Master Course
in Organic Chemistry

2018-19

methods **and design** in organic synthesis

Pere Romea

Rubik's cube

4.1. FG Strategies

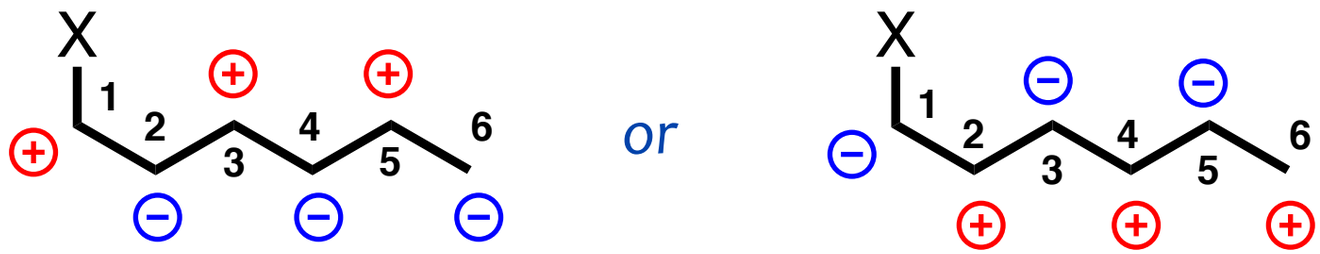
A much more rational approach
to retrosynthetic analysis
involves the analysis of the relationships
among the functional groups located in a molecule.

In this context, a molecule could be viewed as
an ionic aggregate …

1. Inspired by **heterolytic mechanisms**: nucleophile/electrophile

2. Any TGT is formed by a carbon backbone & FG (**heteroatom**)

3. The FG (**heteroatom**) polarizes the carbon backbone



"It might be useful to consider the carbon framework of any molecule as an ionic aggregate, whose origin relies on the presence of functional groups.
The symbol designations, + and –, simply denote potential electrophilic or nucleophilic site reactivity"

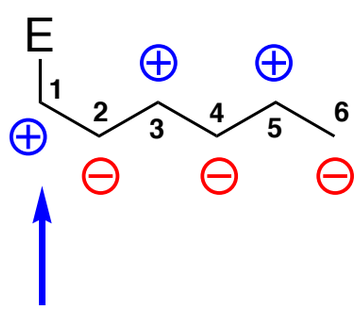
Evans, D. A. *ACR* **1974**, *7*,147. Seebach, D. *ACIEE* **1979**, *18*, 239

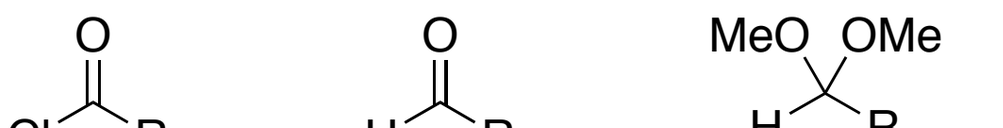
Depending on their nucleophilic / electrophilic role,

synthons can be classified as ***electron donors (d)*** *or* ***acceptors (a)*** *and*

