On the Relationship Between Reactivity and Selectivity

Valerie Shurtleff
MacMillan Group Meeting
July 23, 2014

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

The Reactivity-Selectivity Principle

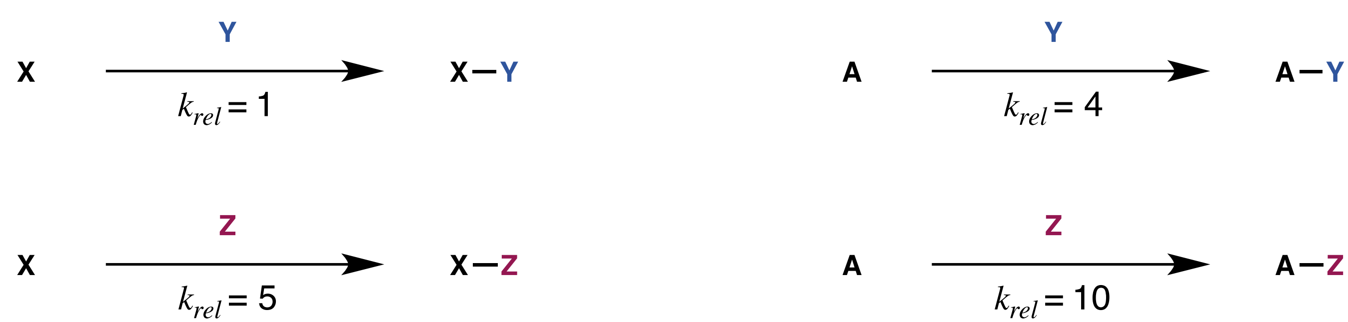
"The more reactive a compound is, the less selective it is."

Relative reactivity:

Relative rate of reaction with a given set of reaction partners, represented by rate constant (k_{rel})

Selectivity:

Measure of a compound's ability to discriminate between different reaction partners, represented by ratio of rate constants (k_1/k_2)

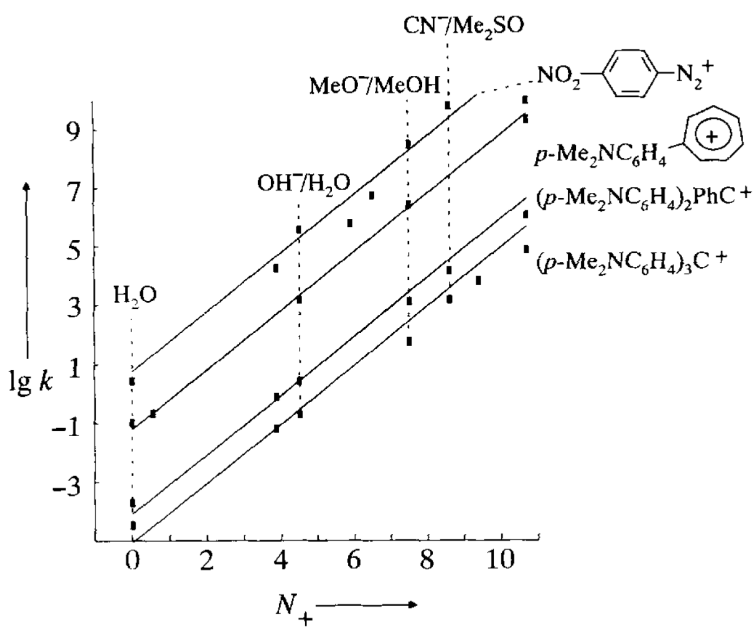


Z is more reactive, Y is more selective

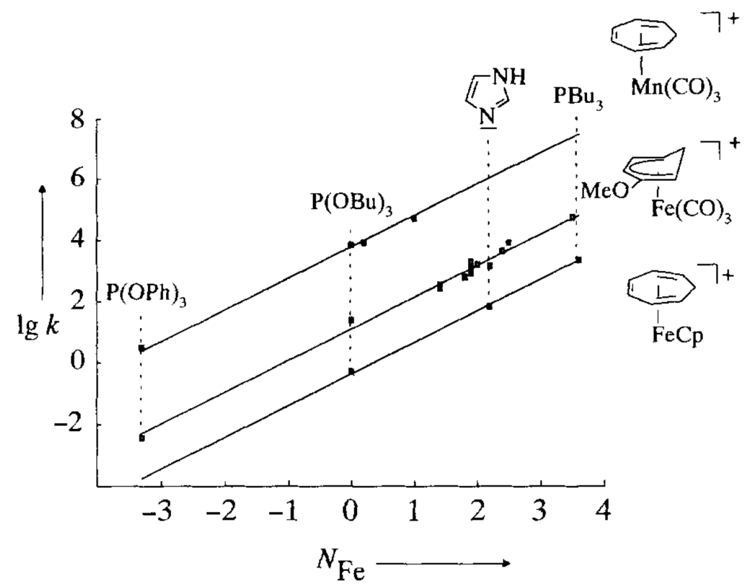
A long time ago in a group meeting far, far away...

Nucleophilicity parameters developed by Ritchie, Kane-Maguire, and Sweigart

Ritchie, 1972



Kane-Maguire, Sweigart, 1984



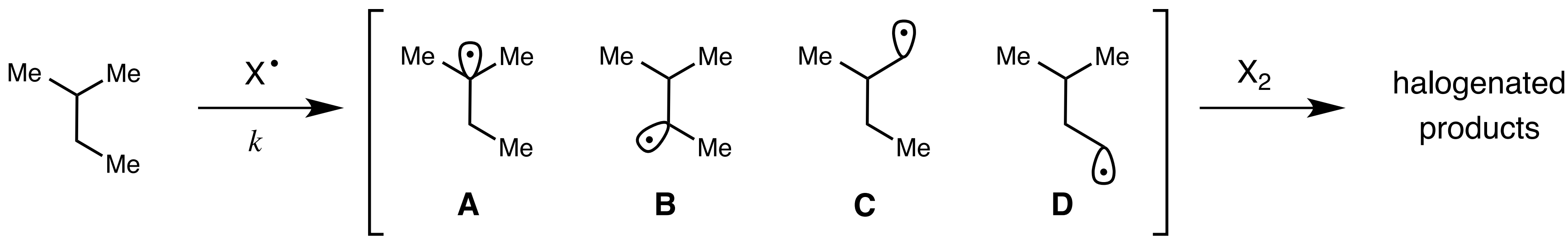
Virtually constant selectivity over reactivity spanning 4 orders of magnitude

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.

