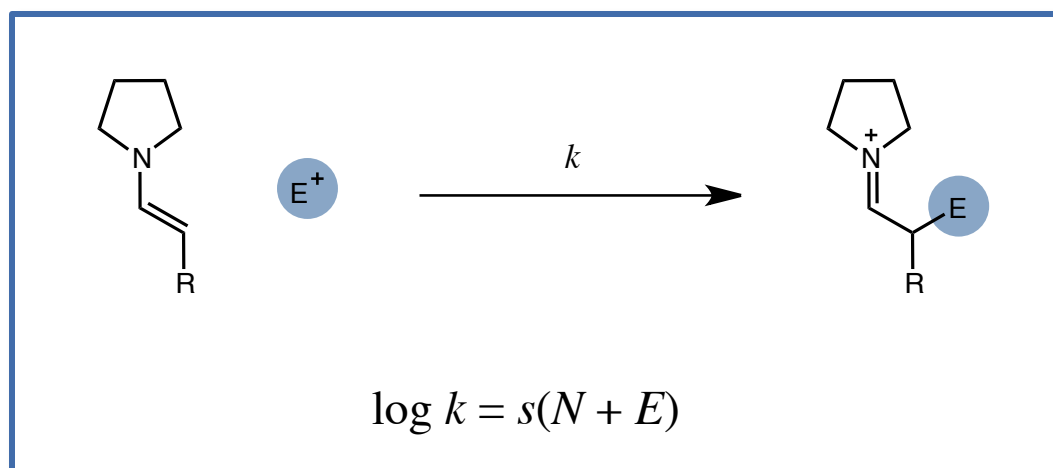


Quantifying Nucleophilicity and Electrophilicity: The Mayr Scales



Valerie Shurtleff
MacMillan Group Meeting
July 10, 2013

A Brief History of Polar Reactivity Scales

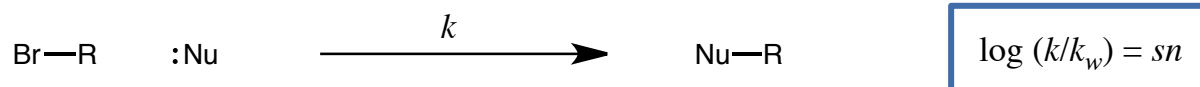
- 1920s: G. N. Lewis presents valence bond theory



- 1930s: Ingold introduces the terms "electrophile" and "nucleophile"



- 1953: Swain and Scott introduce the first method for the quantification of nucleophilicity



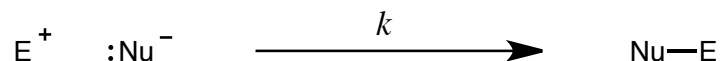
n = nucleophilicity parameter, =0 for H₂O

s = sensitivity of rate constant to changes in the nucleophile, =1 for MeBr

k_w = rate constant for reaction of RBr with H₂O

The Ritchie Relationship

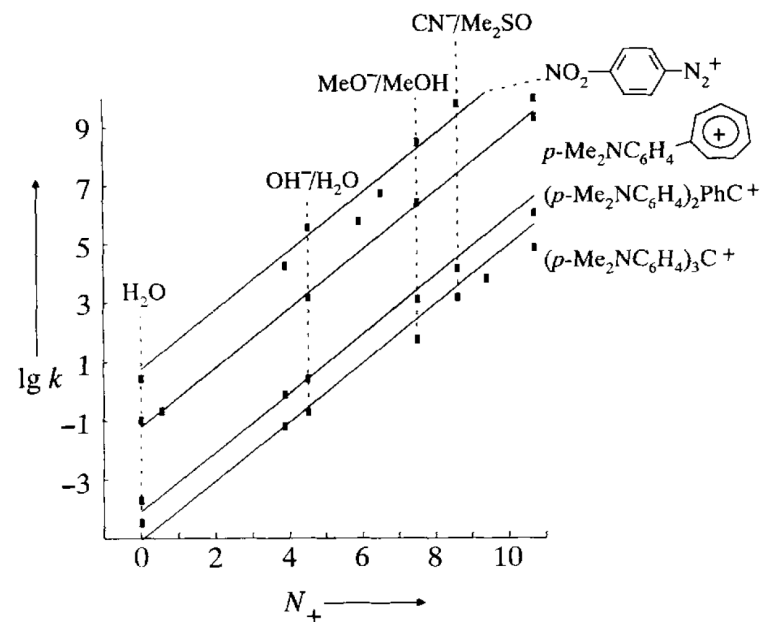
- 1972: Introduction of N_+ for comparison of nucleophiles



$$\log(k/k_w) = N_+$$

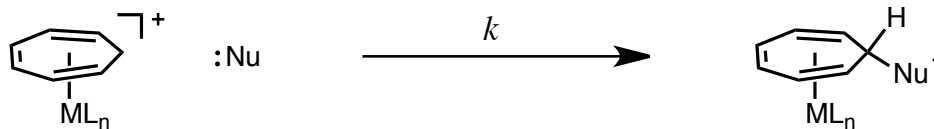
N_+ = nucleophilicity parameter, =0 for H_2O
 k_w = rate constant for reaction of E^+ with H_2O

- N_+ specific to a given solvent (n-nucleophiles)
- Slope represents selectivity of electrophile
- Same slope: "constant selectivity relationship"



Kane-Maguire and Sweigart

1984: Application of Ritchie relationship to organometallic electrophiles

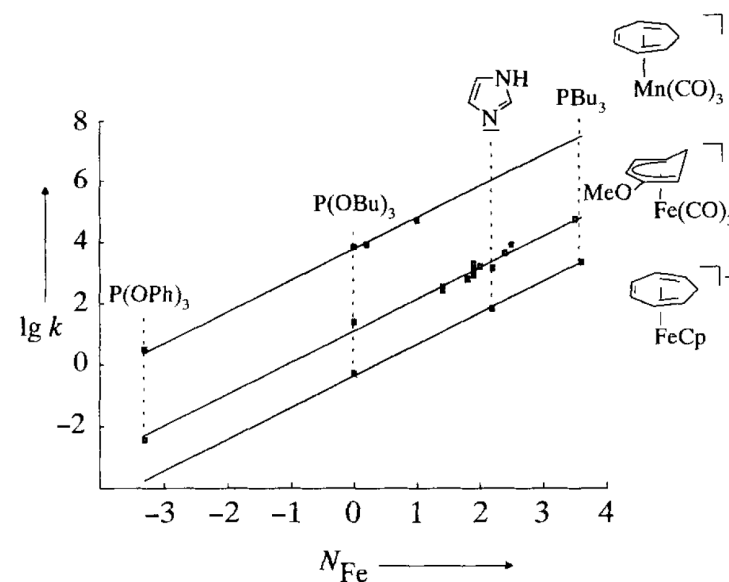


$$\log(k/k_0) = N_{Fe}$$

N_{Fe} = nucleophilicity parameter, =0 for P(OBu)₃

k_0 = rate constant for reaction of L_nMAr⁺ with P(OBu)₃

- Relative reactivities independent of electrophile
- Same relative reactivities found for carbocations
- Constant selectivity relationship



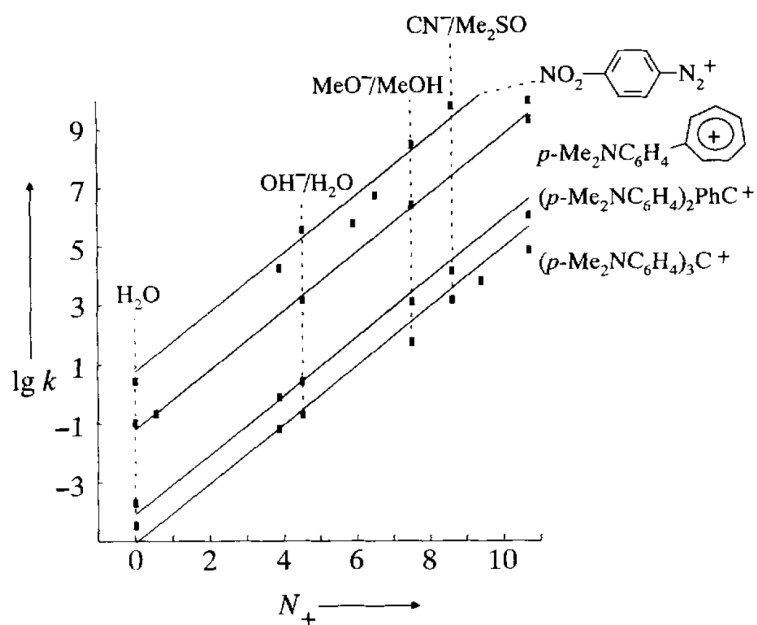
Mayr, H.; Patz, M. *ACIE* **1994**, 33, 938.

Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, 84, 525.

An Aside: The Reactivity-Selectivity Principle

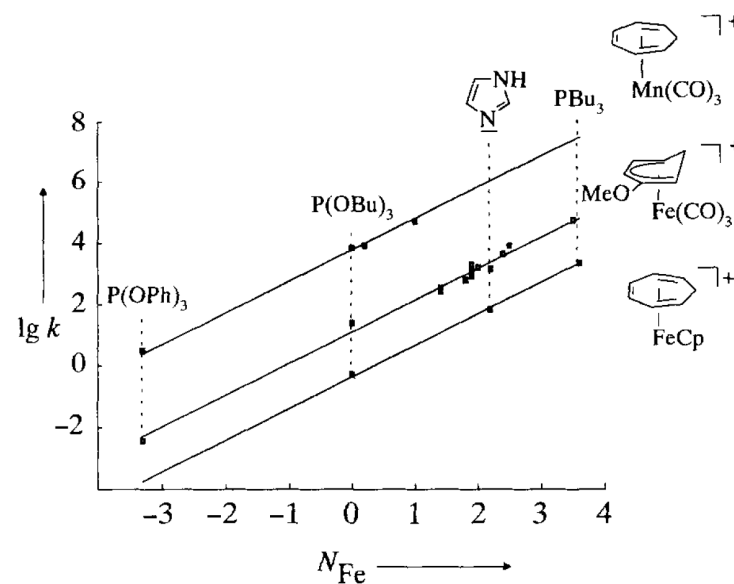
- "The more reactive a compound is, the less selective it is."

Ritchie, 1972



Virtually constant selectivity over reactivity spanning 4 orders of magnitude

Kane-Maguire, Sweigart, 1984



Virtually constant selectivity over reactivity spanning 9 orders of magnitude

Giese, B. *ACIE* **1977**, *16*, 125.

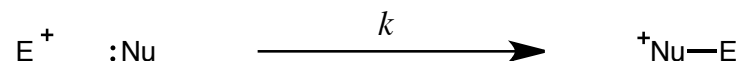
Mayr, H.; Ofial, A. R. *ACIE* **2006**, *45*, 1844.

Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.

Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525.

Expanding the Utility of the Ritchie Relationship

- Can electrophiles also be characterized using constant selectivity relationships?



- From the Ritchie relationship: $\log (k/k_w) = N_+$ (1)

$$\log k - \log k_w = N_+ \quad (2)$$

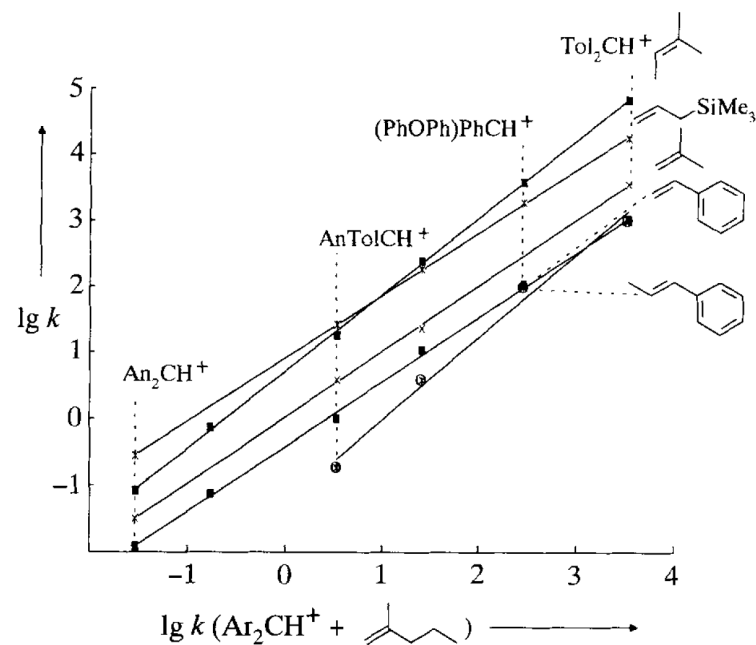
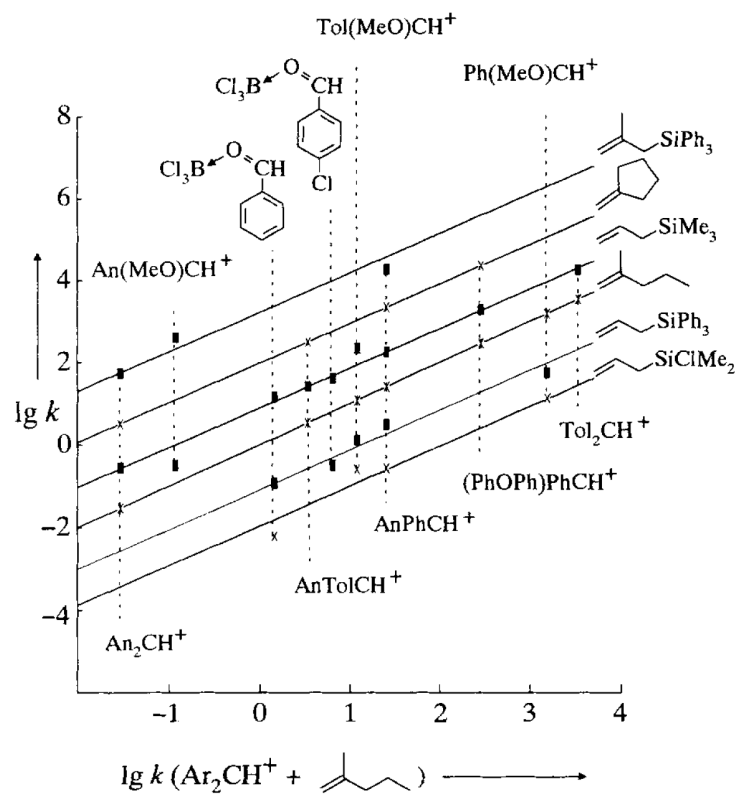
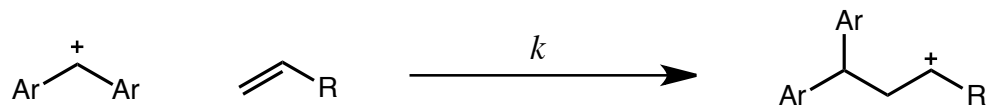
$$\log k = \log k_w + N_+ \quad (3)$$

- Recall, k_w = the rate constant for the reaction of a given electrophile with H₂O
- Thus, k_w is independent of the nucleophile contributing to k and is characteristic of the electrophile
- Let $\log k_w = E_+$ in equation (3) above:

$$\log k = \log k_w + N_+ \quad \xrightarrow{\log k_w = E_+} \quad \boxed{\log k = E_+ + N_+}$$

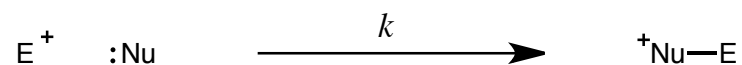
Non-constant Selectivity Relationships

■ Implications of the slope of correlation relationships



The Mayr-Patz Equation

- Introduction of a third parameter to account for differences in selectivity



- The Mayr-Patz equation:

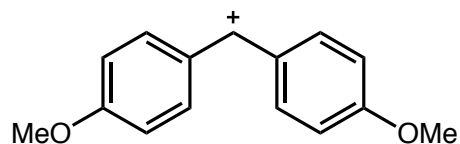
$$\log k = s(N + E)$$

s = nucleophile-specific slope parameter

N = nucleophilicity parameter

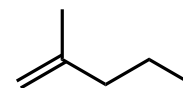
E = electrophilicity parameter

- Reference compounds:



An_2CH^+

$E = 0$



2-methyl-1-pentene

$s = 1$

Towards a Unified Reactivity Scale

■ Nucleophilicity parameters determined for 56 nucleophiles

- π -nucleophiles: alkenes, dienes, alkynes, allylsilanes, -germanes, -stannanes, arenes, enol ethers
- σ -nucleophiles: silanes, germanes, stannanes, BDHNA (nicotinamide derivative)
- n-nucleophiles: phosphines, phosphites, alcohols, amines, heterocycles

■ Conversions for electrophilicity terms determined by Richie and Kane-Maguire/Sweigart

- Richie: $E = 1.24(\log k_w) - 5.80$
- Kane-Maguire/Sweigart: $E = 1.38(\log k_\theta) - 18.2$

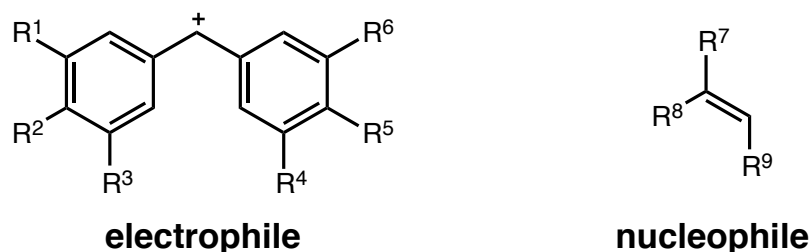
■ Conversions for nucleophilicity parameters determined by Richie and Kane-Maguire/Sweigart

- Richie: $N = 1.20(N_+) + 6.18, s = 0.83$
- Kane-Maguire/Sweigart: $N = 1.51(\log k) + 7.53, s = 0.66$

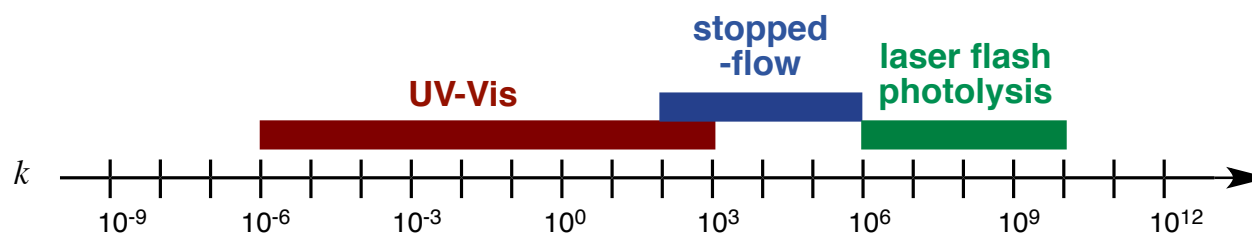
Reference Scales for Parametrization of Polar Reactivity

■ Rate constants measured for the reactions of 23 diarylcarbenium ions with 38 π -nucleophiles

- Pseudo-first-order conditions, [nucleophile] \gg [electrophile]



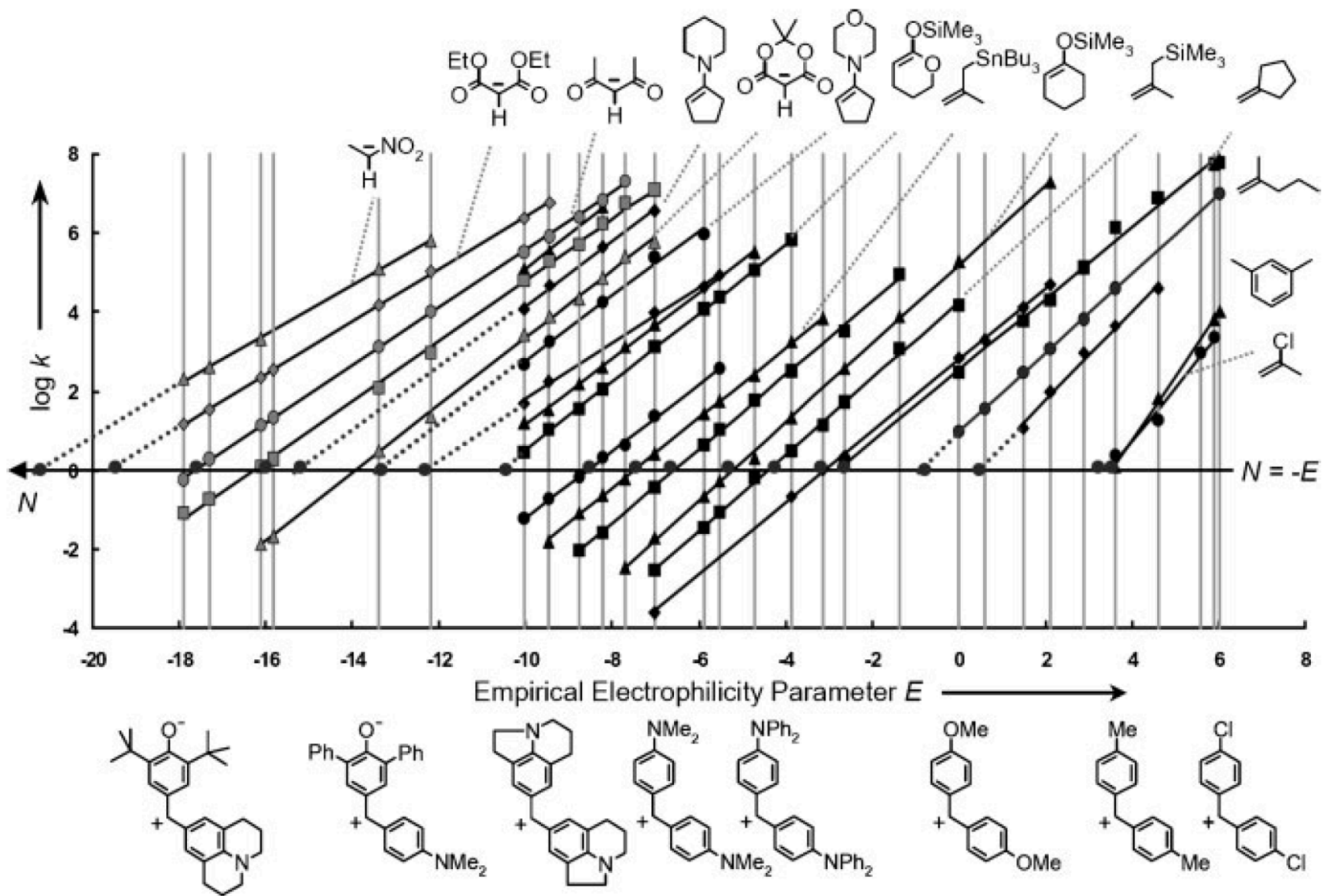
■ Measurement method dependent on the reaction rate:

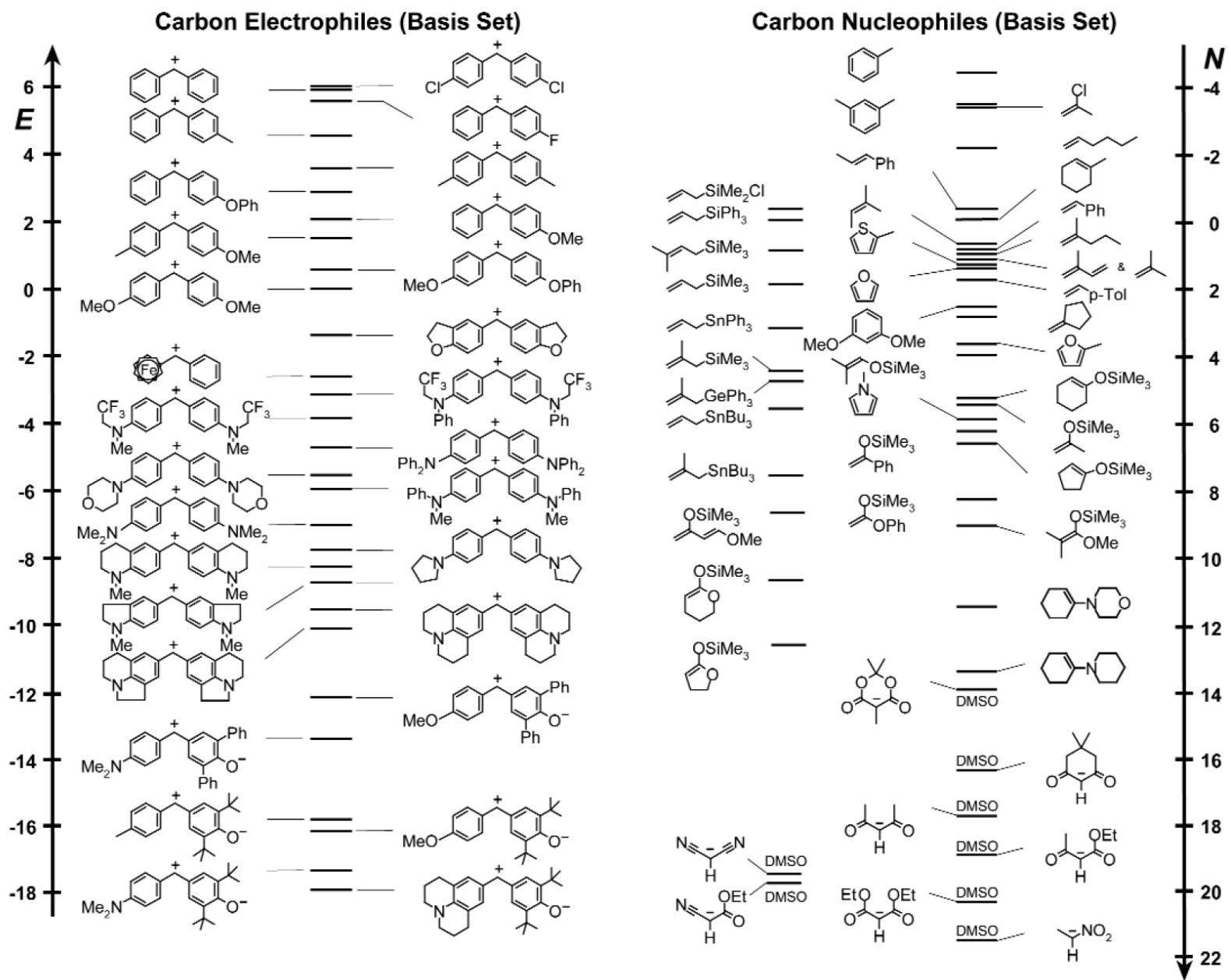


■ Reactivity parameters s , E , N determined by least-squares fitting from the Mayr-Patz equation

- $s = 1$ for 2-methyl-1-pentene, $E = 0$ for An_2CH^+

Reference Scales for Parametrization of Polar Reactivity





Expansion of the Mayr Basis Set

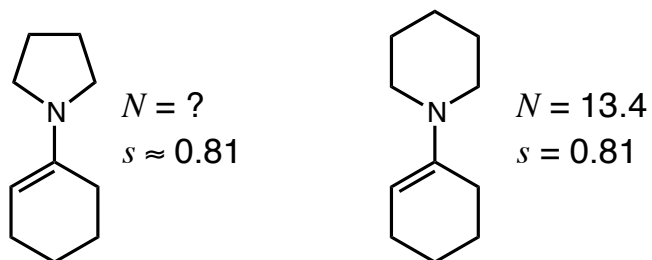
■ Determination of E for new electrophiles

- Measure rate constants for reaction with nucleophiles for which N and s are known, then derive E

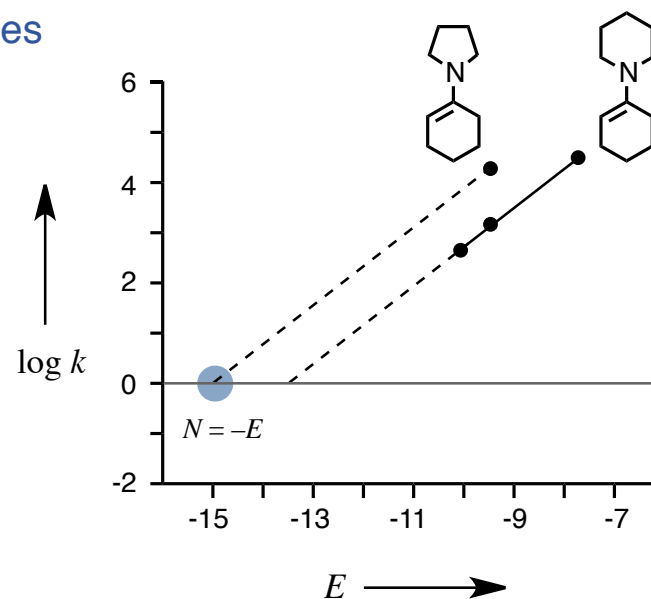
■ Determination of N and s for new nucleophiles

- Measure rate constants for reaction with a variety of electrophiles for which E is known, then derive N and s

■ "Quick and dirty" determination of N for new nucleophiles



- Assume s is similar to a that of a structurally analogous nucleophile
- Measure the rate constant for reaction with a single electrophile for which E is known



Mayr's Online Database of Reactivity Parameters

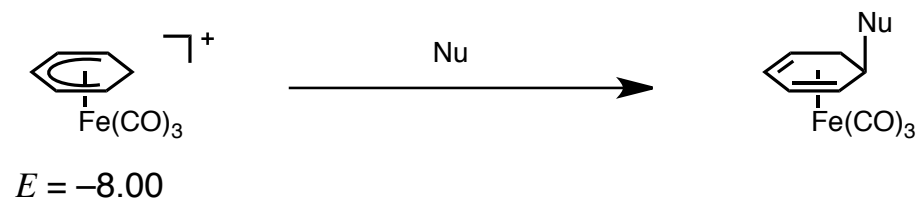
- N , s parameters for 924 nucleophiles; E parameters for 235 electrophiles
- Searchable by molecule class, N parameter, E parameter
- Enamines/Enamides: 42 entries currently listed

Molecule	Solvent	Reactivity Parameters	Classification	Reference (sort by title or year)
 <p>(2S,5S)-5-benzyl-2-(tert-butyl)-3-methyl-1-((E)-styryl)imidazolidin-4-one</p>	MeCN	N Parameter: 5.80 s_N Parameter: 0.87	★★★★	<i>Angew. Chem. Int. Ed.</i> 2012 , 51, 5739-5742 DOI: 10.1002/anie.201201240
 <p>(in MeCN)</p> <p>(cyclohexen-1-yl)prolinate (in MeCN)</p>	MeCN	N Parameter: 18.86 s_N Parameter: 0.70	★★★★	<i>Angew. Chem. Int. Ed.</i> 2010 , 49, 9526-9529 DOI: 10.1002/anie.201004344

Utility of the Mayr Reactivity Scales

■ Will a reaction happen?

