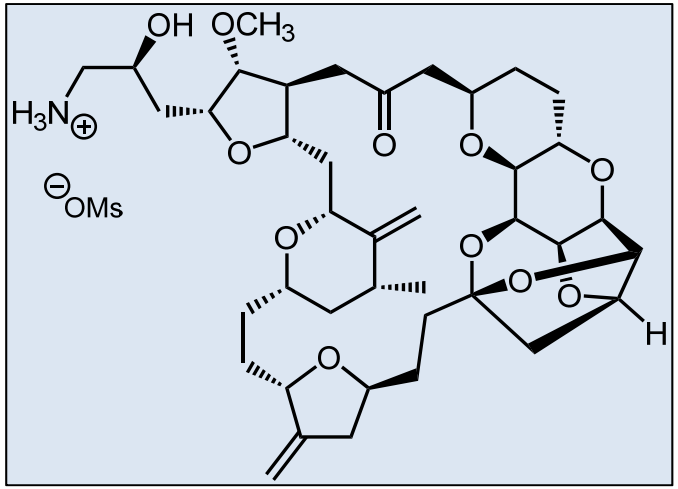
Prof. Dr. Thomas Lindel,
TU Braunschweig, Institute of Organic Chemistry
Class *"Strategies of Synthesis"*

1 Importance of Organic Synthesis
2 Efficiency criteria
3 Non-radical retrosynthesis
4 Selected carbocycles
5 Radical retrosynthesis



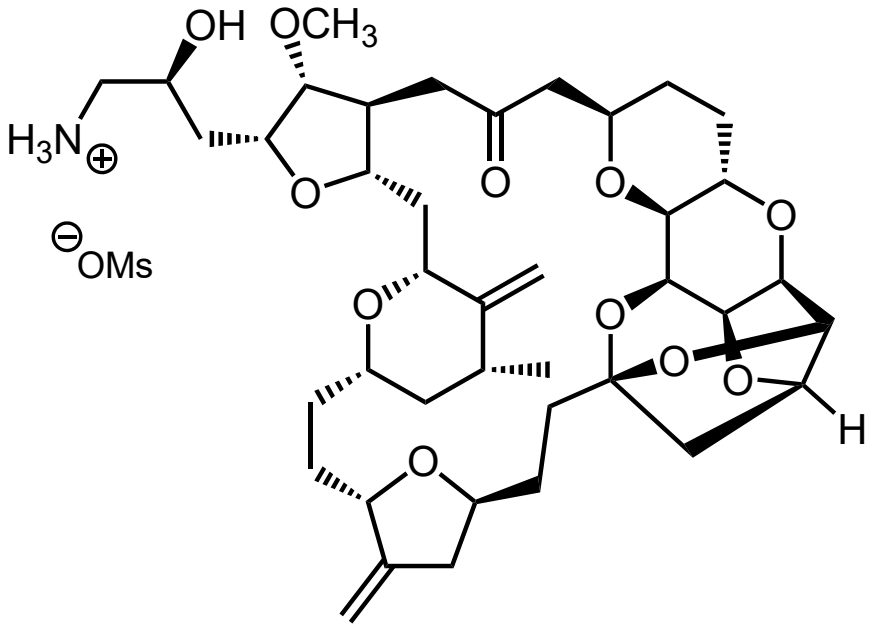
eribulin mesylate: a drug!

Wer nach Promotion und Auslands-Postdoktorat in der chemischen oder pharmazeutischen Industrie forschen will, beschäftige sich möglichst früh mit Organischer Synthese.

Wer Moleküle und deren Eigenschaften jenseits der Möglichkeiten lebender Systeme gezielt verändern möchte, der auch.

Ebenso der, der eigentlich lieber Architekt geworden wäre.

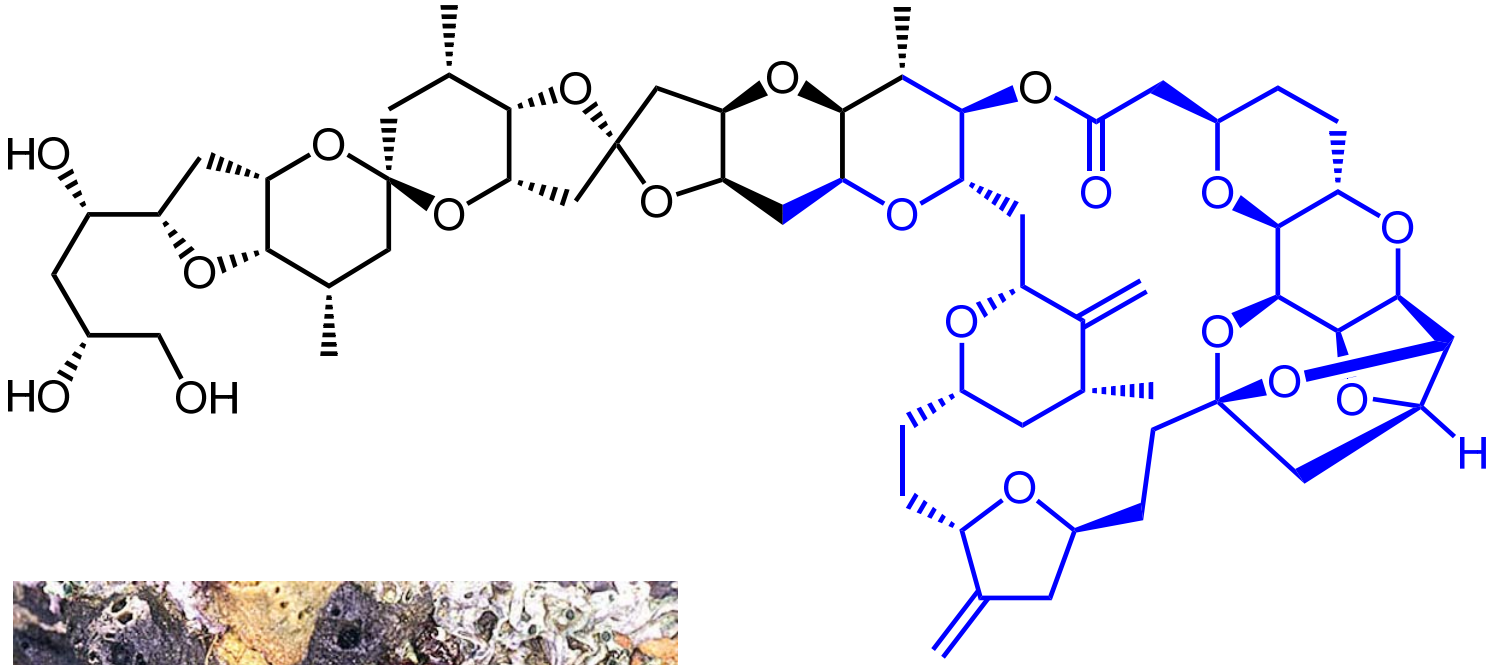
Eribulin mesylate, a microtubule destabilizing agent, has gained approval in the US for patients who have received at least two chemotherapeutic regimens for the treatment of metastatic breast cancer (MBC), with prior therapy including an anthracycline and a taxane.



Eribulin (E7389, Halaven)
antitumor

Mechanism:
suppresses microtubule polymerization, but has no effect on microtubule depolymerization

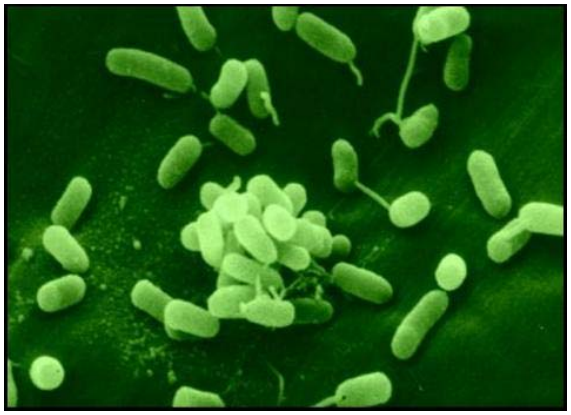
eastern section of halichondrin B, made by Chemical Synthesis (62 steps, based on Kishi's work, *JACS* **1992**, 3162)



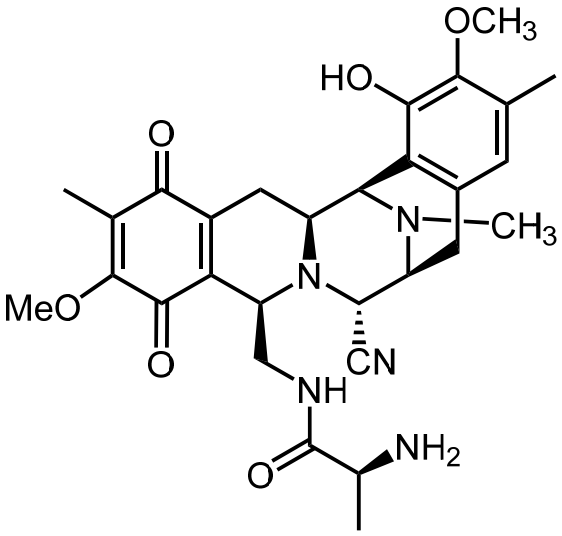
Halichondrin B

from the sponge *Halichondria okadai*, isolation and structure elucidation: Uemura et al. 1985, cytotoxic (IC_{50} < 1 nM)

Sometimes, partial synthesis is better.

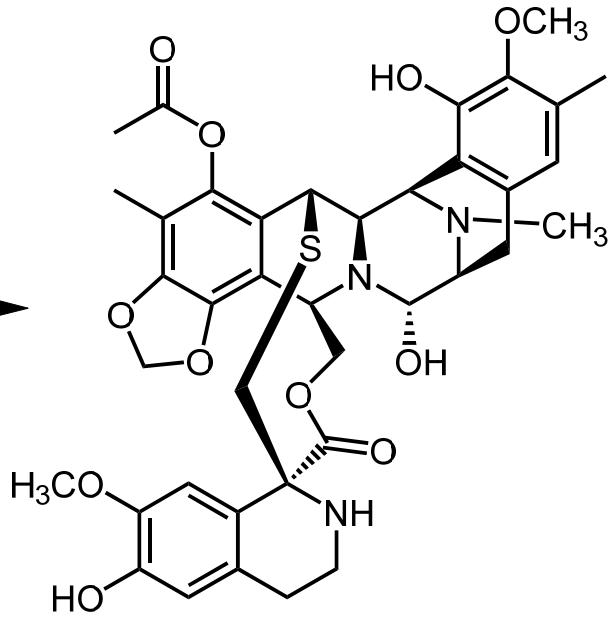


Pseudomonas fluorescens produces cyanosafracin B, used as precursor of ET-743 partial synthesis



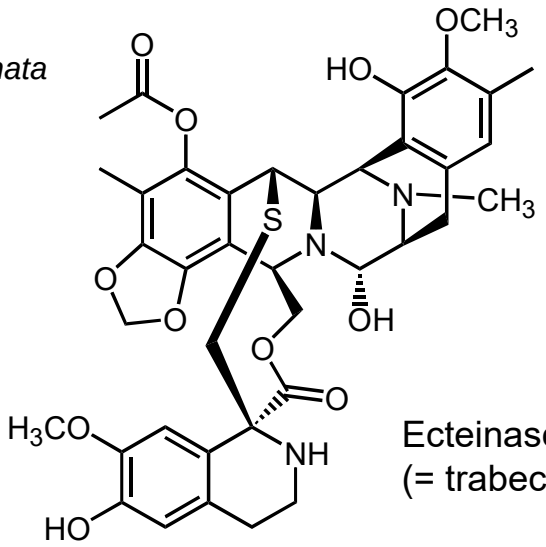
cyanosafracin B

18 steps (instead of originally 46)



ecteinascidin 743

ascidian
Ecteinascidia turbinata
(PharmaMar Inc., Madrid)



Ecteinascidin 743
(= trabectidin, Yondelis)

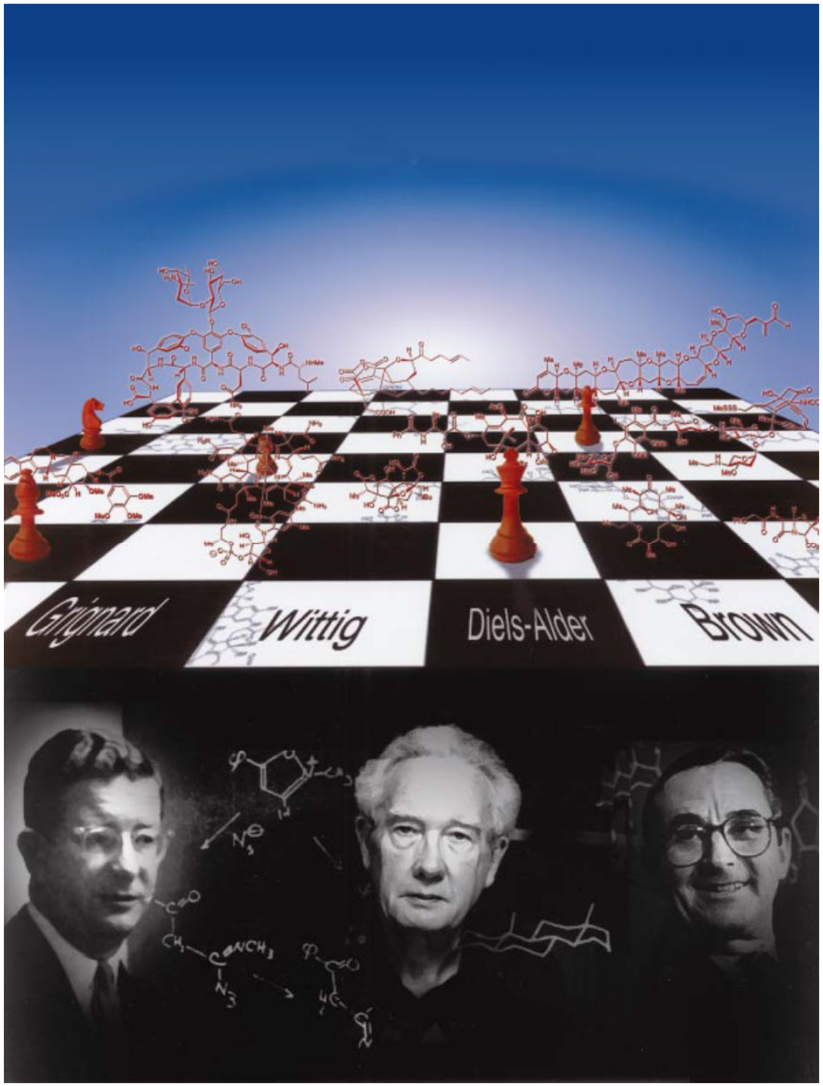
1986: isolation by Rinehart et al.

2007: EC approval for treatment of soft tissue sarcoma after failure of anthracyclines and ifosfamide

2009: EC approval for combination with pegylated liposomal doxorubicin for treatment of relapsed platinum-sensitive ovarian cancer

Review: D'Incalci and Galmarini, *Mol. Cancer Ther.* **2010**, *9*, 2157

1 Importance of Organic Synthesis

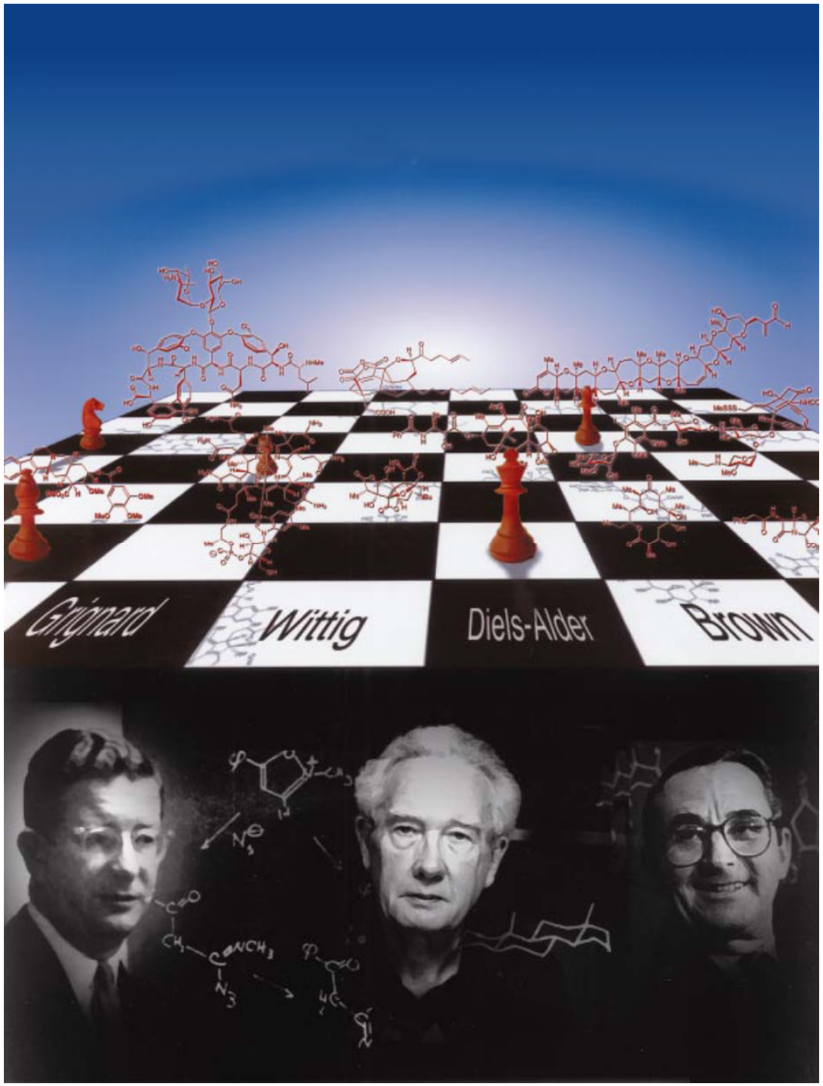


Woodward Barton Corey

from: Nicolaou et al., *Angew. Chem.* **2000**, 46: "Der Stand der Totalsynthese zu Beginn des 21. Jahrhunderts"

Total synthesis comprises the construction of natural products from commercially available starting materials.

1 Importance of Organic Synthesis



Woodward Barton Corey

Why total synthesis?

Quantities of natural products

Structure elucidation

Access to derivatives

Isotopic labeling

Test of new synthetic methods

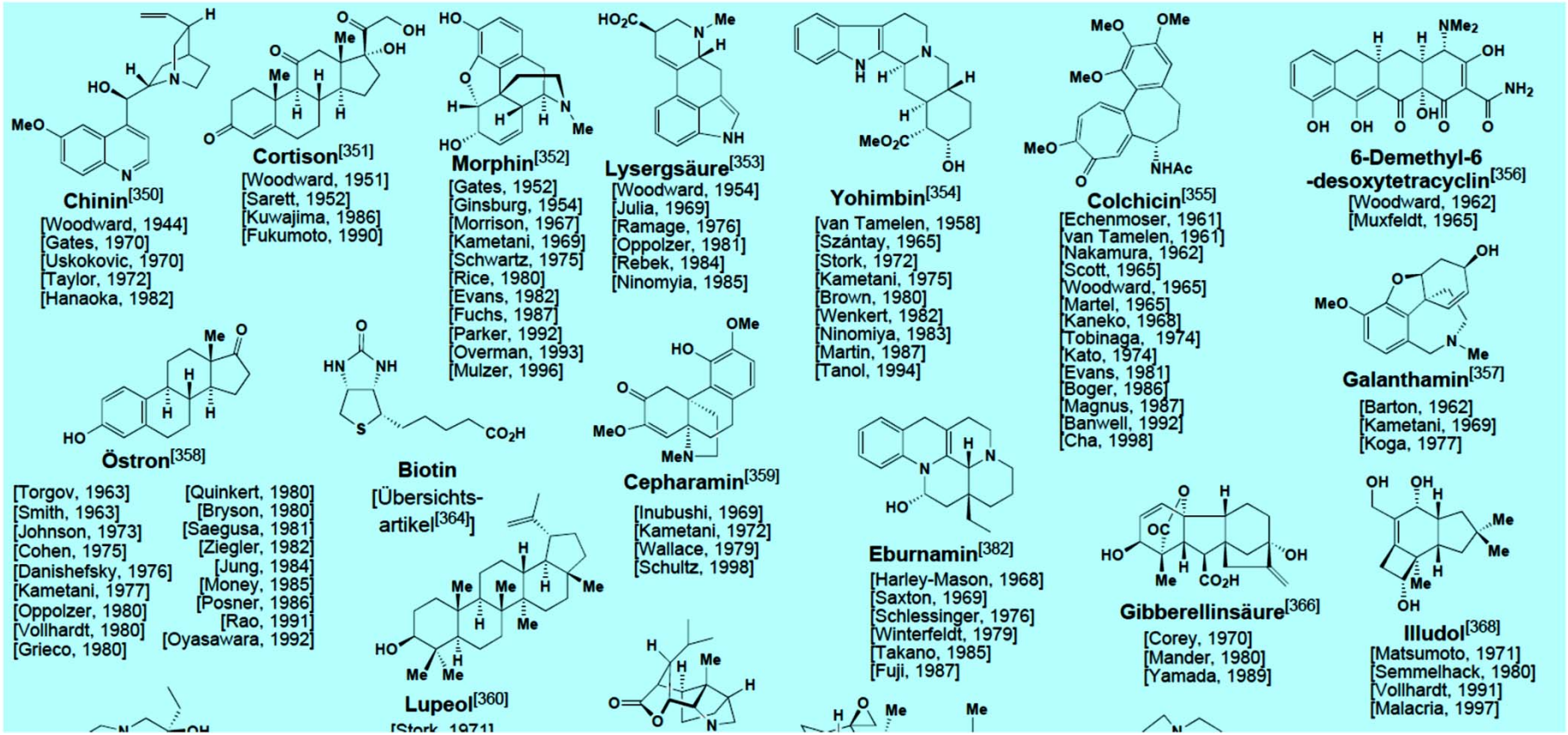
Inspiration for new chemistry

Fun

Education

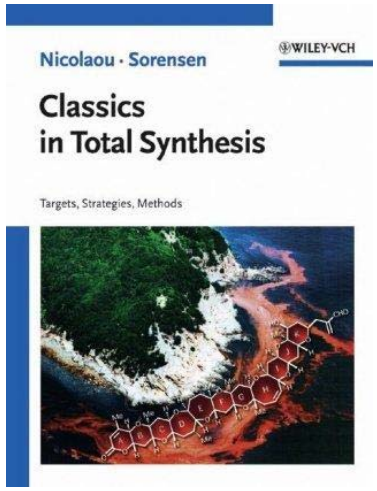
Lindel, *Strategies of Synthesis*

from Nicolaou et al., *Angew. Chem.* **2000**, 46:
"Der Stand der Totalsynthese zu Beginn des 21. Jahrhunderts"

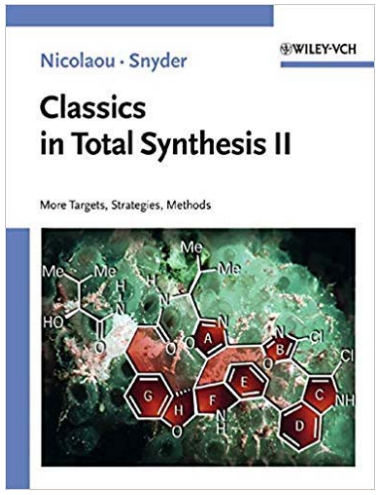


... there are more such Figures in the article ...

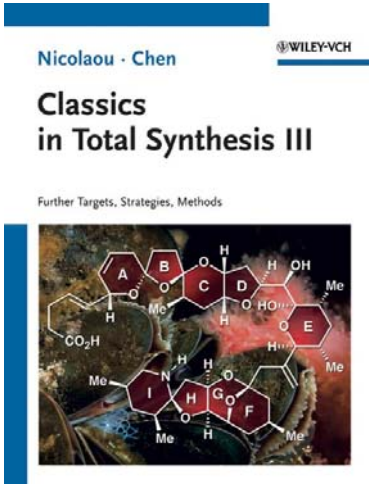
Recommended literature: as cited, but there are also good books on older beautiful examples:



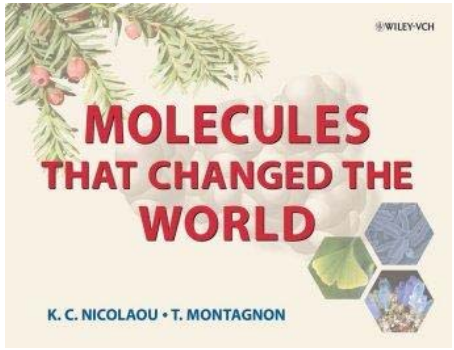
1996



2003



2011



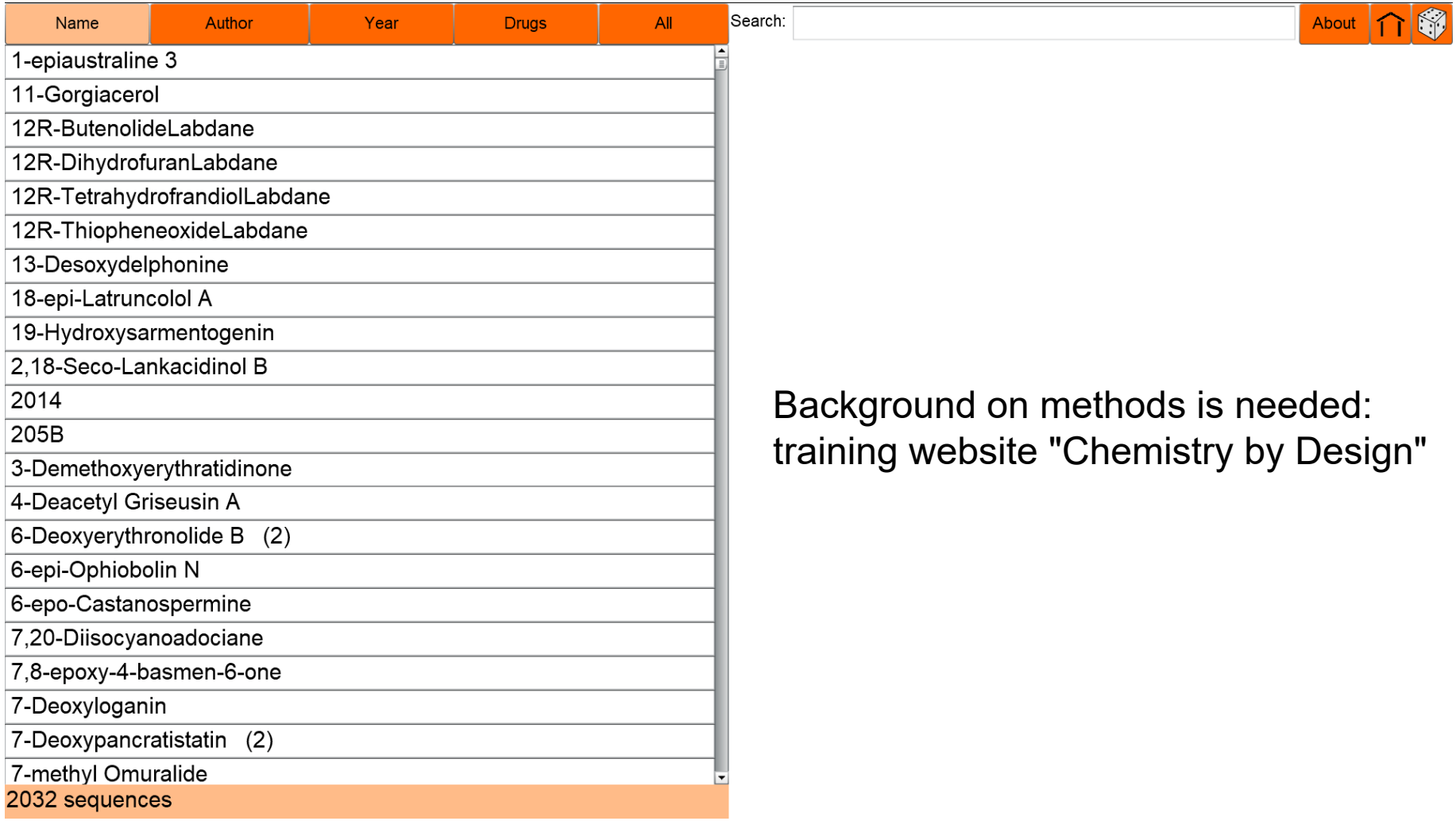
Terpineol, Aspirin, Penicillin, Taxol(TM), D-Glucose, Urea, Camphor, Tropinone, Haemin, Morphine, Strychnine, Penicillin, Longifolene, Prostaglandins, Vitamin B12, Erythronolide, Monensin, Avermectin, Amphotericin, Ginkgolide, Cyclosporin, FK 506, Rapamycin, Calcheamicin, Palytoxin, Taxol, Mevacor, Zaragozic Acid, CP Molecules, Brevetoxin, Ecteinascidin, Epothilones, Resiniferatoxin, Vancomycin, Quinine

1 Importance of Organic Synthesis

2007

1. Allgemeine Einleitung
2. Farbstoffe
2.1 Indigo
2.2 Purpur
2.3 Alizarin
3. Riech- und Aromastoffe
3.1 Damascon
3.2 Jonon
3.3 Jasminoide
3.4 Menthol
3.5 Vanillin
3.6 Muscon
4. Aminosäuren
5. Pharmawirkstoffe
5.1 ACE-Inhibitoren
5.2 β-Lactam-Antibiotika
5.3 Opiate
5.4 Tetrahydrocannabinol
5.5 Aspirin
5.6 Prostaglandine
5.7 Tetrahydrolipstatin
5.8 Coffein
6. Hormone
6.1 Steroide
6.2 Thyroxin
7. Vitamine
7.1 Vitamin-A-Carotinoide
7.2 Vitamin D
7.3 Biotin
8. Pflanzenschutzmittel
8.1 Aminosäureherbizide
8.2 Strobilurine
8.3 Pyrethroide
8.4 Pheromone

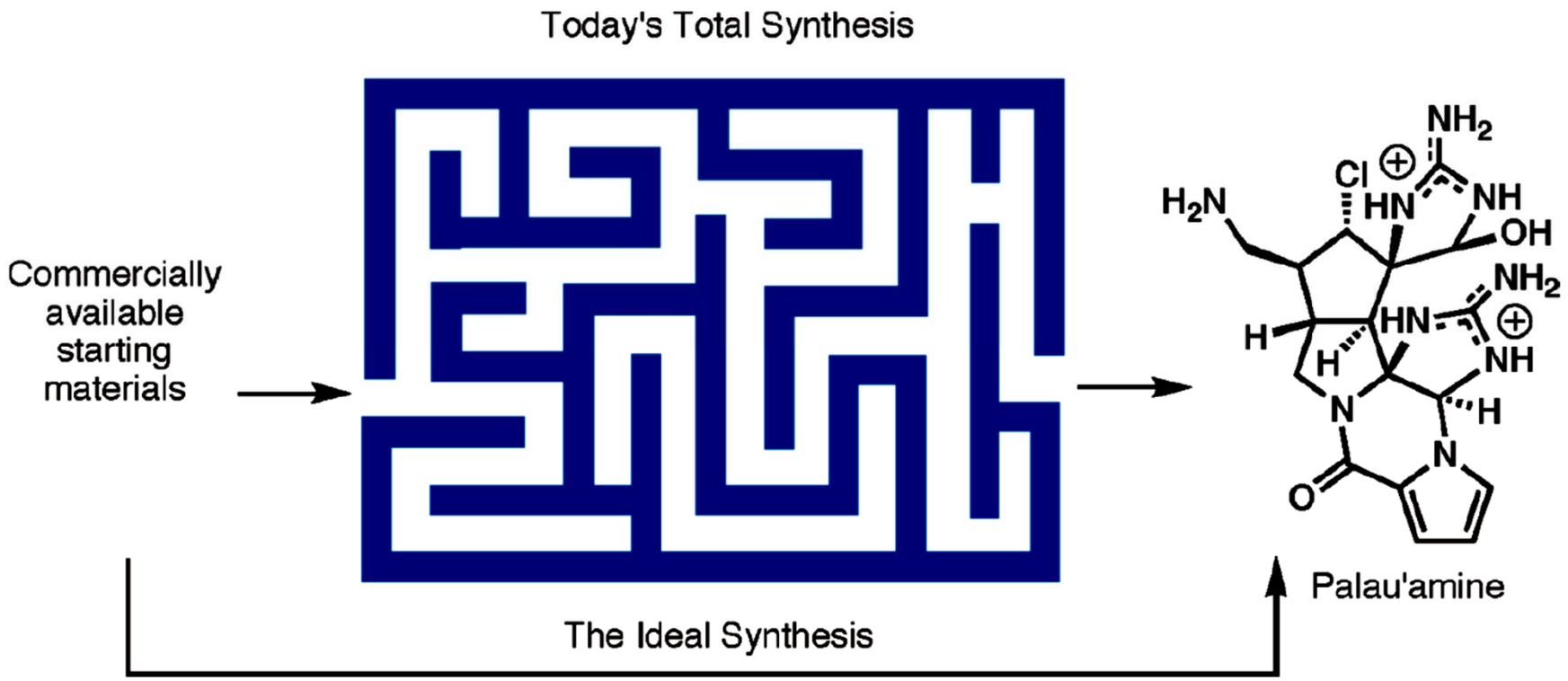
1 Importance of Organic Synthesis



Background on methods is needed:
training website "Chemistry by Design"

http://chemistrybydesign.oia.arizona.edu/app.php

Ideality of a synthesis



from Gaich, Baran, *JOC* **2010**, 4657; DOI: 10.1021/jo1006812

2 Efficiency criteria

One way of defining the ideality of a synthesis:

$$\%\text{ideality} = \frac{[(\text{no. of construction rxns}) + (\text{no. of strategic redox rxns})]}{(\text{total no. of steps})} \times 100$$

Construction reactions, as defined by Hendrickson, are those which form skeletal bonds (C-C and C-heteroatom).

Strategic redox reactions [...] establish the correct functionality found in the final product, such as asymmetric oxidations and reductions or C-H oxidations.

Concession steps: the rest (*e. g.* protecting group operations)

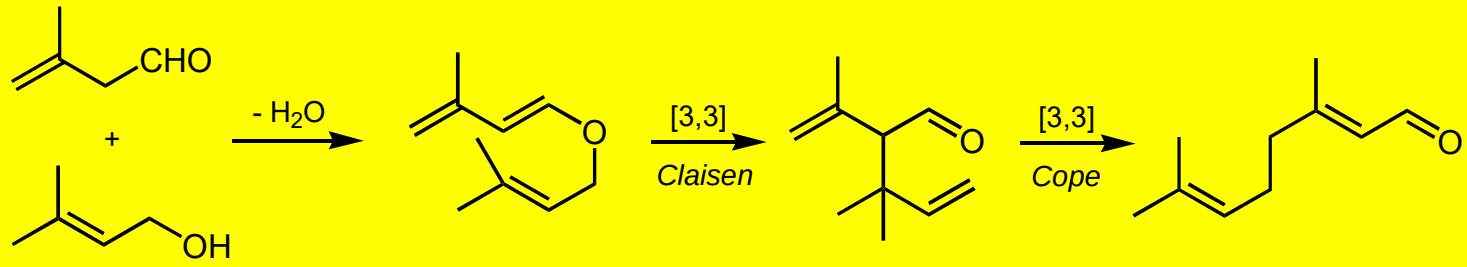
from Gaich, Baran, *JOC* **2010**, 4657; DOI: 10.1021/jo1006812

2 Efficiency criteria

natural product	steps	non-strategic redox	PG manipulation	FGI	strategic redox	construction rxn.	% Ideality
palau'amine (**16**)	25	6	4	7	1	7	32
axinellamines (**18**)	25	5	5	6	2	7	36
massadines (**17**)	25	5	4	7	2	7	36
sceptrin (**19**)	11	2	2	3	1	3	36
stephacidin A (**30**)	16	1	7	2	0	6	38
avrainvillamide (**29**)	17	1	7	2	1	6	41
kapakahine F							
ageliferin (**21**) nagelamide (**2**							
vinigrol (**33**)							
stephacidin B							
chartelline C (							
haouamine (**3**							
4-*epi*-ajanol (**3** hydroxyeudes							
pygmol (**36**)							
eudesmanetetraol (**37**)	15	1	0	4	5	5	66
11-*epi*-eudesmane-tetraol (**37a**)	15	1	0	4	5	5	66
cortistatin A (**32**)	15	1	2	2	6	4	66
fischerindole I (**26a**)	8	0	0	2	2	4	75
hapalindole U (**27a**)	4	0	0	1	1	2	75
psychotrimine (**22**)	4	1	0	0	0	3	75
welwitindolinone A (**25**)	9	0	0	2	3	4	78
ambiguine (**27b**)	6	0	0	1	2	3	83

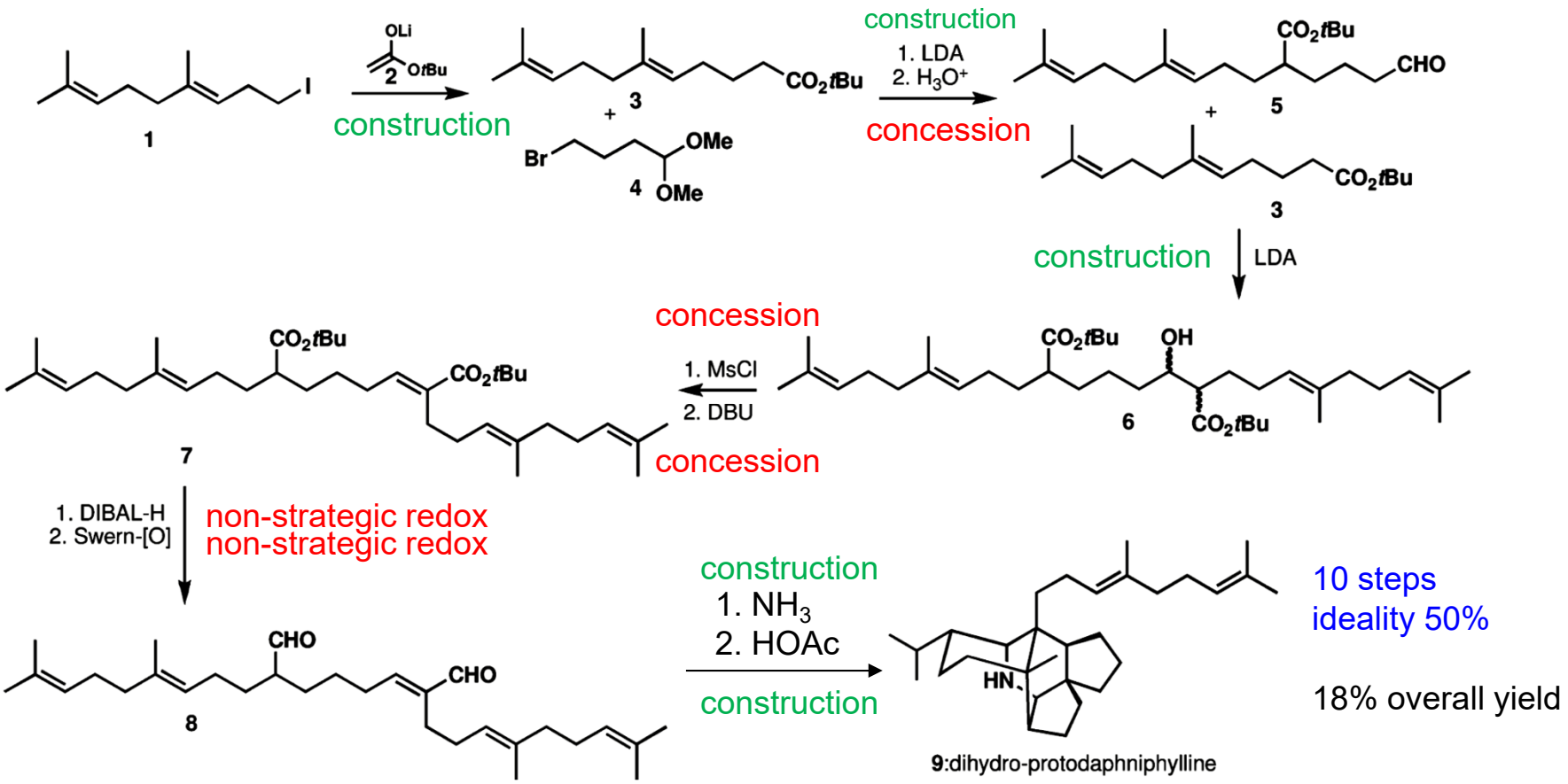
$$\%\text{ideality} = \frac{[(\text{no. of construction rxns}) + (\text{no. of strategic redox rxns})]}{(\text{total no. of steps})} \times 100$$

Industrial synthesis of citral (BASF):



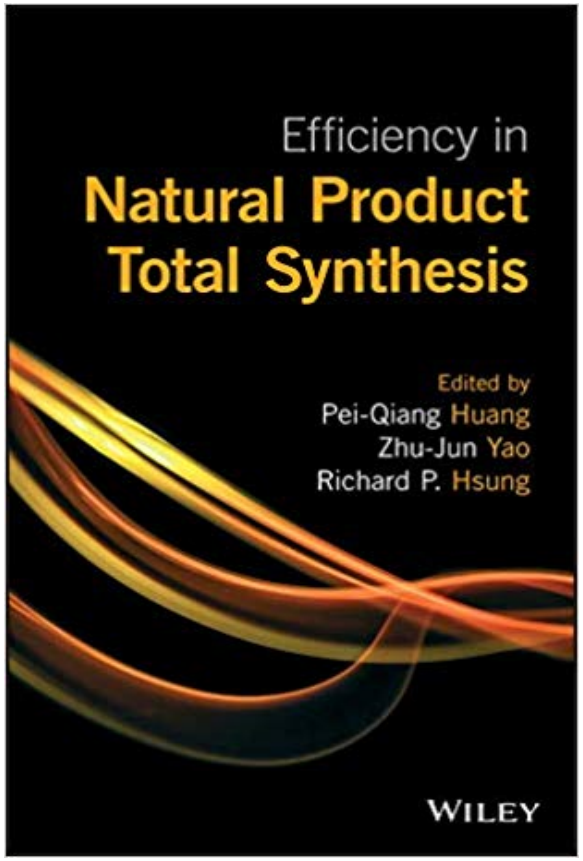
from Gaich, Baran, *JOC* **2010**, 4657; DOI: 10.1021/jo1006812

Heathcock et al., *Science* **1990**, *248*, 1532: 50% Baran ideality



from Gaich, Baran, *JOC* **2010**, 4657; DOI: 10.1021/jo1006812

Another way of defining the ideality of a synthesis: one step, 100%



2018

The key goal of research on the total synthesis of natural product is

EFFICIENCY.

("... to prevent the pursuit from being given up by society.")

Catalysis, no waste.

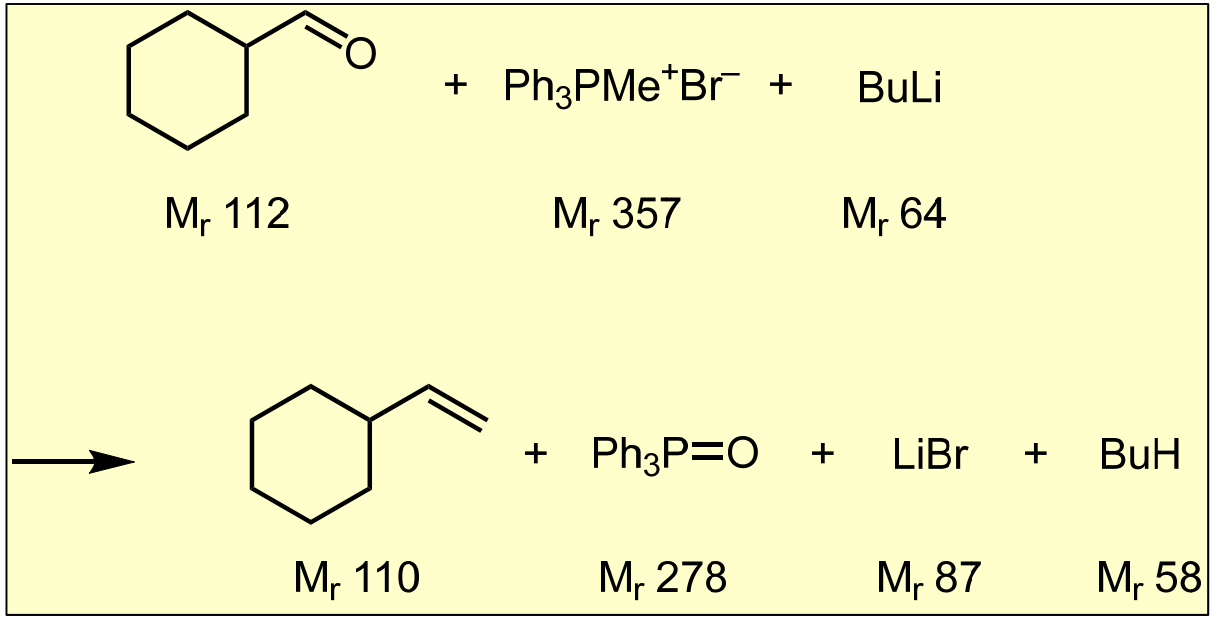
Utopy:

the ideal total synthesis comprises one step of 100% yield.

Atom economy = (molecular weight of desired product) / (molecular weight of all reactants)

Bad atom economy: Wittig olefination, Gabriel synthesis, Cannizzaro reaction, ...

Good atom economy: pericyclic reactions, ...



