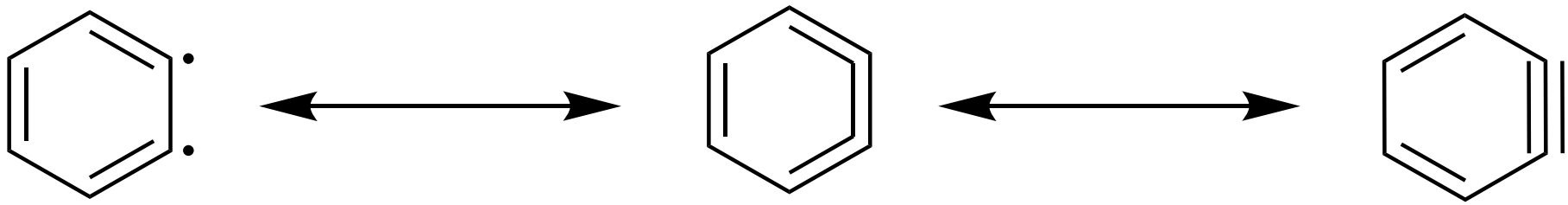


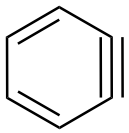
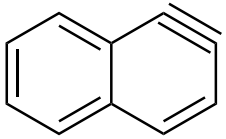
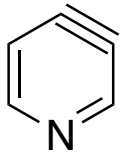
Arynes: History, Reactivity, and Total Syntheses

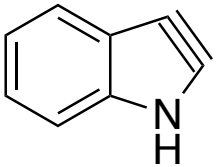
Travis Menard

Group Meeting

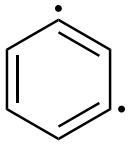
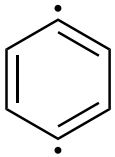
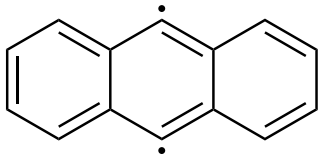
08/13/19

What is an Aryne?

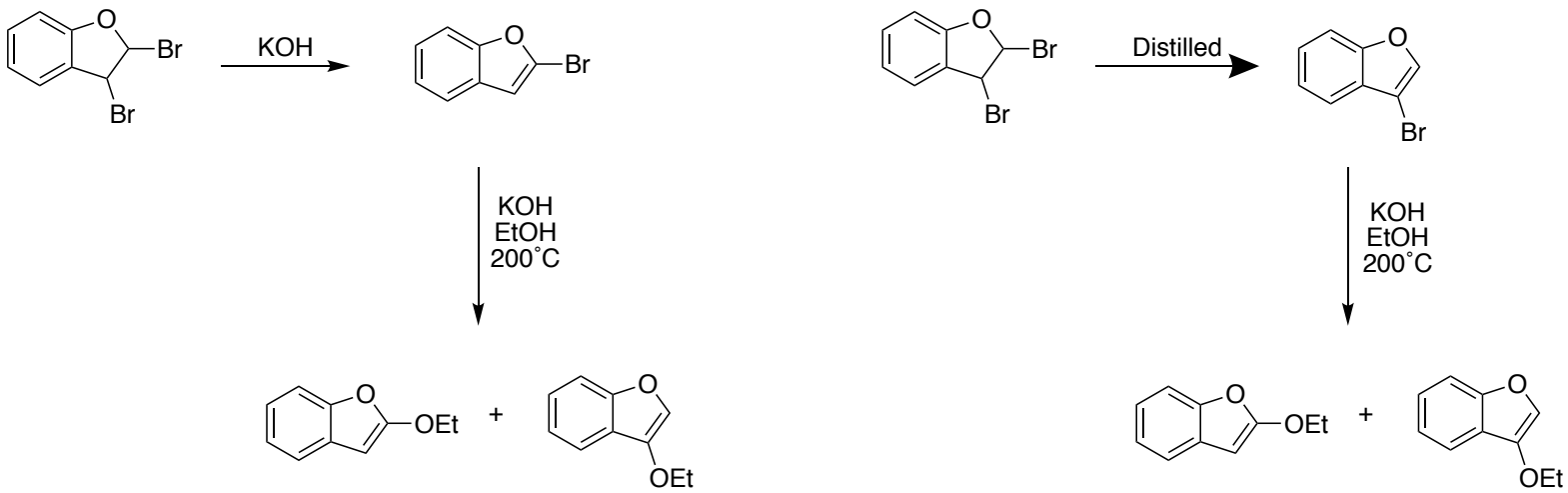




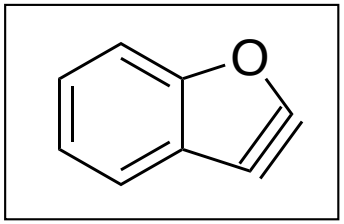


Formally, arynes are any aromatic ring that has undergone the abstraction of at least two hydrogen atoms

First Proposal of Aryne Intermediate (Stoermer and Kahlert, 1902)

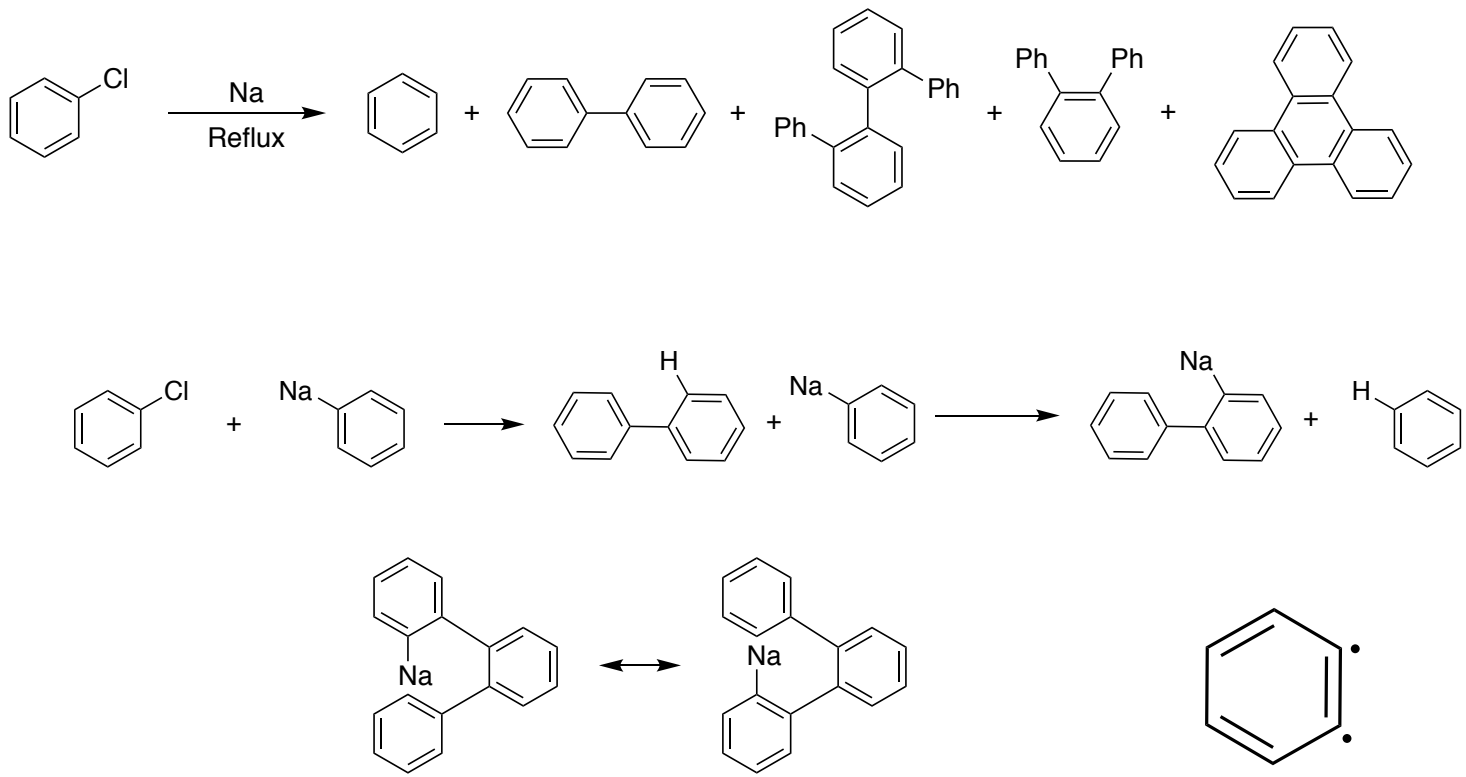




"Perhaps the always observed, strange, somewhat coughing smell of the reaction mixture to be found in the opening of the autoclave is the remains of little remnants of it"

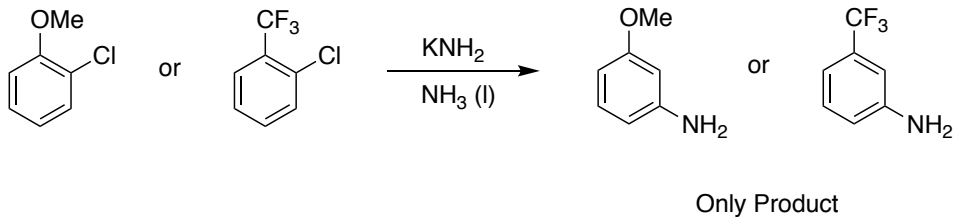
Stoermer, R. and Kahlert, B. (1902), Ueber das 1- und 2-Brom-cumaron. Ber. Dtsch. Chem. Ges., 35: 1633-1640.

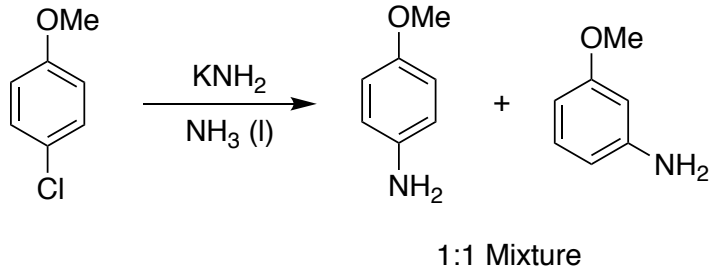
First Proposed Benzyne Intermediate (Bachman and Clarke, 1927)

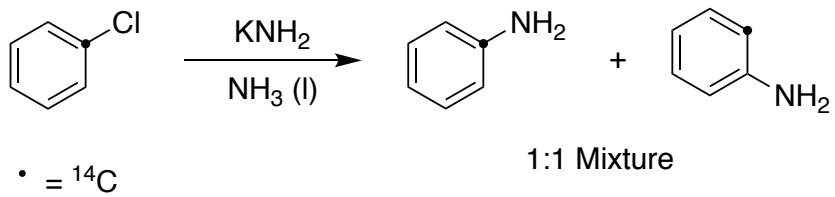


J. Am. Chem. Soc.1927, 49, 8, 2089-2098

Robert's Experiments (1953)



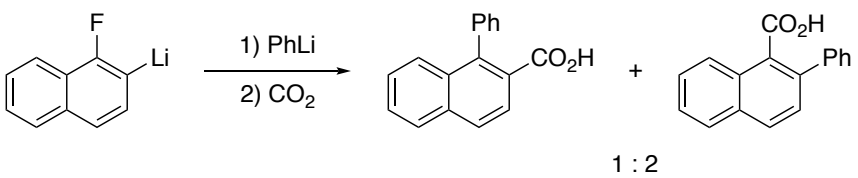


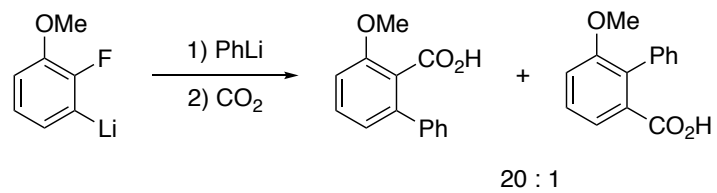


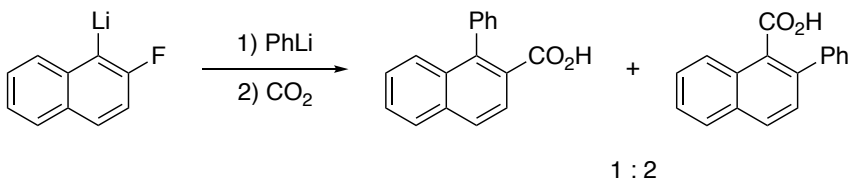
"While this experiment is not considered to "prove" the "benzyne" mechanism, it strongly indicates formation of an intermediate in which the 1- and 2-positions of the ring are, or can become, equivalent."

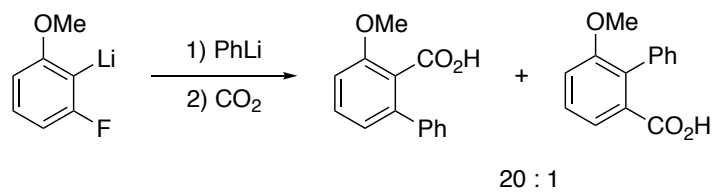
J. Am. Chem. Soc. 1953, 75, 13, 3290-3291

Huisgen's Experiments (1954)



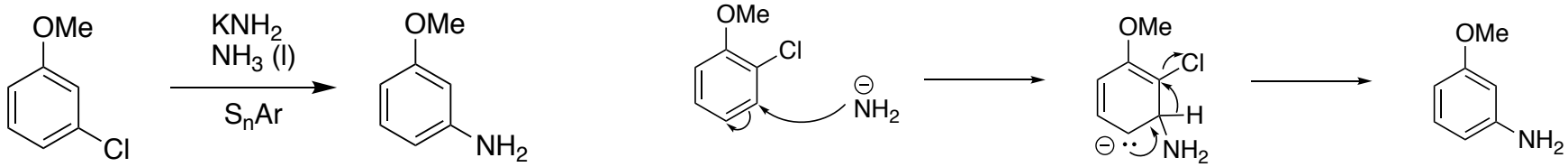


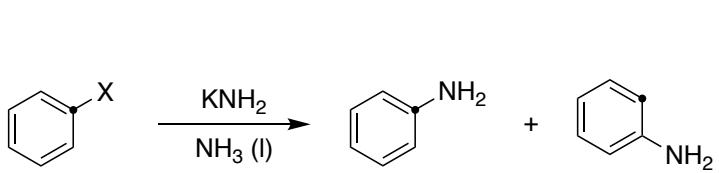




Huisgen, R. & Rist, H. Naturwissenschaften (1954) 41: 358.

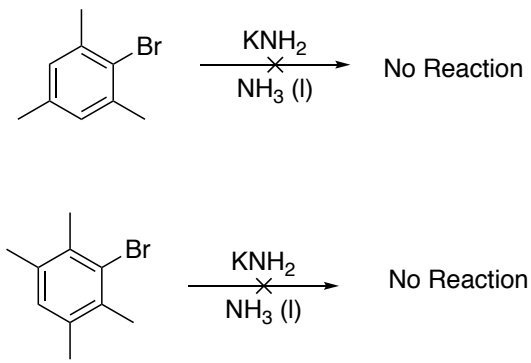
Robert's Experiments (1955)





• = ^{14}C

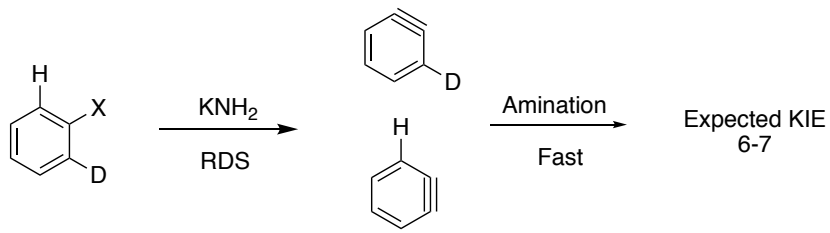
X = Cl, I



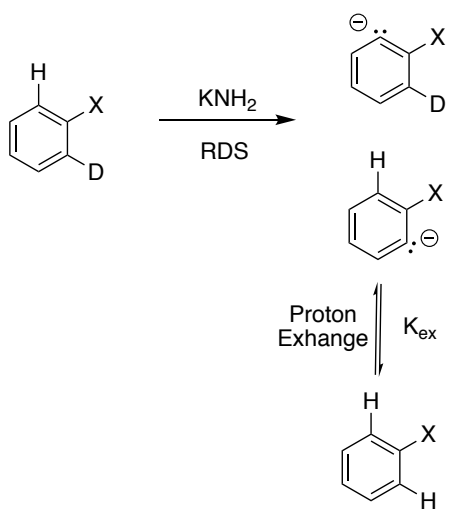
J. Am. Chem. Soc.1956783601-611

Robert's Experiments (1955)

(1)



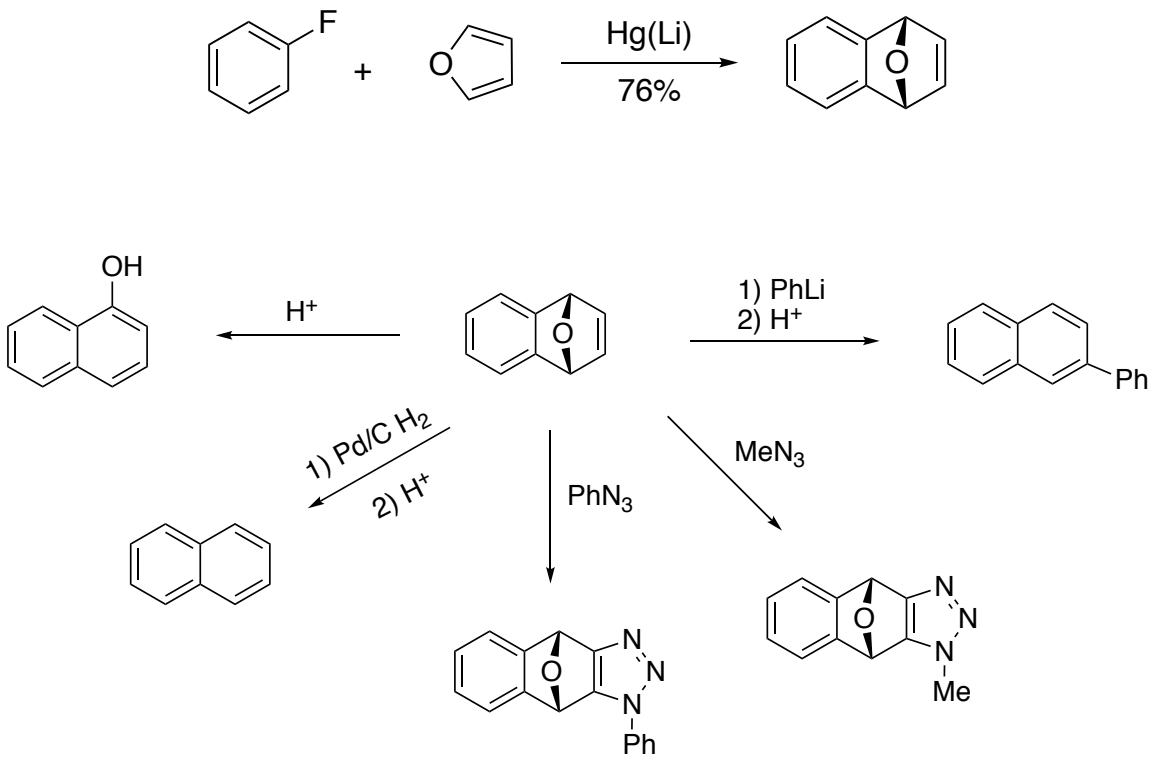
(2)



- F – Only non-deuterated starting material isolated
- Cl – KIE = ~2.5 Significant stepwise character indicated
- Br – KIE = ~6 Concerted mechanism operative

J. Am. Chem. Soc.1956783601-611

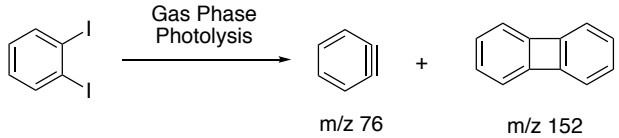
Wittig's Experiments



Georg Wittig und Liselottte Pohmer: Uber das intermediare Auftreten von Dehydrobenzol Eingegangen am 22 Februar 1956

