

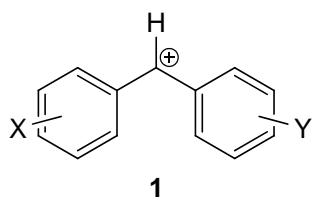
# A Quantitative Approach to Polar Organic Reactivity

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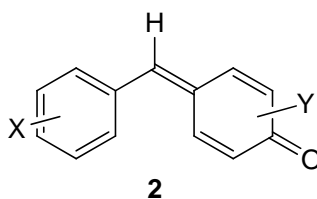
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Organic chemistry is generally organized by the concept of functional groups, and knowledge whether and how different functional groups react with each other is a key qualification of an organic chemist. Since the introduction of this concept, the 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.<sup>1</sup>

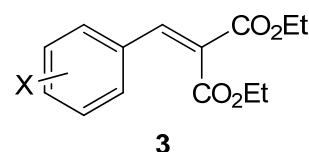
By defining benzhydrylium ions **1**, structurally related quinone methides **2**, and benzylidene malonates **3** as reference electrophiles which differ by 32 orders of magnitude in reactivity (corresponding to relative reaction times of nanoseconds to  $10^6$  times the age of the universe) and using 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.<sup>2</sup>



Characterization of weak nucleophiles, as alkenes, arenes, allylsilanes, silyated enol ethers



Characterization of moderately strong nucleophiles, as stabilized carbanions, amide anions, ylides

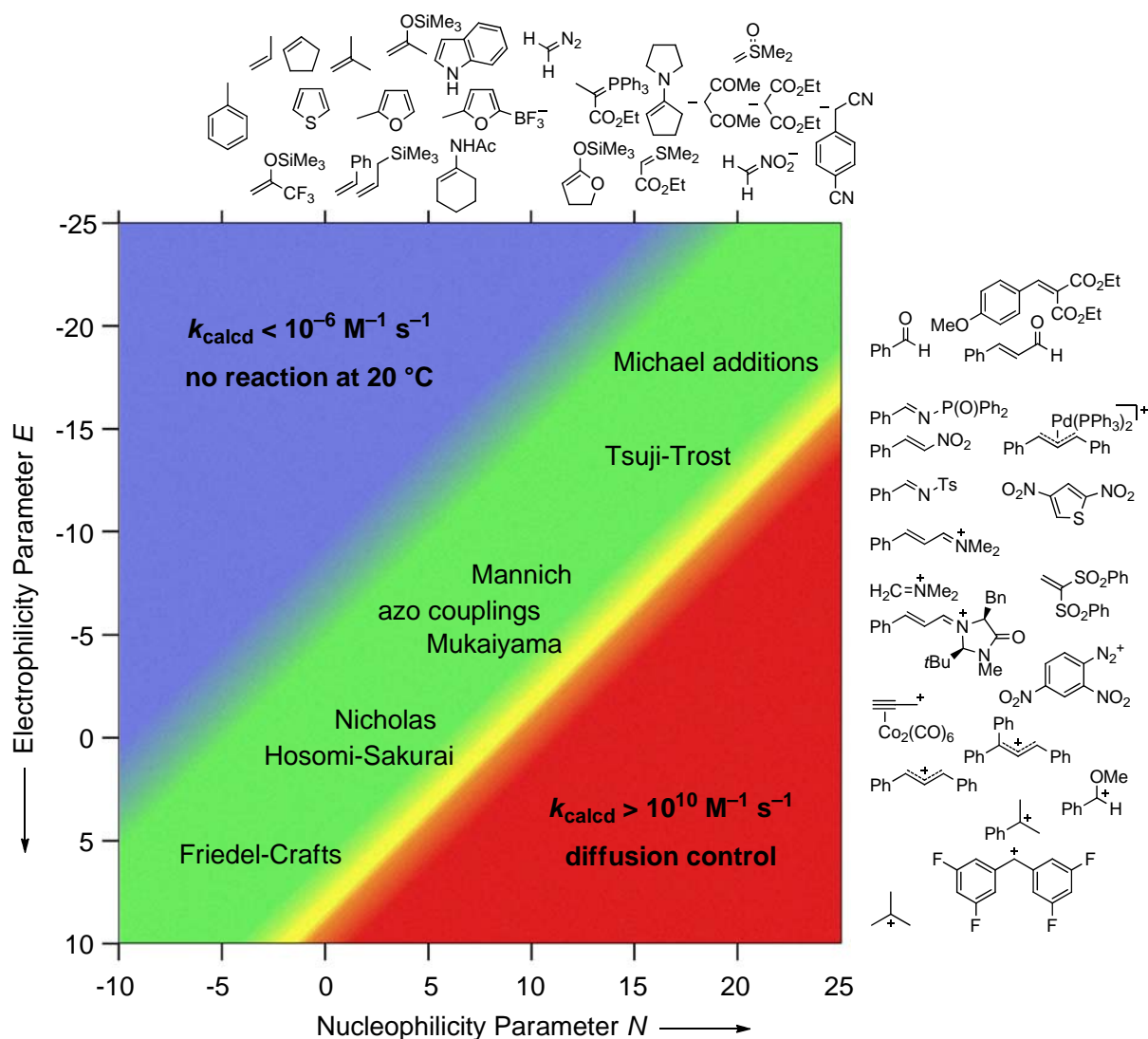


Characterization of strong nucleophiles, as less stabilized carbanions

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.

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

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 the 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 the Figure.



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

Using the freely accessible data base, which presently comprises almost 1000 nucleophiles and 250 electrophiles<sup>1</sup> 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.