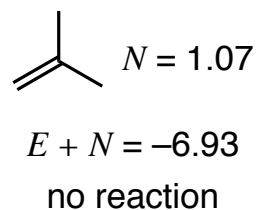
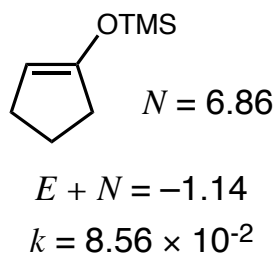
- Consider a reaction at room temperature, 1 M in each reactant:



- For 50% conversion in less than 3 h, $k > 10^{-4}$ is required.
- Rule of thumb:

An electrophile/nucleophile pair can be expected to react at room temperature if $(E + N) > -5$

- Representative examples (reactions at 20 °C):

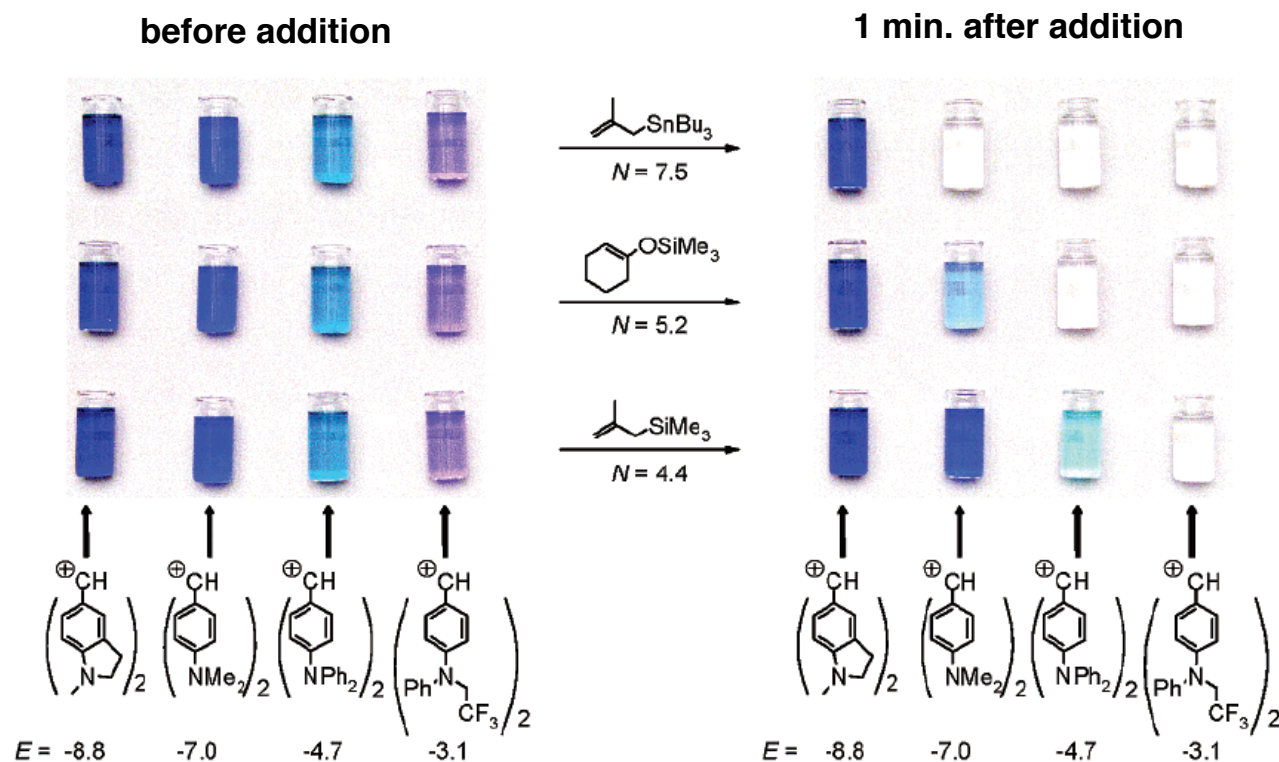


Utility of the Mayr Reactivity Scales

■ Comparison of nucleophilicity/electrophilicity of reaction partners

- Direct comparison of parameters if appropriate E or N and s values are known

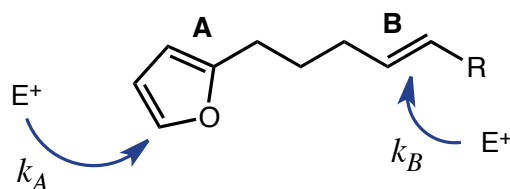
■ "Semiquantitative" nucleophilicity comparison



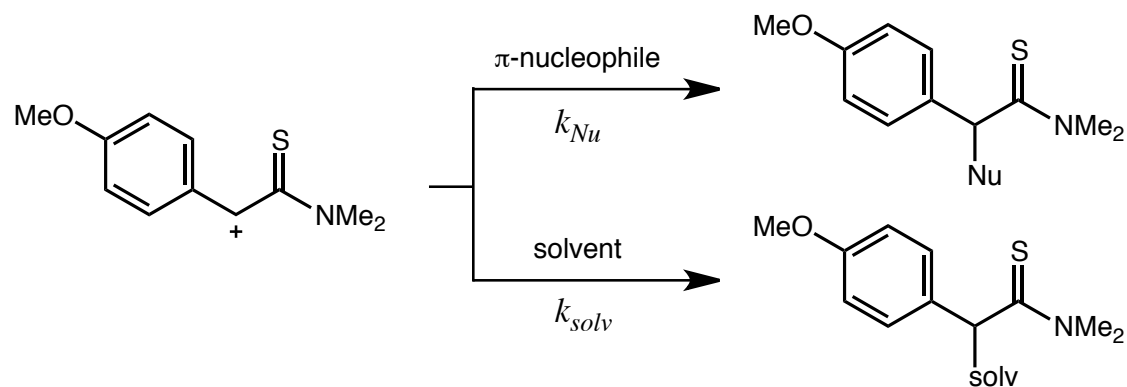
Utility of the Mayr Reactivity Scales

■ Predicting selectivity

- Product ratios for reaction with competing nucleophiles **A** and **B** predicted by calculation of k_A/k_B
- As a corollary, selectivity for competing sites of electrophilic attack may be predicted:



- Nucleophilicity requirement to outcompete solvent trapping



Nu with $N > 6$
compete with solvent

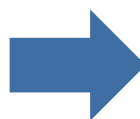
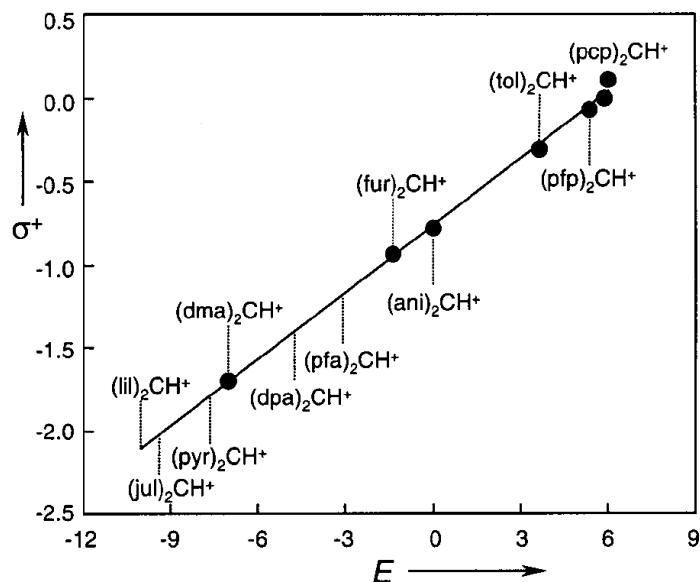
Utility of the Mayr Reactivity Scales