are accordingly numbered with respect to the relative positions of

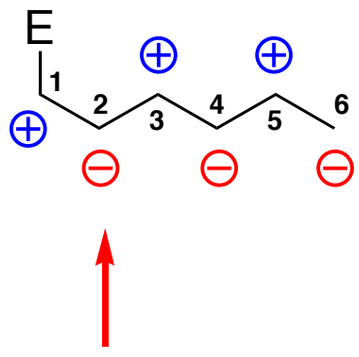
a FG and the reactive carbon atom

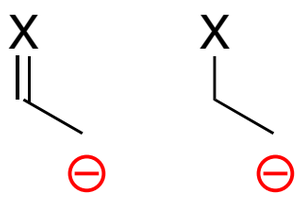


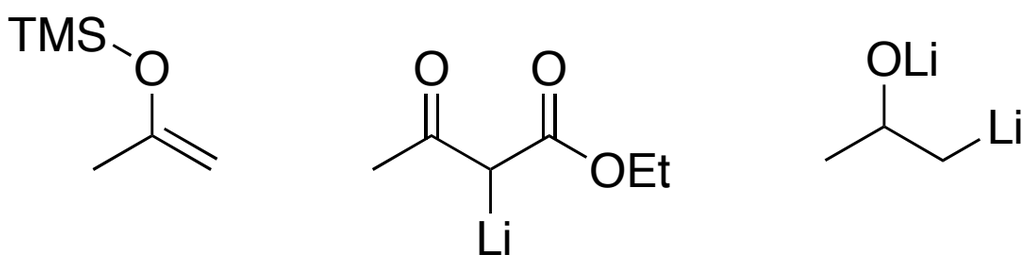


Synthon a^1

Synthetic precursors





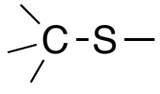


Synthon d^2

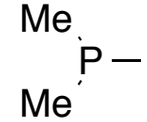
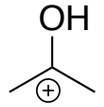
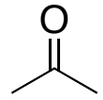
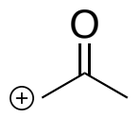
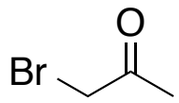
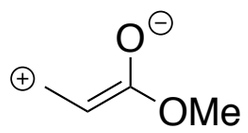
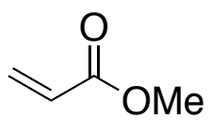
Synthetic precursors

Therefore, synthons can be ***a^0, a^1, a^2, a^3, … or d^0, d^1, d^2, d^3, …***

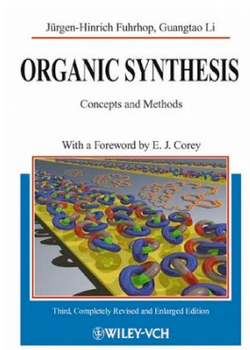
Synthons d

Type	*Example*	*Reacting materials*	*FG*
d^0	$MeS^{\ominus}$	MeSH	
d^1	$^{\ominus}C{\equiv}N$	$KC{\equiv}N$	$-C{\equiv}N$
d^2	$^{\ominus}CH_2CHO$	CH_3CHO	$-CHO$
d^3	$^{\ominus}C{\equiv}C{-}COOMe$	$HC{\equiv}C{-}COOMe$	$-CO_2Me$
Alkyl-d	$Me^{\ominus}$	MeLi	

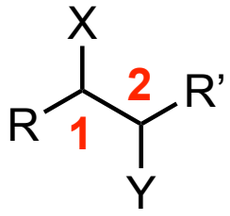
Synthons a

Type	*Example*	*Reacting materials*	*FG*
a^0	$^{\oplus}PMe_2$	$ClPMe_2$	
a^1			$-CO-$
a^2			$-CO-$
a^3			$-CO_2Me$
Alkyl-a	$Me^{\oplus}$	MeI	

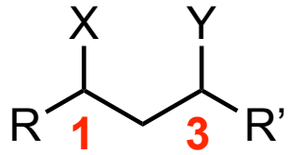
Chaps. 1.1-1.3



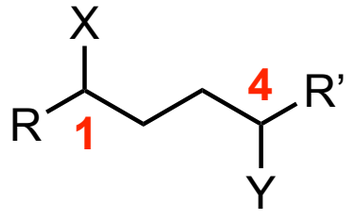
The relationship between two FG depends on how distant they are …