Atom economy

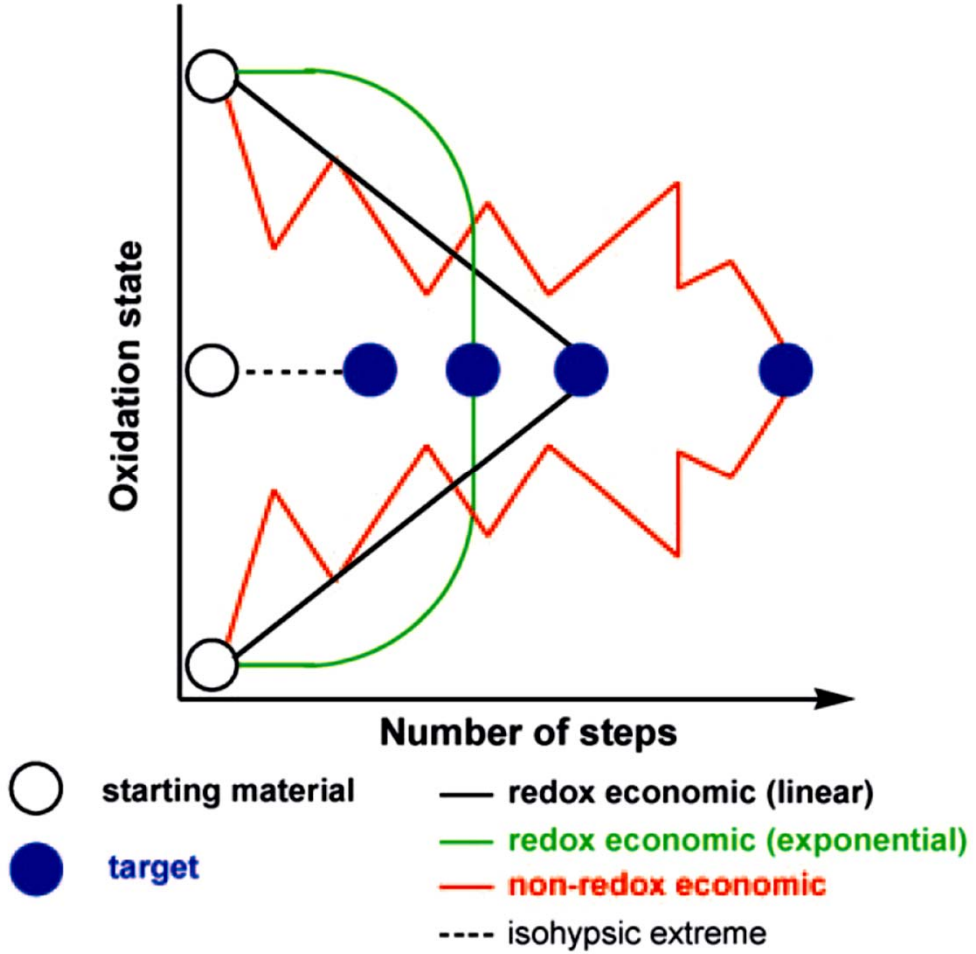
= 110 / (112 + 357 + 64)

21%

And waste.

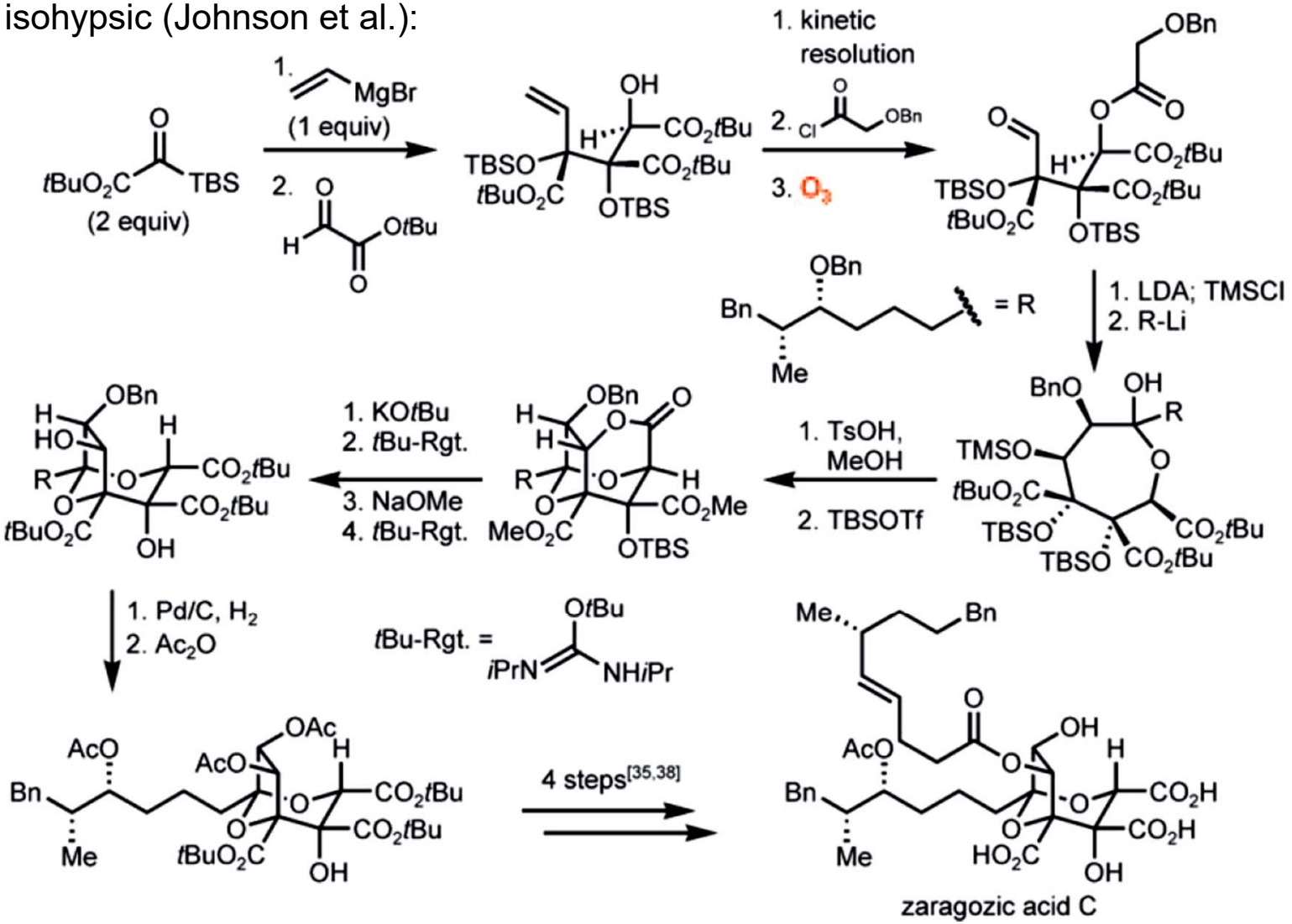
redox economy: "the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework."

isohypsic = redox neutral



from Hoffmann, Baran, *ACIE* **2009**, 2854; DOI: 10.1002/anie.200806086

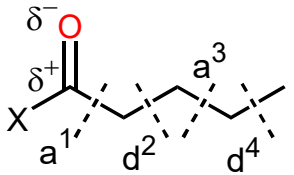
Almost isohypsic (Johnson et al.):



from Hoffmann, Baran, *ACIE* **2009**, 2854; DOI: 10.1002/anie.200806086

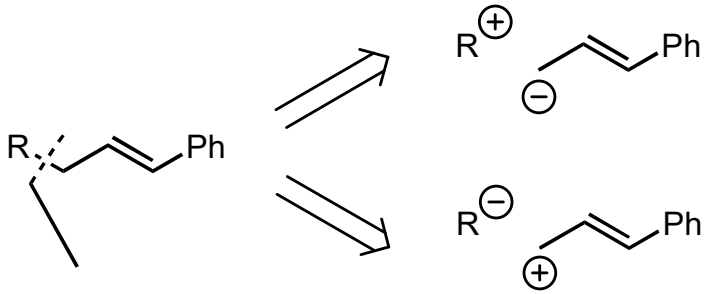
Natürliche Polung: Alternierende Partialladungen, ausgehend von einer polarisierten Bindung.

z. B.



Carbonyl-O-, α-, γ-Position: neg. Partialladung (Donor-Synthon, "**d**")

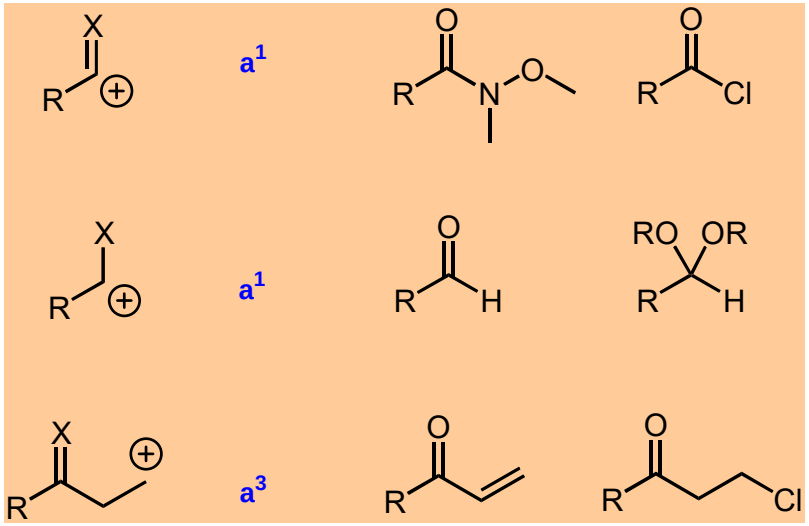
Carbonyl-C-, β-, δ-Position: pos. Partialladung (Akzeptor-Synthon, "**a**")



Polare Bindungsknüpfung: HOMO des Nukleophils + LUMO des Elektrophils (also 2 Möglichkeiten)

Synthon: Verallgemeinerter, durch Retrosynthese erhaltener Synthesebaustein, der ein Reaktionsprinzip verkörpert (*Corey*).

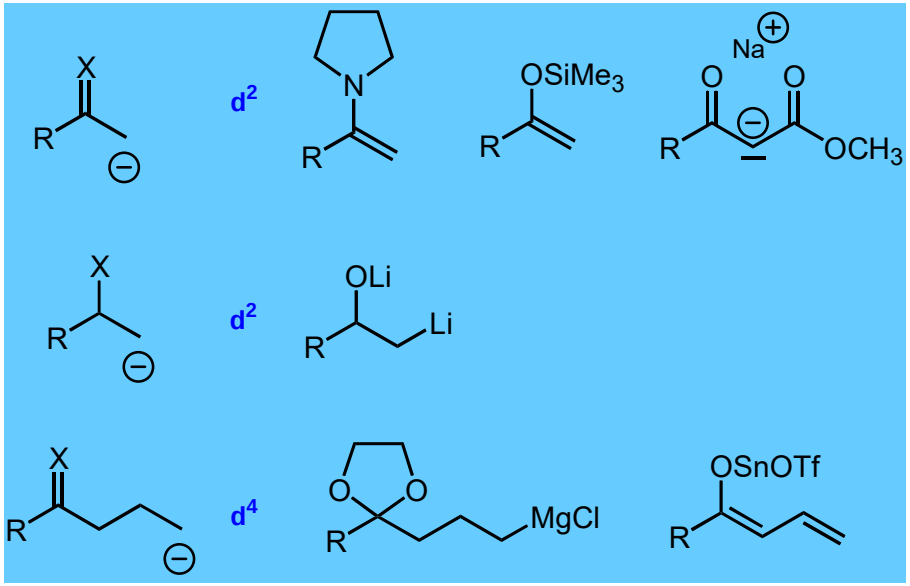
d^{n} und **a**^{m}, (**d:** Donor, **a:** Akzeptor), wobei n und m den Abstand der reaktiven Stelle vom Heteroatom bezeichnen (Seebach). Das Synthon-Konzept beschränkt sich auf $1 \leq n \leq 4$ und $1 \leq m \leq 3$.



e. g., Weinreb amides, acid chlorides

e. g., aldehydes, acetals

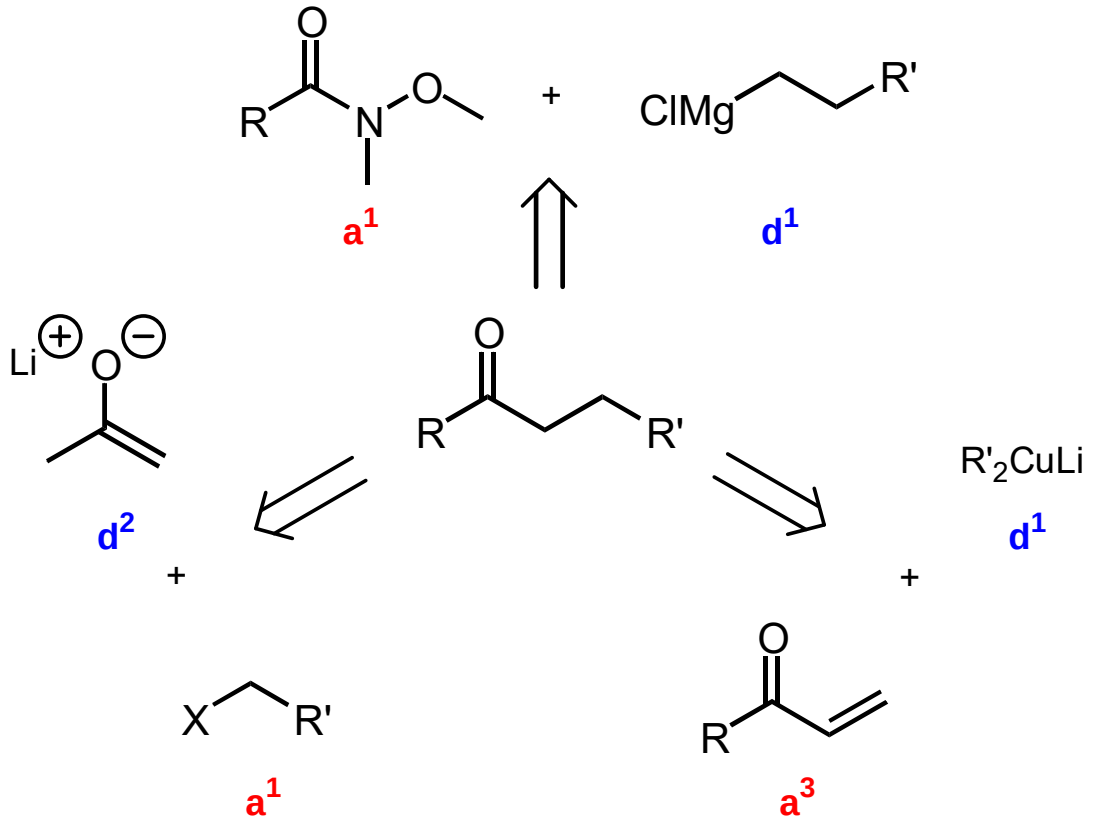
e. g., α,β-unsaturated carbonyl cpds



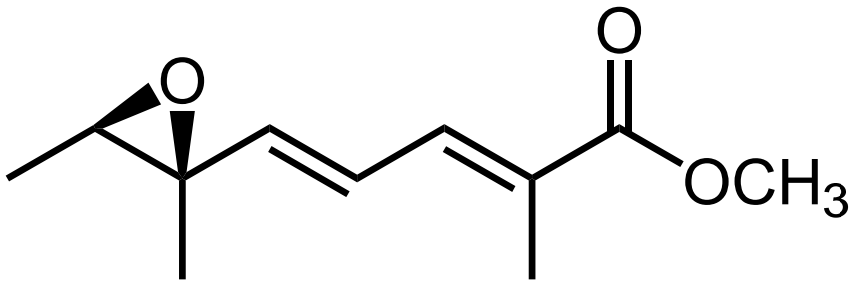
e. g., enamines, silyl enol ethers, β-ketoenolates

e. g., doubly deprotonated alcoholates

e. g., vinylogous metal enolates


O
R
N
O
+
ClMg
R'
a1
d1
Li
O
O
R
R'
d2
R'2CuLi
d1
+
+
X
R'
O
R
a1
a3

How would you make this?

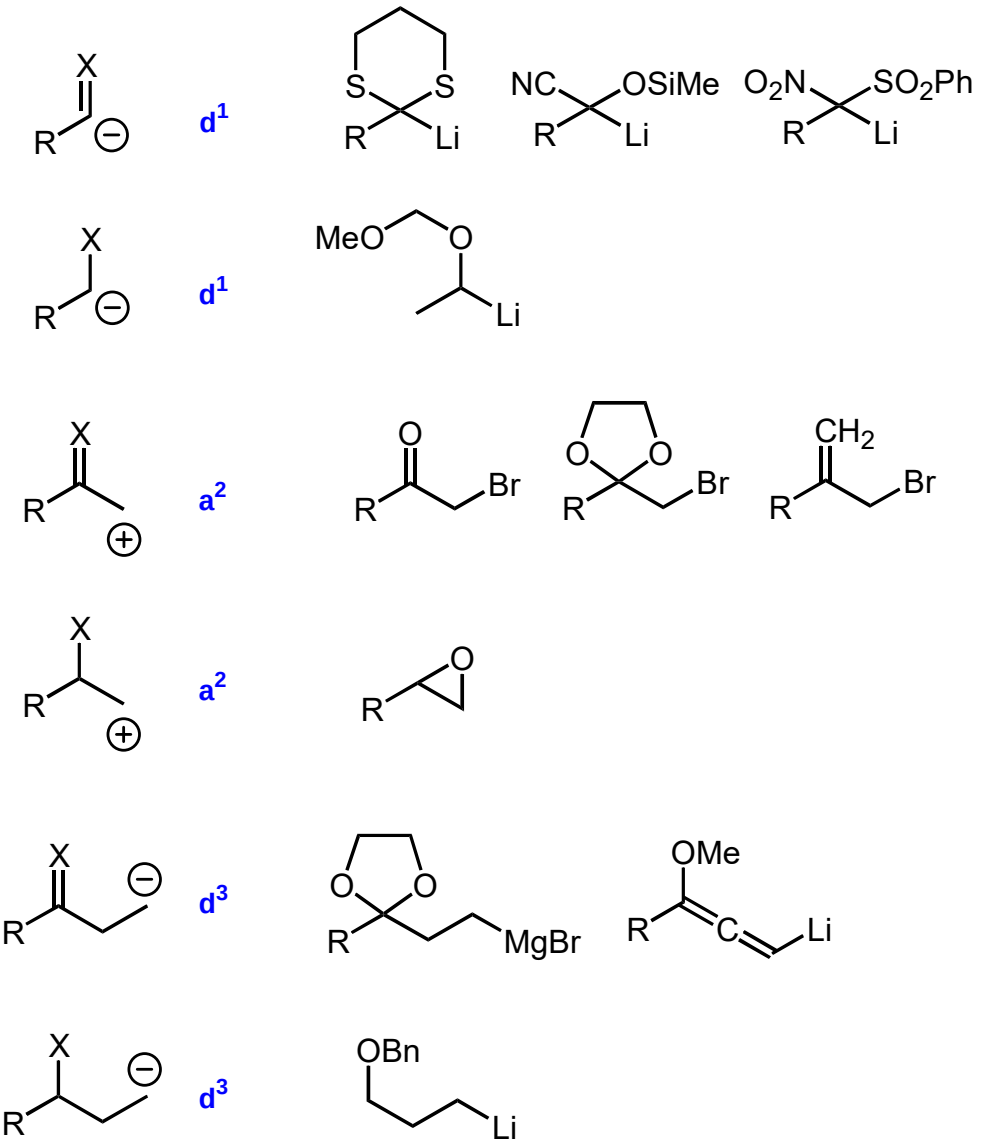


Umpolung:

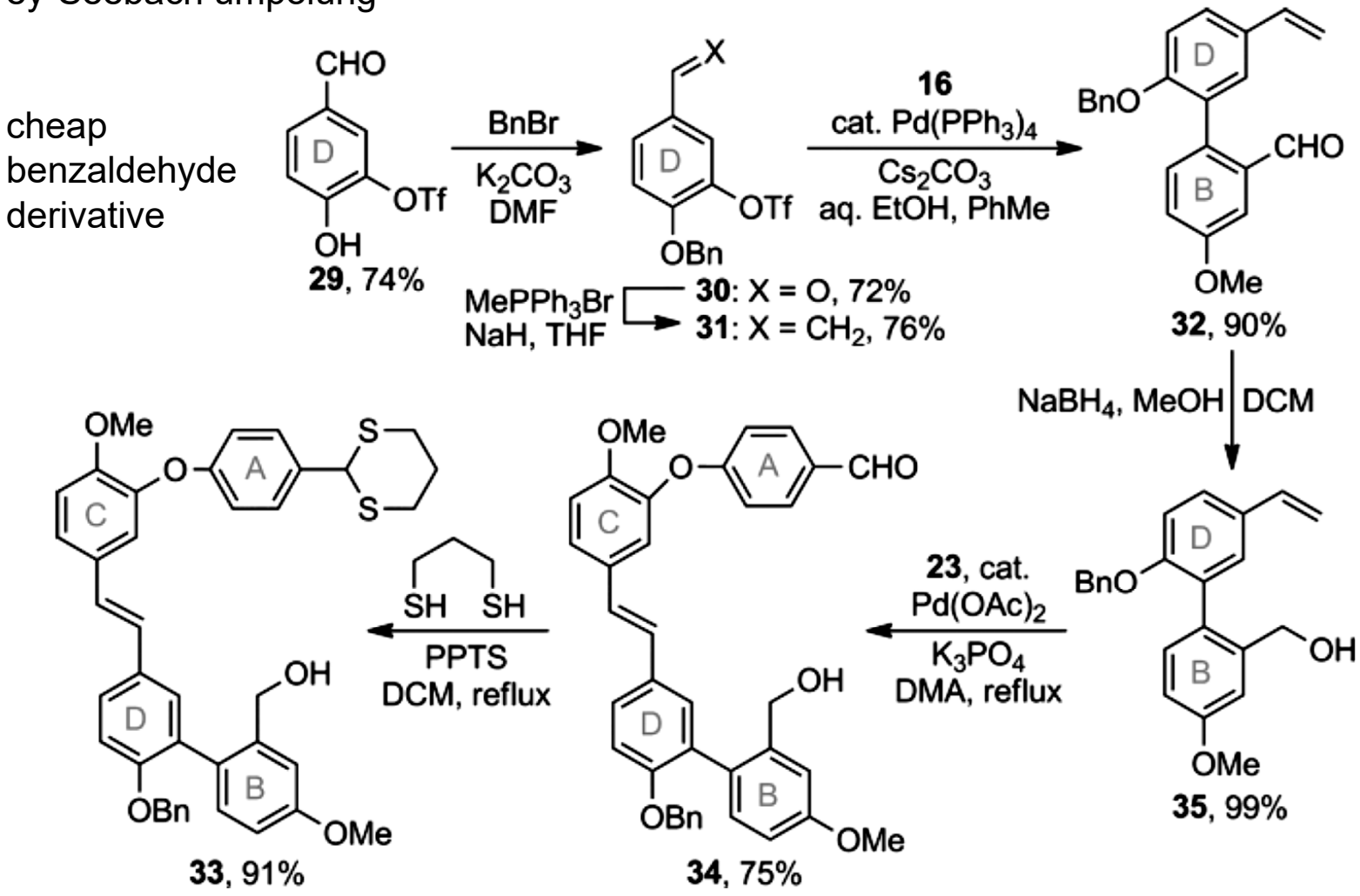
Umwandlung eines Donor-Synthons in ein Akzeptor-Synthon und umgekehrt

Ziel der Verknüpfung eines Donor-Akzeptor-Synthonpaars in geradem Bindungsabstand

Häufigste Redoxumpolung ist die Einführung bzw. Entfernung zweier Elektronen (s. rechts).



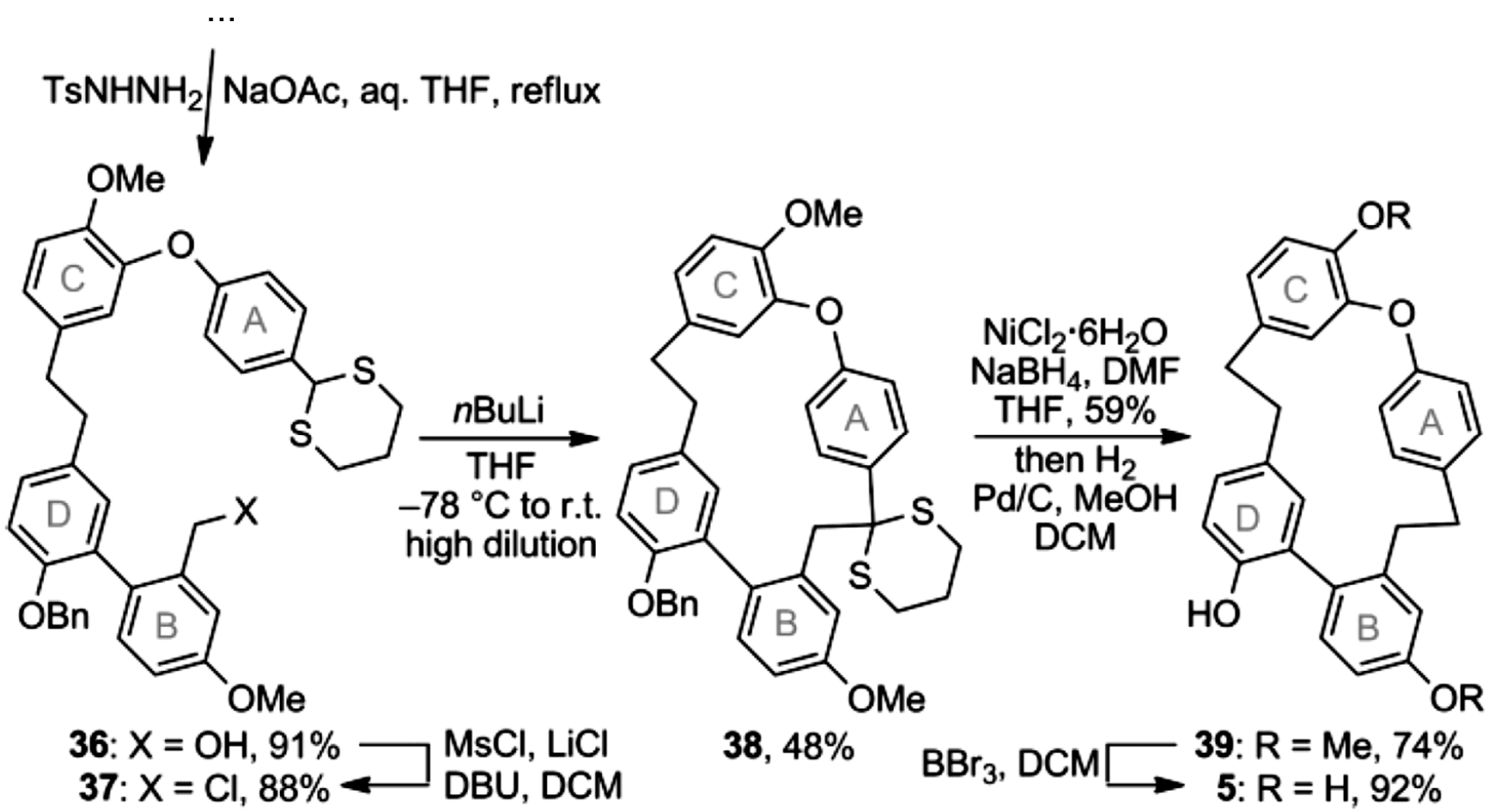
Corey-Seebach umpolung



still not outdated ...

from: Harrowven et al., *EurJOC* **2016**, 5738

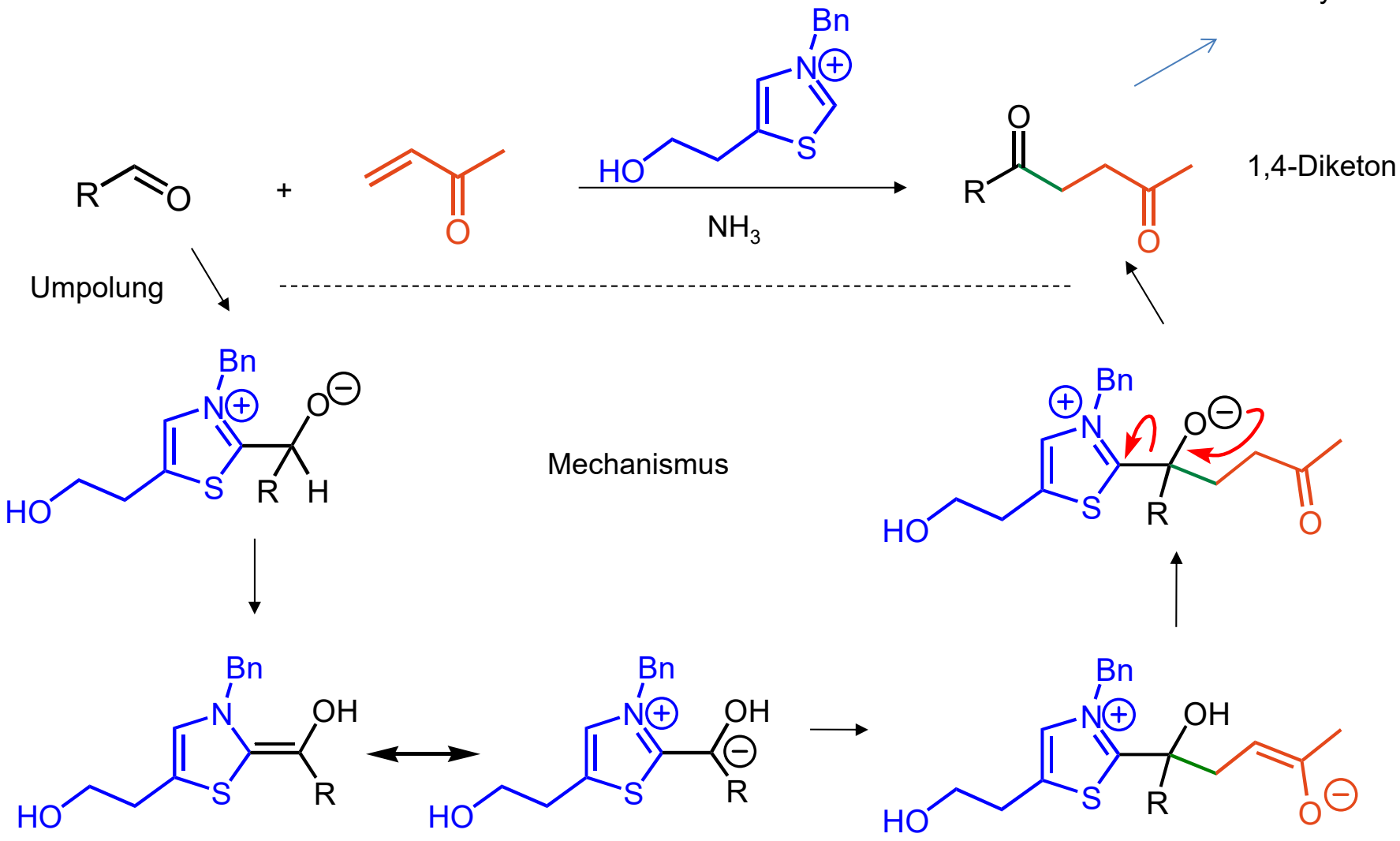
Corey-Seebach umpolung: an old horse



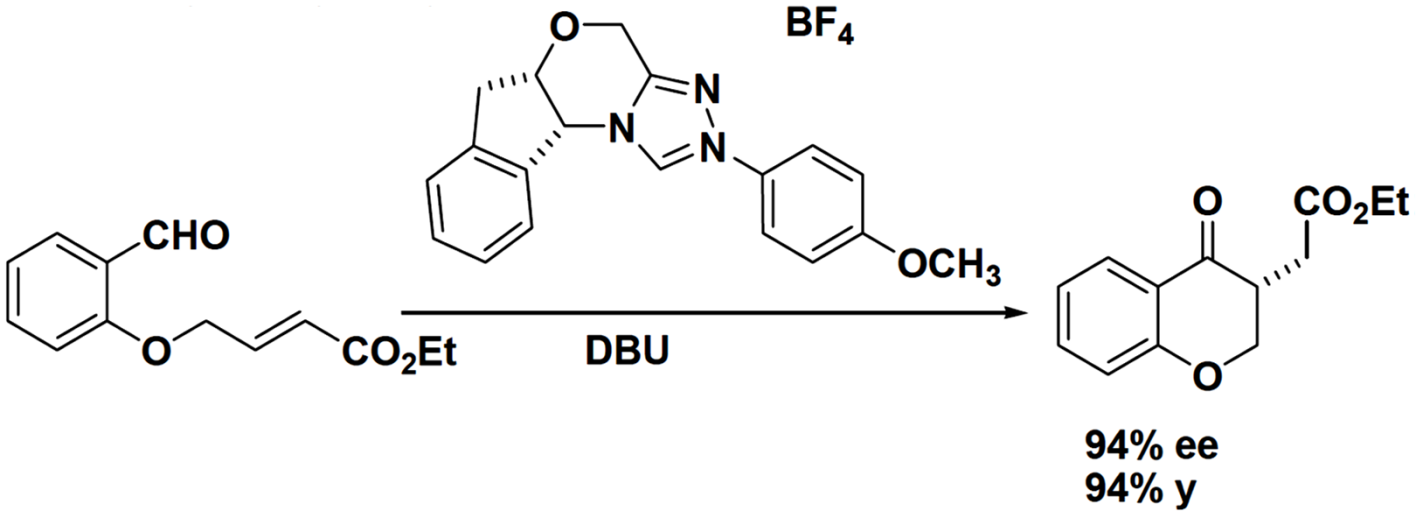
from: Harrowven et al., *EurJOC* **2016**, 5738

Two electron umpolung: *Stetter*-Reaktion catalyzed by N-heterocyclic carbenes

z. B. Pyrrole



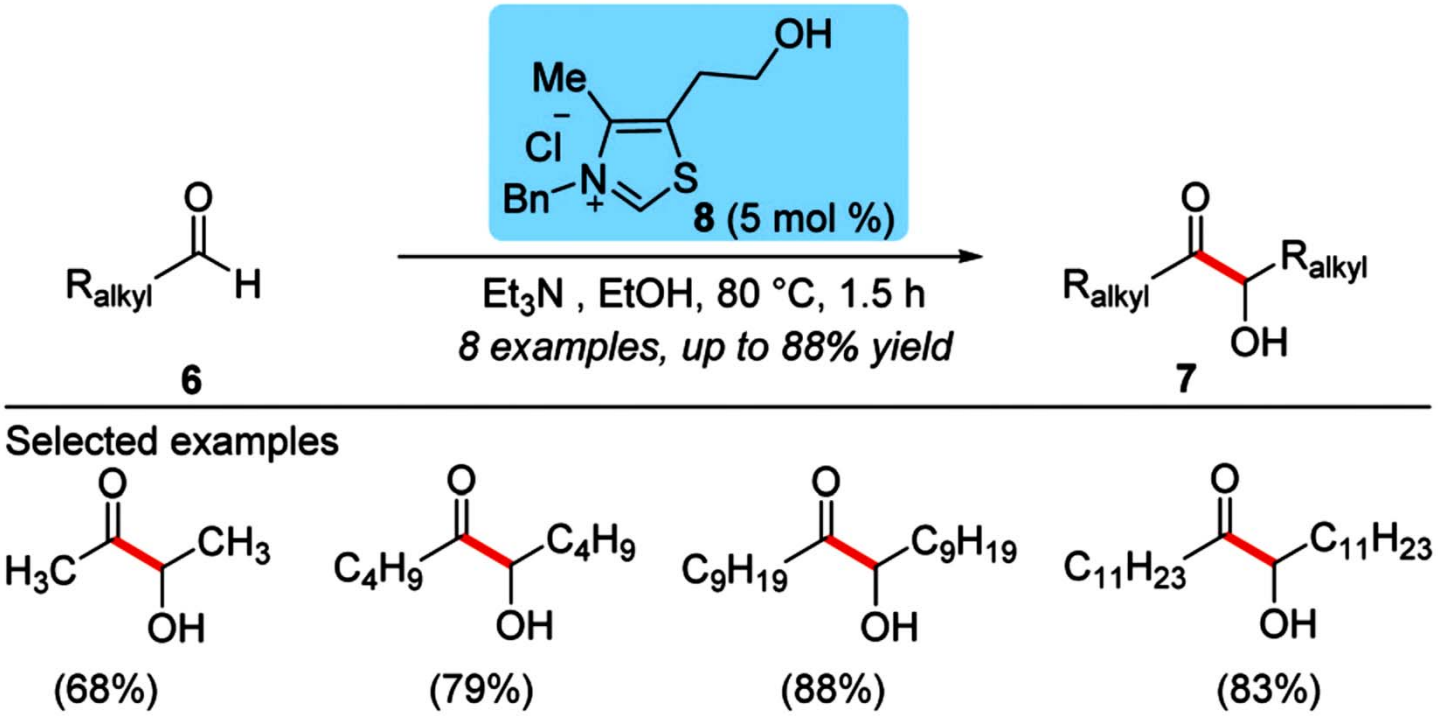
Two electron umpolung: *Stetter*-Reaktion catalyzed by N-heterocyclic carbenes



The formally δ+ aldehyde and β carbons are coupled.

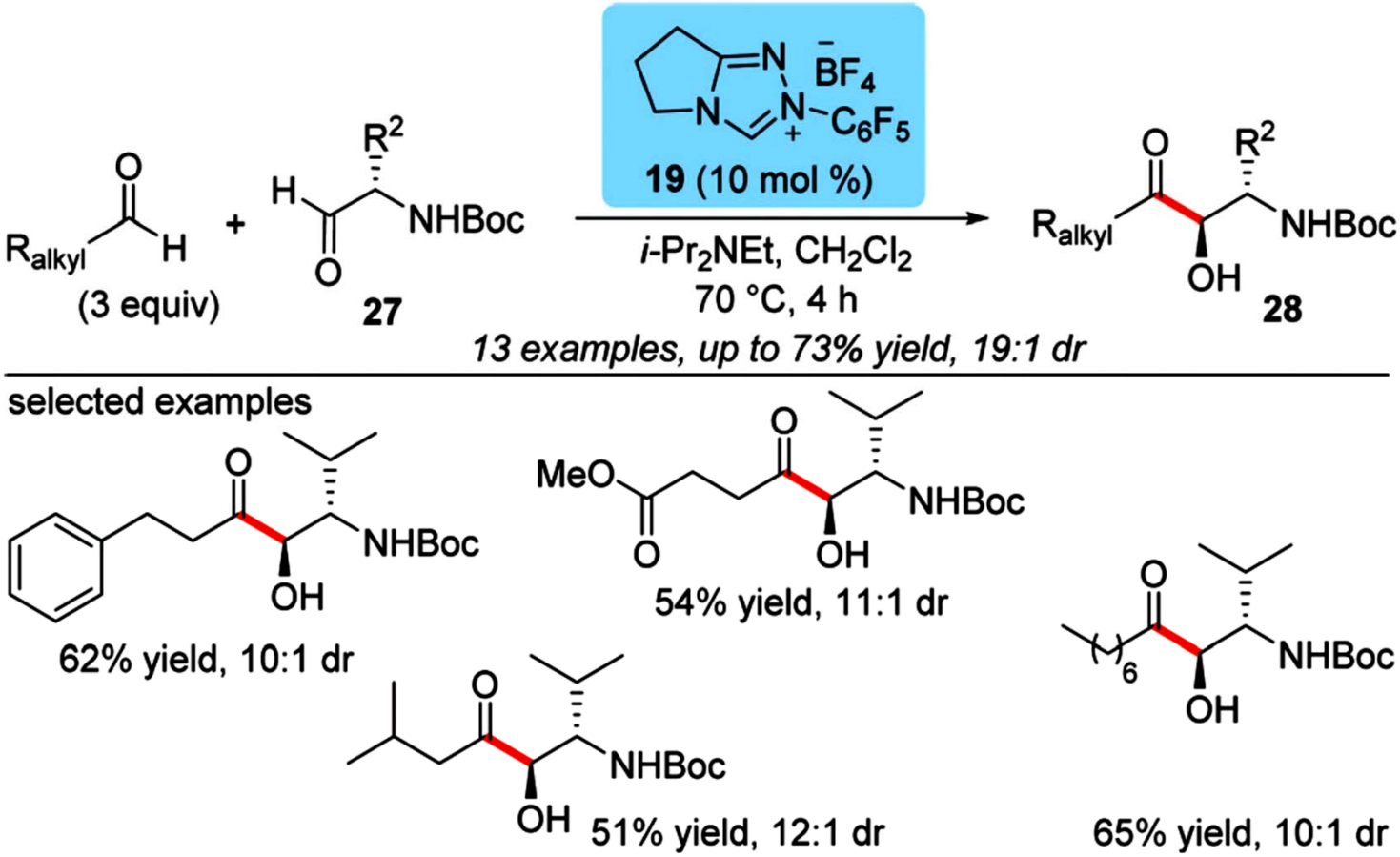
Rovis et al., *JACS* **2002**, 10298

Two electron umpolung: acyloin coupling catalyzed by N-heterocyclic carbenes



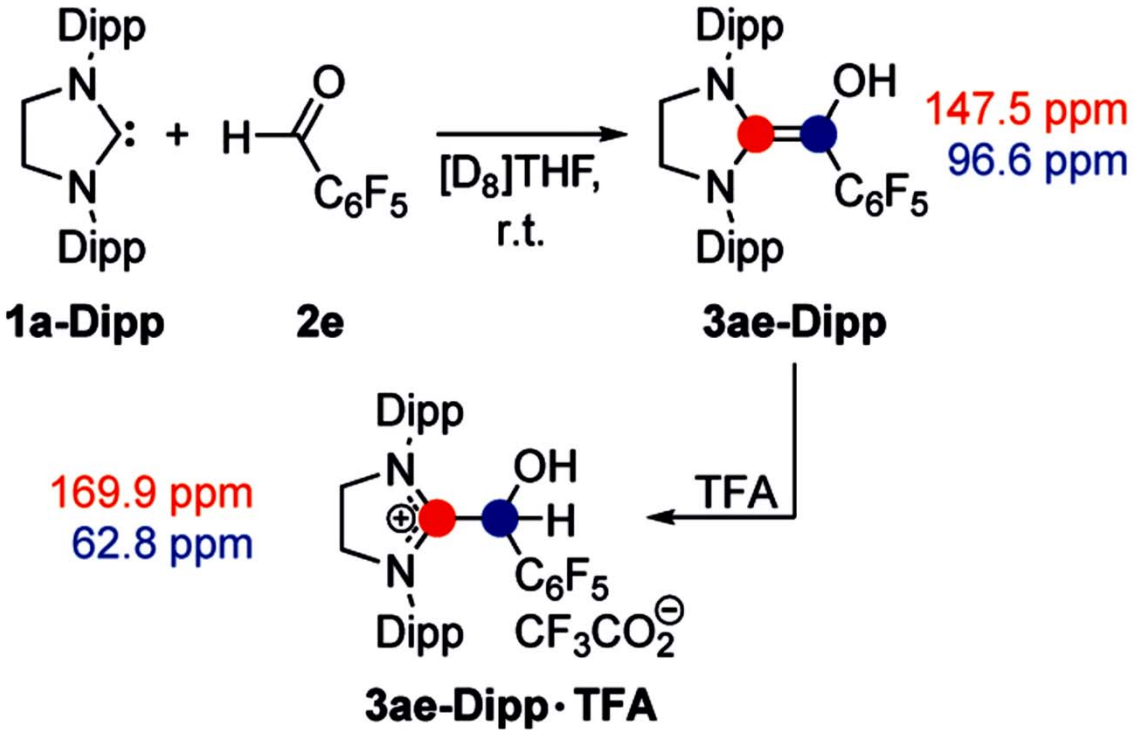
from: Barik and Biju, *Chem. Commun.* **2020**, 15484

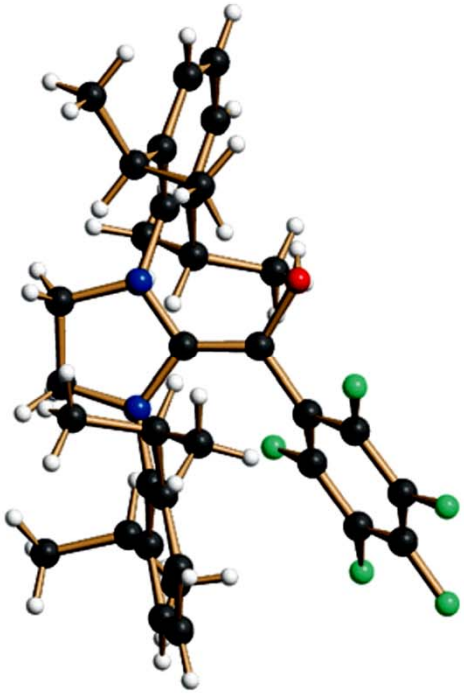
Two electron umpolung: acyloin coupling catalyzed by N-heterocyclic carbenes



from: Barik and Biju, *Chem. Commun.* **2020**, 15484

The Breslow intermediate (postulated in 1958) has been crystallized in 2018!



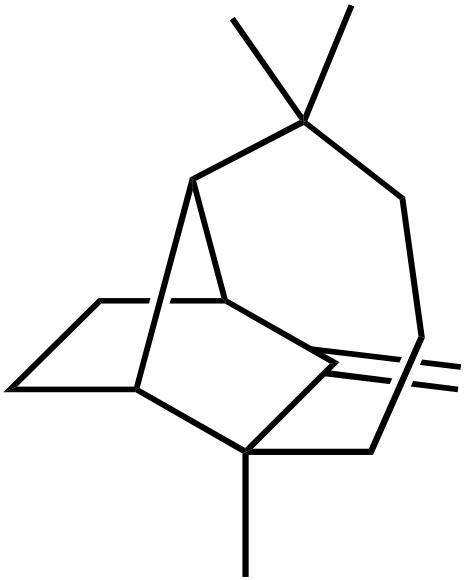


3ae-Dipp

Dipp: 2,6-diisopropylphenyl

from: Berkessel et al., *ACIE* **2018**, 8310

Sesquiterpene (+)-longifolene from *Pinus ponderosa*, one of *Corey*'s early target molecules (1961/4)

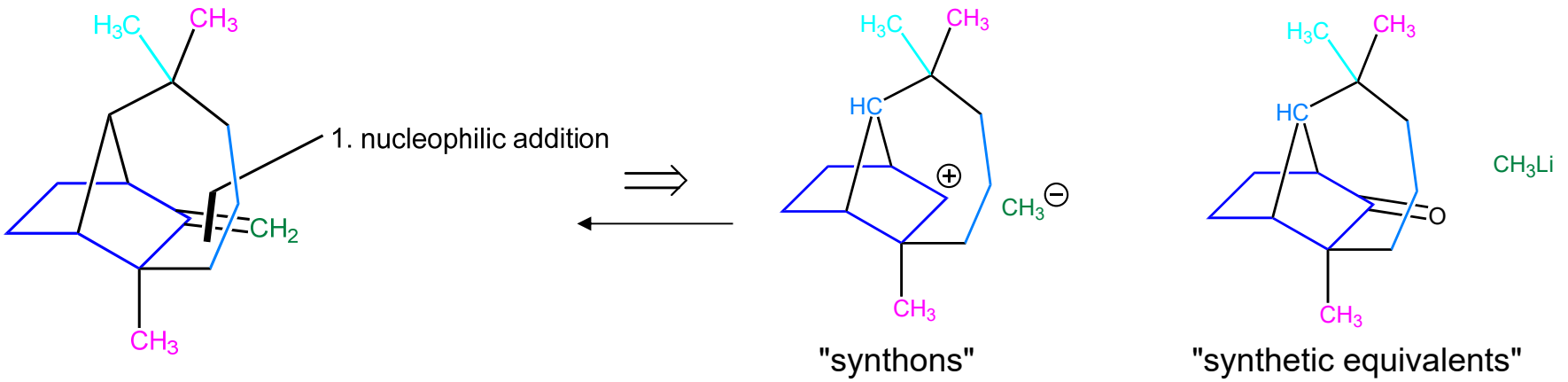


© The Nobel Foundation

"If a definitive history of twentieth century science is ever written, one of the highlights may well be a chapter on the chemical synthesis of complex molecules, especially the total synthesis of naturally occurring substances." E. J. Corey

Nobel Prize 1990 to Elias James Corey for the development of theory and methodology of Organic Synthesis, in particular of retrosynthesis.

