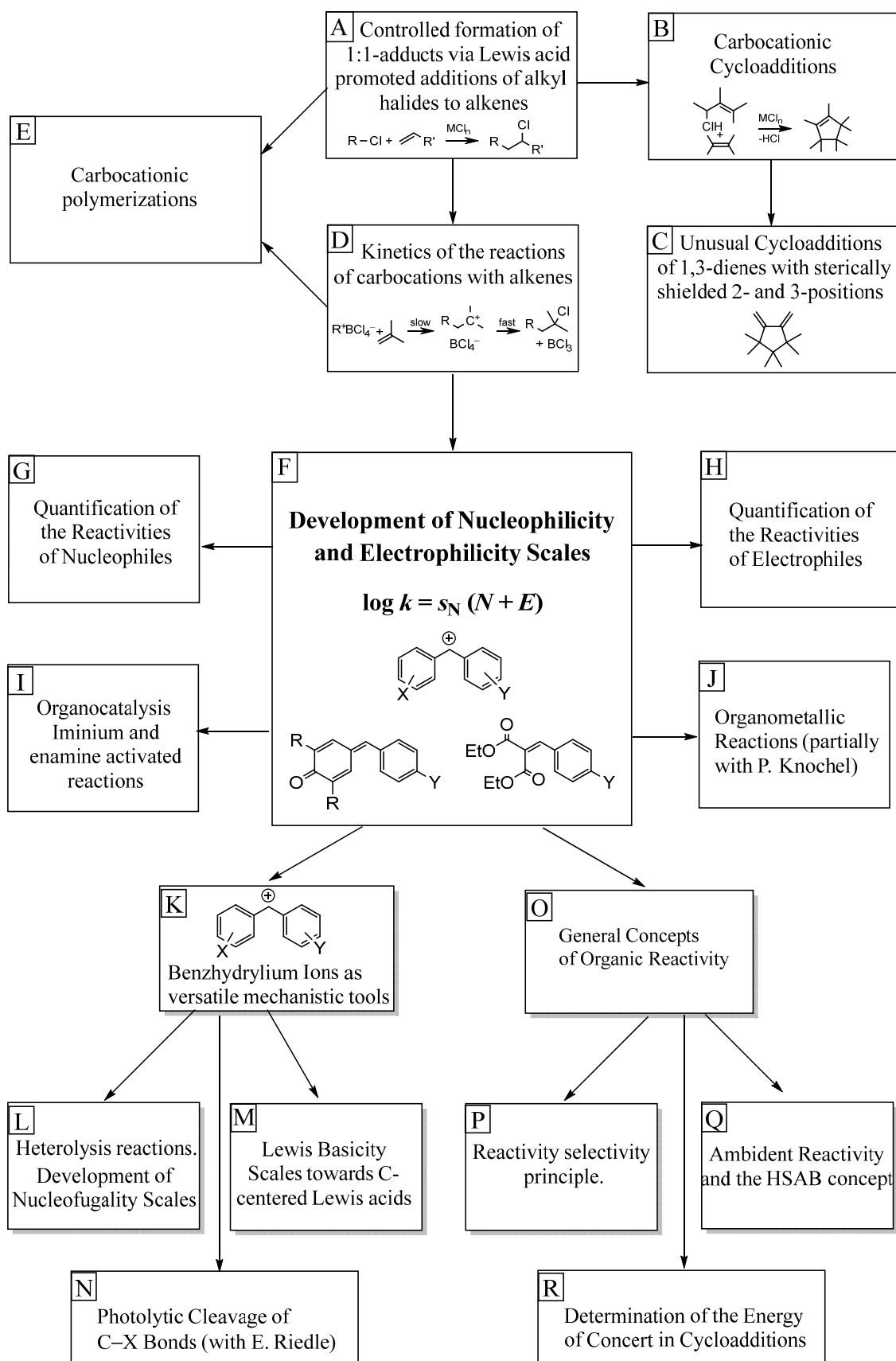


## Research in the Mayr Group 1976 – 2024



## Summary

While electrophilic substitutions of arenes (i.e., Friedel-Crafts reactions) had been a standard method in the toolbox of the organic chemist for more than a century, their aliphatic counterparts (Lewis acid catalysed reactions of alkyl halides with alkenes) played a minor role because of the competing carbocationic polymerizations. A breakthrough in this field was our 1981 discovery that the selective formation of (1:1)-products is possible, when the reactants R-X ionize more readily than the adducts R-C-C-X. Based on this principle, scope and limitations of aliphatic Friedel-Crafts reactions were demonstrated (**A**) and used for designing Lewis acid catalysed reactions of allyl- and propargyl halides with alkenes. These reactions provided a straightforward access to 4 – 7-membered carbocycles via cycloadditions of the intermediate allyl and propargyl cations (**B**). The highly methylated cyclopentenones accessible by this method were used for the investigation of cycloaddition mechanisms (**C**).

Based on the insights of part (**A**), kinetic methods were developed which for the first time provided rate constants for the attack of carbocations at aliphatic and aromatic  $\pi$ -systems (**D**). With these methods initiation, propagation, and termination rate constants of carbocationic polymerizations have been determined (**E**).