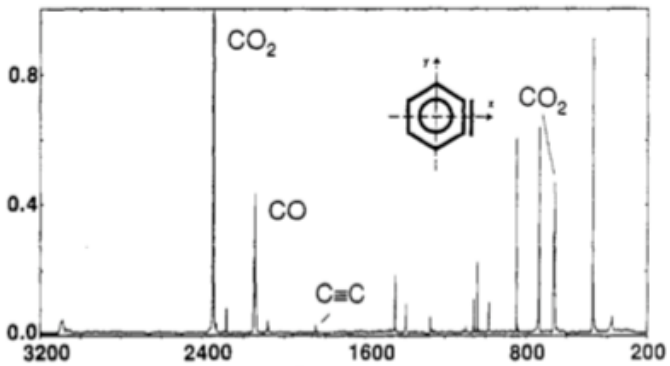
Characterization Milestones

Fisher and Lossin (1963) - Mass Spectrometry



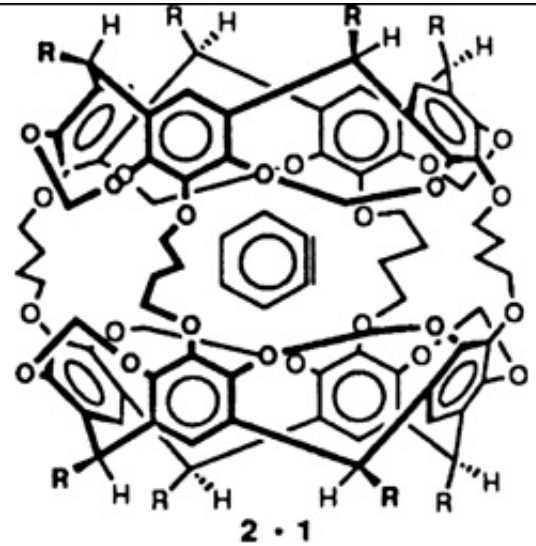
J. Am. Chem. Soc.19638571018-1019

Radziszewski (1990) - IR stretch in Ar Matirx at 8K



J. Am. Chem. Soc.1992114152-57

Warmuth (1997) - ^{1}H and ^{13}C solution NMR in a molecular cage



Angew. Chem. 1997, 109, Nr. 12

Berry, Spokes, and Stilles (1964) - Gas Phase UV

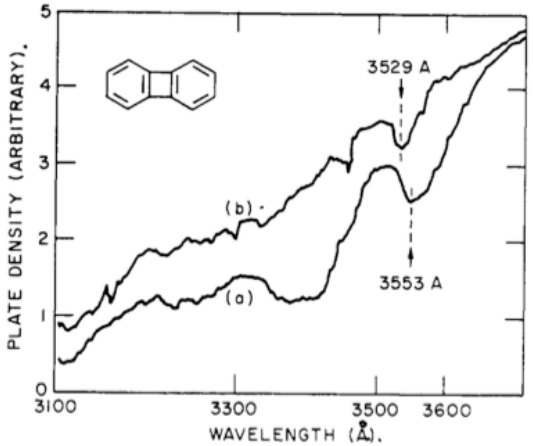
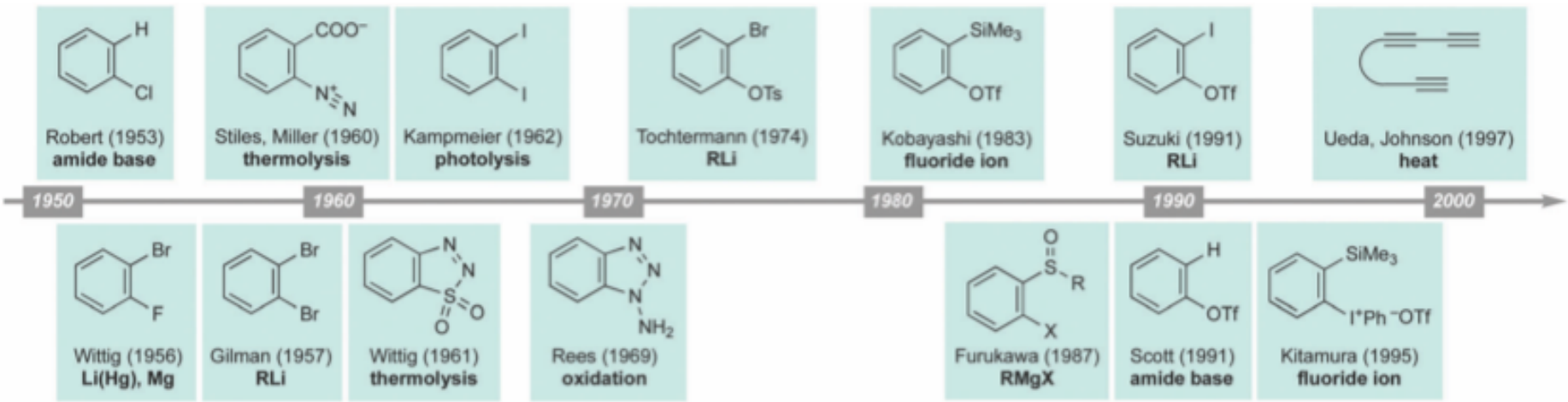


Fig. 2.—Microdensitometer tracings showing shift of long wave length bands of biphenylene with time: (A) 1 millisecond after photolysis of 20 micromoles of benzenediazonium-2-carboxylate; (B) same sample ~2 minutes after photolysis.

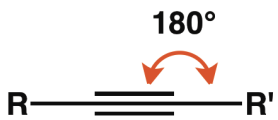
J. Am. Chem. Soc.196284183570-3577

Generation of Arynes

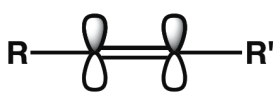


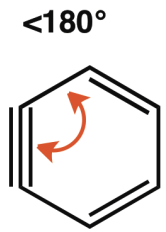
Chem. Soc. Rev., 2018, 47, 8030--8056

General Reactivity

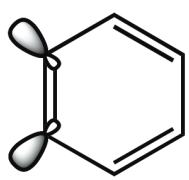


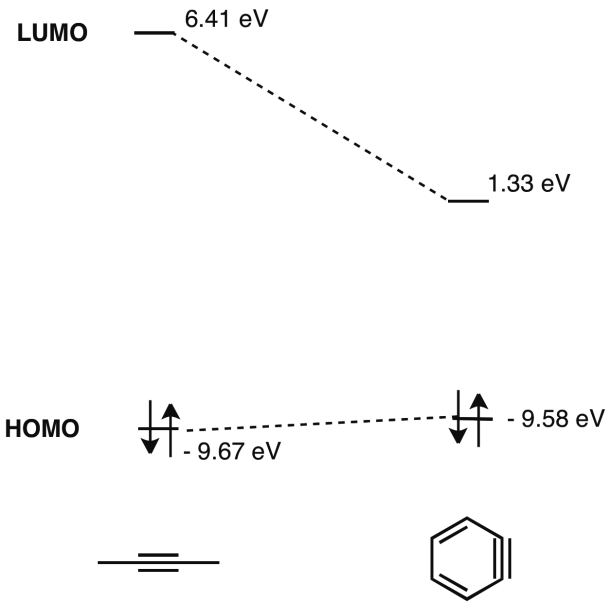
Unstrained alkyne





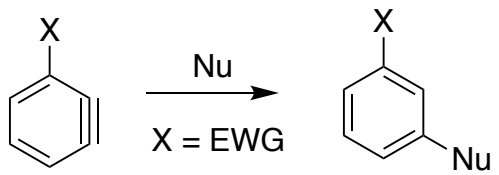
Benzyne



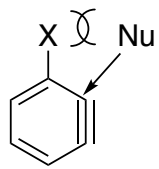


https://commons.wikimedia.org/wiki/File:Homo-lumo_gap.tif https://commons.wikimedia.org/wiki/File:Geometric_constraint2.tif

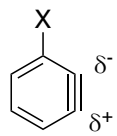
Selectivity of Nucleophilic Attack



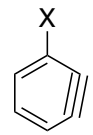
X =	F	Cl	Br	I	OMe
(m vs o)	(only m)	(>20:1)	(13:1)	(9:1)	(only m)



Steric Model



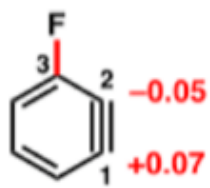
Charge-Controlled Model

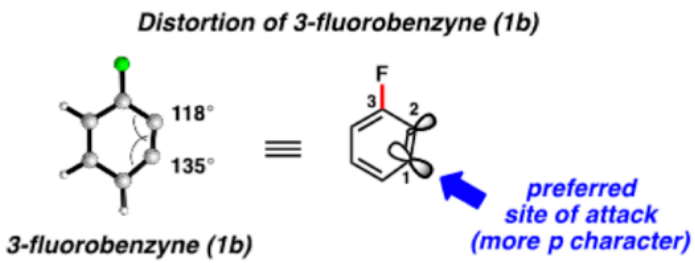


Aryne Distortion Model

F >>> I

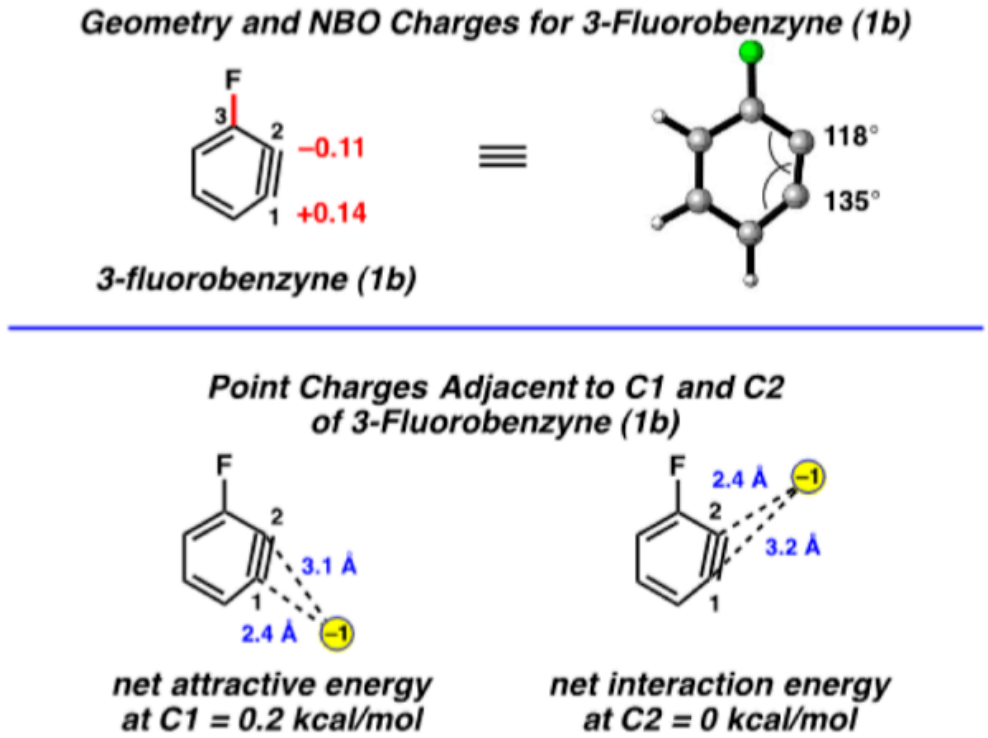
A_F <<< A_I

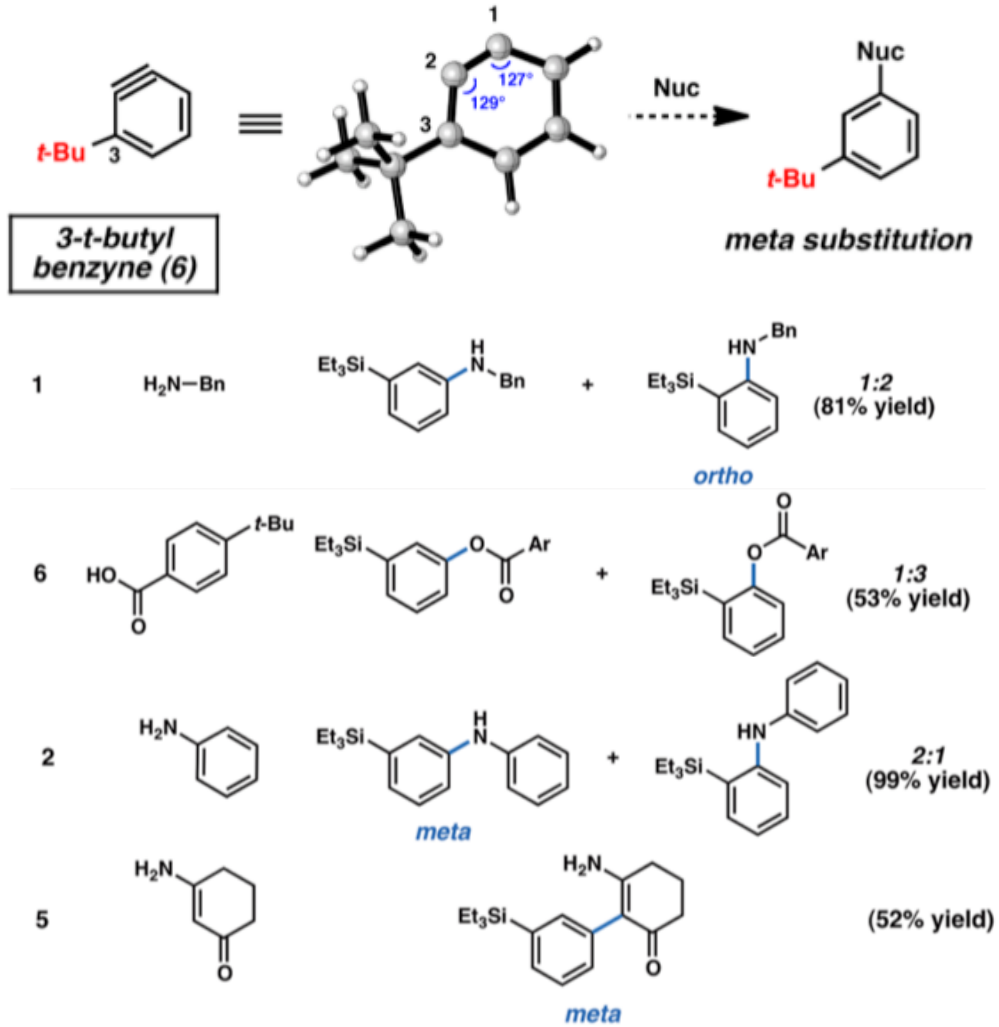




J. Am. Chem. Soc.20141364415798-15805

Charge Controlled vs. Aryne Distortion

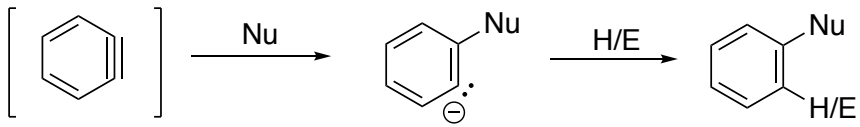




J. Am. Chem. Soc.20141364415798-15805

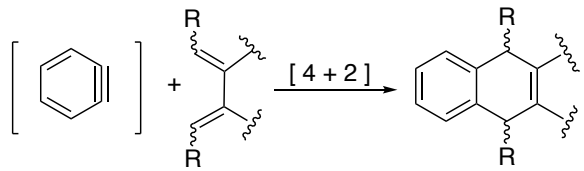
Main Modes of Reactivity

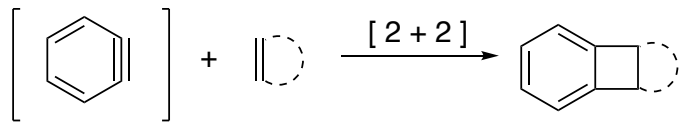
Nucleophilic Additions and Multi-component Reactions

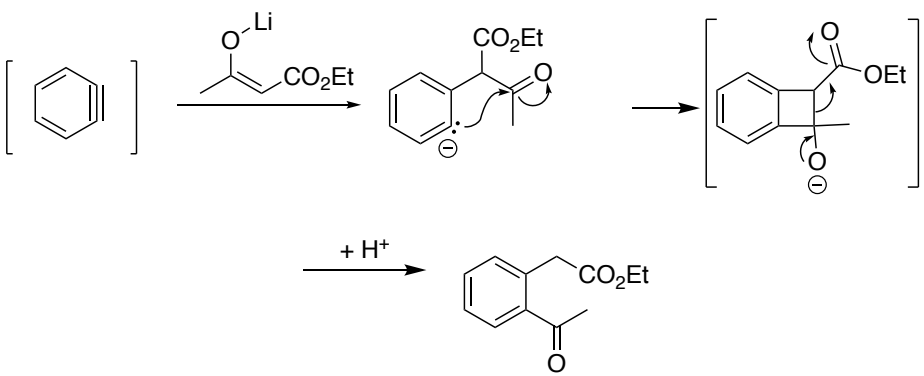


Carbon, Nitrogen, Oxygen, and Enolates/Enamines

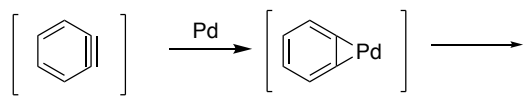
Cycloaddition Reactions

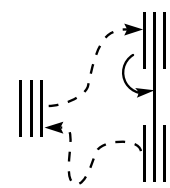






σ-Bond Insertions

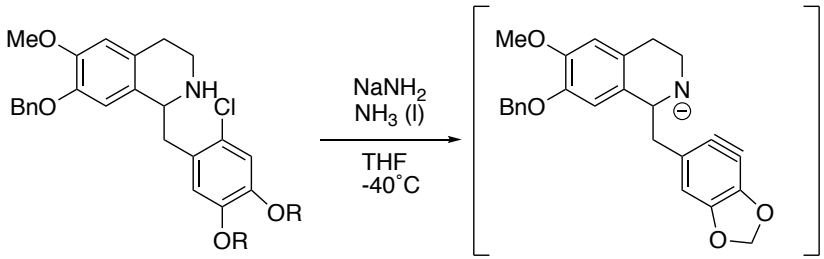




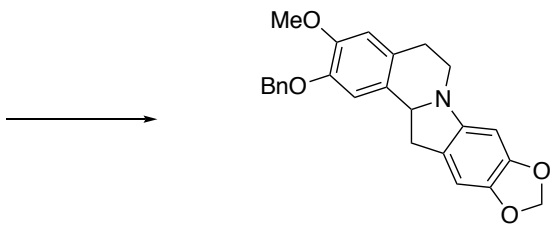
HHDA

Miscellaneous Reactions

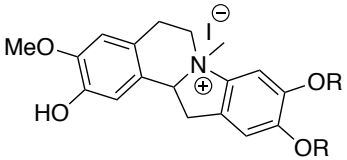
Kametani's Syntheses of Dibenzopyrrocoline Alkaloids (1967 and 1973)



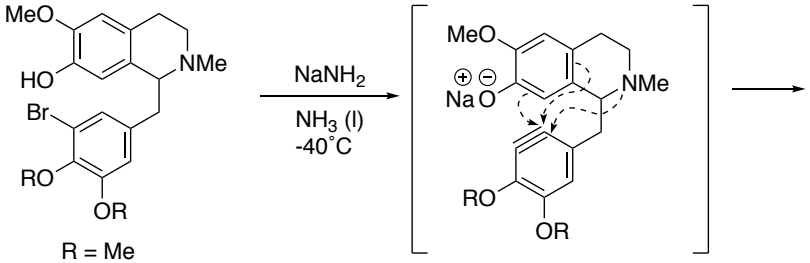
R = Me
R = -CH_2-



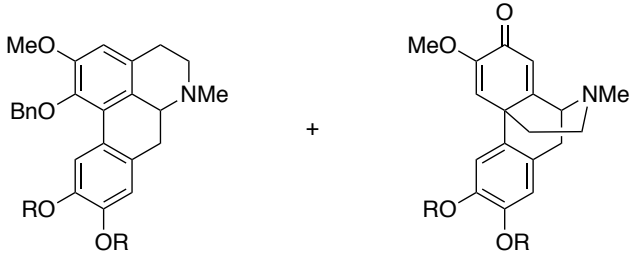
R = Me, 24%
R = -CH_2-, 77%



R = Me, Cryptaustoline
R = -CH_2-, Cryptowoline
After KI

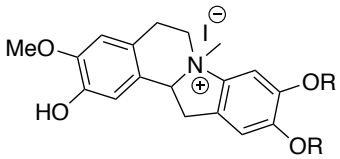


R = Me
R = -CH_2-



R = Me, Thaliporphine (0.14%)
R = -CH_2-, Domesticine (1%)