Caveat. Currently, retrosynthetic analysis will suggest methods and building blocks known to the literature.



Retrosynthese: Mehrstufige Rückführung einer Verbindung auf verfügbare Synthesebausteine.

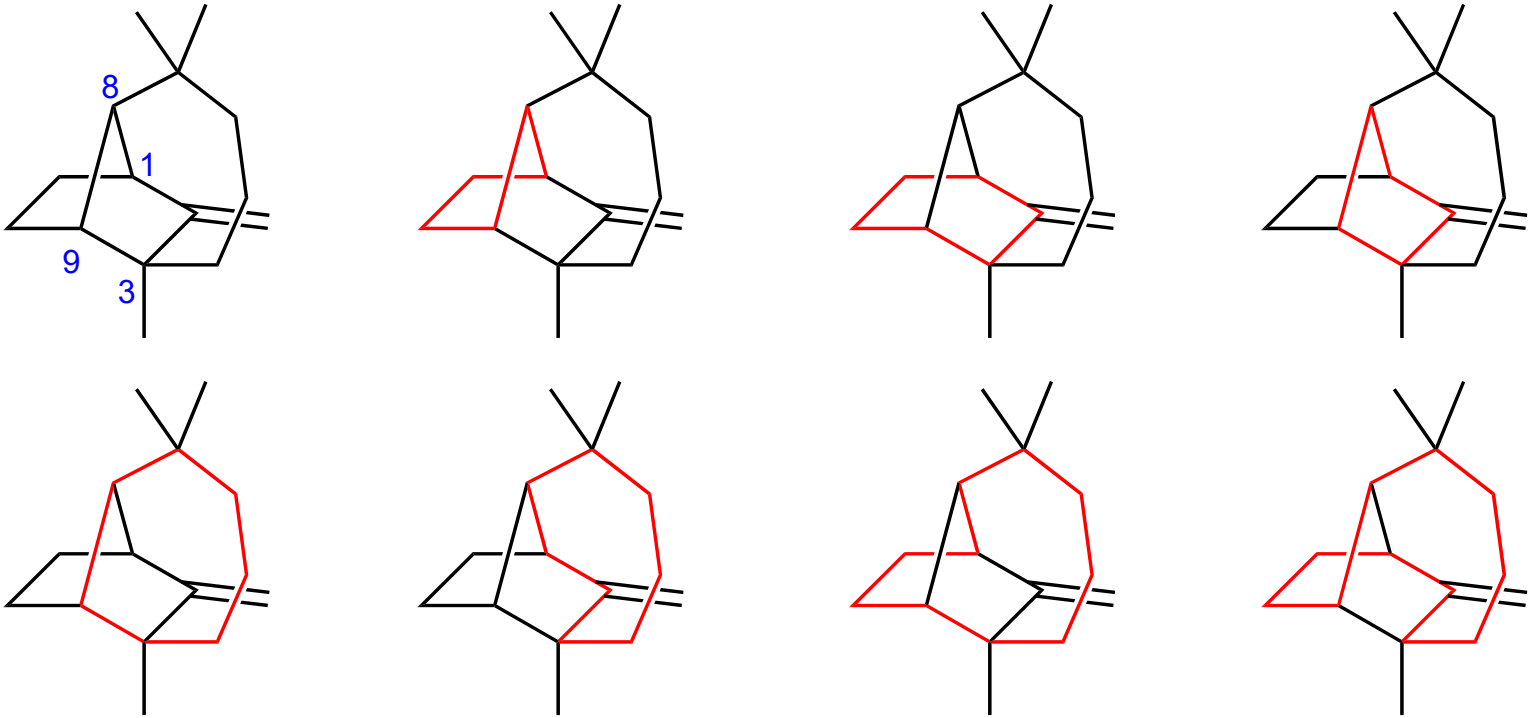
Retrosynthetische Transformation: Einstufige Rückführung einer Verbindung auf Synthesevorstufen.

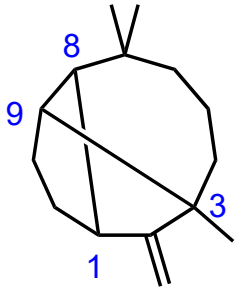
Synthon: Verallgemeinerter, durch Retrosynthese erhaltener Synthesebaustein, der ein Reaktionsprinzip verkörpert (Corey).

Syntheseäquivalent: Realer Baustein mit der durch ein Synthon geforderten Reaktivität, auch mehrvalent (conjunctive reagent, multiple coupling reagent).

FGI (dt. FGU): functional group interchange, Umwandlung einer funktionellen Gruppe in eine andere.

Synthesis of complex carbocyclic skeletons: rings in longifolene





Where to cut first?

4,8,8-trimethyl-9-methylenedecahydro-1,4-methanoazulene (IUPAC)

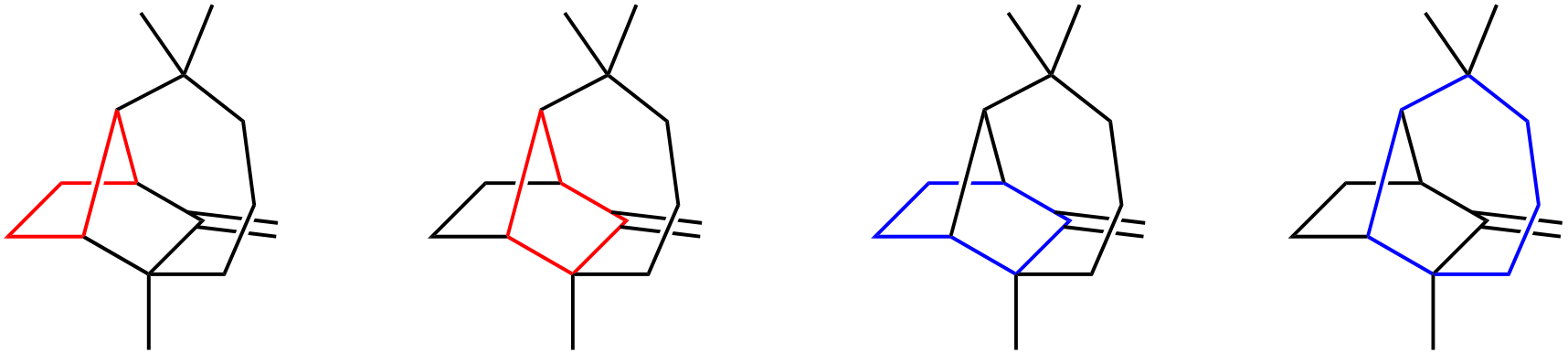
3,7,7-trimethyl-2-methylenetricyclo[6.3.0.$0^{3,9}$]undecane ("tricyclo name")

Synthesis of complex carbocyclic skeletons: strategies

Corey et al., *JACS* **1975**, 6116: *General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures*

"A primary ring is one which cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another."

Secondary rings: all other



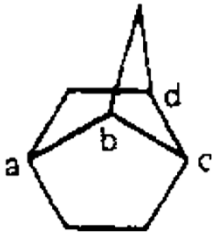
primary rings

secondary rings sized <8

"strategically significant rings"

Corey et al., *JACS* **1975**, 6116: *General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures*

vintage



10

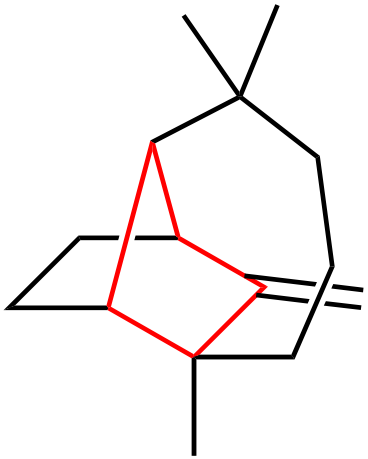
Ring	1	2	3	4	5	6
Times Bridged / Rings Bridged To	4[2, 4, 5, 6]	4[1, 3, 4, 5]	1[5]	2[1, 2]	4[1, 2, 3, 6]	1[5]
Bridgehead Sites (●)	3	4	3	3	3	4
Sites Bridged At (◇)	3	4	2	2	3	2

"Of the six synthetically significant rings comprising structure **10** (primary rings 1-4 and secondary rings 5 and 6), ring 2 is bridged at more sites (four) than any other ring and hence is defined as the maximal bridging ring. Ring 6, which contains as many bridgehead sites as ring 2, is not a maximal bridging ring since it itself is bridged to other rings only at two of these sites (a and d). The above analysis further shows that the number of times a ring is bridged is not a valid criterion for determining maximal bridging character. For example, although ring 5 of structure **10** is bridged by as many other rings as ring 2, it is not a maximal bridging ring since it is bridged at one less site than ring 2."

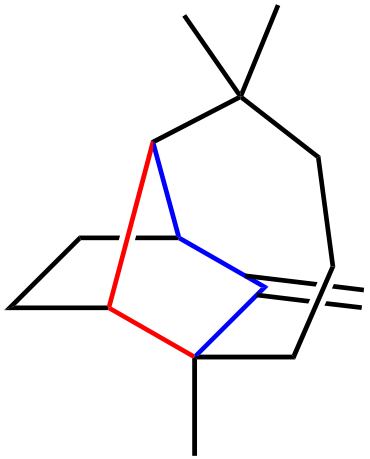
Corey et al., *JACS* **1975**, 6116: *General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures*

"Strategically significant rings": primary rings, secondary rings sized < 8

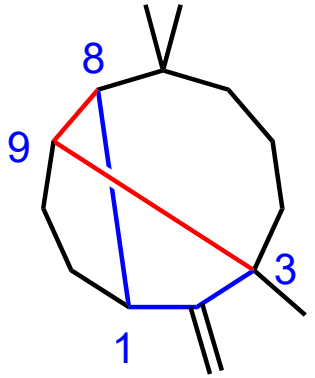
Among them, selection of the "maximum bridging ring" (maximal number of bridgeheads of non-zero bridges):



maximal number (4) of heads of bridges > 0

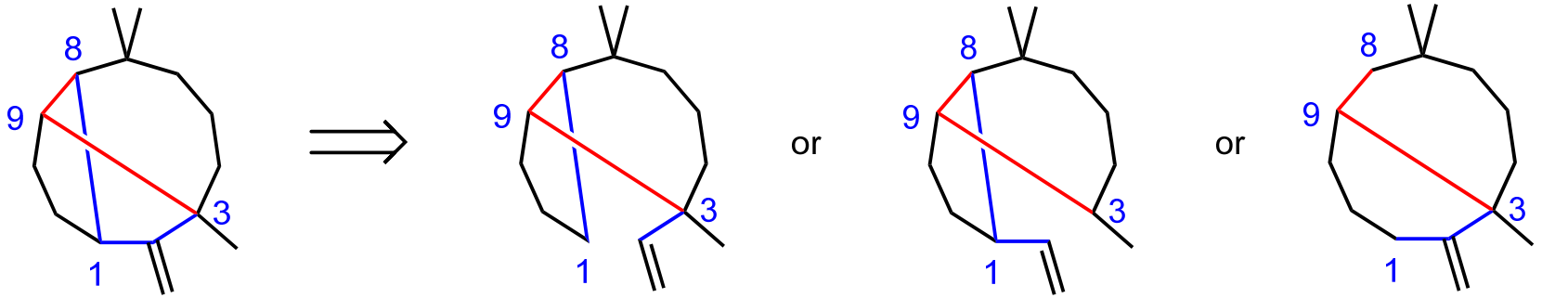


red: core bonds (no retrosynthetic cleavage)
blue: strategic bonds (retrosynthetic cleavage recommended)

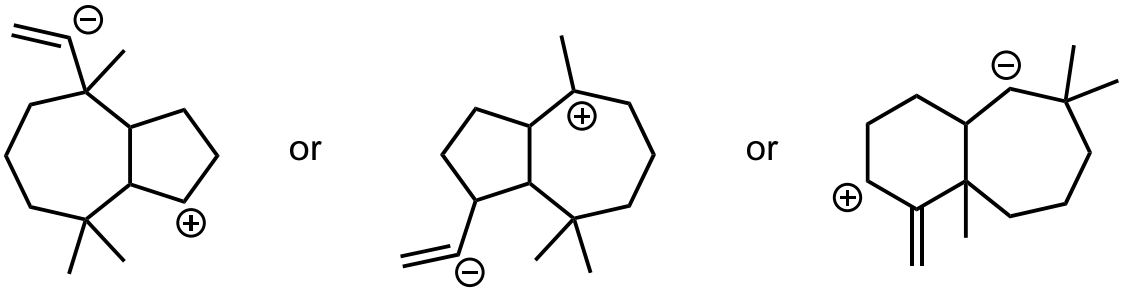


Cleavage of a core bond would generate a primary ring sized > 7.

The first retrosynthetic cut, according to Corey's rules:

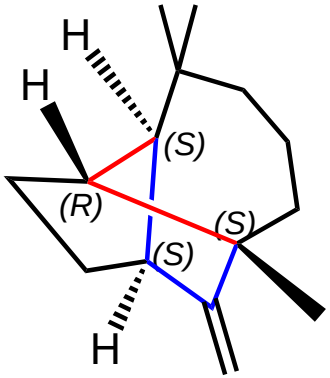


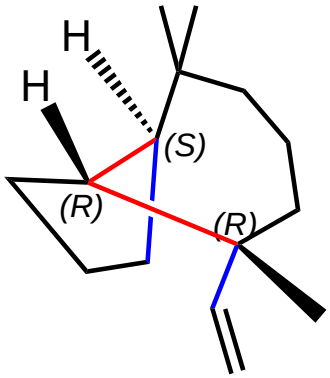
ChemDraw:
use ctrl-alt-c,
then ctrl-alt-p
(SMILES code)

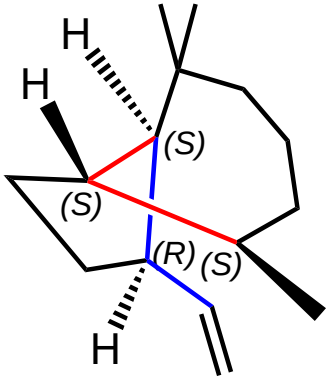


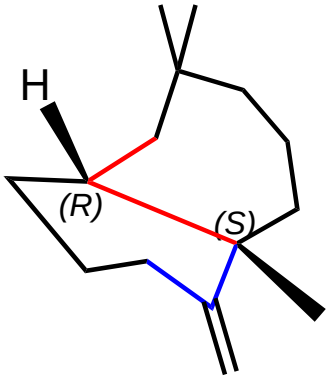
synthons, charges arbitrary

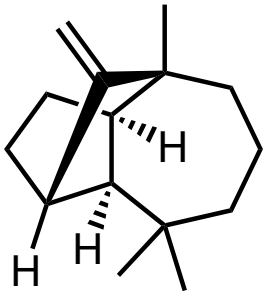
The first retrosynthetic cut, including stereochemistry





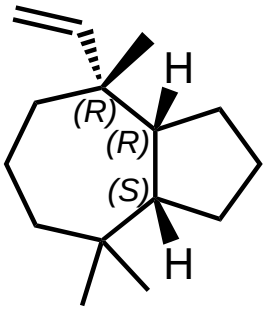




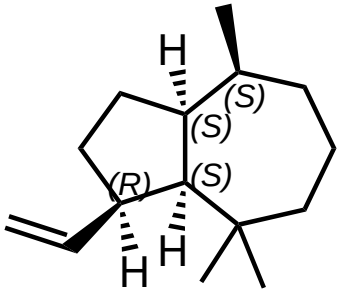


44.8

longifolen

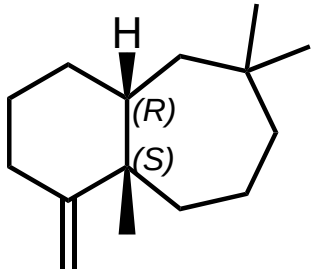


41.8



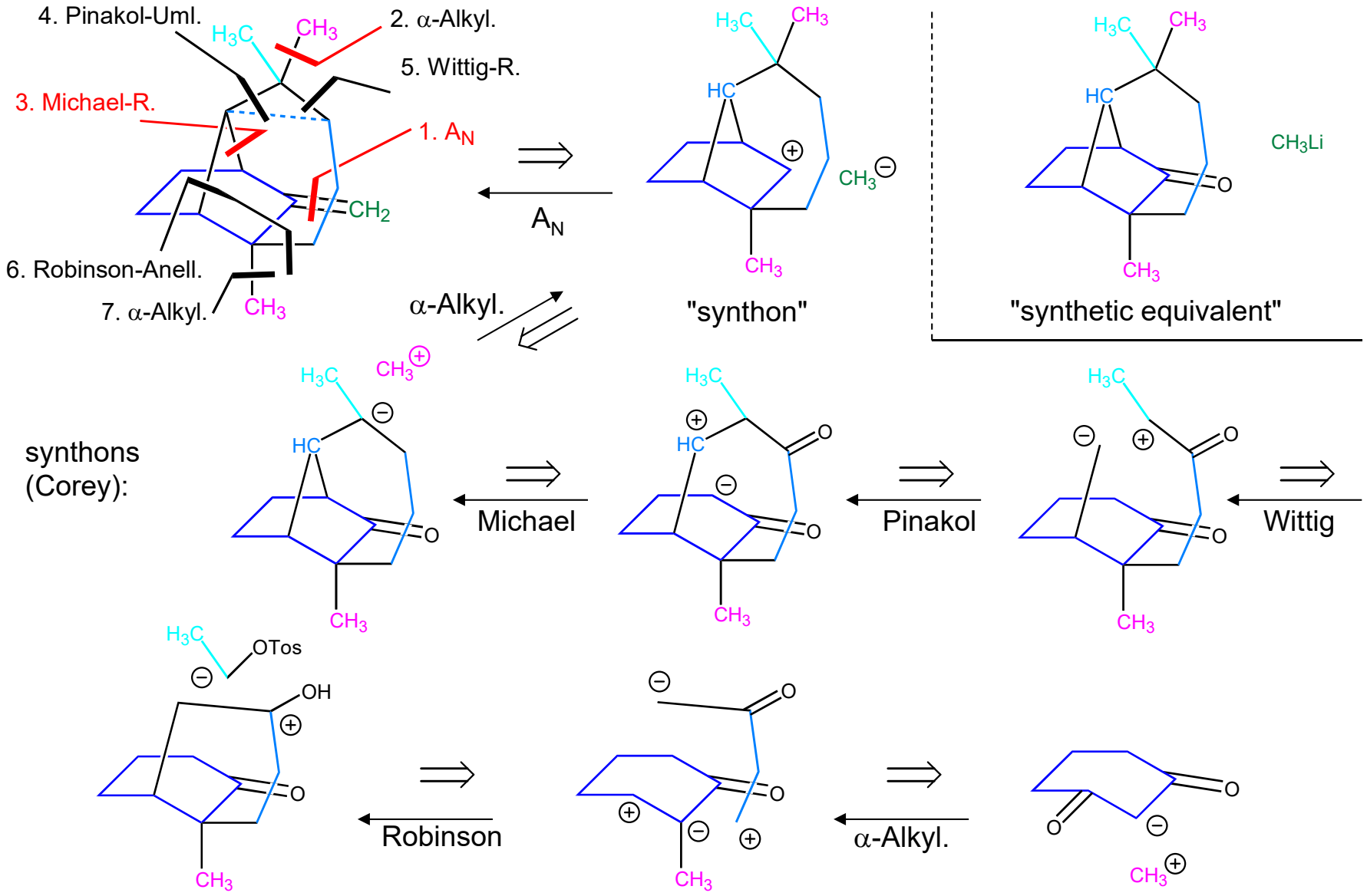
42.7

"cut + 2 H"



33.4

MM2 energies [kcal/mol]


4. Pinakol-Uml.
2. α-Alkyl.
5. Wittig-R.
3. Michael-R.
1. A_N
6. Robinson-Anell.
7. α-Alkyl.
A_N
α-Alkyl.
"synthon"
"synthetic equivalent"
CH_3Li
synthons (Corey):
Michael
Pinakol
Wittig
Robinson
α-Alkyl.
OTos
OH

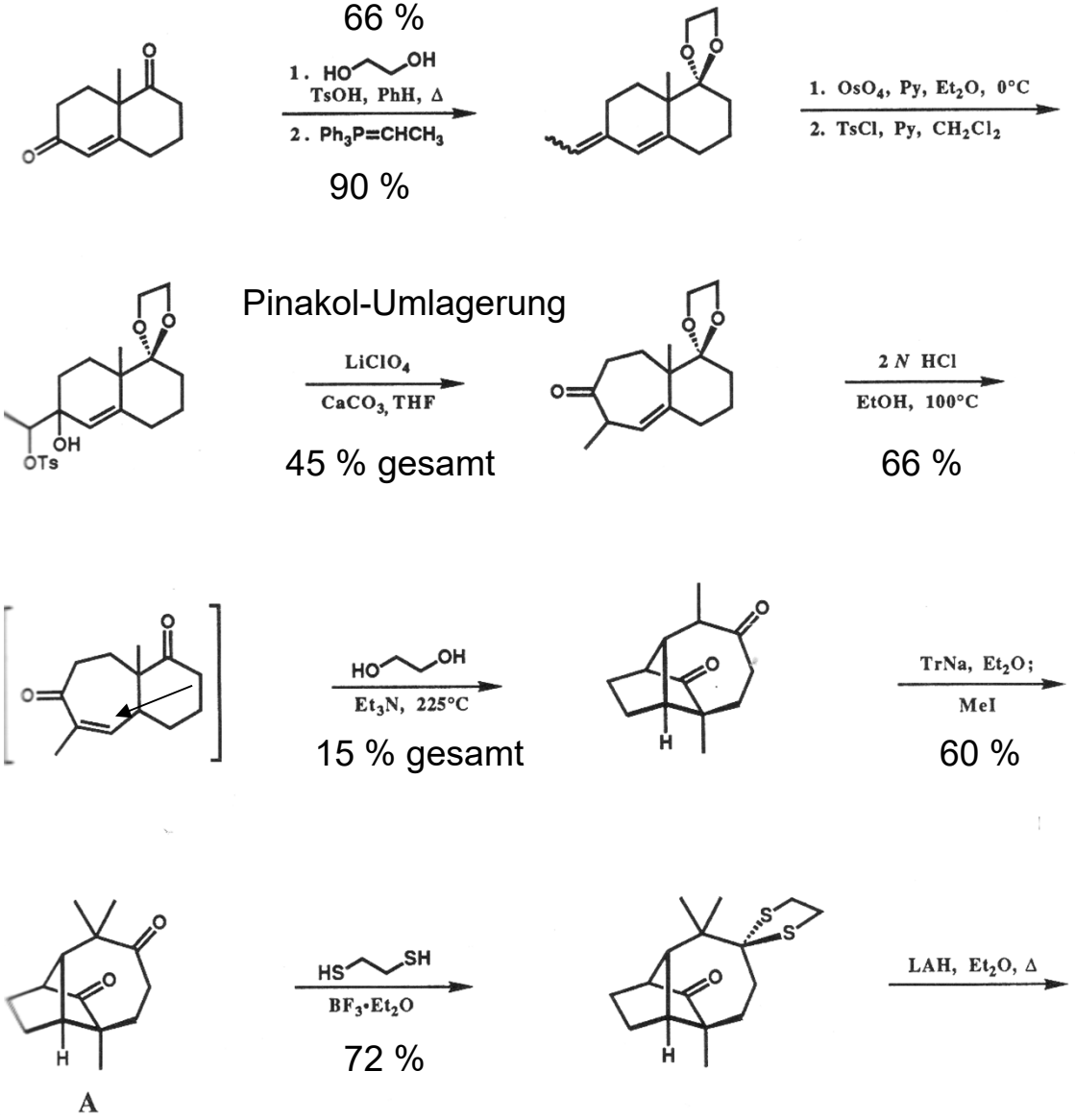
Steps from the basic courses

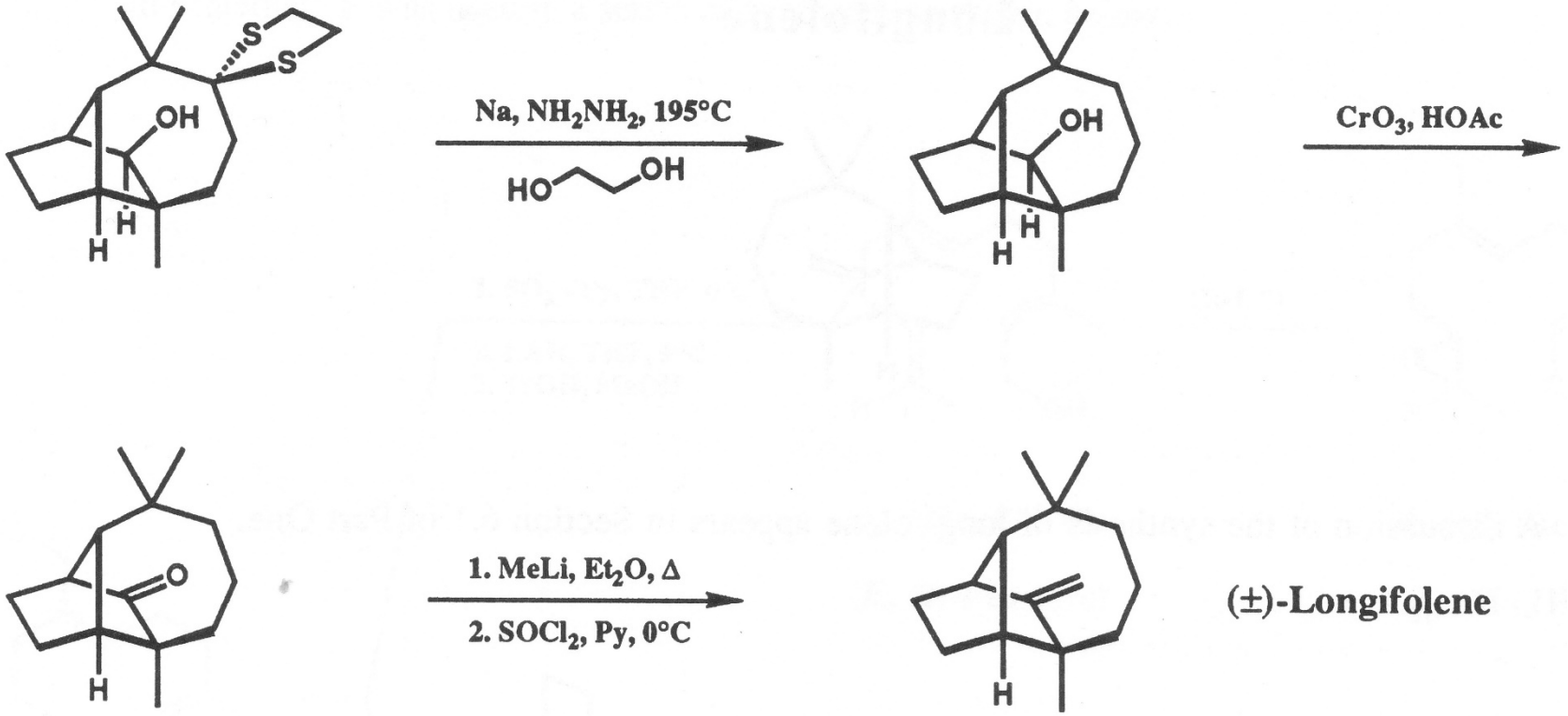
"Ur-Pinakol": 2,3-Dimethyl-2,3-butandiol (Pinakol).

hier: Pinakol-Umlagerung verläuft über das stabilere Allylkation.

0.1 M $LiClO_4$ beschleunigt in Ether die Ionisierung v. Alkyl-tosylaten um 10^5!
0.36 M $LiClO_4$ in Et_2O ionisiert so schnell wie reine HOAc.
Winstein et al., *JACS* **1959**, 5511.

Corey et al.,
JACS **1961**, 1251; *ibid.* **1964**, 478.

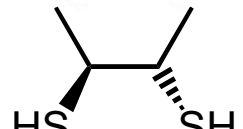




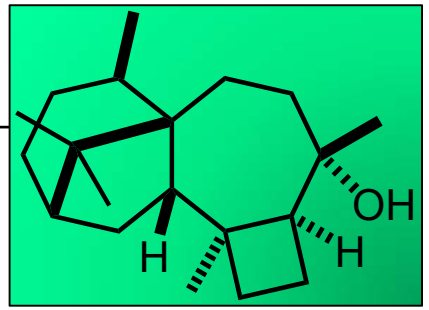
Bredtsche Regel: keine Eliminierung zum Brückenkopf.

70 % gesamt

(+)-Longifolen, wenn (Diastereomerentrennung)

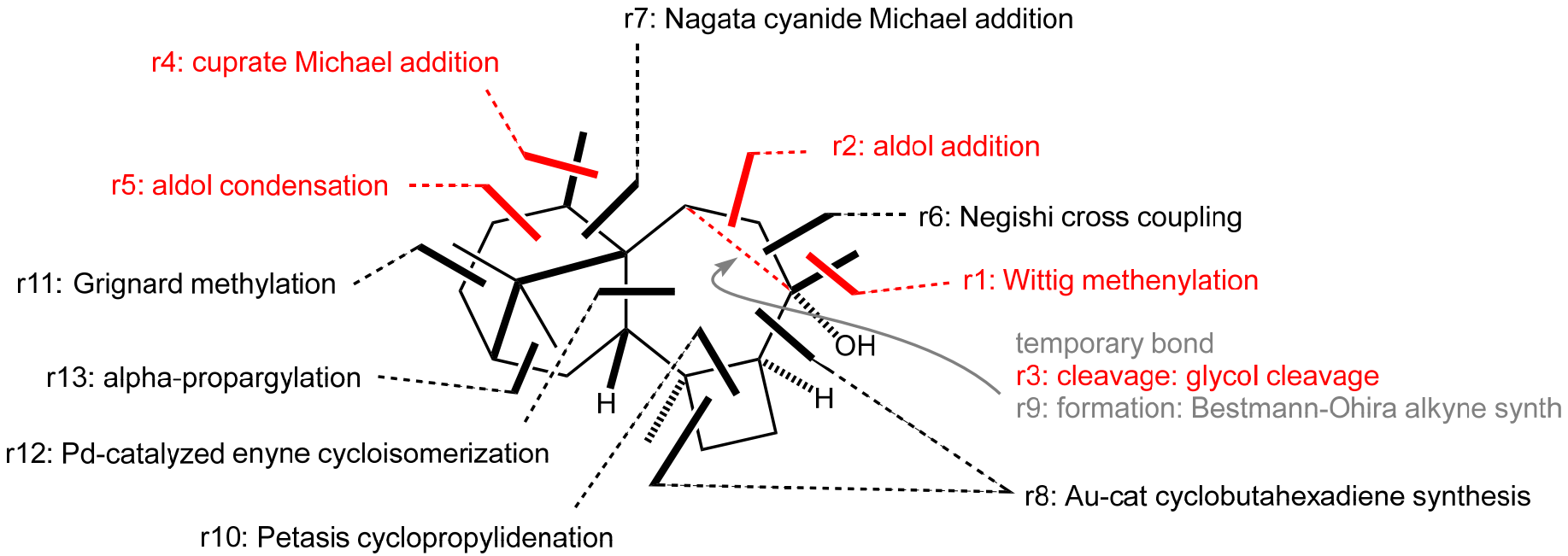


E. J. Corey et al., *JACS* **1961**, 1251; *ibid.* **1964**, 478.



Total Synthesis and Structural Revision of a Harziane Diterpenoid.
Hönig, Carreira, *Angew. Chem. Int. Ed.* **2020**, *59*, 1192–1196

13 carbon-carbon bonds formed, 1 broken:

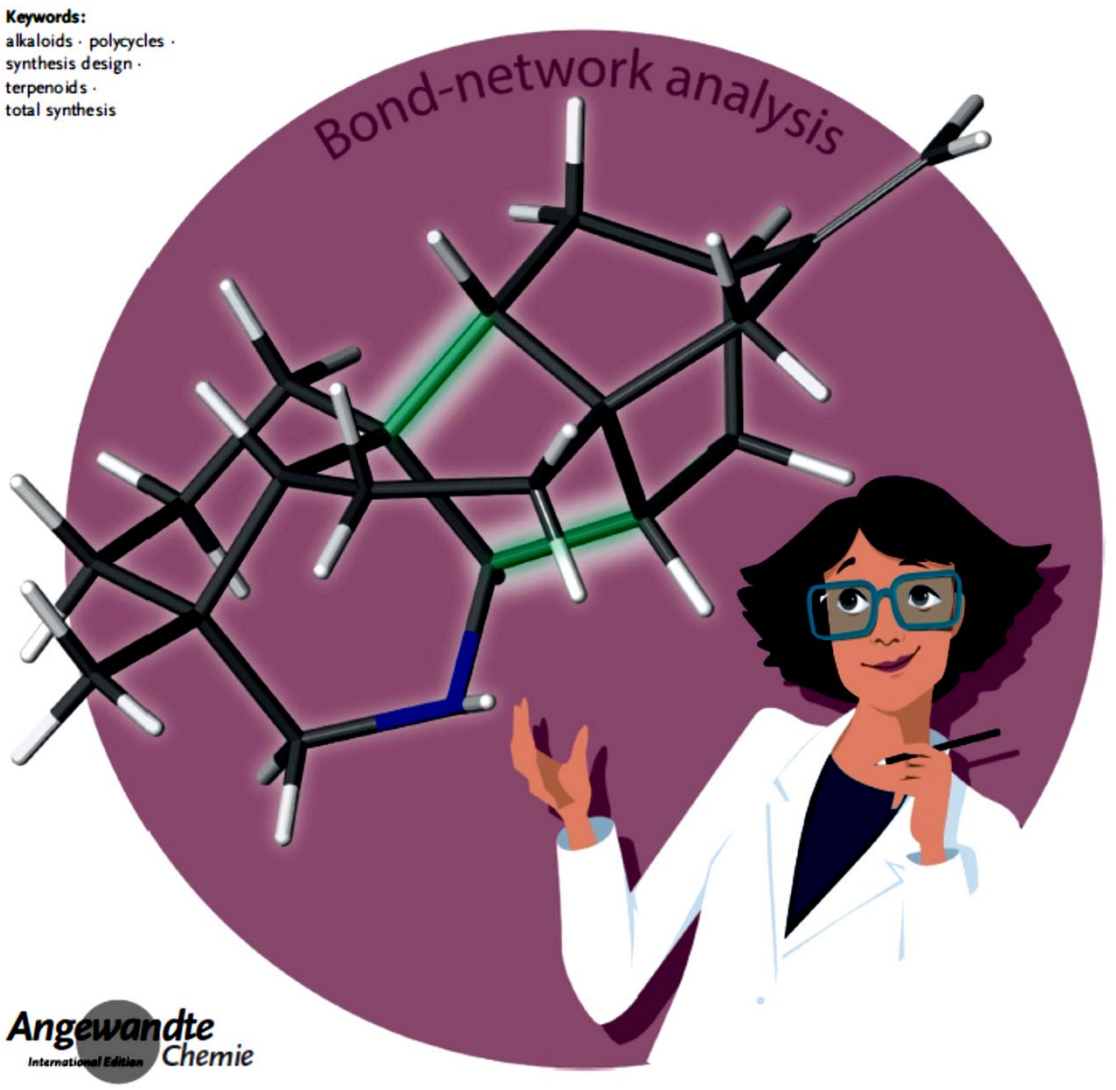


Enjoy reading the article!

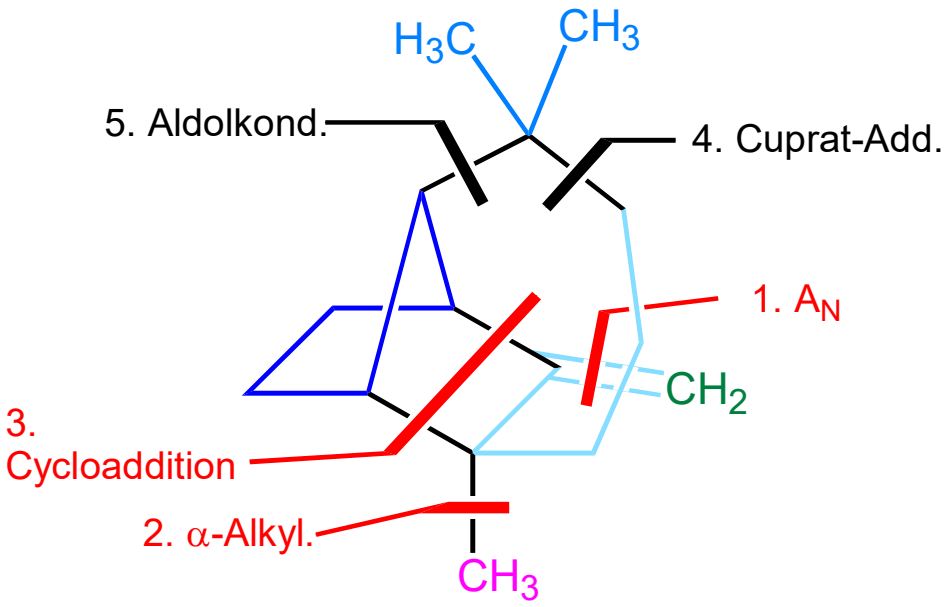
The Corey retrosynthetic analysis of polycyclic systems cuts one bond at a time.

For heterocyclic systems, selection of strategic bonds must be modified.

Reality often sees simultaneous cuts of two or even more bonds (*e. g.*, "retro DAR").

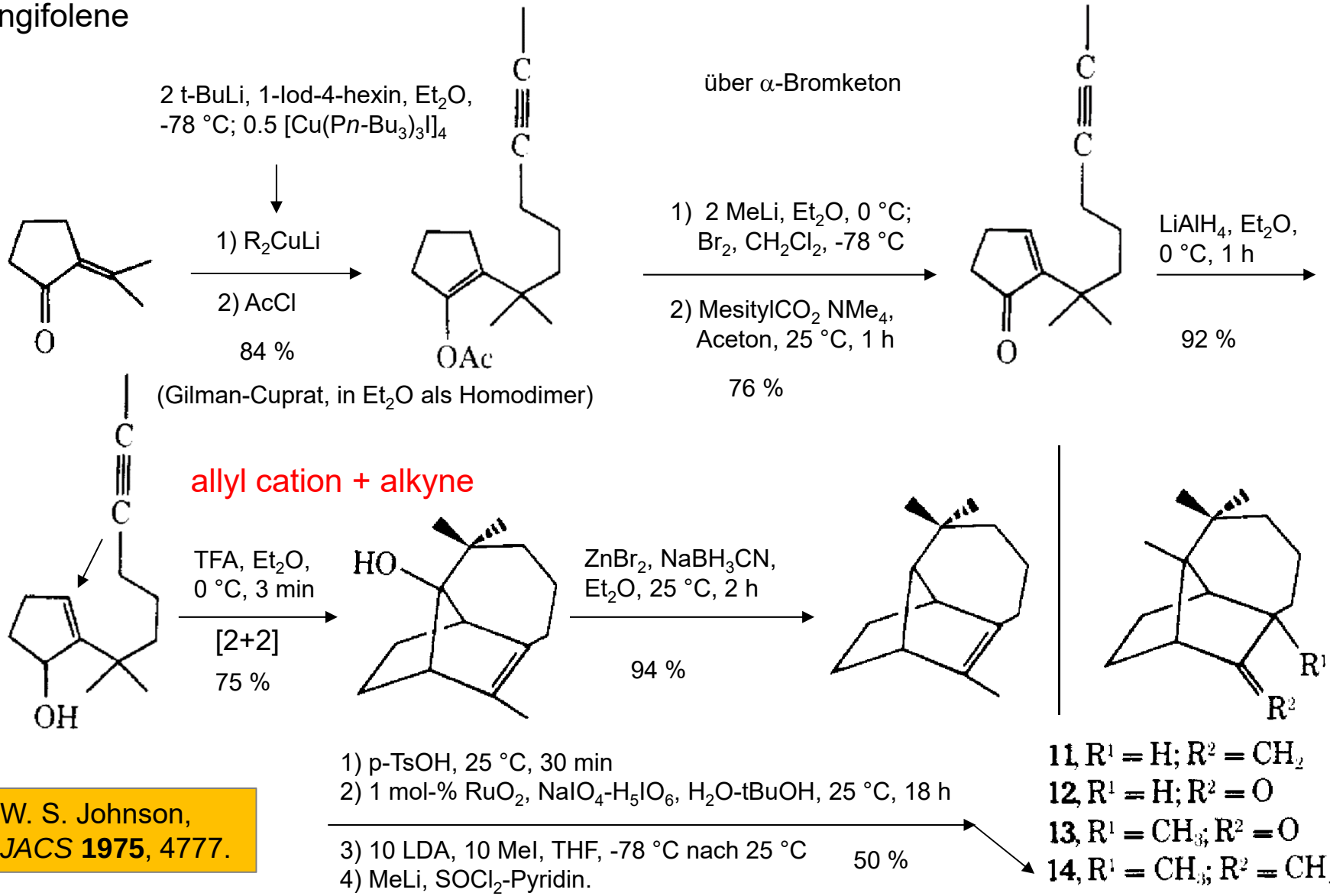


from: Sarpong, Hoffmann, et al., *ACIE* **2020**, 10722

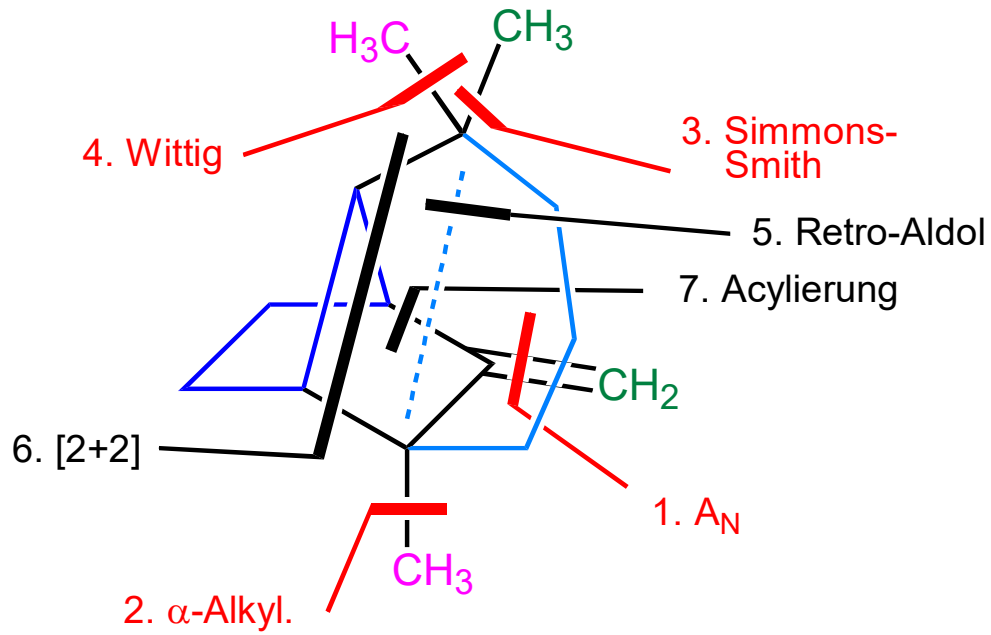


Retrosynthese nach *Johnson*

Longifolene

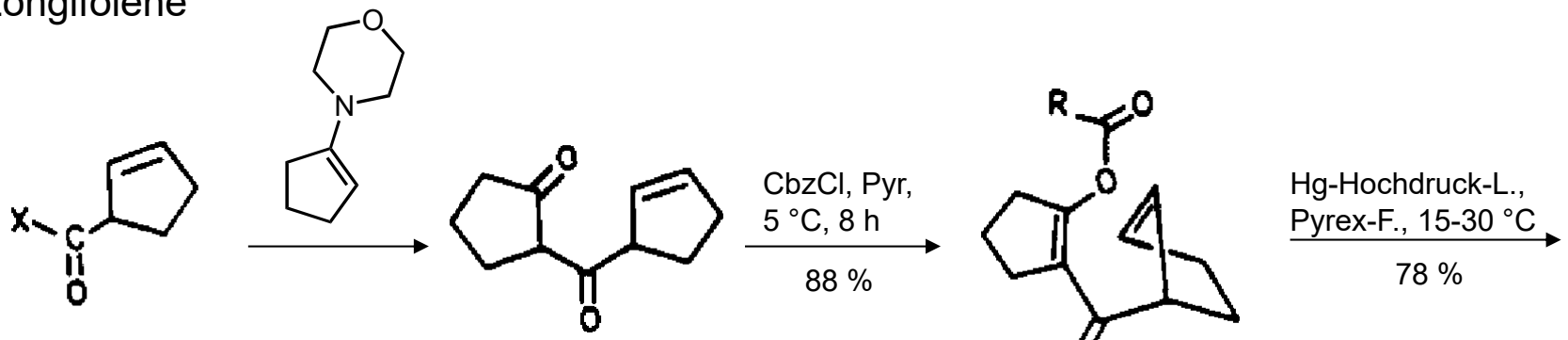


W. S. Johnson, *JACS* **1975**, 4777.



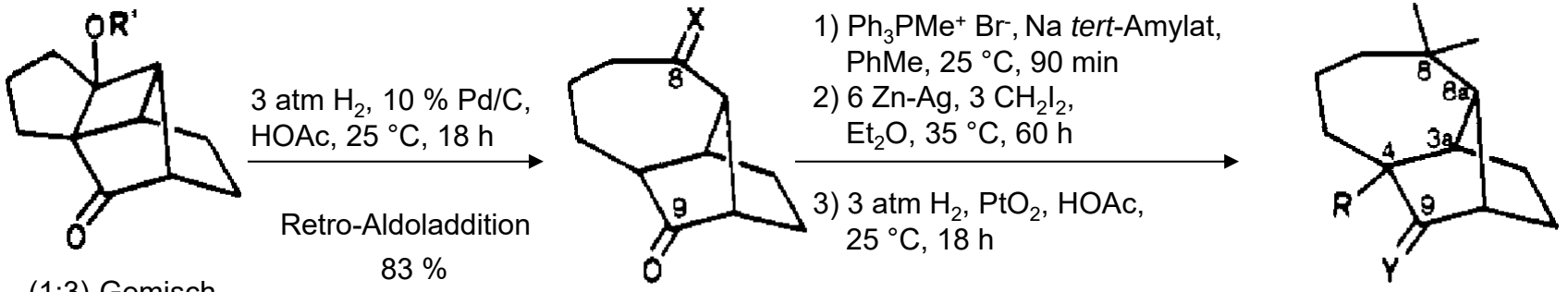
Retrosynthese nach *Oppolzer*

Longifolene



1: X = OH
2: X = Cl

R = OBn



(1:3)-Gemisch

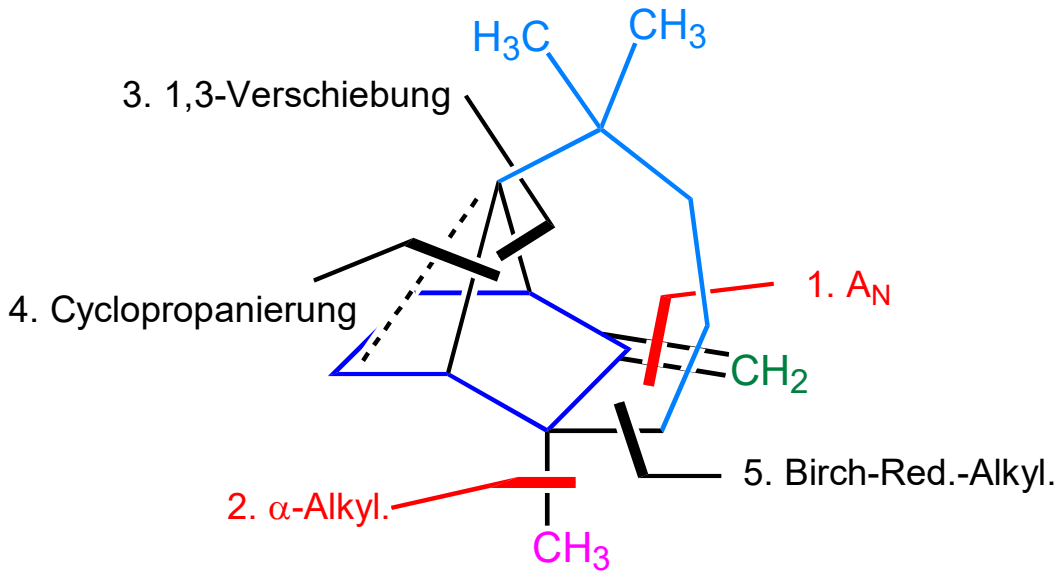
R' = Cbz

6: X = O
7: X = CH_2

Endgame wie Johnson.