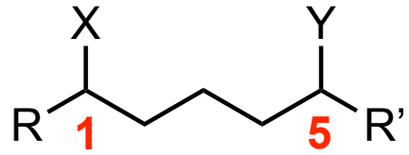
1,2-Relationship



1,3-Relationship

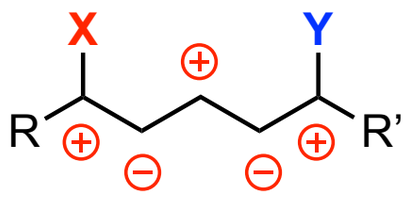


1,4-Relationship

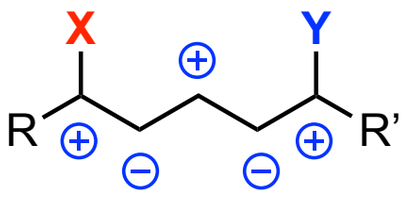


1,5-Relationship

… and the polarization that they impart on the backbone

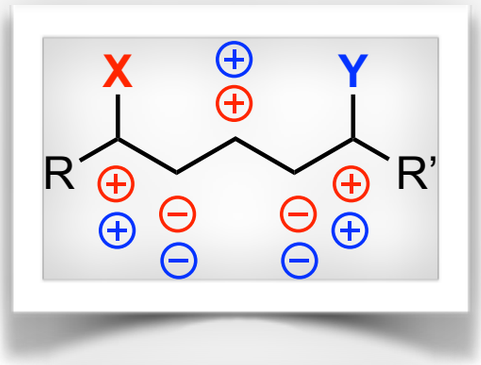


*polar arrangement from **X***

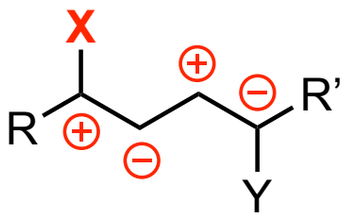


*polar arrangement from **Y***

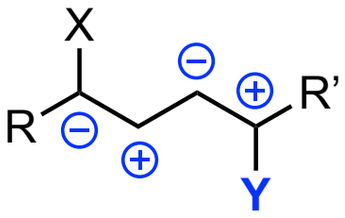
≡



consonant (matched)

