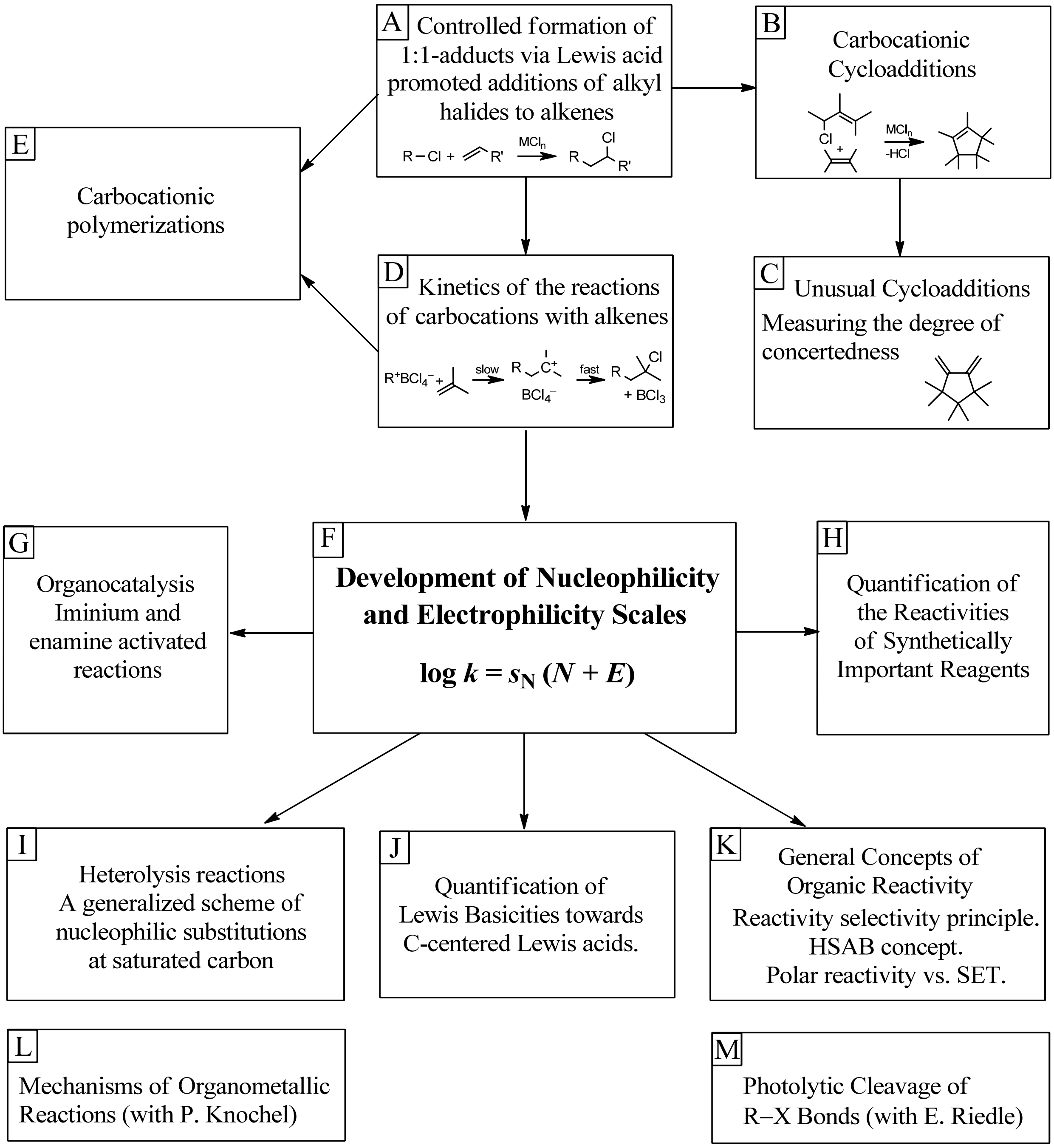
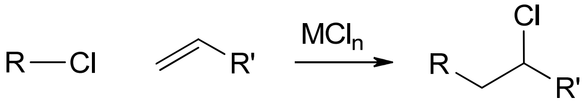
Summary of Research in the Mayr Group 1980 – 2015



A summary of research in the Mayr group has recently been published as a Perspectives Article (*Tetrahedron* **2015**, *71*, 5095-5111). References to original publications are given in the following overview.