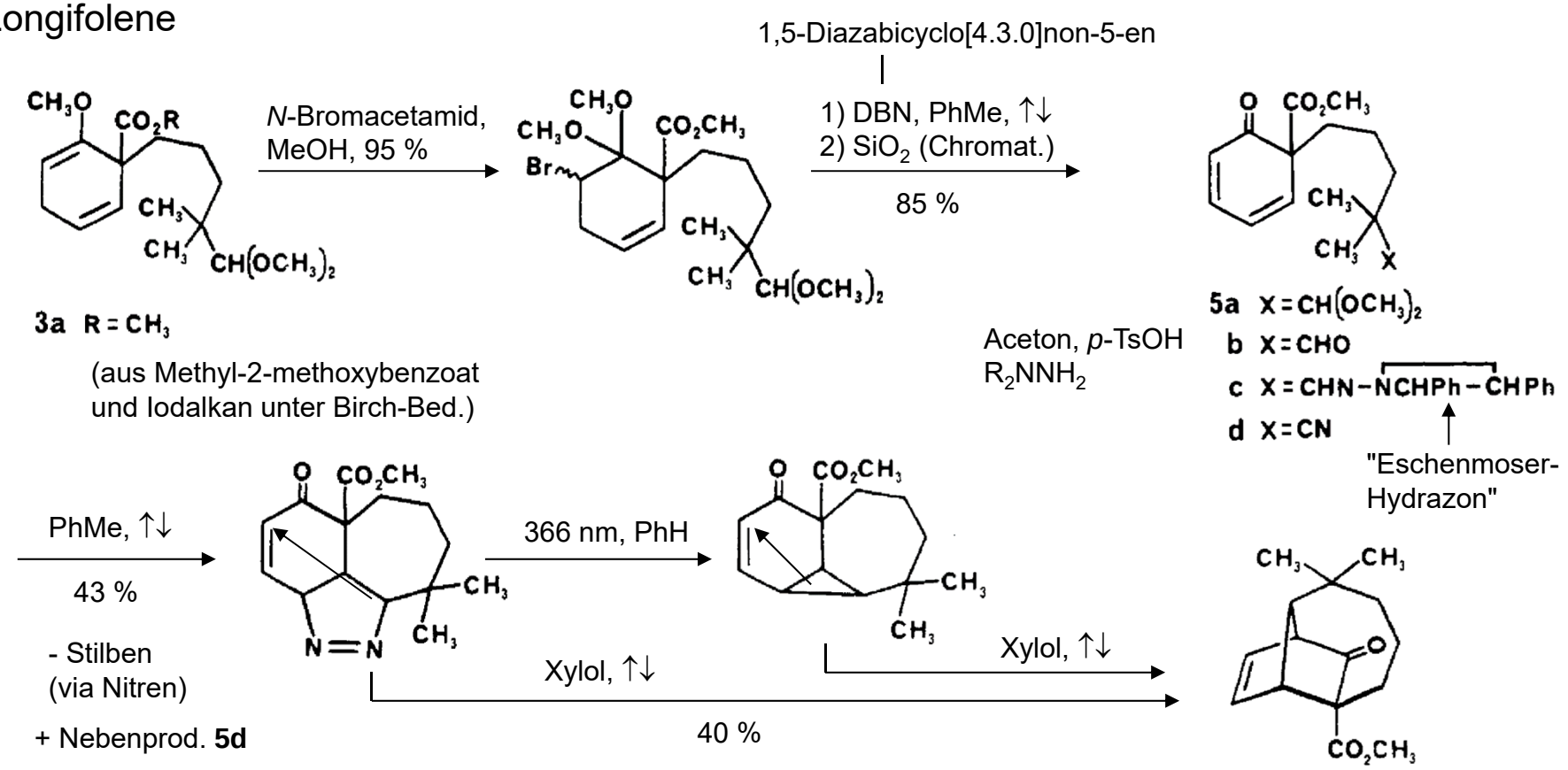
9: Y = O, R=H
10: Y = O, R=CH_3
11: Y =CH_2, R=CH_3

Oppolzer, *JACS* **1978**, 2583.



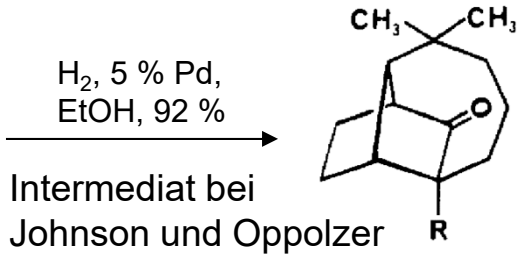
Retrosynthese nach *Schultz*

Longifolene



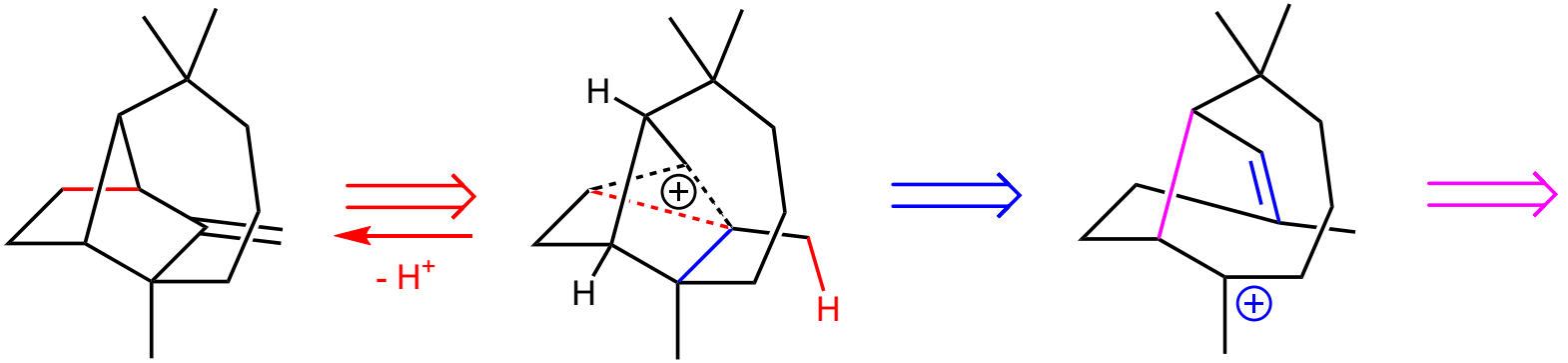
Schultz, *JOC* **1985**, 915.

(7) **CAUTION!** After preparation of 1-amino-2-phenylaziridinium acetate (approximately 10-g scale) by the known procedure (Muller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 114), it exploded during storage at room temperature, causing minor injuries. The cause of the explosion is unclear at present. Thus, it is desirable to use a pentane solution of 1-amino-2-phenylaziridine for the preparation of *N*-aziridinyl imines.



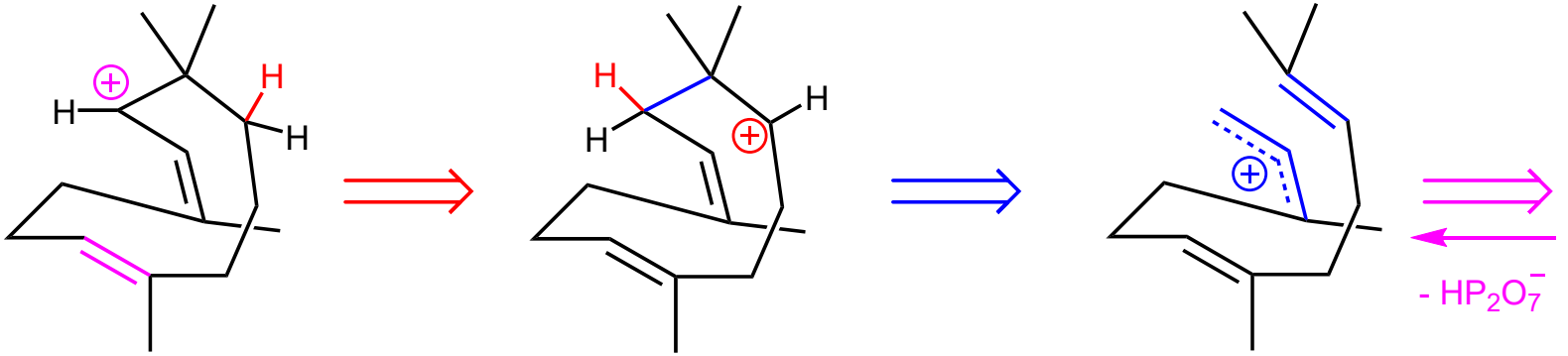
Lindel, *Strategies of Synthesis*

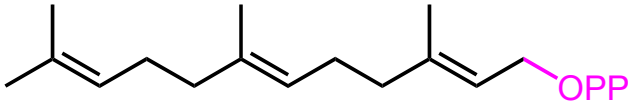
Analysis of the putative or proven biosynthesis



(+)-longifolene

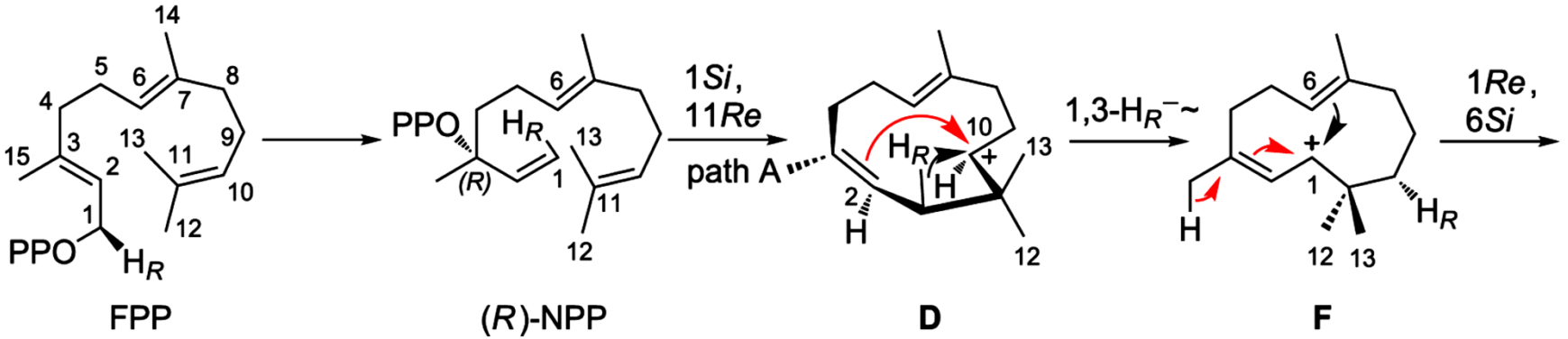
non-classical carbocation

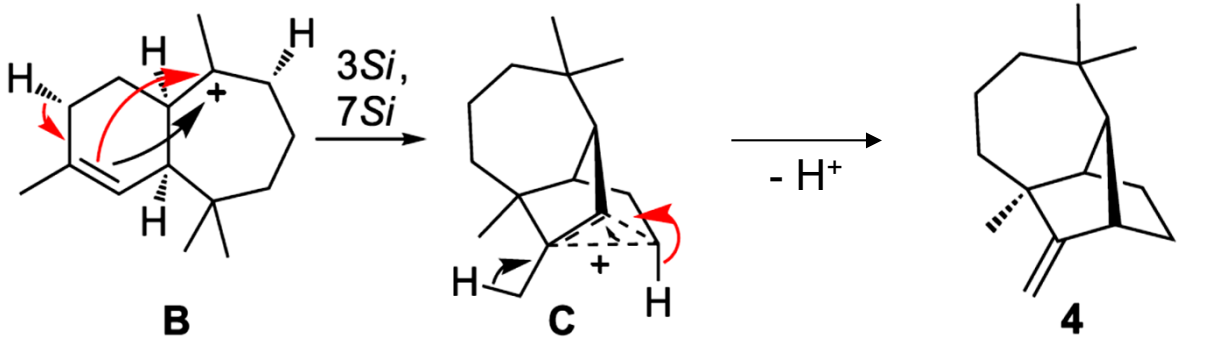




farnesyl pyrophosphate

Biosynthesis of longifolene: done by a single cyclase ...





himachalyl cation

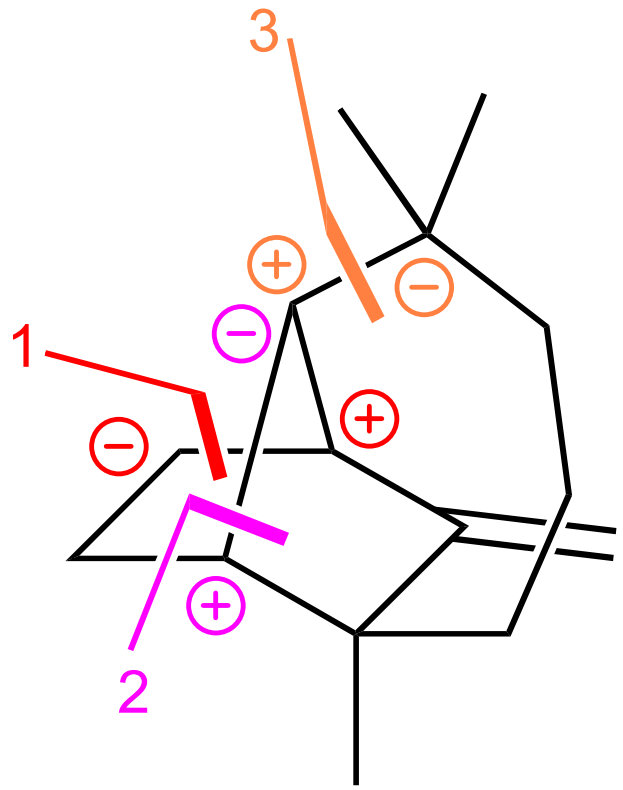
non-classical carbocation

(+)-longifolene

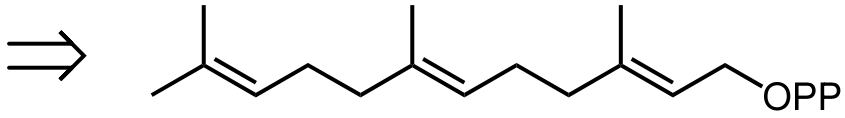
(consider black mechanistic arrows, only)

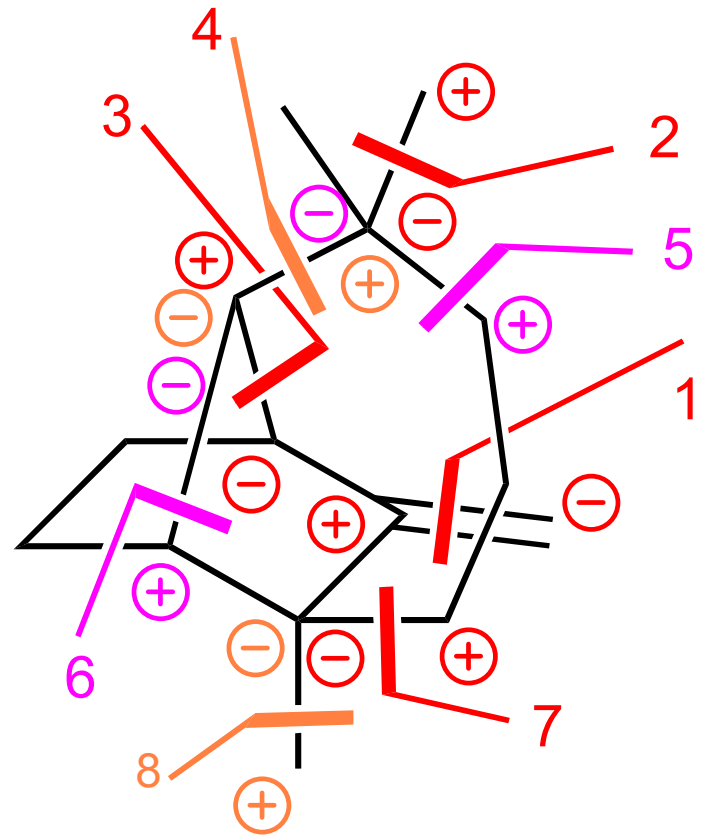
from Rinkel, Dickschat, *Beilstein JOC* **2019**, 1008; doi:10.3762/bjoc.15.99

Polar retrosynthesis (charges indicate the polarity of the retrocut and forward direction)



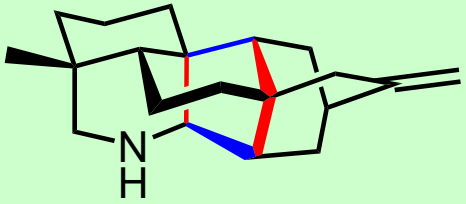
Pinus ponderosa





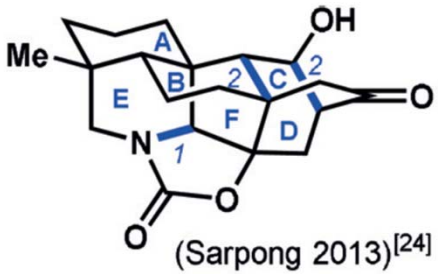
Corey, *JACS* **1961**, 1251.

1,3-cyclohexandione, MeI,
methyl vinyl ketone, ethyl bromide, MeLi



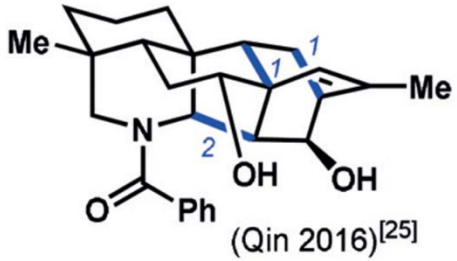
diterpenoid alkaloid hetidine

red: "Corey's core bonds"
blue: "Corey's recommended bonds"



(Sarpong 2013)[24]

Stage	Rings
At Start	A, D
Closure 1)	E
Closure 2)	B, C, F



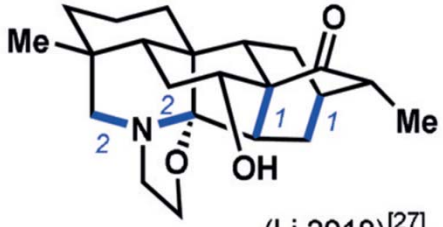
(Qin 2016)[25]

Stage	Rings
At Start	A, E, D
Closure 1)	B, C
Closure 2)	F

Only one of currently known syntheses of hetidine-type compounds exploits Corey's retrosynthetic approach.

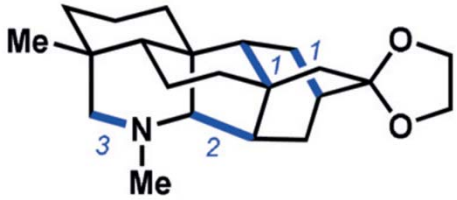
In all of the syntheses, at least one two-bond formation is involved.

Enjoy reading the article!



(Li 2018)[27]

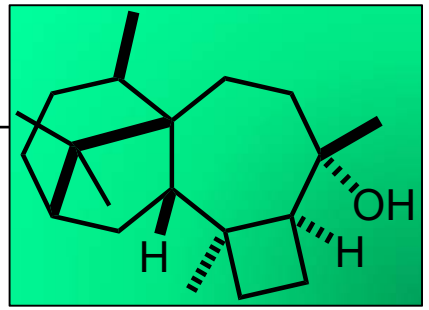
Stage	Rings
At Start	A, B, C
Closure 1)	D, F
Closure 2)	E



(Ma 2018)[28]

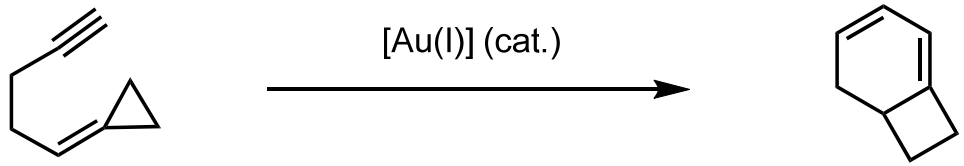
Stage	Rings
At Start	A, D
Closure 1)	B, C
Closure 2)	F
Closure 3)	E

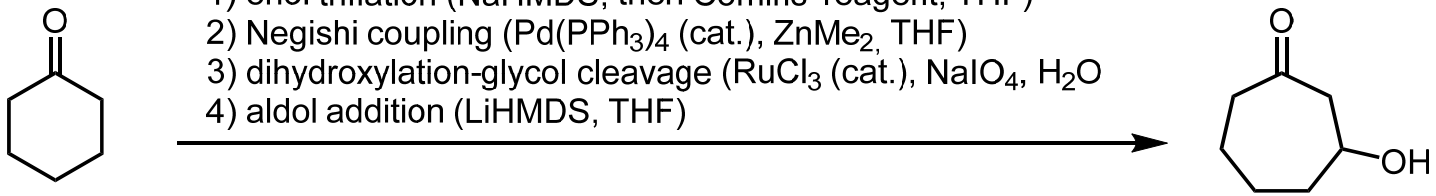
from: Sarpong, Hoffmann, et al., *ACIE* **2020**, 10722

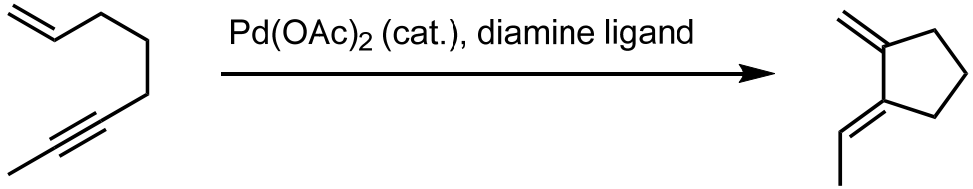


Total Synthesis and Structural Revision of a Harziane Diterpenoid.
Hönig, Carreira, *Angew. Chem. Int. Ed.* **2020**, *59*, 1192–1196

What could be learned?





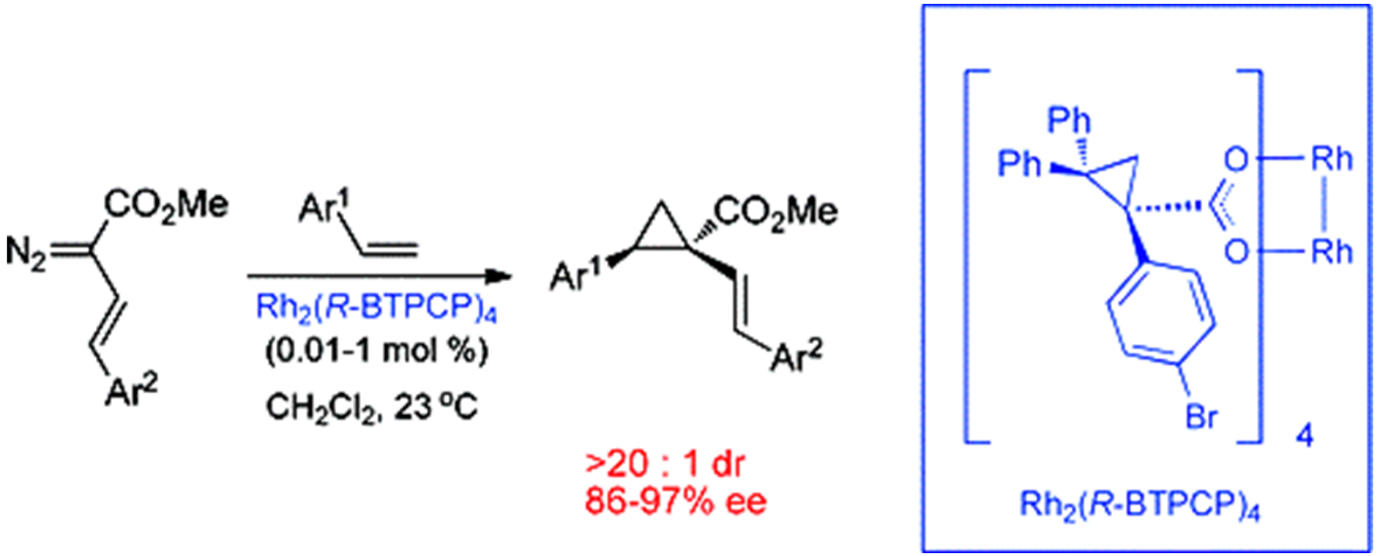


Synthesis of carbocycles (for heterocycles, see class "Heterocycles")

Cyclopropane derivatives

already discussed: Corey-Chaykovsky, Simmons-Smith, Kulinkovich, Wurtz

Rh(II)-catalyzed cyclopropanation of alkenes with α-diazoesters, *e. g.*:



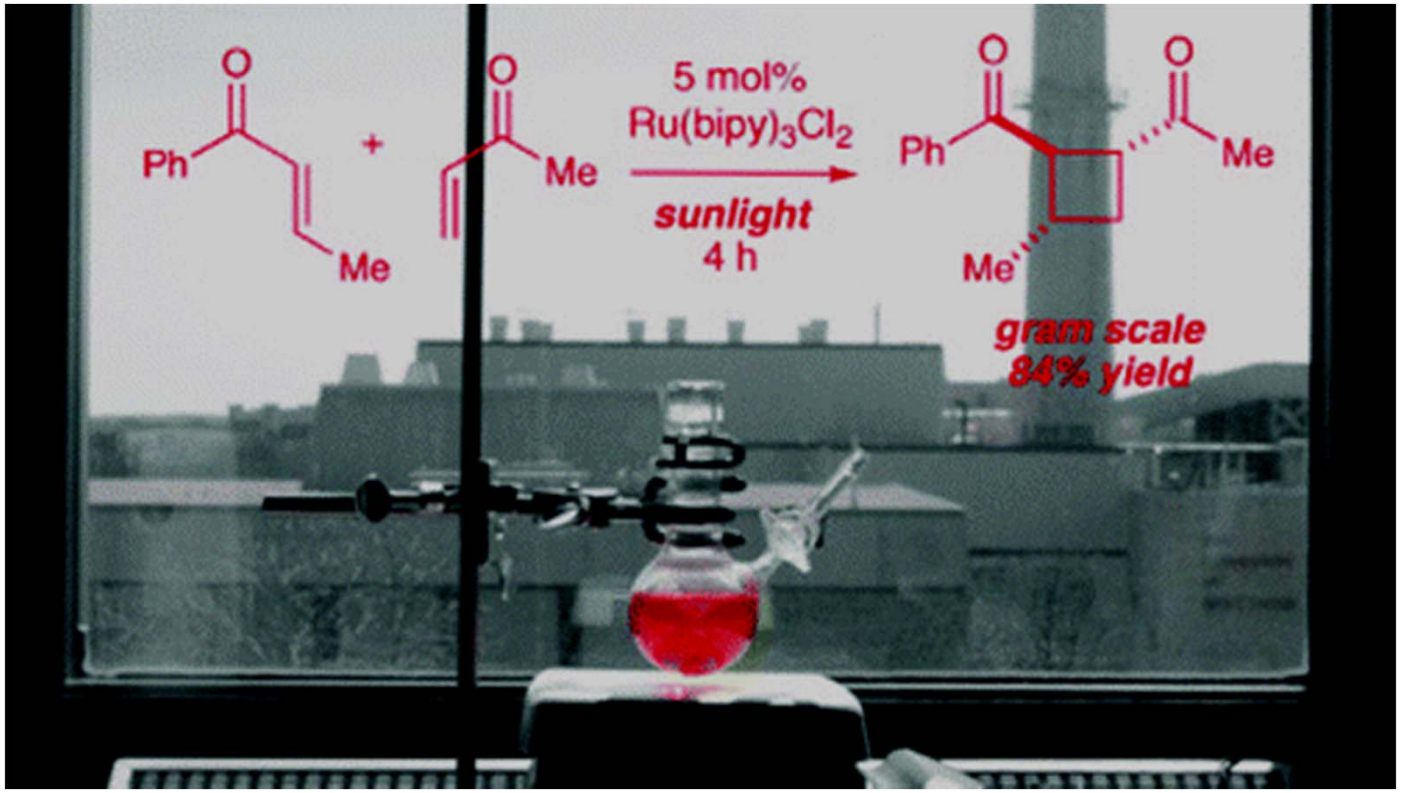
an alkyl cyclopropanecarboxylate ... and many more ...

from Davies et al., *JACS* **2011**, 19198; doi.org/10.1021/ja2074104

Cyclobutane derivatives

already discussed: [2+2] photocycloaddition, cyclization of open-chain precursors

Crossed Intermolecular [2+2] Cycloadditions of Acyclic Enones via Photocatalysis:

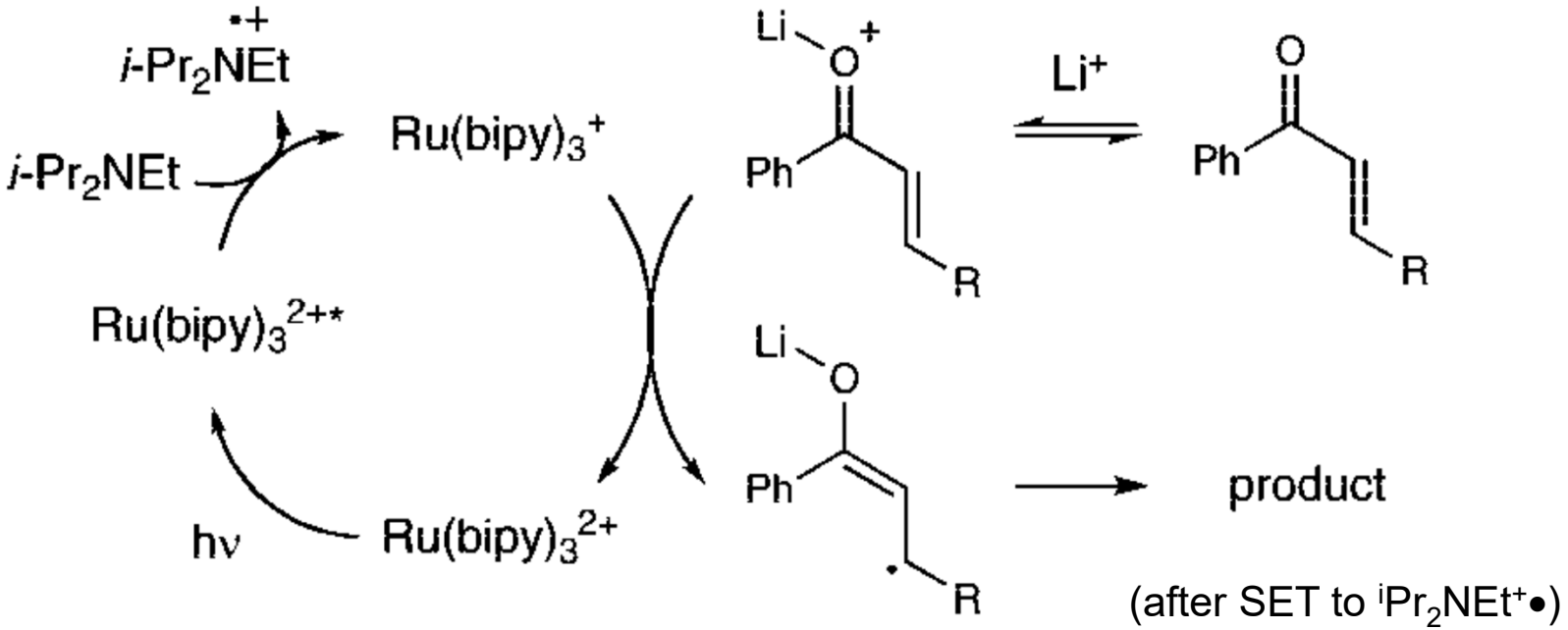


from Yoon et al., *JACS* **2009**, 14604; doi.org/10.1021/ja903732v

Cyclobutane derivatives

already discussed: [2+2] photocycloaddition, cyclization of open-chain precursors

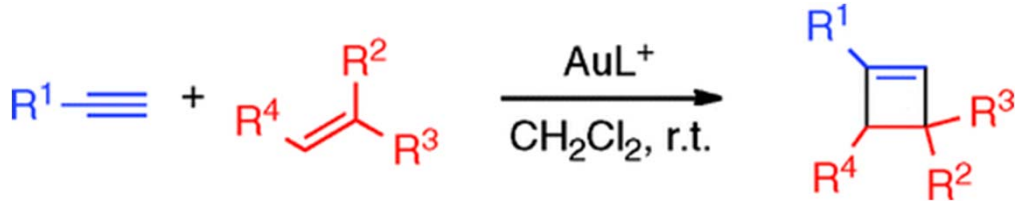
Crossed Intermolecular [2+2] Cycloadditions of Acyclic Enones via Photocatalysis:

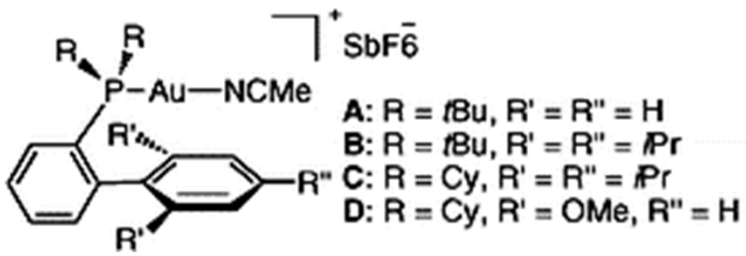


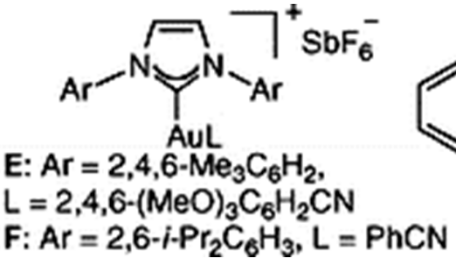
from Yoon et al., *JACS* **2008**, 12887

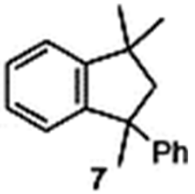
Cyclobutene derivatives

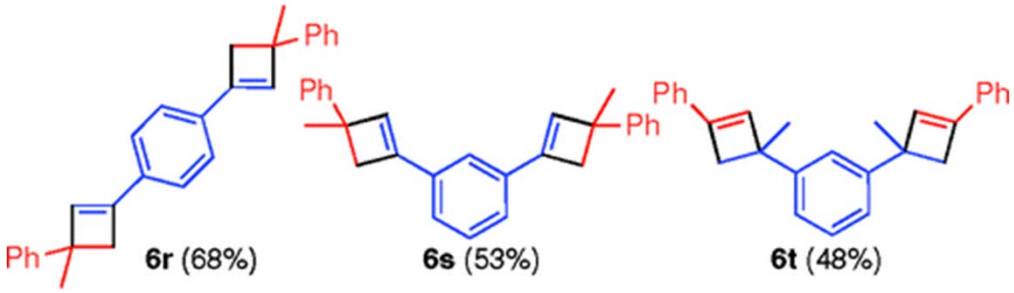
[2+2] cycloaddition of alkene and alkyne components







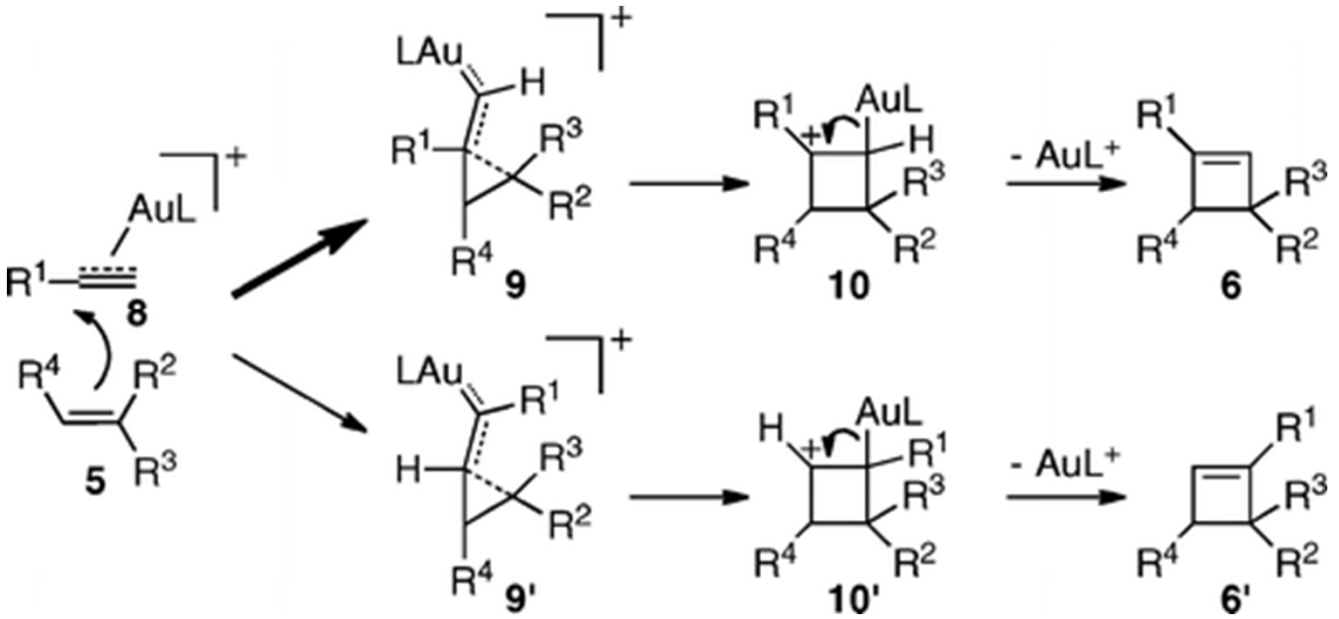




from Echavarren et al., *JACS* **2010**, 9292

Cyclobutene derivatives

[2+2] cycloaddition of alkene and alkyne components

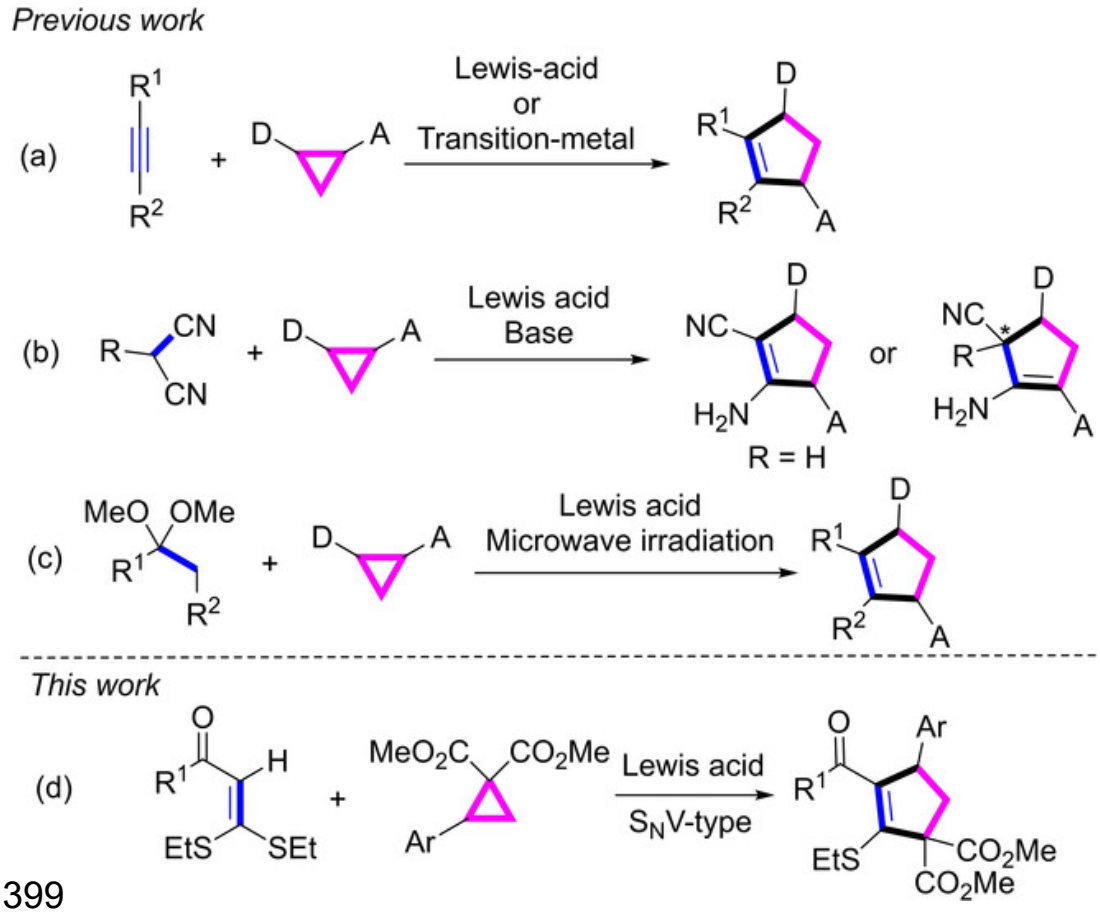


from Echavarren et al., *JACS* **2010**, 9292

Cyclopentene derivatives

already discussed: olefin metathesis, enyne metathesis

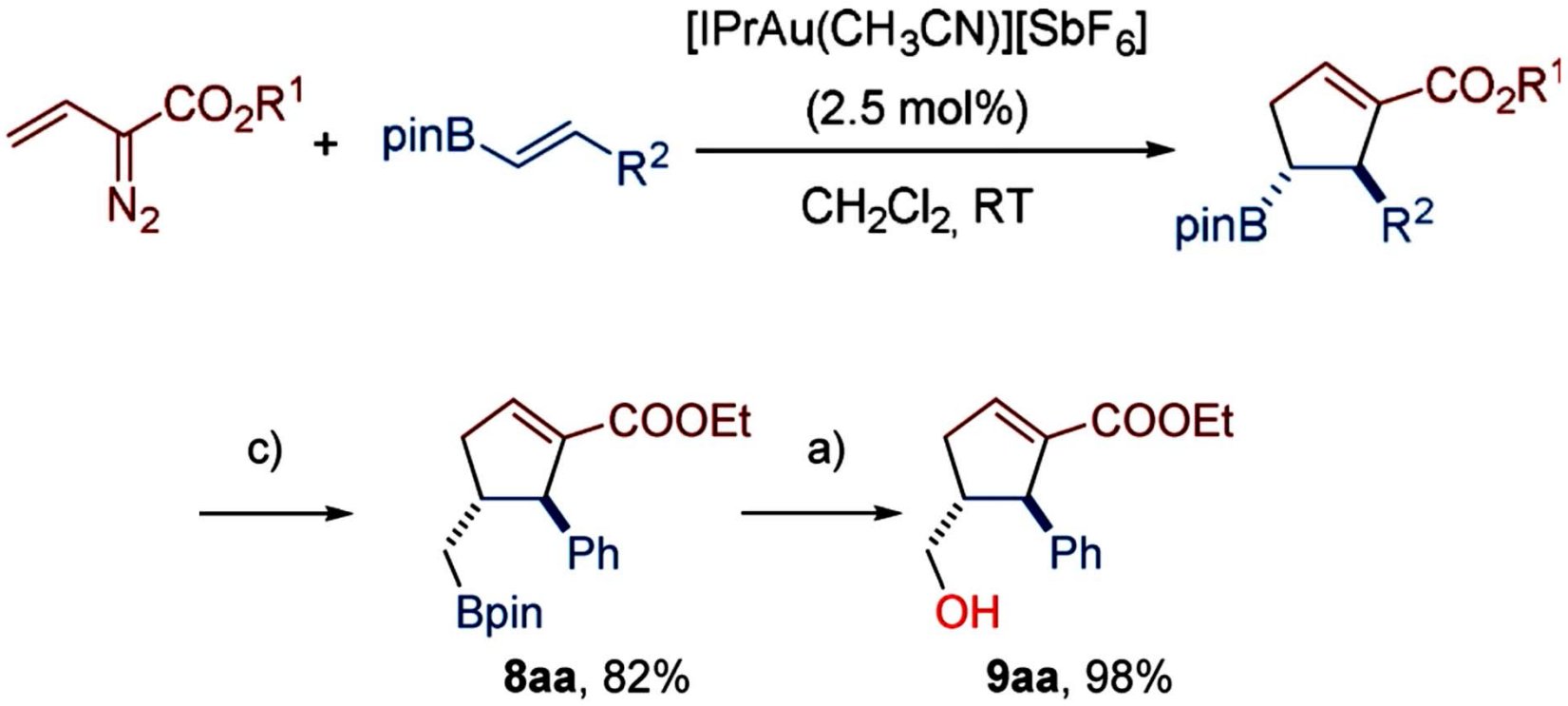
from donor-acceptor cyclopropanes:



from Wang et al., *ChemistrySelect* **2020**, 11399
see also Werz et al., *Eur. J. Org. Chem.* **2020**, 2560