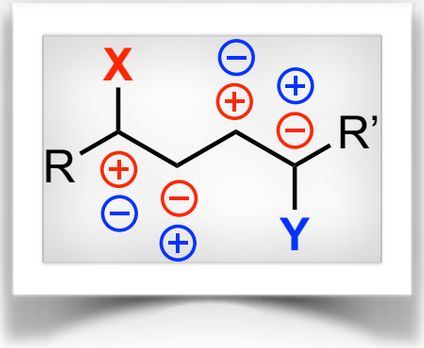


*polar arrangement from **X***



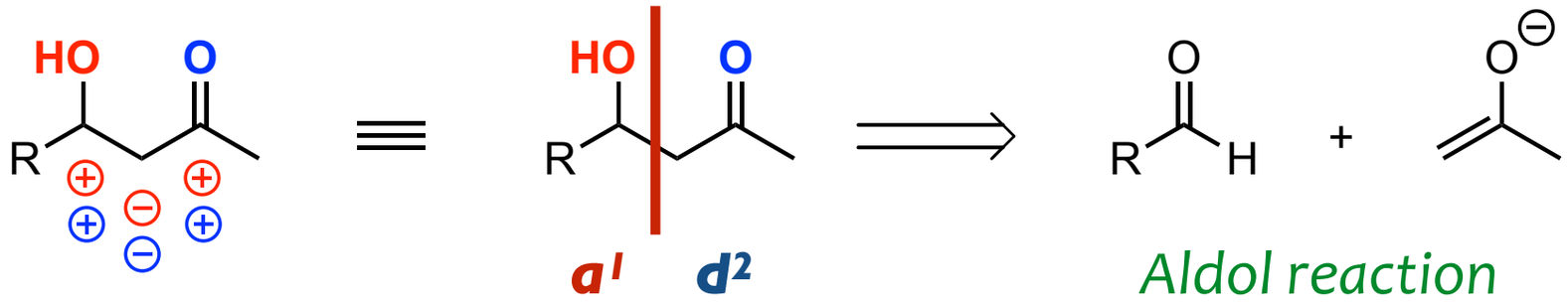
*polar arrangement from **Y***

≡

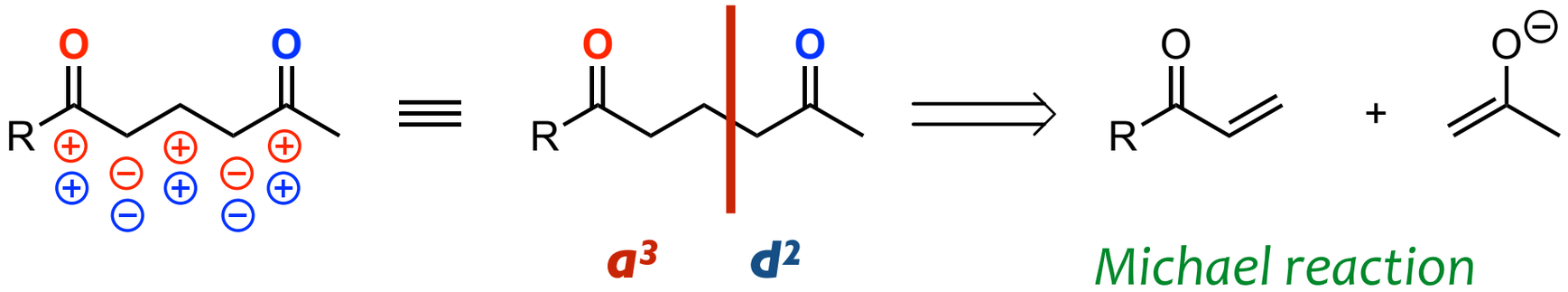


dissonant (mismatched)

Consonant (matched) relationships are quite easy to analyze …



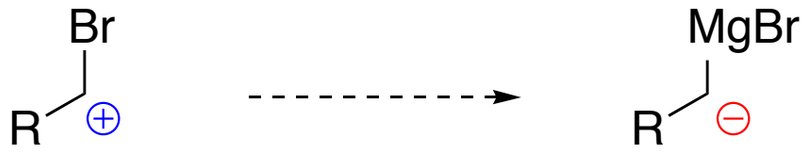
Aldol reaction



Michael reaction

Dissonant *(**mismatched**) relationships are much more complicate and usually require the inversion on the polarity (**UMPOLUNG**) of one of the participants*

UMPOLUNG *refers to the change of the self-reactivity of a synthon*

Acceptor, ***a¹*** 

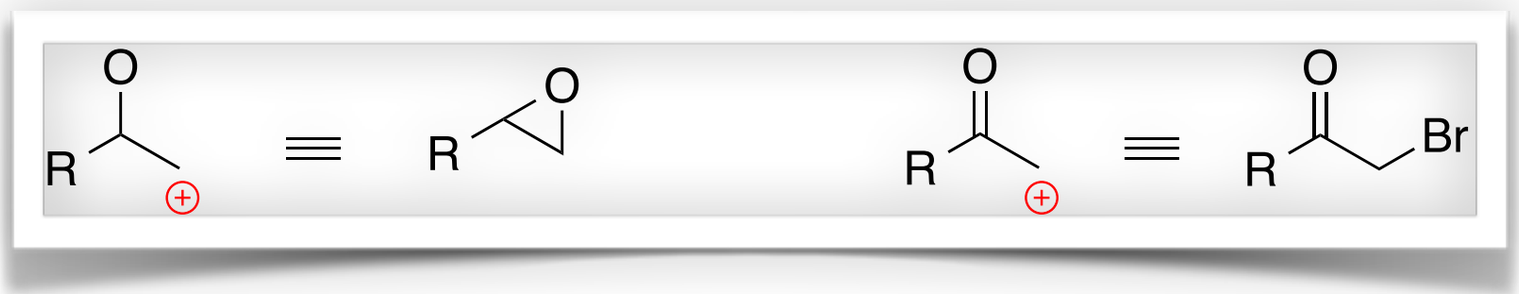
Donor, ***d¹***

Acceptor, ***a¹*** 

Donor, ***d¹***

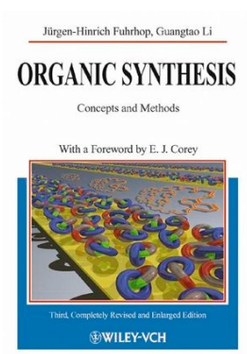
Seebach, D. ACIEE **1969**, *8, 639;* **1979**, *18,* 239
For a seminal application, see Seebach, D.; Corey, E. J. JOC **1975**, *40,* 231