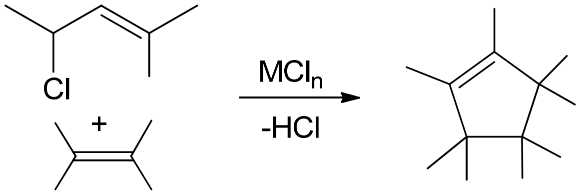
A. Aliphatic Friedel-Crafts Reactions

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): 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 (# 100, 136)



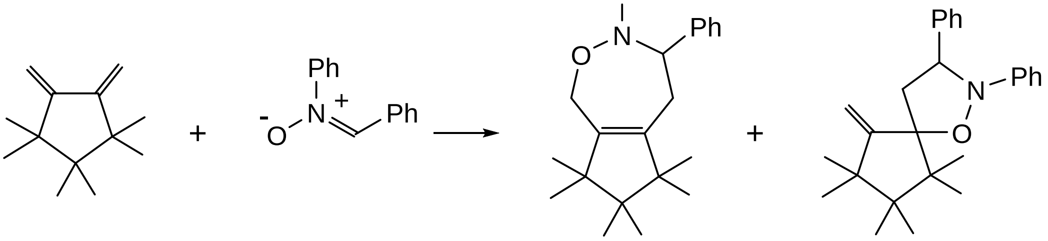
B. Carbocationic Cycloadditions

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)



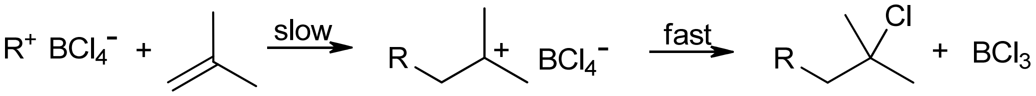
C. Unusual Cycloadditions

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

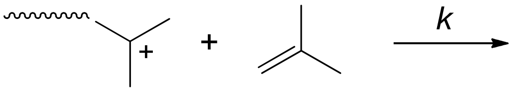
The rules developed in A were used to develop a kinetic method for determining the rates of attack of carbocations at CC-double bonds.



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 analogously employed to determine rate constants for the attack of carbocations and Michael acceptors at various C-nucleophiles (allylsilanes, allylstannanes, carbocyclic and heterocyclic arenes, enol ethers, enamines, enamides, diazoalkanes, metal-π-complexes, carbanions, isonitriles, ylides), hydride donors, halide and pseudohalide anions, N-nucleophiles (amines, pyridines, amide anions, azoles) as well as P-, O-, and S-nucleophiles. By defining benzhydrylium ions, quinone methides, and benzylidene malonates as reference electrophiles, which 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).

