



中国科学技术大学
University of Science and Technology of China

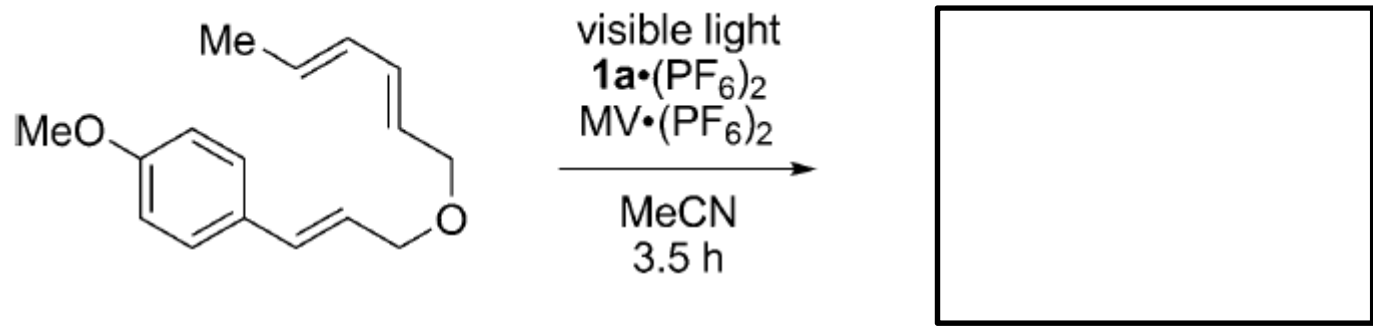
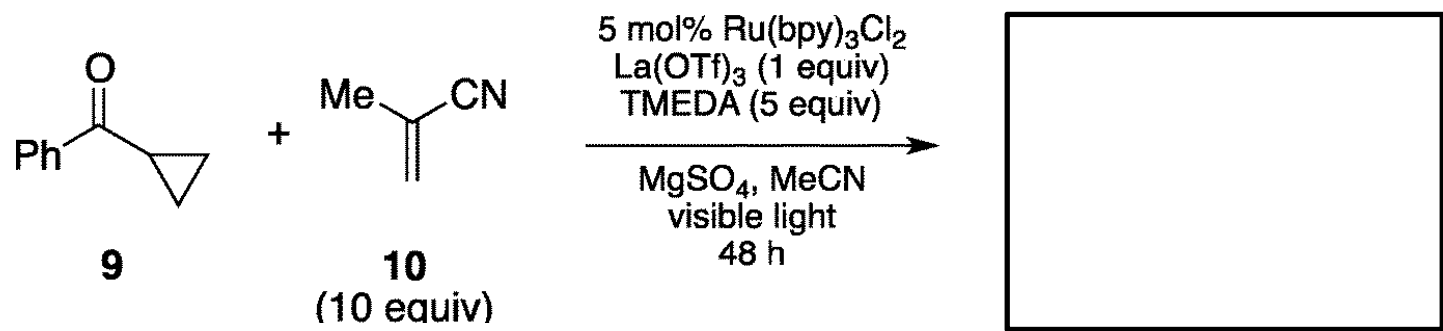
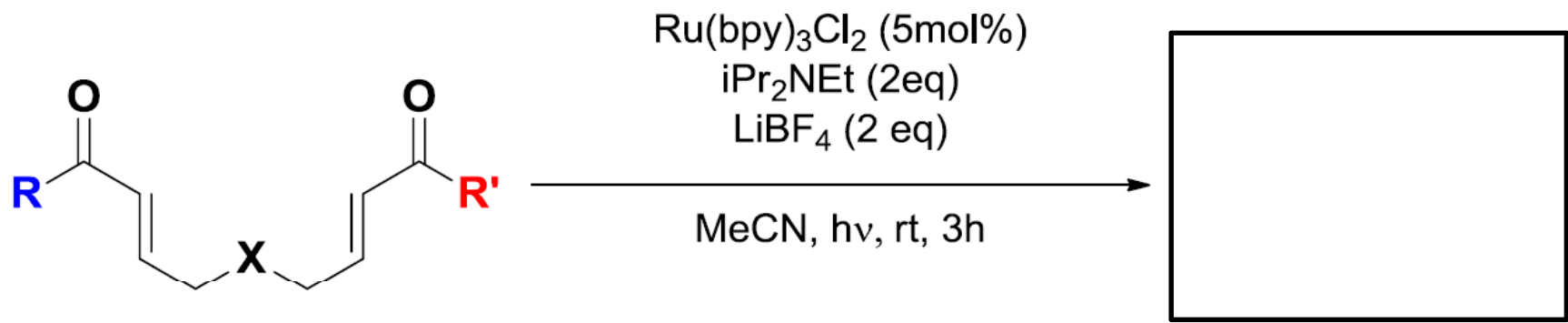
Benzynes: History, Generation & Reaction

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中国科学技术大学高分子科学与工程系







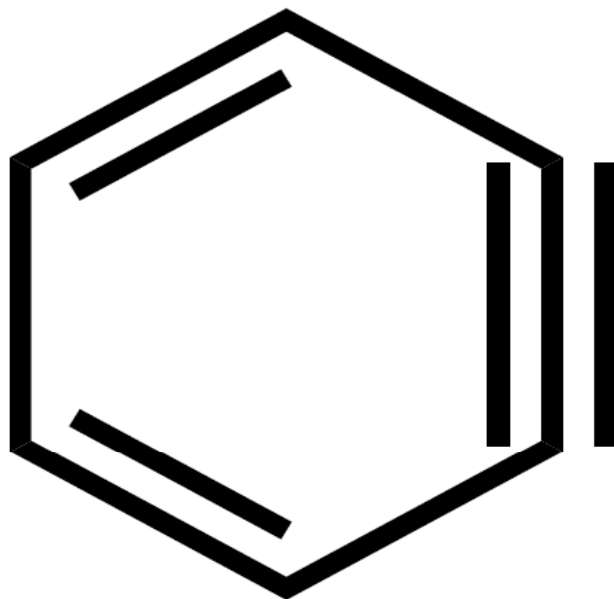
John McAfee
Founder, McAfee Antivirus Software
Eccentric Millionaire







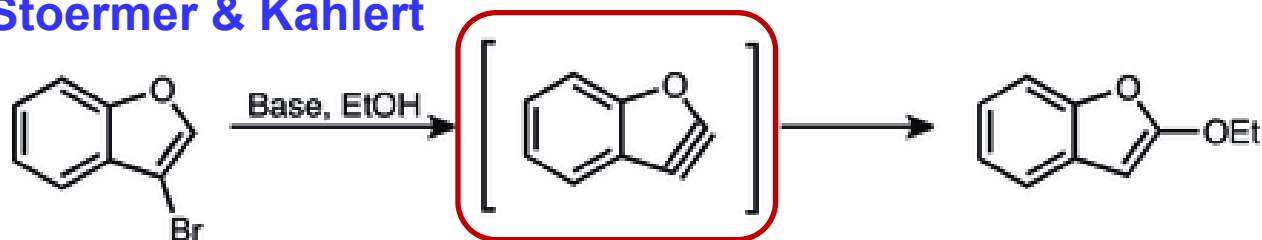
Georg Wittig
1979 Nobel Prize



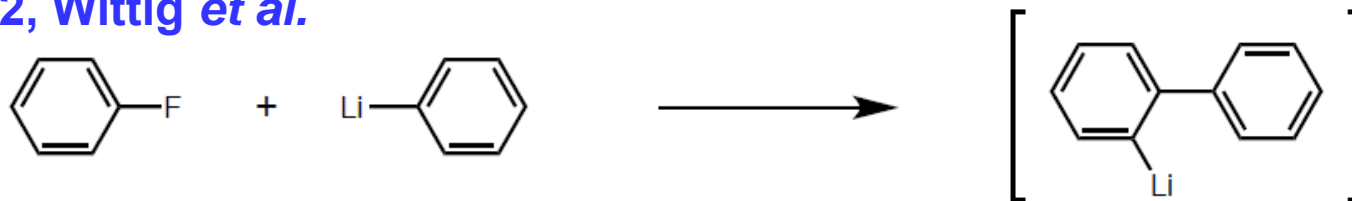
John D. Roberts

History

1902, Stoermer & Kahlert

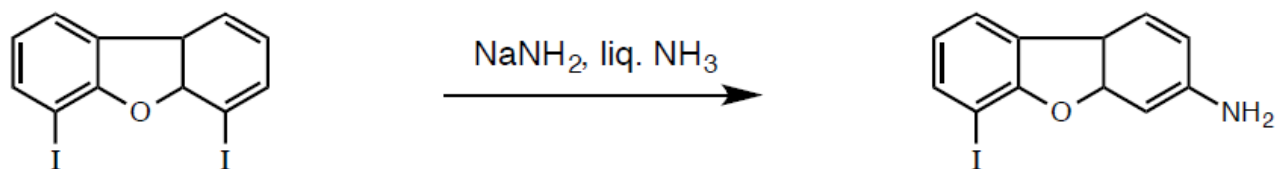


1942, Wittig *et al.*



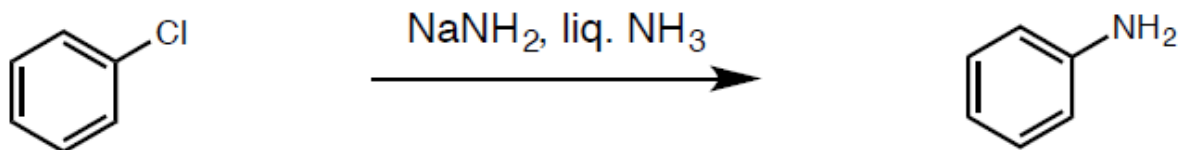
Naturwissenschaften, 1942, 30, 696

1945, Gilman *et al.*



JACS, 1945, 67, 349

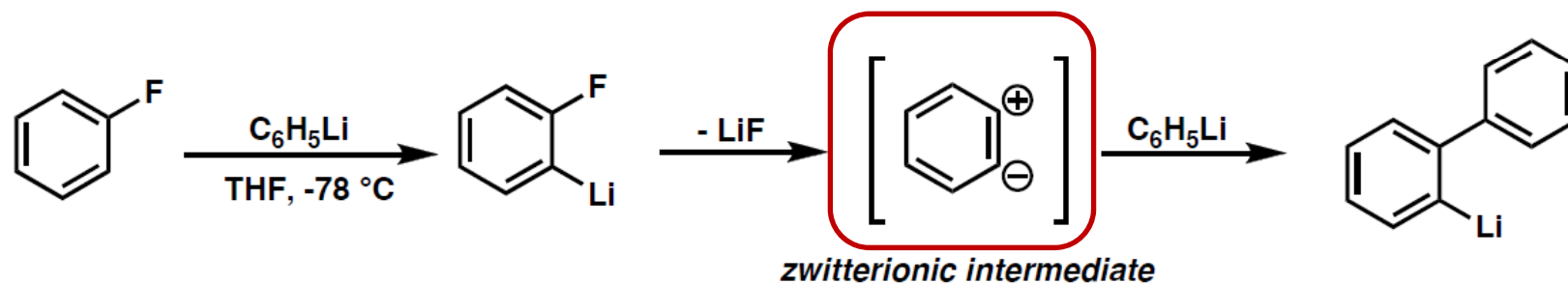
1946, Bergstrom *et al.*



J. Org. Chem., 1946, 11, 334

History

Wittig's Explanation

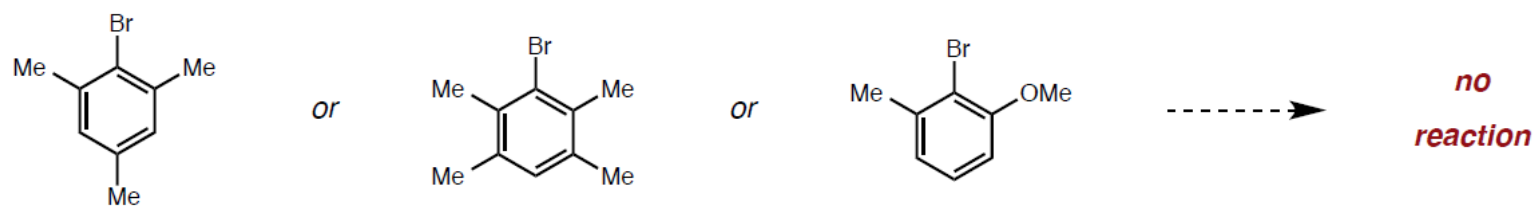
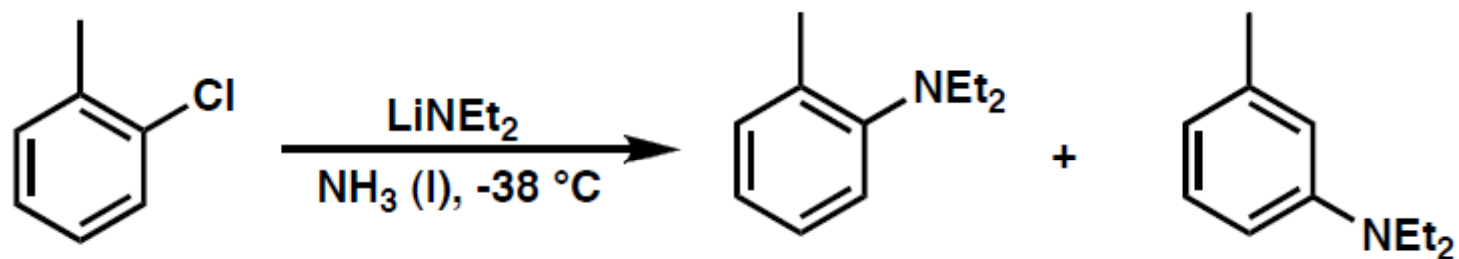


Close but not perfect!

Naturwissenschaften, 1942, 30, 696

History

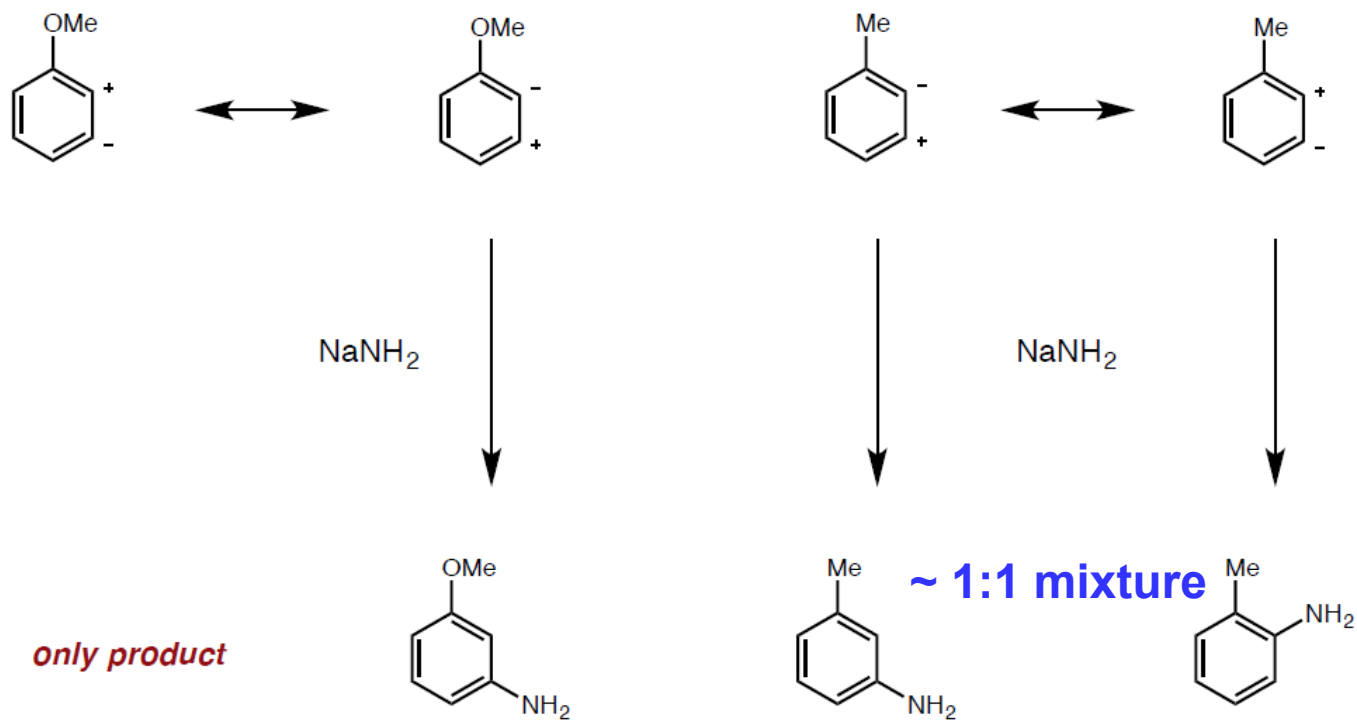
1953, Roberts *et al.*



JACS, 1953, 75, 3290

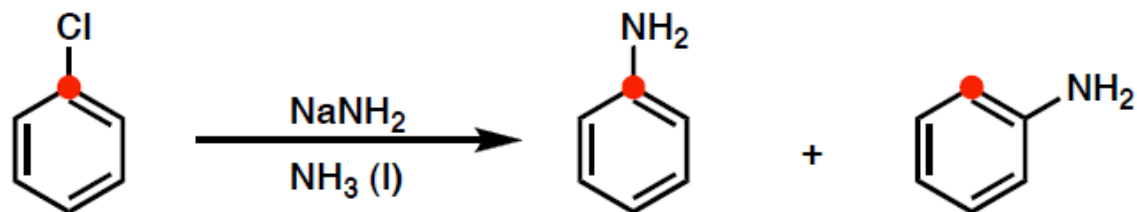
History

Zwitterion failed to explain observed reaction phenomenon



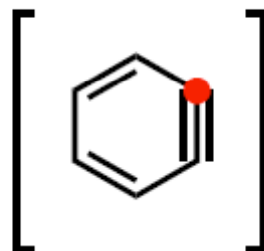
The Classic ^{14}C labeling experiment

Hypothesis: If one started with chlorobenzene-1- ^{14}C , equal amounts of aminobenzenes with the ^{14}C at C-1 and C-2 would be formed.



Nearly 1:1 ratio!

Roberts proposed intermediate: electrically neutral benzyne!



JACS, 1953, 75, 3290

The Classic ^{14}C labeling experiment

REARRANGEMENT IN THE REACTION OF CHLORO-BENZENE-1- C^{14} WITH POTASSIUM AMIDE¹

Sir:

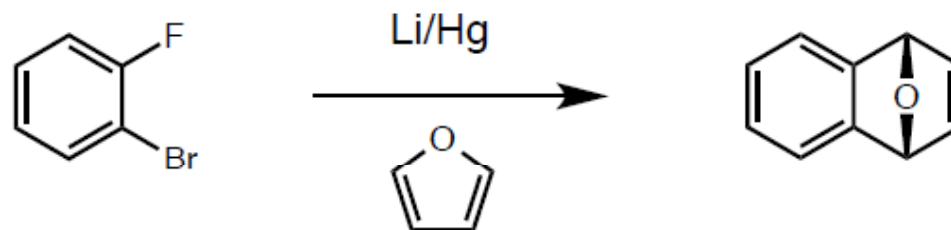
No satisfactory explanation has been published for the rearrangements which often occur in the amination of "non-activated" aryl halides with alkali-metal amides.² The pattern of the rearrangements shows a considerable disregard for the influences governing the usual aromatic substitutions and is well illustrated by the products obtained from the amination of the methoxy- and trifluoromethyl-halobenzenes. Although the methoxy and trifluoromethyl groups orient oppositely in aromatic nitration, *o*- and *m*-methoxy- and trifluoromethyl-halobenzenes with alkali-metal amides yield exclusively *m*-substituted anilines, while the *p*-isomers yield mixtures containing roughly equal amounts of *m*- and *p*-substituted anilines.³

leaving halogen. These facts as well as the orientation data for various substituents can be accommodated by an elimination-addition mechanism involving at least transitory existence of an electrically neutral "benzyne" intermediate (II).