The kinetic methods developed in (**D**) were used for studying the kinetics of the reactions of  $C_{sp^2}$  electrophiles (carbocations and Michael acceptors) with a large variety of well-behaved  $C_{sp^2}$ -nucleophiles. It was shown that the measured rate constants can be expressed by the equation  $\log k_{20^\circ C} = s_N(N + E)$ , where electrophiles are characterized by one parameter ( $E$ ) and nucleophiles by two solvent-dependent parameters  $N$  and  $s_N$  (**F**). This equation also holds for reactions of heteronucleophiles and heteroelectrophiles if the reactive center of the reaction partner is carbon. By correlation analysis, scales of nucleophilicity (> 1300 entries, **G**) and electrophilicity (> 350 entries, **H**) were created, which are freely accessible through <http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html> and allow the prediction of rate constants for electrophile nucleophile combinations with a precision of factor 10 – 100, which is quite remarkable in view of the wide structural variety of substrates and the 40 orders of magnitude (from nanoseconds to 100 000-times the age of the universe) covered by these scales. This precision is sufficient for synthetic chemists to check whether projected reactions have a chance to take place (have sufficient rates) and to predict selectivities (which of several competing processes is preferred) of polar reactions. Particular attention was paid to topics of current interest, as catalysts and intermediates of organocatalytic cycles (**I**), nucleophilicities of organoborates and ylides (**G**), as well as electrophilicities of common fluorinating N-F reagents (**H**).

Benzhydrylium ions with substituents in 4- and 3-position, which have widely differing demand of electrons while their steric requirements are almost the same, have also been used as references for the construction of nucleofugality and Lewis basicity scales (**K**, **L**, **M**). Equilibrium constants for the reactions of benzhydrylium ions provided a Lewis basicity scale with respect to C-centered Lewis acids (cover page in JACS), which was suggested by Jack

Hine in 1965, but has not been realized before. Correlations of rate with equilibrium constants revealed variable Marcus intrinsic barriers as origin for the breakdown of linear free energy relationships (**L**, **M**). Thus high intrinsic barriers were found to account for the counterintuitive observation that vinyl cations are weak electrophiles, i.e., react slowly with nucleophiles, in contrast to the expectation based on the low  $S_N1$  reactivities of vinyl derivatives (**H**, **L**). Solvolysis reactions were designed which allowed “carbocation watching”, i.e., solvolyses where fast ionizations lead to visible concentrations of colored carbocations, which subsequently undergo slow reactions with the solvent. Evidence was provided that  $S_N1$  and  $S_N2$  reactions are not extremes of a continuum, but distinct processes which may coexist side by side. The borderline between both mechanisms has been derived from the corresponding reactivity scales (**L**). Femtosecond spectroscopy revealed that photolyses of benzhydryl halides and phosphonium salt proceed with homolytic and heterolytic bond cleavage yielding benzhydryl radicals and ions. The initially formed radicals may undergo electron transfer to give the benzhydryl cations, which were investigated by nanosecond spectroscopy (**N**).

By combining different kinetic methods (conventional UV-Vis spectroscopy, stopped flow, and laser flash techniques) Gibbs energy relationships of unprecedented lengths became available, which allowed to examine some allegedly general concepts of Organic Reactivity (**O**). It was found that rate equilibrium correlations stay linear up to rate constants of  $10^8 \text{ Lmol}^{-1}\text{s}^{-1}$  and do not even bend when the enthalpy of activation becomes zero, and enthalpy control is replaced by entropy control. These observations confirm that Leffler’s  $\alpha$  is not an indicator of the position of the transition state. It was demonstrated why the Reactivity Selectivity Principle cannot be a general rule (**P**) and that the Klopman-Salem “Concept of Charge and Frontier Orbital Control” does not even properly predict ambident reactivity while Marcus theory does (**Q**).

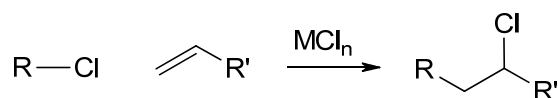
The rates of stepwise cycloadditions via zwitterionic intermediates can be predicted from the nucleophilicity and electrophilicity parameters from **D-G**. As a consequence the energy of concert of concerted cycloadditions equals the difference between the experimentally observed rate constants and those calculated for the formation of zwitterionic intermediates (**R**).

## Research Topics

Numbers in the following text refer to the list of publications: <http://www.cup.uni-muenchen.de/oc/mayr/CDpublika.html>

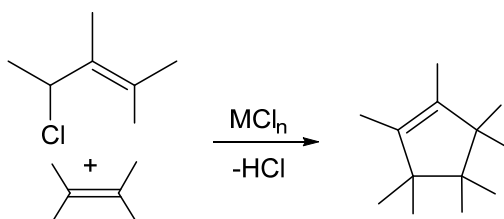
### A. Aliphatic Friedel-Crafts Reactions

Lewis acid induced reactions of alkyl halides with alkenes may either yield 1:1 adducts or lead to polymers. In the early 1980s, rules were developed how to selectively produce [1:1]-adducts and avoid the formation of polymers (# 19, 34, 75, 119, 120): When catalytic amounts of Lewis acids are employed, the reactant  $RX$  must ionize more readily than the product  $R-C-C-X$ . With stoichiometric quantities of strong Lewis acids, this rule must be reversed (# 67, 100)