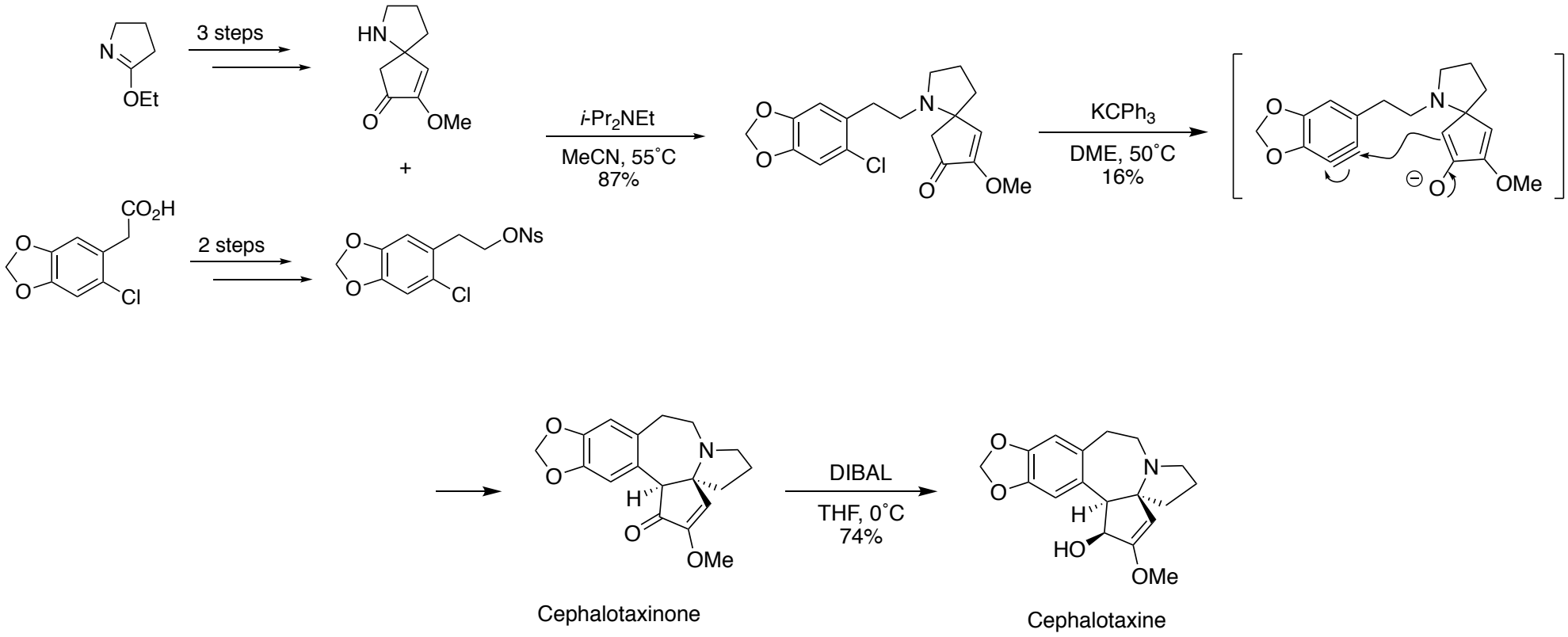
R = Me, O-methylflavinantine (0.1%)
R = -CH_2-, Amurine (0.3%)



R = Me, Cryptaustoline (0.7%)
R = -CH_2-, Cryptowoline
After KI

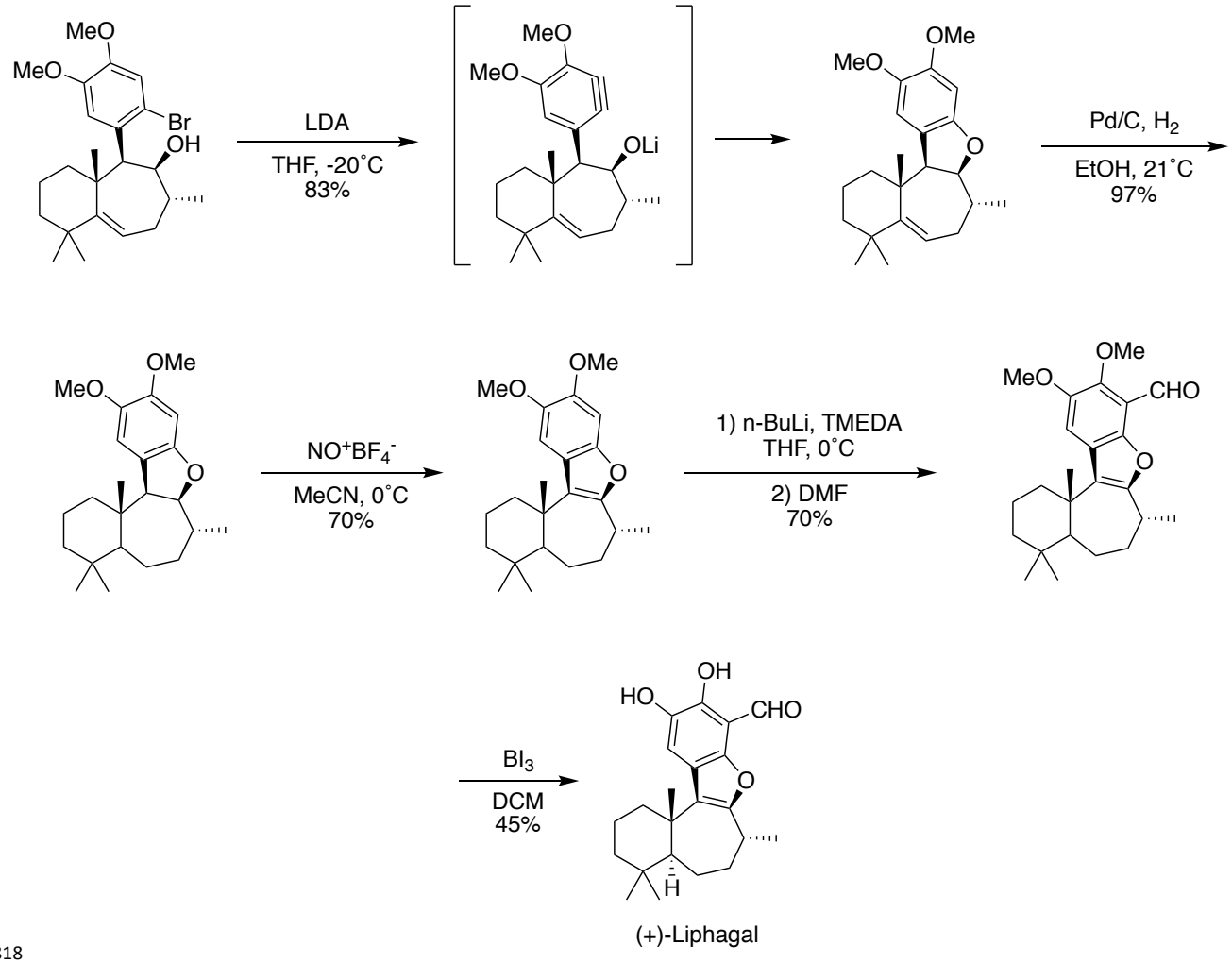
J. Chem. Soc. C, 1967, 2208-2212, K. Chem. Pharm. Bull. 1973, 21, 766

Semmelhack's Synthesis of Cephalotaxinone and Cephalotaxine (1972)



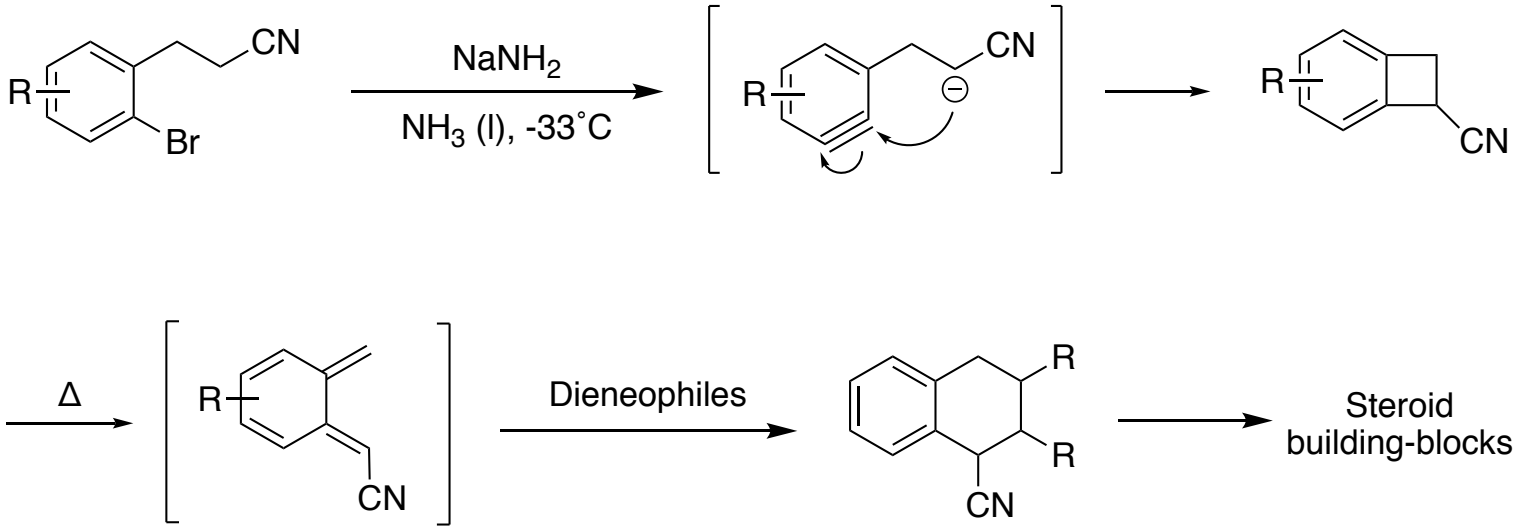
J. Am. Chem. Soc.197294248629-8630

Stoltz's Synthesis of (+)-Liphagal (2011)



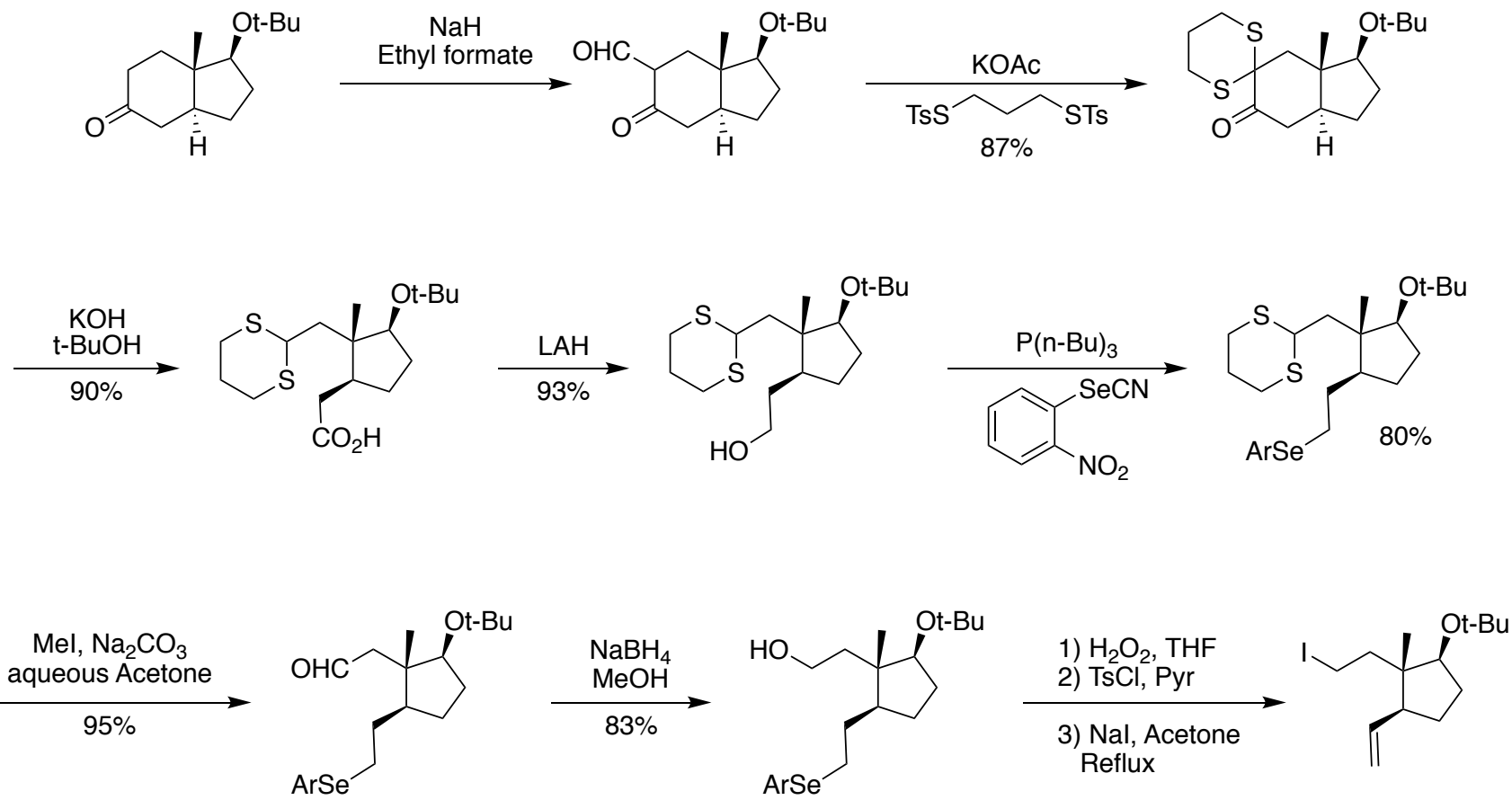
Angew. Chem. Int. Ed.2011,50, 6814 –6818

Kametani's Synthesis of Benzocylobutanes (1977)



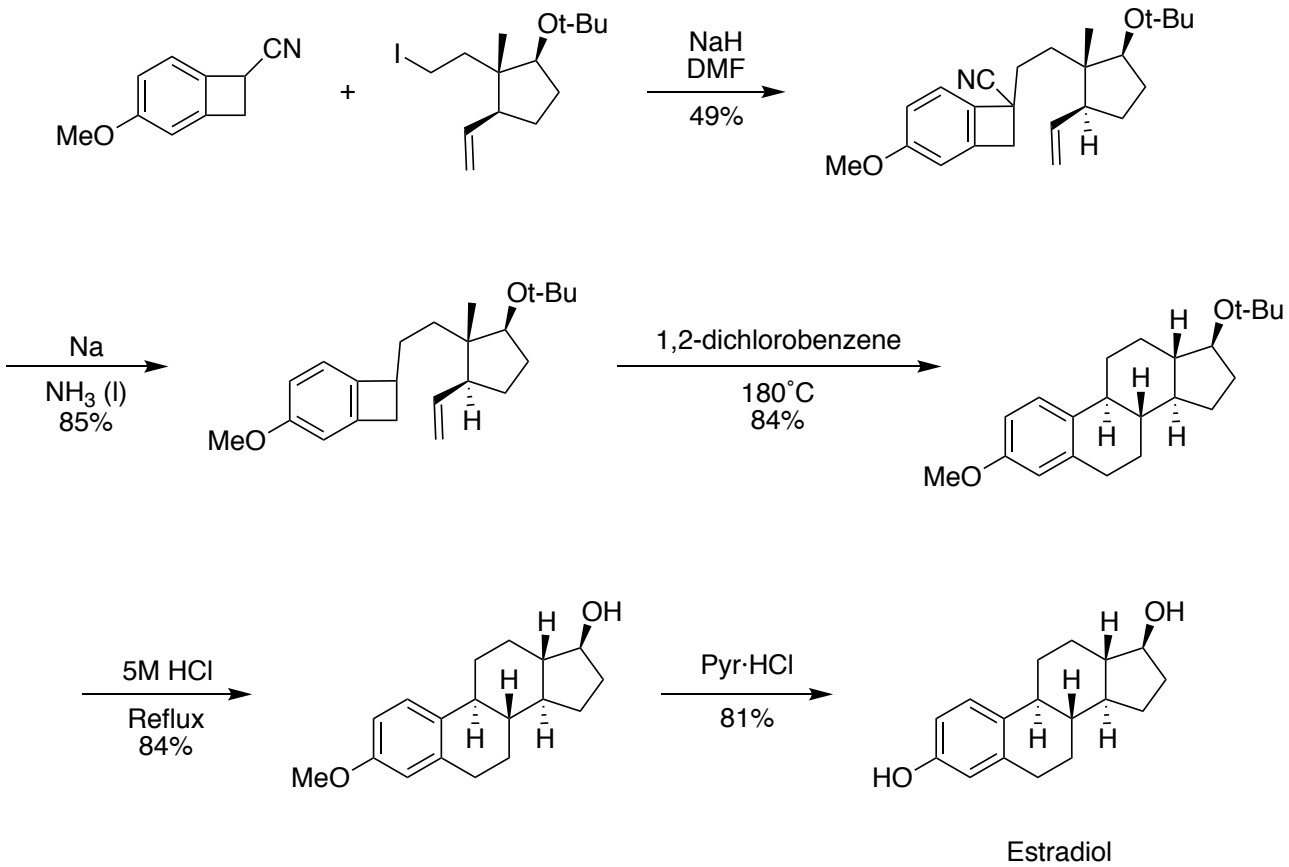
J. Am. Chem. Soc. 1977, 99, 3461

Kametani's Synthesis of Estradiol (1978)



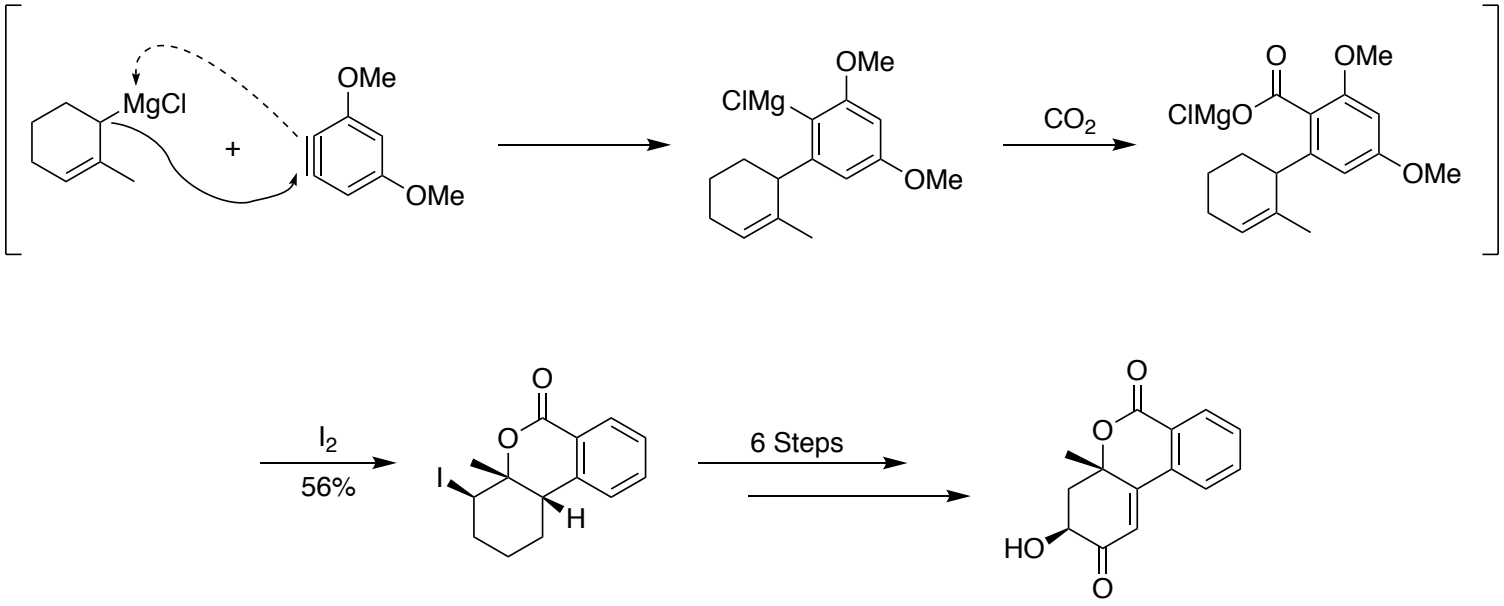
J. Am. Chem. Soc.1978100196218-6220

Kametani's Synthesis of Estradiol (1978)



J. Am. Chem. Soc.1978100196218-6220

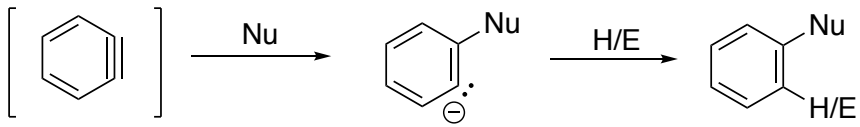
Barret's (Multi-Component) Synthesis of Dehydroaltenuene B (2008)



Org. Lett. 2008, 10, 3833.