J. Am. Chem. Soc. 1953, 75, 3290

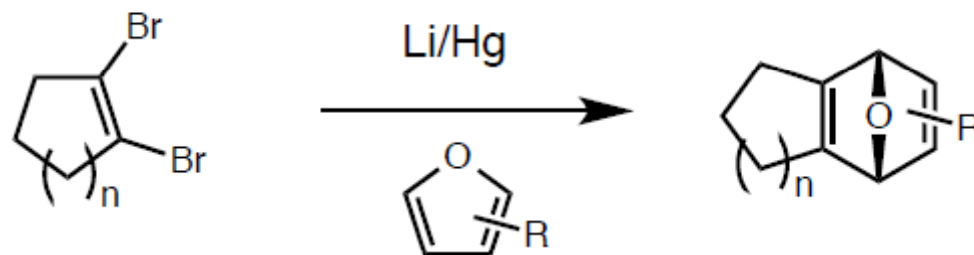
Following Experiments

1955, the first Benzyne Diels-Alder Reaction



Angew. Chem. 1955, 67, 348

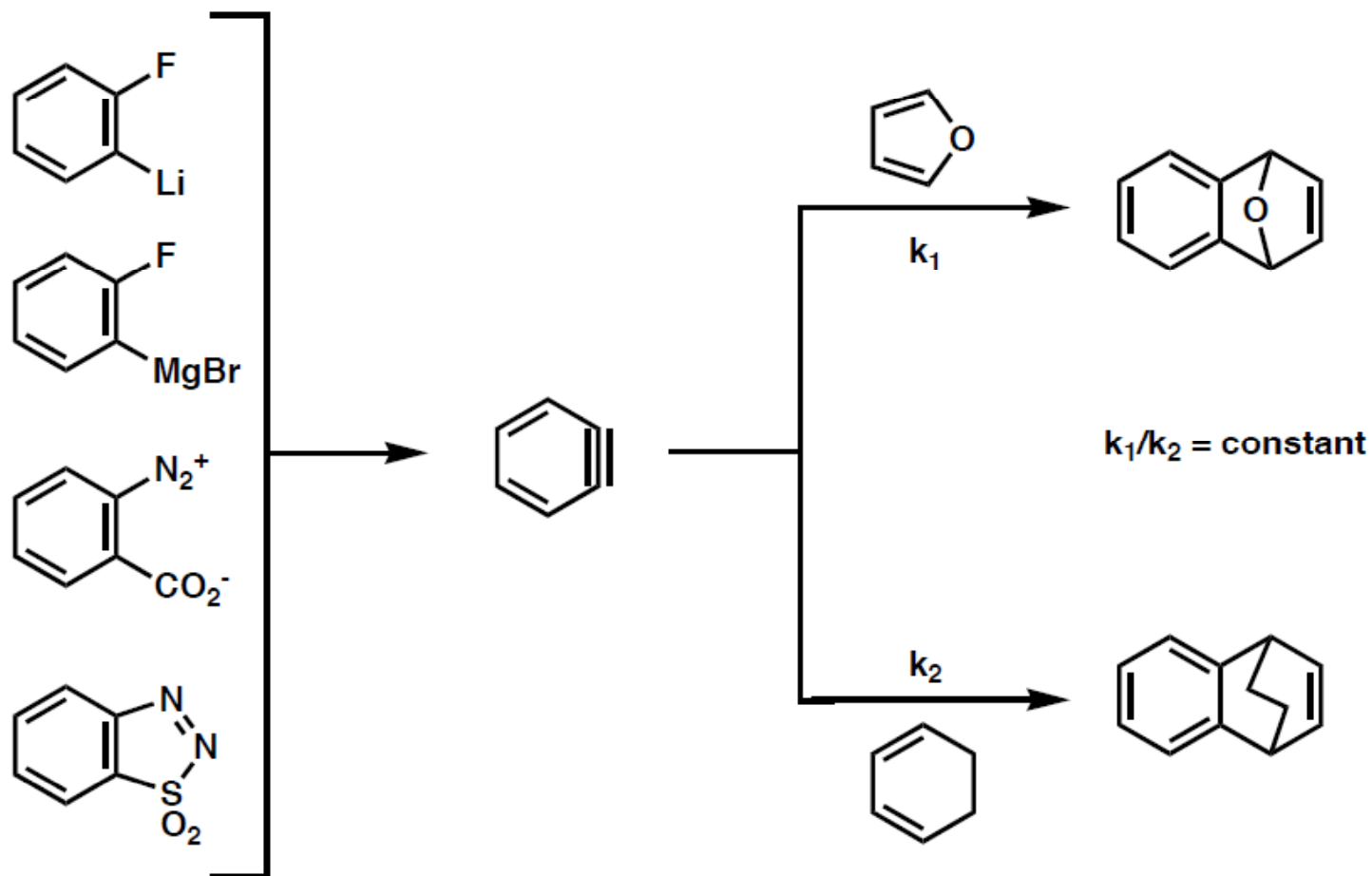
1960, aliphatic cycloalkynes postulated



$n = 1$: "low yield"; $n = 2$: 25%; $n = 3$: 35%

Angew. Chem. 1960, 72, 324

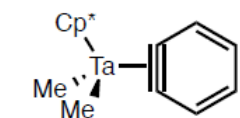
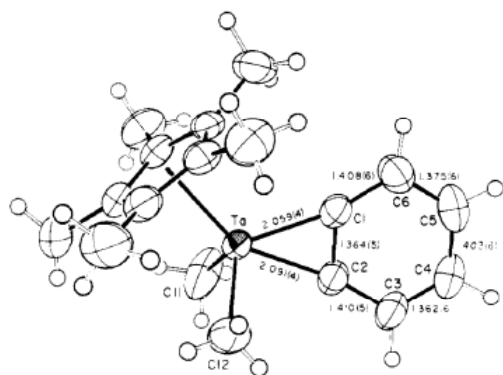
Following Experiments



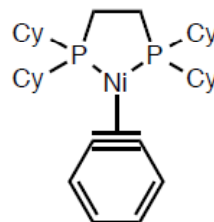
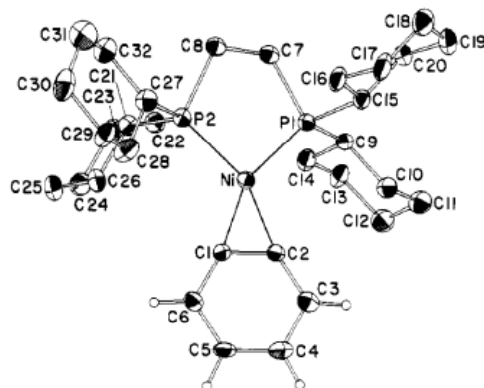
Benzyne generated from different precursors have identical reactivity

Following Experiments

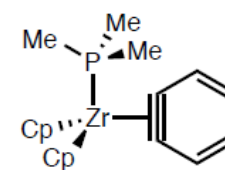
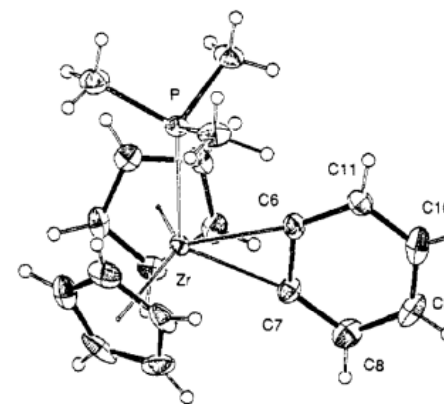
Crystal structure of metal-bound benzyne obtained.



1979, Shrock

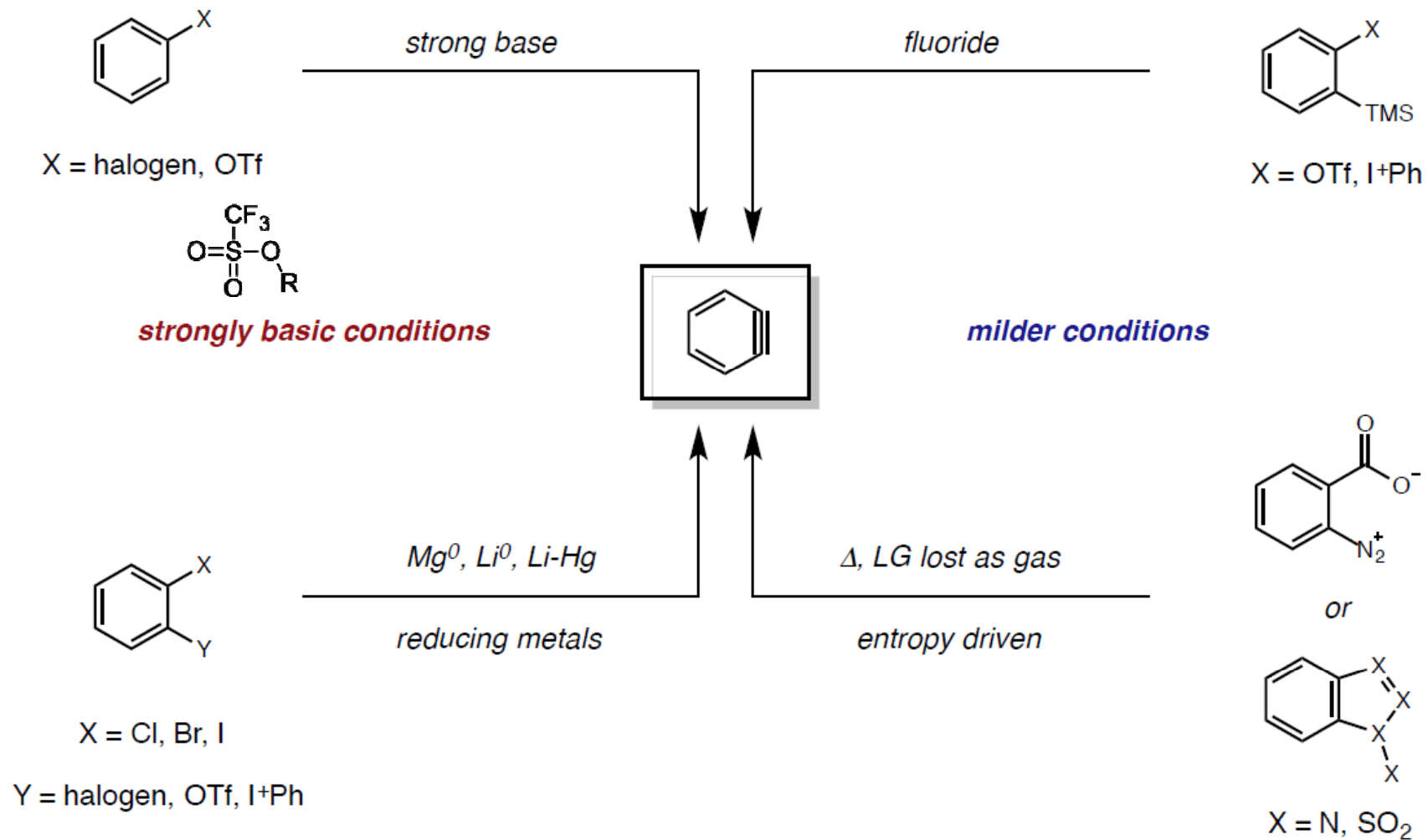


1985, Bennett



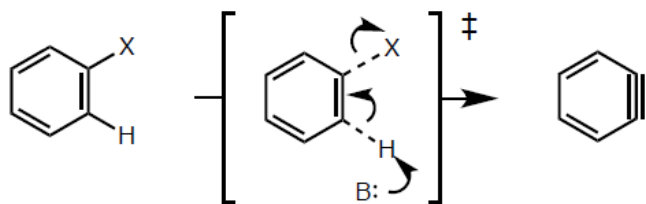
1986, Buchwald

Generation of Benzynes



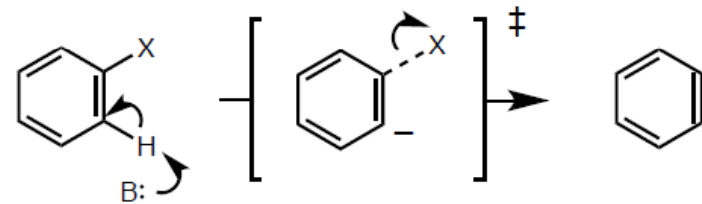
Generation of Benzyne

protic solvents (质子化溶剂)



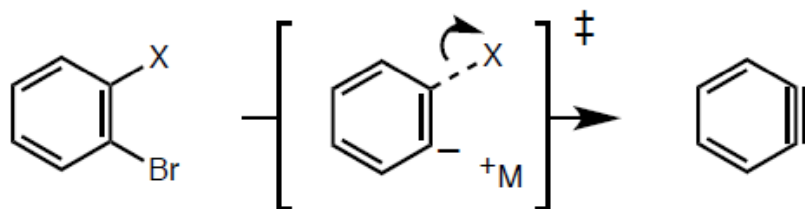
rate: $Br > I > Cl > F$

aprotic solvents: stepwise



rate: $F > Cl > Br > I$

Dihalides: determined by choice of metal

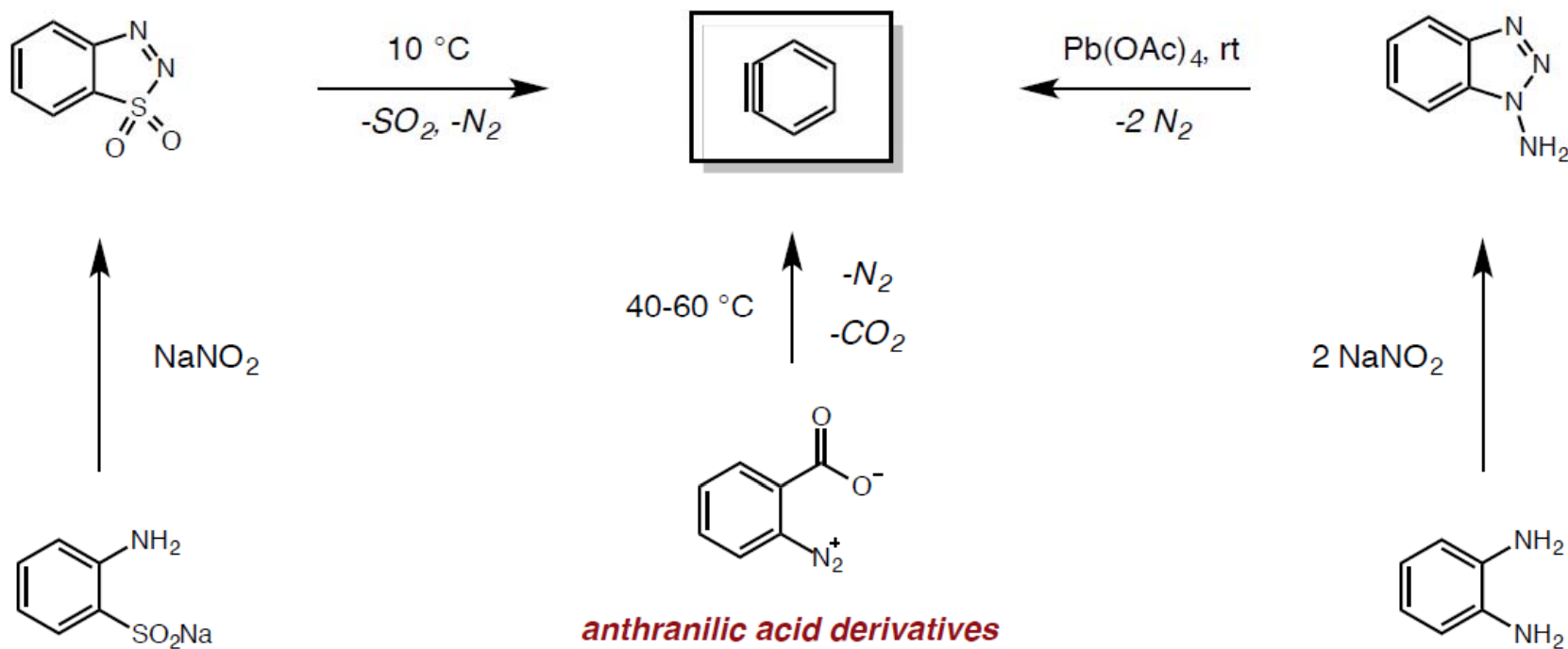


X = F, Cl, Br, I, OTf, I⁺Ph

rate: $Na > Mg > Li$

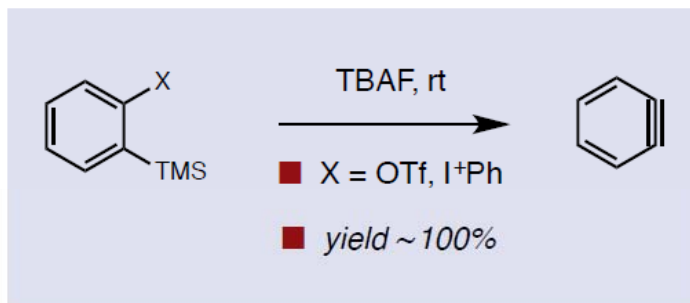
Generation of Benzyne

Loss of gas molecules drives benzyne formation under relatively mild conditions

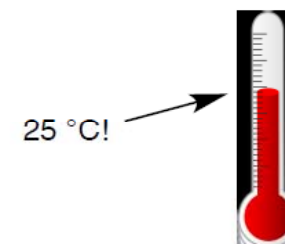


Generation of Benzynes

- avoid use of pyrophoric/
highly reactive bases



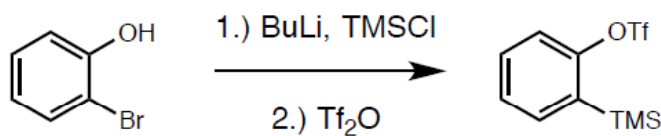
- facile yet controlled at rt



- not shock-sensitive



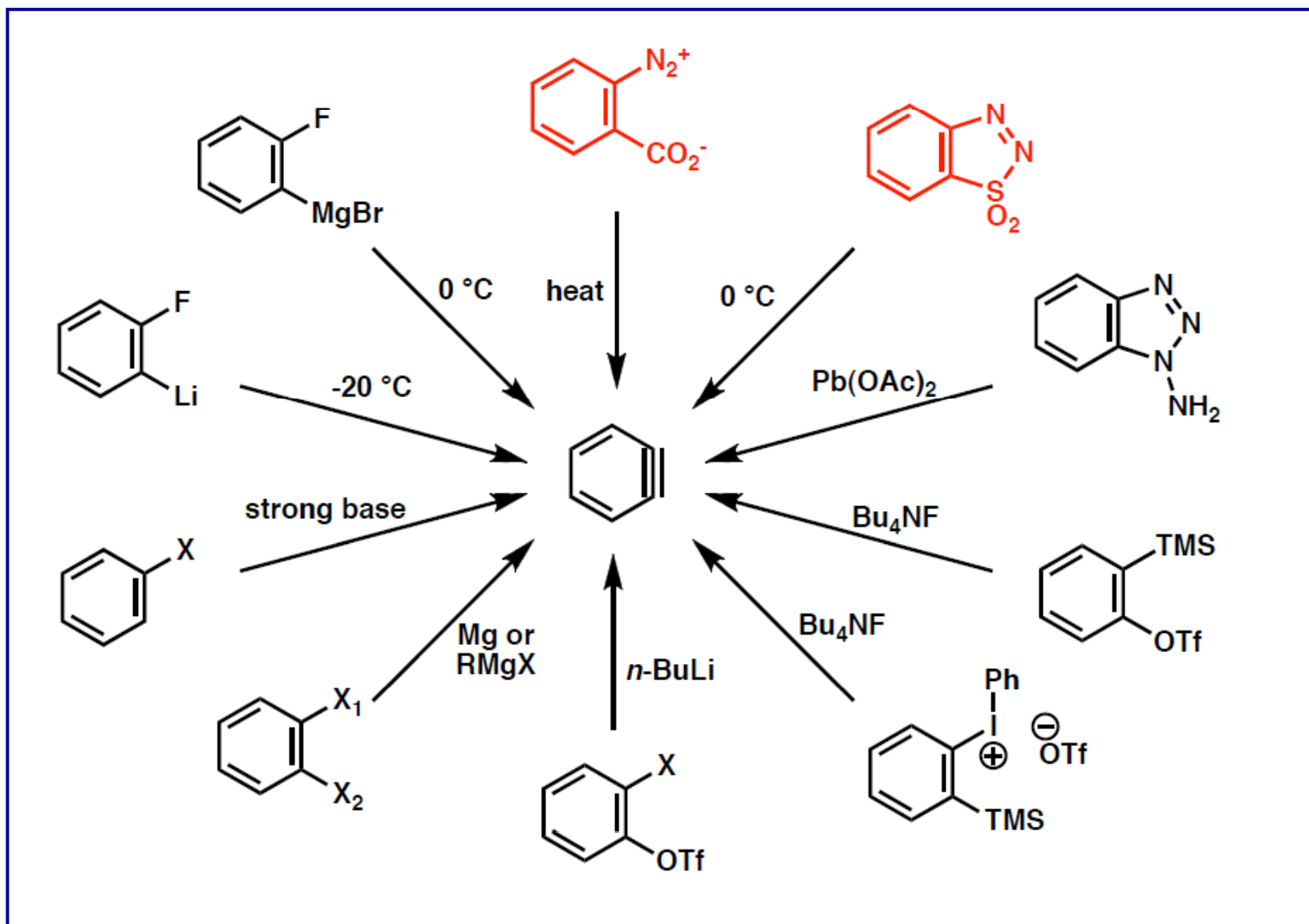
- easily synthesized



- avoid use of toxic
oxidants [$\text{Pb}(\text{OAc})_4$]