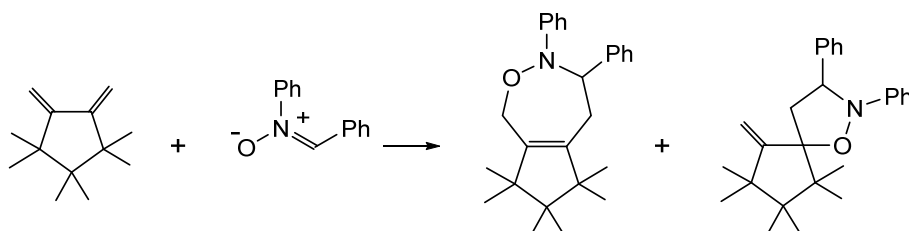
### B. Carbocationic Cycloadditions

The rules developed in **A** were employed to realize carbocationic cycloadditions. Selective formations of 4-, 5-, 6-, and 7-membered carbocycles were achieved by Lewis acid catalyzed reactions of propargyl and allyl halides with alkenes and 1,3-dienes (# 17, 18, 20, 29-33)



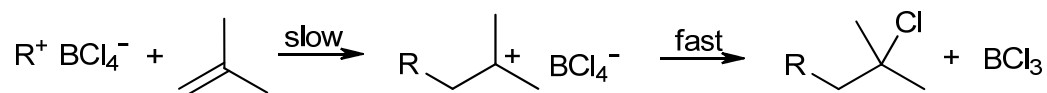
### C. Unusual Cycloadditions

Octamethylcyclopentene, synthesized as described in **B**, was transformed into a *s-cis* fixed 1,3-diene with sterically shielded 2- and 3-positions. The investigation of unusual cycloadditions of this diene (review # 106), e.g. [4+3]-cycloadditions of nitrones (# 65, 94), [4+1]-cycloadditions of carbenes (# 43), [4+2]-cycloadditions of ketenes (# 69), [4+3]-cycloadditions of 2-azaallyl anions (# 117), and noncatalyzed [4+4]-cyclodimerizations of 1,4-dienes (# 93) gave insight in the “concertedness” of various cycloadditions.



#### D. Kinetics of the Reactions of Carbocations with Alkenes

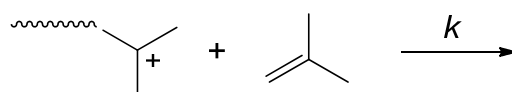
The rules developed in A were used to develop a kinetic method for determining the rates of attack of carbocations at CC-double bonds.



Though this type of reaction represents the key-step of many transformations in organic and macromolecular chemistry as well as in biochemistry, prior to our work, rate constants for such processes were essentially unknown. Three communications in *Angewandte Chemie* (# 47, 56, 57) and three back to back full papers in *J. Am. Chem. Soc.* (# 95, 96, 97) changed this situation abruptly. Nowadays, hundreds of rate constants, mostly by us, are available, and electrophilic alkylations of alkenes are now among the best understood CC-bond forming reactions (# 100).

#### E. Carbocationic Polymerizations

The methods developed in A and D were used in Macromolecular Chemistry for designing initiators, coinitiators, and comonomers in carbocationic polymerizations (# 137, 152, 157, 186, 206). As reviewed by Puskas (*J. Polymer Science: Part A: Polymer Chem.* **2005**, 43, 5394) our work changed the previously accepted value for the propagation rate constant of cationic isobutylene polymerization by several orders of magnitude. The diffusion-clock method, a well-established tool in Physical Organic Chemistry, was introduced into Macromolecular Chemistry (# 140) and has been used for determining numerous propagation rate constants (Faust et al.).



#### F. Nucleophilicity and Electrophilicity Scales

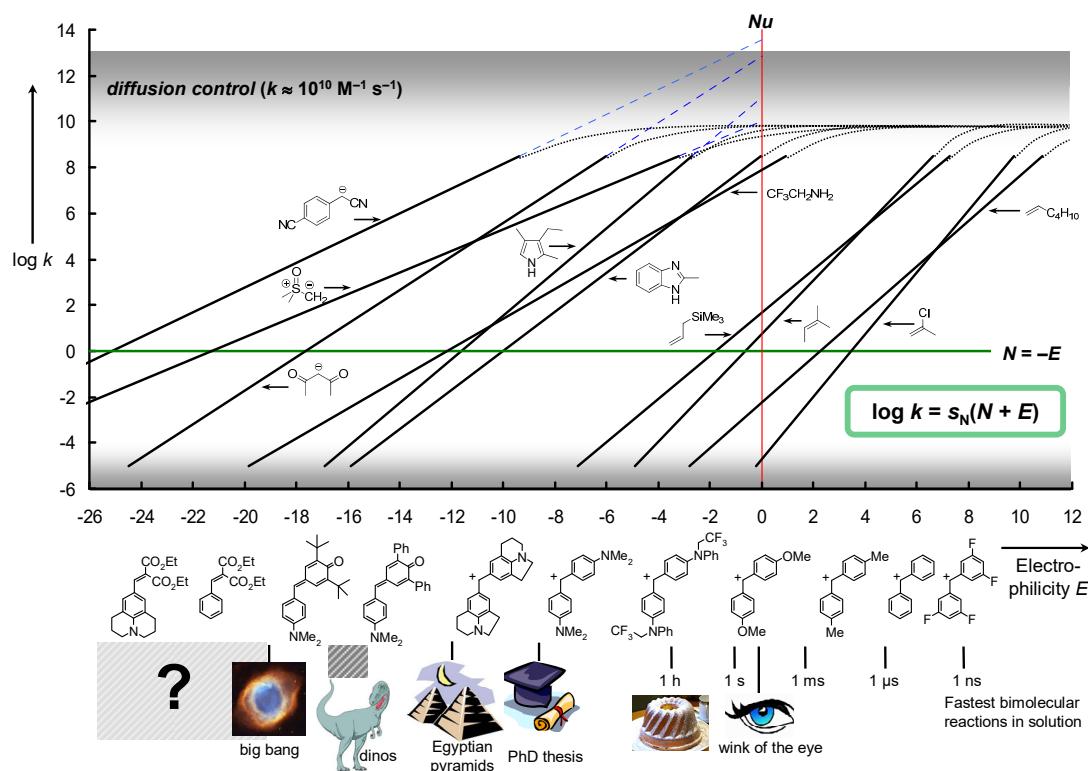
The kinetic methods developed in D were employed to determine rate constants for the reactions of carbon-centered nucleophiles with carbon-centered electrophiles. By using para- and meta-substituted benzhydrylium ions, as well as structurally related quinone methides and benzylidene malonates as reference electrophiles (# 261, 271, 374), which have similar steric demand and cover a reactivity range of more than 30 orders of magnitude, it has become possible to generate the most comprehensive nucleophilicity scale, presently available (reviews: # 124, 191, 219, 250, 262). Analogously, alkenes, allylsilanes, silylated enol ethers,