Cyclopentene derivatives

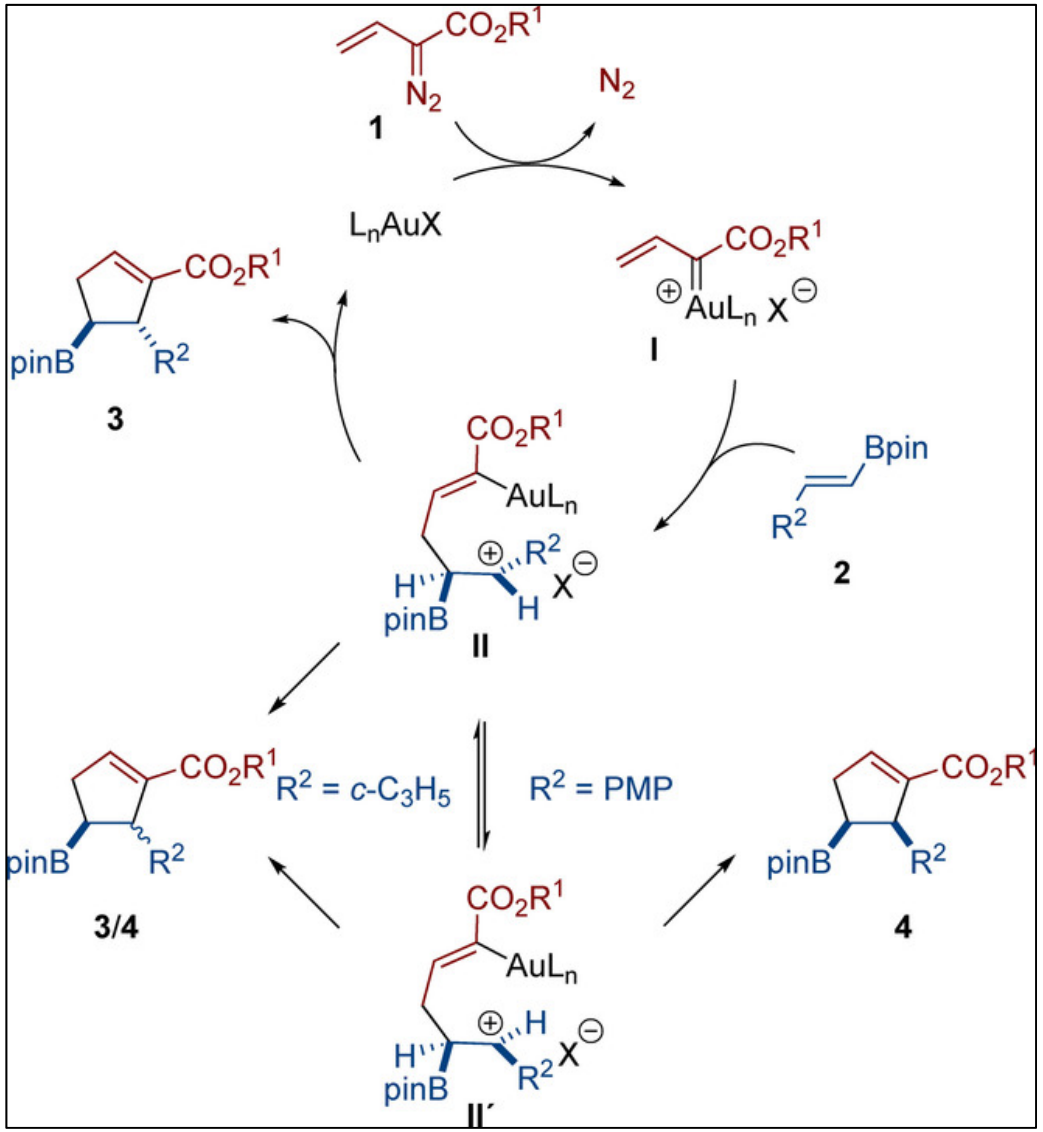
Au(I)-catalyzed [3+2] carbocycloaddition



from López et al., *Chem. Eur. J.* **2020**, 6999

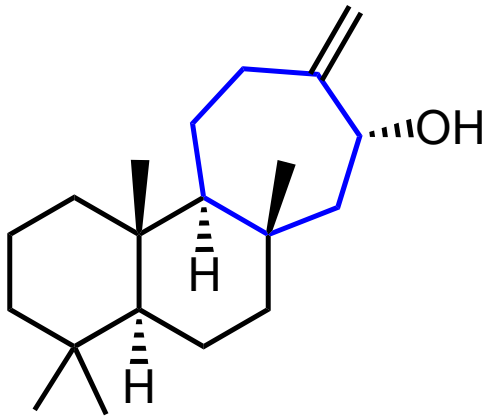
Cyclopentene derivatives

Au(I)-catalyzed [3+2] carbocycloaddition

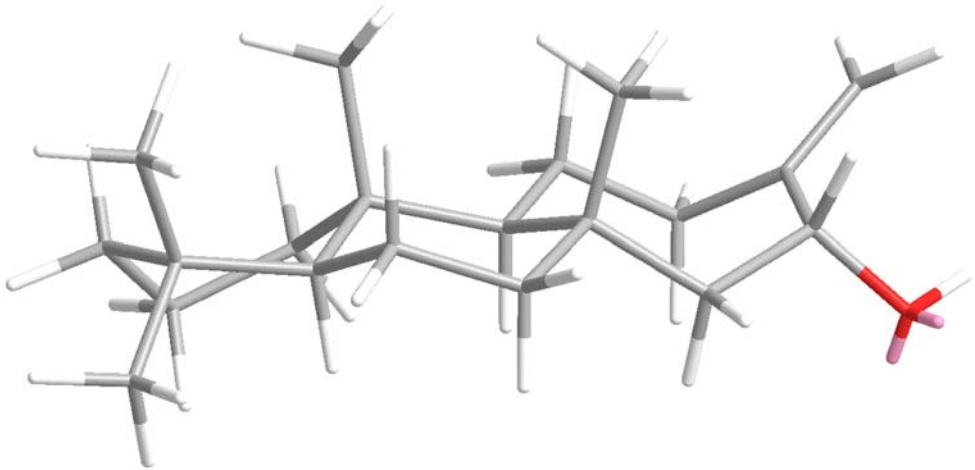


from López et al., *Chem. Eur. J.* **2020**, 6999

Cycloheptadiene derivatives by [4+3] cycloaddition



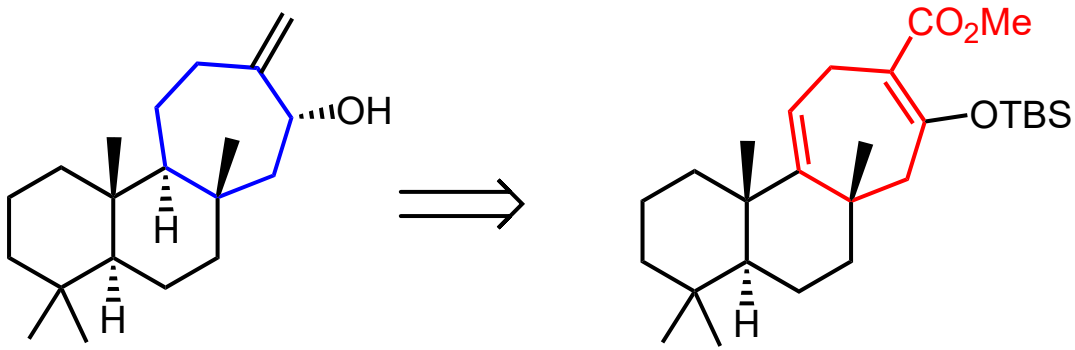
(–)-barekol



This is no cycloheptadiene.

Sarpong, Davies, et al., *JACS* **2010**, 12422

Cycloheptadiene derivatives by [4+3] cycloaddition

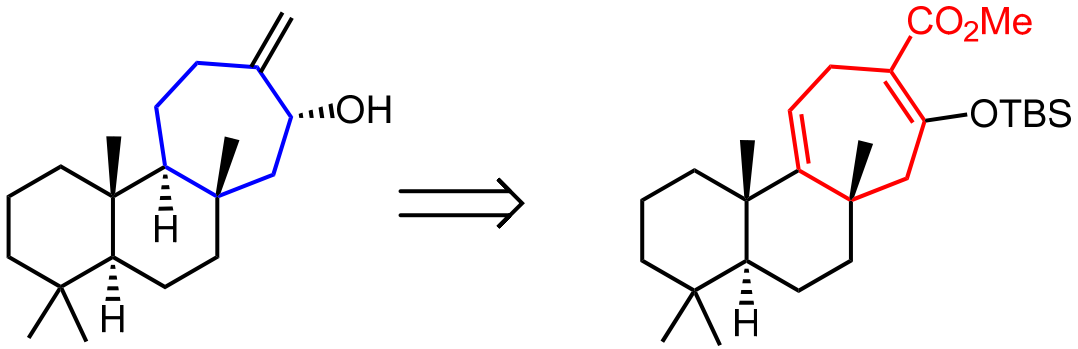


(–)-barekol

a 1,4-cycloheptadiene precursor

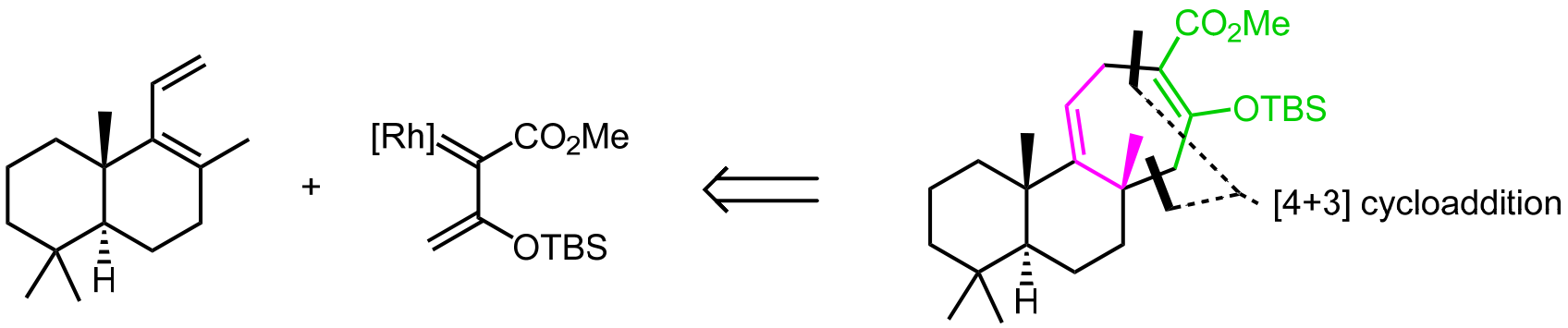
Sarpong, Davies, et al., *JACS* **2010**, 12422

Cycloheptadiene derivatives by [4+3] cycloaddition



(–)-barekol

a 1,4-cycloheptadiene precursor



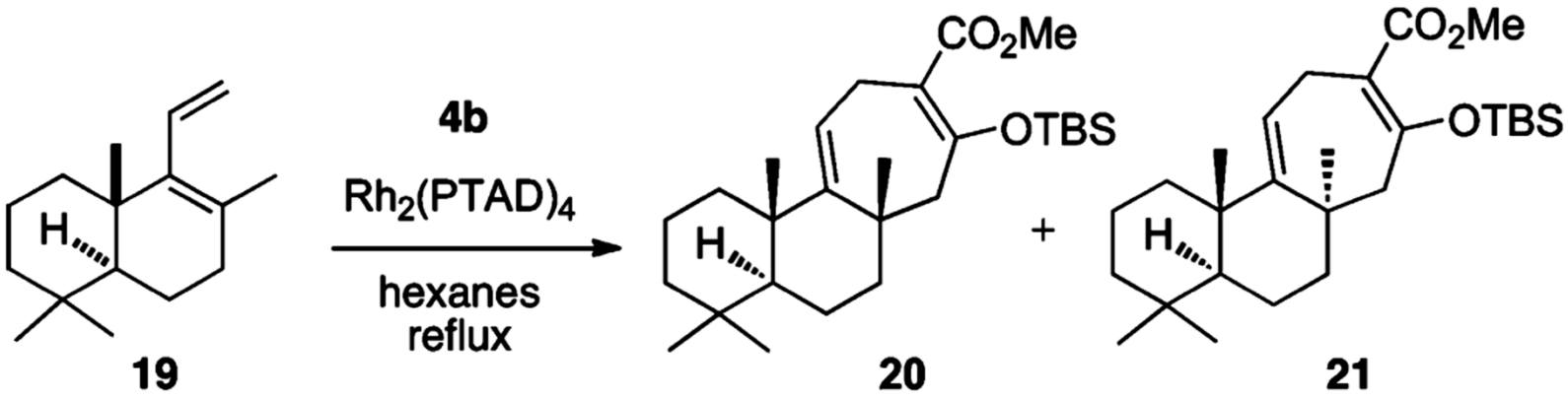
what the master may have to look up

what the master knows

Sarpong, Davies, et al., *JACS* **2010**, 12422

Cycloheptadiene derivatives by [4+3] cycloaddition

via the divinylcyclopropane and [3,3]



19 **20** **21**

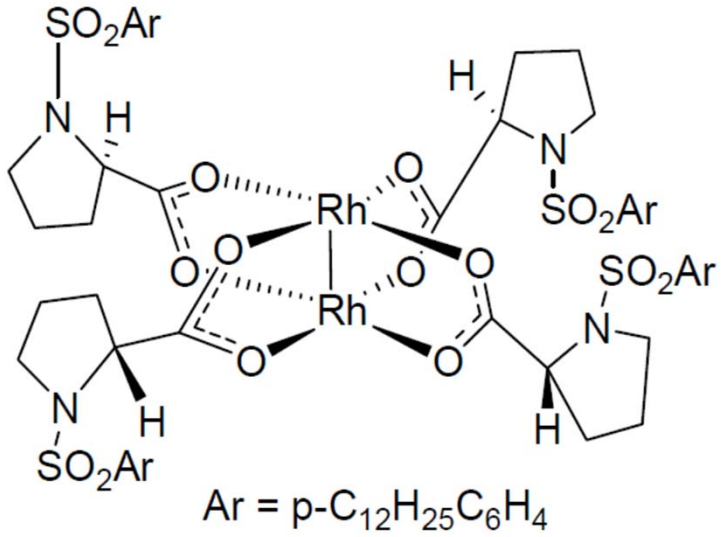
catalyst	ratio (**4b**/**19**)	dr (**20**/**21**)	yield (**20** + **21**, %)
Rh_2(*R*-PTAD)$_4$	5:1	6:1	65 (47[a])
Rh_2(*S*-PTAD)$_4$	3:1	1:9	63

[a] Isolated yield of pure **20**.

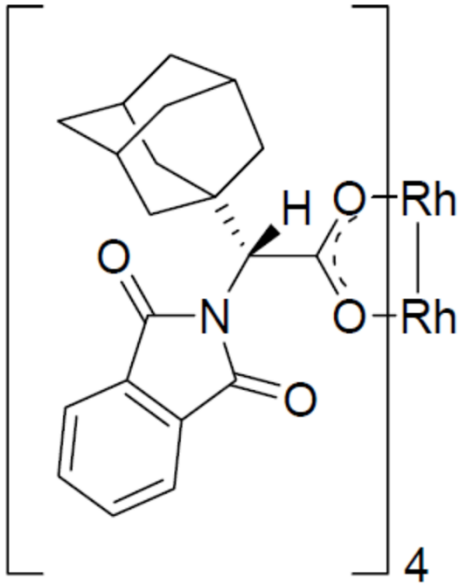
what the master still has to investigate

from: Sarpong, Davies, et al., *JACS* **2010**, 12422

Cycloheptadiene derivatives by [4+3] cycloaddition



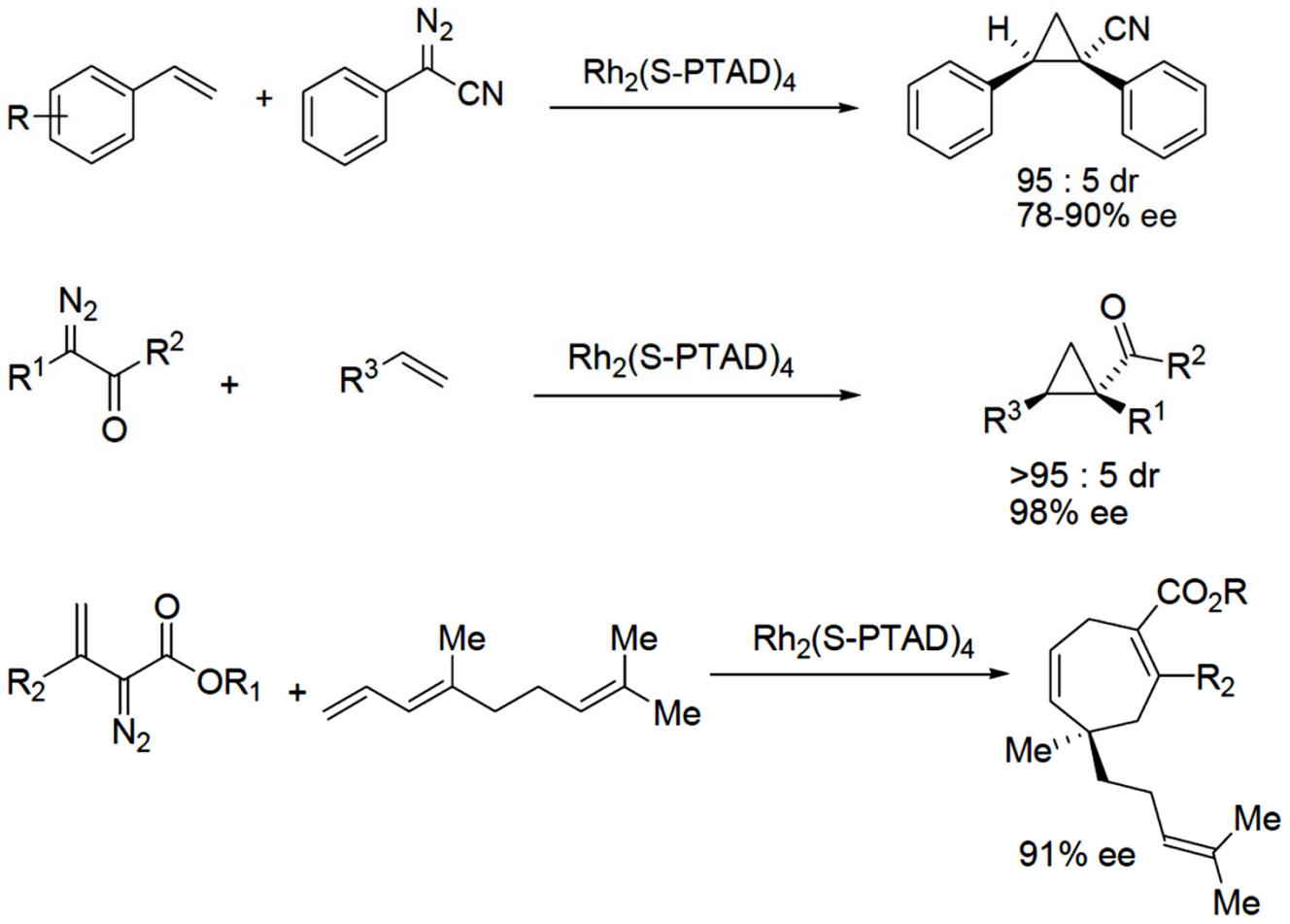
Tetrakis[(*R*)-(+)-*N*-(*p*-dodecylphenylsulfonyl)-prolinato]dirhodium(II)
Rh_2(*R*-DOSP)$_4$



Tetrakis[(*R*)-(-)-(1-adamantyl)-(*N*-phthalimido)acetato]dirhodium(II)
Rh_2(*R*-PTAD)$_4$

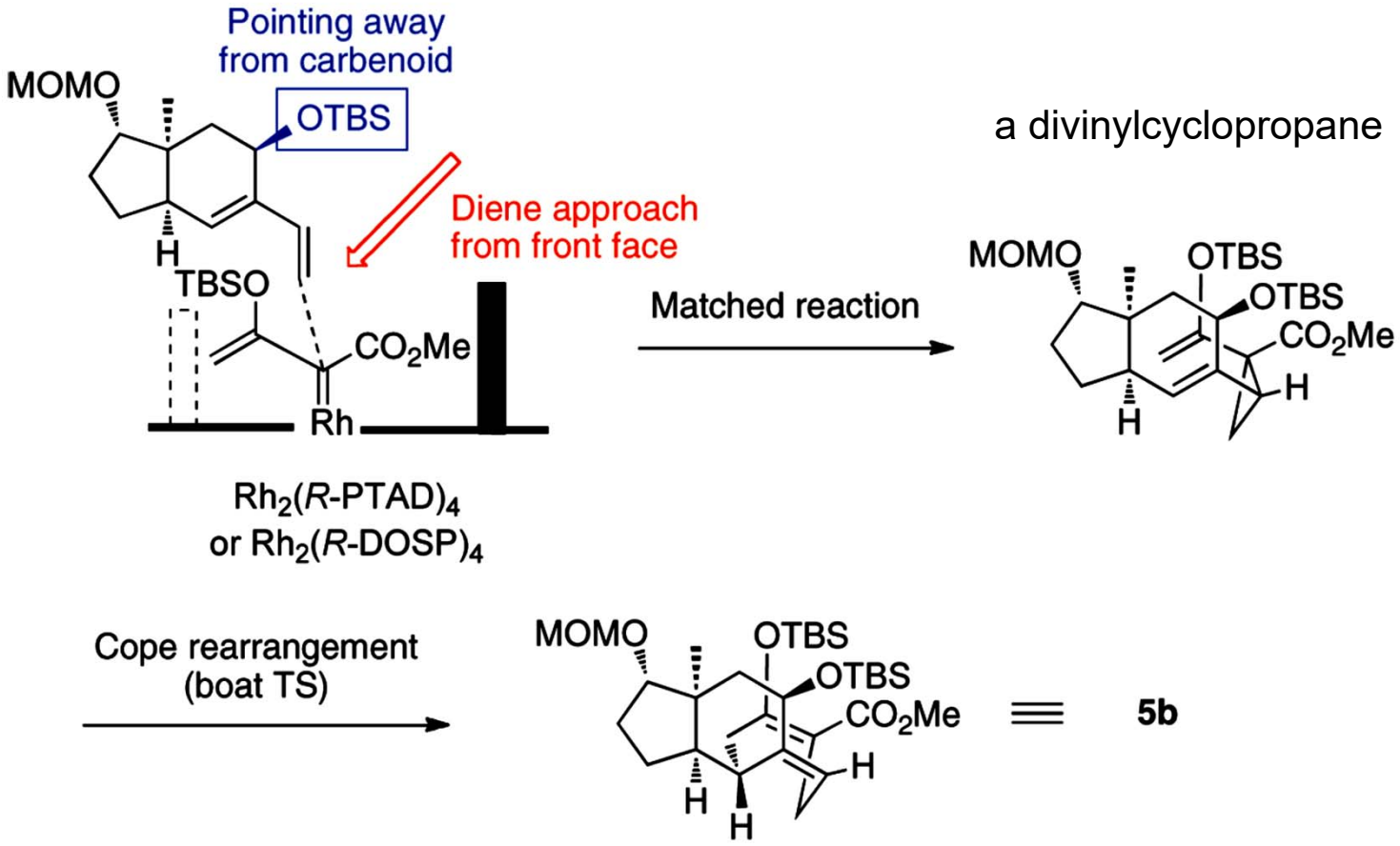
STREM Chemicals

Cycloheptadiene derivatives by [4+3] cycloaddition



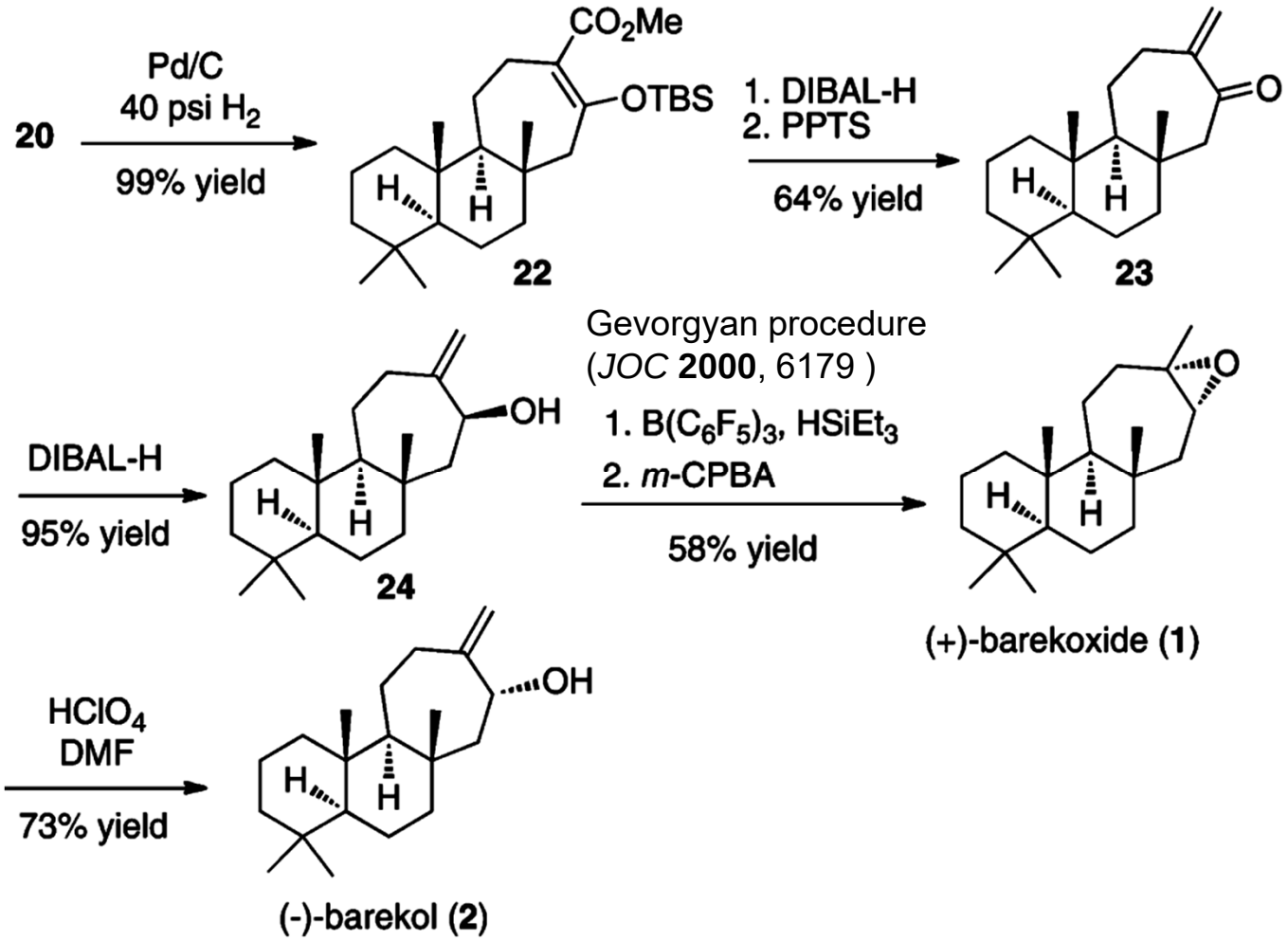
STREM Chemicals

Cycloheptadiene derivatives by [4+3] cycloaddition



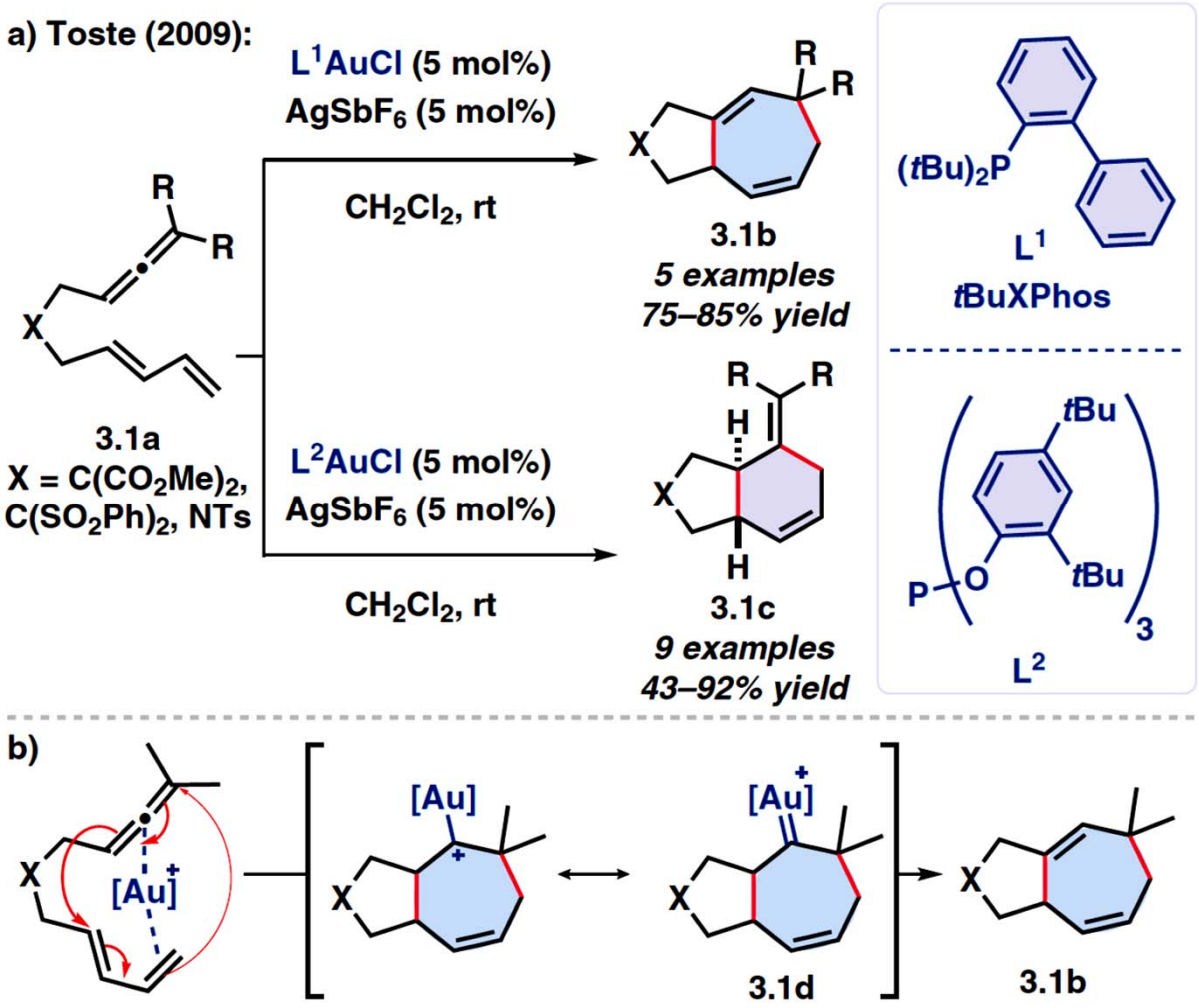
from: Sarpong, Davies, et al., *JACS* **2010**, 12422

Cycloheptadiene derivatives by [4+3] cycloaddition



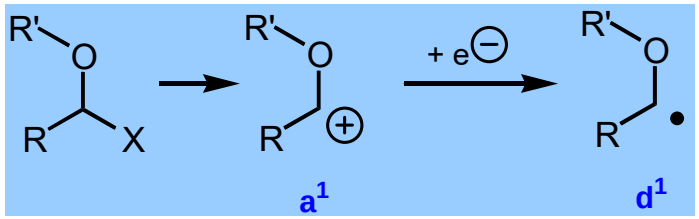
from: Sarpong, Davies, et al., *JACS* **2010**, 12422

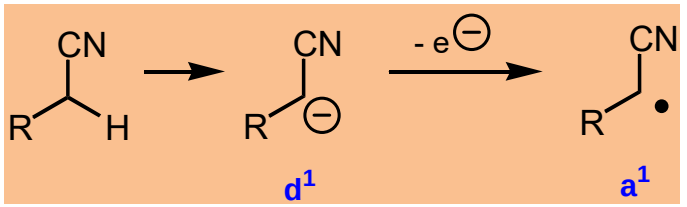
Cycloheptadiene derivatives by [4+3] cycloaddition



from: Lam and Lautens, *Synthesis* **2020**, 2427; 10.1055/s-0039-1690875

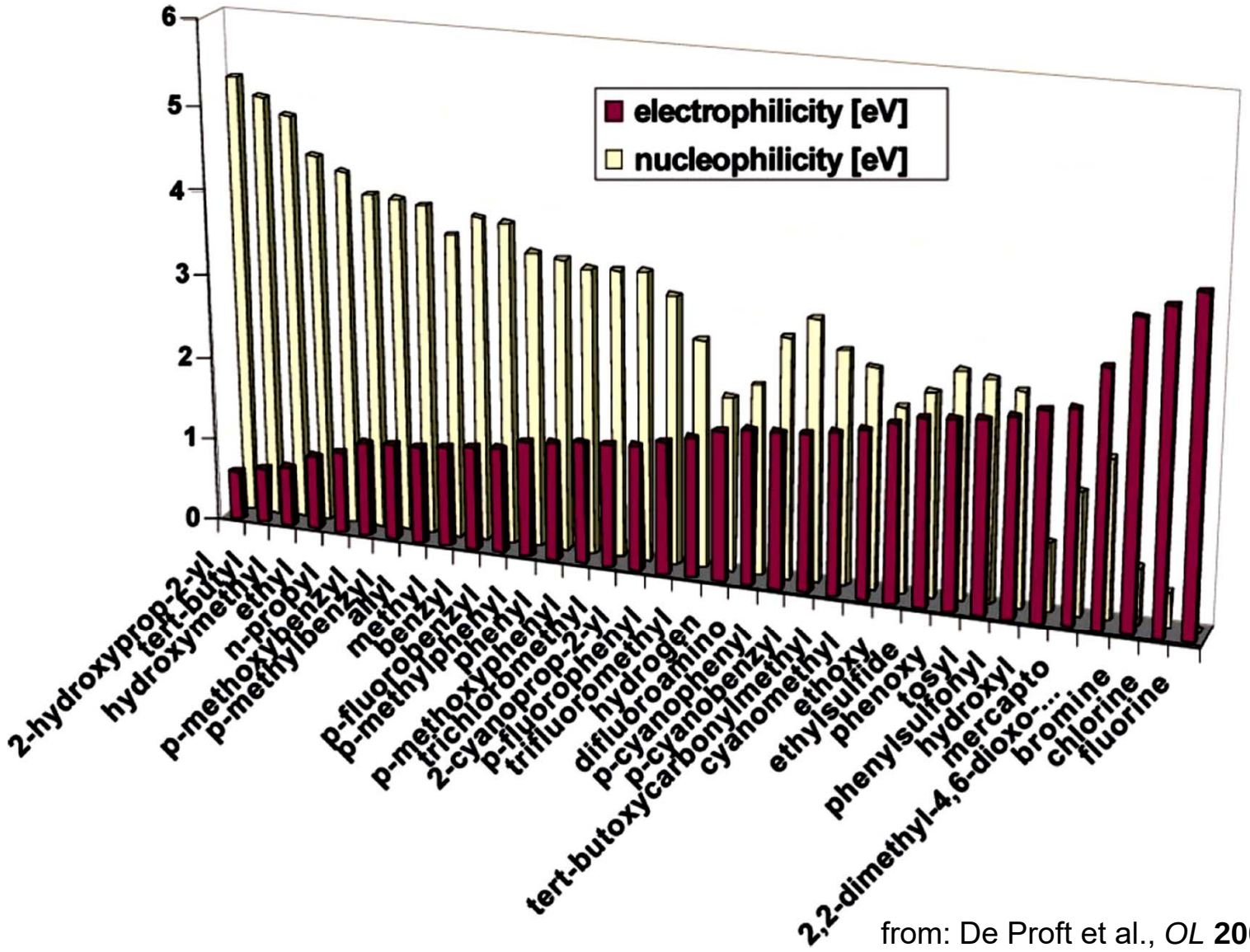
It is sufficient to introduce or remove one electron, which leads to the formation of nucleophilic radicals from electrophiles or of electrophilic radicals from nucleophiles (one-electron polarity reversal).





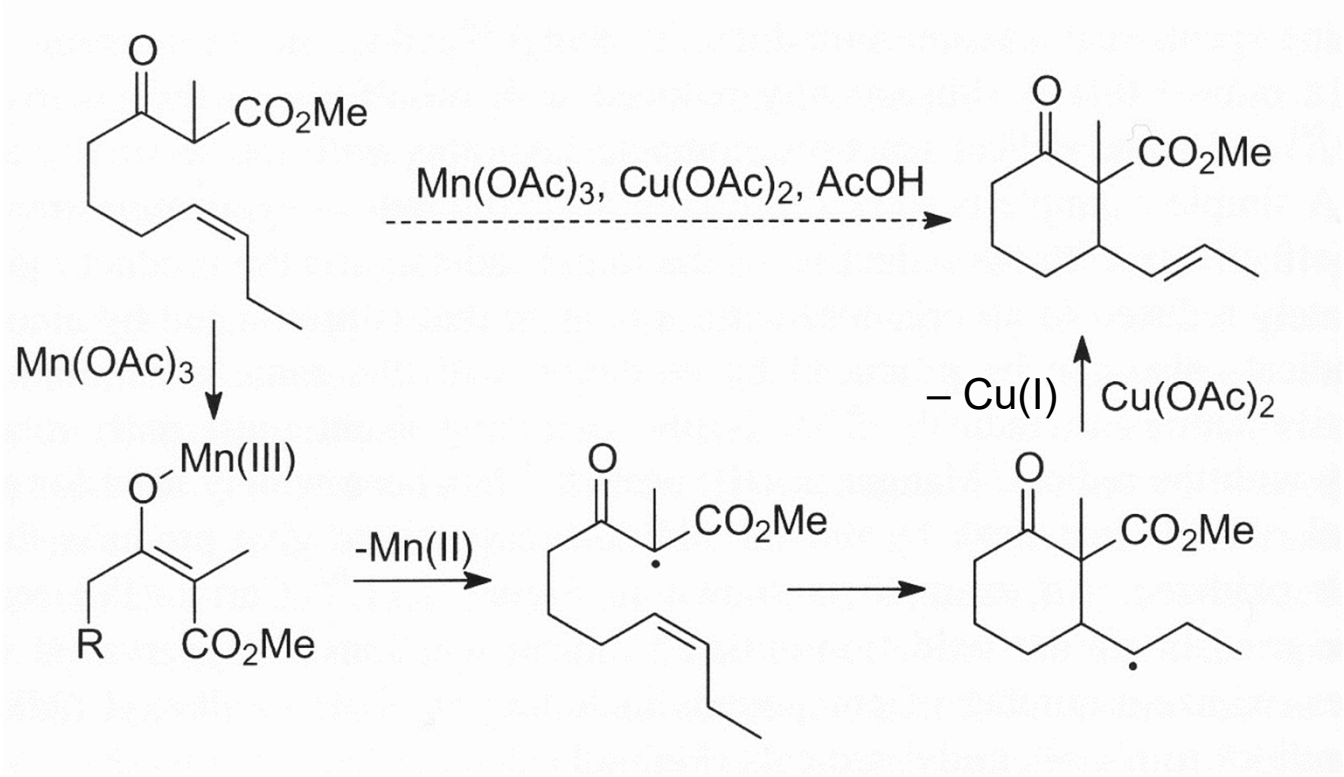
A qualitative approach to determining the "philicity" of a radical

1. Consider the oxidized (cationic) and reduced (anionic) forms of A•
2. Determine which of the forms is more stable
3. Assign the "philicity" of the radical:
    a. If A+ is more stable, A• is a nucleophilic radical because it wants to lose an e–
    b. If A– is more stable, A• is an electrophilic radical because it wants to gain an e–

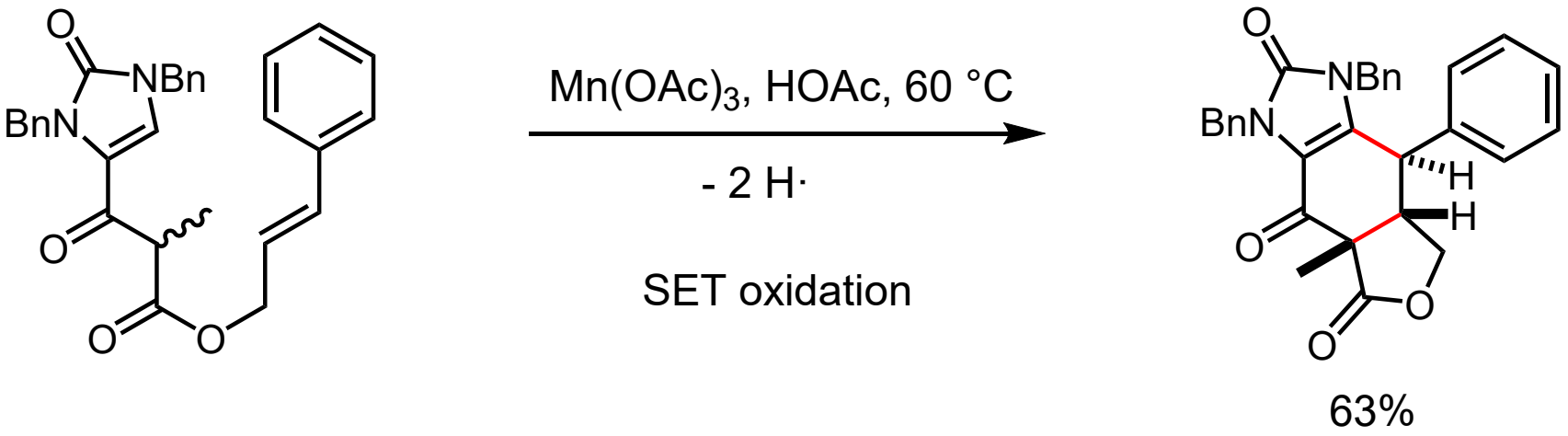


from: De Proft et al., *OL* **2007**, *9*, 2721

E. g., Mn(III) enolate -> Mn(II) + enoyl radical



nucleophilic enolate *electrophilic* enoyl radical



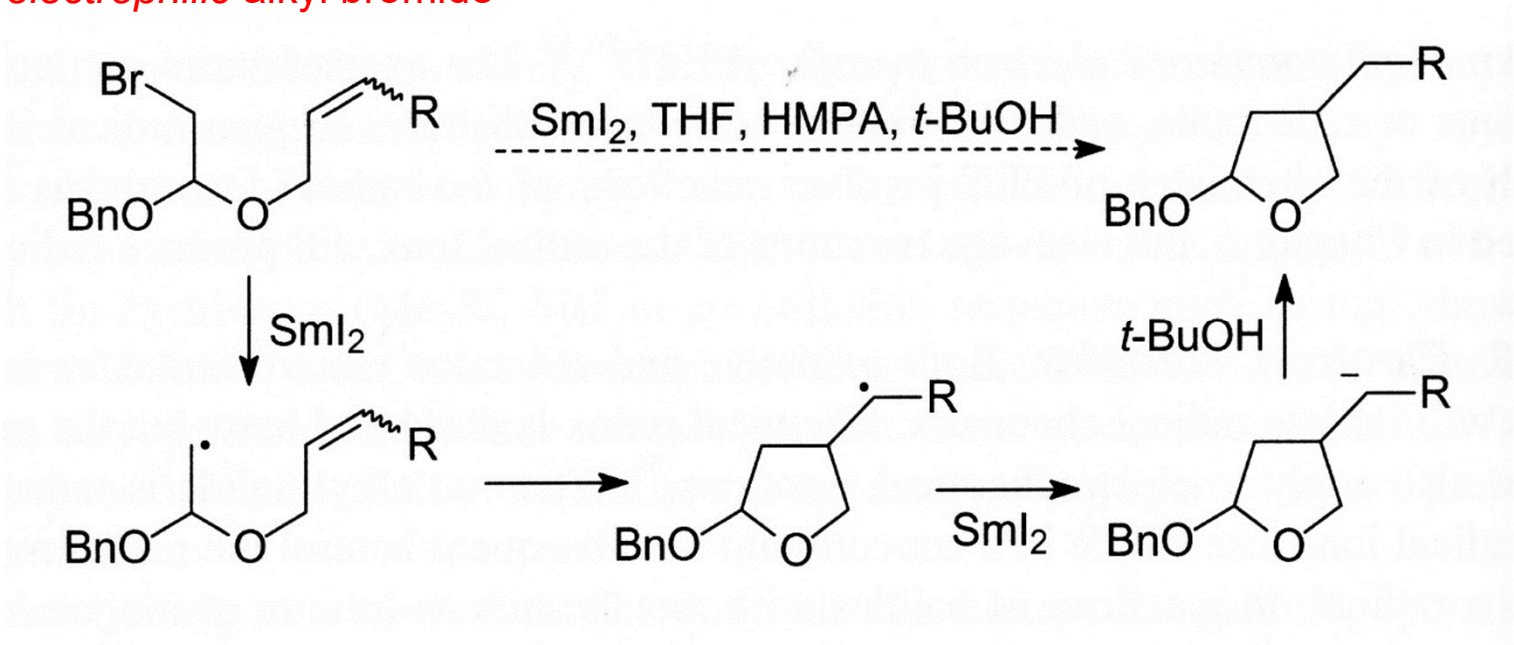
63%

Mechanism?