Pay an especial attention to a² synthons



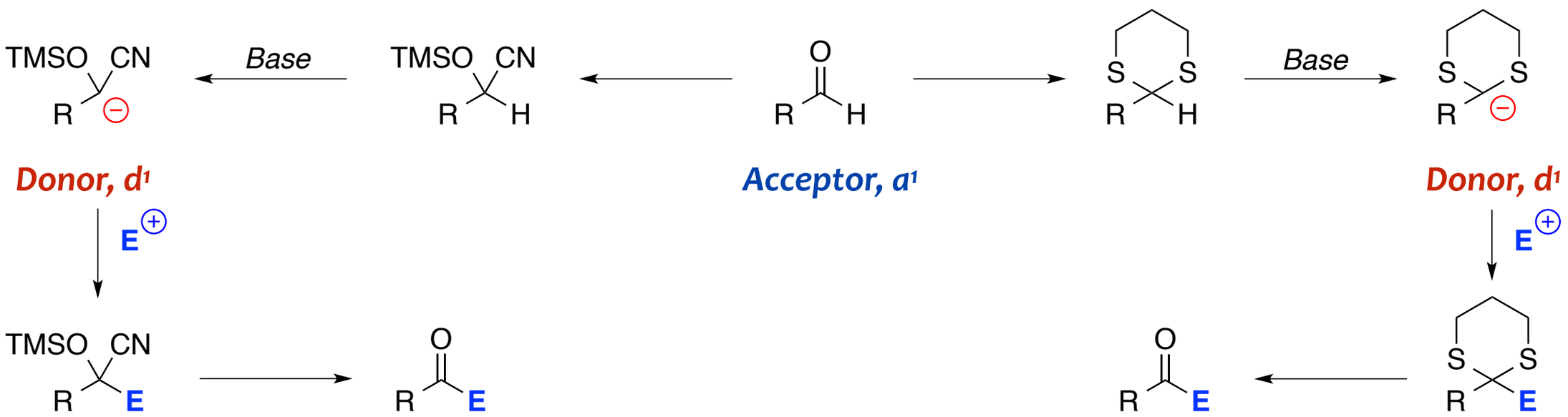
a² Synthons

Chaps. 1.1-1.3

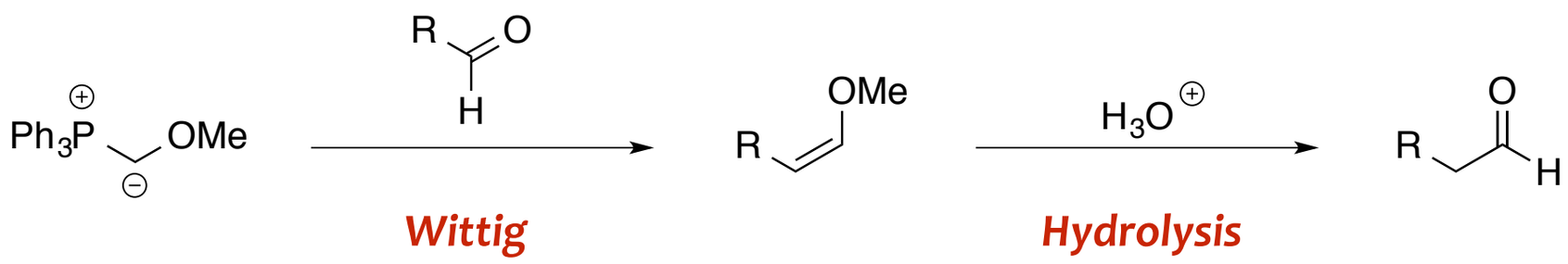


CARBONYL EQUIVALENTS

refers to modifications on the carbonyl FG that producing an inversion on reactivity



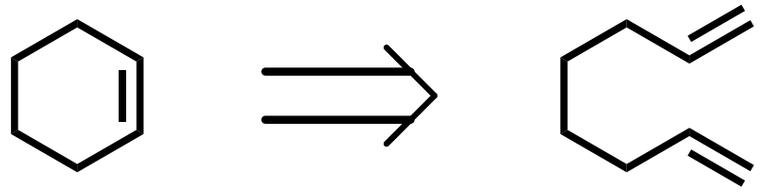
MASKED CARBONYL COMPOUNDS



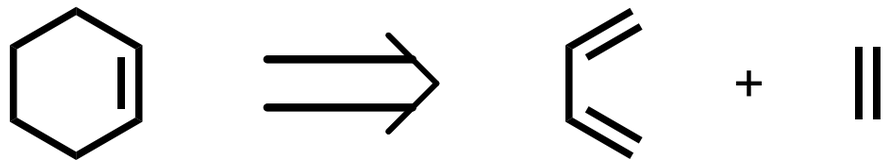
CAVEATS

The heterolytic character of the disconnections associated to FGs precludes the use of some organometallic transforms