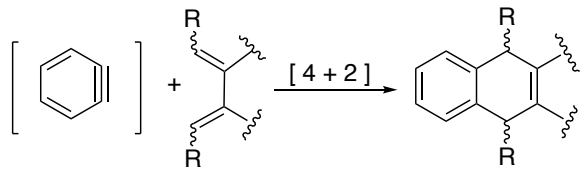
Main Modes of Reactivity

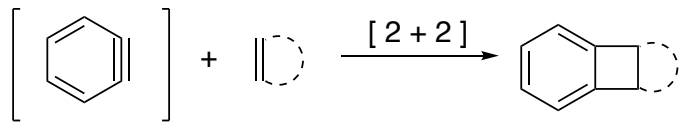
Nucleophilic Additions and Multi-component Reactions

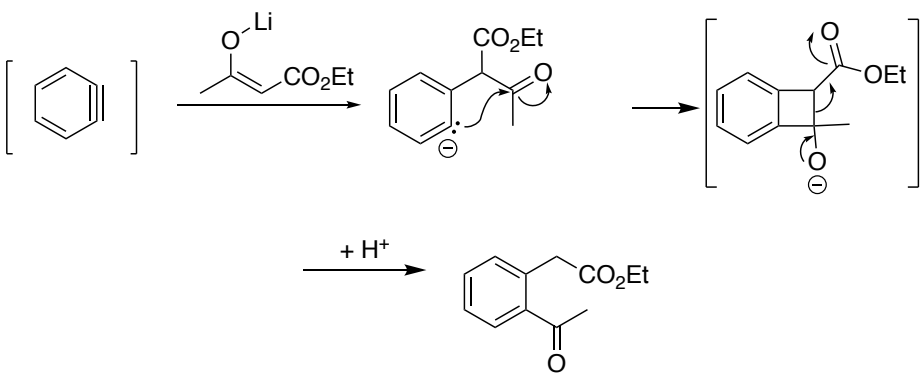


Carbon, Nitrogen, Oxygen, and Enolates/Enamines

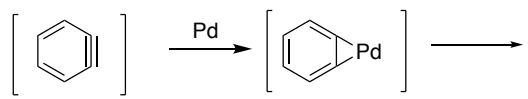
Cycloaddition Reactions

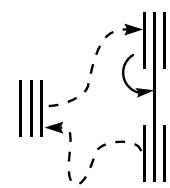






σ-Bond Insertions





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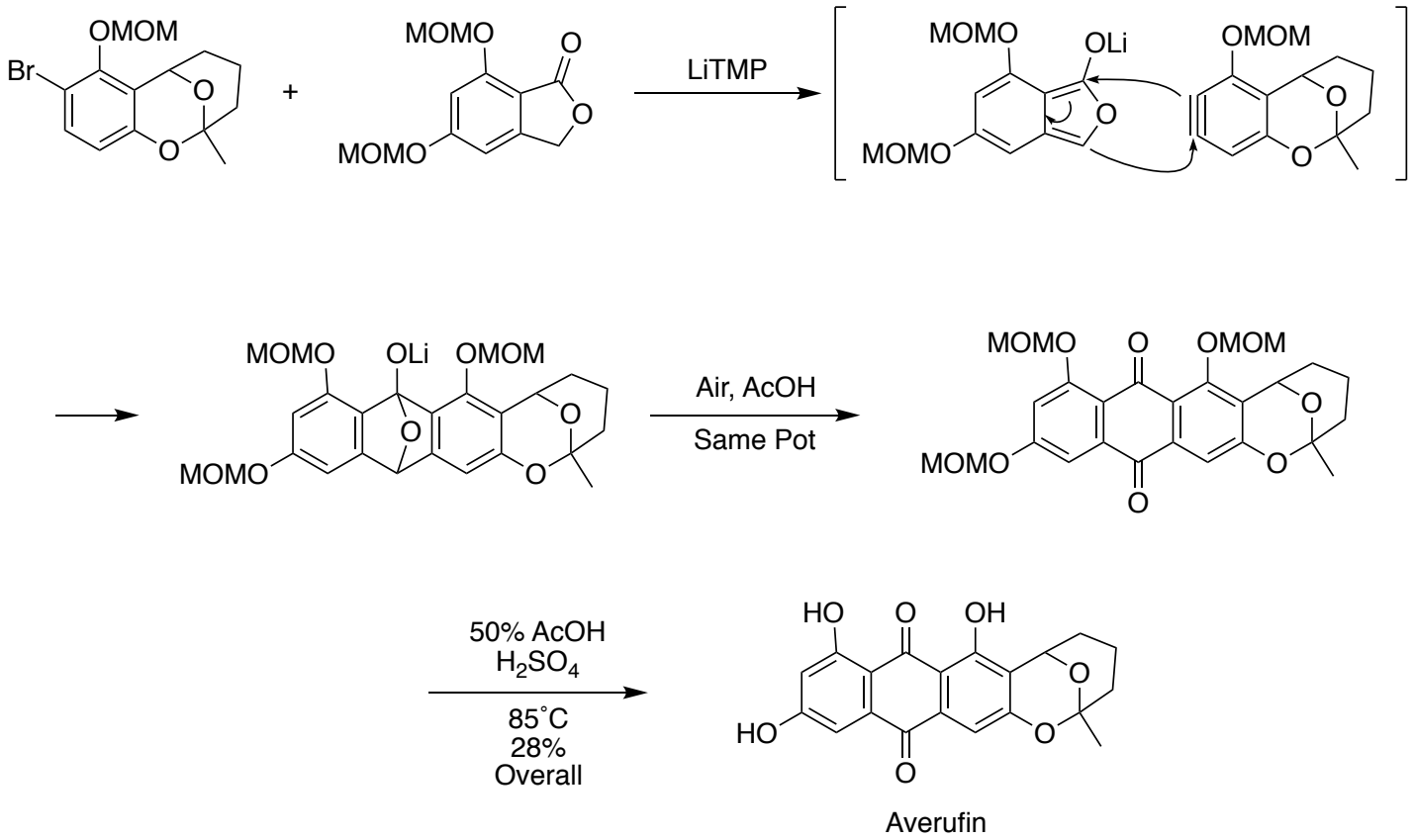
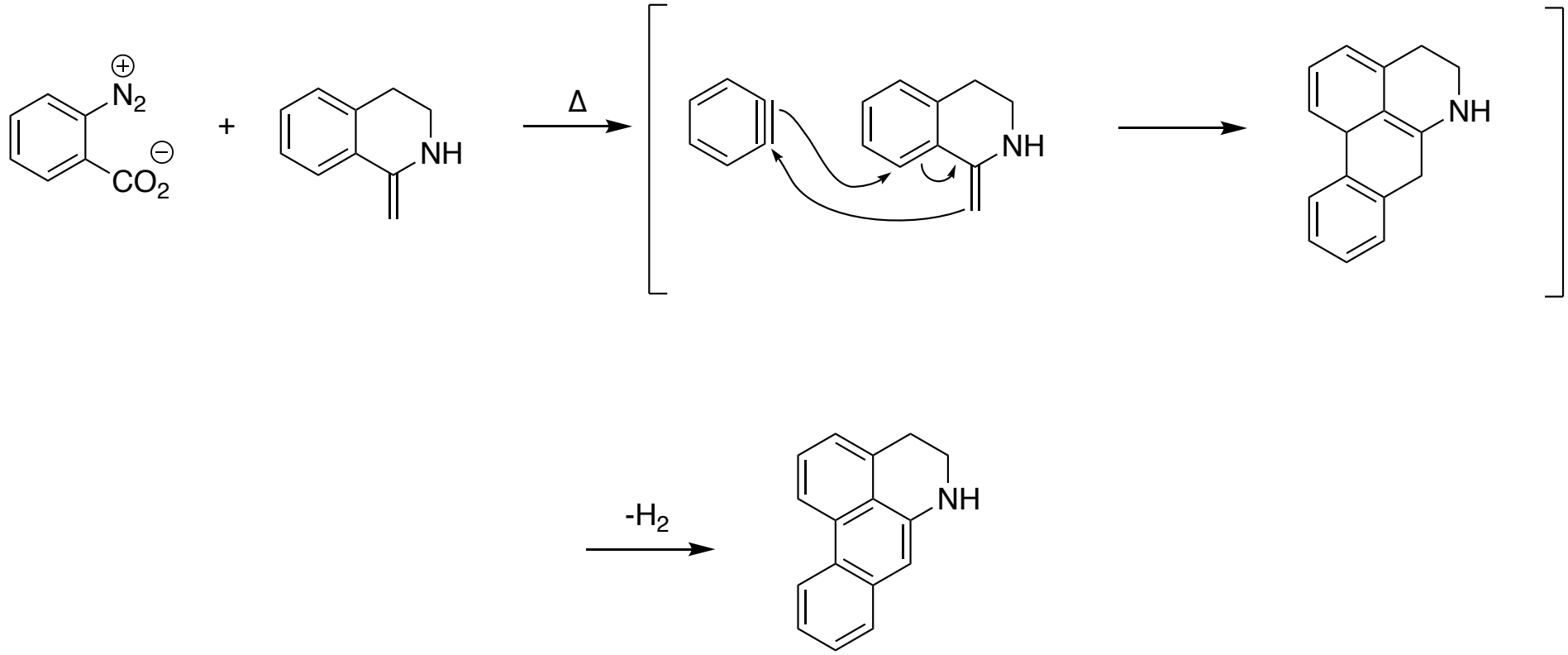
Miscellaneous Reactions

Townsend's Synthesis of Averufin (1981)



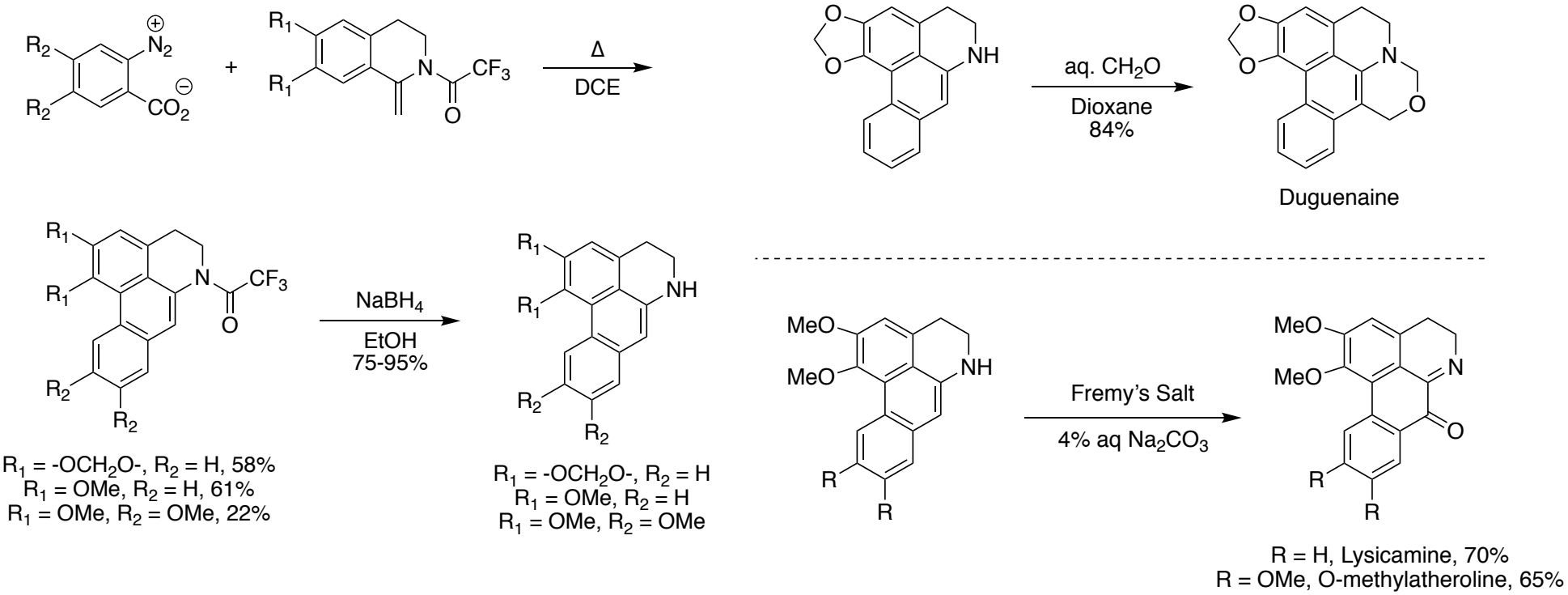
J. Am. Chem. Soc. 1981, 103, 6885.

Castedo's Synthesis of Aporphinoid Alkaloid Scaffolds (1983)



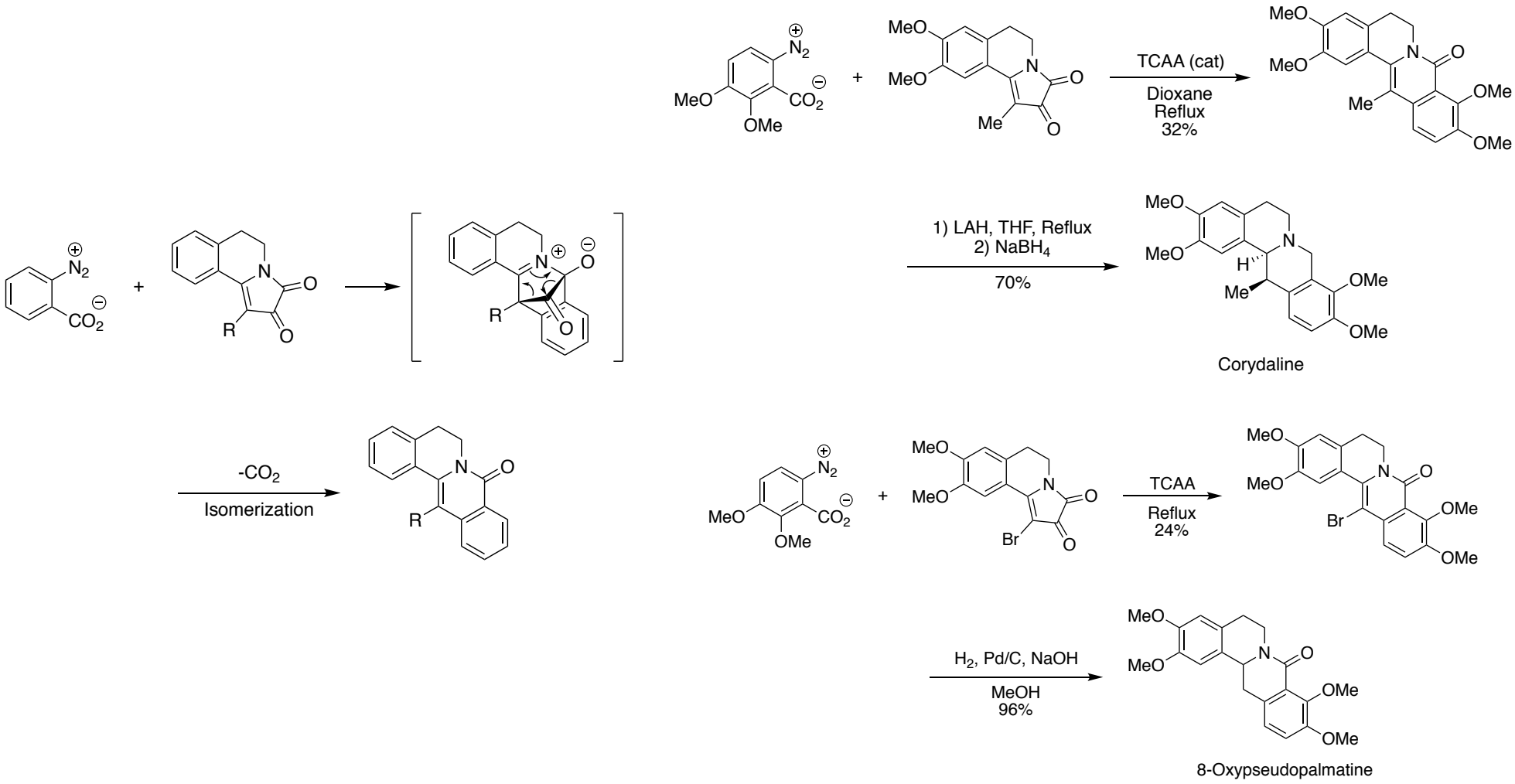
Tetrahedron Letters,Vol.24,No.20,pp 2107-2108,1983

Castedo's Synthesis of Aporphinoid Alkaloid Scaffolds



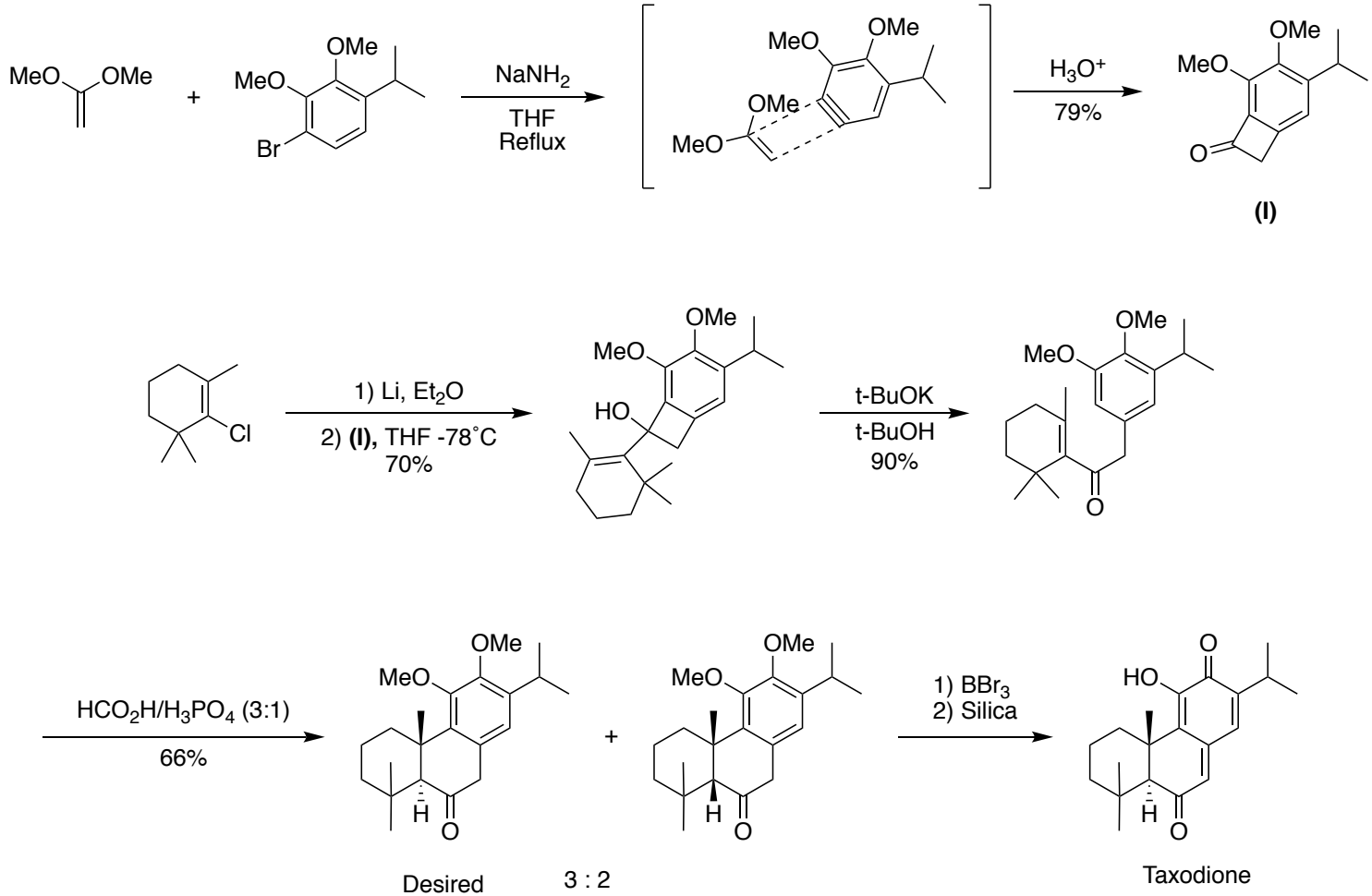
J. Org. Chem. 1991, 56, 2984

Castedo's Synthesis of Protoberberine Scaffolds (1988)