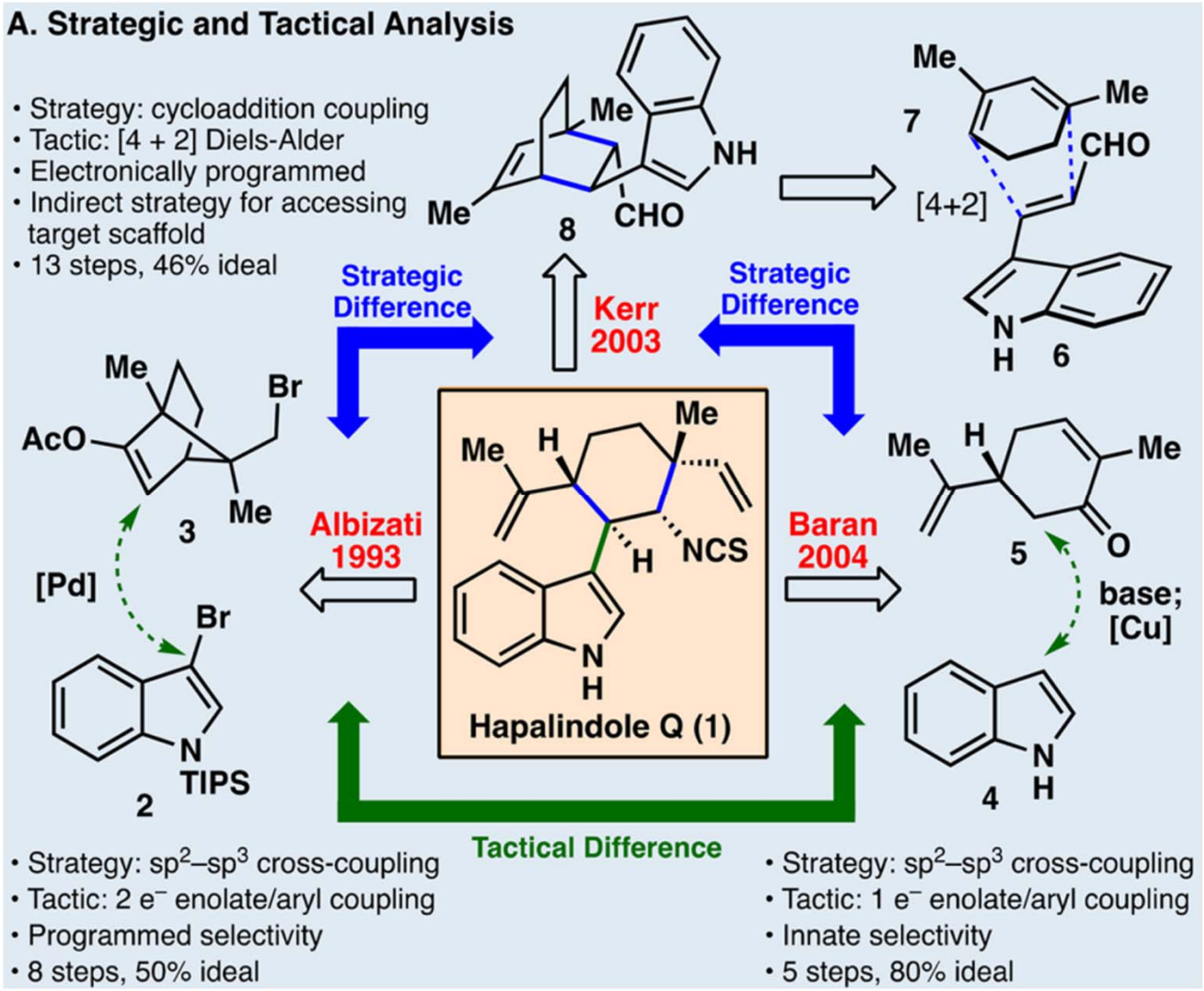
Chuo Chen et al., *JACS* **2012**, 18834

E. g., SmI_2 + alkyl bromide -> Sm(III) + nucleophilic radical

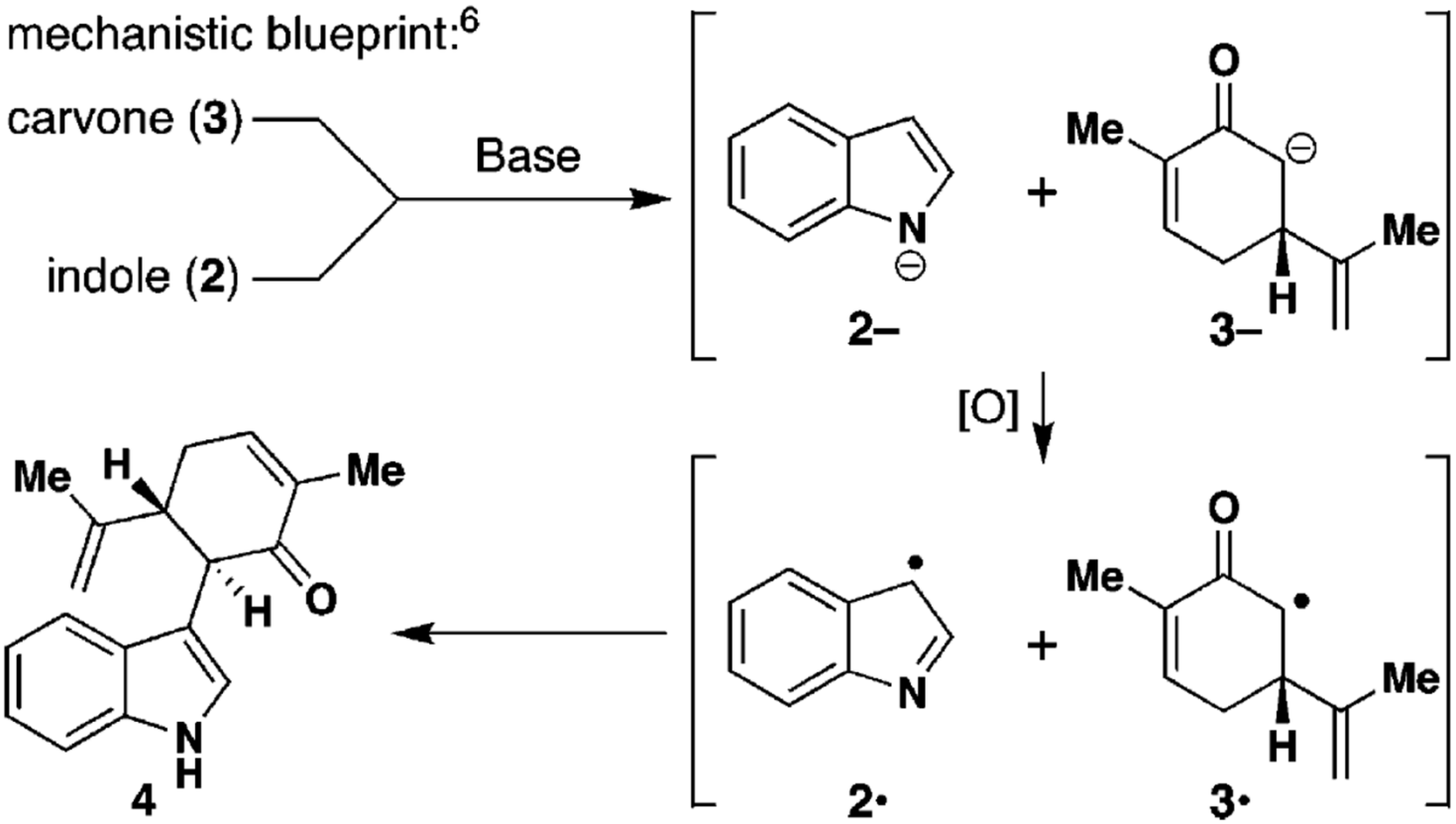
electrophilic alkyl bromide



nucleophilic alkyl radical

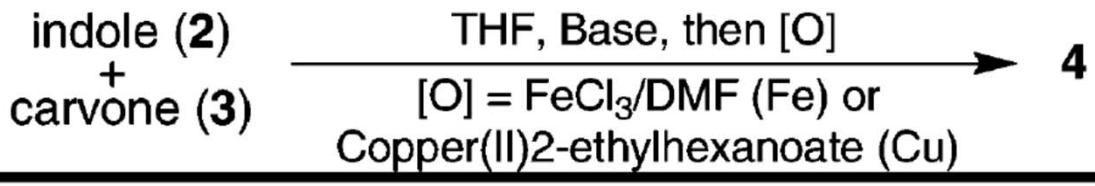


from: Baran et al., *Acc. Chem. Res.* **2018**, 1807



Baran et al., *JACS* **2004**, 7450

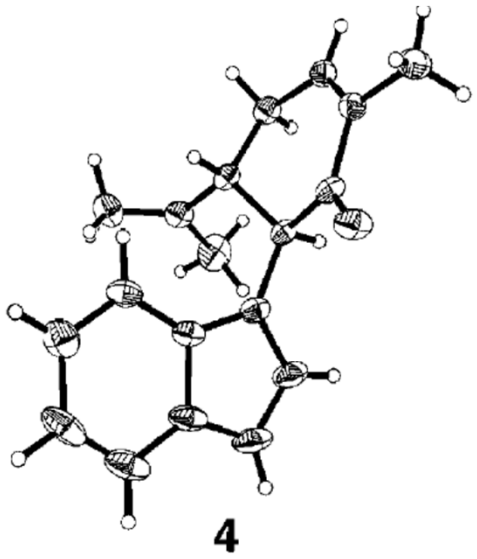
Table 1. Selected Optimization Results of **2** + **3** → **4**



Entry	Conditions	Yield (%)[a]
1	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Fe (4.0 eq), –78 to 23 °C	*ca* 15
2	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 23 °C	24
3	**2** (1.0 eq), **3** (1.0 eq), LDA (2.0 eq), Cu (2.0 eq), –78 to 0 °C	24
4	**2** (3.0 eq), **3** (1.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 0 °C	32
5	**2** (2.0 eq), **3** (1.0 eq), LHMDS (3.0 eq), Cu (1.5 eq), –78 °C	53 (70)[b]

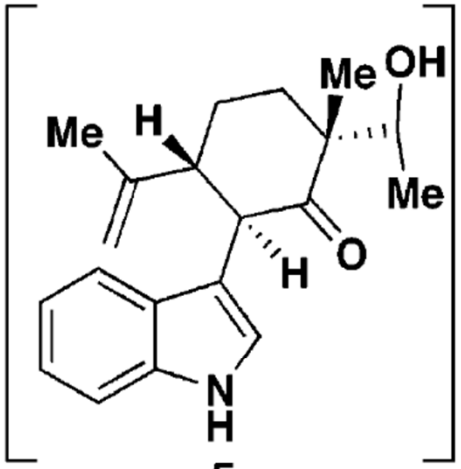
[a] Isolated yield after chromatography. [b] Yield based on recovered sm.

Baran et al., *JACS* **2004**, 7450



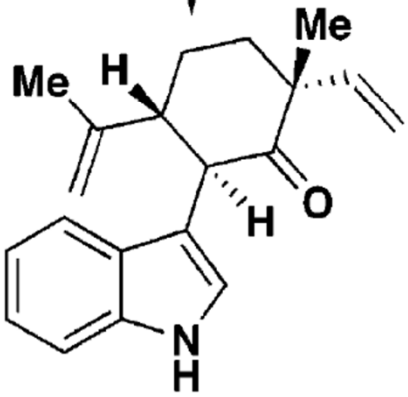
4

a. LHMDS,
L-Selectride
then CH_3CHO



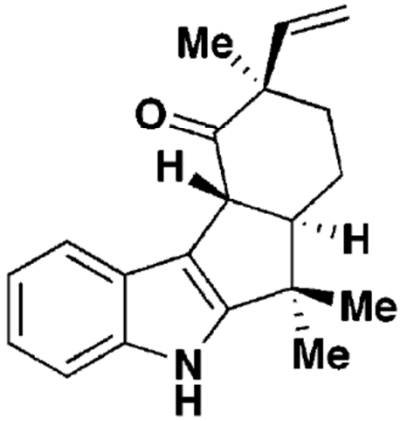
5

b. Martin
sulfurane



6 (75% overall, dr = >20:1)

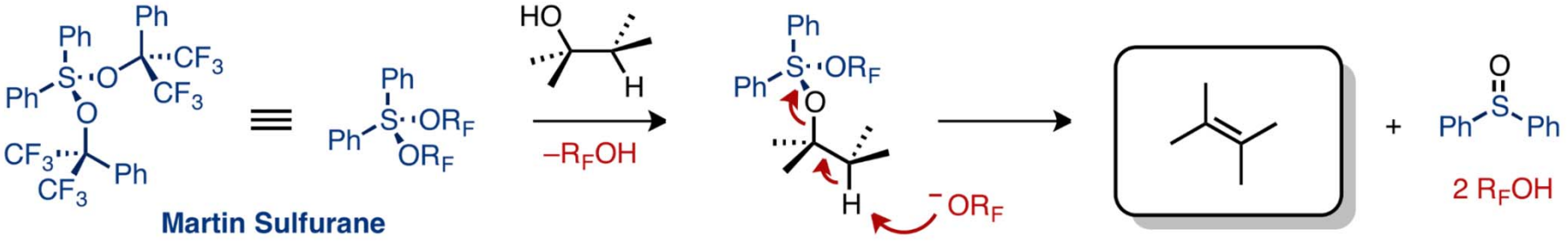
c. TMSOTf



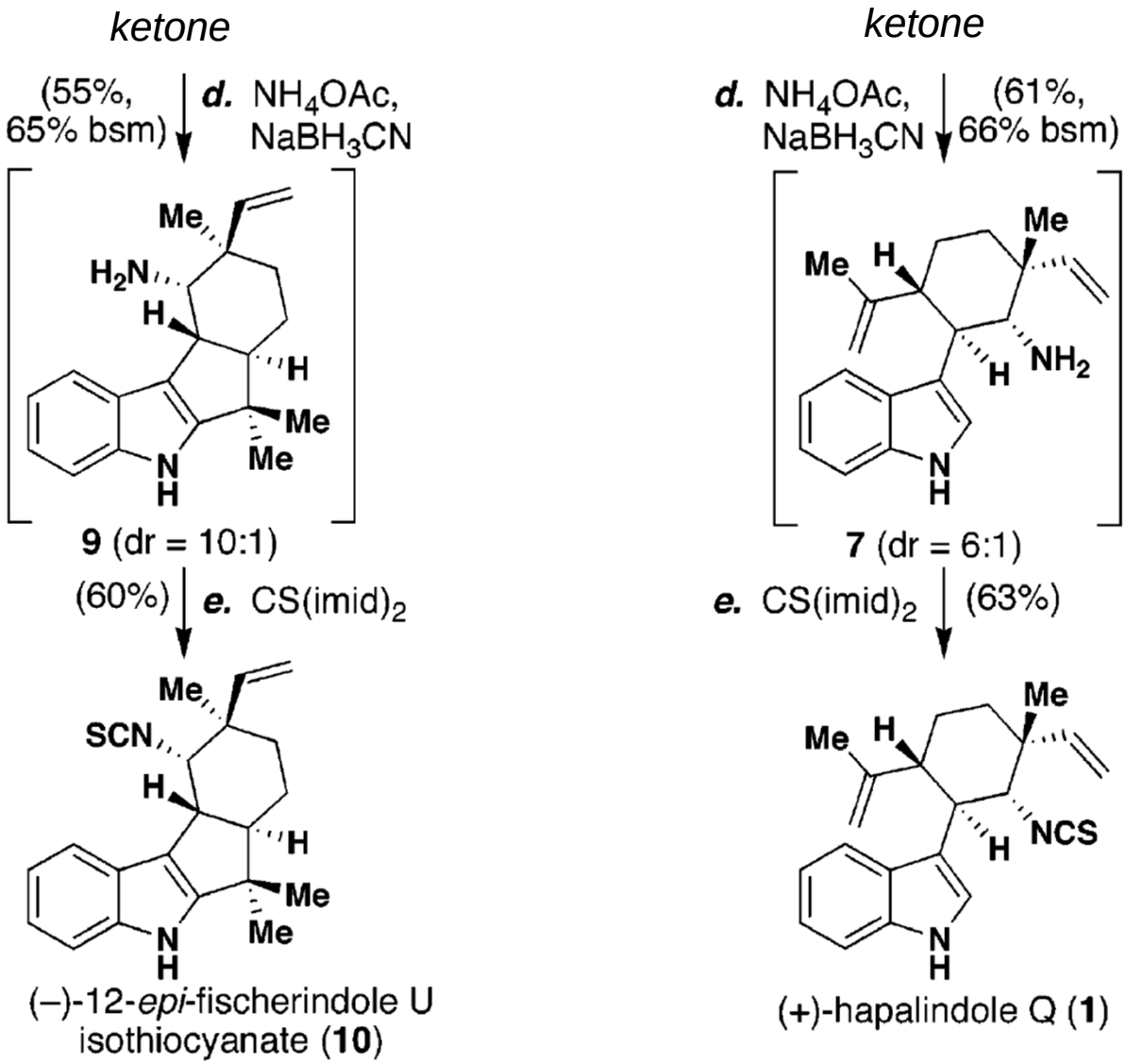
8 (75%)

Baran et al., *JACS* **2004**, 7450

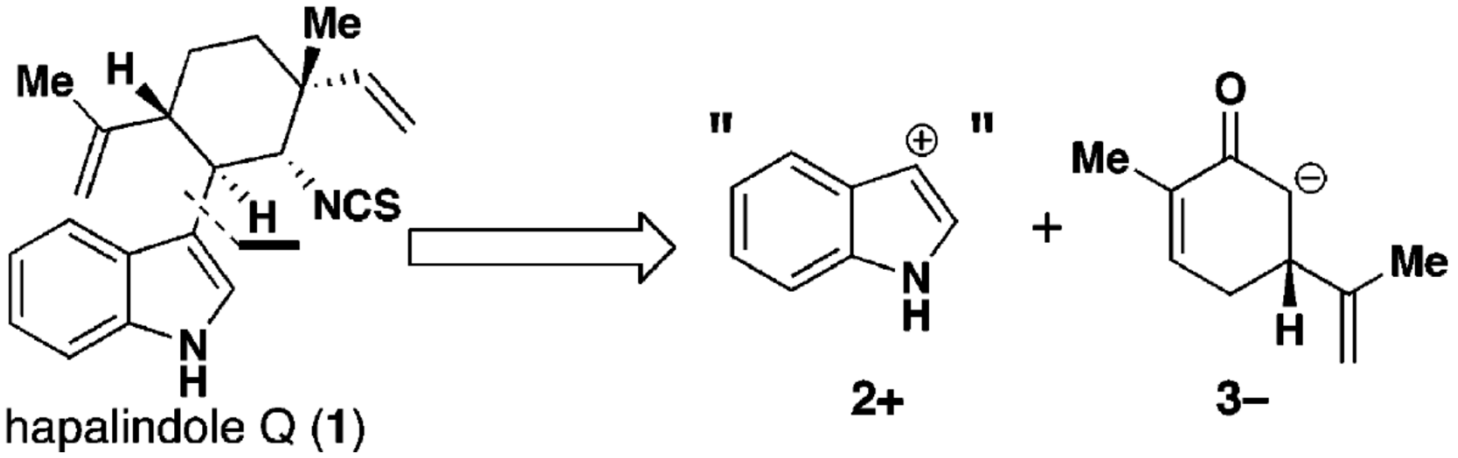
Dehydration of alcohols and of *trans*-diols to epoxides



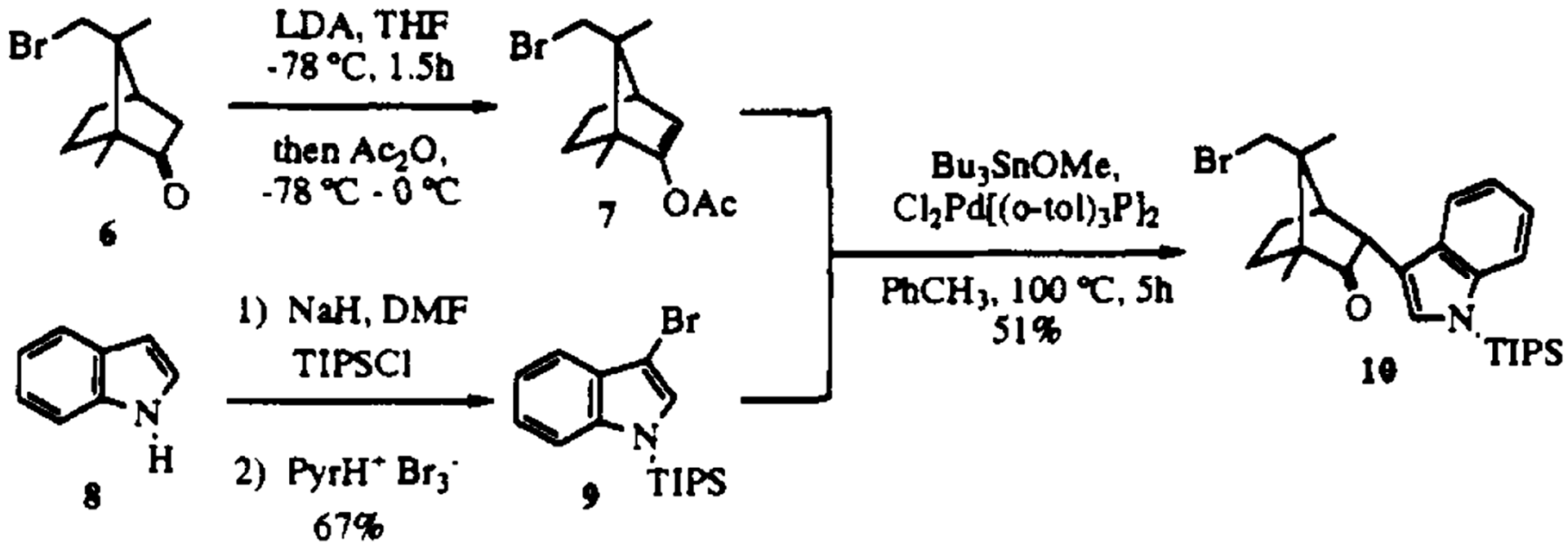
Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, 4327



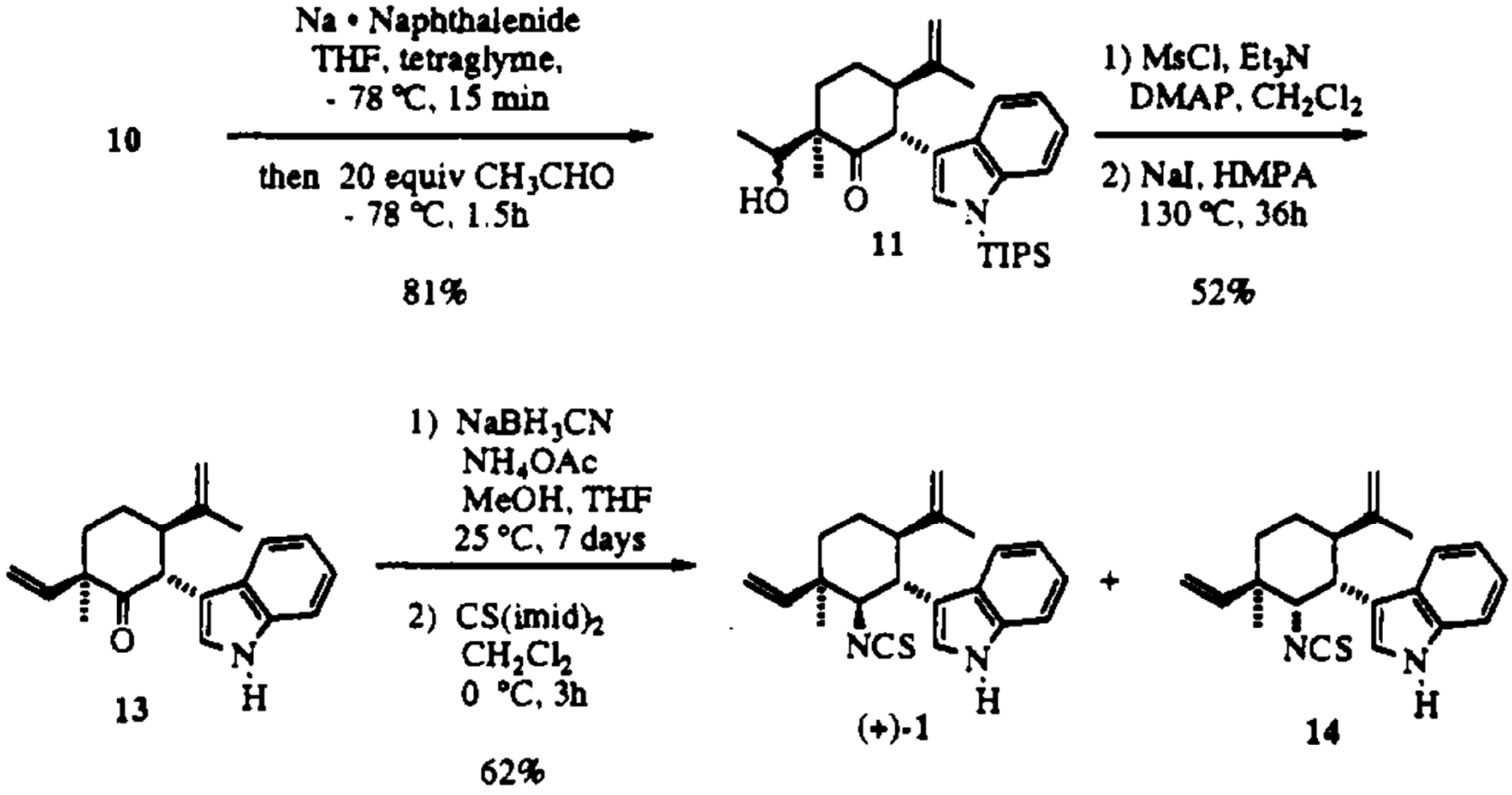
Baran et al., *JACS* **2004**, 7450



Albizati et al., *JACS* **1993**, 3499; Baran et al., *JACS* **2004**, 7450

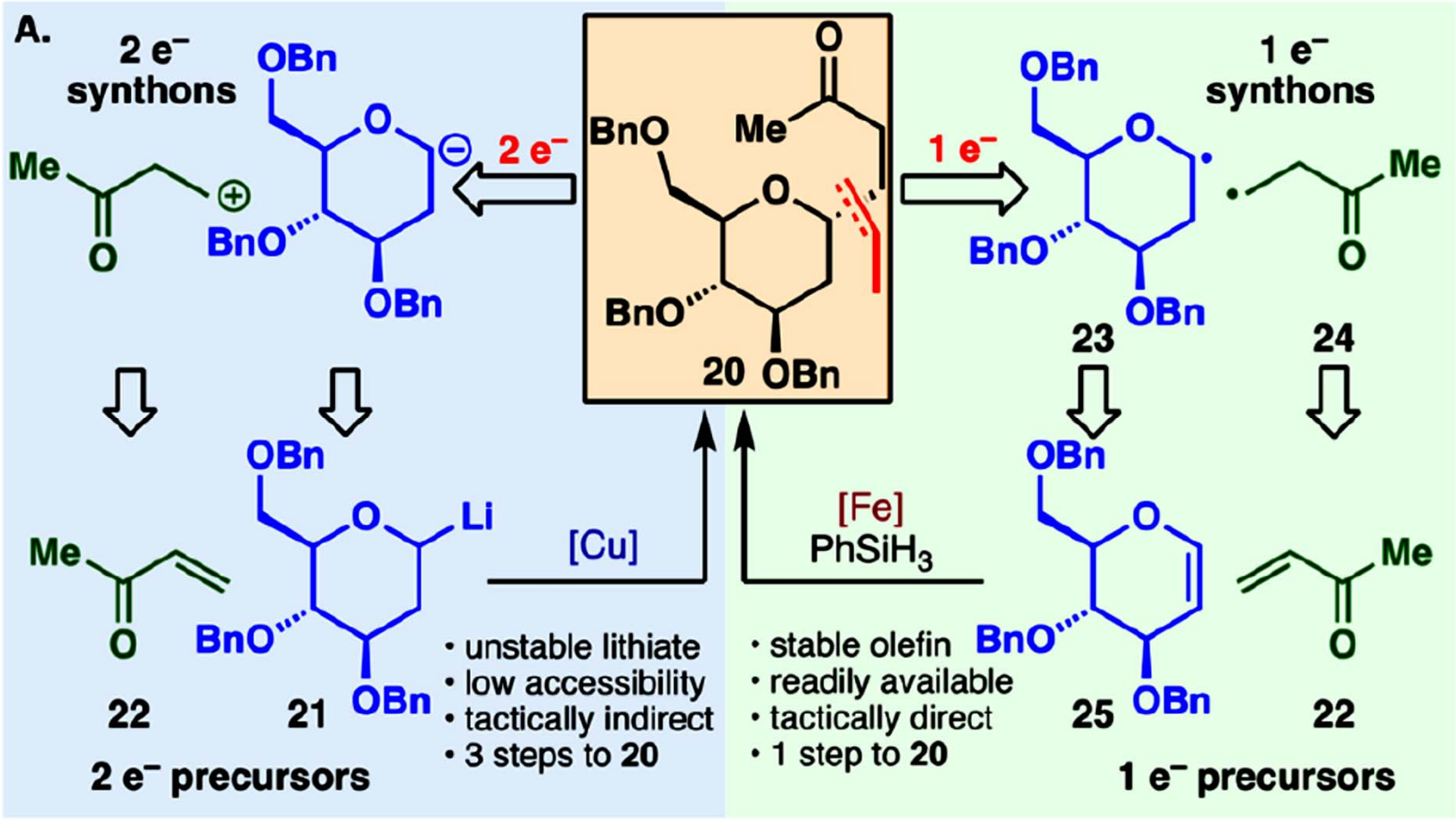


Albizati et al., *JACS* **1993**, 3499



Albizati et al., *JACS* **1993**, 3499

Functionalized olefin cross coupling via hydrogen atom transfer

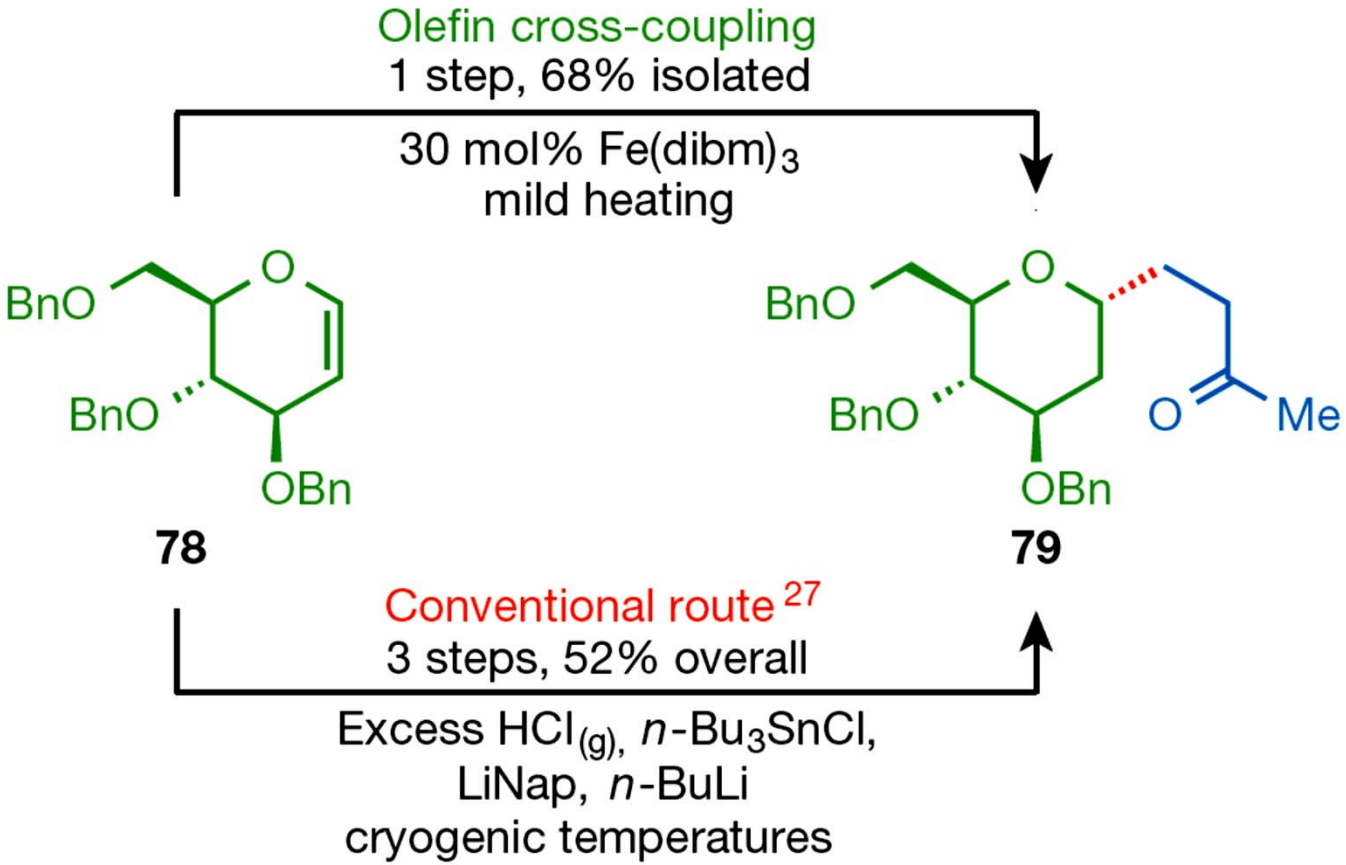


Noguchi et al., *JACS* **2007**, 758

Baran et al., *Nature* **2014**, 343

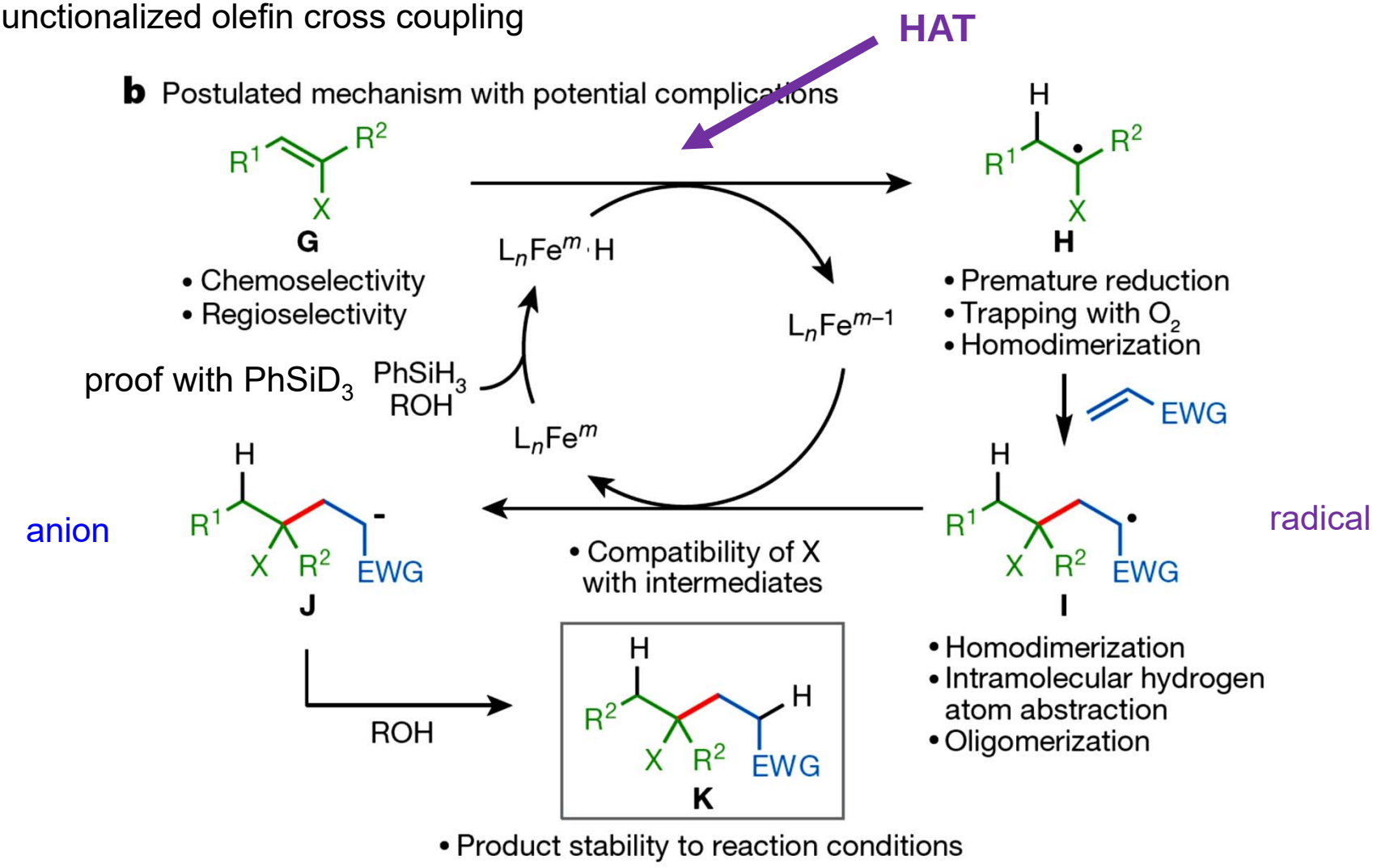
from: Baran et al., *Acc. Chem. Res.* **2018**, 1807

Functionalized olefin cross coupling



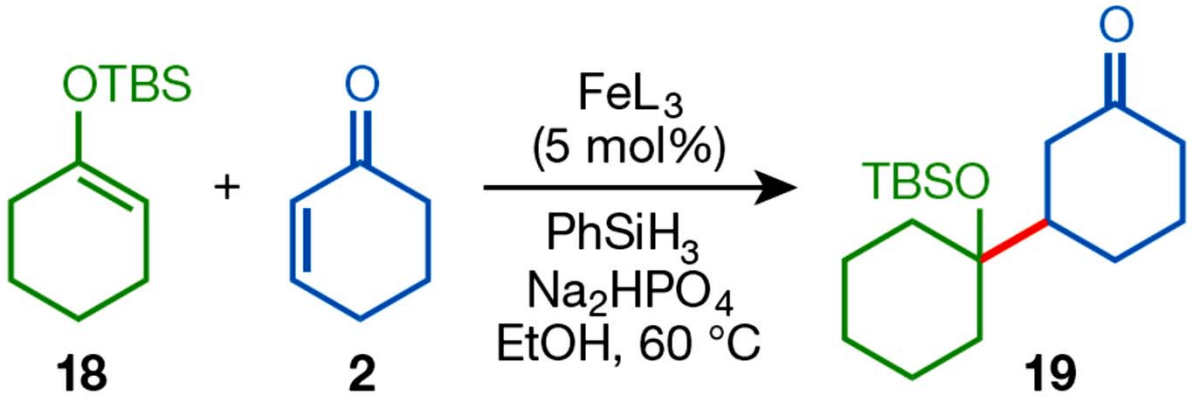
from: Baran et al., *Nature* **2014**, 343

Functionalized olefin cross coupling

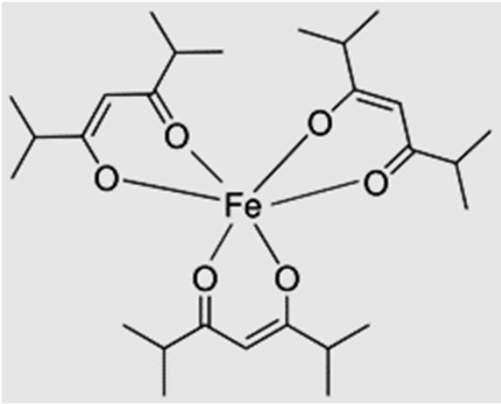


from: Baran et al., *Nature* **2014**, 343

Functionalized olefin cross coupling



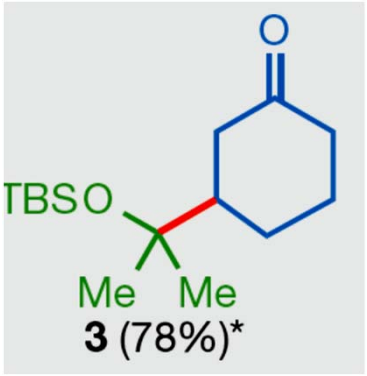
Catalyst	Yield
$Fe(acac)_3$	<1%
$Fe(dibm)_3$	32%



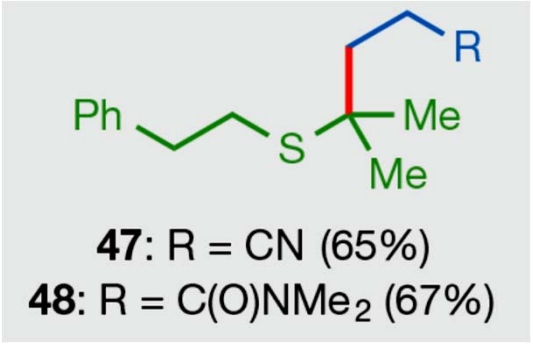
dibm: diisobutyrylmethane

from: Baran et al., *Nature* **2014**, 343

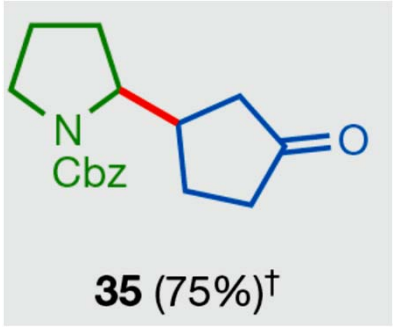
Functionalized olefin cross coupling



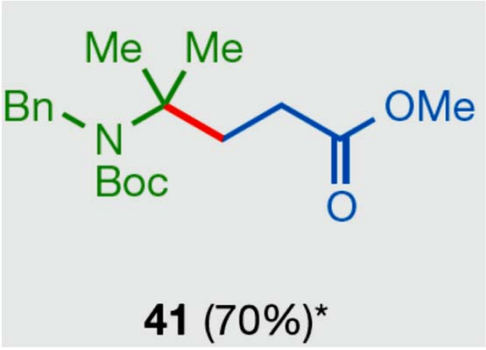
3 (78%)*



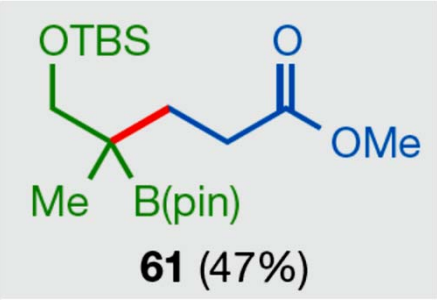
47: R = CN (65%)
48: R = C(O)NMe$_2$ (67%)