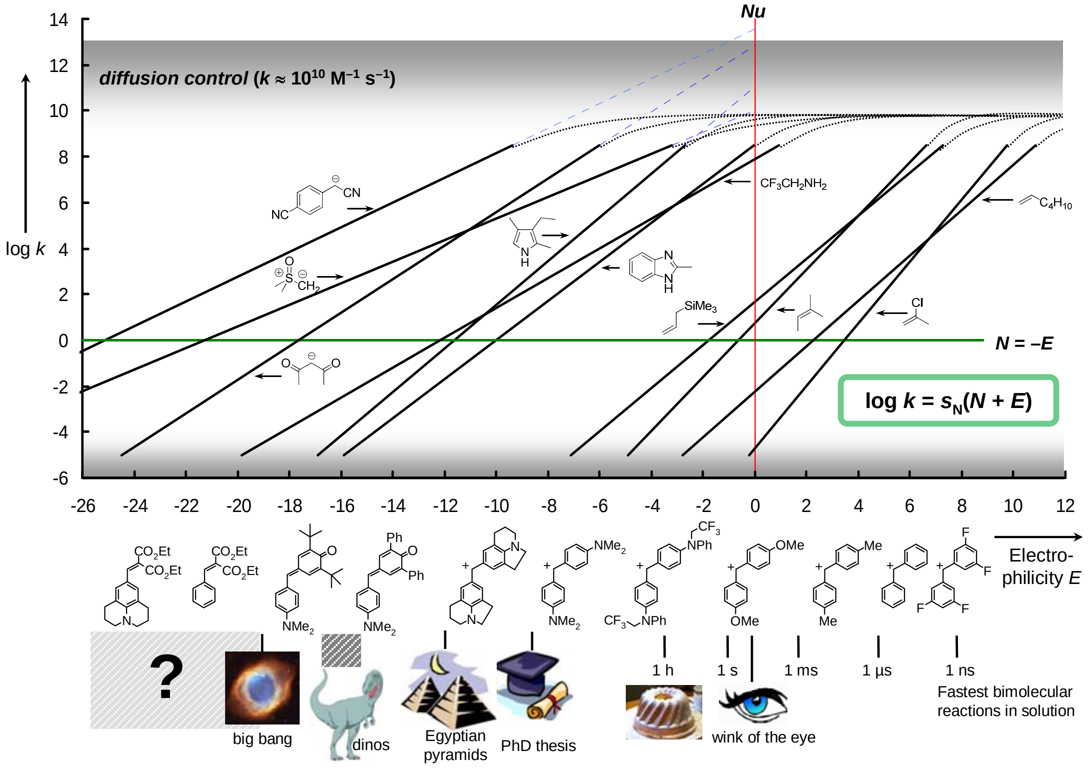


Figure 1. Rate constants for Electrophile-Nucleophile Combinations

It has been shown that equation 1, where electrophiles are characterized by one parameter (E) while 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.

$$\log k_{20°} = s_N (N + E) \qquad (1)$$

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 $k = 10^9 - 10^{10}$ $M^{-1}s^{-1}$, 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.