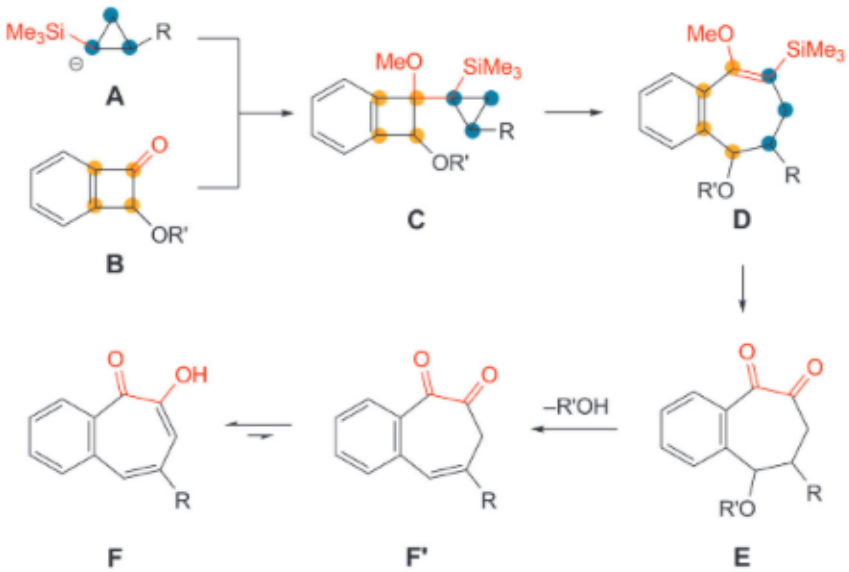
J.Org. Chem. 1986, 51, 2781. -- Tetrahedron Lett.1988,29,2491

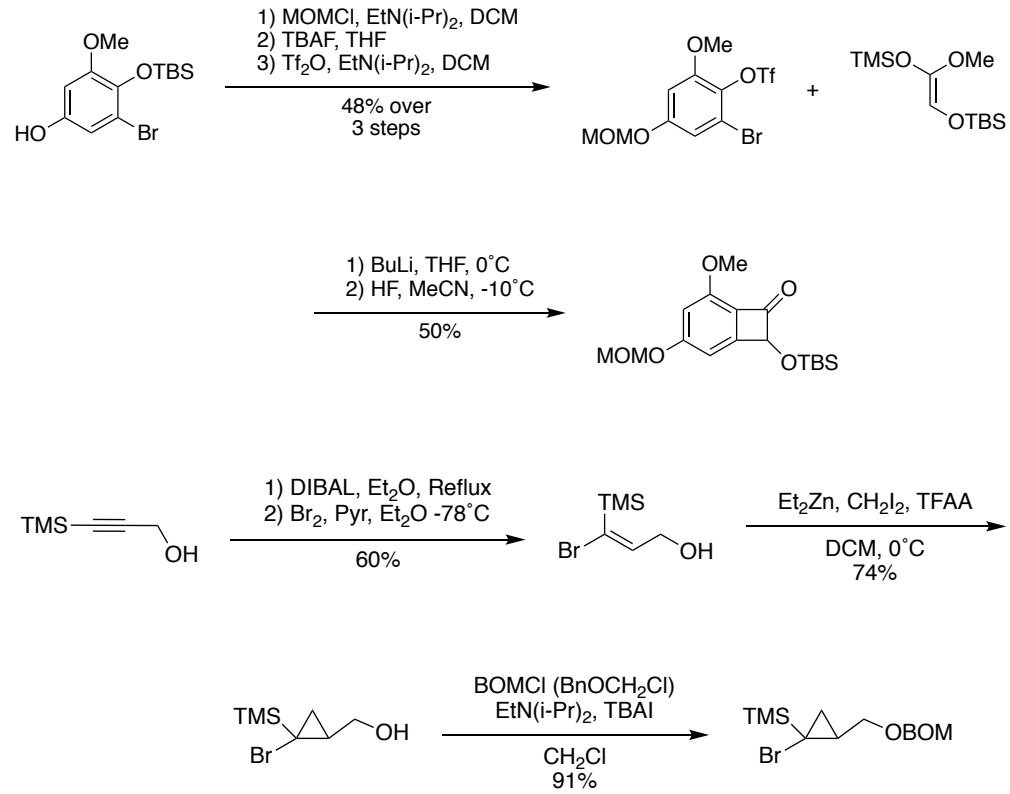
Steven's Taxodione Synthesis (1982)



J. Org. Chem., Vol. 47, No. 12, 1982

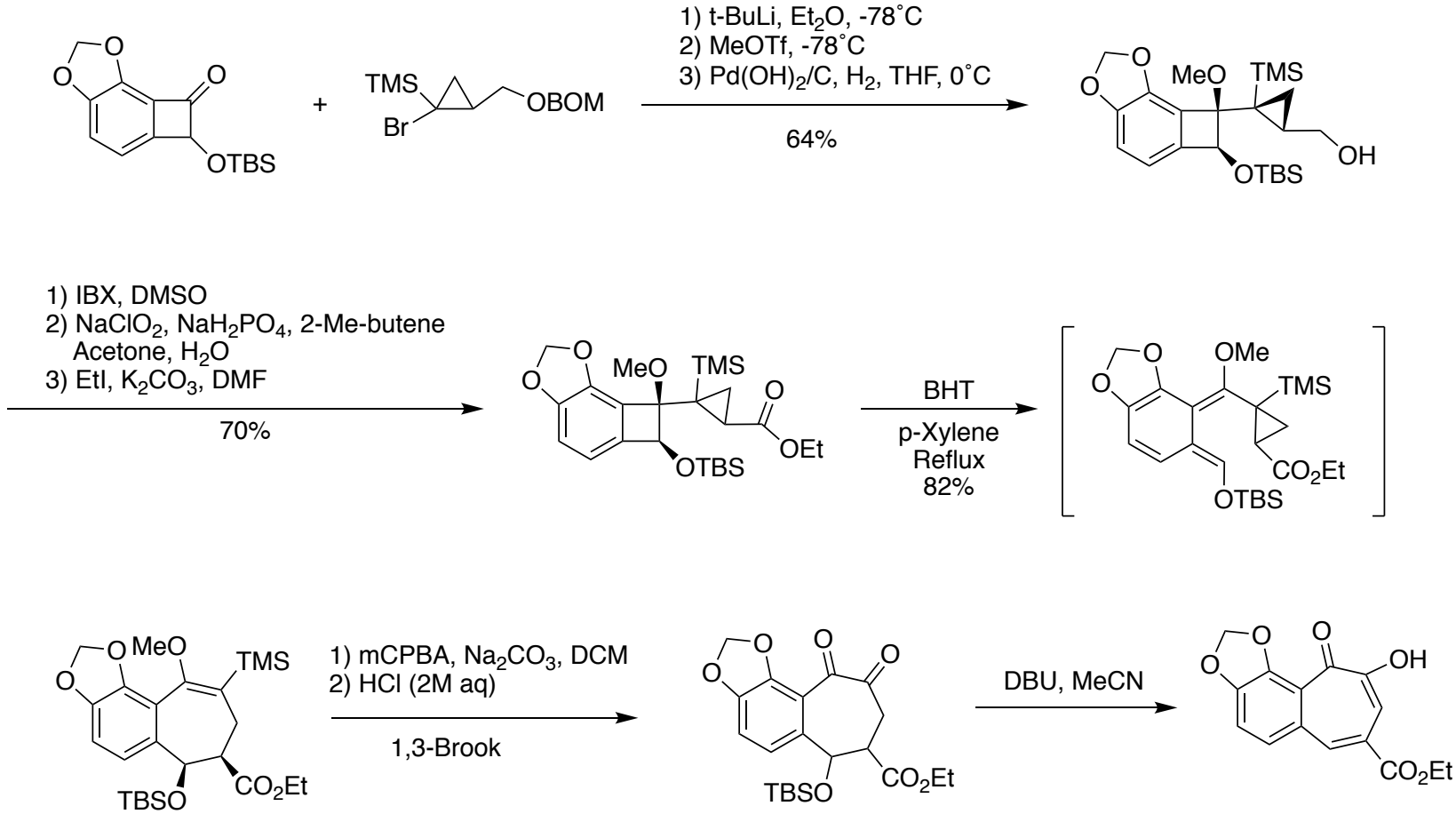
Suzuki's Route to Tropolone Scaffolds (2012)





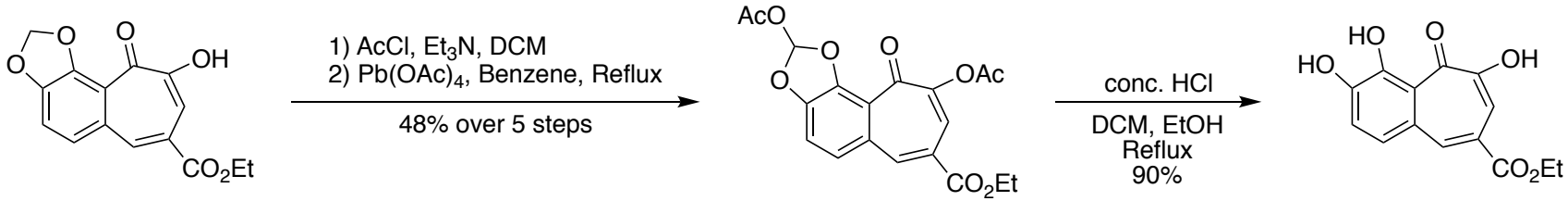
Helv. Chim. Acta, 2012, 95, 2194–2217.

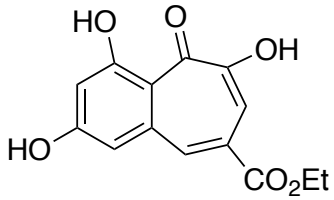
Suzuki's Synthesis of Goupiolone A



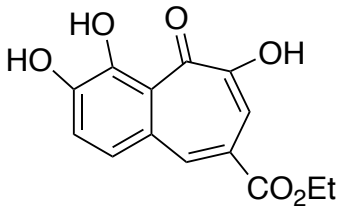
Helv. Chim. Acta, 2012, 95, 2194–2217.

Suzuki's Synthesis of Goupiolone A





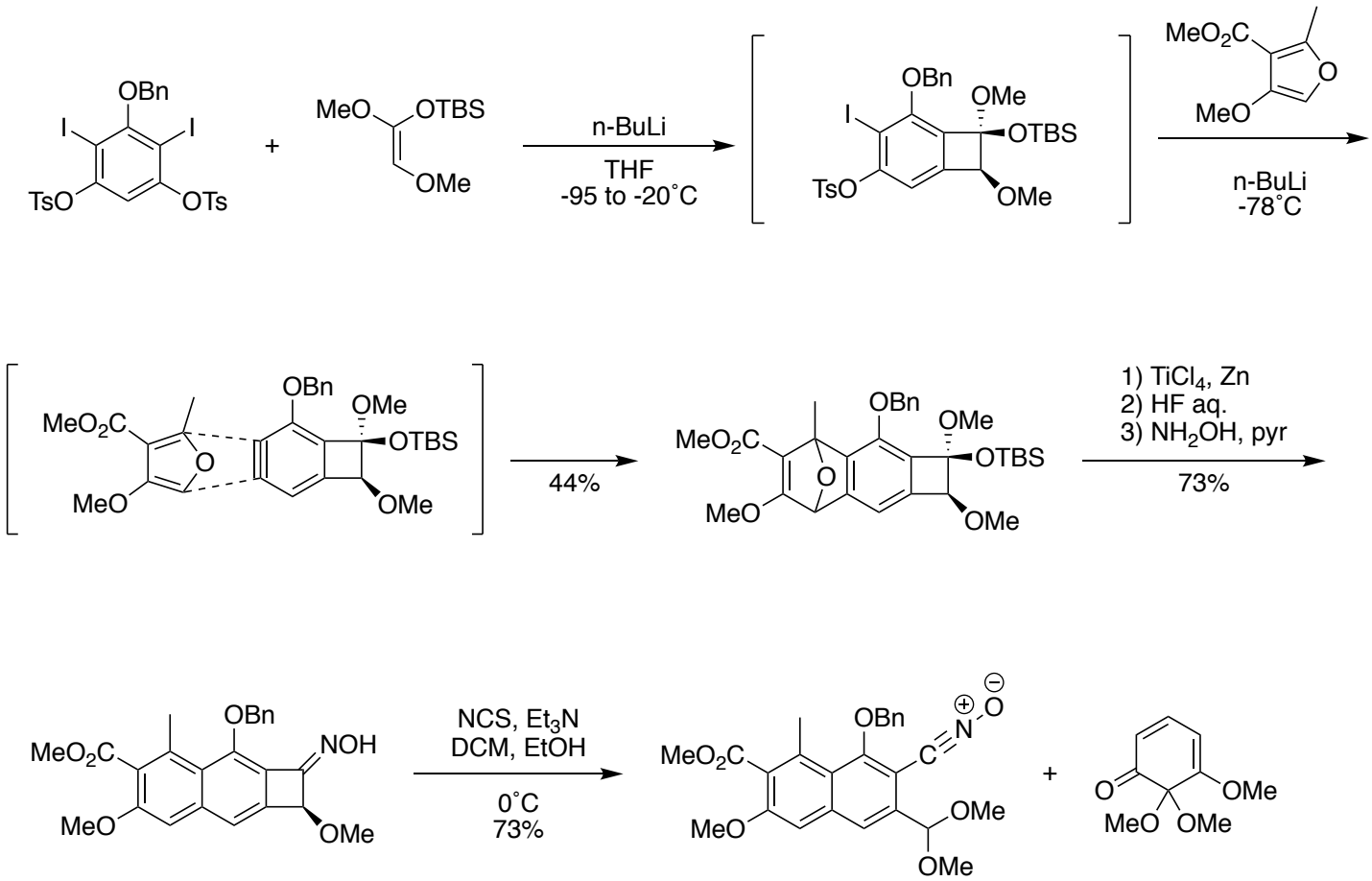
Goupiolone A
(Reported)



Goupiolone A
(Corrected)

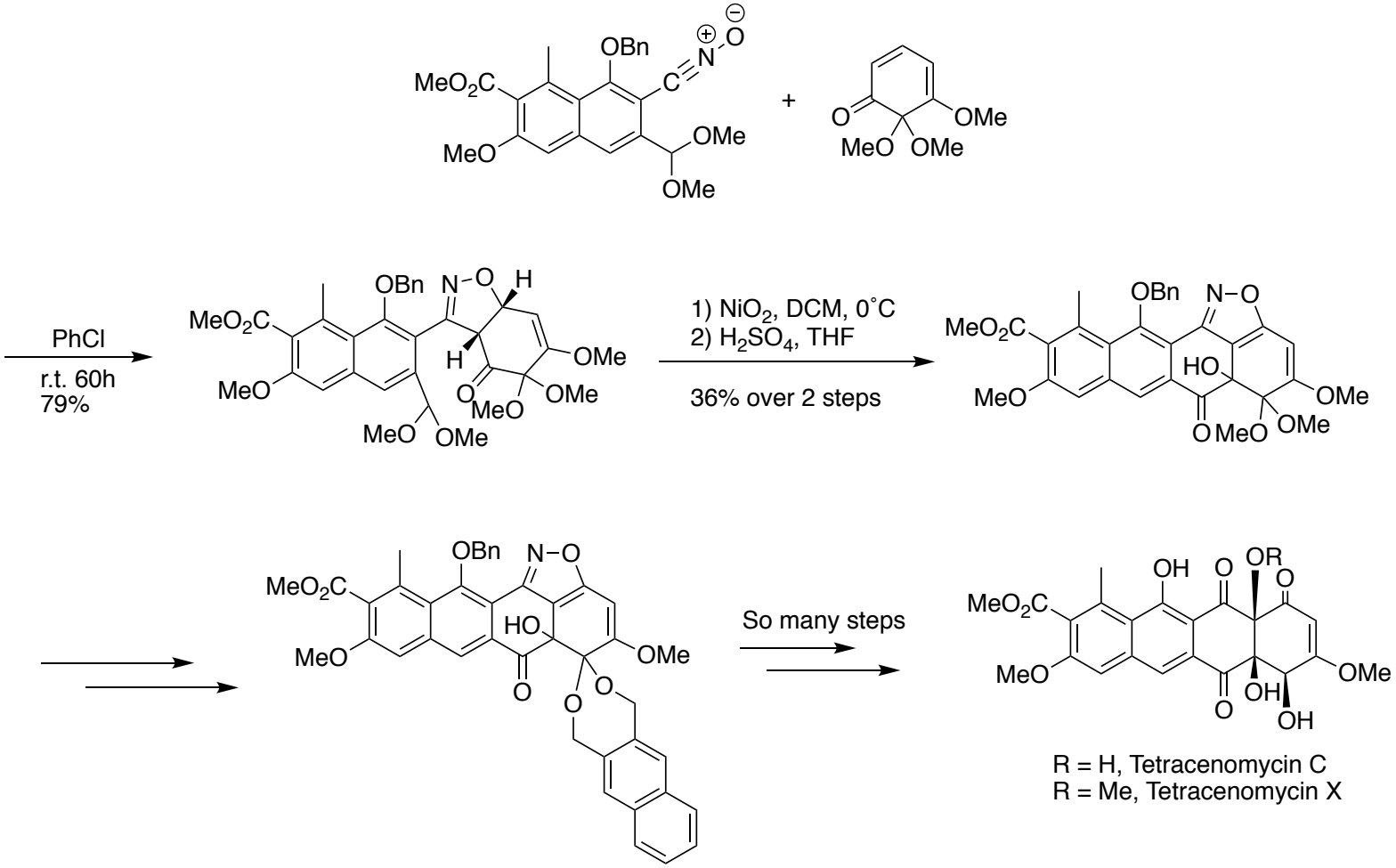
Helv. Chim. Acta, 2012, 95, 2194–2217.

Suzuki's Synthesis of Tetracenomycins C and X (2017)



Angew.Chem.Int.Ed.2017,56,12608–12613

Suzuki's Synthesis of Tetracenomycins C and X



Angew.Chem.Int.Ed.2017,56,12608–12613

Main Modes of Reactivity

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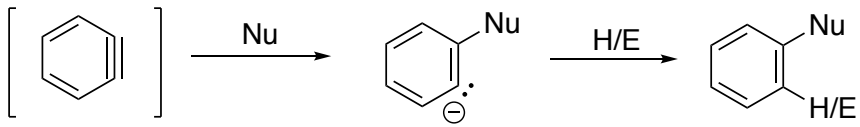
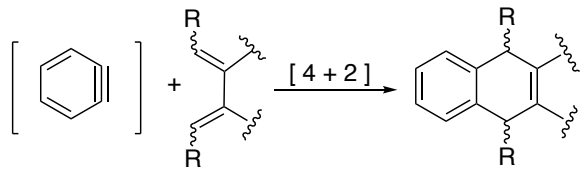
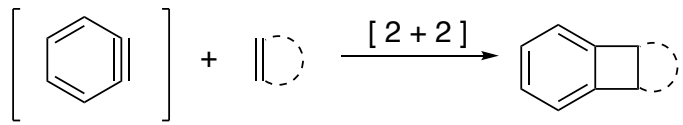
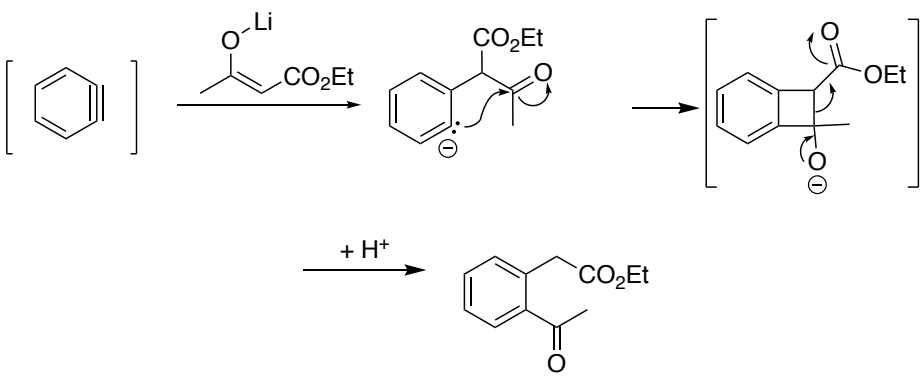