35 (75%)†



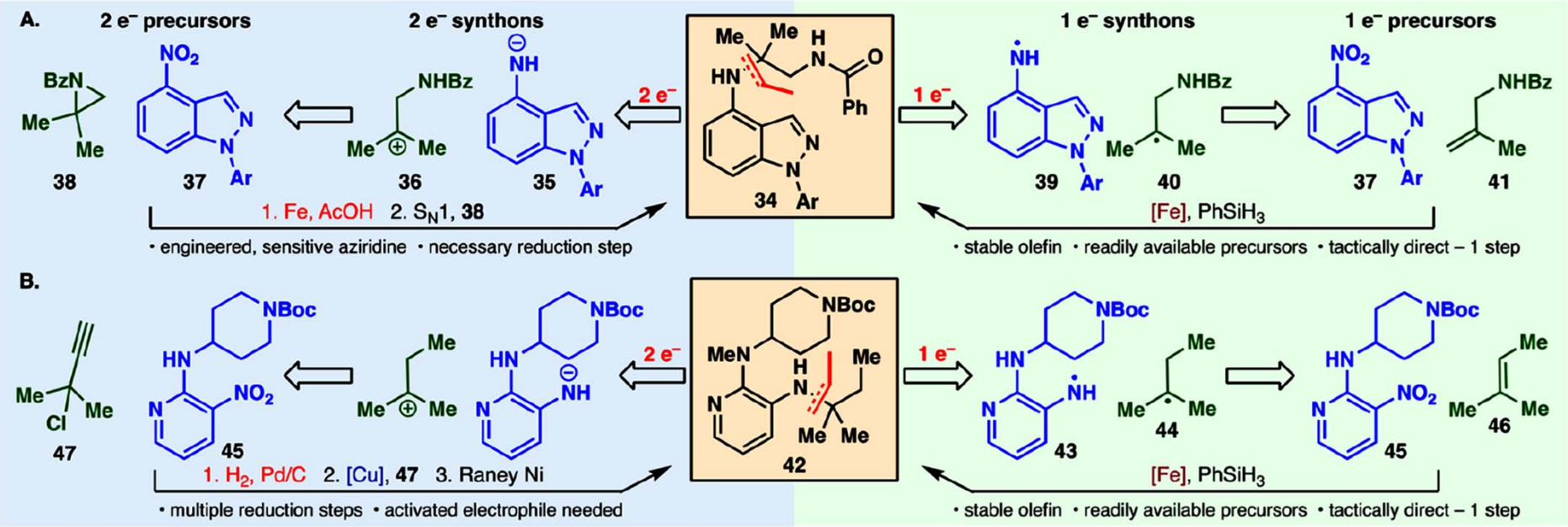
41 (70%)*



61 (47%)

from: Baran et al., *Nature* **2014**, 343

Olefin hydroamination with nitroarenes

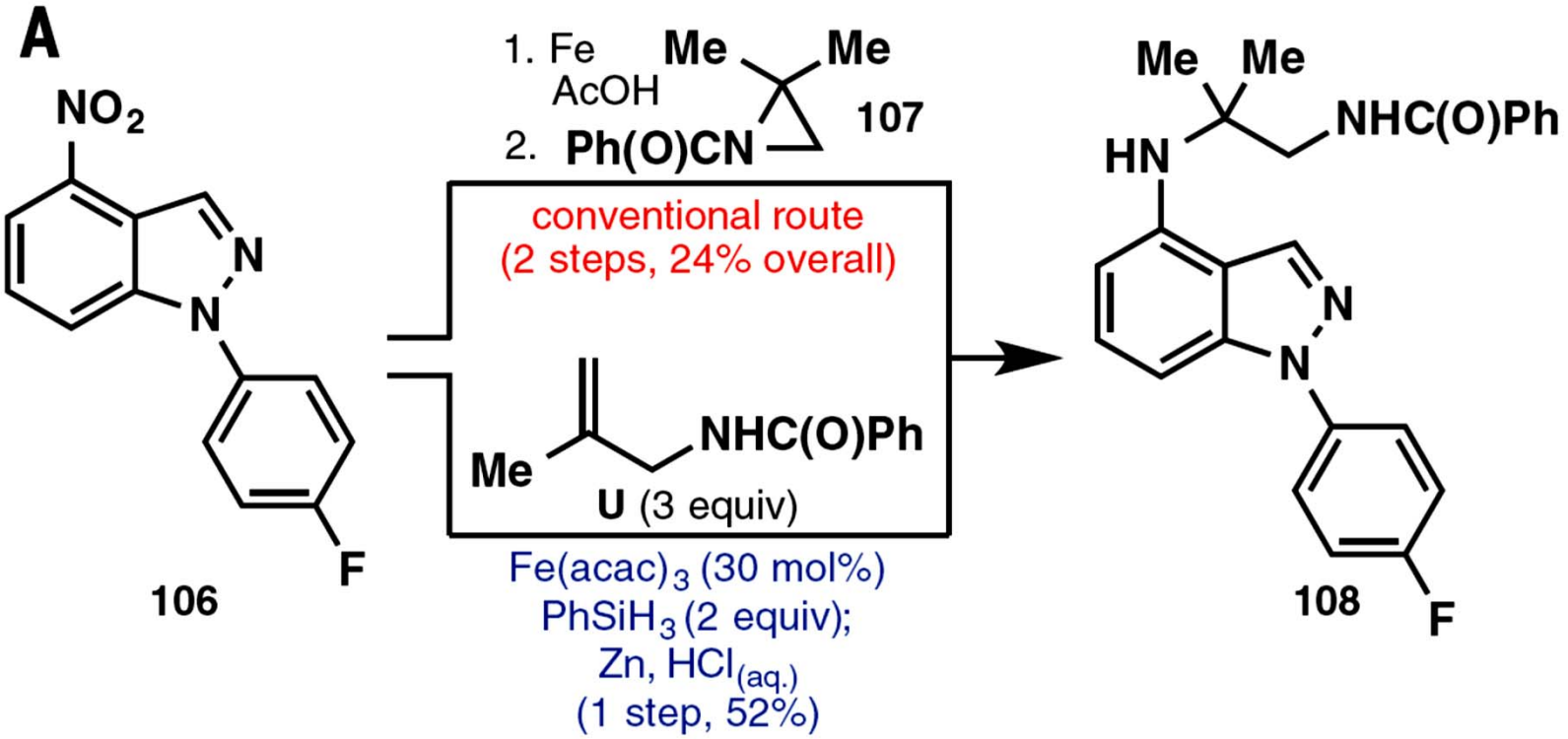


PCT Int. Appl. WO 2007046747, 2007

Baran et al., *Science* **2015**, *348*, 886

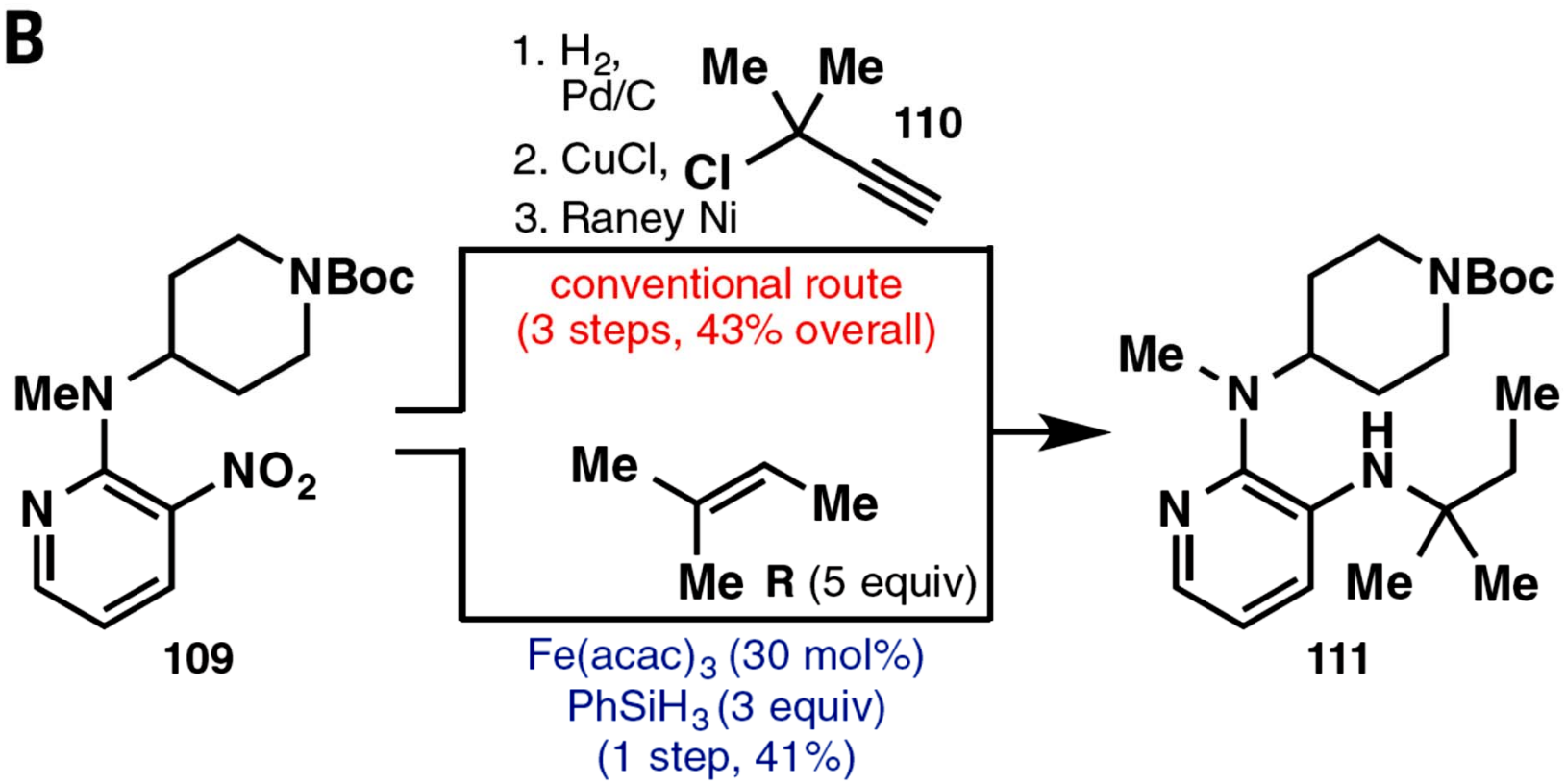
from: Baran et al., *Acc. Chem. Res.* **2018**, 1807

Olefin hydroamination with nitroarenes



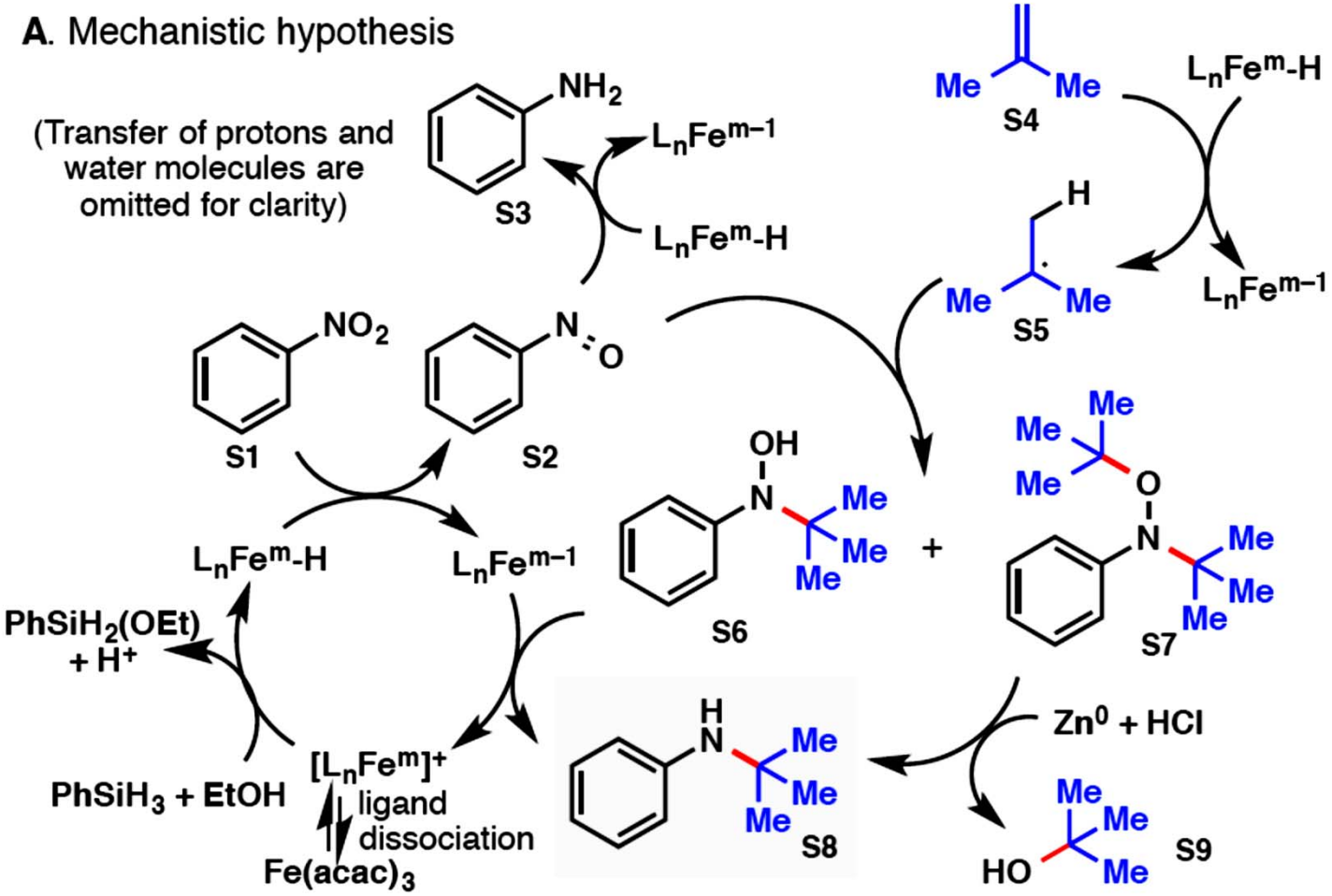
from: Baran et al., *Science* **2015**, *348*, 886

Olefin hydroamination with nitroarenes



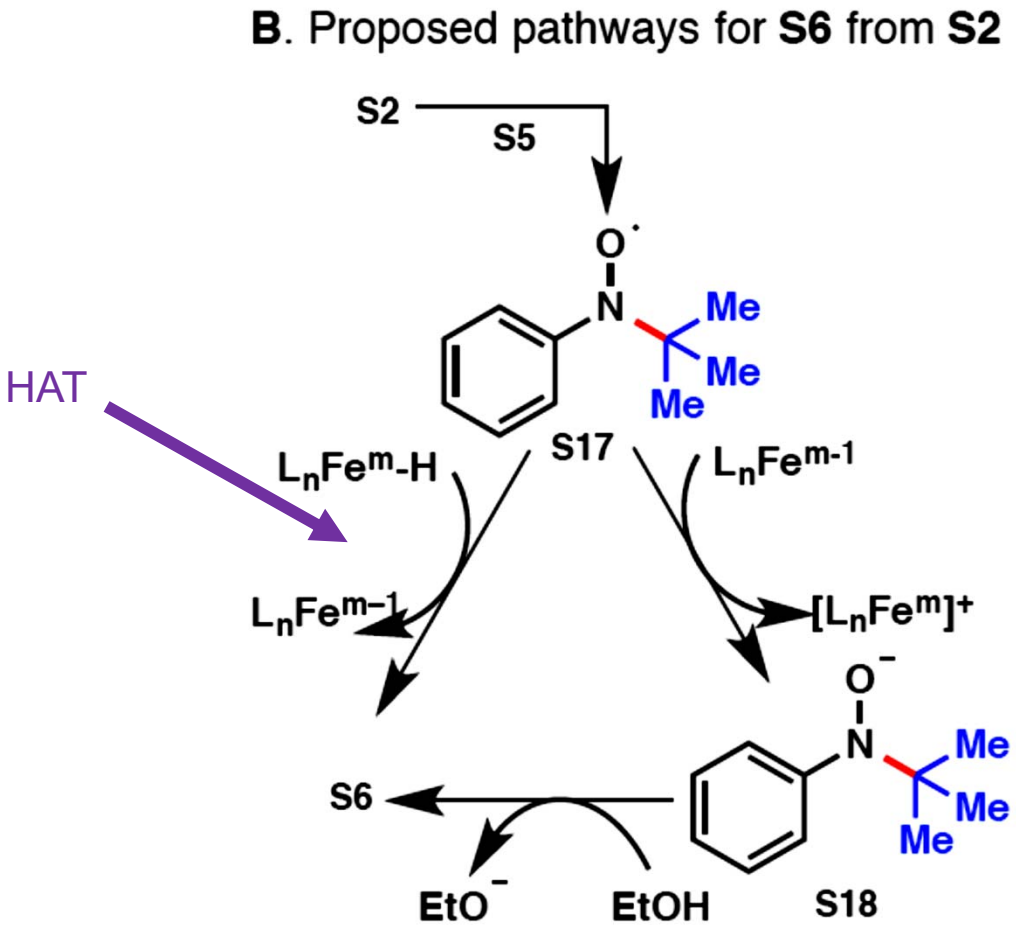
from: Baran et al., *Science* **2015**, *348*, 886

Olefin hydroamination with nitroarenes



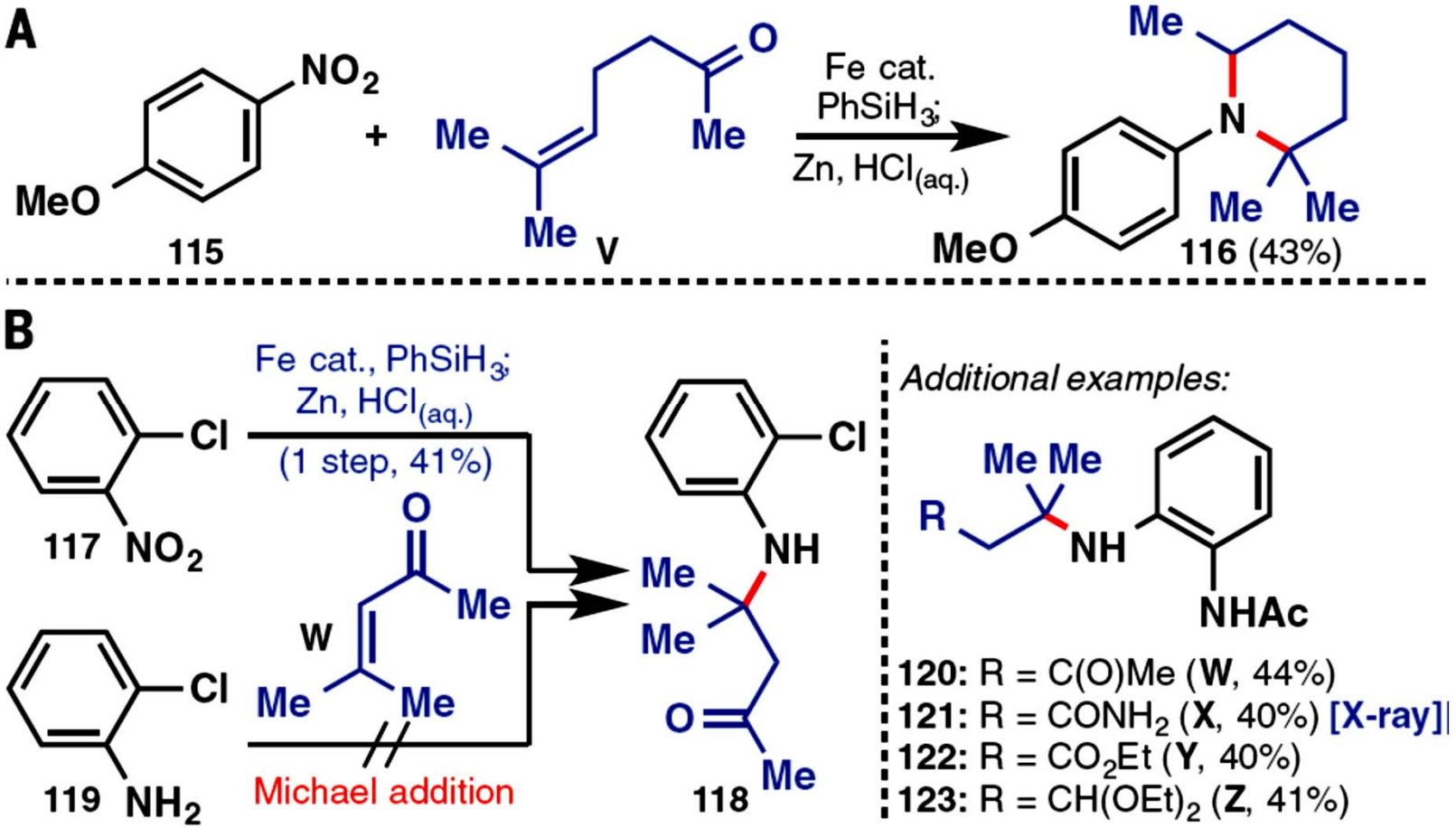
from: Baran et al., *Science* **2015**, *348*, 886

Olefin hydroamination with nitroarenes

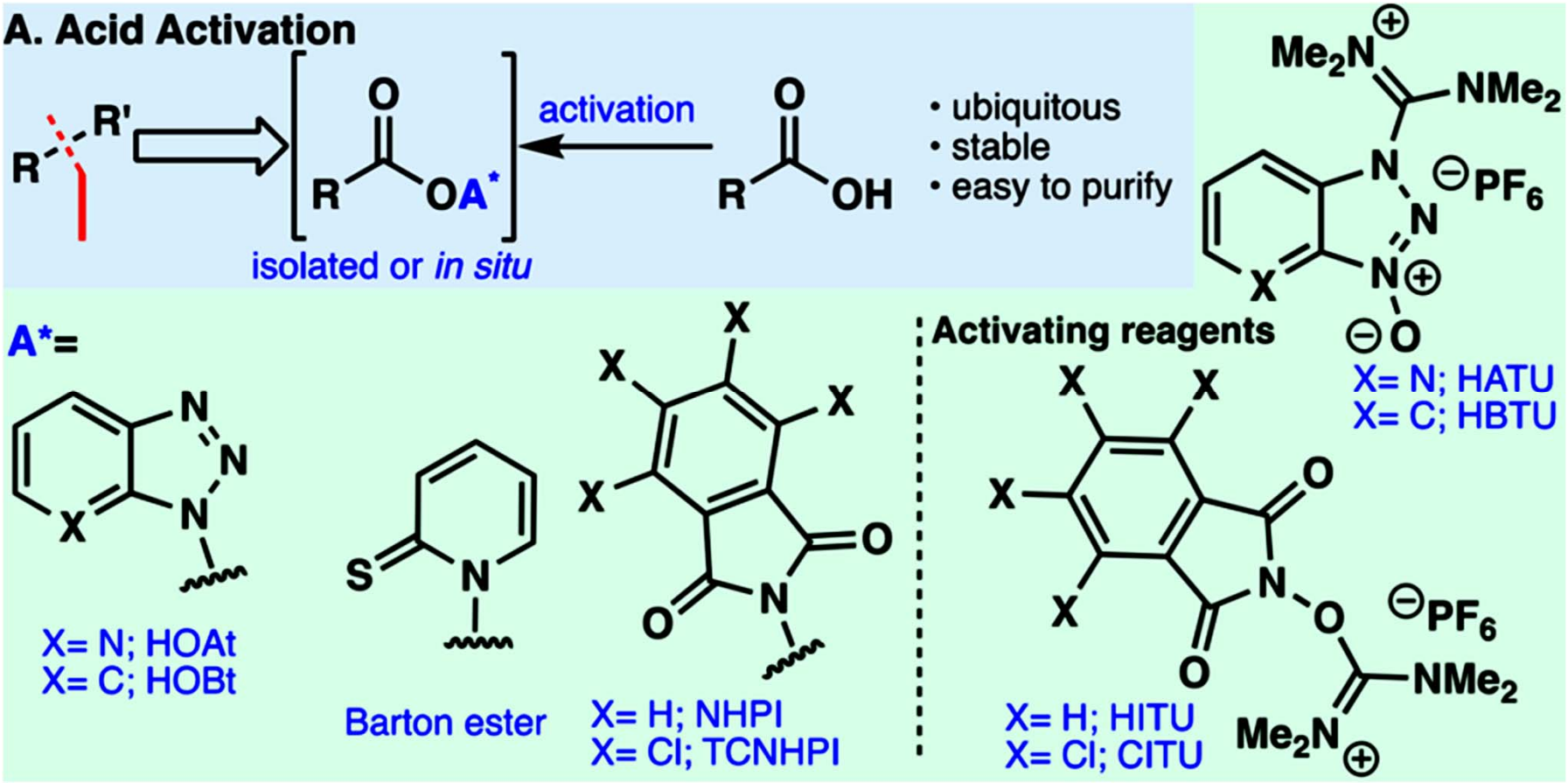


from: Baran et al., *Science* **2015**, *348*, 886

Olefin hydroamination with nitroarenes

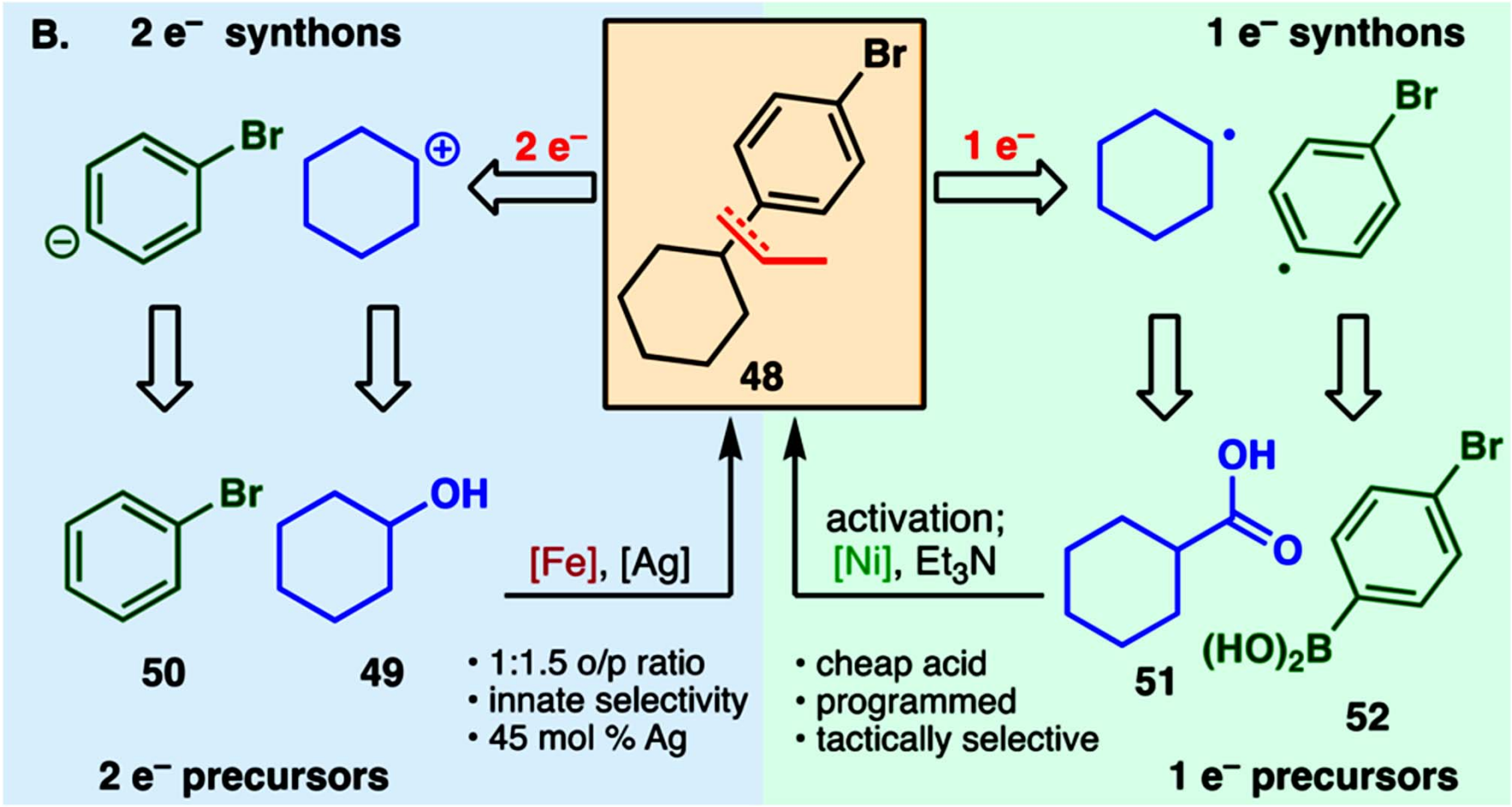


from: Baran et al., *Science* **2015**, *348*, 886



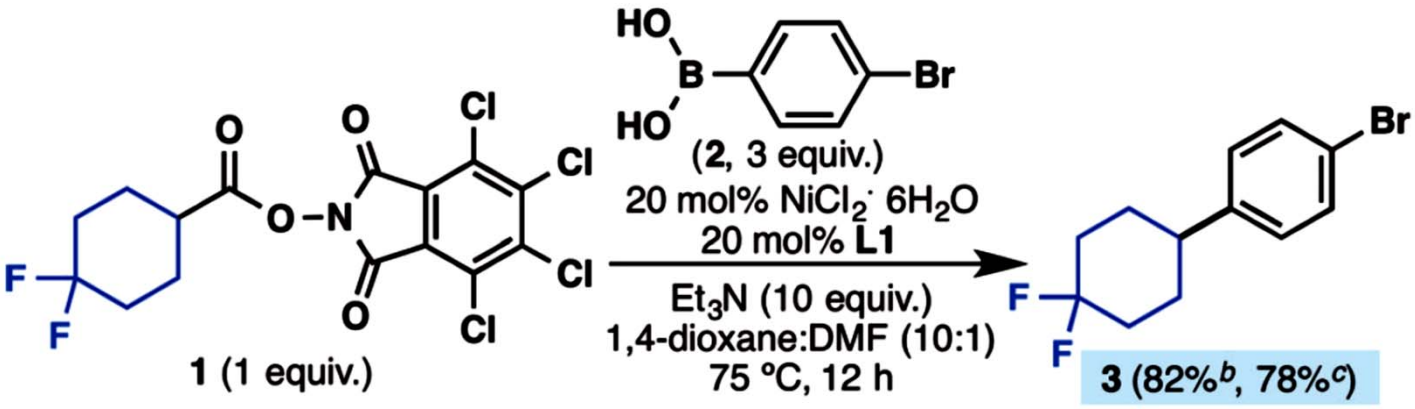
TCNHPI: *N*-Hydroxytetrachlorophthalimide

from: Baran et al., *Acc. Chem. Res.* **2018**, 1807

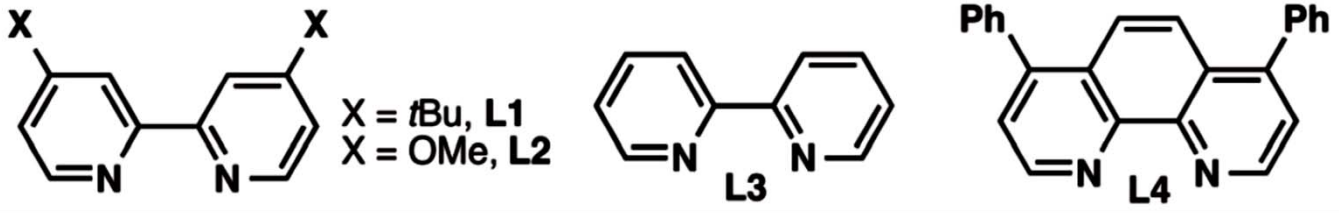


Friedel-Crafts alkylation-type

from: Baran et al., *Acc. Chem. Res.* **2018**, 1807



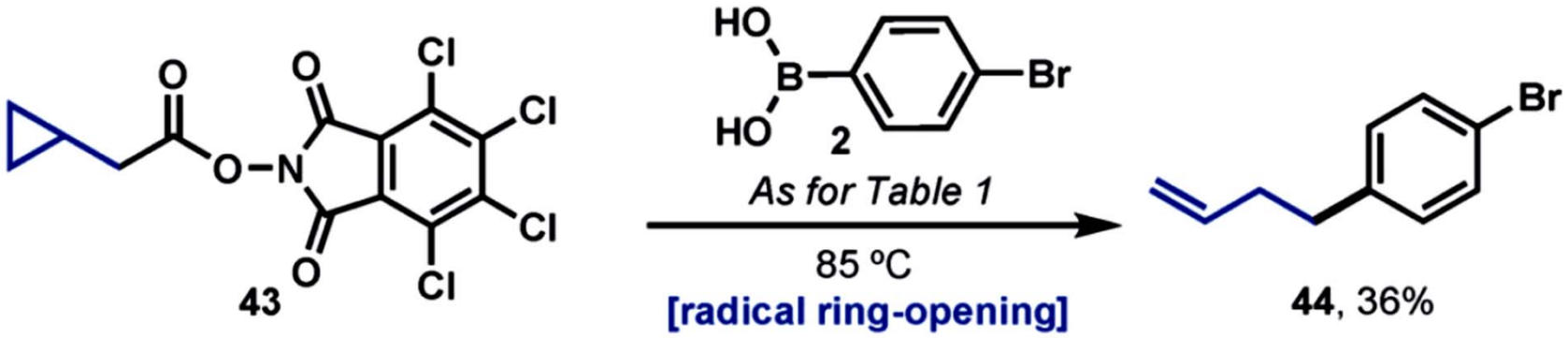
entry	deviation from above	yield (%)[b]	entry	deviation from above	yield (%)[b]
1	1,4-dioxane	20[c]	8	**L2**	64
2	THF:DMF (10:1)	10	9	**L3**	58
3	DIPEA	68	10	**L4**	82
4	Bu_3N	43	11	NHPI ester	<5
5	K_3PO_4	<5	12	w/o **L1**	<5
6	Cs_2CO_3	<5	13	w/o $NiCl_2 \cdot 6\,H_2O$	<5
7	40 mol% **L1**	44	14	w/o Et_3N	40



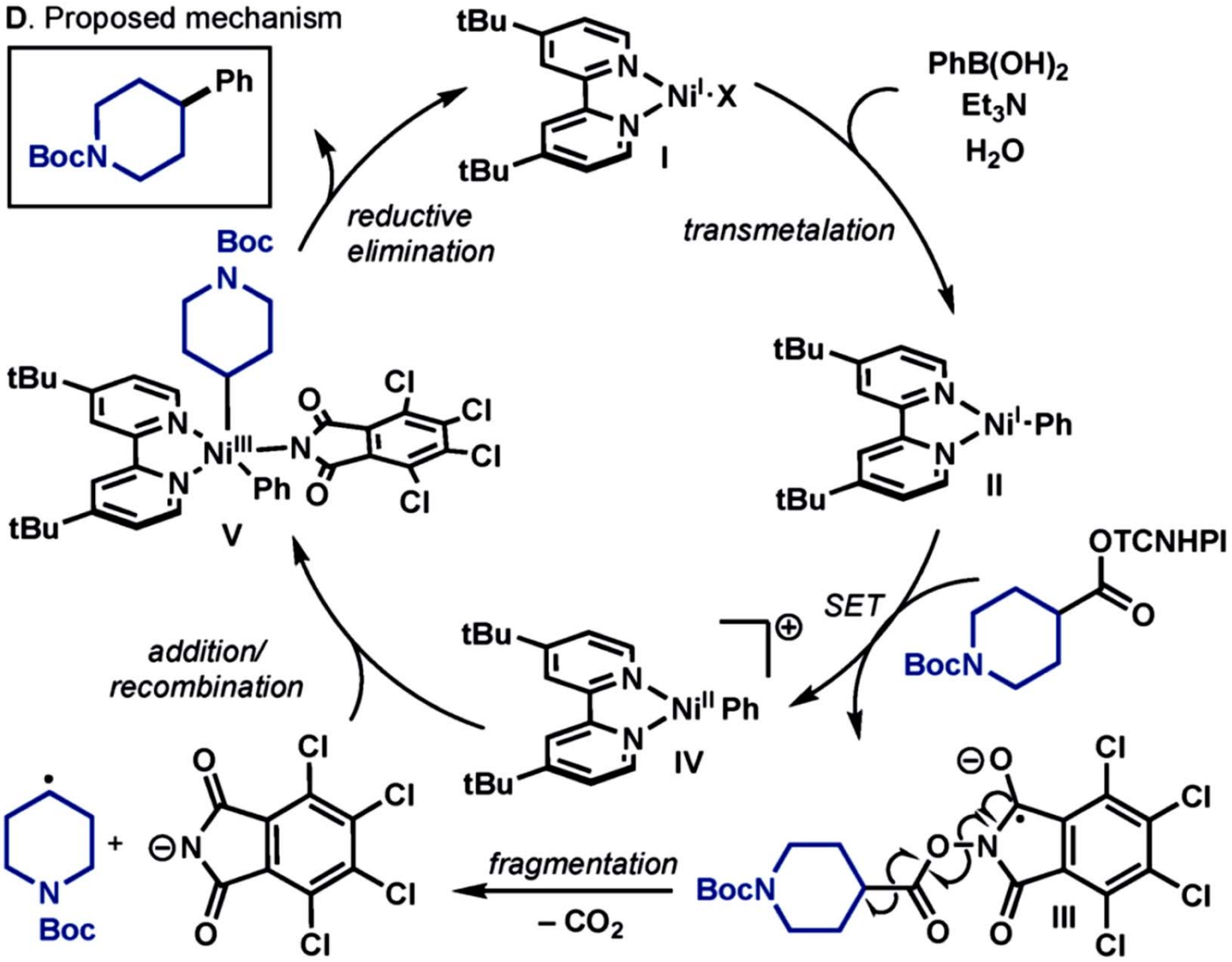
[a] 0.1 mmol. [b] Yield determined by GC using dodecane as internal standard. [c] Isolated yield.

from: Baran et al., *ACIE* **2016**, 9676

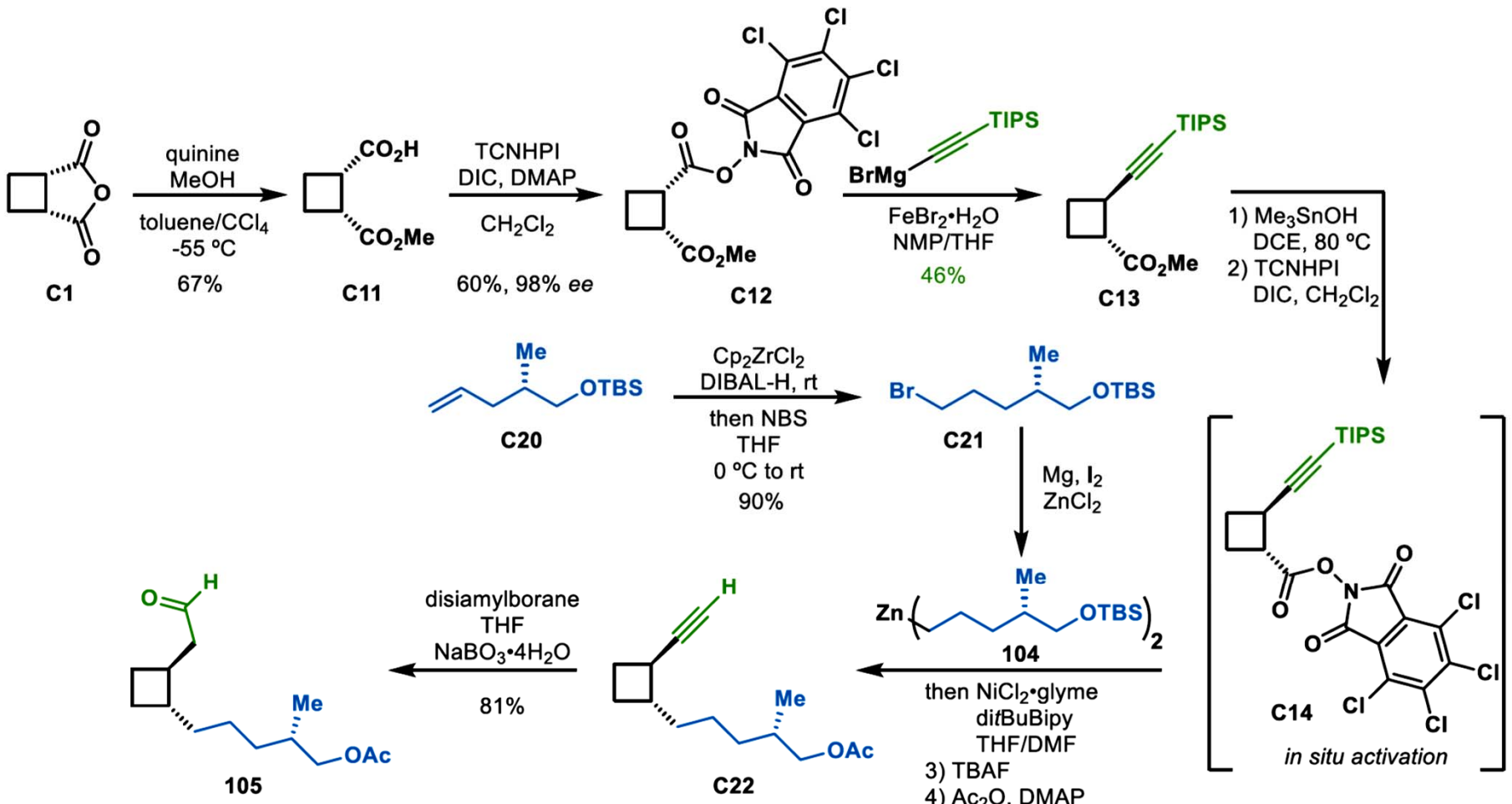
C. Cyclopropyl opening experiment



from: Baran et al., *ACIE* **2016**, 9676

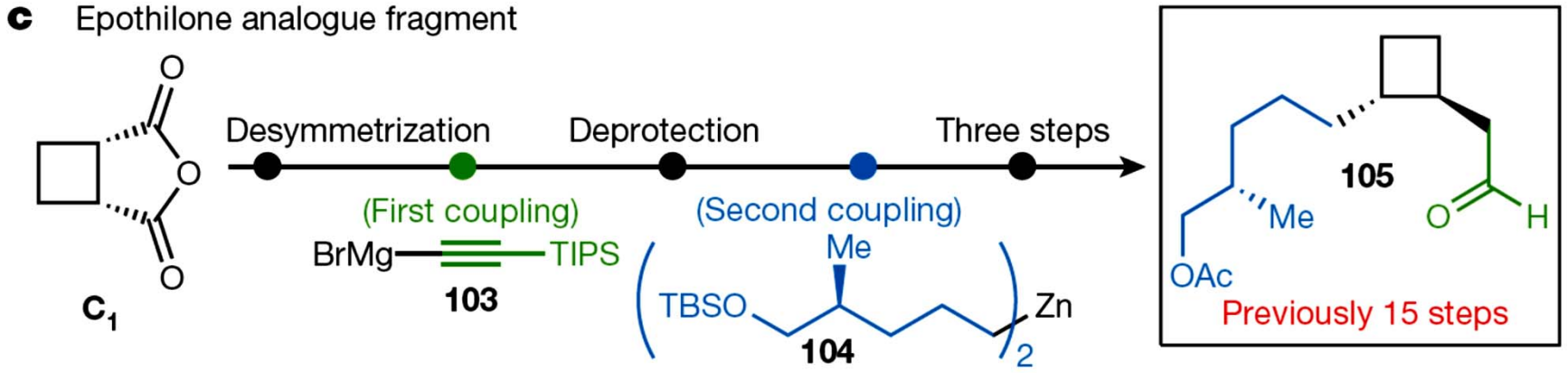


from: Baran et al., *ACIE* **2016**, 9676

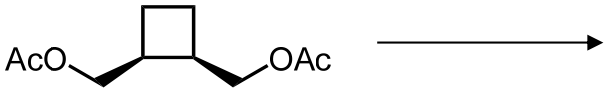


TCNHPI: *N*-Hydroxytetrachlorophthalimide

from: Baran et al., *Nature* **2018**, *560*, 350 (si)



from: Baran et al., *Nature* **2018**, *560*, 350



a much longer sequence

(a) lipase

(b) $(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), Et_3N (5.0 equiv), DCM, -78 °C; then Et_3N, 25 °C, 5 d, 88% (2 steps)

(c) $MeOCH_2PPh_3Cl$ (1.15 equiv), NaHMDS (1.10 equiv), THF, -78 to 25 °C, 89%

(d) 0.12 N HCl (aq):acetone (1:9), rf, 1 h, 94%

(e) **Wittig salt** (2.0 equiv), NaHMDS (3.8 equiv), THF, 0 °C, 2 h; then TMSCl (2.0 equiv), 25 °C, 20 min; then **sm**, THF, -78 to 25 °C, 20 h, 83%

(f) $(NCO_2K)_2$ (20 equiv), AcOH (40 equiv), py:MeOH (5: 1), 25 °C, 48 h; then PtO_2 (0.05 equiv), H_2 (1 atm), MeOH, 25 °C, 20 min, 82%

(g) 10 wt % Pt/C (0.02 equiv), H_2 (1 atm), EtOAc, 25 °C, 8 h, 96%

(h) TBSOTf (1.0 equiv), 2,6-lutidine (2.5 equiv), DCM, -78 to 0 °C, 20 min

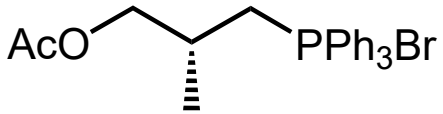
(i) DIBAL (2.0 equiv), DCM, -78 °C, 5 min, 90% for 2 steps

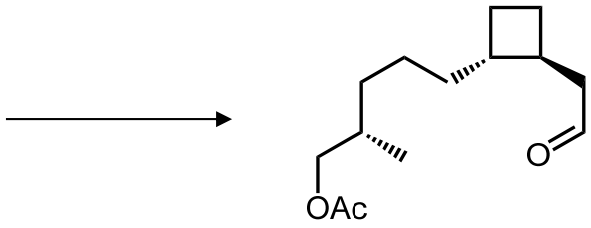
(j) $(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), Et_3N (5.0 equiv), DCM, -78 to 25 °C, 97%

(k) $MeOCH_2PPh_3Cl$ (1.15 equiv), NaHMDS (1.10 equiv), THF, -78 to 25 °C

(l) 0.12 N HCl (aq):acetone (1:9), rf, 1 h

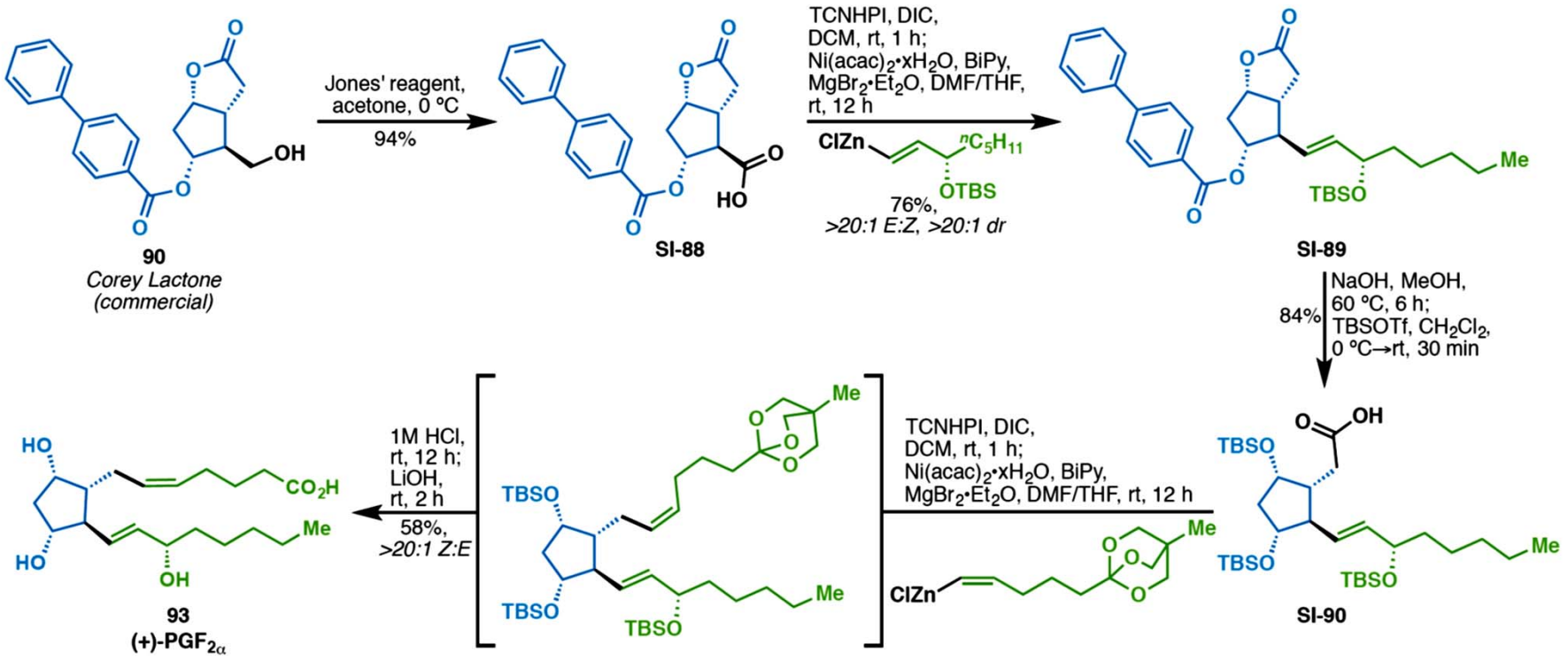
(m) Ac_2O (1.1 equiv), Et_3N (2.5 equiv), 4-DMAP (0.02 equiv), DCM, 0 °C, 20 min, 62% (3 steps)





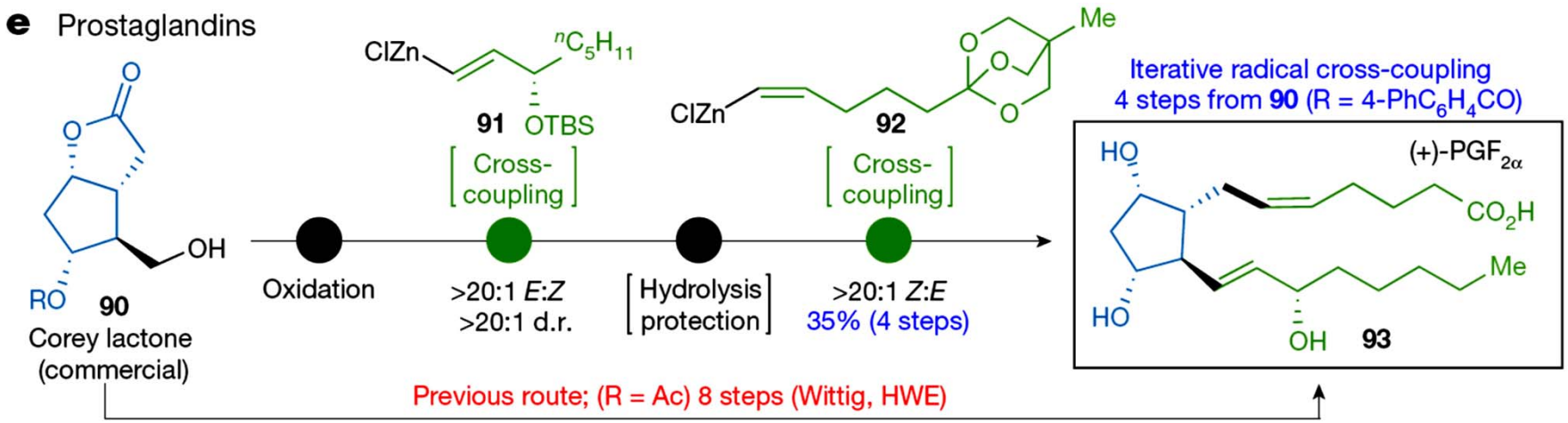
detail the steps!