The Classic Example: Free-Radical Halogenation

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



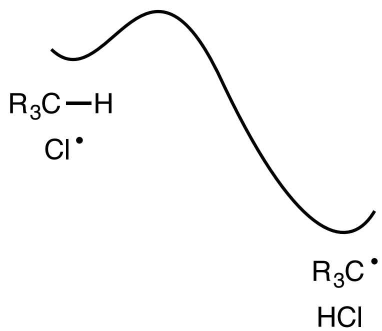
$k_{Cl} > k_{Br}$

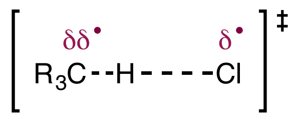
	A	B	C	D
X = Cl	28%	35%	24%	12%
X = Br	90%	9%	0.3%	0.2%

chlorine is more reactive and less selective than bromine

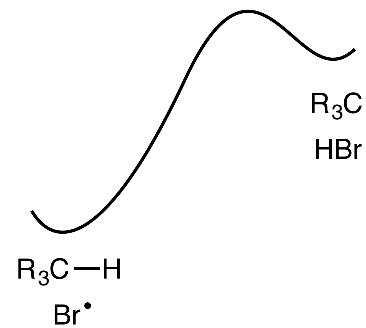
Mayr, H.; Ofial, A. R. *ACIE* **2006**, *45*, 1844.

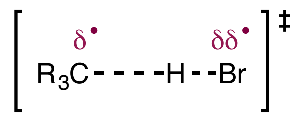
The Classic Example: Free-Radical Halogenation





"early" transition state
little radical character on carbon
radical stability has little effect





"late" transition state
significant radical character on carbon
radical stability has large effect

chlorine is more reactive and less selective than bromine

Theoretical Foundation of the RSP

■ Bell-Evans-Polanyi Relationship

Based on data for homolytic atom transfer reactions:

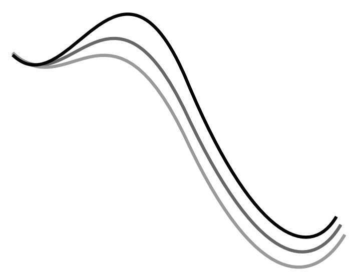
$$E_a = E_0 + \alpha \Delta H$$

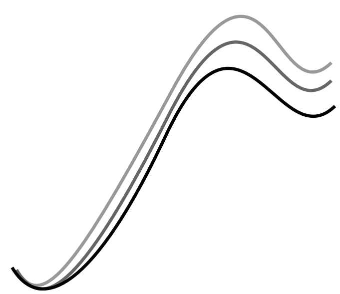
E_0 = activation energy for reference reaction

more exothermic

⇩

faster reaction





more endothermic

⇩

slower reaction

Sundberg, R. J.; Carey, F. A. In *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 5th ed.; Springer: New York, 2007; pp. 288–289.

Theoretical Foundations of the RSP

Leffler, 1953

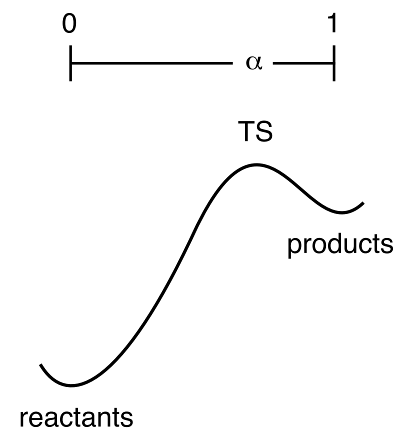
$$\delta\Delta G^{\ddagger} = \alpha(\delta\Delta G^{0})$$

$0 \leq \alpha \leq 1$

α = measure of "lateness" of the TS

more exergonic reaction, α closer to 0

more endergonic reaction, α closer to 1



Hammond, 1955

"If two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures."

> more exothermic reactions tend to have earlier transition states;
> more endothermic reactions tend to have later transition states

Leffler, J. E.; *Science* **1953**, *117*, 340.

Hammond, G. S.; *J. Am. Chem. Soc.* **1955**, *77*, 334.

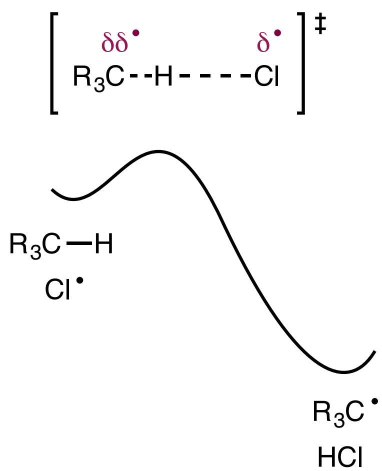
Theoretical Foundations of the RSP

fast-reacting compounds tend to undergo exothermic reactions (Bell–Evans–Polanyi)

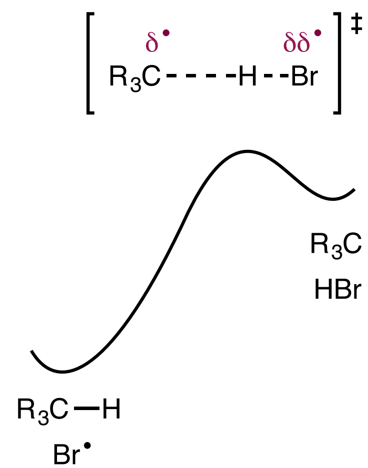
exothermic reactions tend to have reactant-like transition states (Hammond–Leffler)

reactant-like transition states do not differentiate significantly between varying reactants