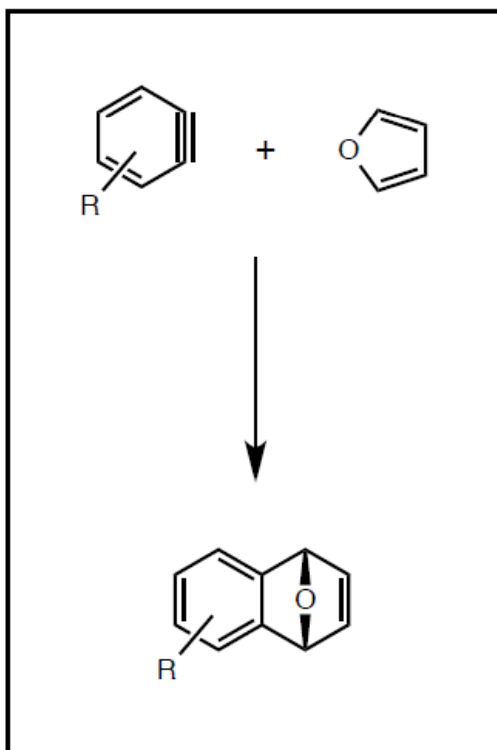


Generation of Benzynes

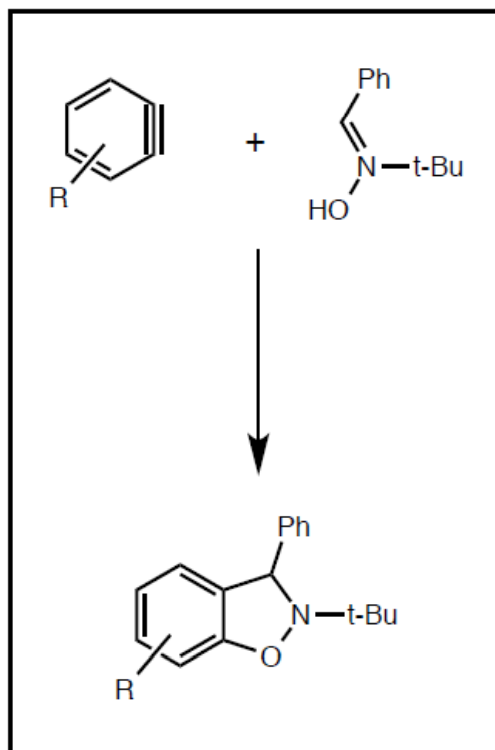


Reaction of Benzyne

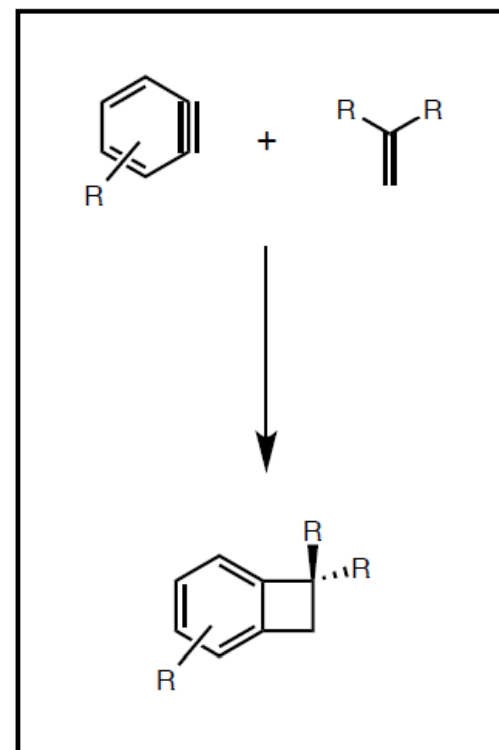
[4+2] cycloaddition



[3+2] cycloaddition

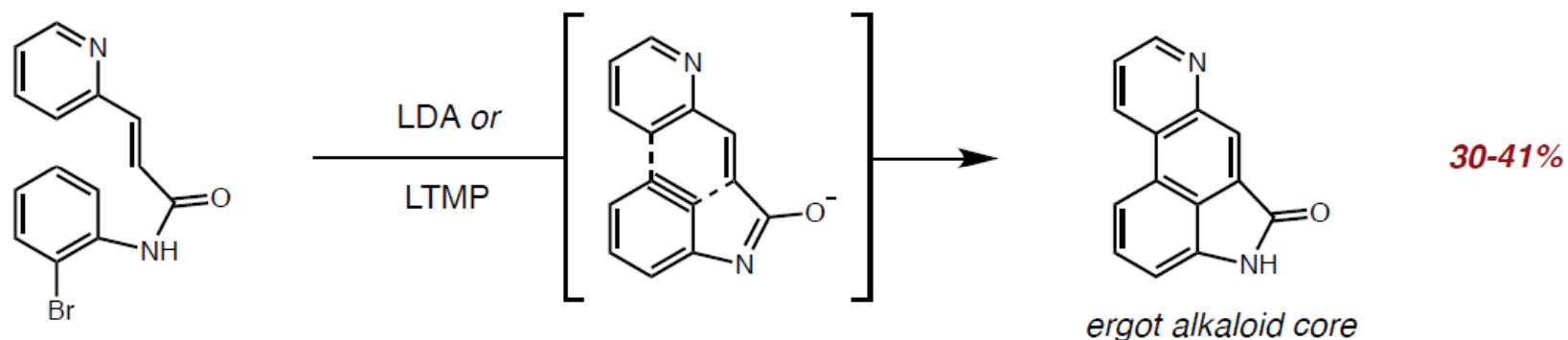


[2+2] cycloaddition



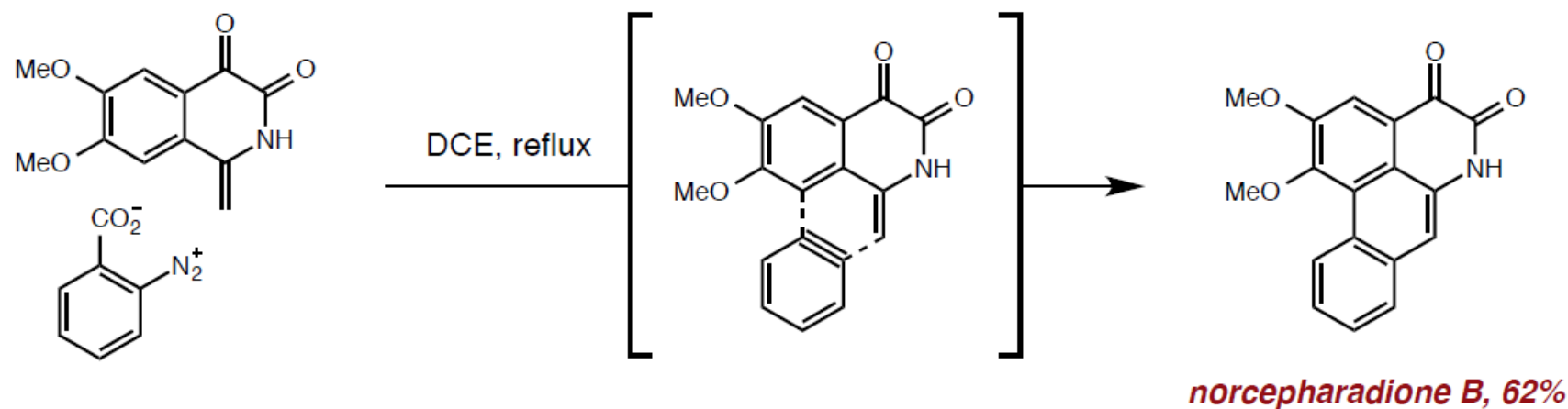
Reaction of Benzyne

Intramolecular reaction



Synlett, 1992, 903

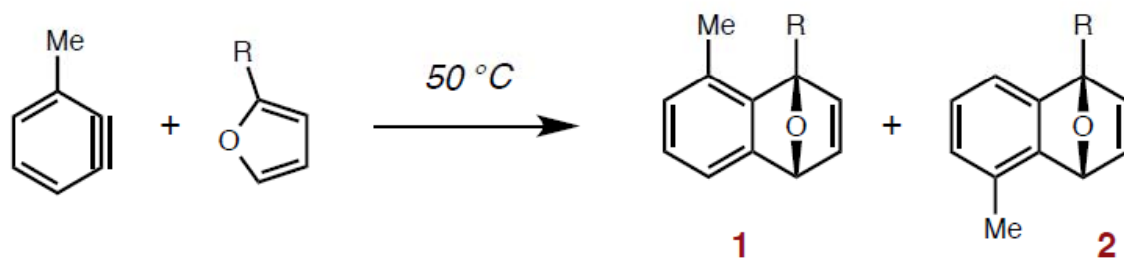
Intermolecular reaction



Tetrahedron Lett, 1992, 903

Reaction of Benzyne

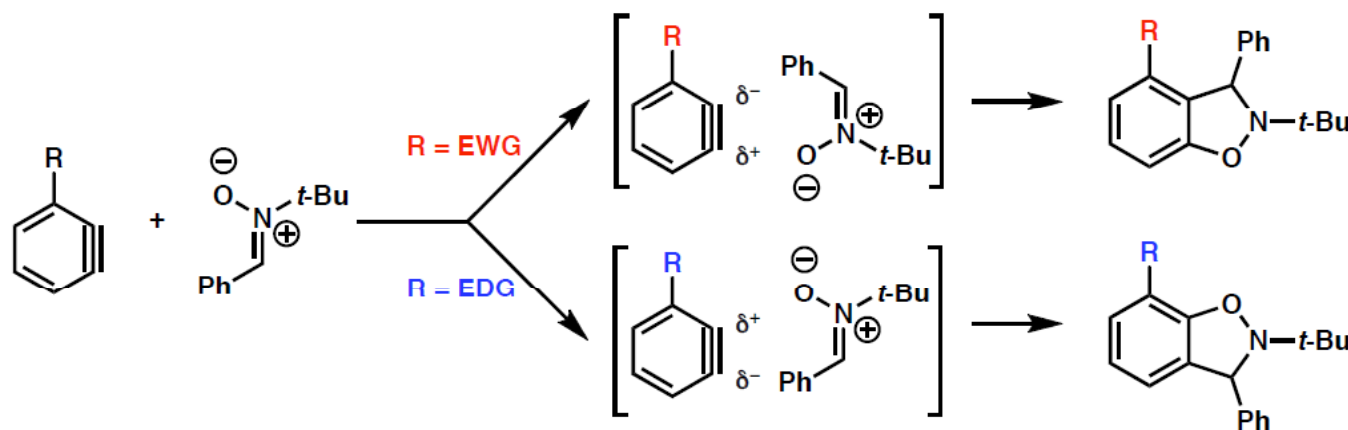
non-symmetrical dienes often display little selectivity



R	1 : 2
Me	42 : 58
<i>t</i> -Bu	36 : 64
CO ₂ Me	43 : 57
	39 : 61

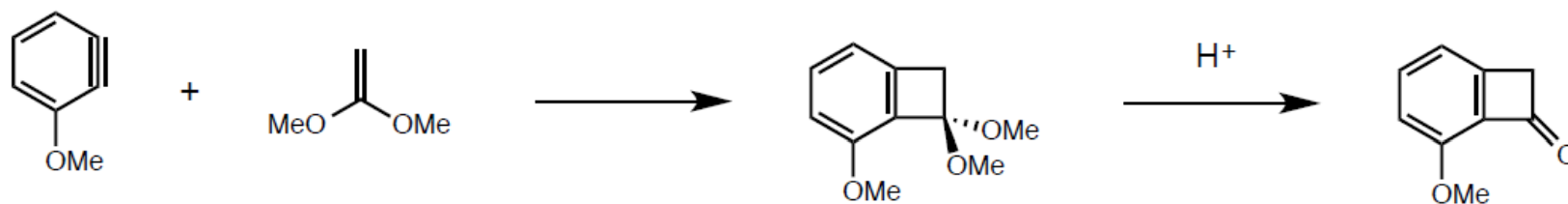
J. Org. Chem. 1976, 41, 3356

But, when EWG or EDG present....

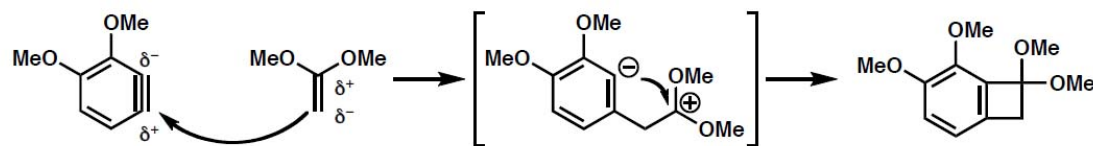


Reaction of Benzyne

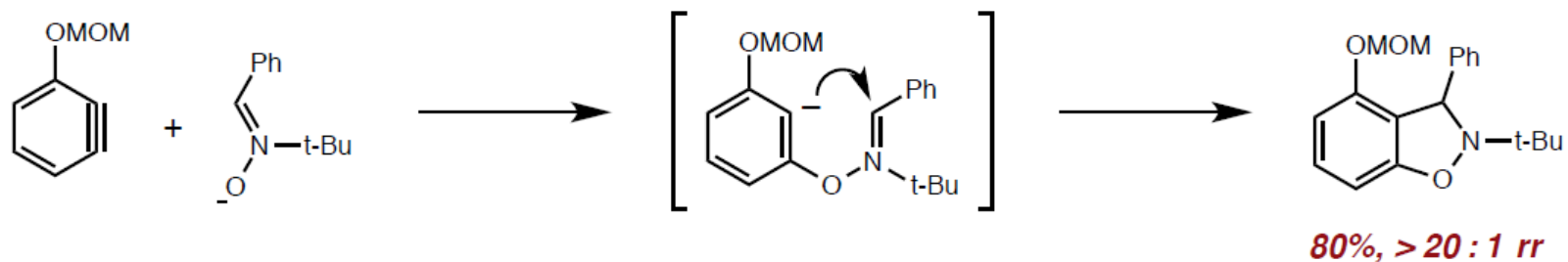
[2+2] cycloaddition with enol ethers provide convenient access to benzocyclobutenones



76%, single regioisomer

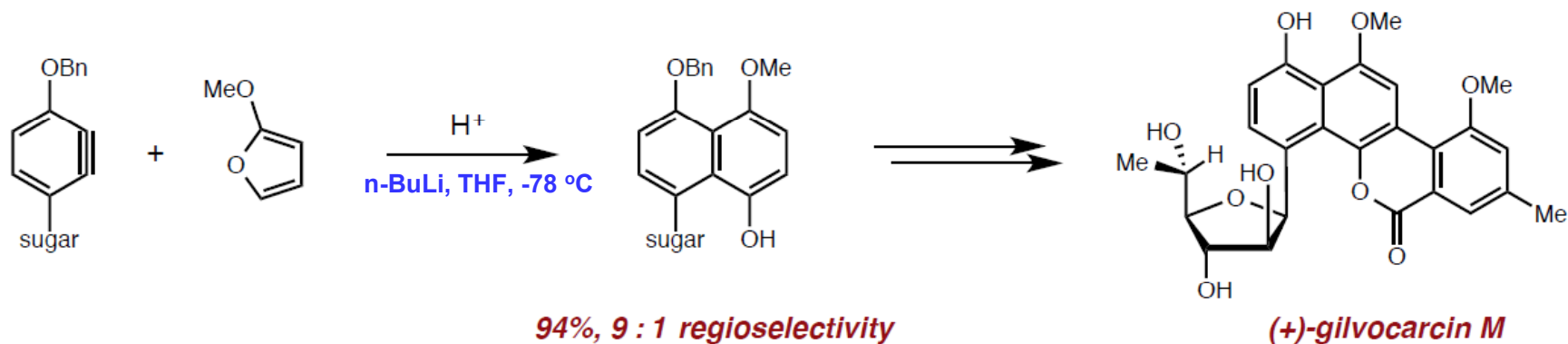


stepwise [3+2] cycloaddition proceeds with similar regiochemistry

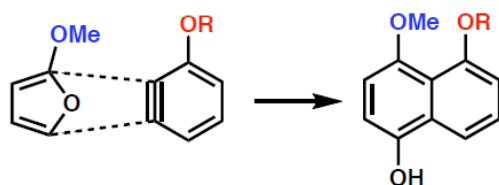


80%, > 20 : 1 rr

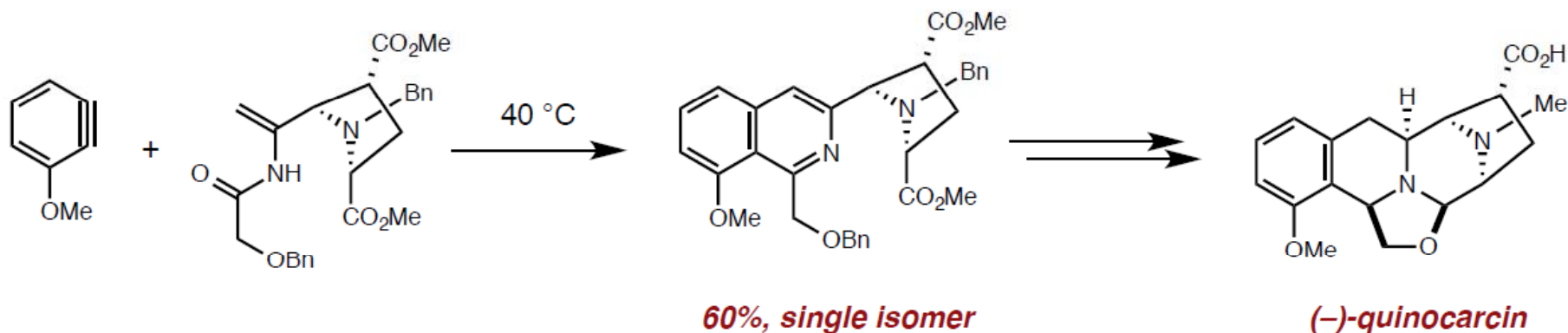
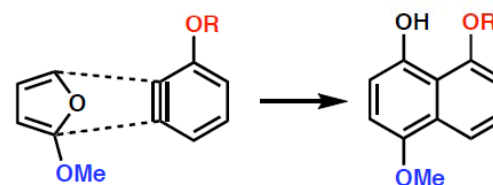
Reaction of Benzyne in Total Synthesis



