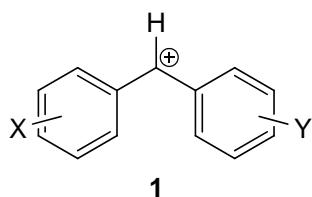# A Quantitative Approach to Polar Organic Reactivity
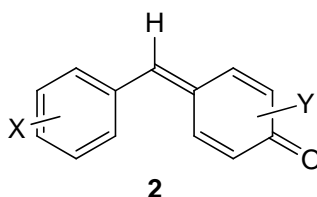
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Organic chemistry is generally organized by the concept of functional groups, and knowledge whether and how different functional groups react with each other is a key qualification of an organic chemist. Since the introduction of this concept, the number of functional groups has grown so tremendously that a new organizing principle appeared necessary. The basis for this approach was laid in the 1930s by C. Ingold who recognized that most organic reactions can be considered as combinations of electron-surplus (nucleophiles) with electron-deficient compounds (electrophiles). Numerous attempts to quantify nucleophilicity and electrophilicity have been reported since the 1950s, but most of them cover only a narrow group of compounds. The most comprehensive nucleophilicity and electrophilicity scales presently available have been created by the Munich group in the past two decades.[1]
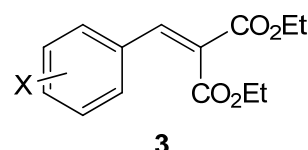
By defining benzhydrylium ions **1**, structurally related quinone methides **2**, and benzylidene malonates **3** as reference electrophiles which differ by 32 orders of magnitude in reactivity (corresponding to relative reaction times of nanoseconds to 10^6 times the age of the universe) and using the method of overlapping correlation lines it has become possible to directly compare nucleophiles of different functionality, which allows one to transfer knowledge from one field of chemistry into another.[2]

1	**2**	**3**
Characterization of weak nucleophiles, as alkenes, arenes, allylsilanes, silyated enol ethers	Characterization of moderately strong nucleophiles, as stabilized carbanions, amide anions, ylides	Characterization of strong nucleophiles, as less stabilized carbanions

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 sensitivity parameter s_N allows one to predict absolute rate constants with an accuracy of factor 10-100 in a reactivity range of more than forty orders of magnitude.