more reactive compounds are less selective

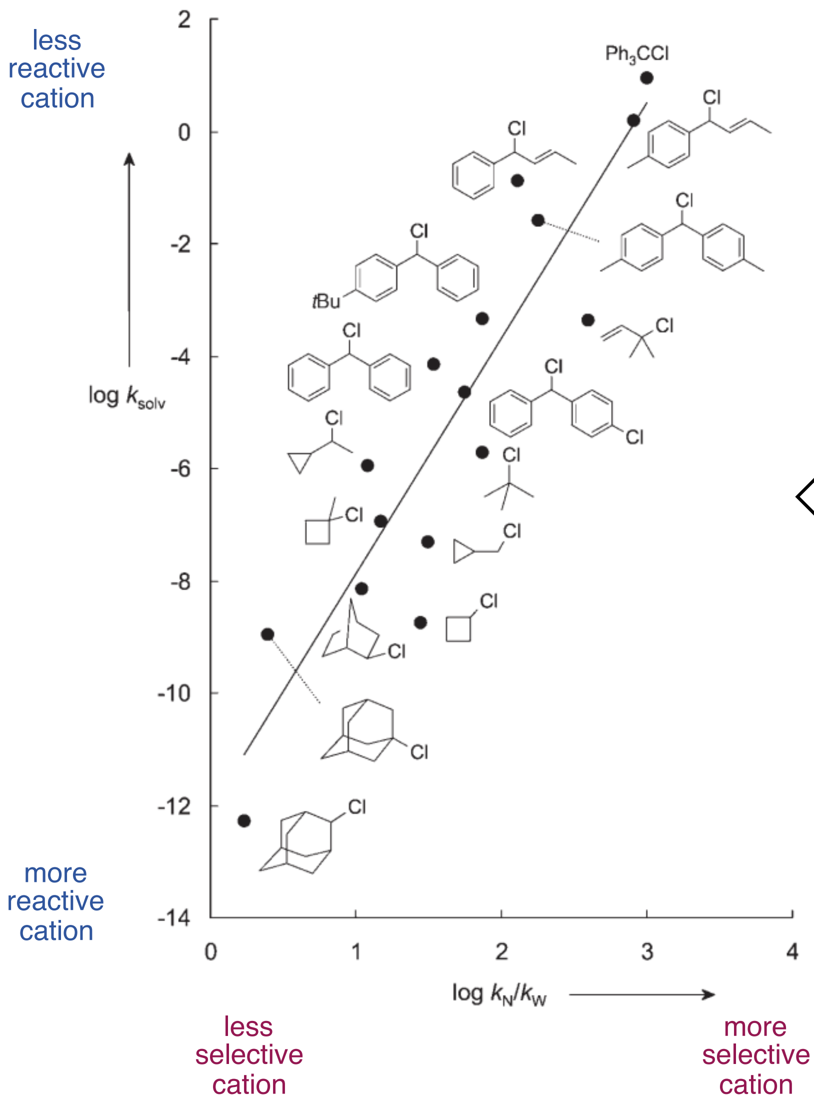


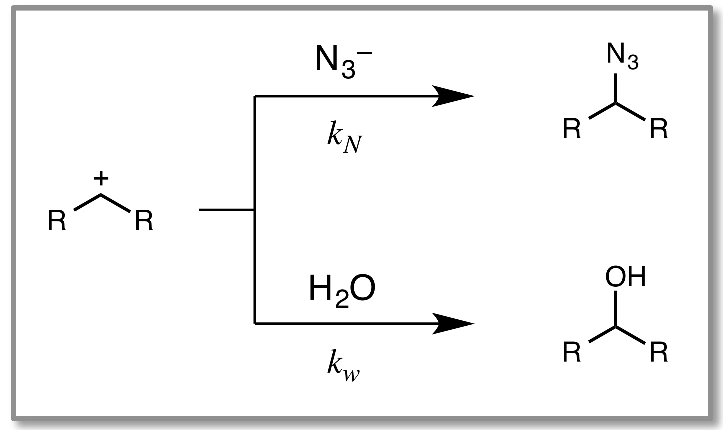
chlorine: more reactive, less selective



bromine: less reactive, more selective

The Curious Case of Carbocations





Raber, Harris, Hall, Schleyer, 1971:

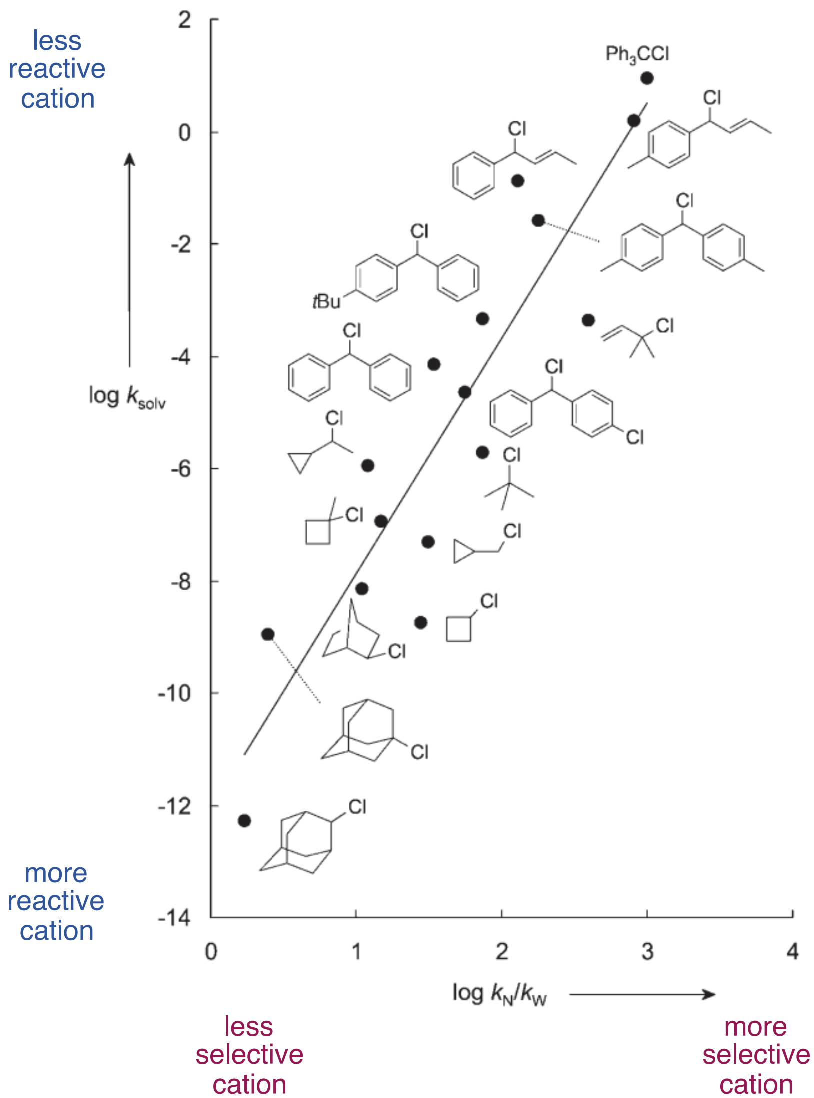
using azide as nucleophile, more reactive cations found to be less selective (consistent with reactivity-selectivity principle)

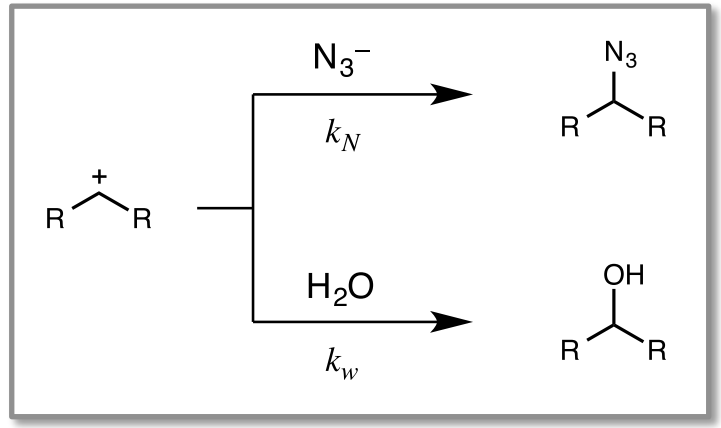
Ritchie, 1972:

using methoxide, hydroxide, cyanide, and other nucleophiles, constant selectivity observed (inconsistent with reactivity-selectivity principle)

Ritchie, C. D.; *Acc. Chem. Res.* **1972**, *5*, 348.
Mayr, H.; Ofial, A. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 1844.
Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1971**, *93*, 4821.