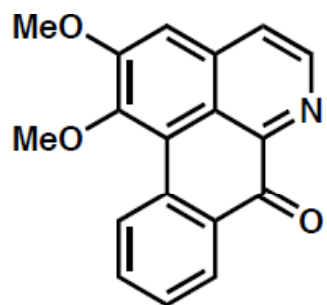
Head-to-head Product



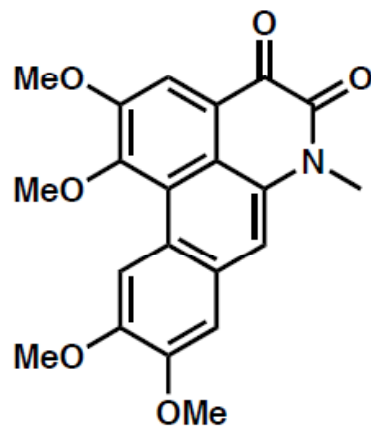
Head-to-tail Product



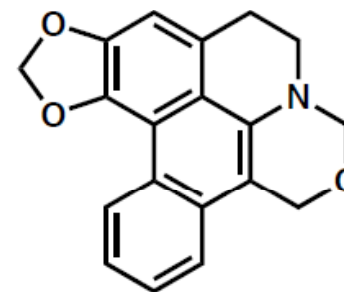
Reaction of Benzyne in Total Synthesis



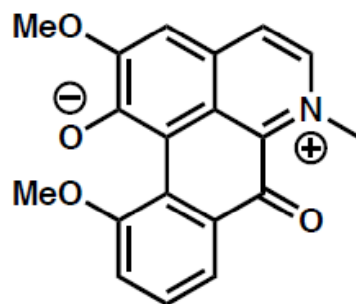
lysicamine



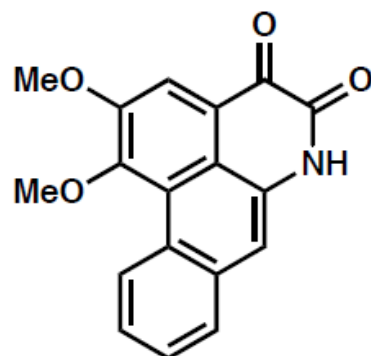
pontevedrine



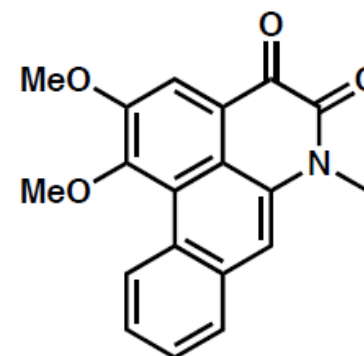
duguenaine



alkaloid PO-3

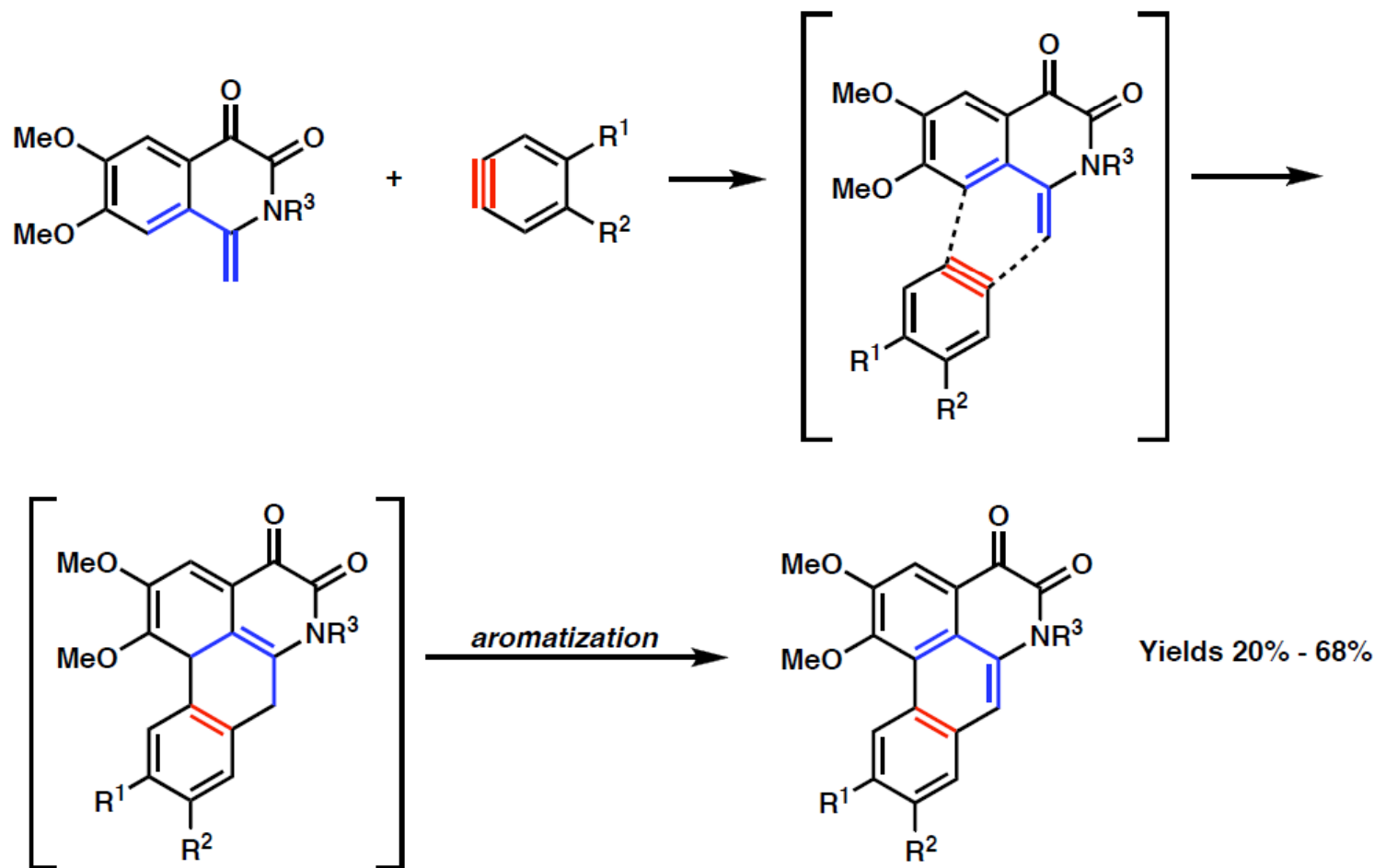


norcepharadione B



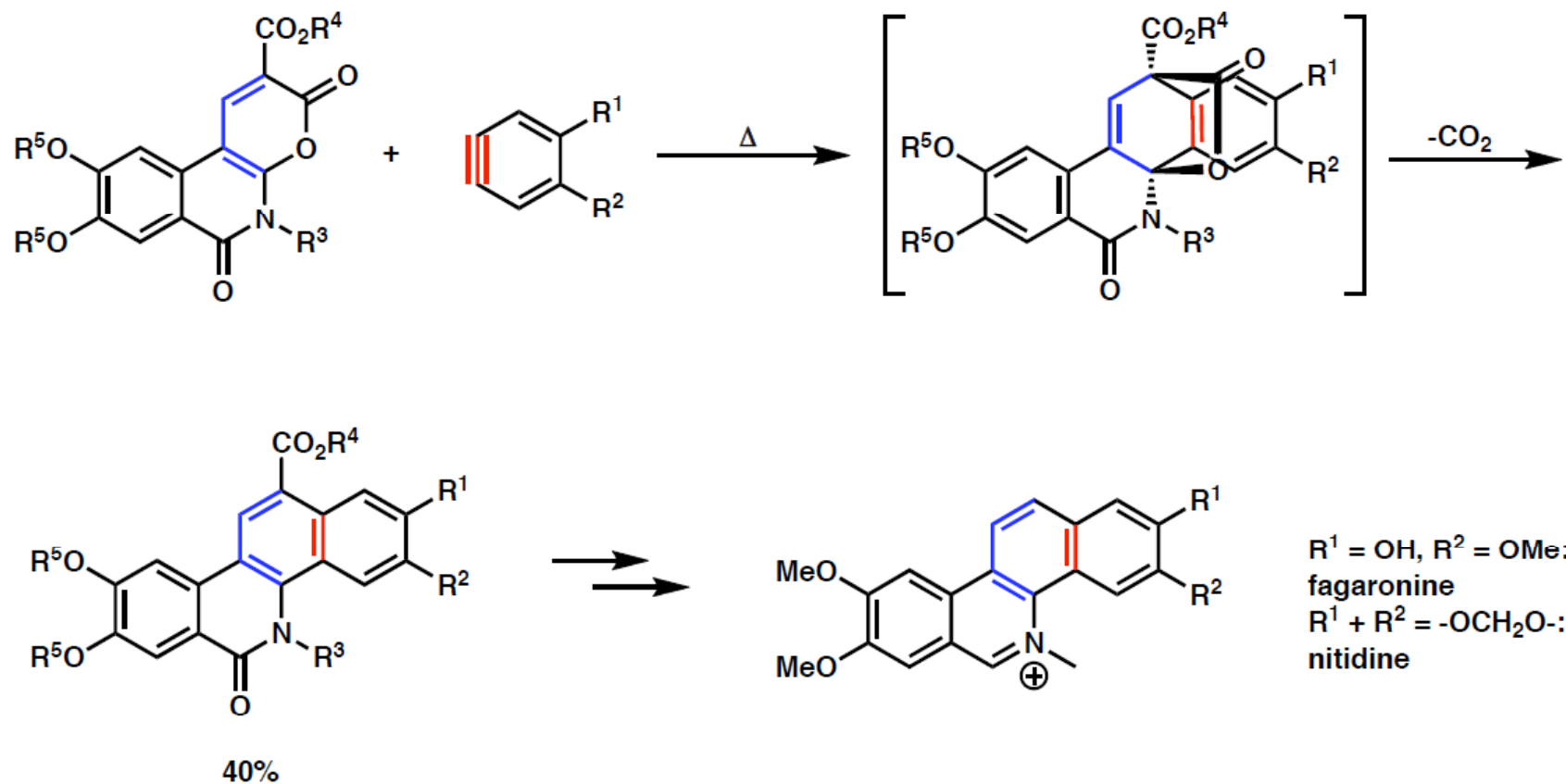
cepharadione B

Reaction of Benzyne in Total Synthesis

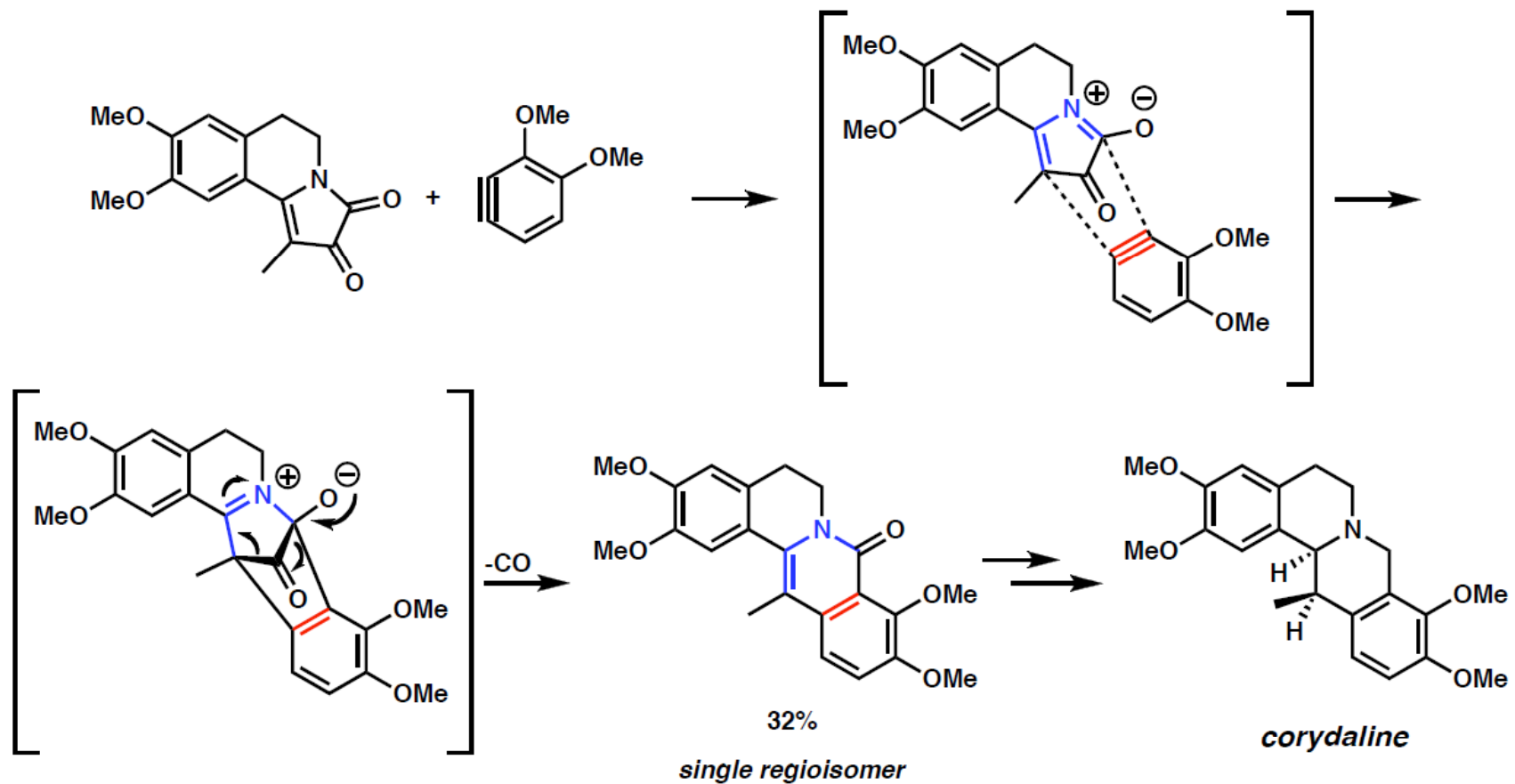


R¹ = R² = R³ = H: norcepharadione B
R¹ = R² = OMe, R³ = Me: pontevedrine
R¹ = R² = H, R³ = Me: cepharadione B

Reaction of Benzyne in Total Synthesis



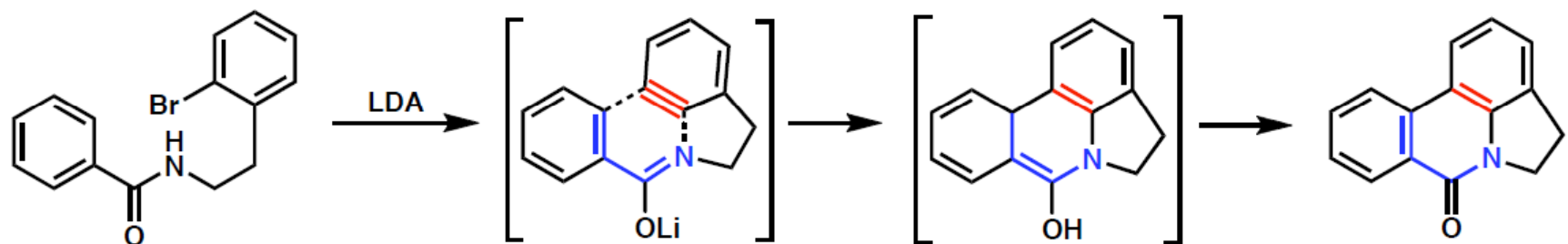
Reaction of Benzyne in Total Synthesis



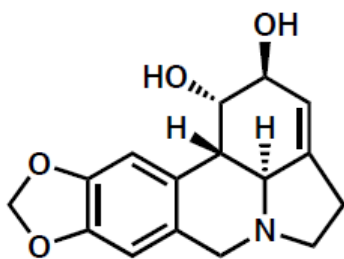
J. Org. Chem. 1986, 51, 2781

J. Org. Chem. 1992, 57, 6765

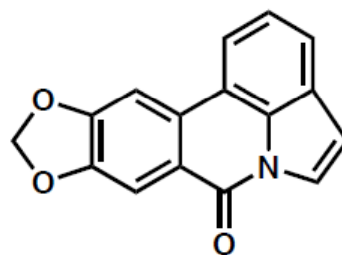
Reaction of Benzyne in Total Synthesis



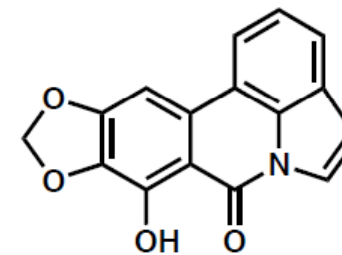
Yields 61% - 91%



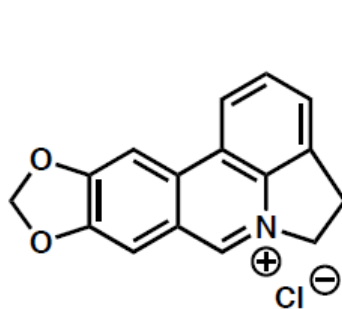
lycorine



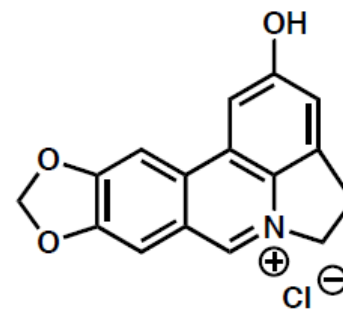
hippadine



kalbretorine

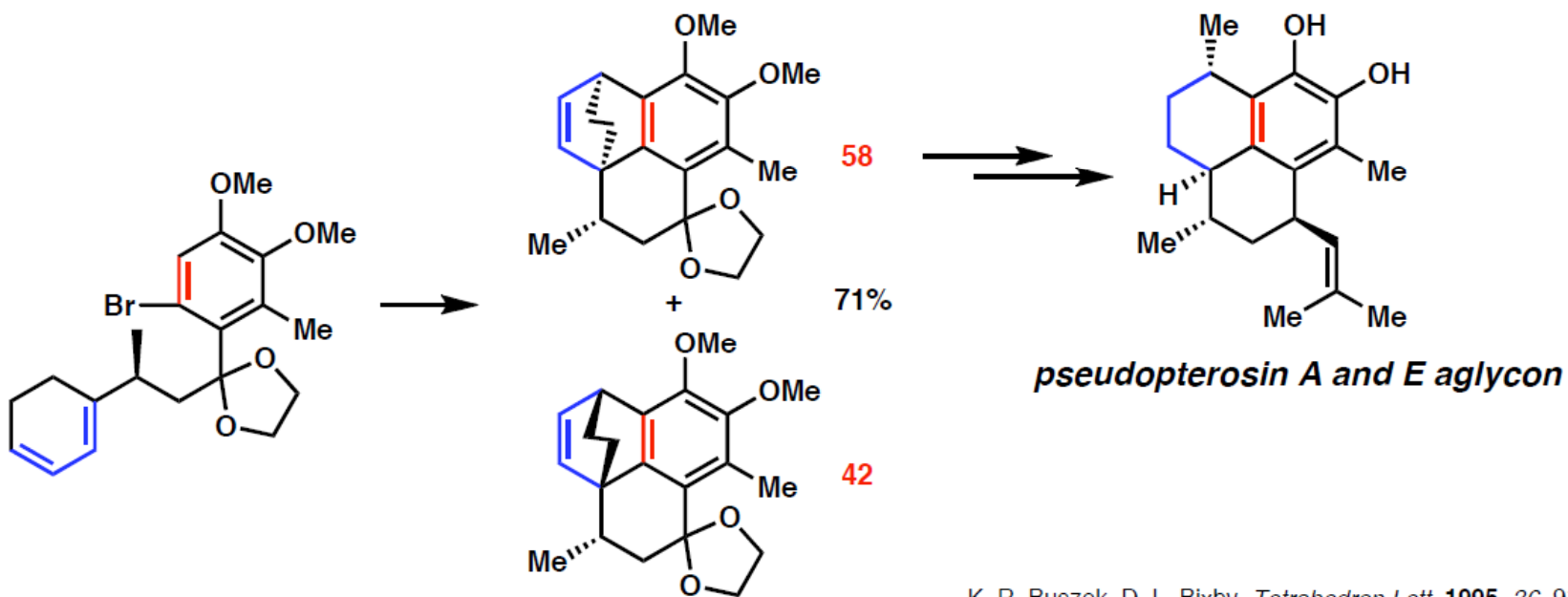
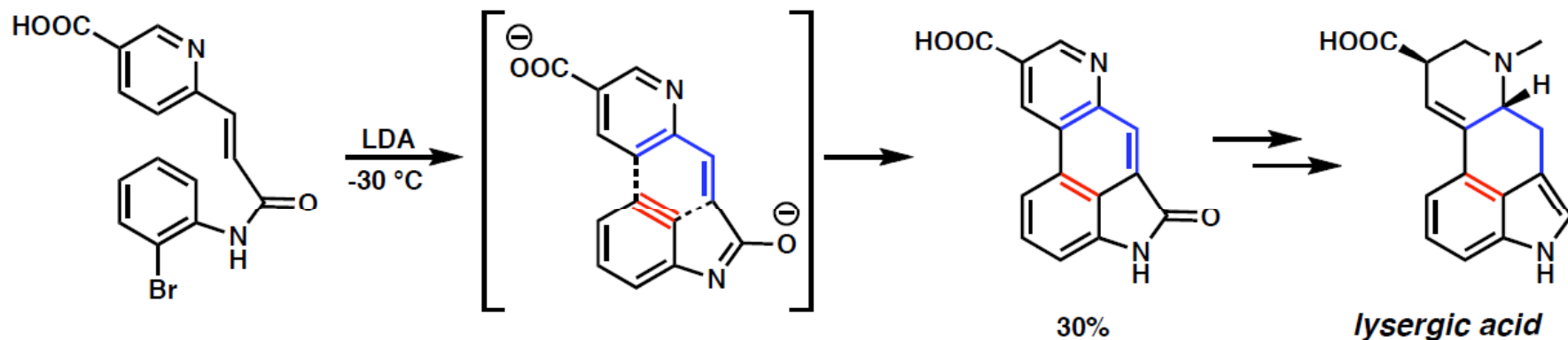