Carbon, Nitrogen, Oxygen, and Enolates/Enamines

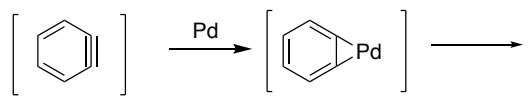
Cycloaddition Reactions

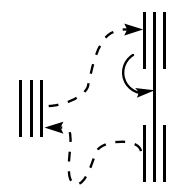






σ-Bond Insertions





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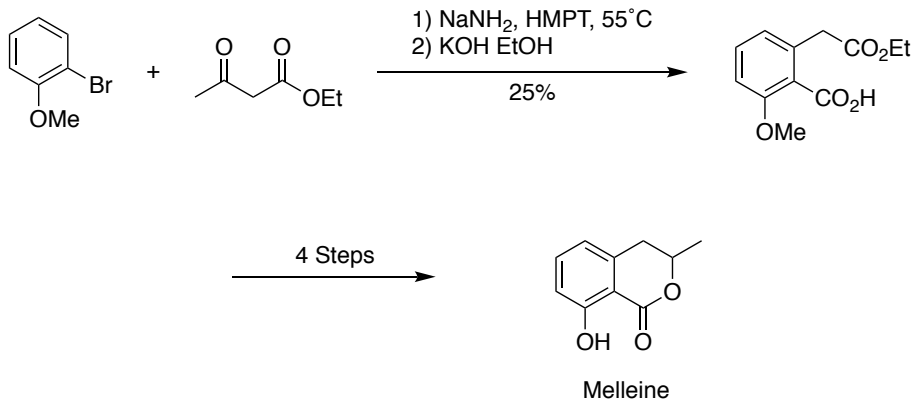
Miscellaneous Reactions

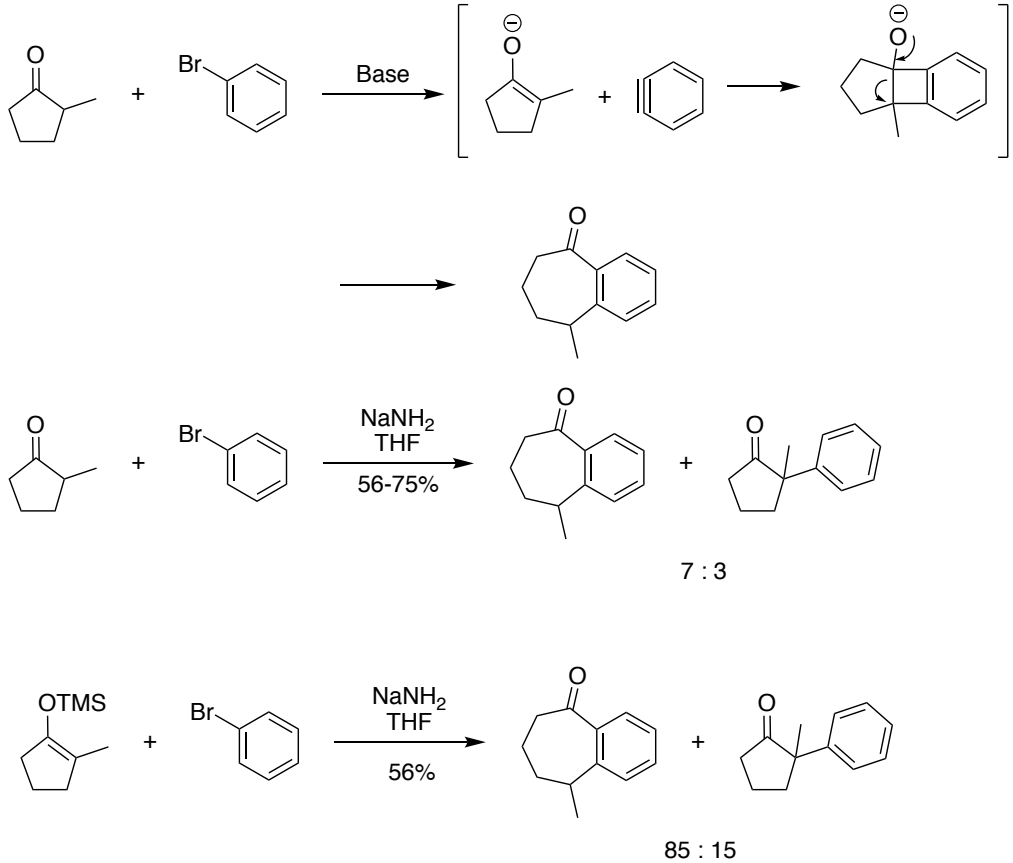
σ-Bond Insertion Reactions



Guyot's Synthesis of Melleine (1973)

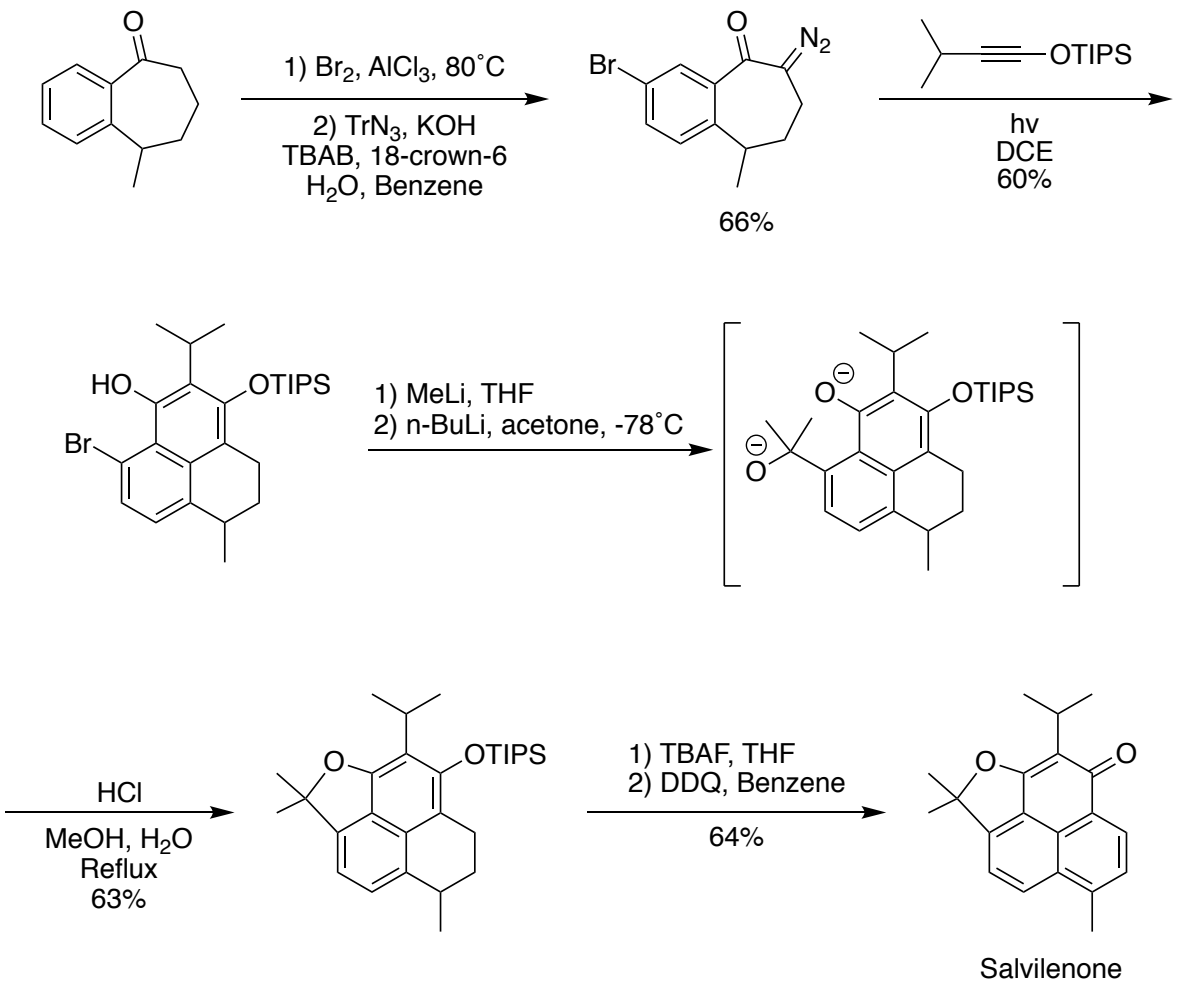
Tetrahedron Letters No. 36, pp 3433 - 3136, 197

Danheiser's Ring Expansion with 2-Methyl Cyclopentanone (1994)



J. Am. Chem. Soc. 1994, 116, 9471.

Danheiser's Synthesis of Salvilenone (1994)



J. Am. Chem. Soc. 1994, 116, 9471.

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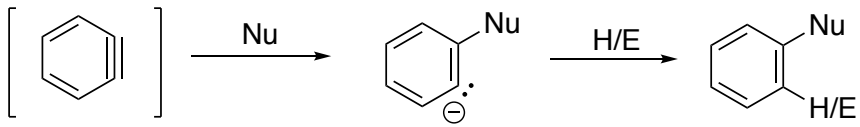

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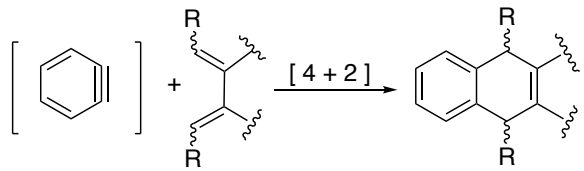
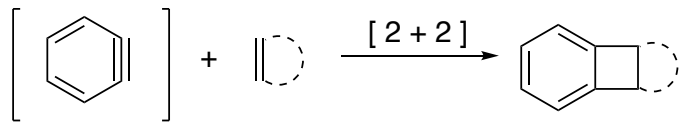
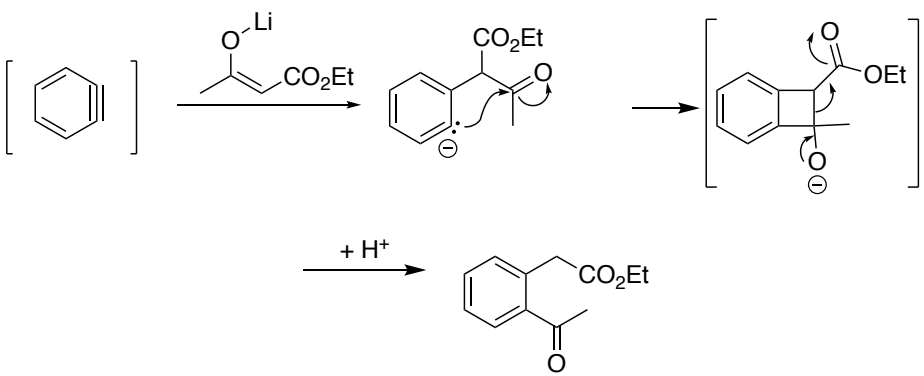
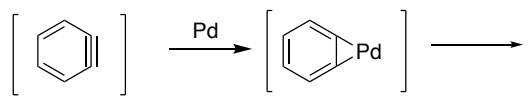
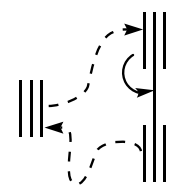






σ-Bond Insertions

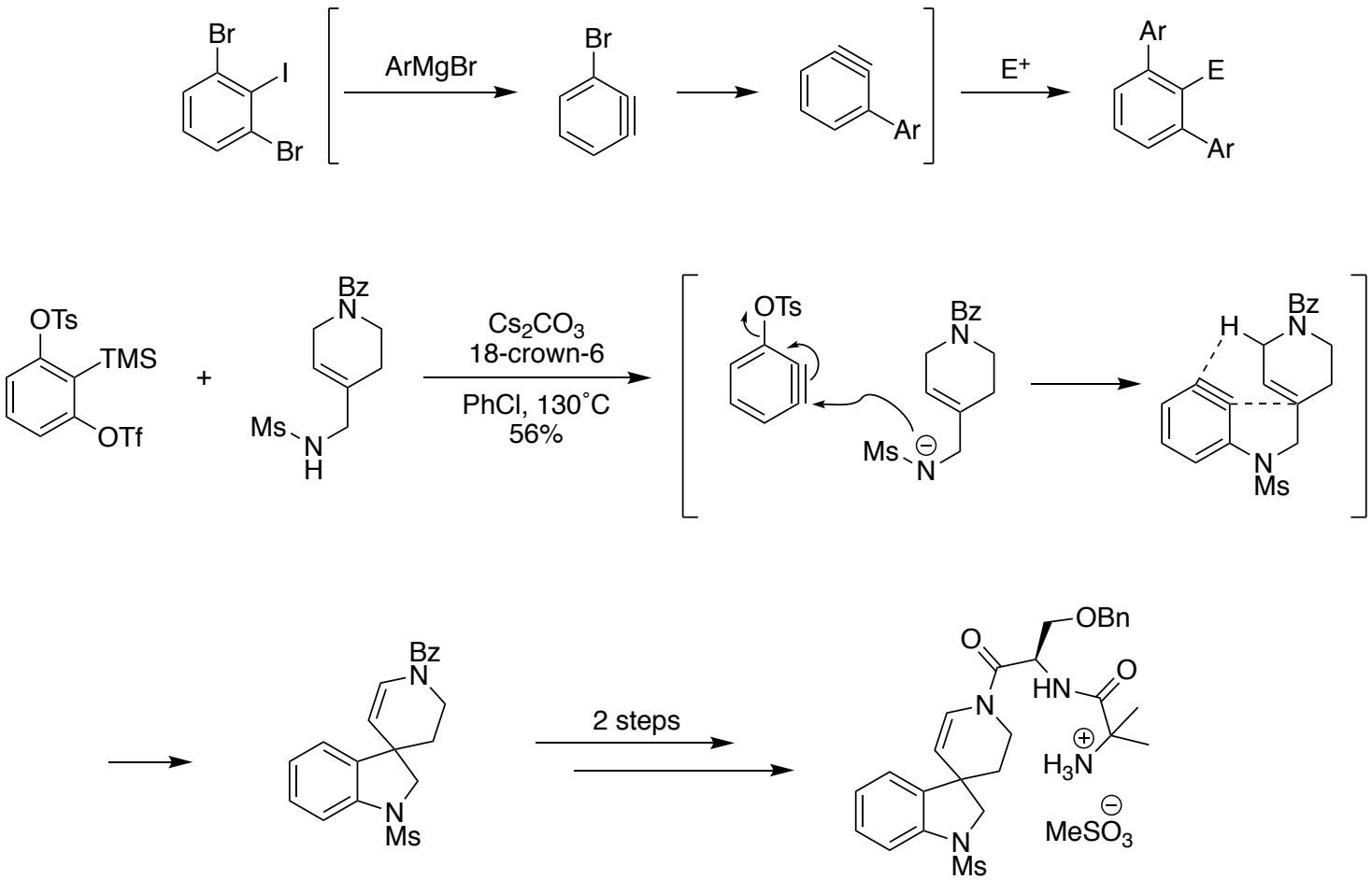




HHDA

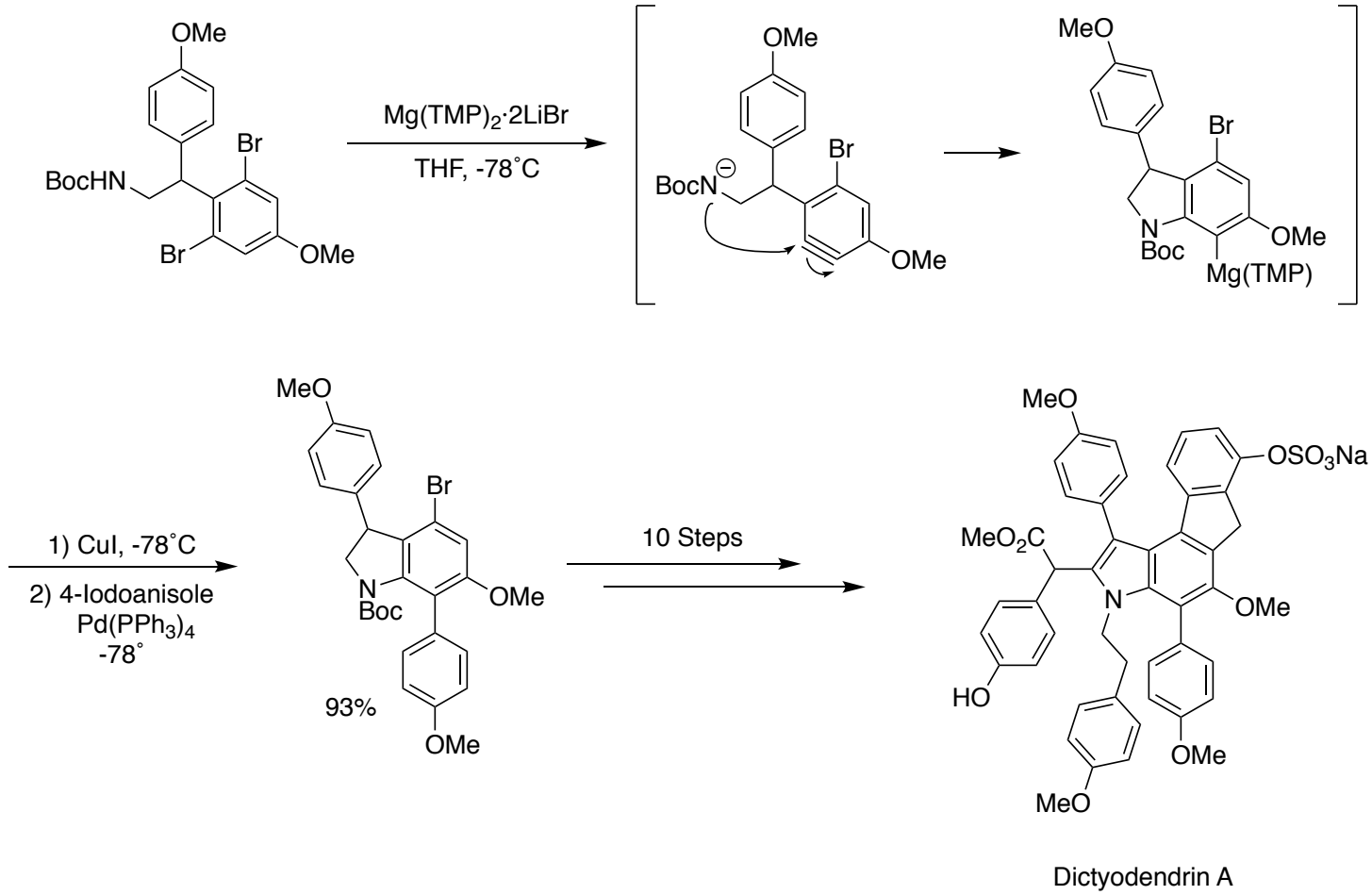
Miscellaneous Reactions

Li's Aryne-ene Cascade Synthesis of Ibutamoren (2018)



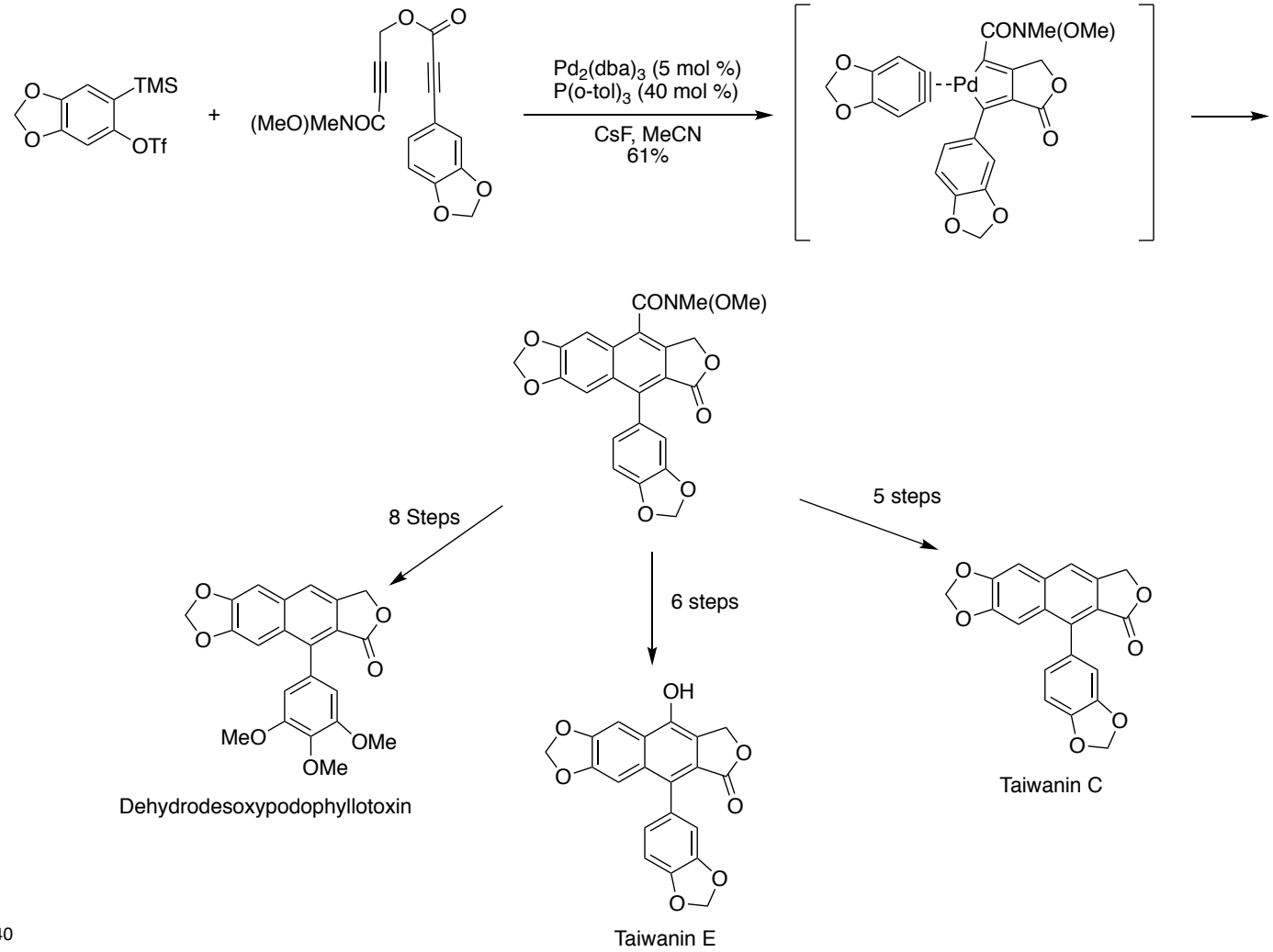
J. Am. Chem. Soc.2018140103555-3559

Tokuyama's Synthesis of Dictyodendrin A (2010)