Correlation with Hammett parameters

- Few σ^+ parameters available for electron-donating groups stronger than alkoxy
- Strong correlation between σ^+ and E for symmetrical diarylcarbenium ions

$$\sigma^+ = 0.134E - 0.767$$

$$r = 0.9986$$

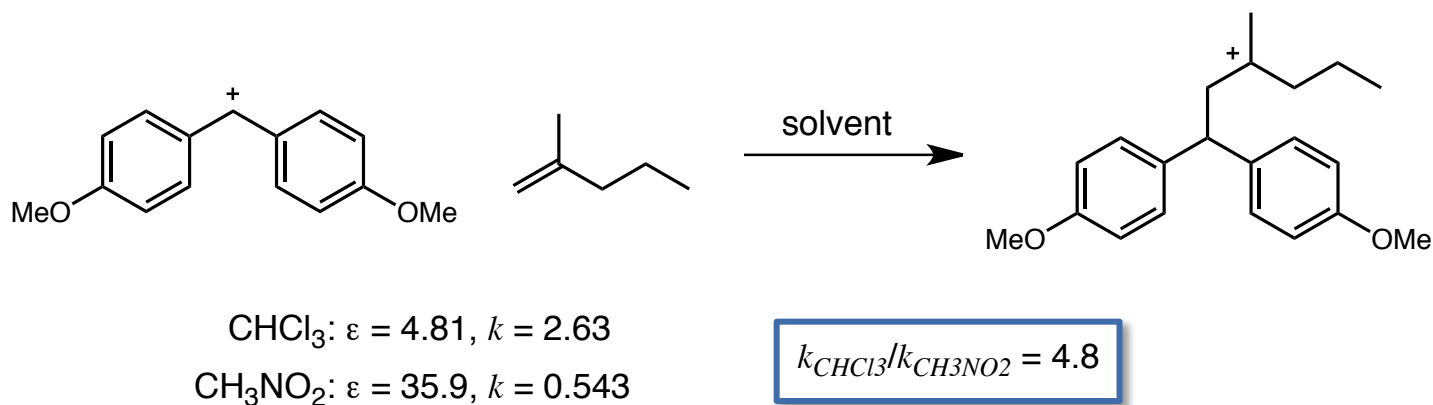


$\text{Ar}_2\text{CH}^+{}^a$	substituent at 	σ^+
(lil) ₂ CH ⁺		-2.11
(jul) ₂ CH ⁺		-2.03
(ind) ₂ CH ⁺		-1.94
(thq) ₂ CH ⁺		-1.87
(pyr) ₂ CH ⁺	4-N 	-1.80
(dma) ₂ CH ⁺	4-NMe ₂	-1.70 ^b
(mpa) ₂ CH ⁺	4-N(Ph)Me	-1.56
(mor) ₂ CH ⁺	4-N 	-1.51
(dpa) ₂ CH ⁺	4-NPh ₂	-1.40
(mfa) ₂ CH ⁺	4-N(Me)CH ₂ CF ₃	-1.28
(pfa) ₂ CH ⁺	4-N(Ph)CH ₂ CF ₃	-1.19

Solvent Effects

Reactions of π -nucleophiles and σ -nucleophiles

- Changes in solvent have little effect on rate constants
- Presumably due to preservation of charge in the combination step



Reactions of n-nucleophiles

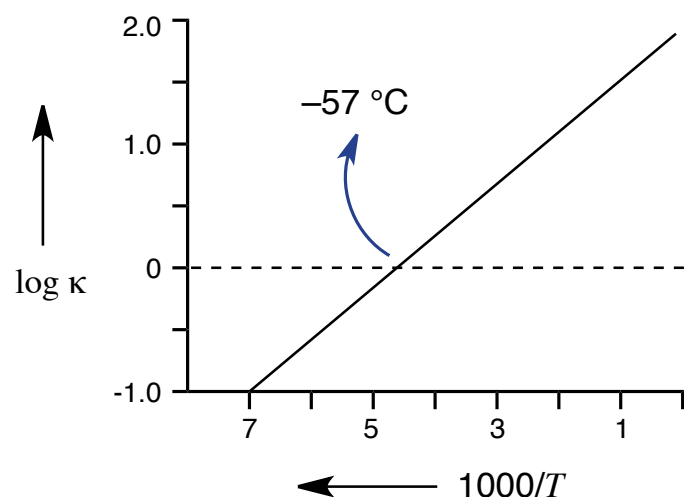
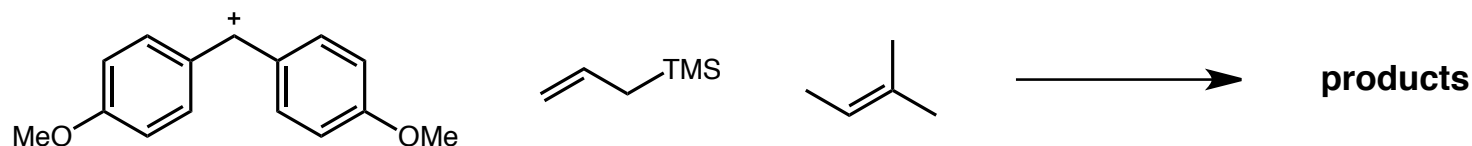
- Rate constants can be very different in aprotic vs. protic solvents due to H-bonding
- N , s parameters are solvent-specific

Reactions of diazonium electrophiles

- Electrophilicity dependent on donor number of solvent, E is solvent-specific

Temperature Effects

- Nucleophilicity scales can be affected by changes in temperature



$$\kappa = \frac{k(\text{allyl-TMS})}{k(\text{2-methyl-2-butene})}$$

- $T > -57\text{ }^\circ\text{C}$: allyltrimethylsilane is more nucleophilic
- $T < -57\text{ }^\circ\text{C}$: 2-methyl-2-butene is more nucleophilic
- $T = -57\text{ }^\circ\text{C}$: aselective reaction

- Nucleophiles with very different reaction enthalpies/entropies should be compared cautiously

- Reaction entropy seems to be influenced most heavily by nucleophile structure

A Few Caveats

■ Rate constants for combination reactions

- N , s , and E are **kinetic** parameters – unfavorable equilibrium can prevent productive reaction
- Reactions for which electrophile–nucleophile combination is not the RDS may not be amenable to analysis

■ Steric effects

- N and s reflect a combination of steric and electronic effects
- Reactions of bulky compounds can show deviation from linearity

■ Very fast reactions

- Reactions with rates approaching diffusion control begin to deviate from linearity
- The Mayr-Patz equation holds only for $k < 1 \times 10^8$