Nicolaou et al., *JACS* **2001**, 9313



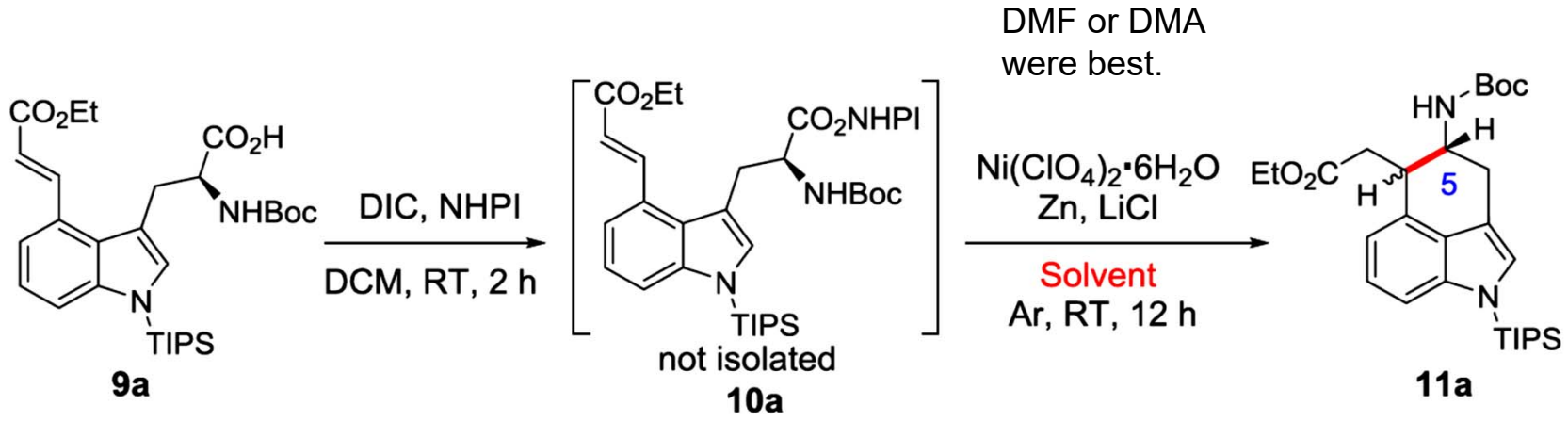
TCNHPI: *N*-Hydroxytetrachlorophthalimide

from: Baran et al., *Nature* **2017**, *545*, 213 (si)



from: Baran et al., *Nature* **2017**, *545*, 213

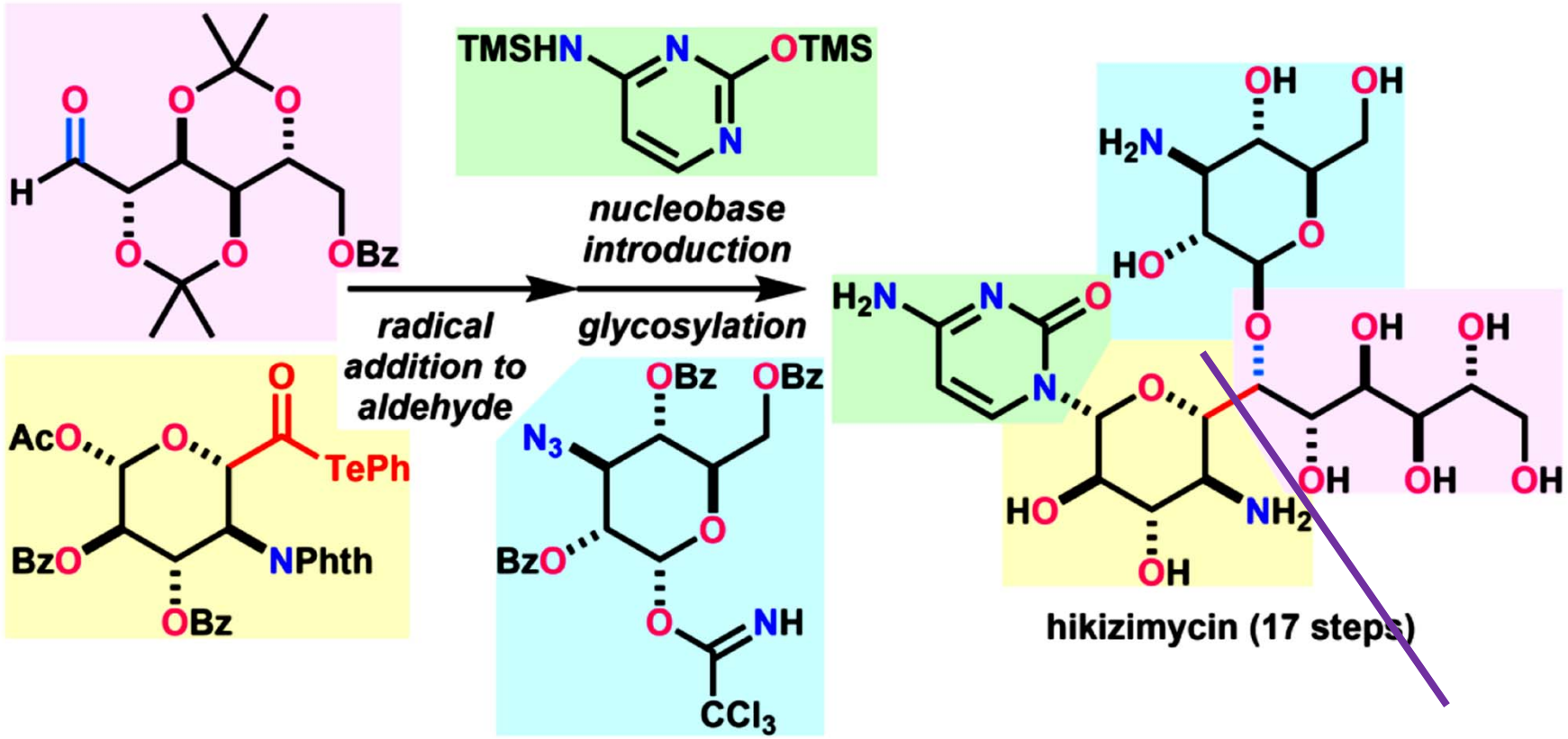
Decarboxylative Giese coupling



DIC: diisopropylcarbodiimide; NHPI: N-hydroxyphthalimide

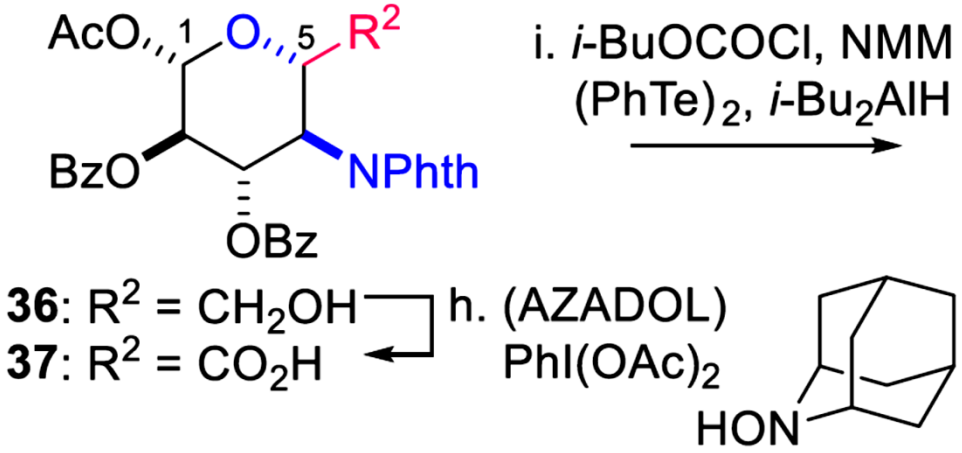
from: Yuhua Ge et al., *OL* **2021**, 370

Intermolecular decarbonylative radical addition to an aldehyde

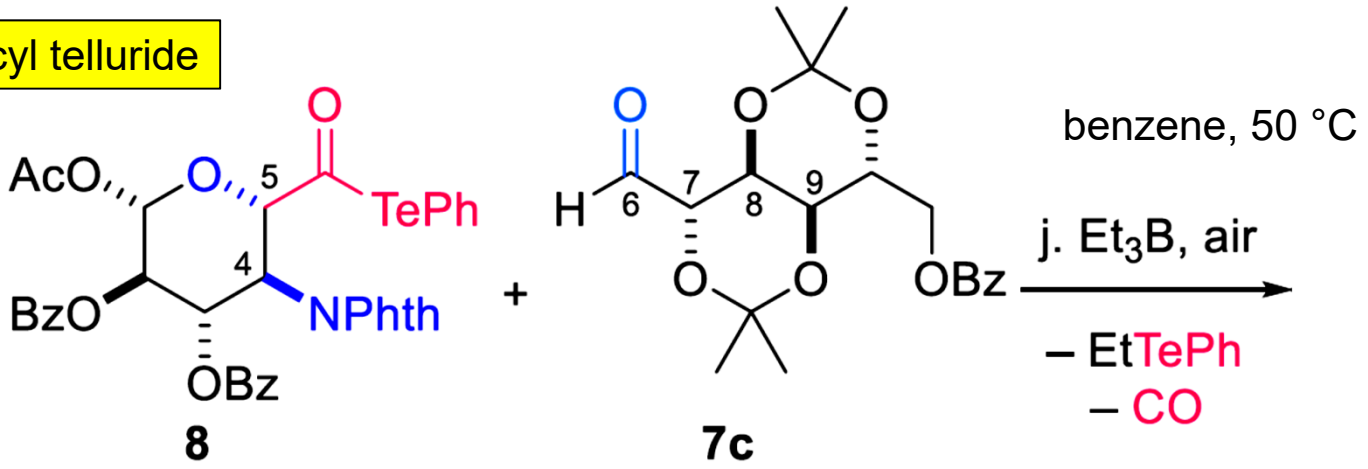


from: Masayuki Inoue et al., *JACS* **2020**, *142*, 13227

Intermolecular decarbonylative radical addition to an aldehyde

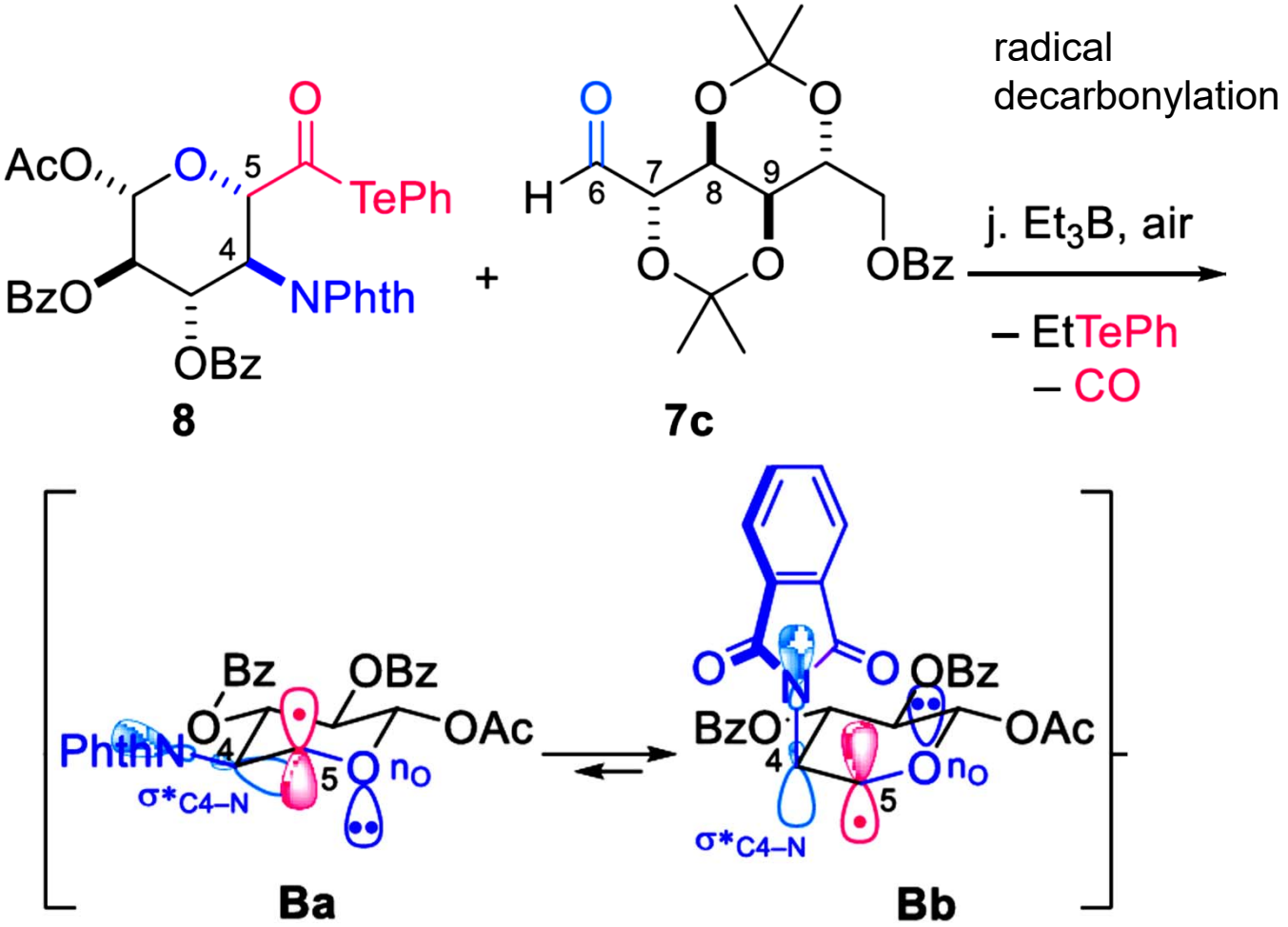


an alkoxy acyl telluride



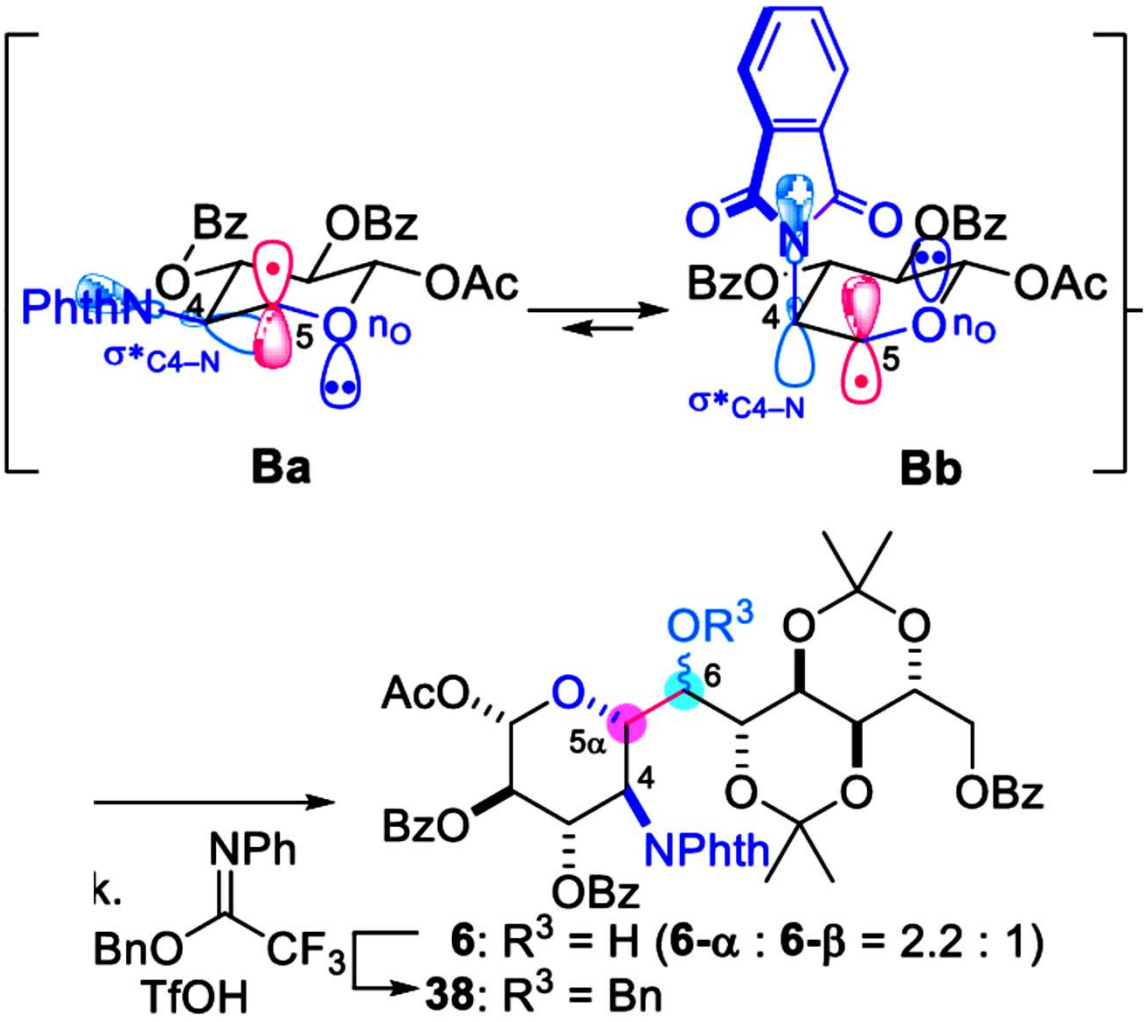
from: Masayuki Inoue et al., *JACS* **2020**, *142*, 13227

Intermolecular decarbonylative radical addition to an aldehyde



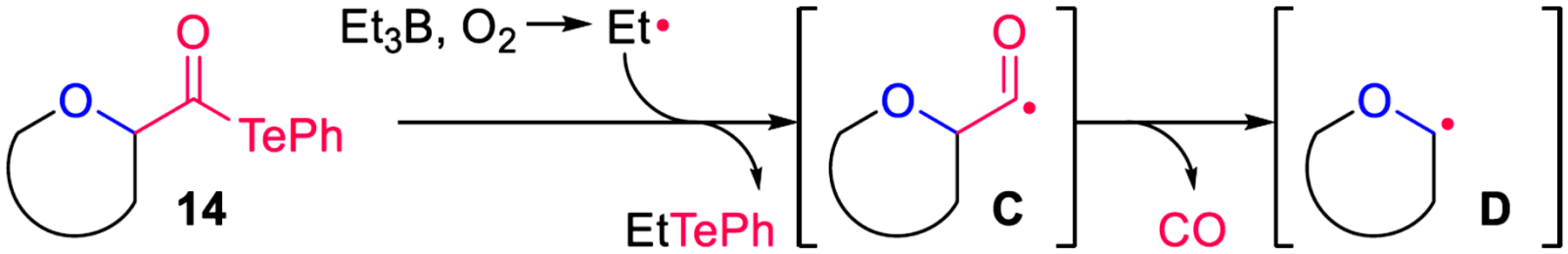
from: Masayuki Inoue et al., *JACS* **2020**, *142*, 13227

Intermolecular decarbonylative radical addition to an aldehyde



from: Masayuki Inoue et al., *JACS* **2020**, *142*, 13227

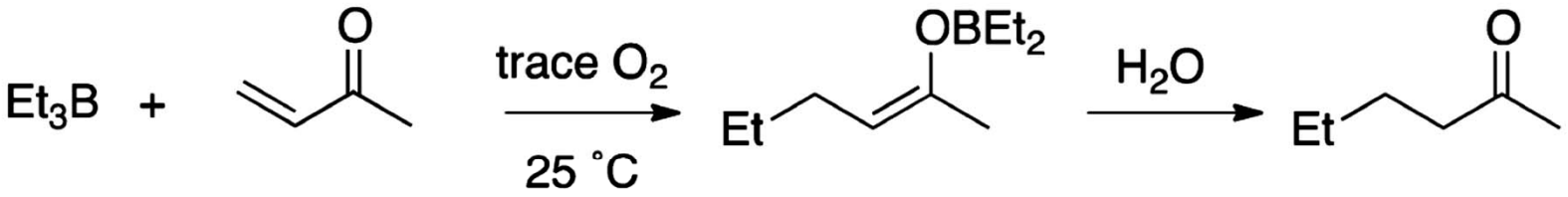
Radical decarbonylation



from: Masayuki Inoue et al., *JACS* **2020**, *142*, 13227

Triethylborane liberates ethyl radicals (and $Et_2BOO\cdot$) in the presence of air oxygen.

(a) Brown, Et_3B initiates its own reactions 1960s



(b) Utimoto, Et_3B initiates other reactions 1980s

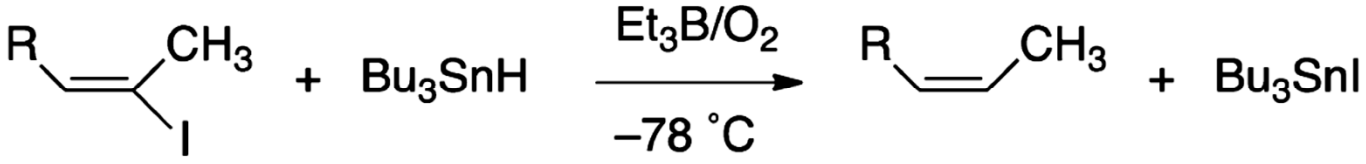
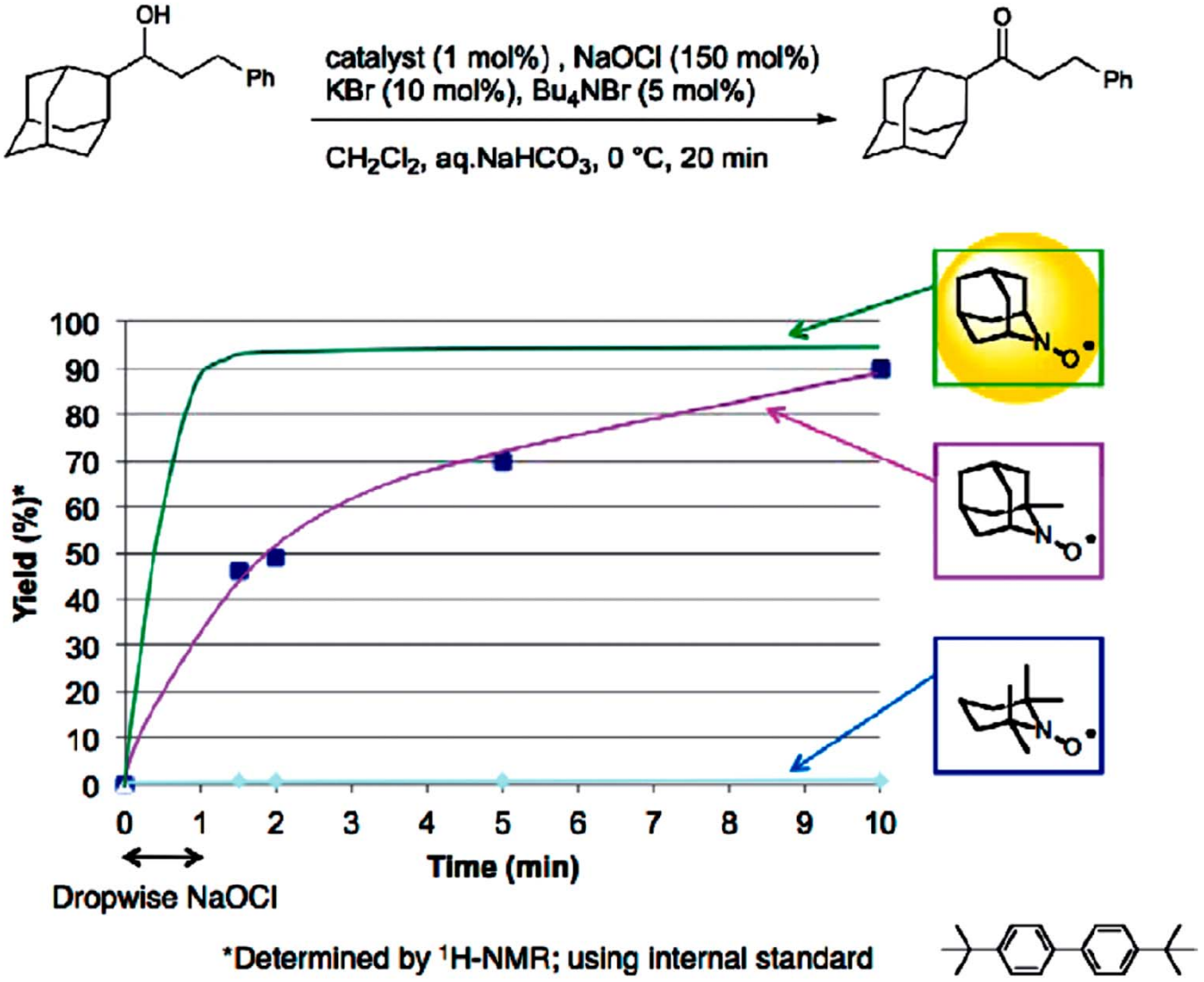


Figure 1. Key early contributions in the preparative radical chemistry of triethylborane.

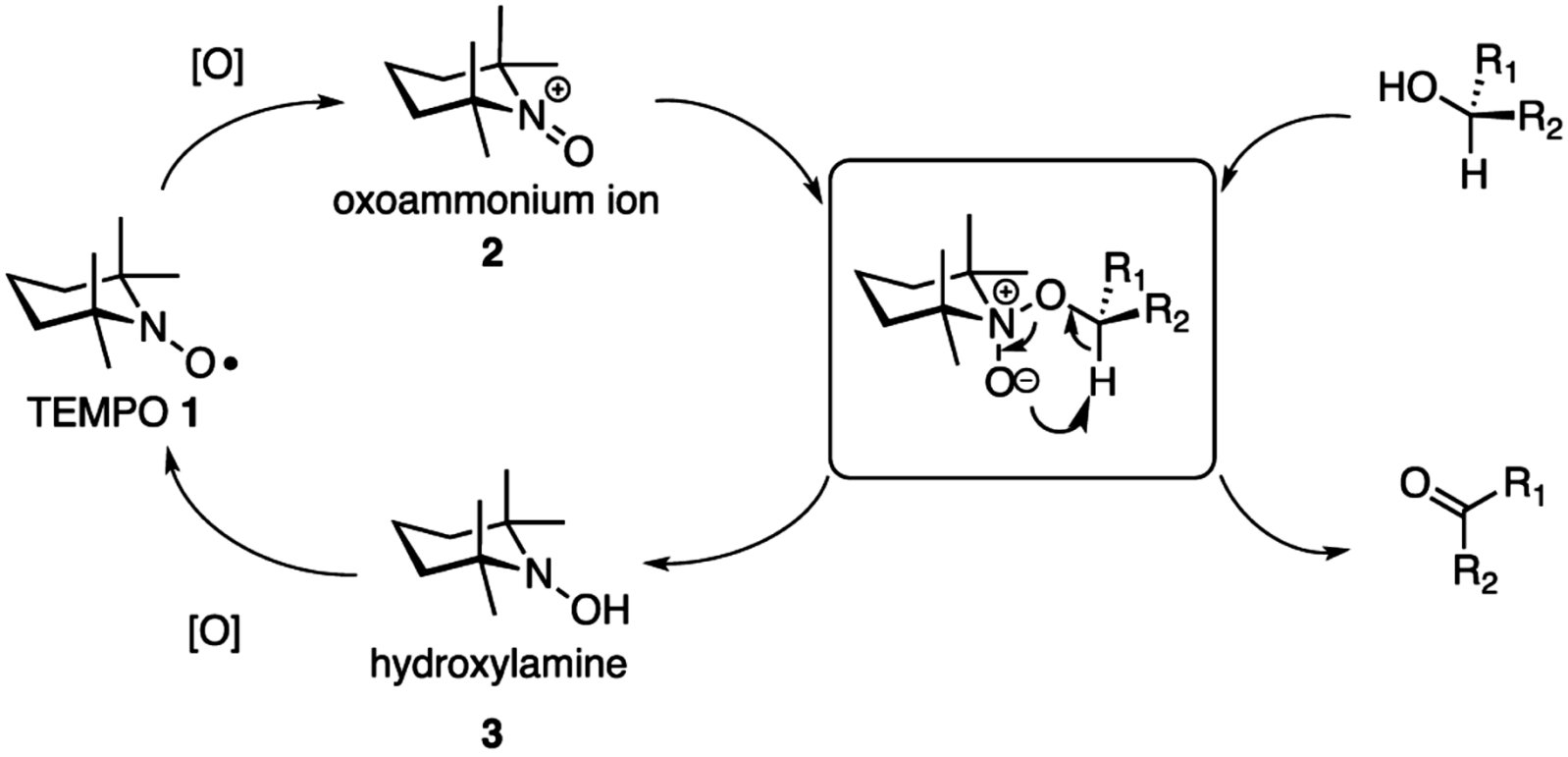
kinetics: Curran et al., *JACS* **2016**, 7741 (10.1021/jacs.6b04014)

AZADO:
the better TEMPO



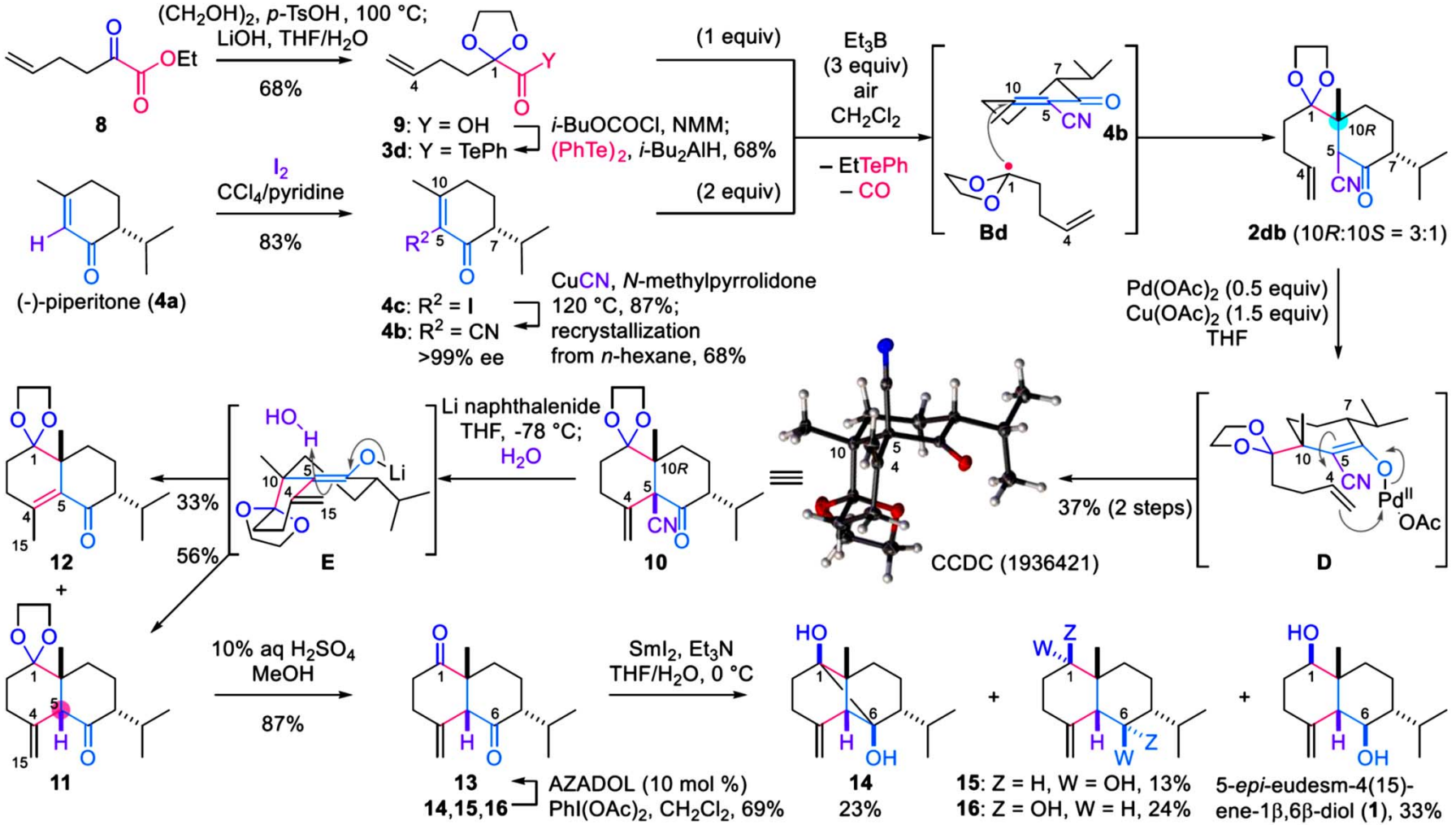
review: Yoshiharu Iwabuchi, *Chem. Pharm. Bull.* **2013**, 1197

TEMPO: mechanism

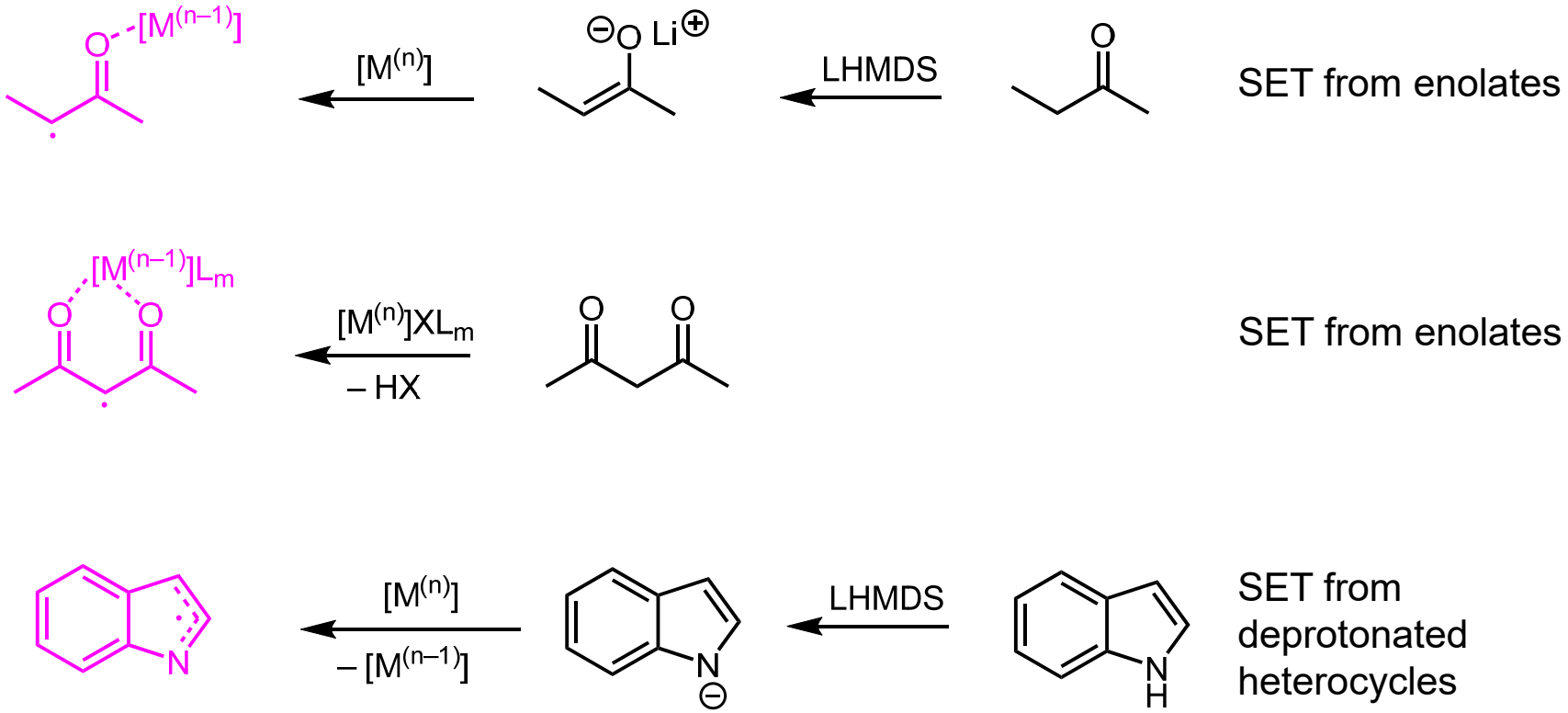


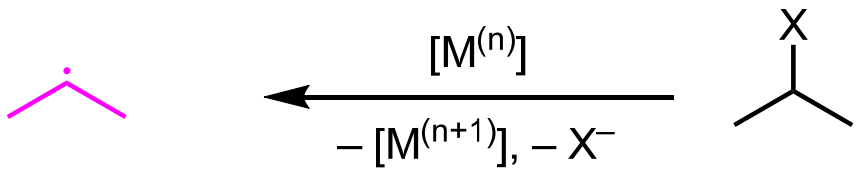
review: Yoshiharu Iwabuchi, *Chem. Pharm. Bull.* **2013**, 1197

Intermolecular decarbonylative radical addition to a cyclohexenone

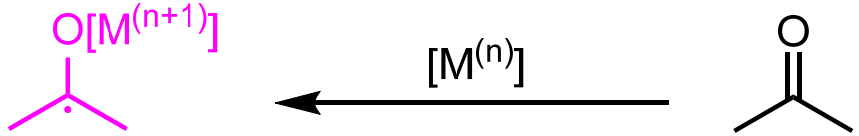


from: Masayuki Inoue et al., *OL* **2019**, 7619

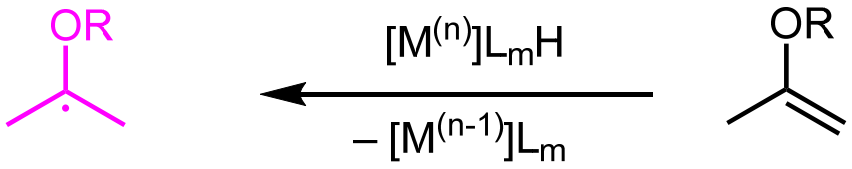

[M(n–1)]
[M(n)]
Li
LHMDS
SET from enolates
[M(n–1)]Lm
[M(n)]XLm
– HX
SET from enolates
[M(n)]
– [M(n–1)]
LHMDS
SET from deprotonated heterocycles



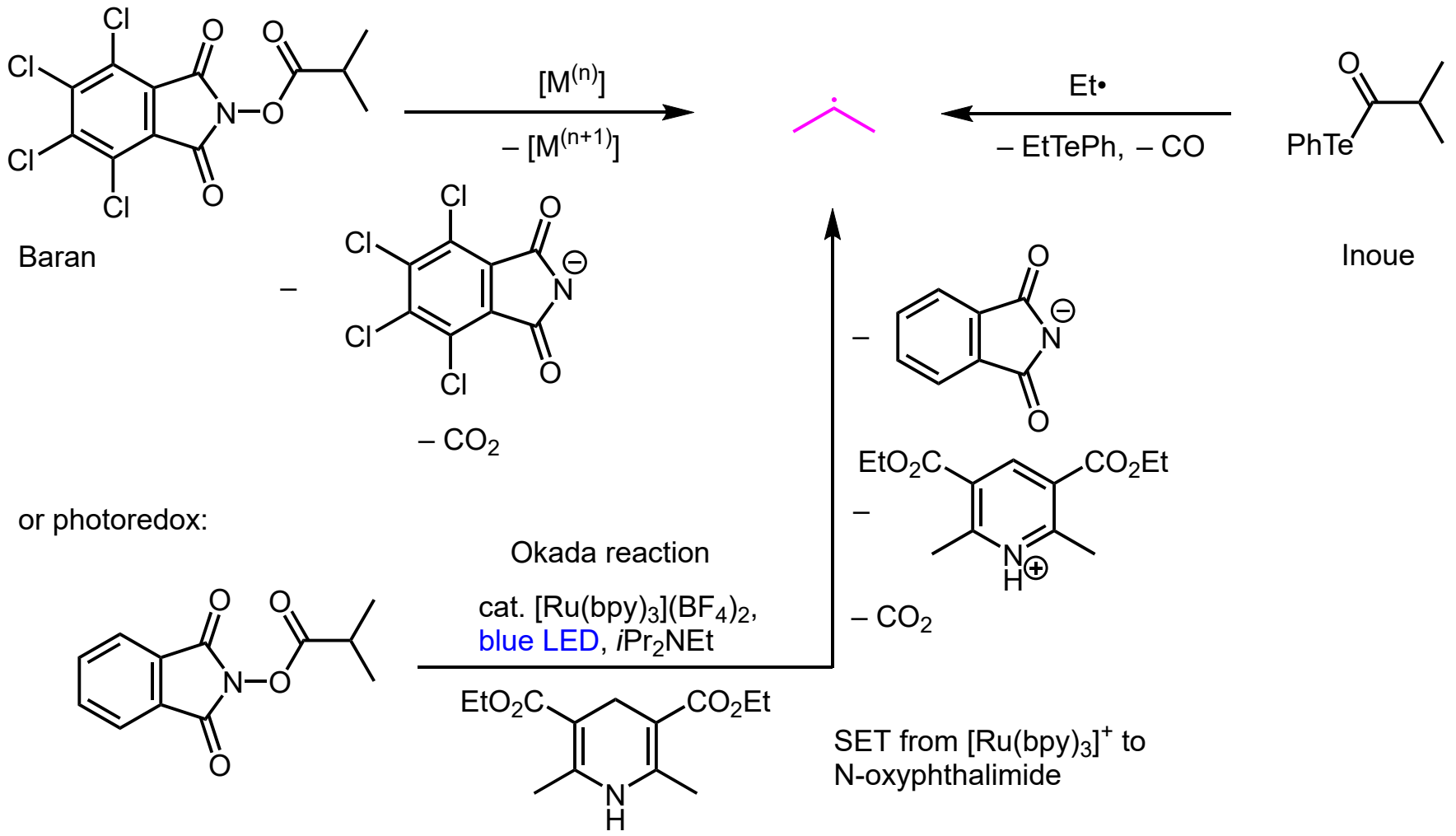
SET to alkyl halide



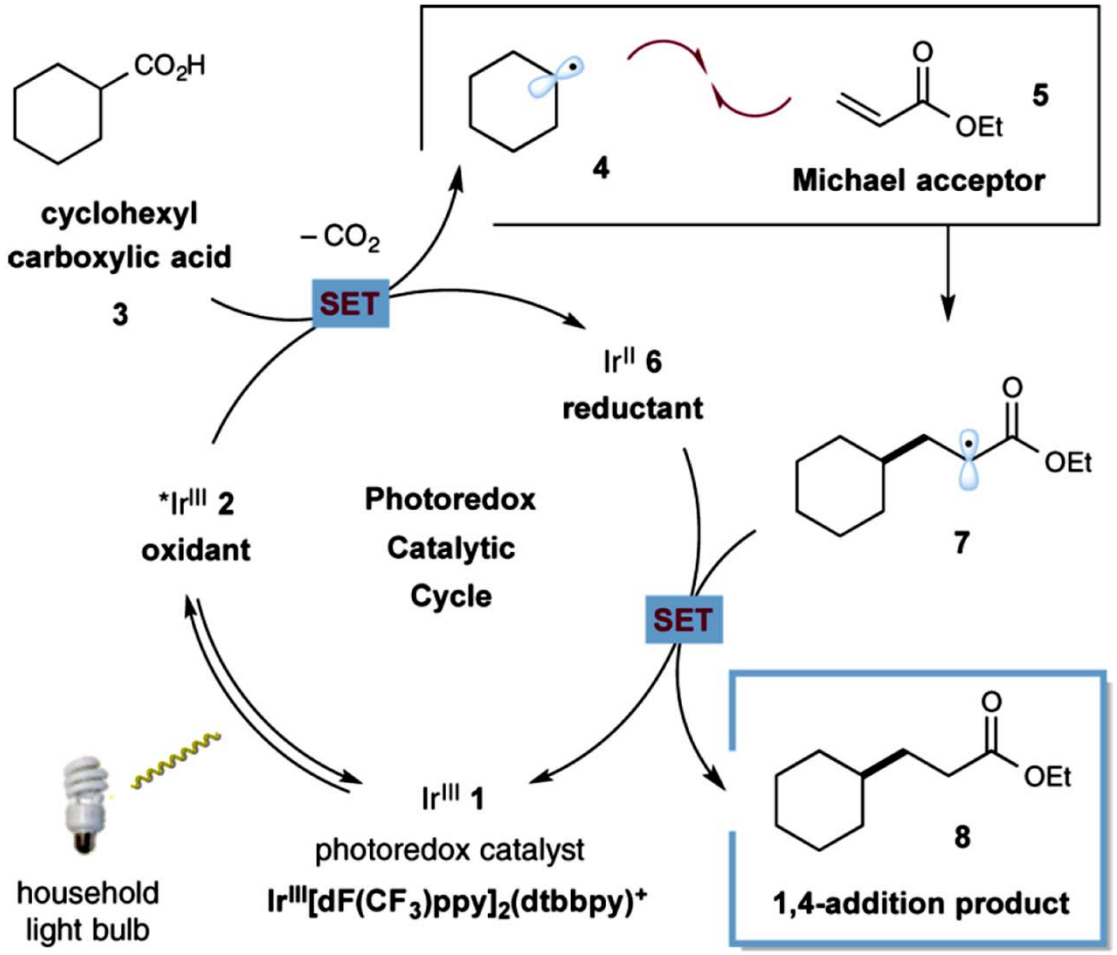
ketyl radical anion



hydrogen atom transfer



see class "reaction mechanisms" ...



see class "reaction mechanisms" ...

from: MacMillan et al., *JACS* **2014**, 10886; dx.doi.org/10.1021/ja505964r