secondary carbanions, and structurally related C-nucleophiles (#180, 183) have been used as reference nucleophiles for characterizing the reactivities of electrophiles.

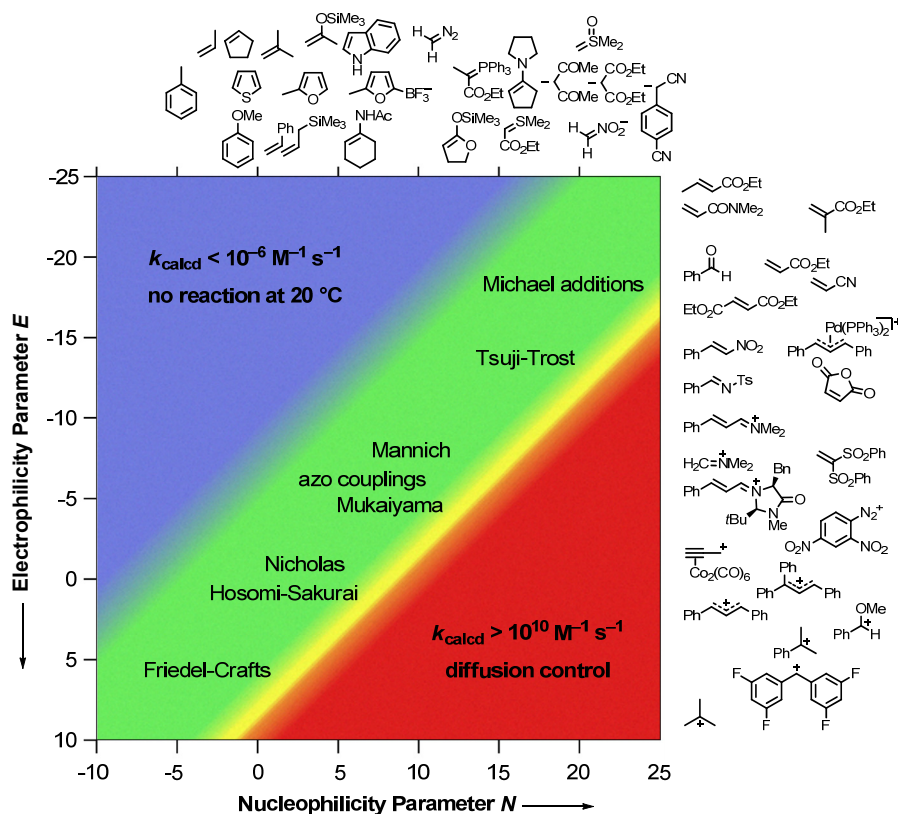
It has been shown that equation 1, where electrophiles are characterized by one parameter ( $E$ ) and nucleophiles are characterized by the solvent-dependent nucleophilicity parameter  $N$  and the nucleophile-specific sensitivity parameter  $s_N$  can be used to predict absolute rate constants with an accuracy of factor 10 – 100 in an overall reactivity range of 40 orders of magnitude.

$$\log k_{20^\circ} = s_N (N + E) \quad (1)$$

For qualitative analyses, the sensitivity factor  $s_N$  can be neglected, and as a rule of thumb one can expect electrophile-nucleophile combinations to take place at room temperature if  $(N + E) > -5$ . Since diffusion limit is reached at  $k = 10^9 - 10^{10} \text{ M}^{-1}\text{s}^{-1}$ , chemo-, regio- and stereoselectivity often break down when  $(N + E) > 10$ . As a consequence, most synthetically used reactions are found in the green corridor of Figure 2.



**Figure 1.** Rate constants for Electrophile-Nucleophile Combinations



**Figure 2.** Where to find synthetically useful reactions

Open access to our database of electrophilicity and nucleophilicity parameters is provided at <http://www.cup.lmu.de/oc/mayr/DBintro.html>.