■ Crossover in nucleophilicity scales

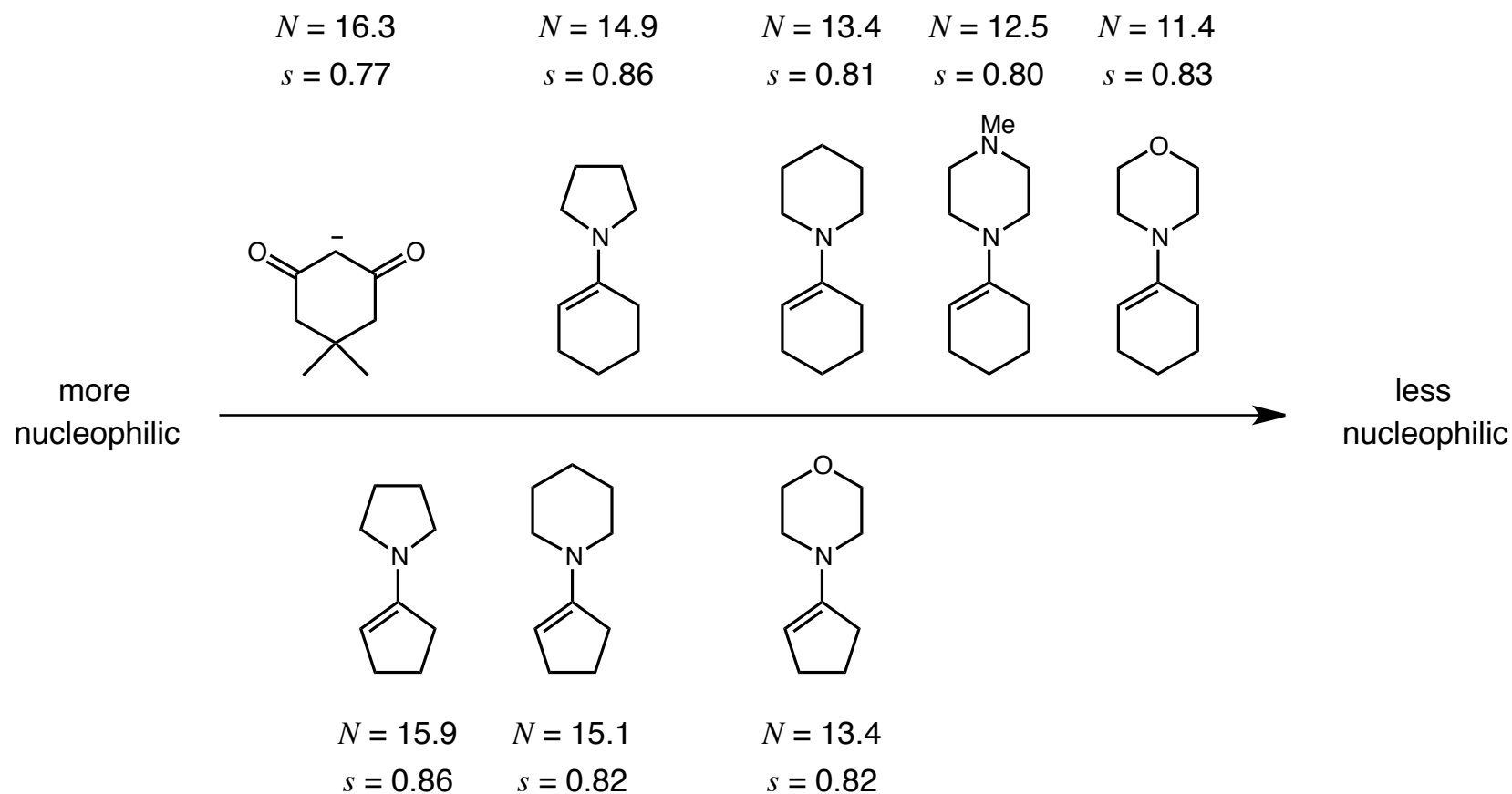
- Nucleophiles with significantly different s values must be compared with caution
- Crossover is most likely to occur when N values are very similar

Mayr, H.; Patz, M. *ACIE* **1994**, *33*, 938.

Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

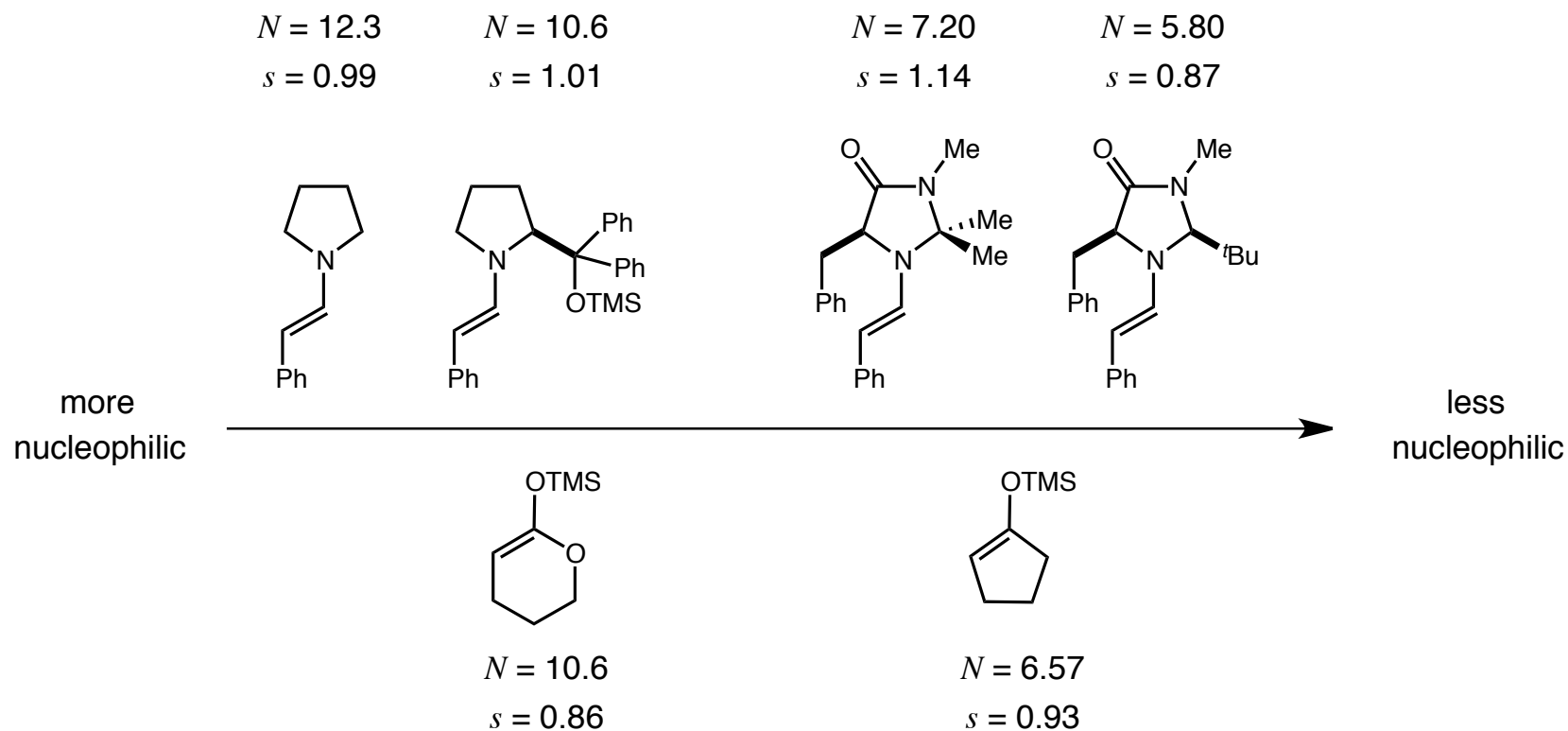
Nucleophilicity of Enamines

■ N and s determined using weak electrophiles



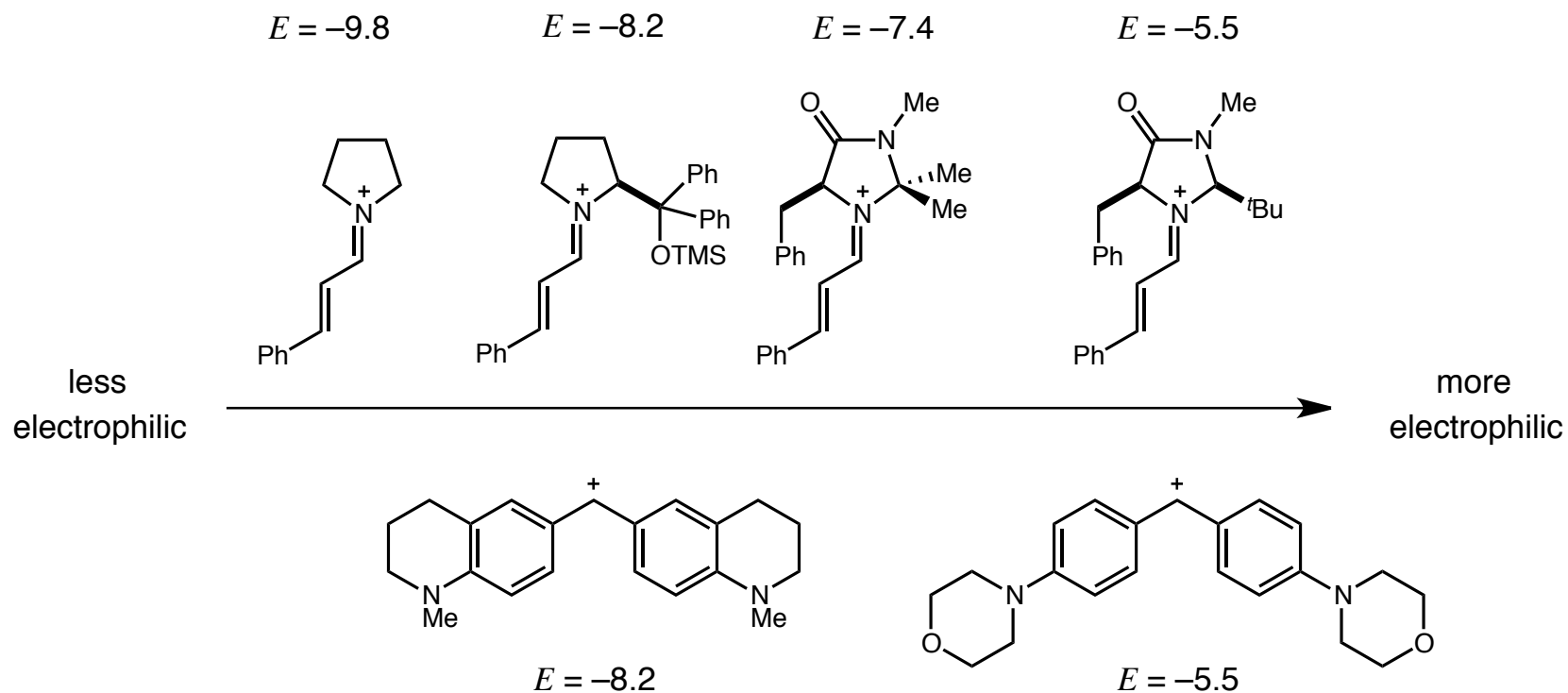
Nucleophilicity of Enamines

■ Enamines derived from prolinol and imidazolidinone organocatalysts



Electrophilicity of α,β -Unsaturated Iminiums

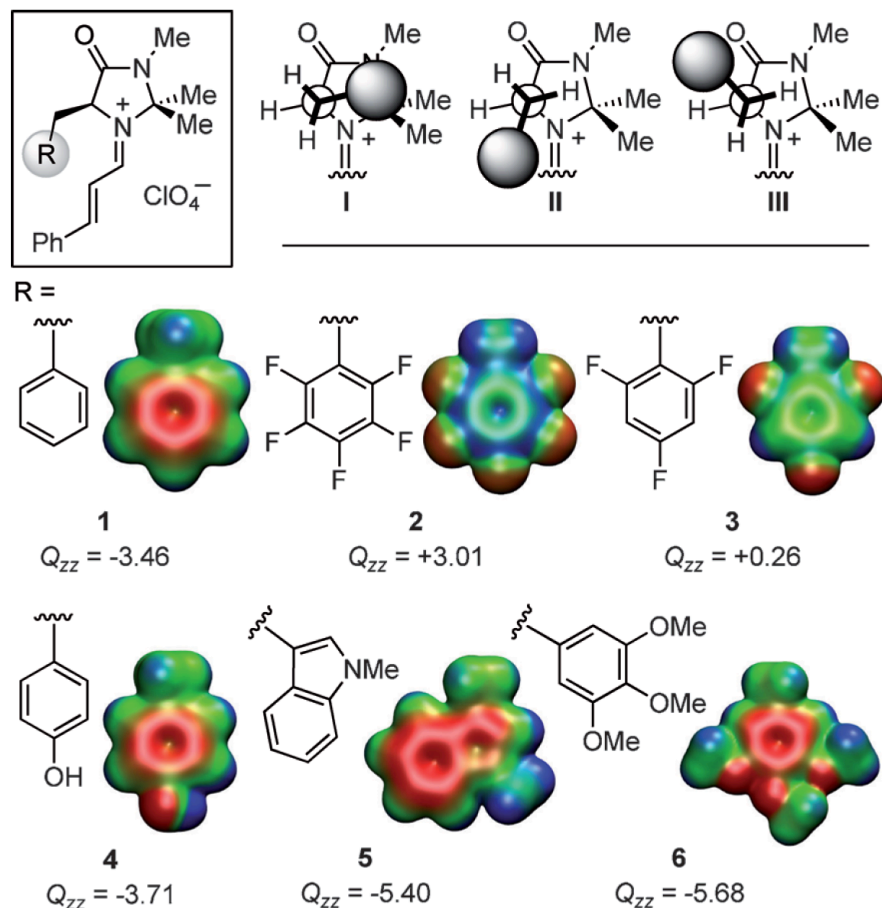
Iminiums derived from prolinol and imidazolidinone organocatalysts



Lakhdar, S.; Ammer, J.; Mayr, H. *ACIE* **2011**, *50*, 9953.
Lakhdar, S.; Tokuyasu, T.; Mayr, H. *ACIE* **2008**, *47*, 8723.
Mayr, H., *et al.* *JACS* **2001**, *123*, 9500.

And Now for Something (Not) Completely Different

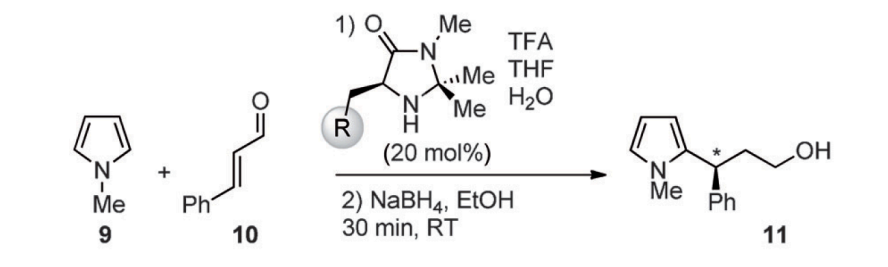
■ Design of electronically differentiated imidazolidinone catalysts



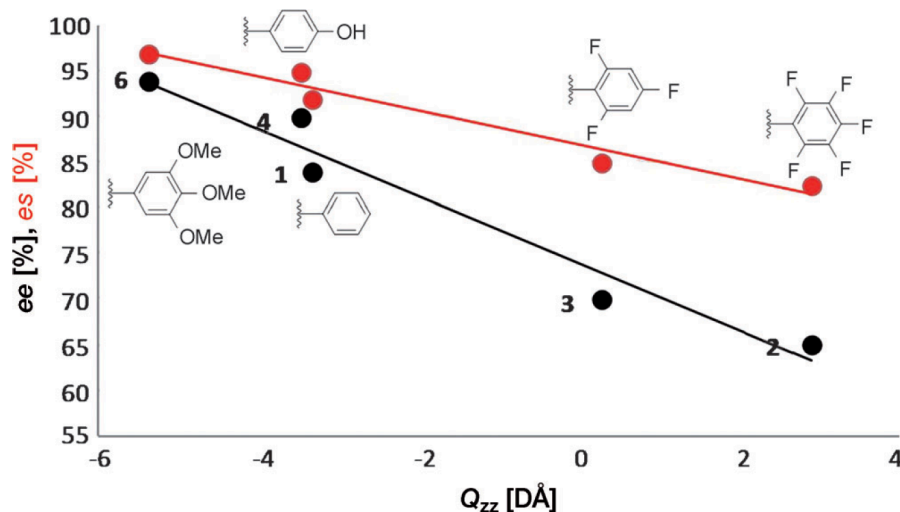
- E for **2** = -6.0
- E for **6** = -7.0
- Q_{zz} = component of the traceless quadrupole moment orthogonal to the aromatic ring
- More EWG, Q_{zz} more positive
- More EDG, Q_{zz} more negative
- Electron-rich catalysts tend to populate conformation **I** preferentially (**1, 4, 5, 6**)
- Electron-poor catalysts tend to populate conformation **III** preferentially (**2, 3**)

And Now for Something (Not) Completely Different

■ Performance of new catalysts in an organocatalytic Friedel–Crafts alkylation



- Using first generation imidazolidinone: –30 °C, 42 h, 87% yield, 93% ee
- Reaction via iminium **6**: rt, 3 h, "completion," 94% ee



- Significant correlation between Q_{zz} and enantioselectivity