The Curious Case of Carbocations





Rappoport, Ta-Shma, 1983:

for sufficiently reactive electrophiles, N_3^- undergoes diffusion-controlled reactions ($k_N = 5 \times 10^9\ M^{-1}s^{-1}$)

⇩

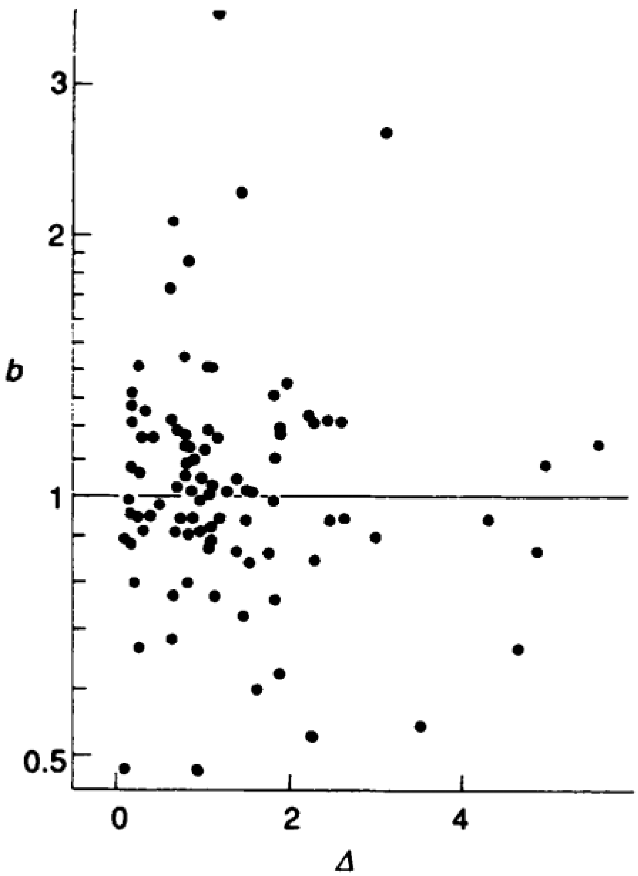
decreasing selectivity is caused by changing rate of reaction with water

Mayr, H.; Ofial, A. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 1844.
Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082.

The RSP as a General Rule

■ How often does the RSP "work?"

analysis of kinetic data for 100 reactions: if $b \geq 1$, RSP does not hold



$b > 1$: selectivity increases with reactivity
54 out of 100 cases

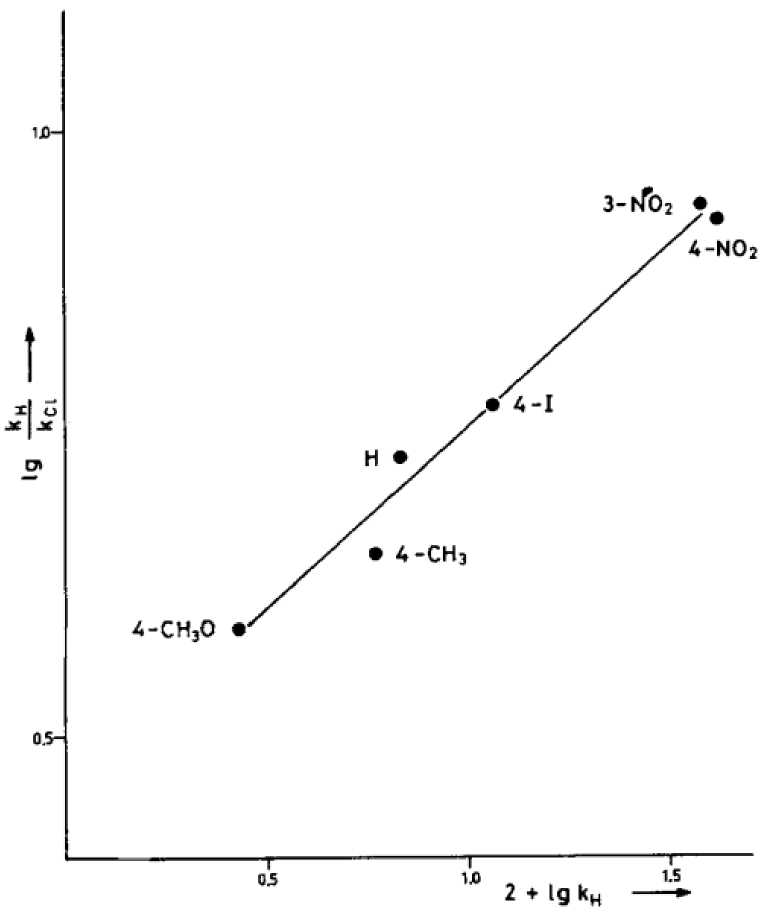
$b = 1$: no change in selectivity as reactivity varies

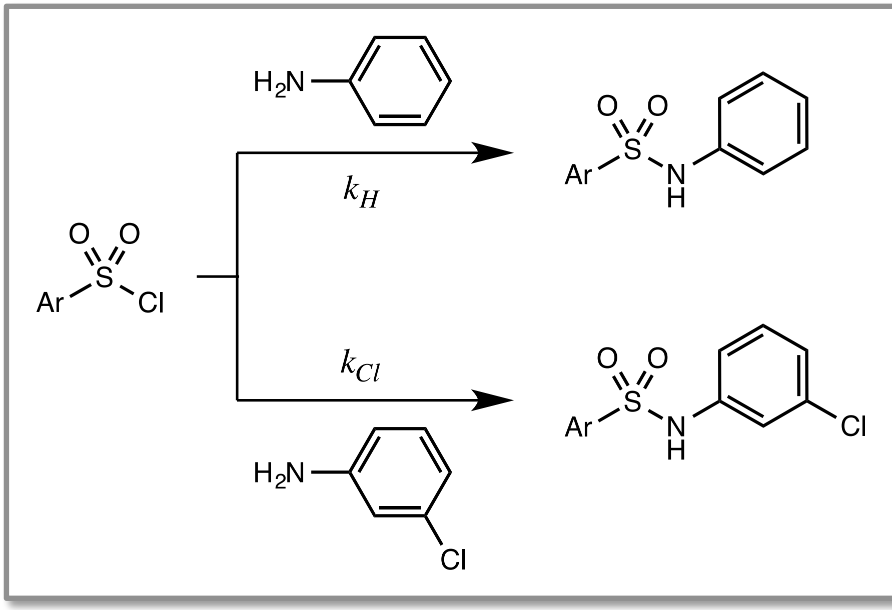
$b < 1$: selectivity decreases as reactivity increases
46 out of 100 cases

Exner, O. *J. Chem. Soc. Perkin Trans. 2* **1993**, *5*, 973.