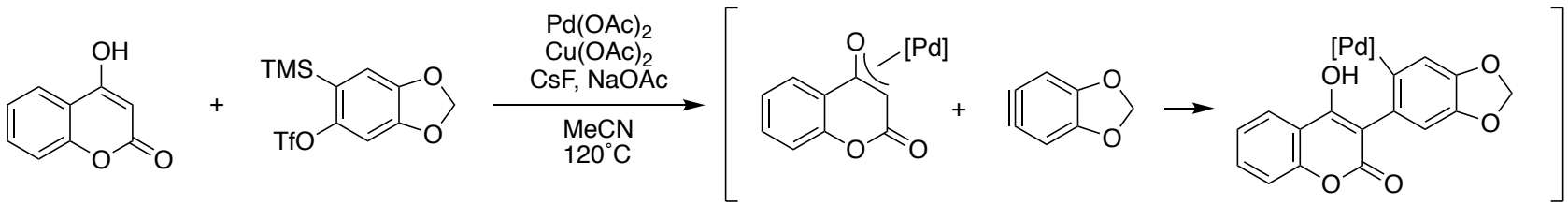
Angew. Chem. Int. Ed.2010,49, 5925 –5929

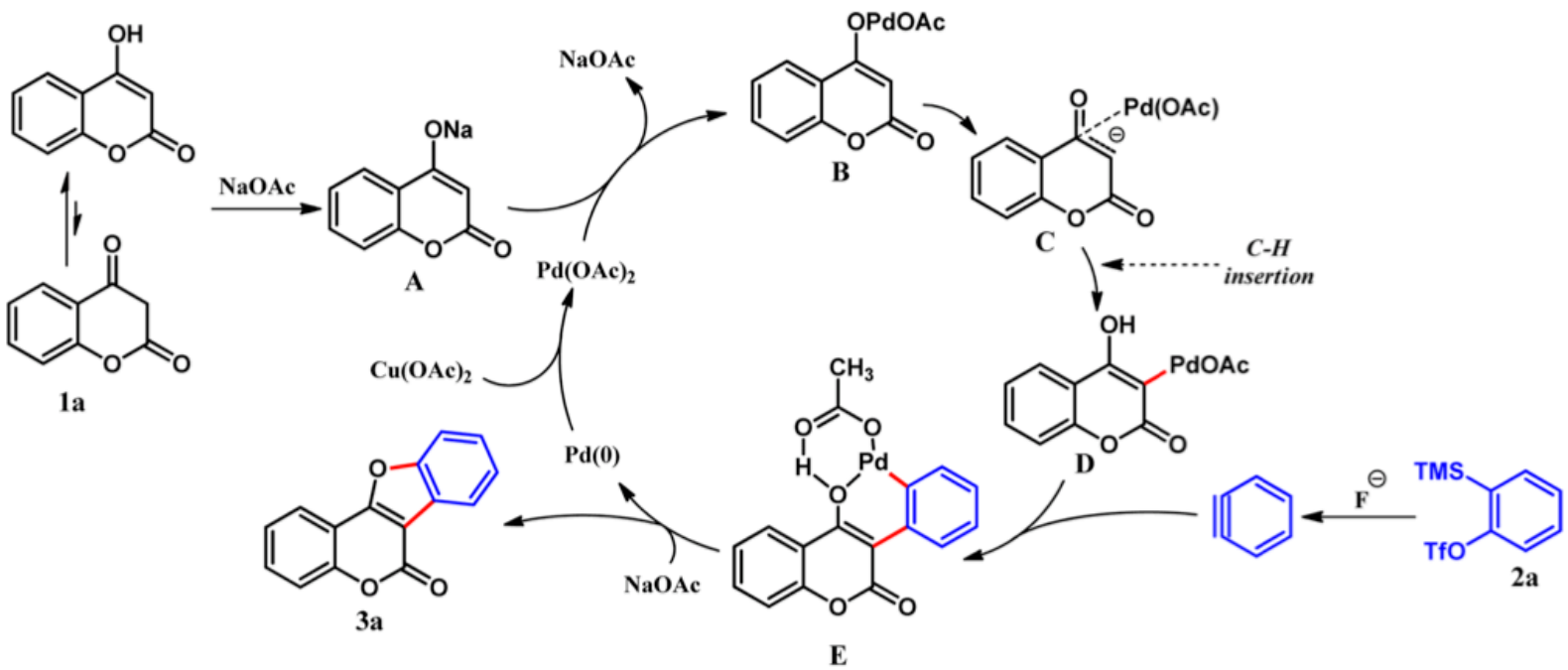
Mori's Synthesis of Taiwanins (2004)



Angew.Chem.Int.Ed.2004,43,2436–2440

Gogoi's Pd Catalyzed Synthesis of Coumestan Core

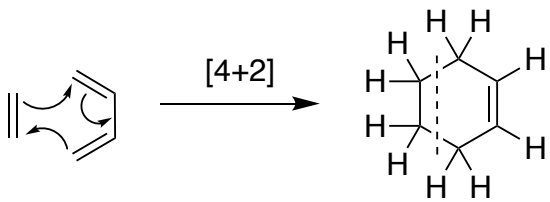




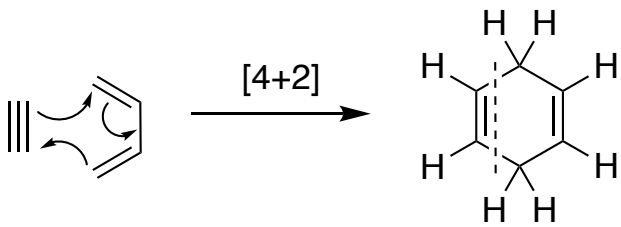
J. Org. Chem.2016812311971-11977

The Hexadehydro-Diels-Alder Reaction

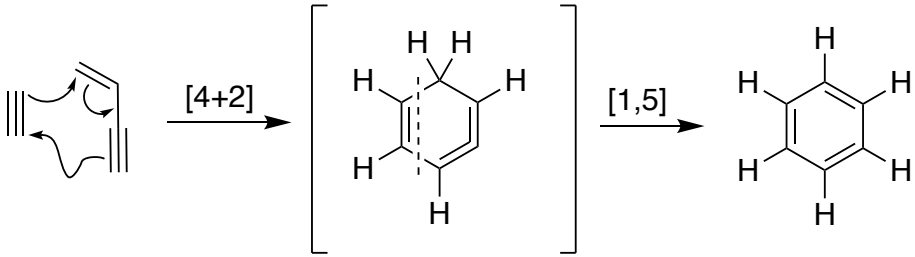
Diels-Alder



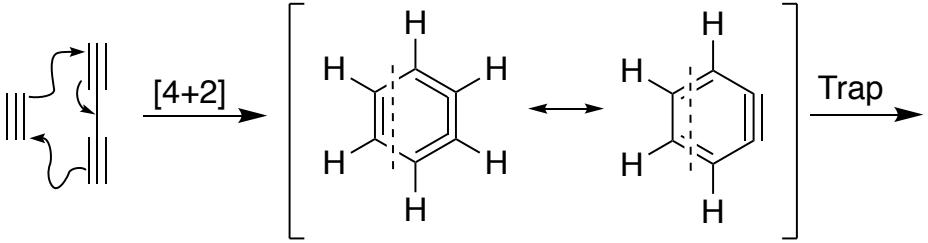
Didehydro-Diels-Alder



Tetradehydro-Diels-Alder



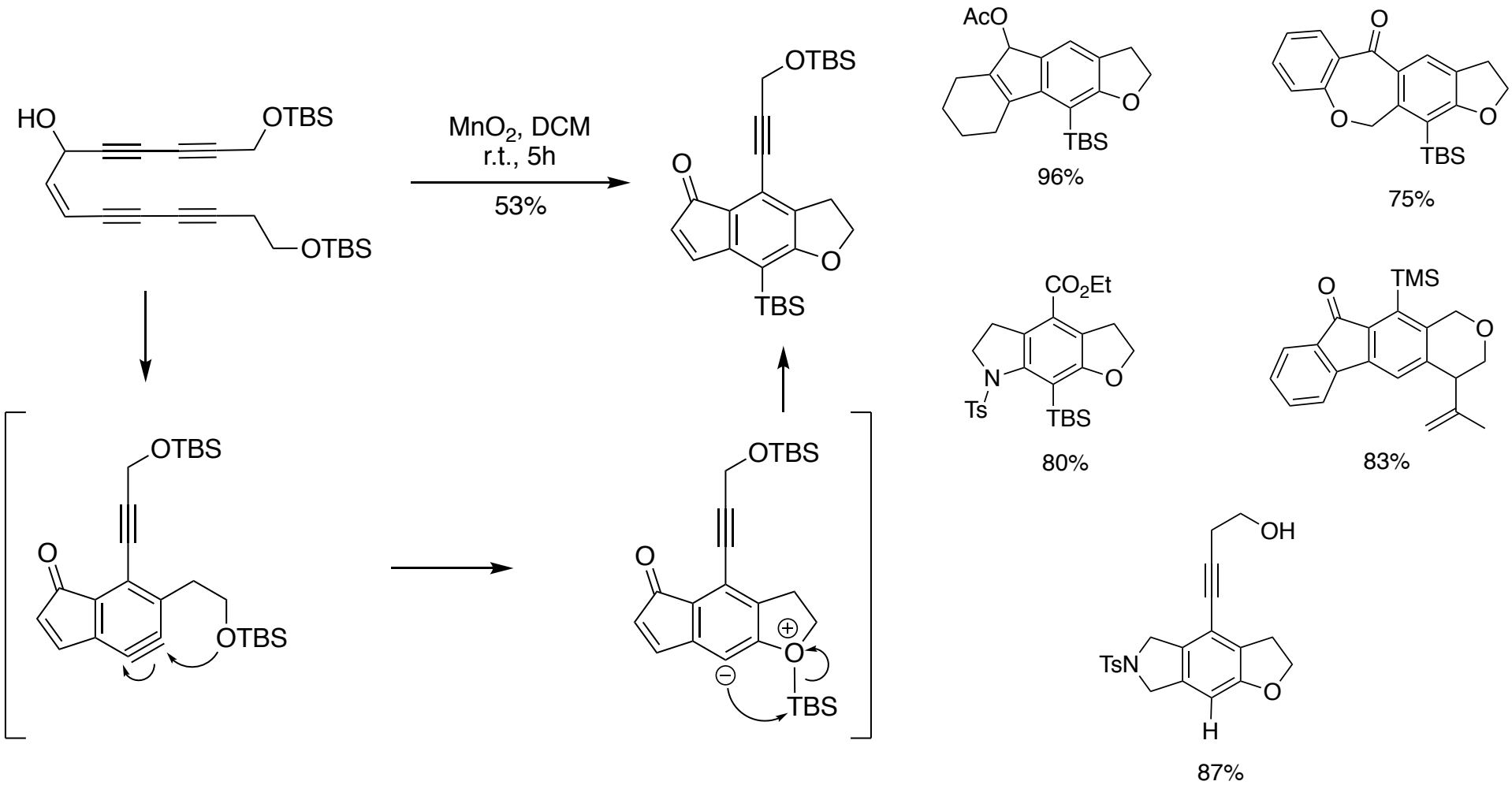
Hexadehydro-Diels-Alder



Ueda and Johnson (1997)

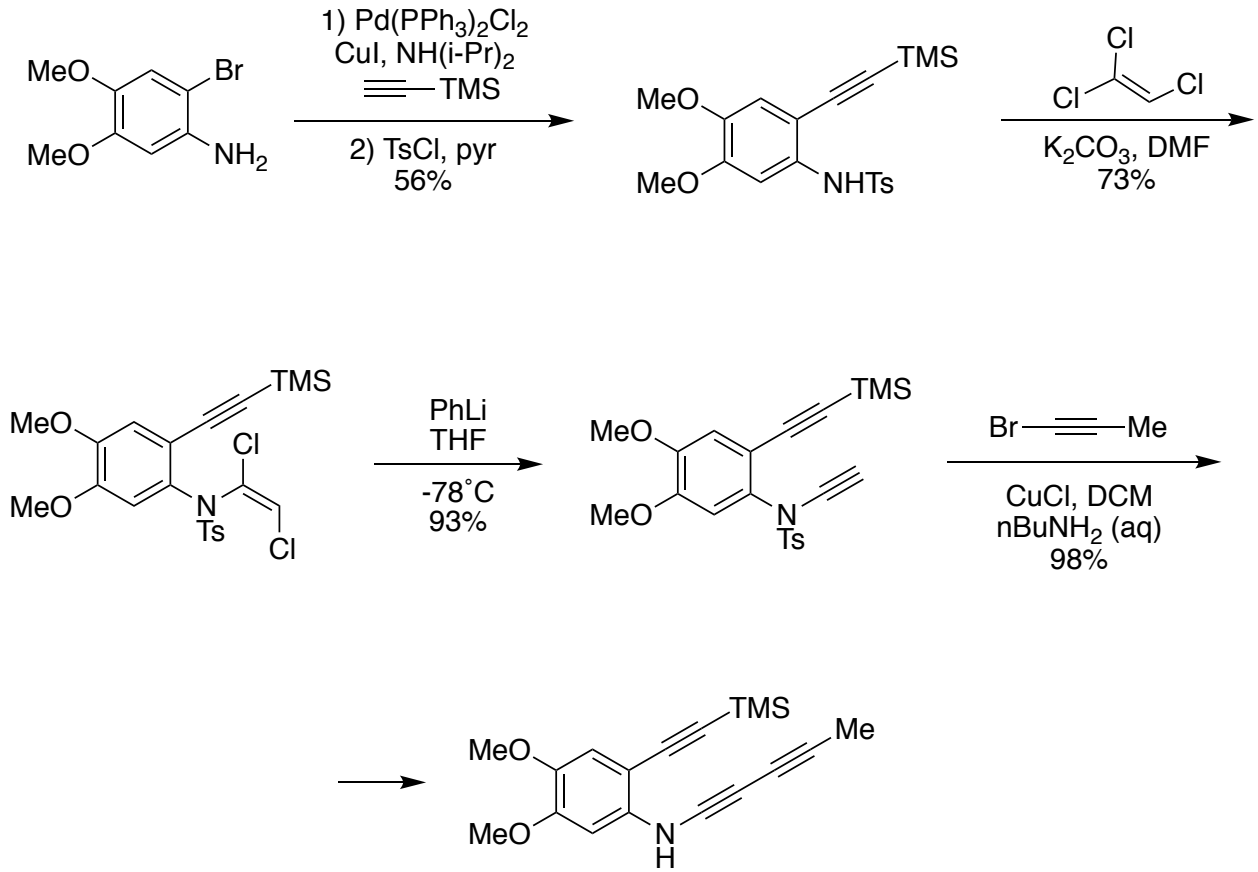
J. Am. Chem. Soc., 1997, 119, 9917, Tetrahedron Lett., 1997, 38, 3943