anhydrolycorinium chloride

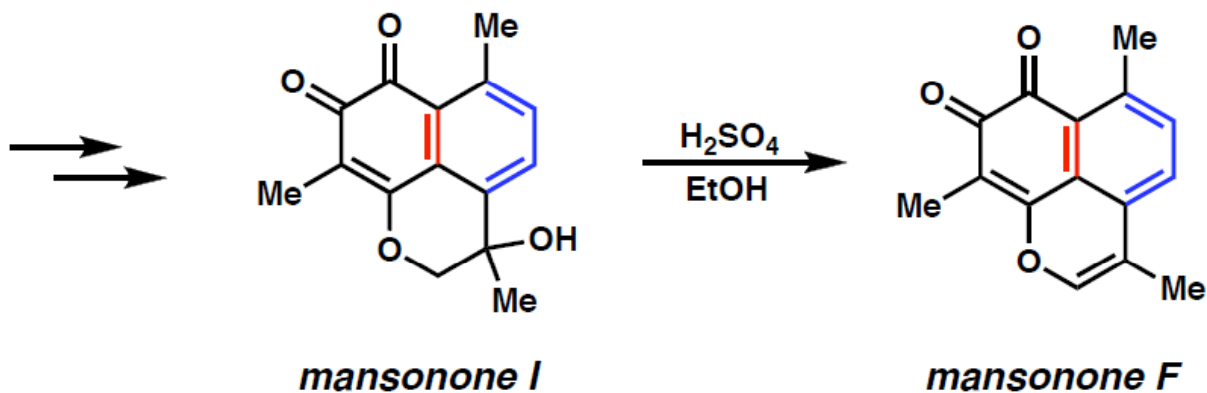
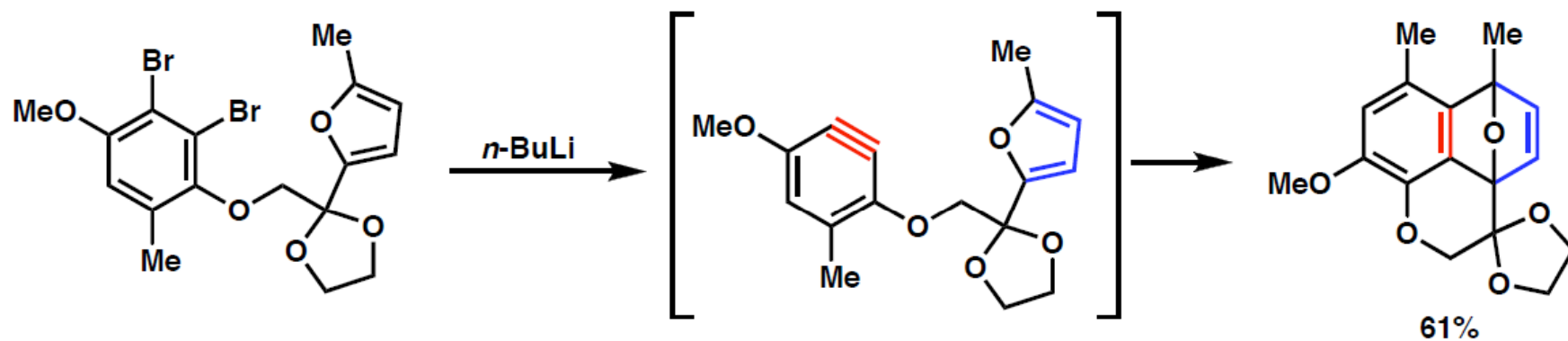


ungeremine

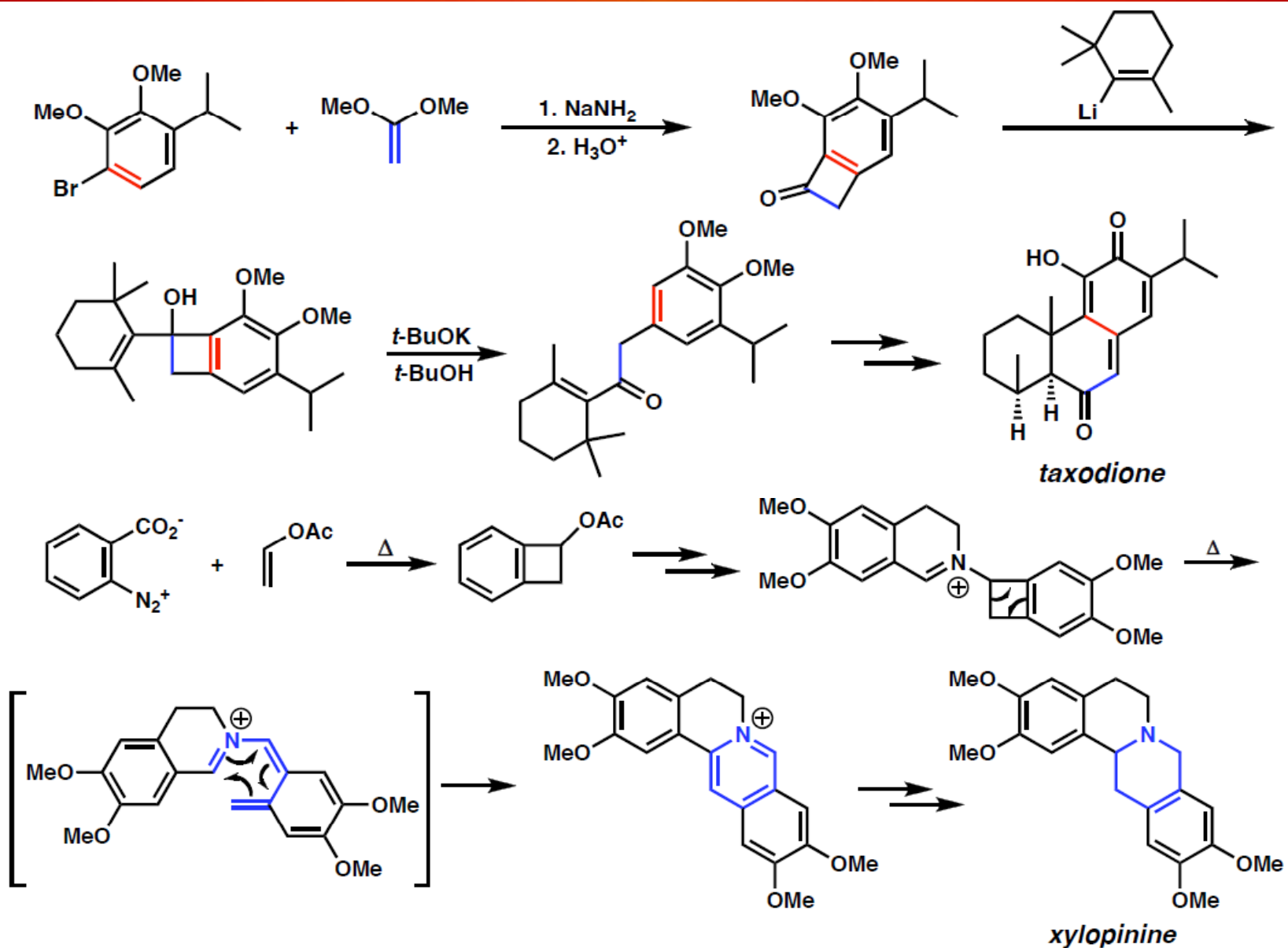
Reaction of Benzynes in Total Synthesis



Reaction of Benzyne in Total Synthesis

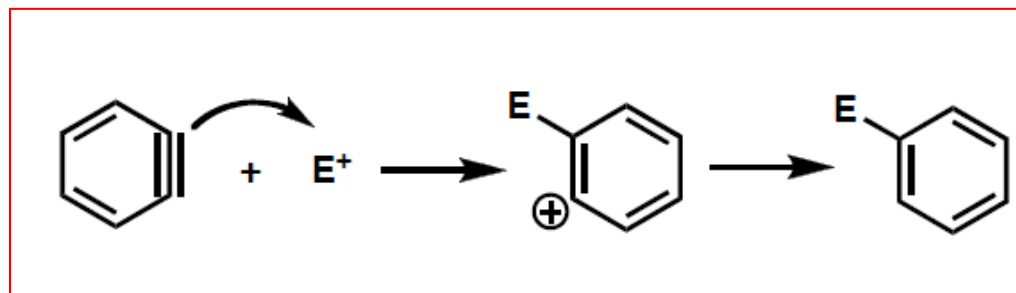
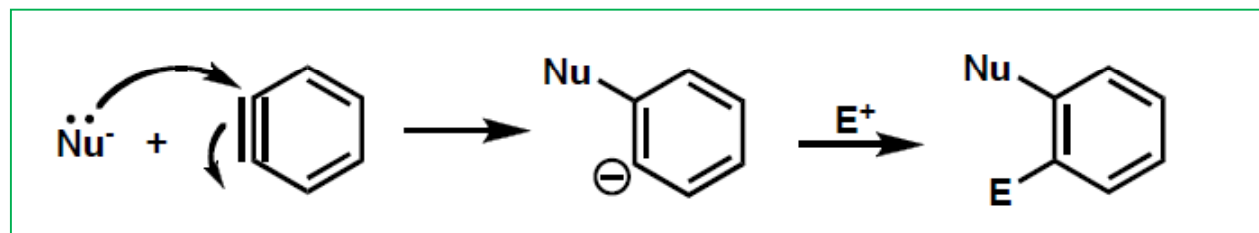
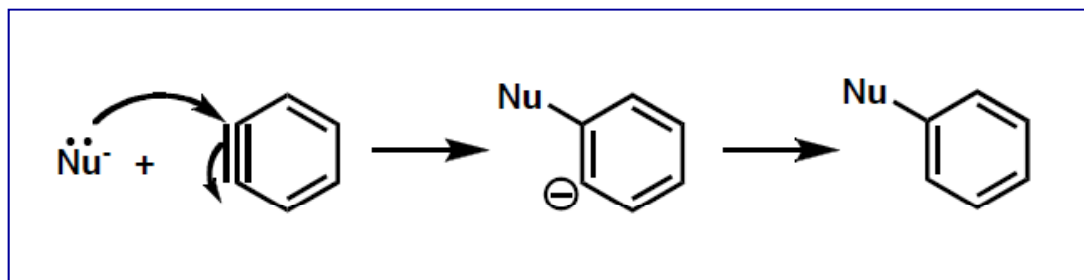


Reaction of Benzyne in Total Synthesis



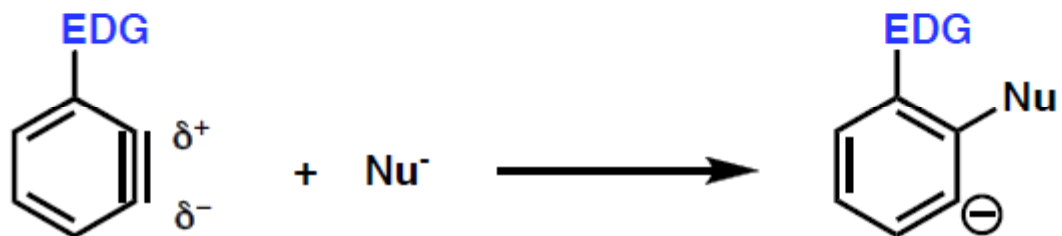
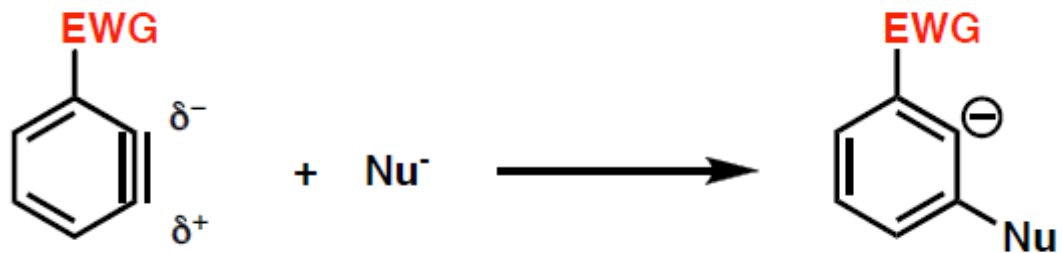
Reaction of Benzyne

Benzyne reacts both as nucleophile and electrophile



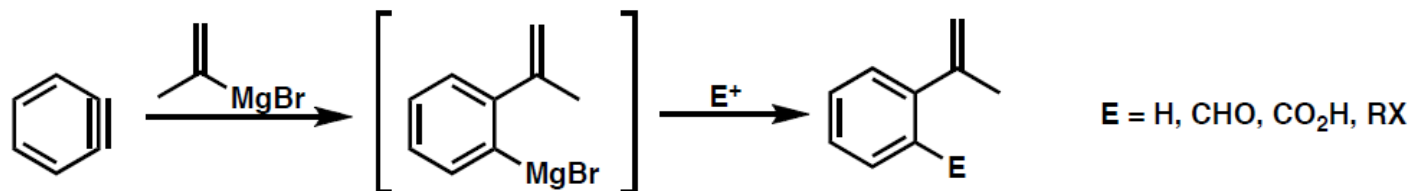
Reaction of Benzyne

Nucleophilic addition to Benzyne



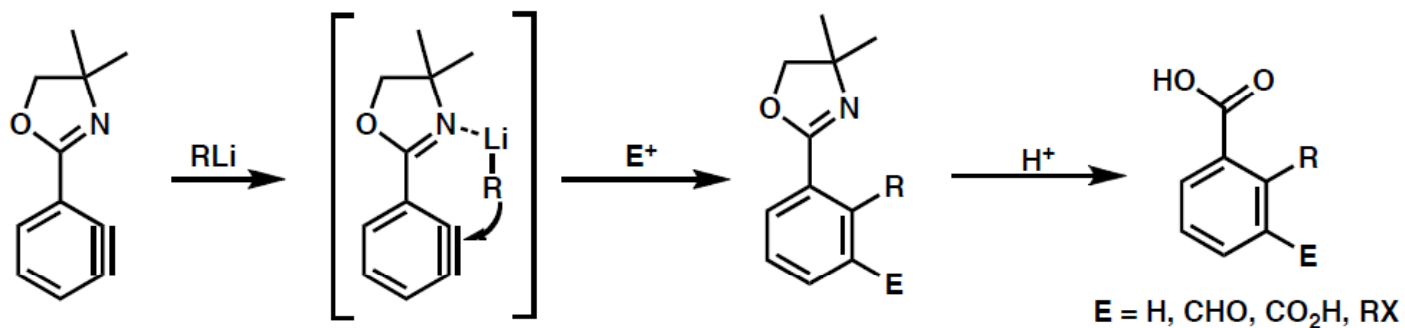
Reaction of Benzyne

Grignard reagents:

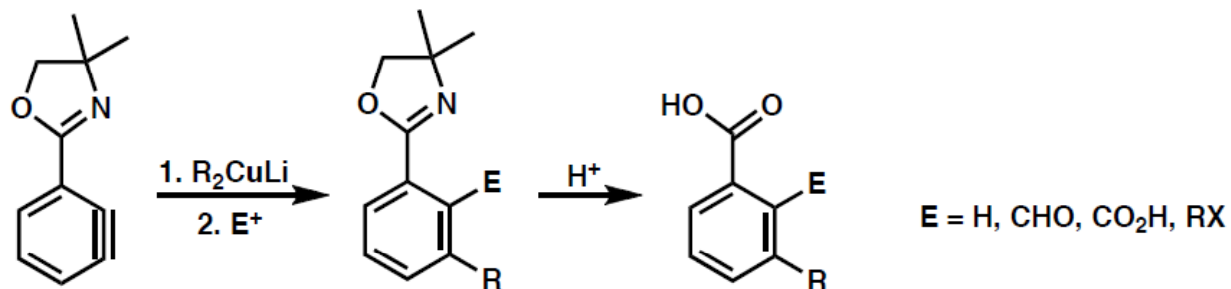


H. Hart, A. Saednya, *Synth. Commun.* 1988, 18, 749.

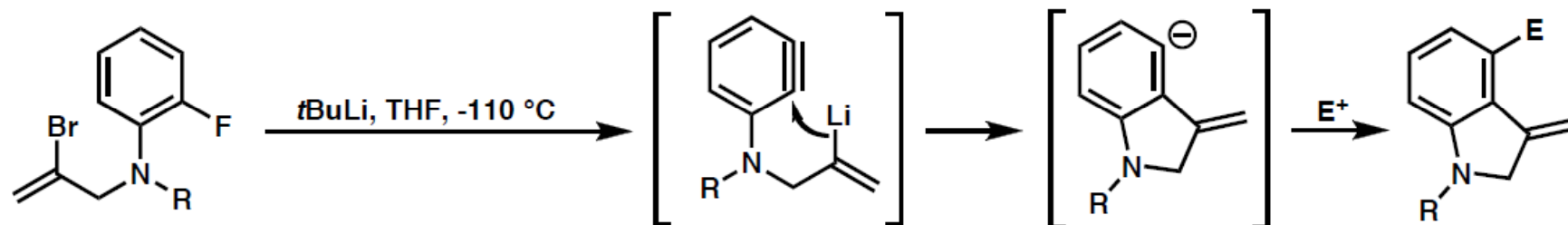
Organolithium reagents:



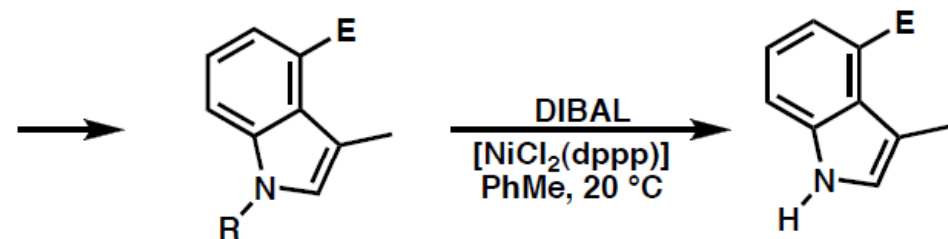
Copper-lithium reagents:



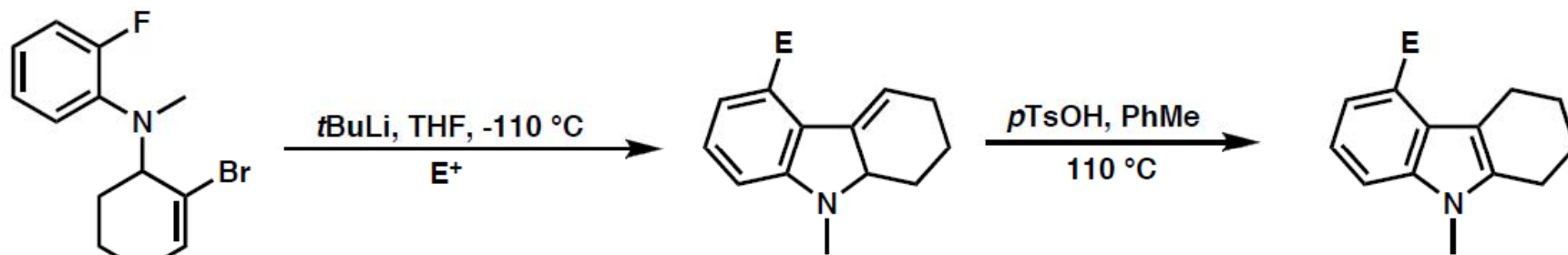
Reaction of Benzynes



R = Me, allyl

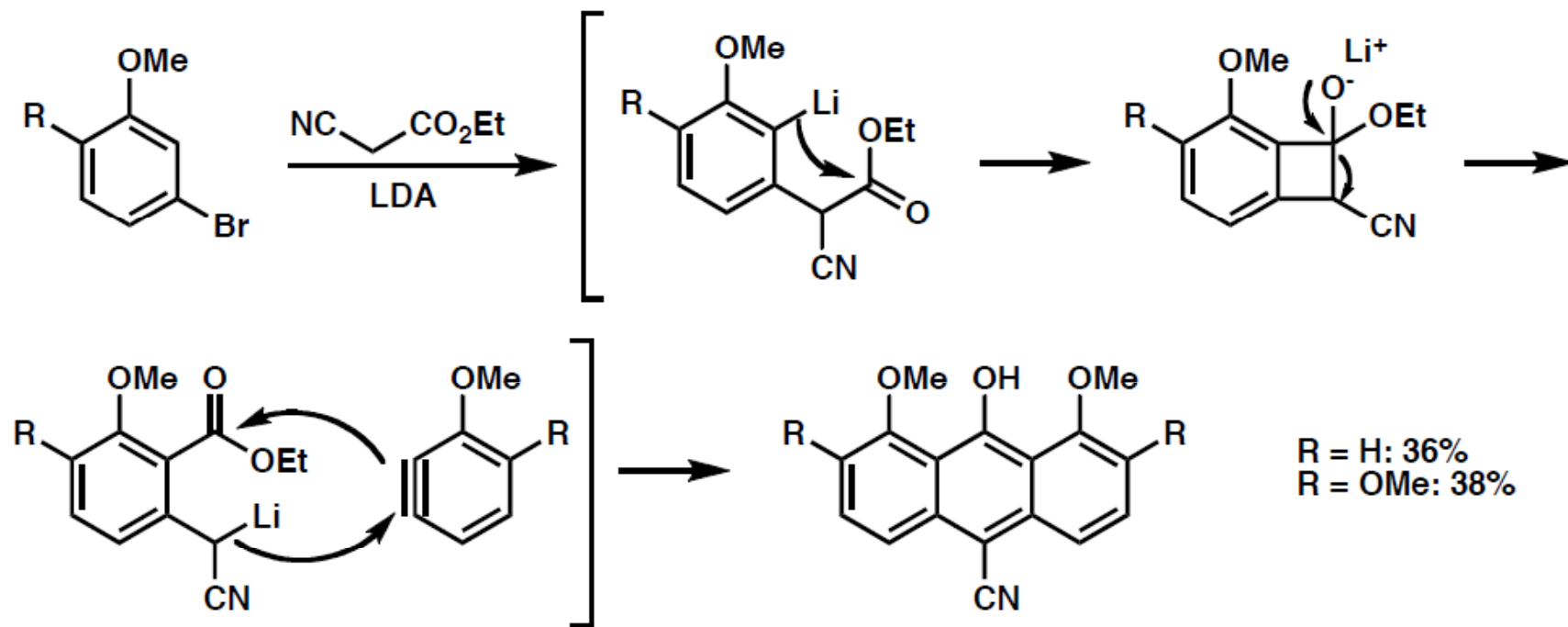


R	E^+	E	Yield
Me	H_2O	H	75%
Me	PhCHO	PhC(H)OH	69%
allyl	Bu_3SnCl	SnBu ₃	52%
Me	Bu_3SnCl	SnBu ₃	67%

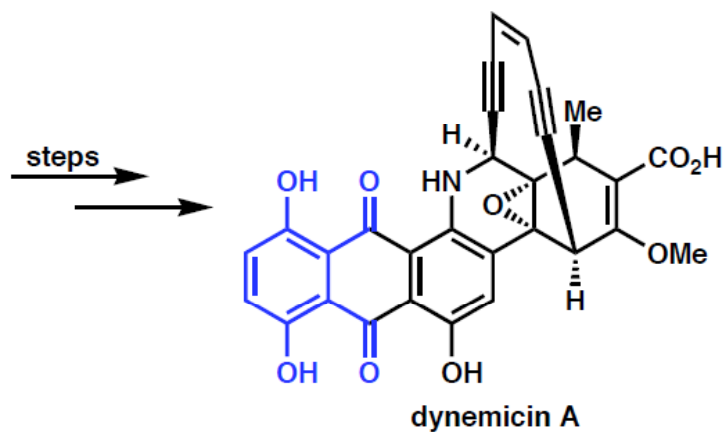
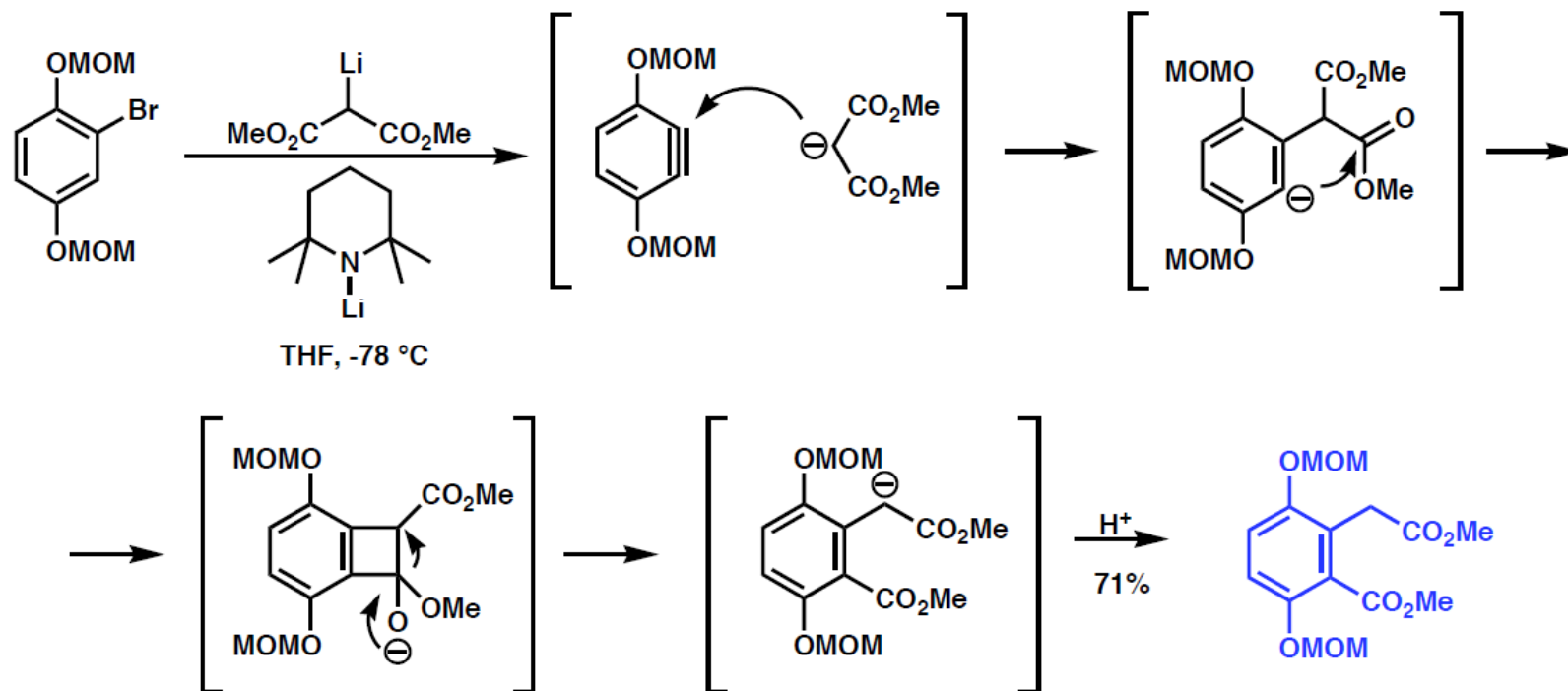


E = Br: 59%
E = CO_2Et : 65%

Reaction of Benzyne



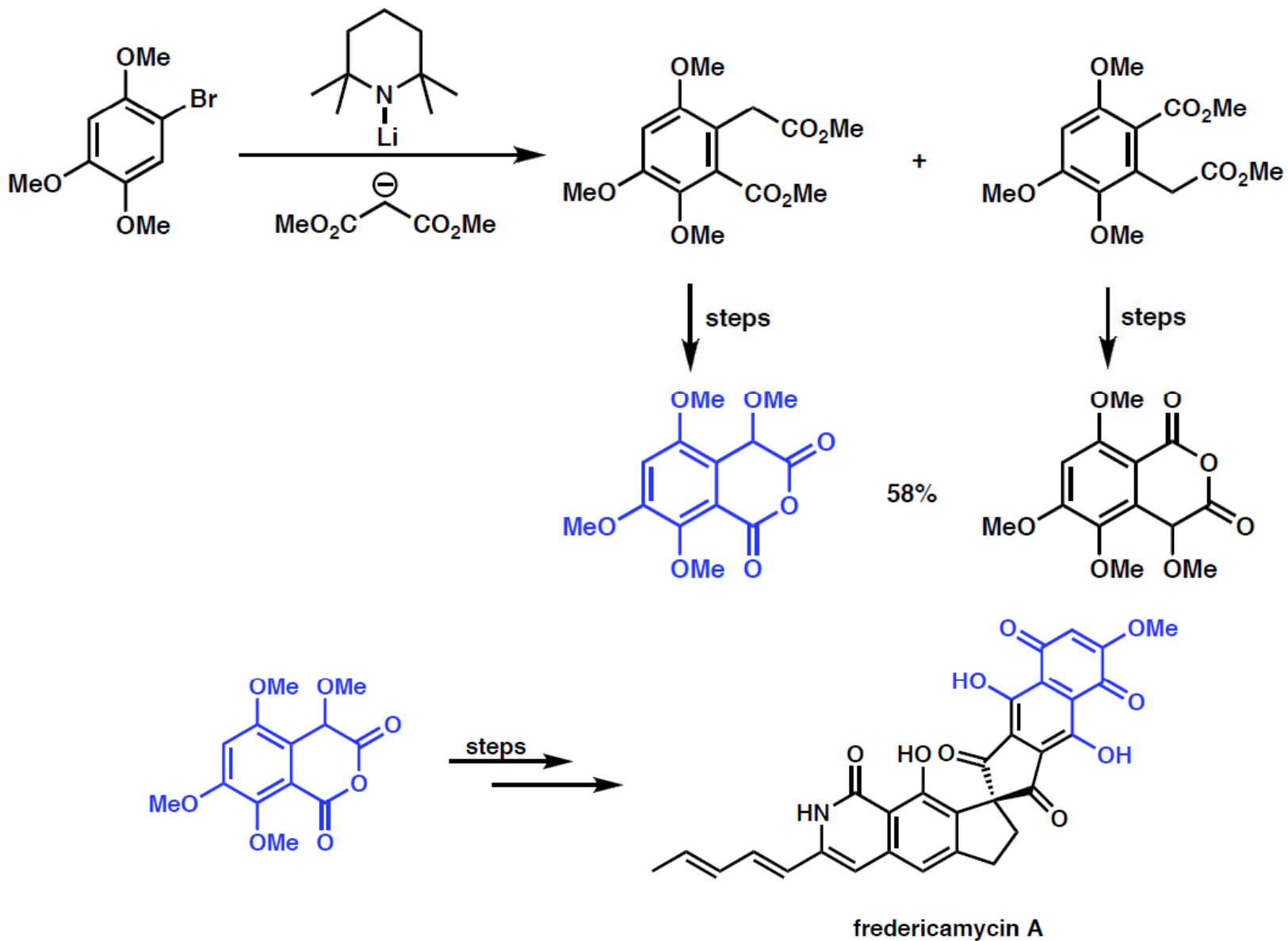
Reaction of Benzyne



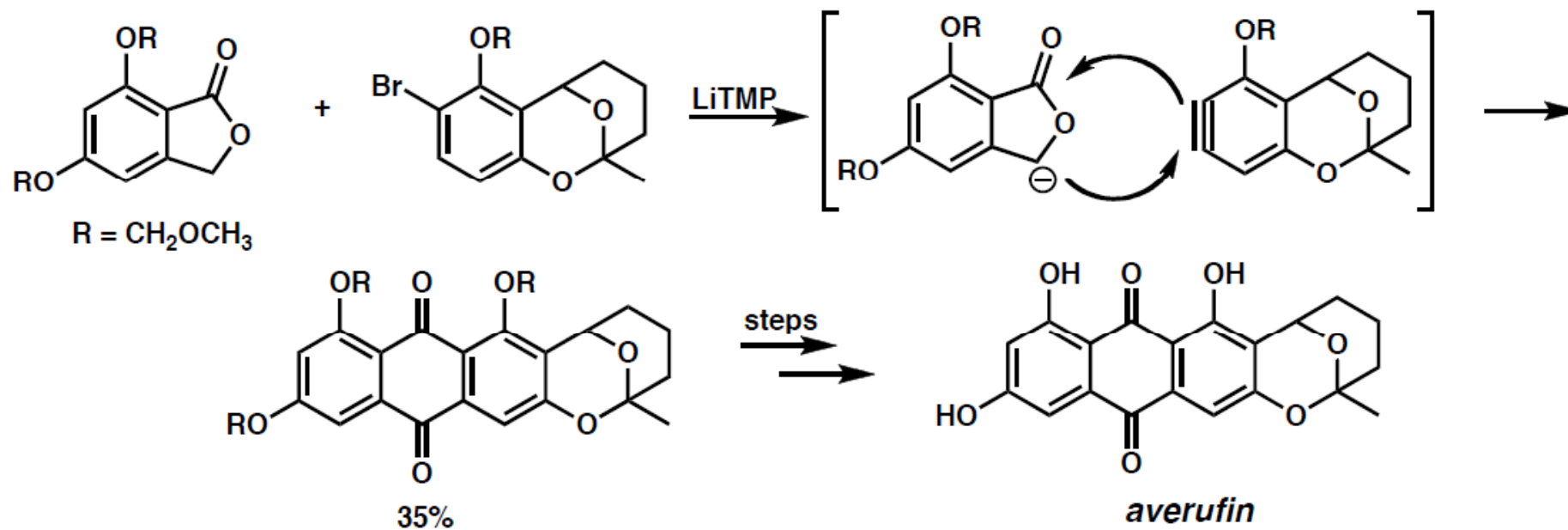
M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509.

K. C. Nicolaou, S. A. Snyder, Dynemicin A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; 75-108.

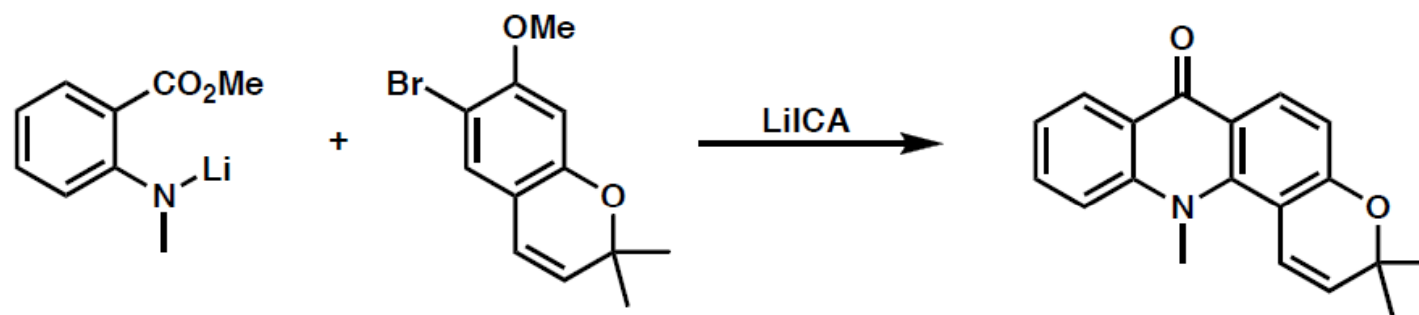
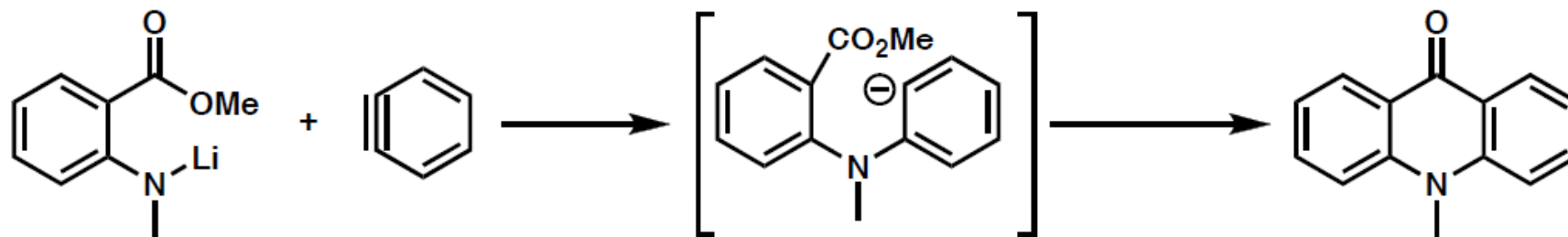
Reaction of Benzyne