Reversal of the Reactivity-Selectivity Principle: Case Study 1

Reaction of various sulfonyl chlorides with aniline and 3-chloroaniline

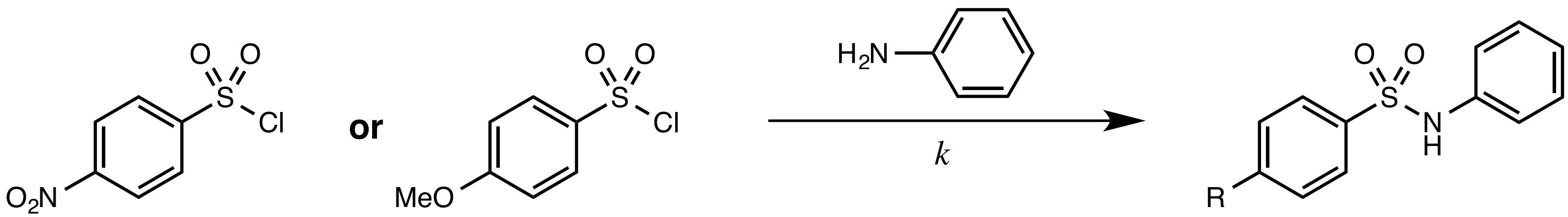


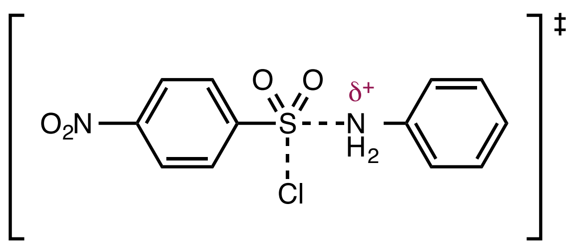


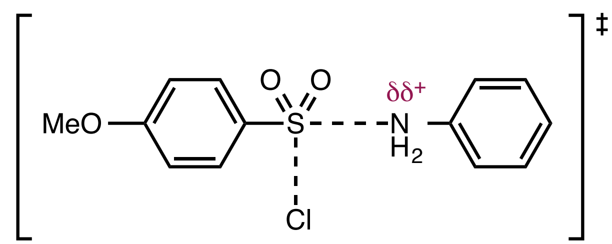
selectivity increases with increasing reactivity

Giese, B. *Angew. Chem. Int. Ed.* **1977**, *16*, 125.

Reversal of the Reactivity-Selectivity Principle: Case Study 1







more reactive, more selective

- slight S–Cl bond cleavage
- extensive S–N bond formation
- significant charge buildup on N

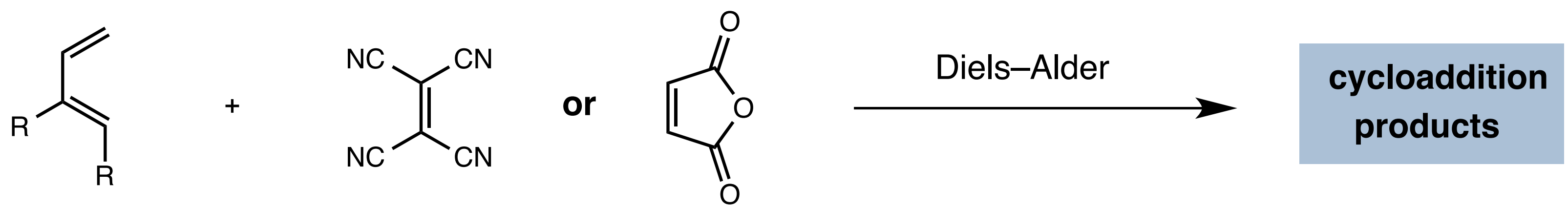
less reactive, less selective

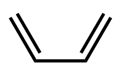
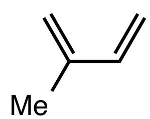
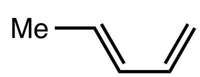
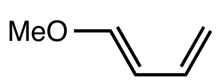
- extensive S–Cl bond cleavage
- slight S–N bond formation
- little charge buildup on N

changes in reactant structure may cause non-obvious deformations in the transition state that determine selectivity and reactivity

Giese, B. *Angew. Chem. Int. Ed.* **1977**, *16*, 125.

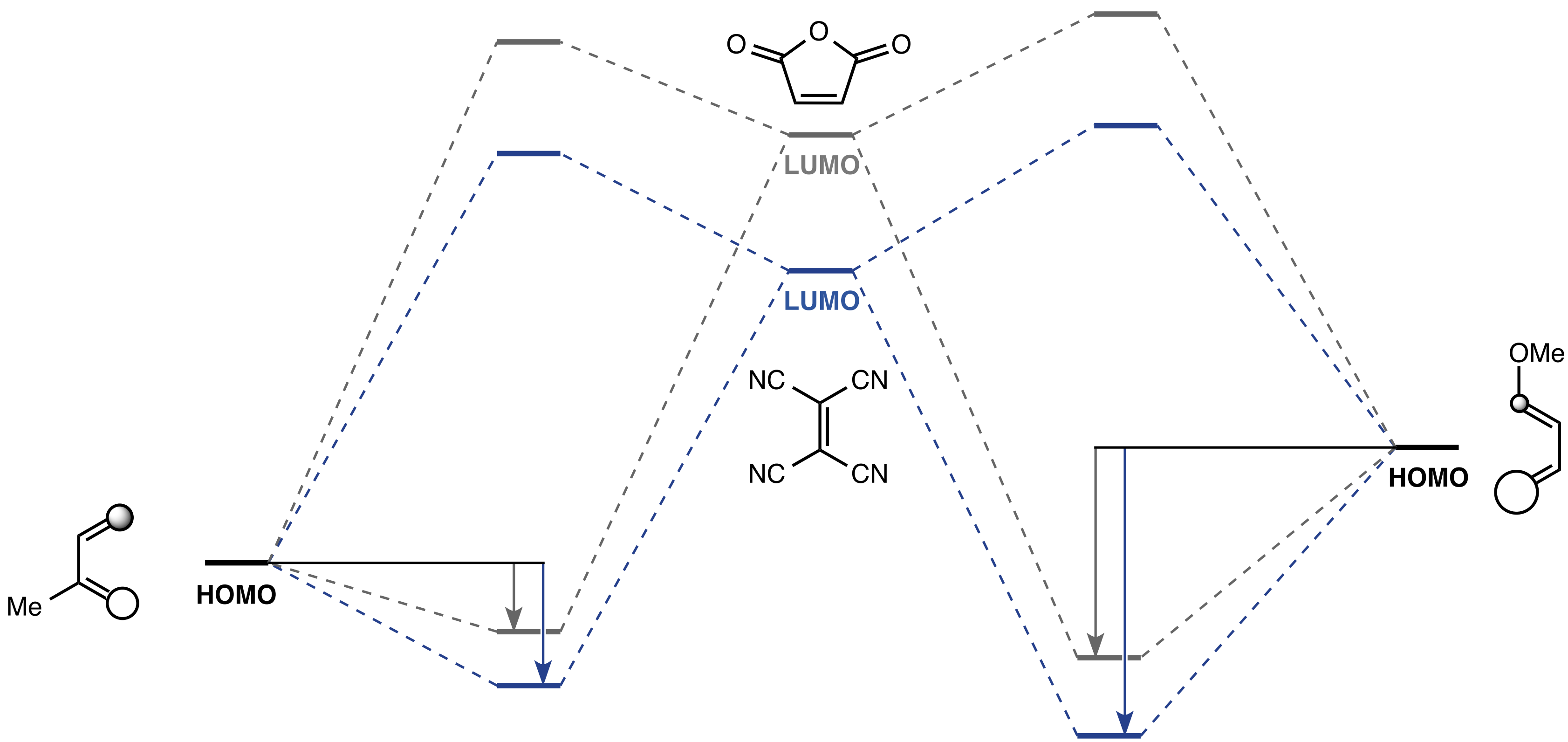
Reversal of the Reactivity-Selectivity Principle: Case Study 2



diene	$k_{rel,TCNE}$	$k_{rel,MA}$	$k_{TCNE} : k_{MA}$
	1	1	1:1
	45	2.3	20:1
	103	3.3	31:1
	50900	12.4	4104:1

Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* **1980**, *113*, 1663.
Sundberg, R. J.; Carey, F. A. In *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 5th ed.; Springer: New York, 2007; pp. 288–289.