Poster presentations of our reactivity scales which can be used for synthesis planning can be downloaded (<http://www.cup.lmu.de/oc/mayr/CDmayrPoster.html>).

## G. Quantification of the Reactivities of Nucleophiles

Apart from species which were used for establishing the reactivity scales (Section F), we have studied the nucleophilic reactivities of arenes (# 114, 163, 234, 417), allyl-, hetaryl- and vinylsilanes (#105, 177, 358), organoborates (# 318, 346, 370, 372), N-heterocyclic carbenes (# 308, 329), P-, S-, N-, I-ylides (# 264, 293, 299, 357, 386), stabilized carbanions (# 213, 229, 238, 263, 347, 378, 389, 391, 392), isocyanides (# 236), diazoalkanes (# 196, 425), and most recently, mesoionic N-heterocyclic olefins (# 427). The reference electrophiles used for the characterization of C-nucleophiles were analogously used for the characterization of heteronucleophiles as hydride donors (#319, 339, 363), alcohols (# 209), alkoxides (# 224), carboxylates (# 248), peroxides (# 396), phosphines (# 214), dialkyl sulphides (# 416) and a large variety of N-nucleophiles mentioned in Section I (review #429) as well as nucleobases (# 316).

## H. Quantification of the Reactivities of Electrophiles

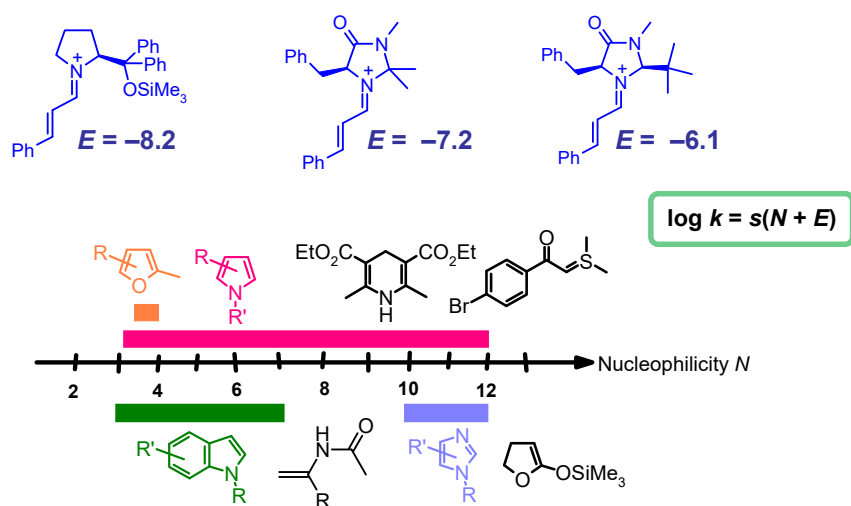
Unlike the situation in **G**, where colored benzhydrylium ions, quinone methides and benzylidene malonates with similar steric demand and widely differing electrophilicities were used as reference compounds, we could not establish a homogeneous set of reference nucleophiles for the quantification of electrophilic reactivities. For that reason, the determination of electrophilicity parameters  $E$  is less straightforward than the characterization of nucleophiles. In order to exclude anomeric effects, only C-nucleophiles, preferentially allylsilanes, silylated enol ethers, secondary carbanions, and various ylides with small steric demand were used as reference nucleophiles. Apart from benzhydrylium ions, 1,3-diaryl-allyl cations (# 314), tritylium ions (# 311, 332 hydride donors as references), ordinary Michael acceptors (# 315, 324, 359, 380, 395), ketones (# 400), heteroallenes (# 412), diazonium ions (# 145), diazoalkanes (# 421), and azo dicarboxylates (# 295) were characterized. Electrophilicity parameters  $E$  were also accessible for N-F fluorinating agents (# 402),  $\text{CF}_3\text{S}$  transfer agents (# 401), and Umemoto's trifluoromethylating agents (# 428). For including  $\text{S}_{\text{N}}2$  reactions, equation (1) must be expanded by an additional electrophile-specific susceptibility factor  $s_{\text{E}}$  (# 231).

Though some reactions of quinones with  $\pi$ -nucleophiles were found to proceed via inner sphere electron transfer processes, the rate constants of the reactions of DDQ and halogen-substituted quinones with amines and  $\pi$ -nucleophiles were found to follow eq. (1), which allowed us to define the synthetic potential of quinones (# 355, 364). Different pathways for hydride abstractions from C-H, B-H, and Sn-H groups by DDQ were established (# 365).

## I. Nucleophilic Organocatalysis (Reviews #334, 429)

The key-steps in many organocatalytic cycles are electrophile-nucleophile combinations as investigated in part **F**. Benzhydrylium ions and structurally related quinone methides have been employed to compare nucleophilicities ( $k$ ) and Lewis basicities of tertiary amines (# 239, 275, 287), pyrrolidines and imidazolidinones (# 409) pyridines (# 235, 302), amidines (# 255), guanidines (#328), isothiourea derivatives (# 309, 320), and phosphines (# 214), i. e., nucleophilic organocatalysts. We have also determined reactivity parameters of intermediates, e. g. iminium ions (# 260, 310, 349, 361) or enamines (# 195, 295, 325, 326), as well as of potential substrates of iminium and enamine activated reactions. Since nucleophilic substrates suitable for iminium activated reactions must react fast with iminium ions, but not with the precursor carbonyl compounds, nucleophiles with  $3 < N < 12$  (Figure 3) appear to be the most suitable substrates (# 290, 334). Particular attention has been paid to the unique reactivities of N-heterocyclic carbenes (# 308) and the resulting intermediates (# 329, 333, 353).