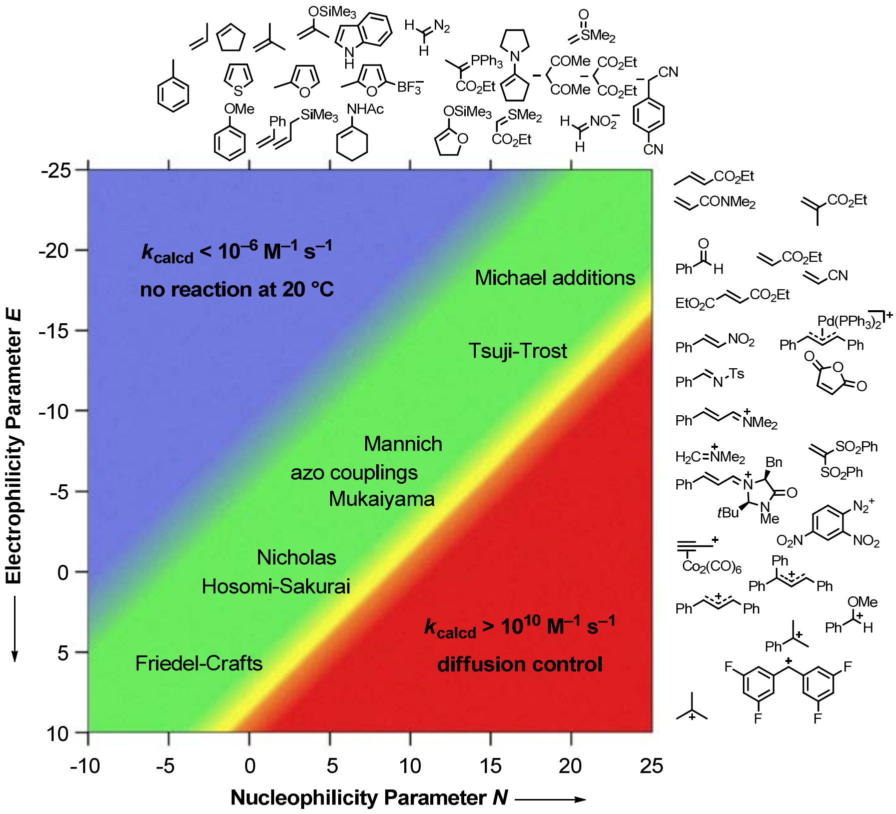


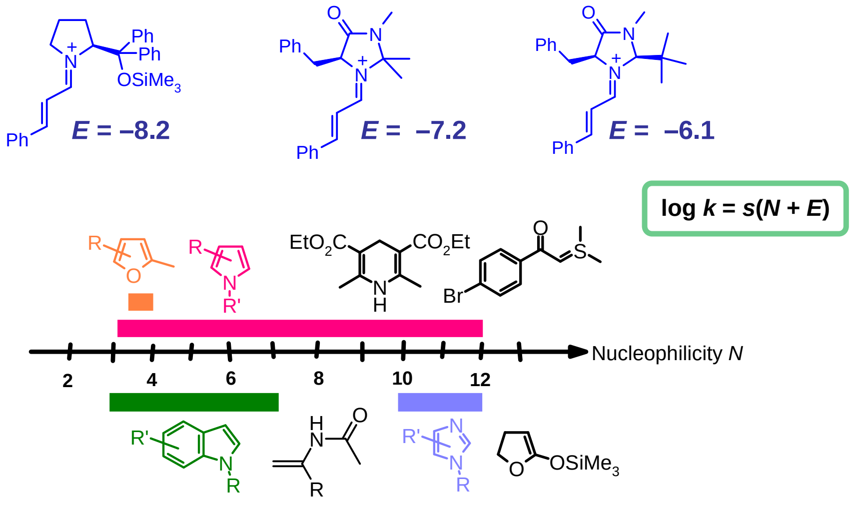
Figure 2. Where to find synthetically useful reactions

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. **Nucleophilic Organocatalysis** (Review #334)

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), 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 (# 270, 284, 295, 315, 321, 324, 356, 366). Since nucleophilic substrates suitable for iminium activated reactions must react fast with iminium ions, but not with the precursor carbonyl compounds, nucleophiles with $3 < N < 12$ 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

H. Quantification of the Reactivities of Synthetically Important Reagents

Apart from species which are relevant for organocatalytic processes (Section G), recent studies have focused on the nucleophilic reactivities of hydride donors (#319, 339, 363), nucleobases (# 316), P-, S-, N-ylides (# 264, 293, 299, 307, 357), allyl and vinylsilanes (and organoborates (# 318, 346, 370, 372) and the comparison with stabilized carbanions (#. Though some reactions of quinones with π-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 π-nucleophiles were found to follow eq. (1), which allows 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. 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). While it was already clear that nucleofugality is not the inverse of nucleophilicity, we have now found that differences in intrinsic barriers also account for the fact that electrofugality is not the inverse of electrophilicity (# 343).

Solvolysis rate constants of combinations of poor electrofuges with good nucleofuges as well as of good electrofuges with poor nucleofuges (Figure 4) have been determined to provide a semiquantitative scheme of heterolysis rates (Figure 5).

poor electrofuge
good nucleofuge

intermediate electrofuge
intermediate nucleofuge

good electrofuge
poor nucleofuge

Figure 4. 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 5, which indicates the experimentally accessible range.

As illustrated in Figure 6, it has become possible to quantitatively predict the mechanistic change from S_N2 reactions over ordinary S_N1 reactions with and without ion return to heterolytic cleavages with formation of persistent carbocations (# 272, 268). Studies with chiral allyl derivatives even allowed us to derive rate constants for internal and external ion-pair recombination (# 341).