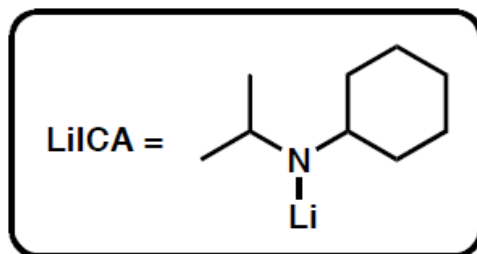
Reaction of Benzyne



Reaction of Benzyne

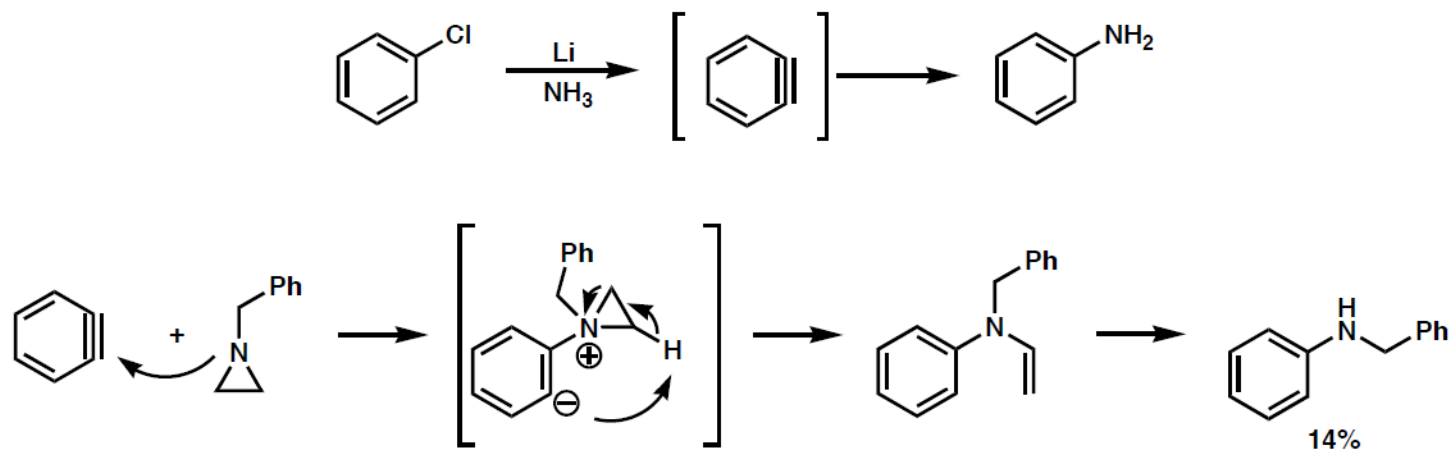


acronycine, 41%

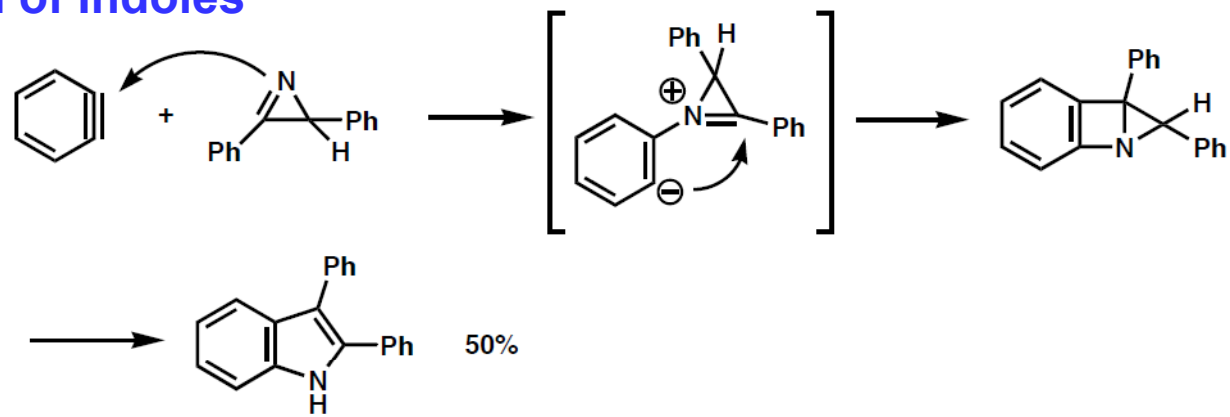


Reaction of Benzyne

Preparation of anilines

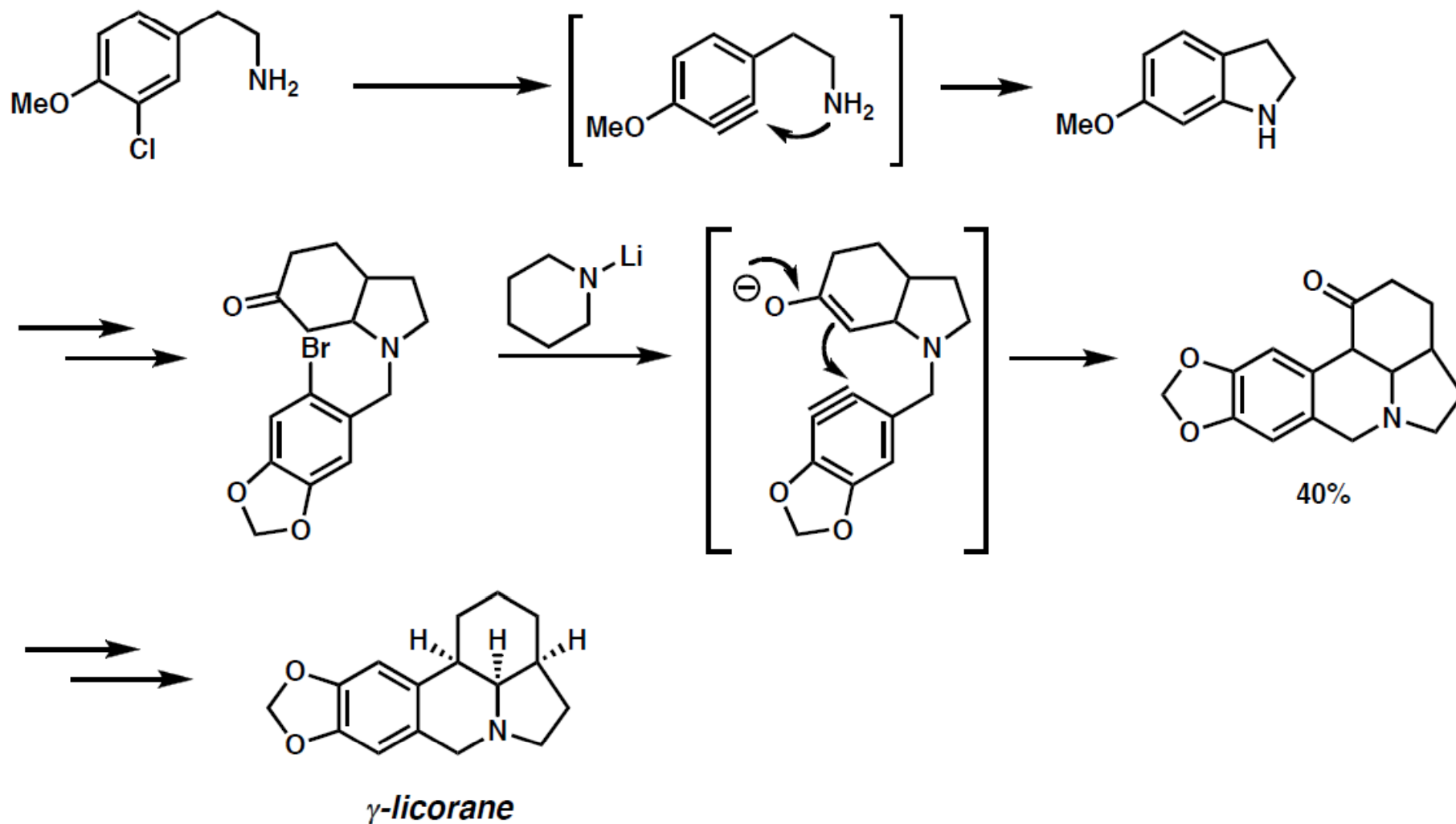


Preparation of Indoles

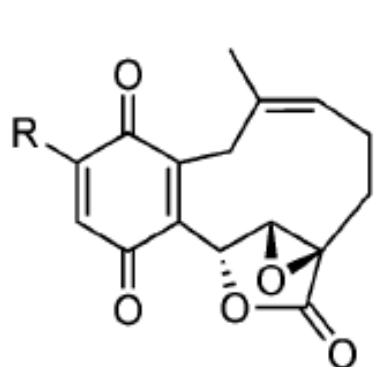


Reaction of Benzyne

Two Benzyne cyclization reactions complete the skeleton



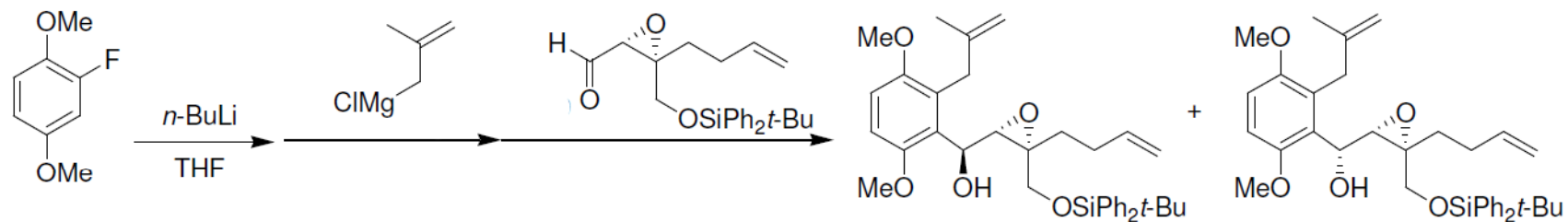
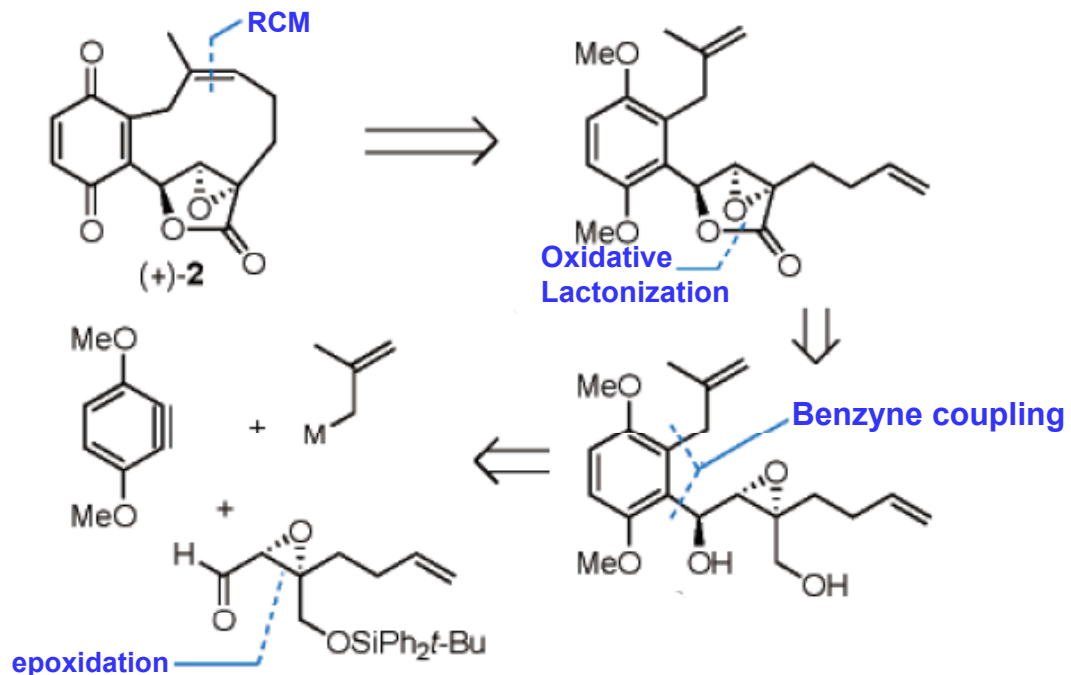
Reaction of Benzyne



ent-Clavilactone B

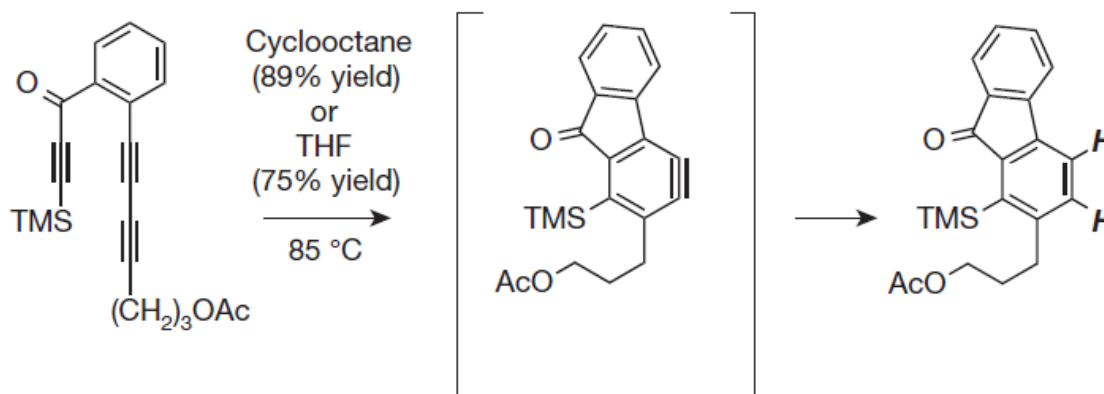
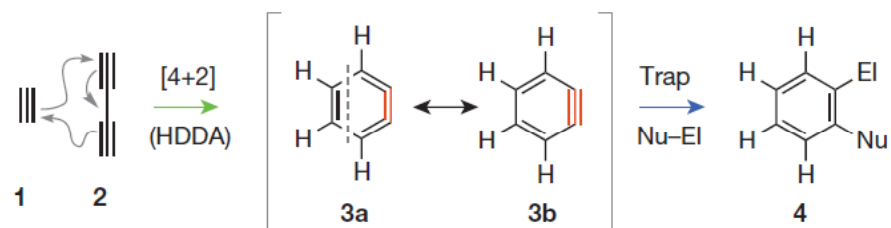
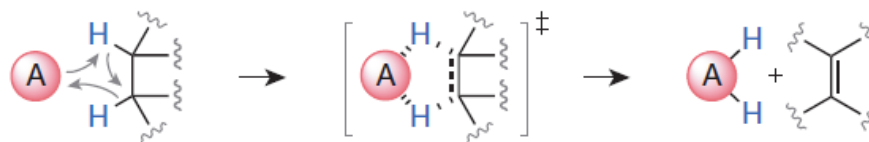
antifungal, antibacterial

J. Am. Chem. Soc. 2006, 128, 14042.

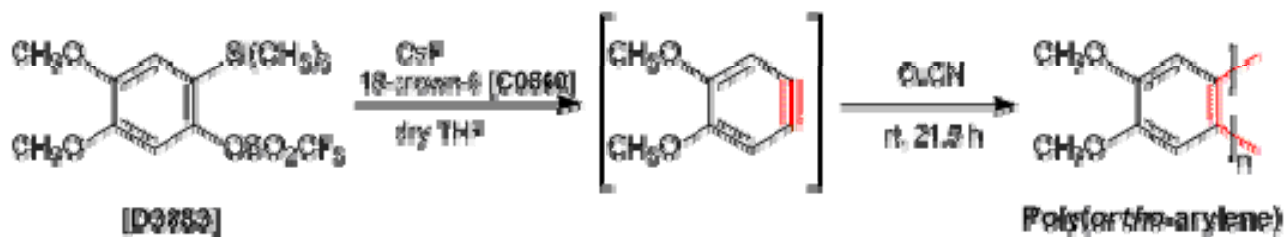
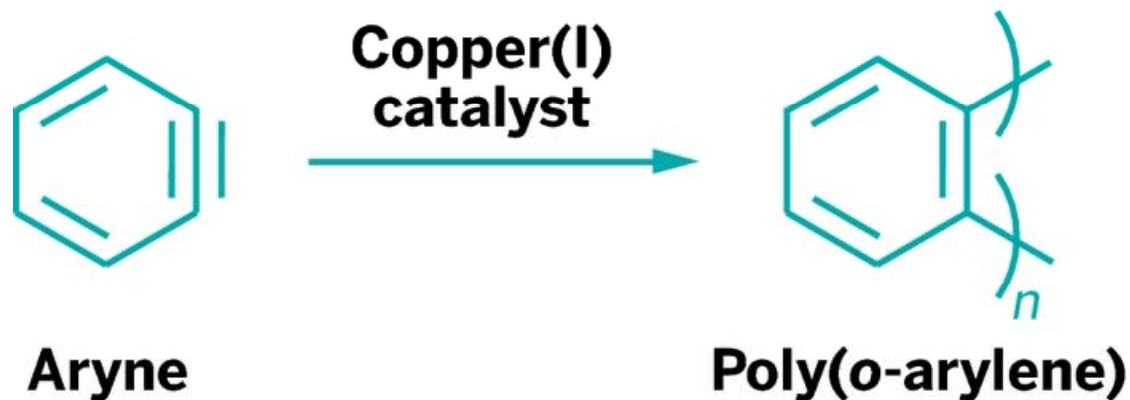


Reaction of Benzyne

The removal of two vicinal hydrogen atoms from an alkane to produce an alkene is a challenge for synthetic chemists



Reaction of Benzyne



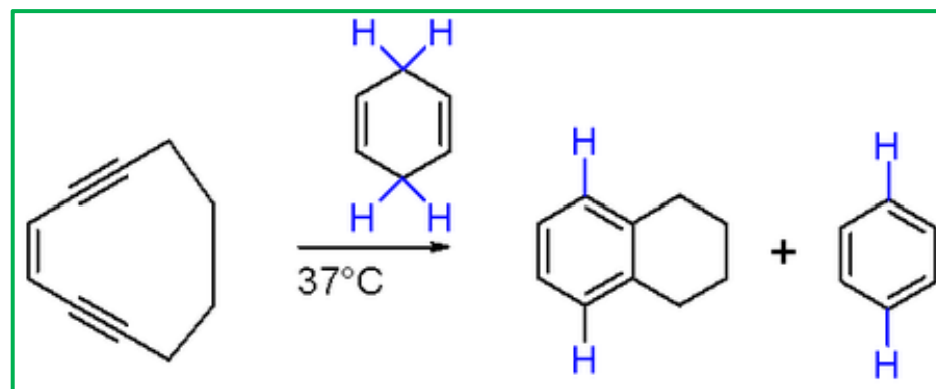
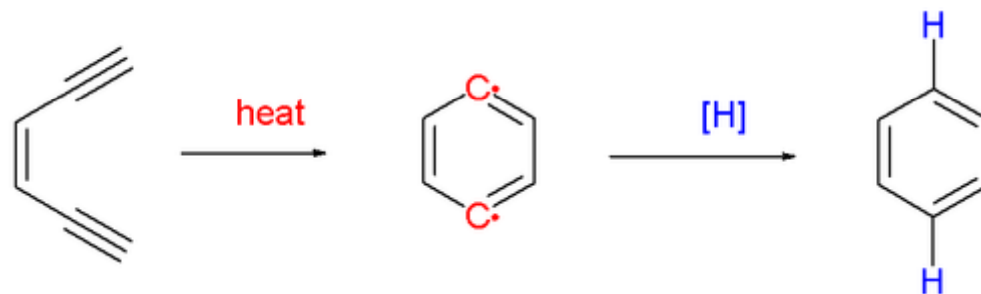
Bergman Cyclization



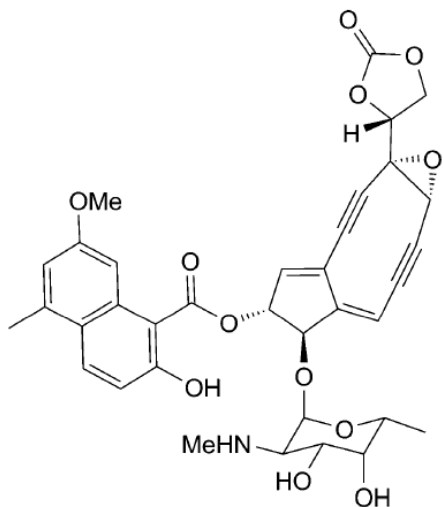
Robert G. Bergman

Bergman Cyclization

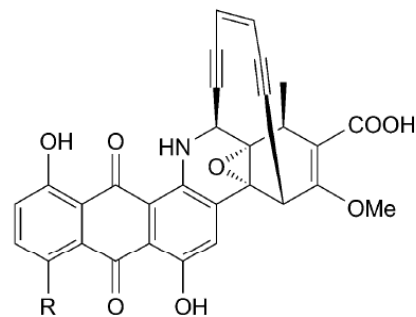
A rearrangement reaction taking place when an enediyne is heated in presence of a suitable hydrogen donor.