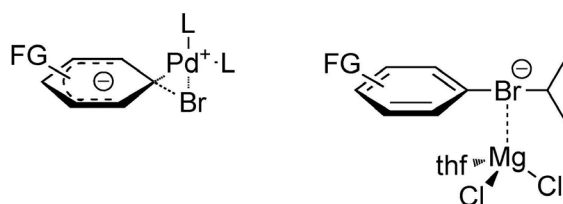


Nucleophiles must be strong enough to react with iminium ions and weak enough not to react with the precursor carbonyl compounds.

**Figure 3.** Nucleophiles suitable for iminium activated reactions

## J. Organometallic Reactions

Following the standard methods used in sections **F**, **G**, **H**, nucleophilic (#180, 191, 383) as well as electrophilic transition metal complexes (# 191, 322) have been characterized. In collaboration with the Knochel group, we have investigated structure-reactivity relationships in organometallic reactions. Competition experiments on magnesium/halide exchange reactions in haloarenes with *i*PrMgCl–LiCl (# 246, 269, 274) and in Negishi cross-couplings (# 279) have revealed the different transition states in the corresponding metallation steps (Figure 4); furthermore, we have quantified the difference in reactivity between carbanions and organometallics (#371).



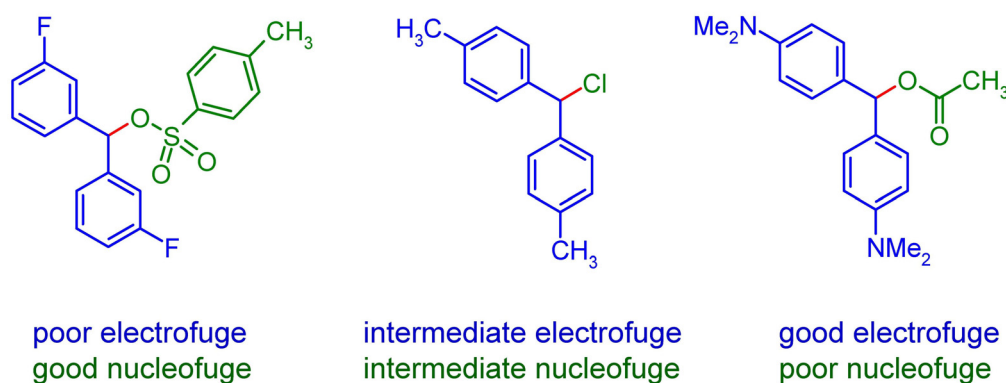
**Figure 4.** Comparison of the transition states of the oxidative addition of  $\text{PdL}_2$  and of the Br–Mg exchange with *i*PrMgCl·LiCl.

## K. Benzhydrylium ions as Versatile Mechanistic Tools

The unique role, benzhydrylium ions have played for the construction of nucleophilicity scales (**F**, **G**) suggested to use them also as reference electrofuges (**L**), as reference Lewis acids (**M**), and tools for the mechanistic study of photolytic cleavage of C–X bonds (**N**).

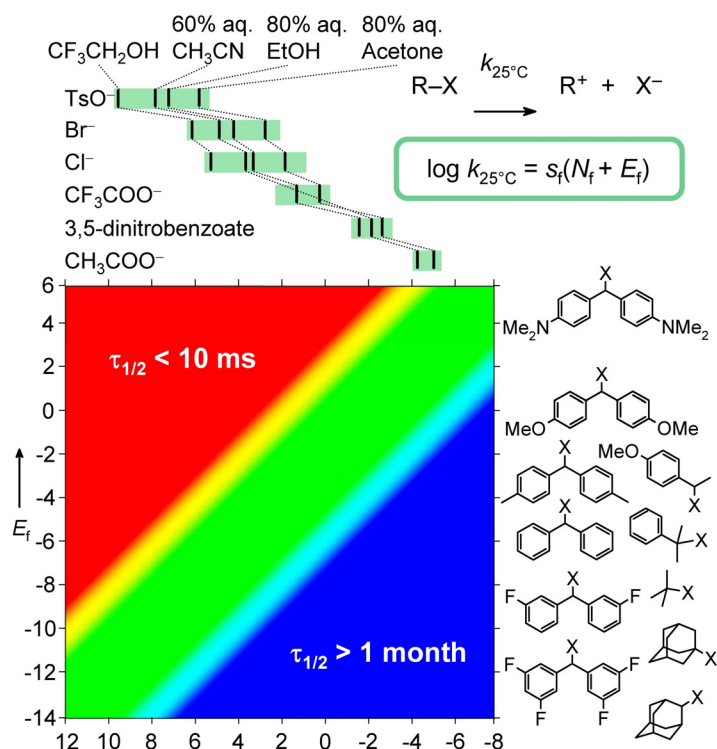
## L. Heterolytic Cleavages: The $S_N1$ – $S_N2$ -Spectrum

The method of overlapping correlation lines, which allowed us to develop the comprehensive nucleophilicity and electrophilicity scales in section F, has analogously been employed to develop nucleofugality scales (leaving group abilities) (# 300). Solvolysis rate constants of combinations of poor electrofuges with good nucleofuges as well as of good electrofuges with poor nucleofuges (Figure 5) have been determined to provide a semiquantitative scheme of heterolysis rates (Figure 6).