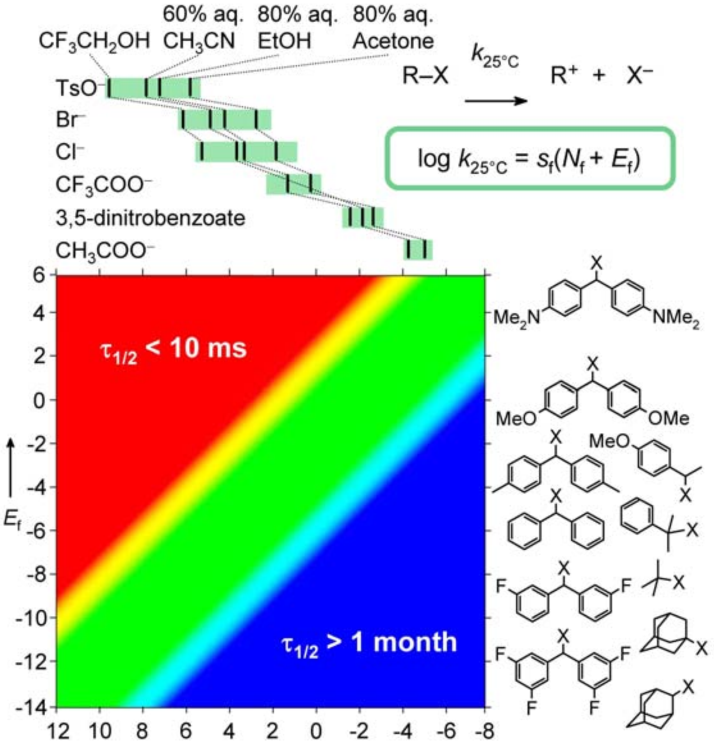


Figure 5. A practical guide for estimating rates of heterolysis reactions

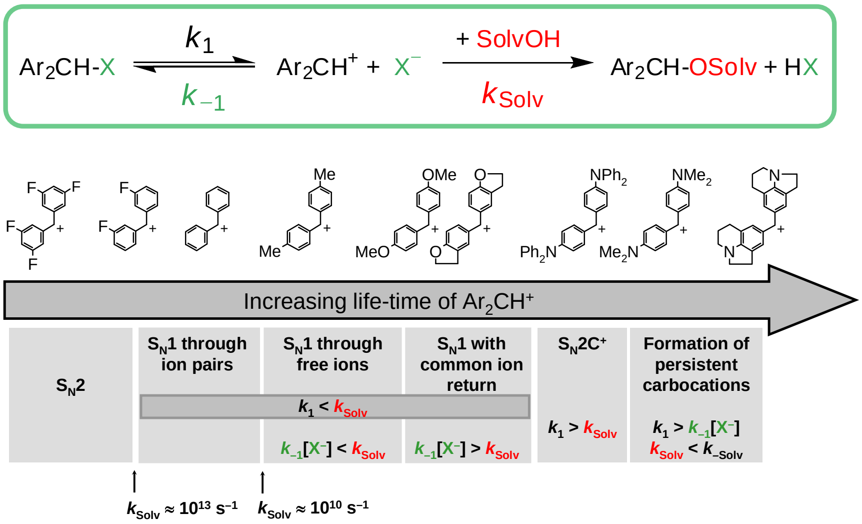


Figure 6. Changing Solvolysis Mechanisms

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_N1 reactions, showing that *m*-values cannot be used as a criterion to differentiate between S_N1 and S_N2 mechanisms (review # 332).

J. Lewis Basicities

The widely variable stabilization of m- and p-substituted benzhydrylium ions, which enabled their use as reference electrophiles for the construction of nucleophilicity scales (Section F) and as reference electrofuges for the construction of nucleofugality scales (Section I) has recently been used for the construction of Lewis basicity scales with respect to C-centered Lewis acids of equal steric shielding (Figure 7, #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.