The Hoye HDDA Aryne Method



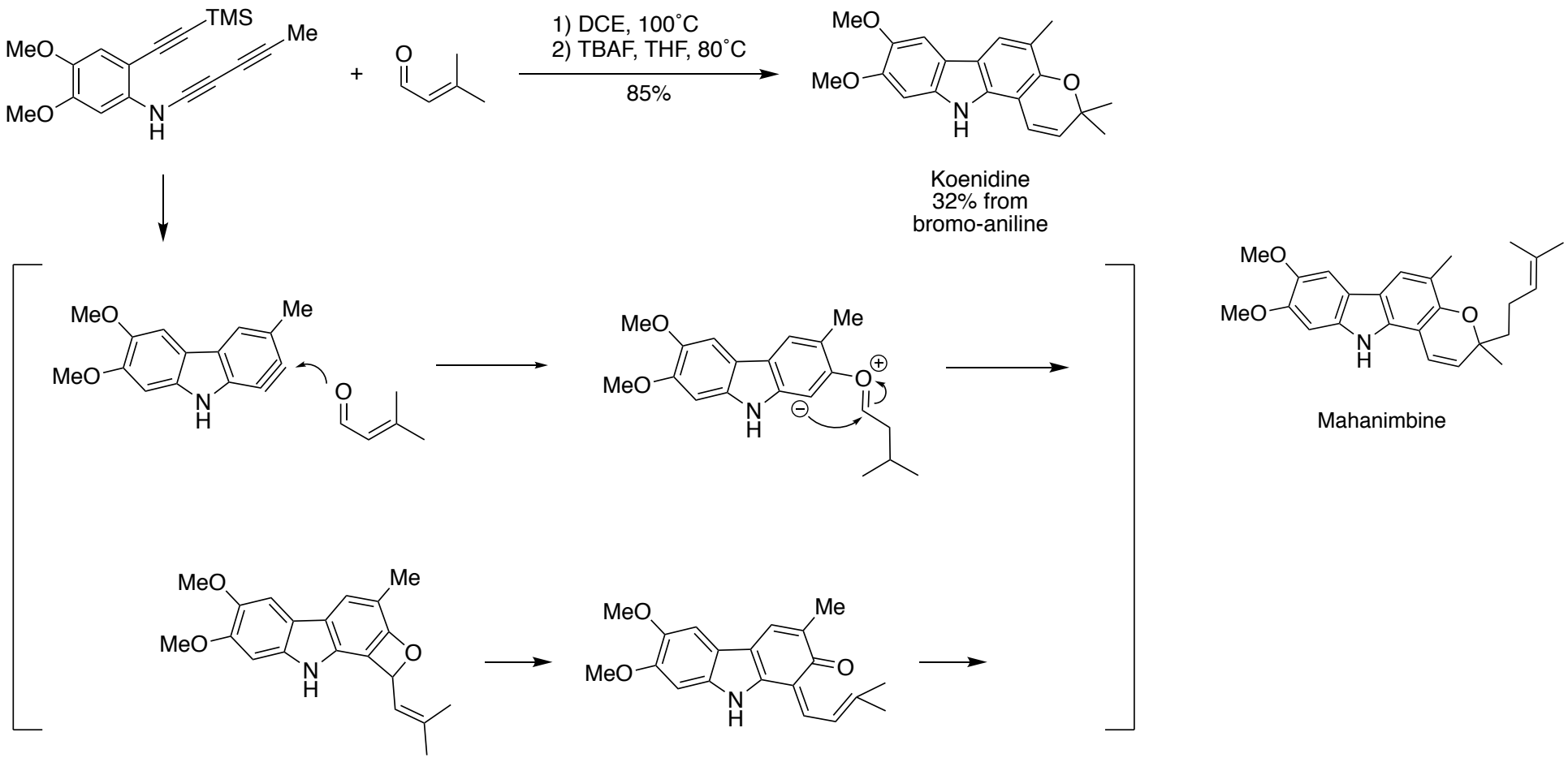
Nature 2012, 490, 208–212

Hoye's Synthesis of Koenigii Alkaloids



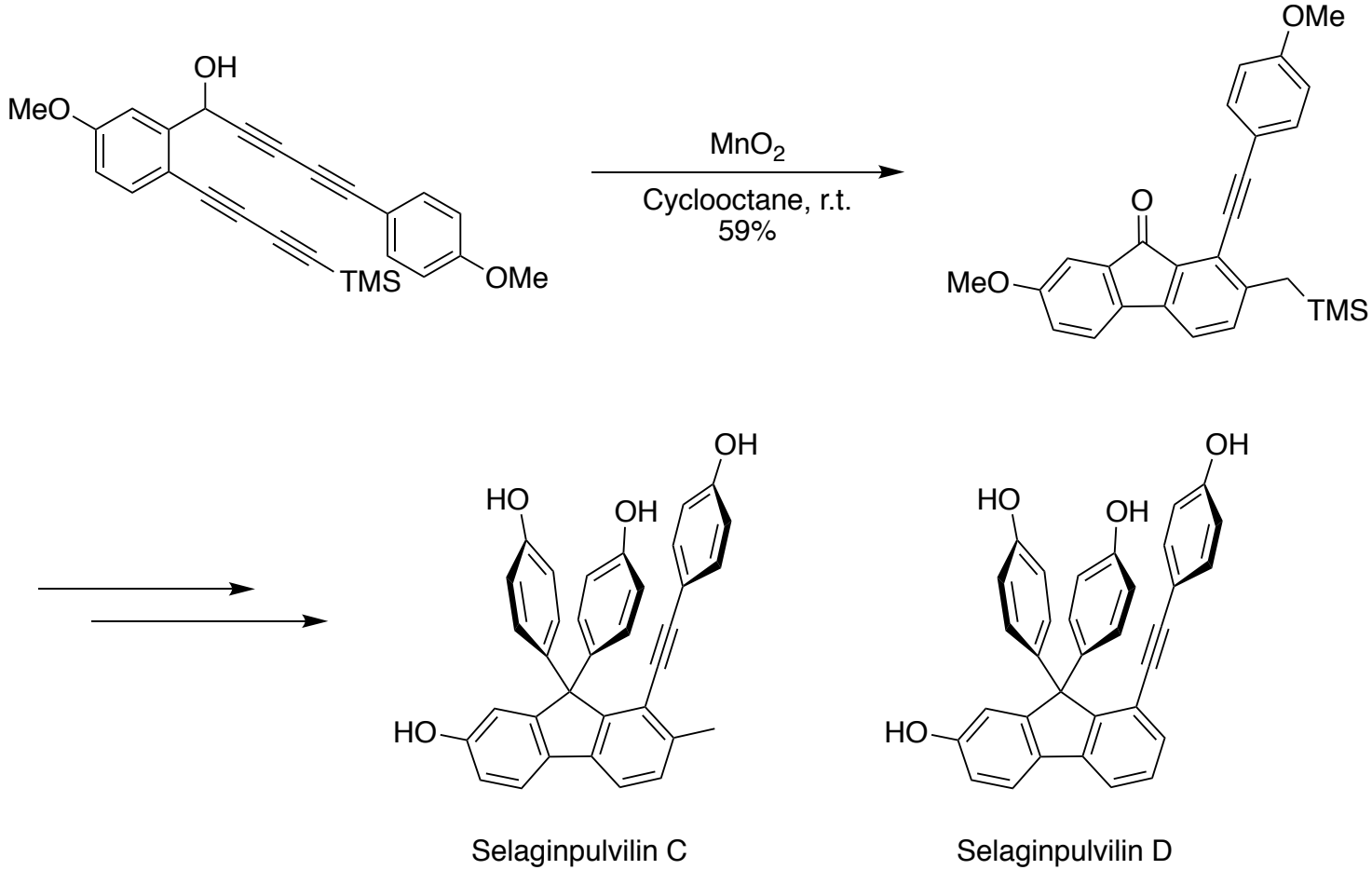
J. Am. Chem. Soc.20161384213870-13873

Hoye's Synthesis of Koenigii Alkaloids



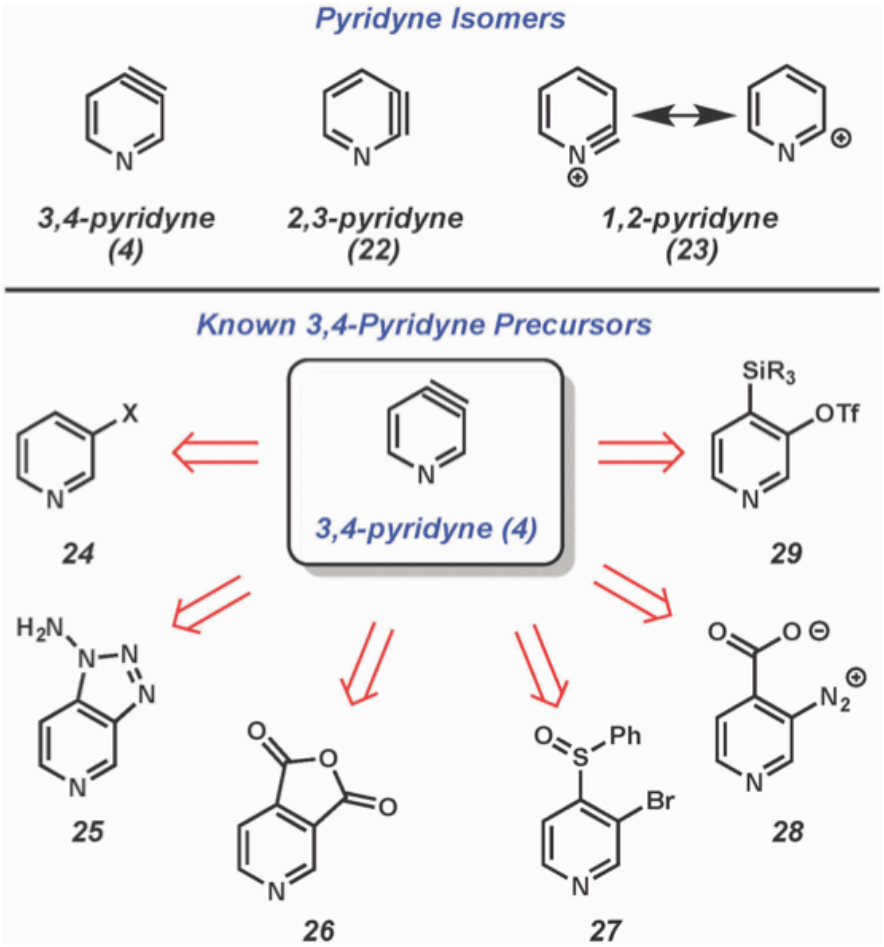
J. Am. Chem. Soc.20161384213870-13873

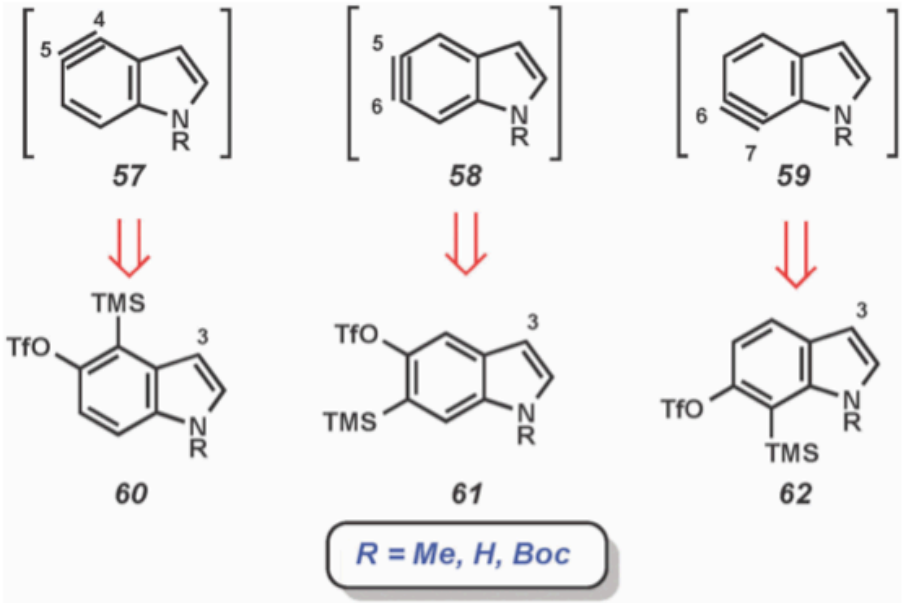
Lee's Synthesis of Selaginpulvilin C and D



Org. Lett.201618236105-6107

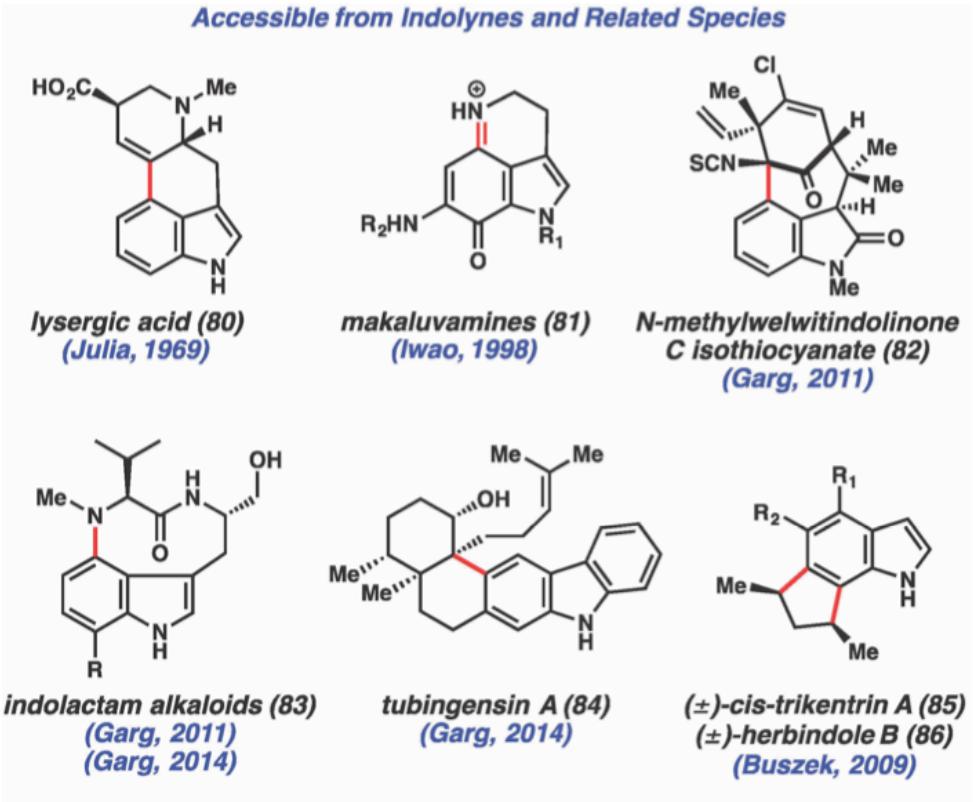
Heteroarynes

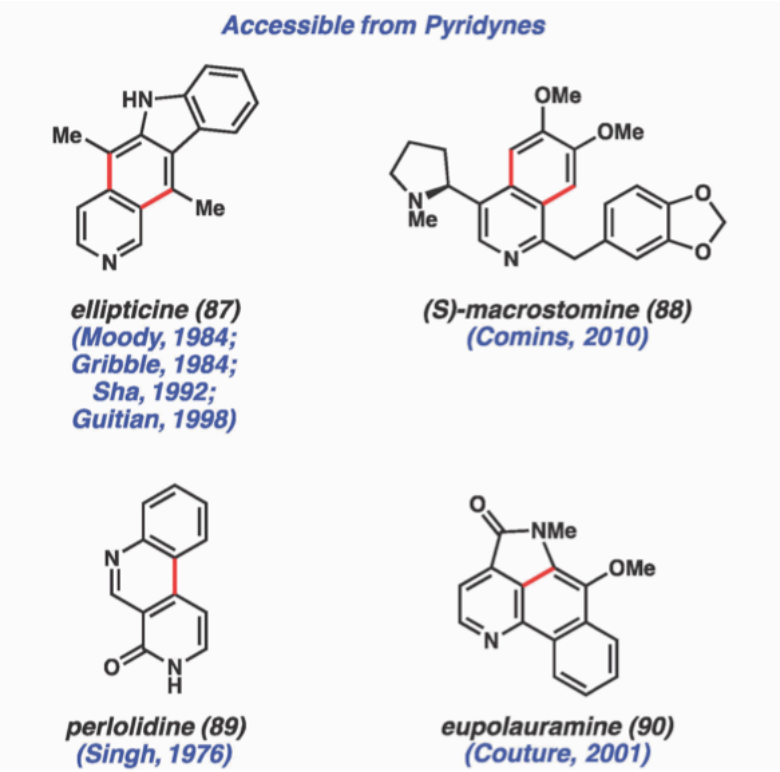




Chem. Commun., 2015, 51, 34

Total Syntheses Utilizing Heteroarynes

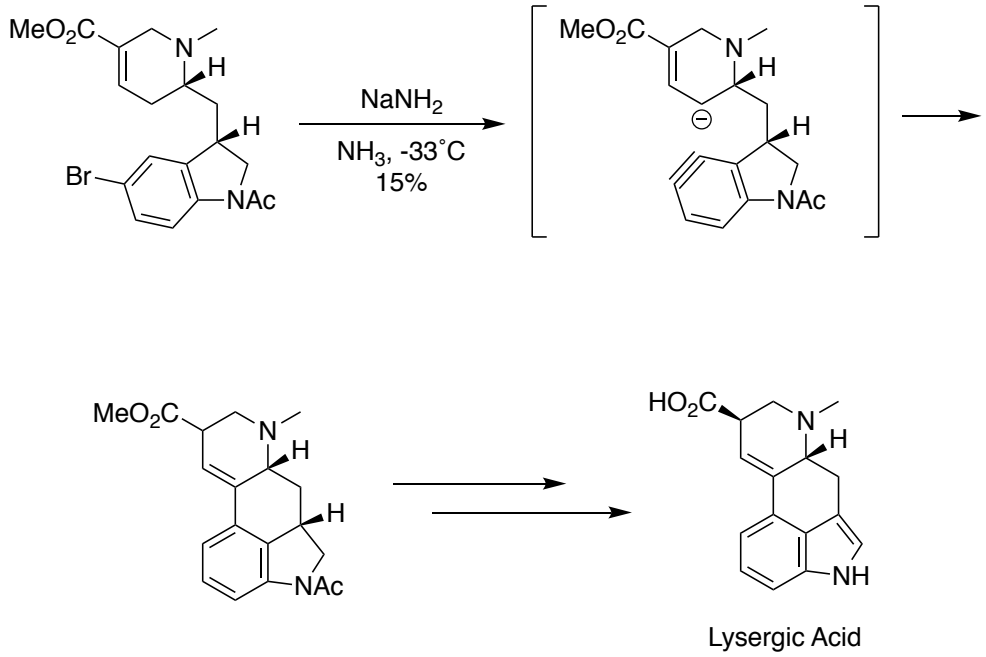




Chem. Commun., 2015, 51, 34

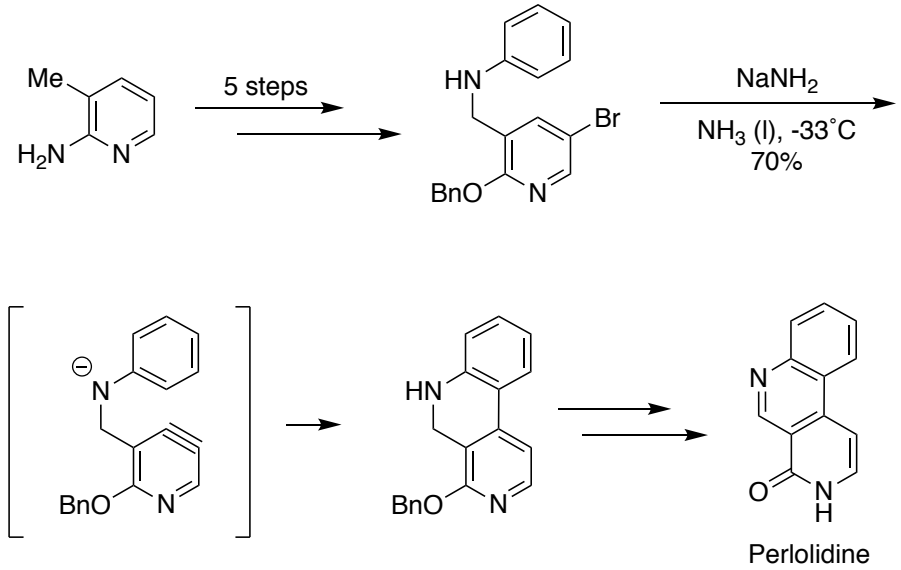
Historical Heteroaryne Total Syntheses

Julia's Synthesis of Lysergic Acid (1969)



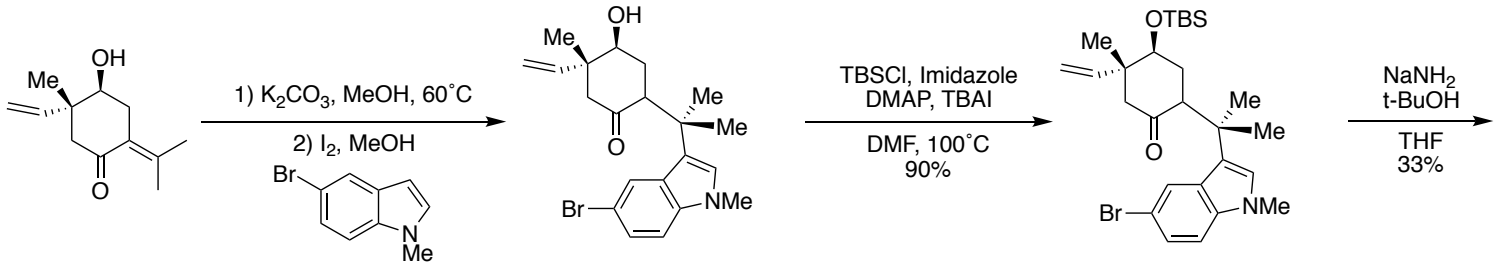
Acad. Sci., Ser. C, 1967, 265, 110–112.

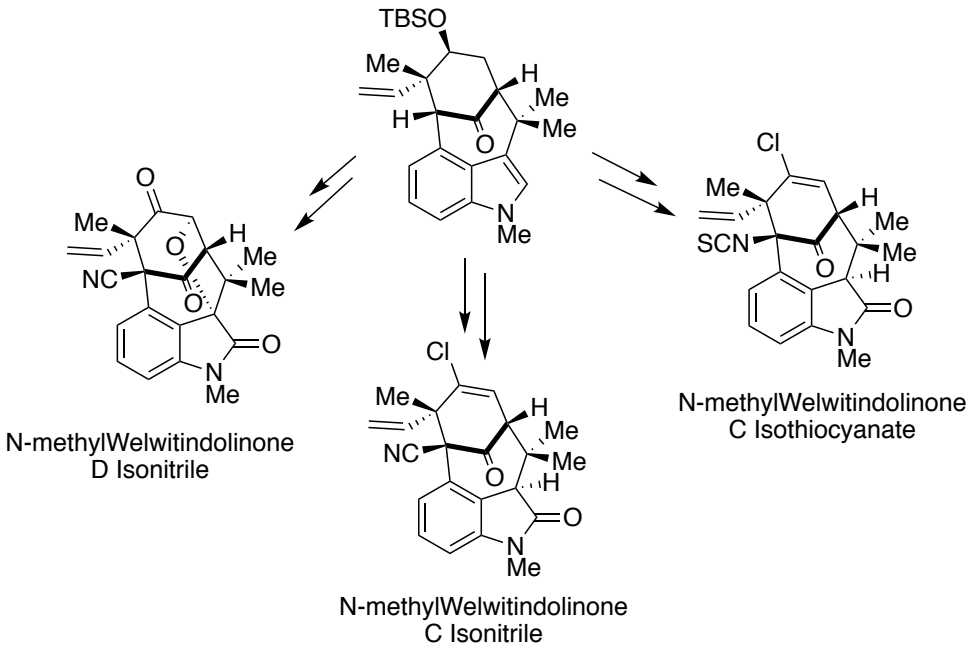
Singh's Synthesis of Perlolidine (1976)



Tetrahedron Lett., 1976, 17, 3207–3208

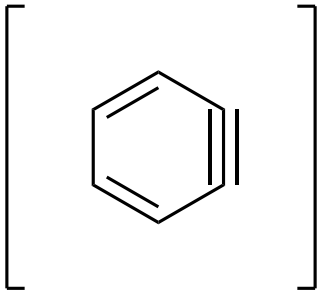
Garg's Synthesis of Welwitindolinones (2011-2013)





Angew. Chem. Int. Ed. **2012**, *51,* 3758–3765

Conclusions



- Arynes are versatile and highly reactive intermediates
- Both the forming and trapping of arynes affords many synthetic opportunities
- Despite their high reactivity they are incredibly selective
- Still highly underdeveloped modes of action that will further increase their synthetic utility

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