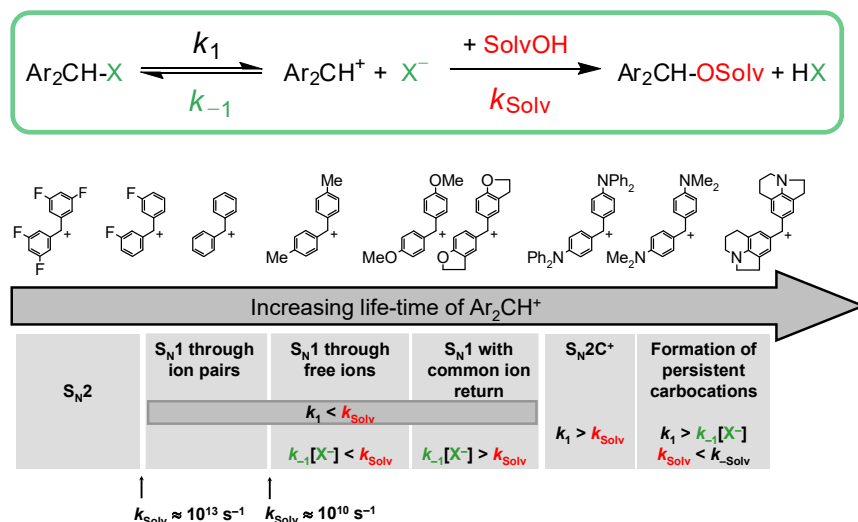
**Figure 5.** Electrofuge-nucleofuge combinations which dissociate with measurable rates

By developing a stopped-flow technique, which allows one to investigate solvolysis rate constants in the millisecond time scale (# 248), we have almost doubled the width of the green corridor of Figure 6, which indicates the experimentally accessible range for investigating rates of heterolytic cleavages. It was shown that differences in intrinsic barriers do not only account for the well-known fact that nucleofugality is not the inverse of nucleophilicity, but also for the observation that electrofugality is not the inverse of electrophilicity (# 248, 343). Thus high intrinsic barriers account for the counterintuitive observation that vinyl cations are weak electrophiles, in contrast to the expectation based on the low  $S_N1$  reactivities of vinyl derivatives (# 390).



**Figure 6.** A practical guide for estimating rates of heterolysis reactions

As illustrated in Figure 7, it has become possible to quantitatively predict the mechanistic change from  $\text{S}_{\text{N}}2$  reactions over ordinary  $\text{S}_{\text{N}}1$  reactions with and without ion return to heterolytic cleavages with formation of persistent carbocations (# 272, 268). Studies with chiral allyl derivatives allowed us to derive rate constants for internal and external ion-pair recombination (# 341).



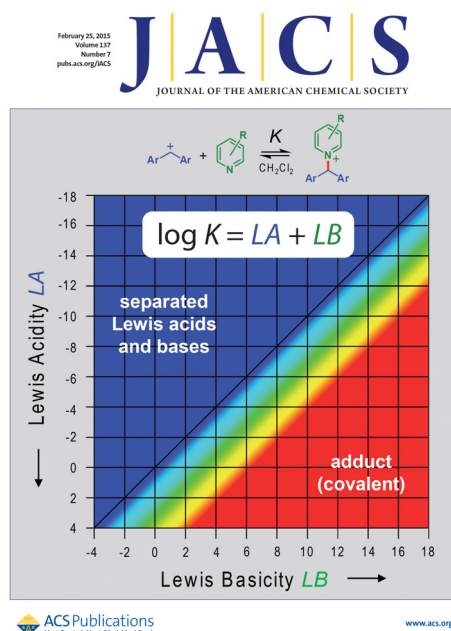
**Figure 7.** Changing Solvolysis Mechanisms

The newly developed methods have also been employed for studying solvolysis rates of trityl derivatives, which have only rarely been studied before because of the high rates of these

heterolyses. Winstein-Grunwald *m*-values between 0.2 and 0.6 have been measured for these S<sub>N</sub>1 reactions, showing that *m*-values cannot be used as a criterion to differentiate between S<sub>N</sub>1 and S<sub>N</sub>2 mechanisms (review # 332, 426).

## M. Lewis Basicities

The widely varying stabilization of *m*- and *p*-substituted benzhydrylium ions, which made them suitable reference electrophiles for the construction of nucleophilicity scales (Section F) and reference electrofuges for the construction of nucleofugality scales (Section L) has also been used for the construction of Lewis basicity scales with respect to C-centered Lewis acids of equal steric shielding (Figure 8, #369). Hine's concept of "Carbon basicity" developed in JACS 1965, 87, 3387 thus found a broad experimental basis, which can be used for a systematic analysis of rate-equilibrium relationships.