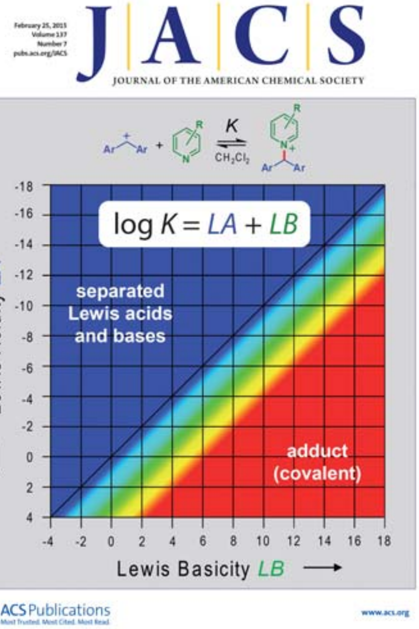


Figure 7. Frontispiece of Feb. 25, 2015 issue of the Journal of the American Chemical Society.

K. General Concepts of Organic Chemistry.

The reactivity scales developed in Section F have been employed for a rigorous examination of common concepts of Organic Chemistry. Though the reactivity selectivity principle has been abandoned as a general rule more than 30 years ago through the work of several authors, 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).

Detailed experimental studies on the ambident reactivities of SCN^- (# 204), CN^- (# 215), NO_2^- (# 221), OCN^- (# 256), $PhSO_2^-$ (# 283), pyridone anions (# 297), hydrazines (# 317), and hydrazones (# 356) 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 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 8 and demonstrates that the application of PMO theory on reactivities of ambident anions toward carbocations often implies extrapolations to transition states of reactions, which do not have a transition state as they undergo diffusion-controlled combinations (review # 305).

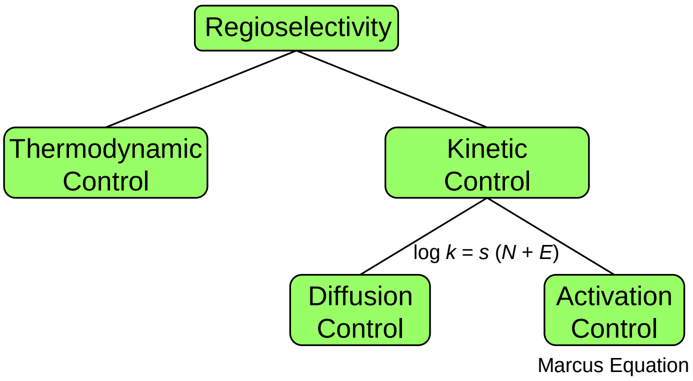


Figure 8. A systematic analysis of ambident reactivity.

The question polar reactivity versus SET processes, which has been attracting our attention for many years (# 130, 198), has recently been examined for the reactions of quinones with a variety of π-nucleophiles and amines (# 355, 364).

Another long lasting research interest, the differentiation between concerted and stepwise cycloadditions (# 146, 171, 189, see also Section C) has recently gained new actuality by our demonstration that the rate constants of stepwise 1,3-dipolar cycloadditions are correctly reproduced by our reactivity parameters (# 357, 359). For that reason, the energy of concert can be derived from the ratio of measured vs. calculated (by eq. 1) rate constants.

L. Mechanisms of Organometallic Reactions

In collaboration with the Knochel group, we are investigating 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 9); furthermore, we have quantified the difference in reactivity between carbanions and organometallics (#371).

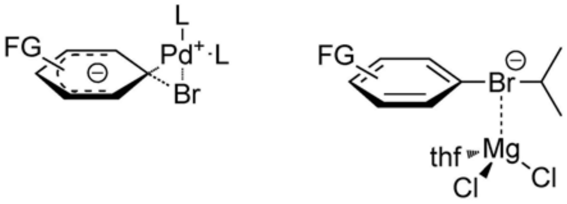


Figure 9. Comparison of the transition states of the oxidative addition of PdL_2 and of the Br–Mg exchange with *i*PrMgCl·LiCl.

M. Photolytic Cleavage of R-X Bonds

Photolysis of benzhydryl derivatives generally leads to mixtures of radicals $Ar_2CH^{\cdot}$ and carbocations Ar_2CH^+. The efficiency and mechanism of the photo-cleavage were studied by nanosecond laser flash photolysis and femtosecond spectroscopy. The radical/carbocation ratio depends on the photoelectrofuge (Ar_2CH), 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).