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

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 the 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 the Figure.
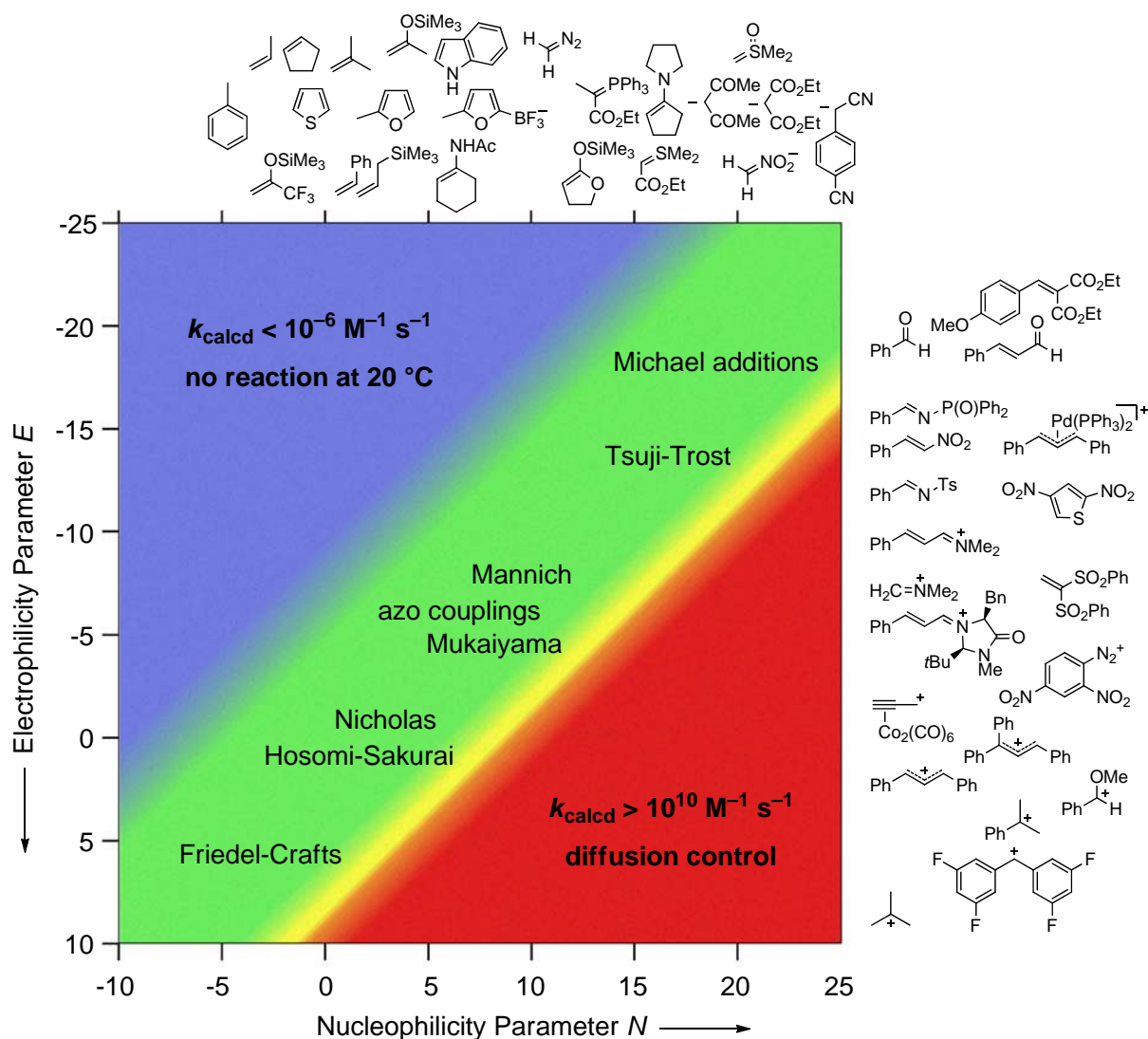
Figure. Where to find synthetically useful reactions

Using the freely accessible data base, which presently comprises almost 1000 nucleophiles and 250 electrophiles[1] one can examine the likeliness of designed synthetic transformations, derive suggestions for novel reactions, and examine the plausibility of patent claims.

An analogous approach to estimate rates of heterolytic cleavages is described in ref. 3.

1) Data collection and download of a reactivity scales poster:
   http://www.cup.uni-muenchen.de/oc/mayr/
2) Reviews: a) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807-1821; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77. c) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21,* 584-595.
3) N. Streidl, B. Denegri, O. Kronja, H. Mayr, *Acc. Chem. Res.* **2010**, *43*, 1537-1549.

Herbert Mayr studied chemistry at the University of Munich (LMU) and obtained his PhD in 1974 under the direction of R. Huisgen. After postdoctoral studies with G. A. Olah at Case Western Reserve University in Cleveland, Ohio, he joined the group of P. v. R. Schleyer at the University of Erlangen-Nürnberg, where he completed his habilitation in 1980. After professorships in Lübeck (1984 – 1991) and Darmstadt (1991 – 1996) he returned to the LMU Munich in 1996, where he has been serving as the Dean of the Faculty of Chemistry and Pharmacy and the Director of the Department of Chemistry and Biochemistry. He received the Alexander von Humboldt Honorary Fellowship of the Foundation for Polish Science (2004) and the Liebig Denkmünze of the German Chemical Society (2006). He is a member of the Bavarian Academy of Sciences and the German National Academy of Sciences Leopoldina. His research interests focus on quantitative approaches to organic reactivity, including the development of reactivity scales which are applied on organometallic and organocatalytic reactions as well as on ionic polymerizations.