**Figure 8.** Frontispiece of Feb. 25, 2015 issue of the Journal of the American Chemical Society.

## N. Photolytic Cleavage of C-X Bonds

Photolysis of benzhydryl halides and phosphonium ions generally leads to mixtures of radicals Ar<sub>2</sub>CH· and carbocations Ar<sub>2</sub>CH<sup>+</sup>. The efficiency and mechanism of the photocleavage were studied by nanosecond laser flash photolysis and femtosecond spectroscopy. The radical/carbocation ratio depends on the photoelectrofuge (Ar<sub>2</sub>CH), the photonucleofuge (X), the counterion (in case of onium precursors), and the solvent (# 331). As electron transfer interconverts radicals and carbocations during the first nanoseconds (#344), the

radical/carbocation ratio observed by nanosecond spectroscopy does not reflect the real ratio of homolytic vs. heterolytic bond cleavage. Recipes, how to obtain an optimal ratio of carbocations on the nanosecond time-scale have been summarized (review # 351).

## **O. General Concepts of Organic Chemistry.**

The availability of reaction series of unprecedented lengths ranging from slow reactions on the hour time-scale to the diffusion limit revealed inadequacies of several common concepts of Organic Chemistry, which are specified in Sections **P**, **Q**, and **R**.

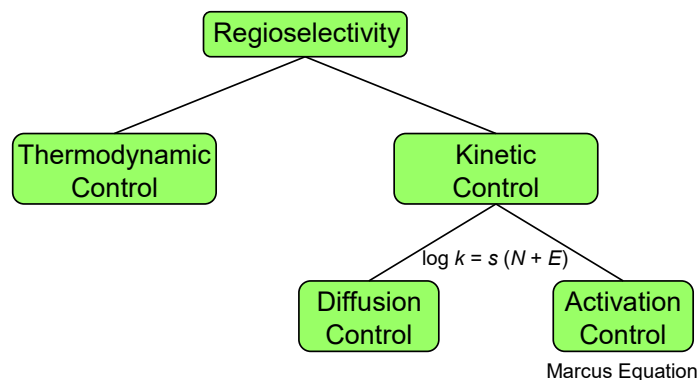
## **P. Reactivity-Selectivity-Principle**

Though the reactivity selectivity principle had been abandoned as a general rule through the work of several authors in the 1970s, many chemists still believe that it is generally applicable rule, violated just by a few exceptions. In a review, we have shown why it is impossible that selectivity generally decreases with increasing reactivity and in which cases a decrease of selectivity with increasing reactivity can reliably be expected (# 228).

## **Q. HSAB Treatment of Ambident Reactivity**

Experimental studies on the ambident reactivities of  $\text{SCN}^-$  (# 204),  $\text{CN}^-$  (# 215),  $\text{NO}_2^-$  (# 221),  $\text{OCN}^-$  (# 256),  $\text{PhSO}_2^-$  (# 283), pyridone anions (# 297), hydrazines (# 317), hydrazones (# 356), and phenolates (# 407) showed that the “principle of hard and soft acids and bases” or the related Klopman-Salem concept of “frontier- and charge controlled reactions” does not even correctly describe the regioselectivities of the prototypes of ambident nucleophiles. In a quantum chemical investigation we have demonstrated that a consistent description of activation-controlled reactions can be based on Marcus theory (# 288).

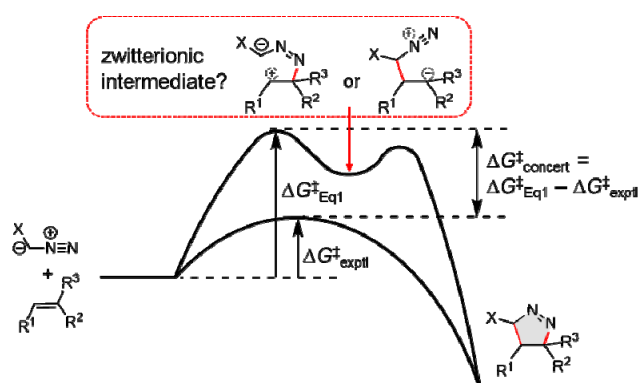
An extensive review on ambident reactivity provides a consistent analysis of ambident reactivity on the basis of Figure 9 and notes that PMO theory is often incorrectly applied to diffusion-controlled reactions of ambident anions with carbocations, i. e., barrier-less reactions which do not pass through a transition state (review # 305).



**Figure 9.** A systematic analysis of ambident reactivity.

### R. Energy of Concert in Cycloadditions

Equation (1) in Section F is only applicable to reactions of electrophiles with nucleophiles, when one and not more than one new bond is formed in the rate-determining step. It cannot be applied to multibond reactions, e. g., concerted cycloadditions. Rates of stepwise 1,3-dipolar cycloadditions via ionic or zwitterionic intermediates, which undergo fast subsequent cyclizations, have been shown to be predictable by equation (1), however (# 357, 403, 414), and in case of concerted cycloadditions of diazoalkanes with Michael acceptors the relative reactivities follow the electrophilicity parameters  $E$  of the dipolarophiles. Figure 10 shows how the comparison of the observed cycloaddition rate constants with the rate constants calculated for the formation of zwitterions can be used for measuring the degree of concertedness (# 425). Mechanisms of Diels-Alder reactions can analogously be analyzed (# 146, 171, 189).



**Figure 10.** Determination of the energy of concert by comparison of experimentally determined rate constants and rate constants calculated by equation (1).

Previous PMO treatments of diazoalkane cycloadditions have been revised because the role of  $\pi^*_{N=N}$ , the real LUMO of diazoalkanes, had been overlooked (# 419, 425).