Reversal of the Reactivity-Selectivity Principle: Case Study 2

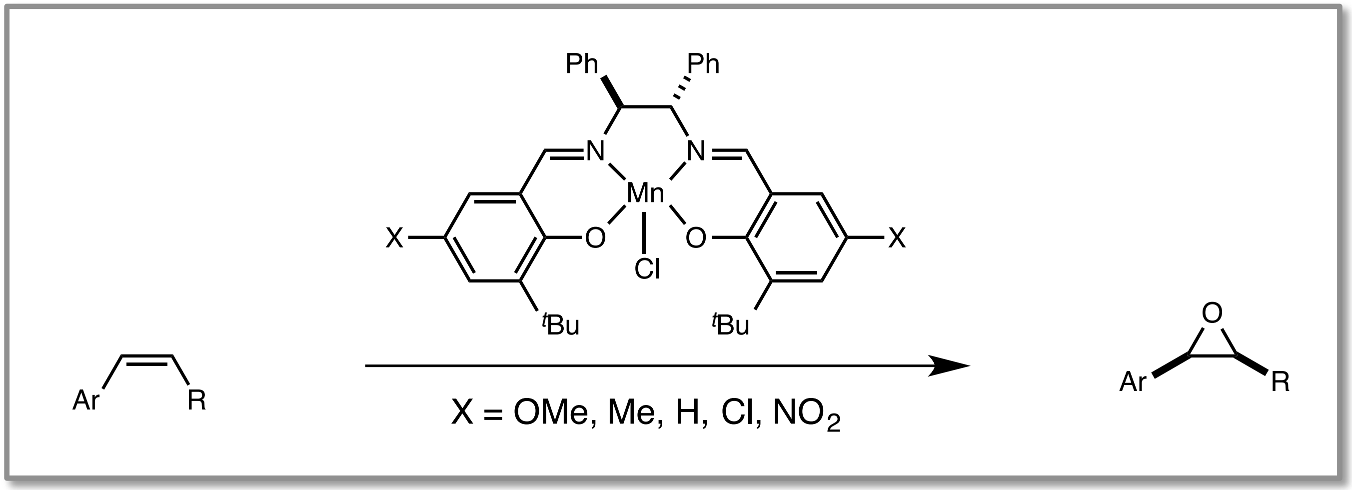


frontier molecular orbital effects dominate:
smaller HOMO-LUMO gap leads to faster rate, and orbitals of more similar energy overlap more effectively (better selectivity)

Giese, B. *Angew. Chem. Int. Ed.* **1977**, *16*, 125.
Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; Wiley, 2009.

An RSP-Consistent Reaction: Case Study 3

■ Jacobsen (salen)Mn-catalyzed epoxidation

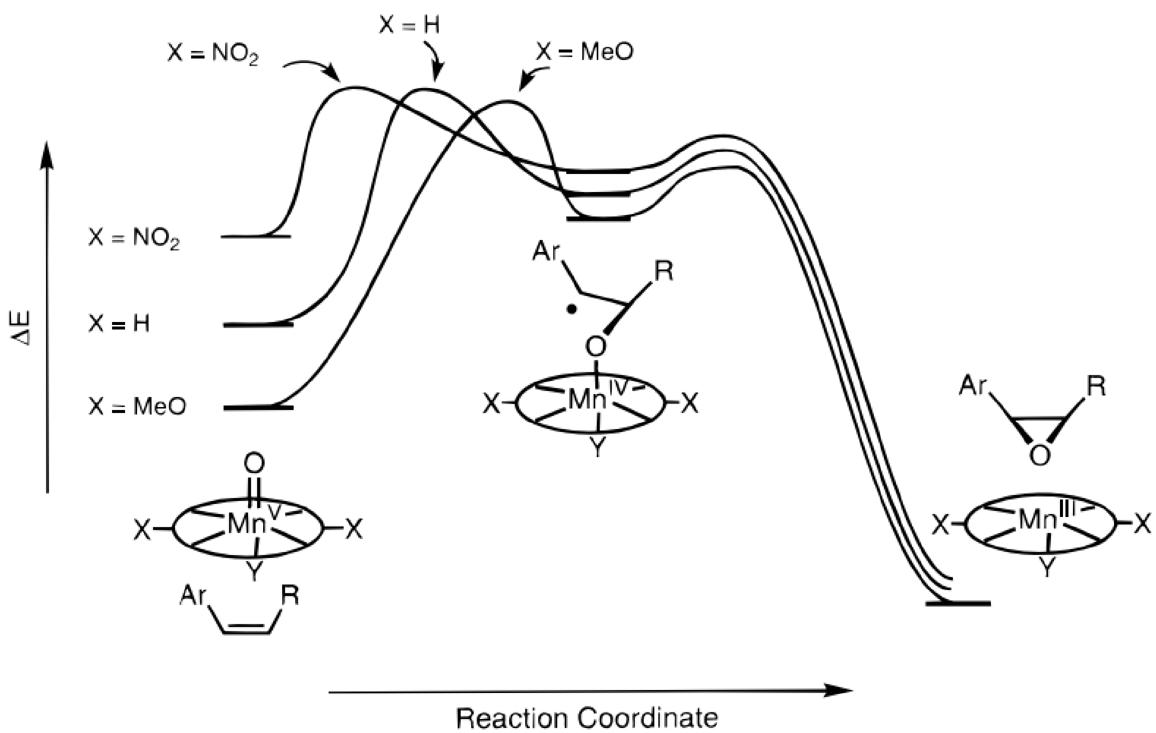


ligands bearing more electron-donating groups produce higher enantioselectivities

Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

■ Proposed mechanism providing rationale for observed selectivity

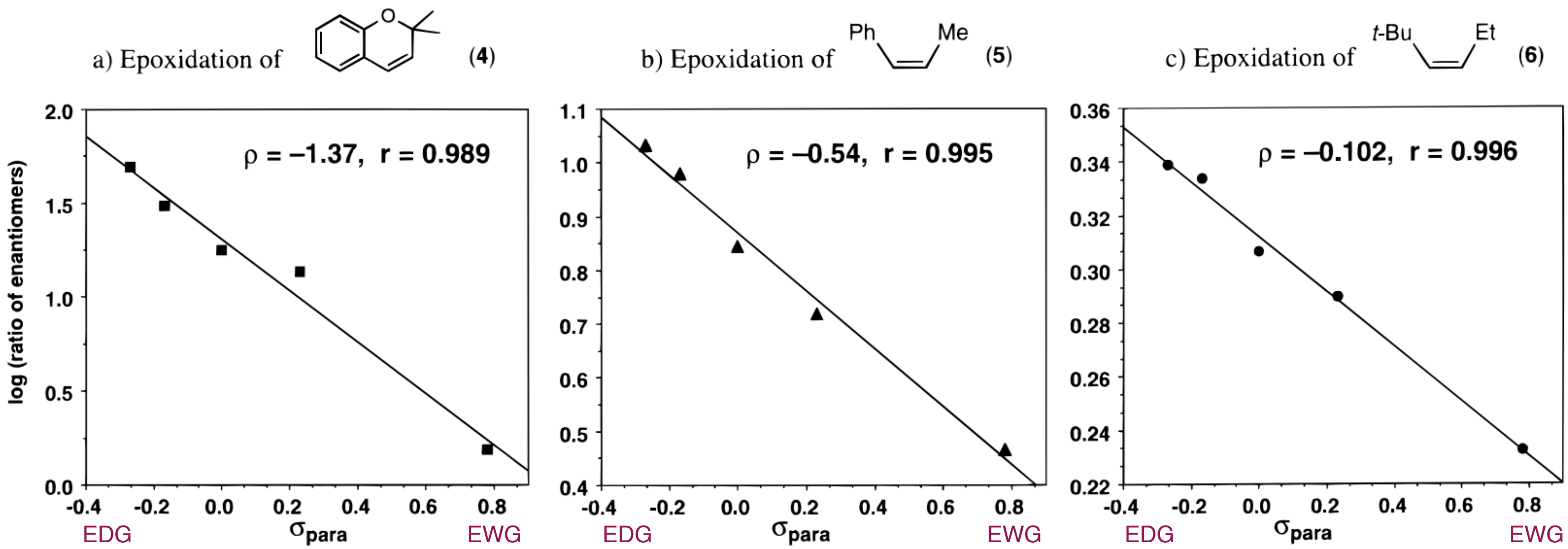


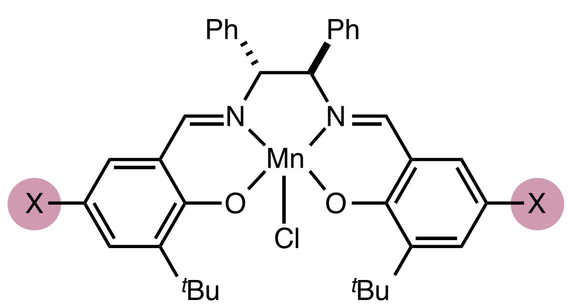
hypothesis: "electron-donating groups attenuate the reactivity of the oxo species, leading to a comparatively late transition state and concomitantly higher enantioselectivity"

Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

Hammett plots reveal the influence of electronics on enantioselectivity





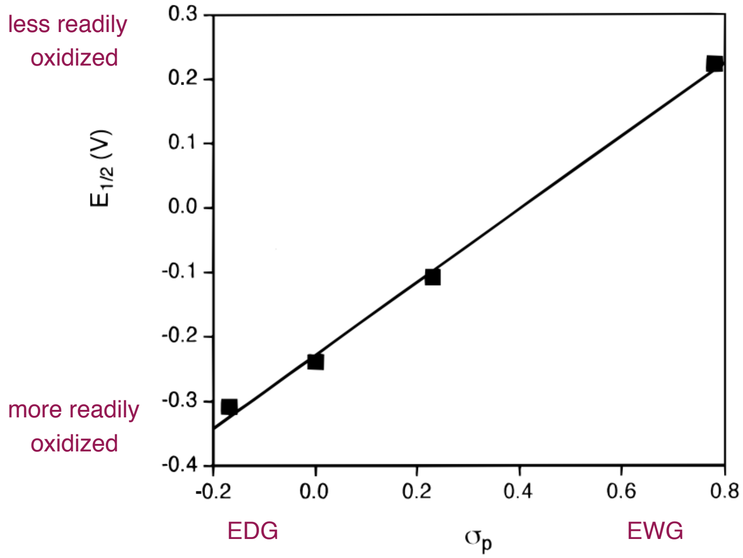
X = OMe, Me, H, Cl, NO_2

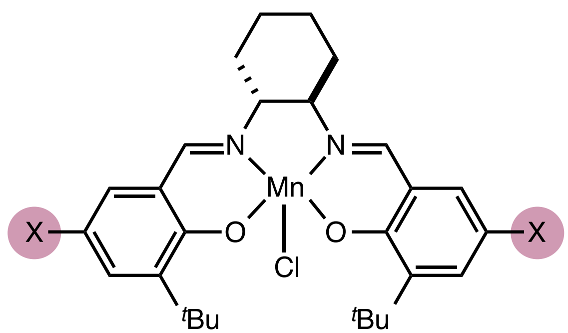
strong correlation observed between electronic nature of ligand (σ) and ee

Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

Evidence in support of stabilization of Mn(V) oxo complex





X = OMe, Me, H, Cl, NO_2

for Mn(II)/Mn(III) redox couple, strong correlation observed between electronic nature of ligand (σ) and redox potential

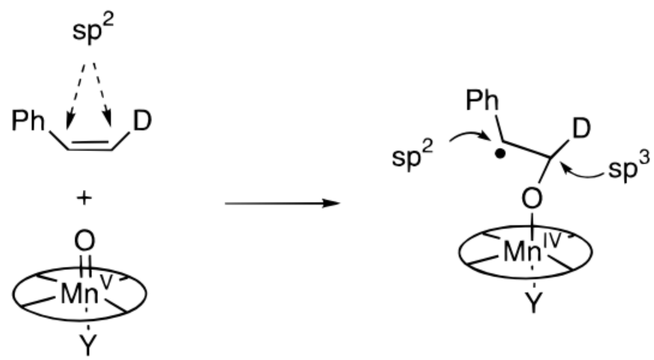
⇩

more electron-donating substituents appear to stabilize more highly oxidized catalyst systems