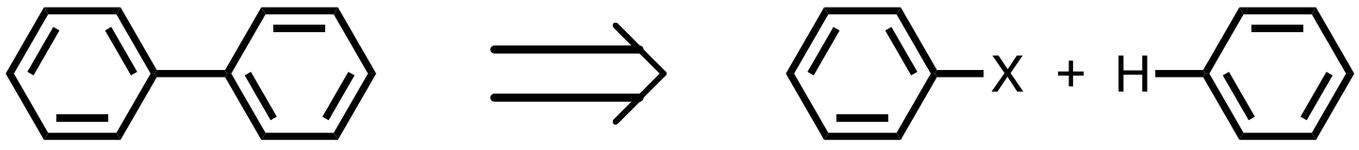
Pericyclic & radical transforms are also excluded



Ring-Closing-Metathesis



Diels-Alder



C–H Activation

For a recent account on the use of radical transforms in retrosynthetic analysis, see

ACCOUNTS of chemical research

Article

Cite This: *Acc. Chem. Res.* 2018, 51, 1807–1817

pubs.acs.org/accounts

Radical Retrosynthesis

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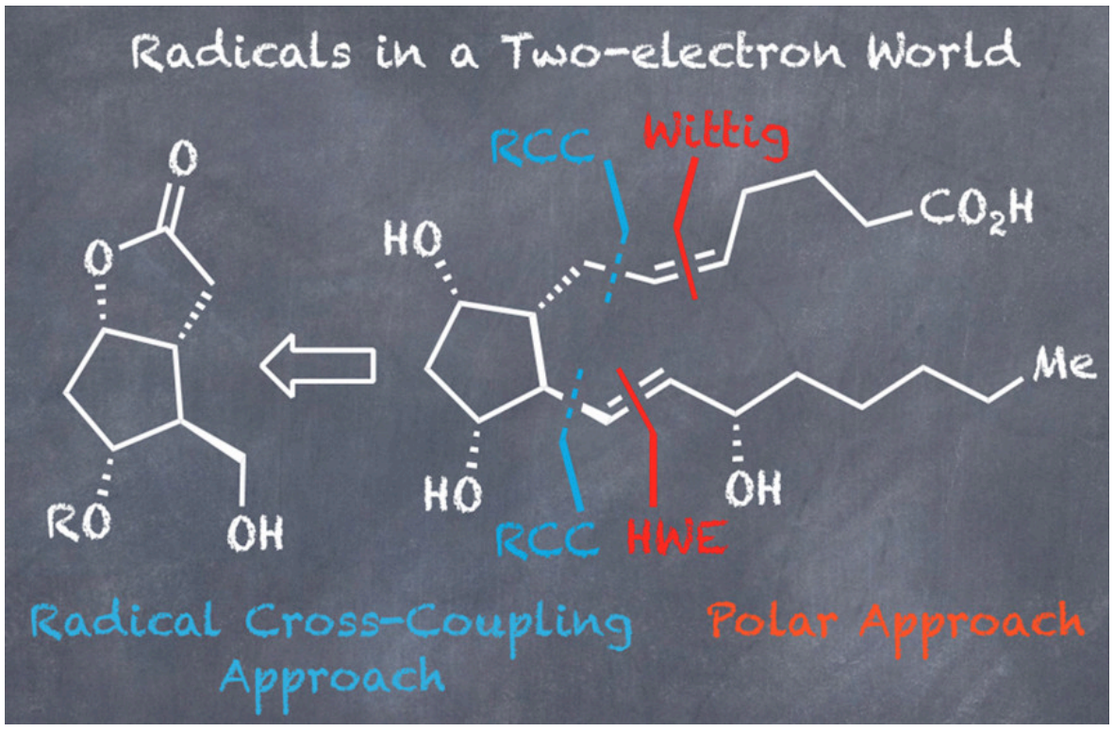

Baran, P. S.
ACR **2018**, *51*, 1807