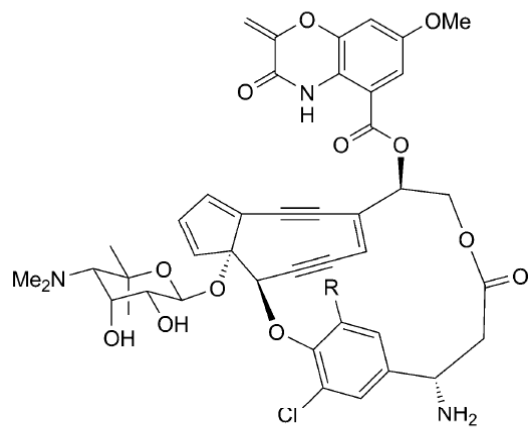
Natural Products Containing Ene-diynes



Neocarzinostatin (**6**)

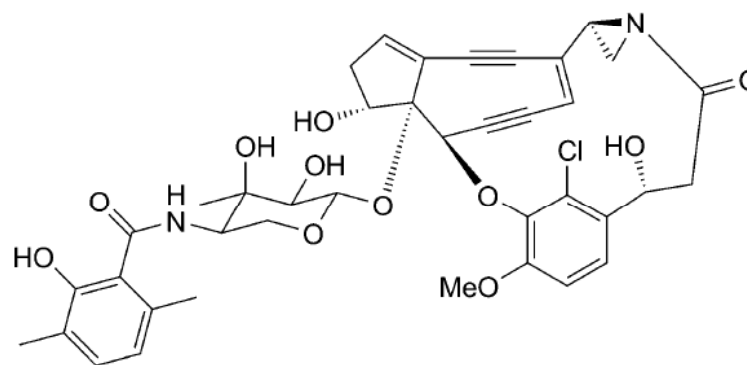


Dynemicin A (**4**) R = OH
Deoxydynemicin A (**5**) R = H



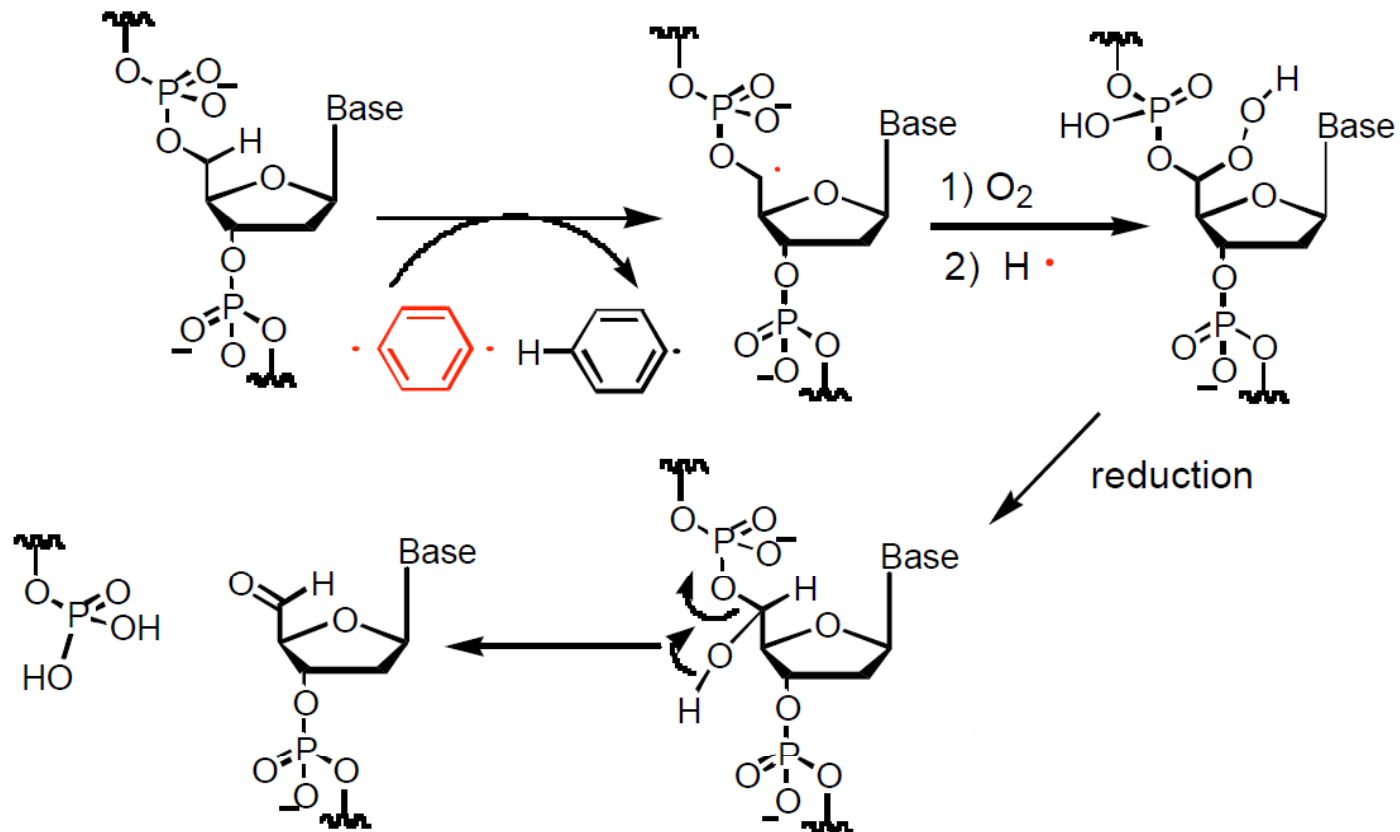
C-1027 Chromophores

8 R = H
9 R = OH



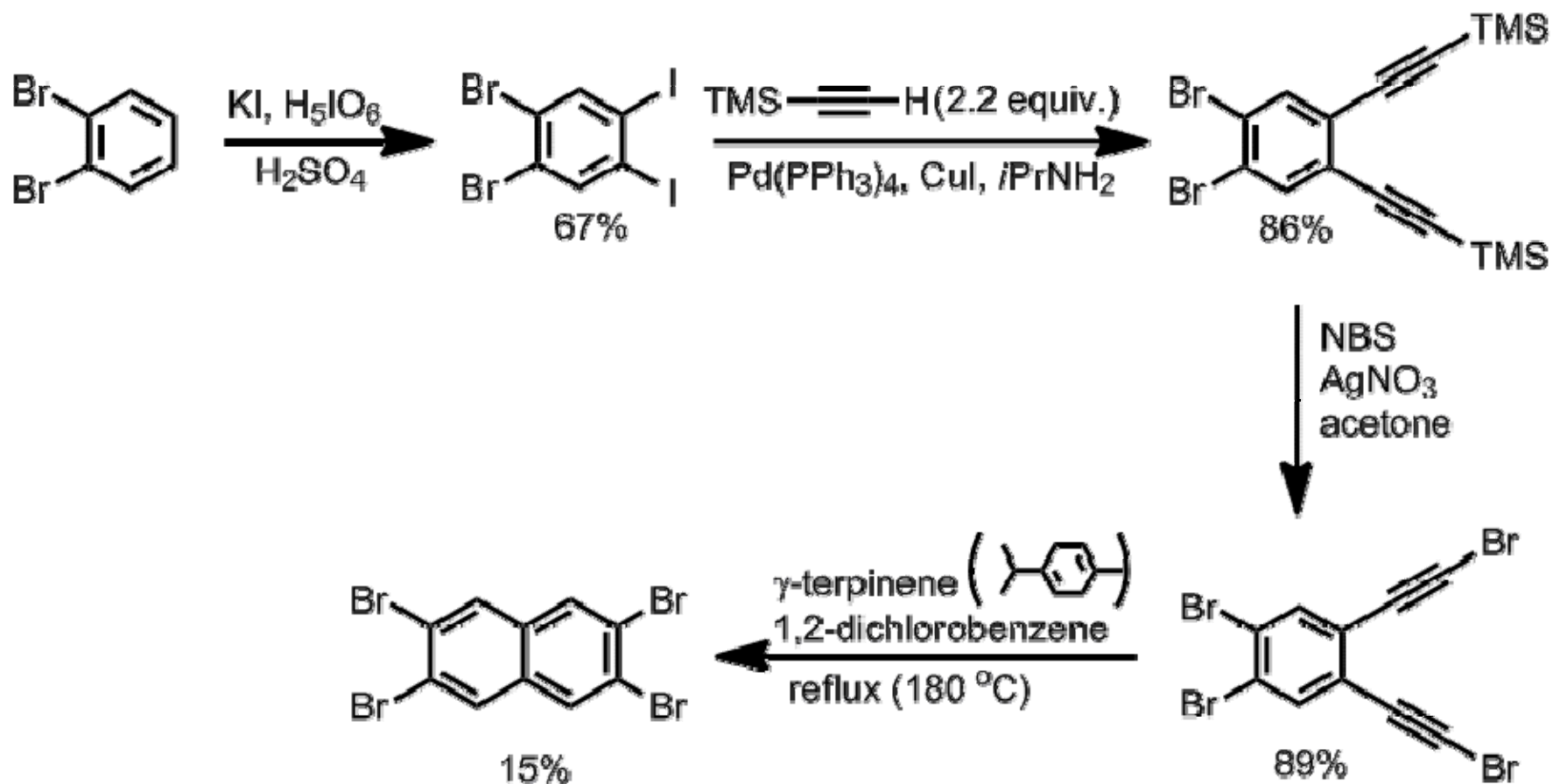
Maduropeptin (**12**)

Natural Products Containing Ene-diynes

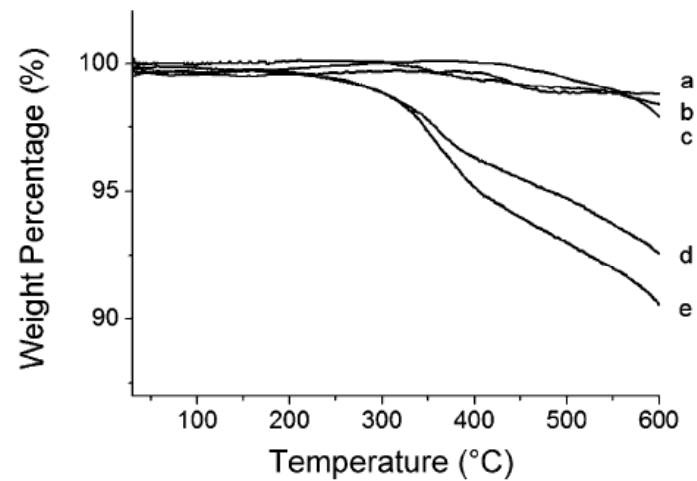
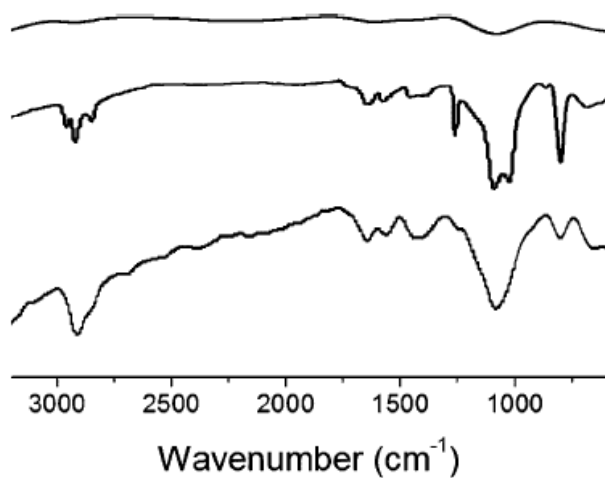
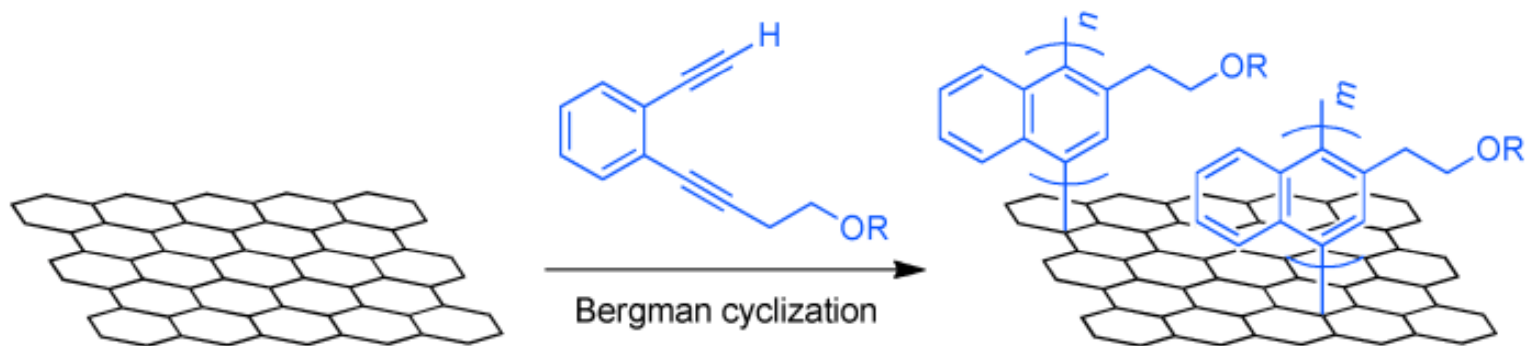


Bergman Cyclization is the reaction nature uses to generate lethal fragments to DNA

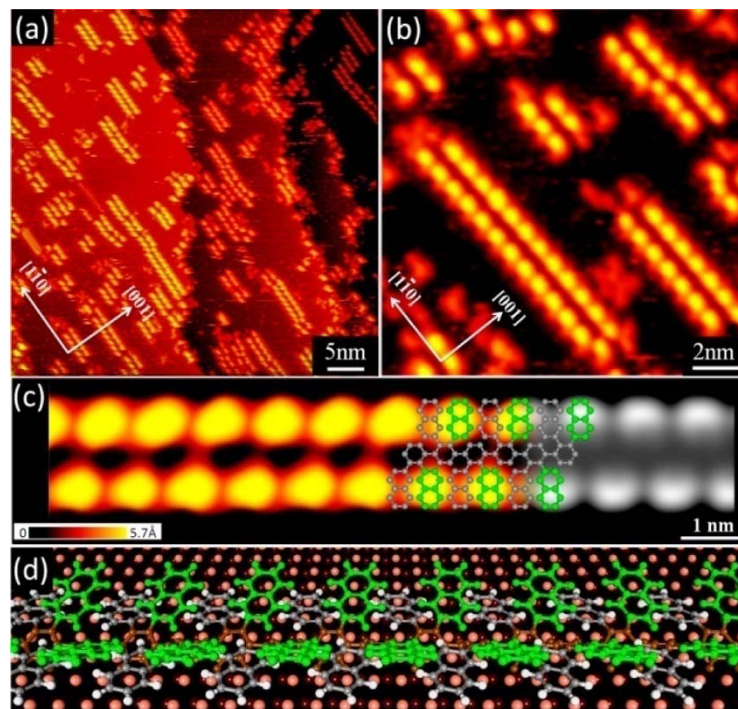
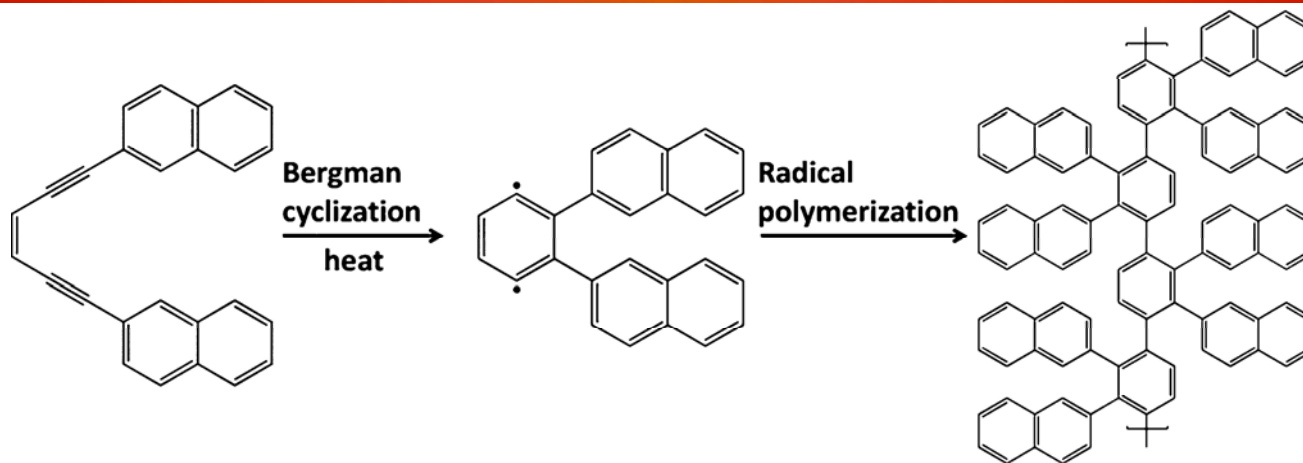
Reactivity of Ene-diynes



Reactivity of Ene-diynes



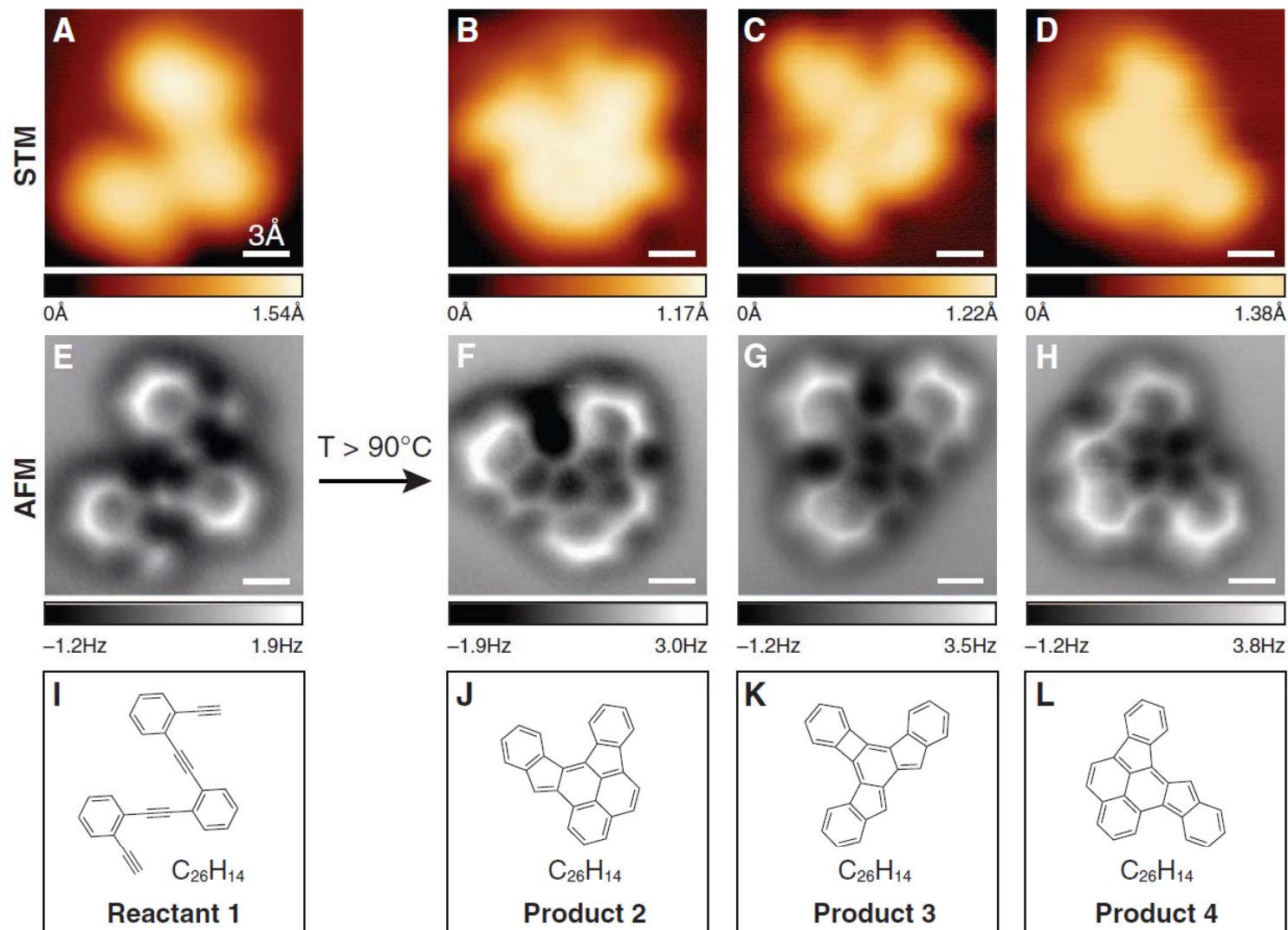
Enediynes for Surface Science



J. Am. Chem. Soc., 2013, 135, 8448.

Ene-diynes for Surface Science

Direct Imaging Covalent Bond in Single-Molecule Chemical Reactions



Science, 2013, 340, 1434.