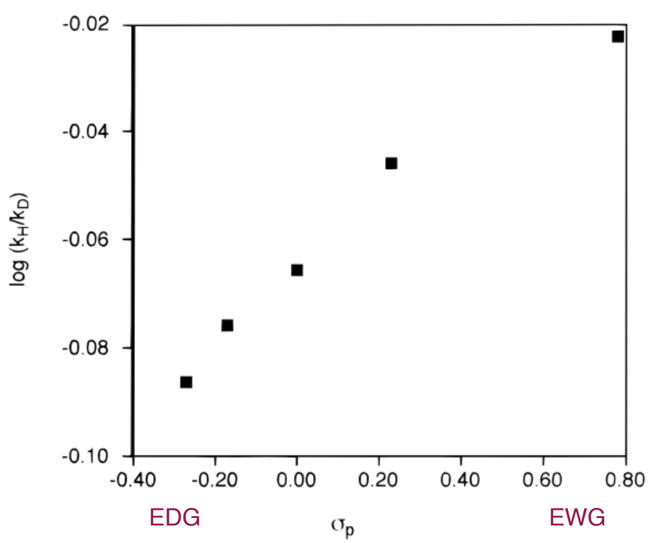
Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

■ Examination of "lateness" of transition states via kinetic isotope effects



"later" transition state should possess more sp^3 character, and therefore exhibit a more significant inverse secondary KIE



more electron-donating substituents produce a more pronounced KIE, suggesting a later transition state

Paluck, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

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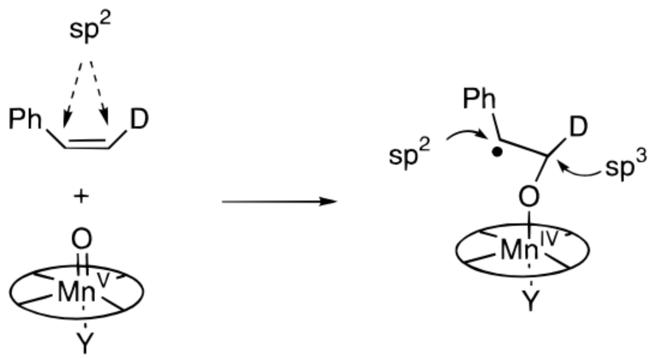

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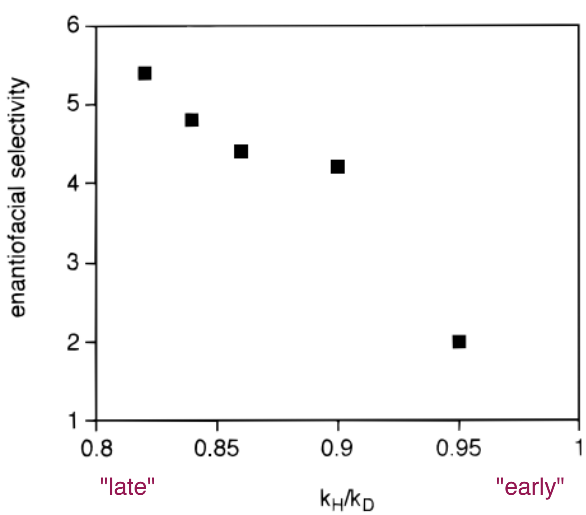
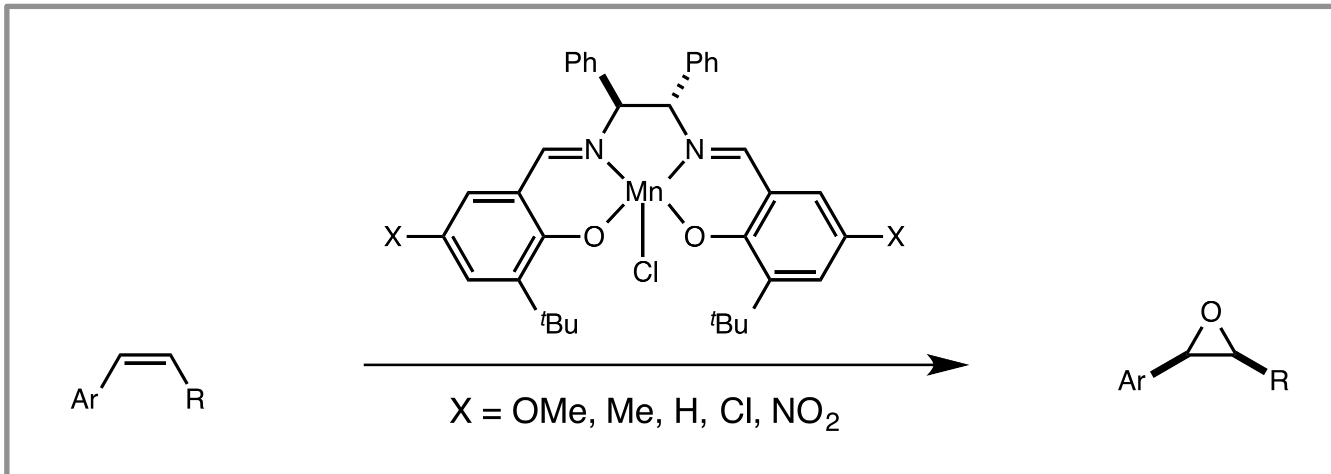


reactions that exhibit a more pronounced KIE ("later" TS) are more enantioselective

Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

An RSP-Consistent Reaction: Case Study 3

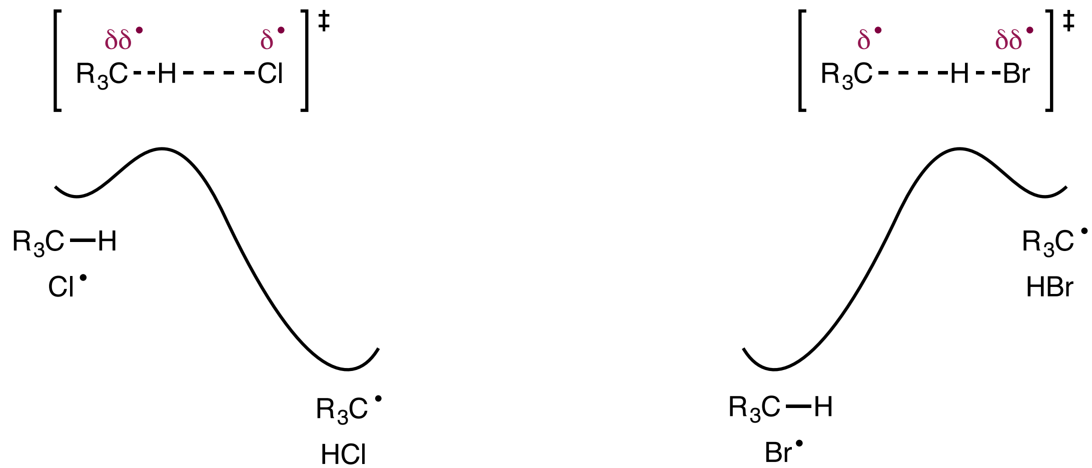
■ Jacobsen (salen)Mn-catalyzed epoxidation



mechanistic data are consistent with the theoretical foundations of the reactivity-selectivity principle

Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

Reactivity and Selectivity



The reactivity-selectivity principle cannot be applied as a general rule of thumb.

- however, the theoretical basis of the RSP may be useful in cases where it is supported by experiment
- specialized analysis of reaction classes may offer more useful frameworks for understanding selectivity
- a general theory to explain any relationship between reactivity and selectivity remains elusive