"Flatland": Logic and Methods in the Synthesis of Benzenoids

Steven McKerrall

Introduction

-Scope: -The synthesis and substitution chemistry of simple and complex benzenoid aromatics
-Logic in the synthesis of complex polycyclic benzenoids

-Not covered: Heterocyclic aromatics, Polymer chemistry, etc.
-See Also:
Directed Metalation (Krawczuk, 2008)
Atropselective Biaryl Synthesis (Gulder, 2008)
Direct sp3-sp2 Coupling (Lin, 04)

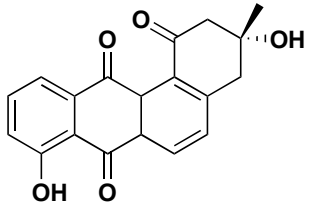
Background:

-Benzene was first isolated by Michael Faraday in 1825
-1:1 Hydrogen to carbon ratio and unusual chemistry was perplexing to chemists who proposed a variety of possible polycyclic and/or polyene structures

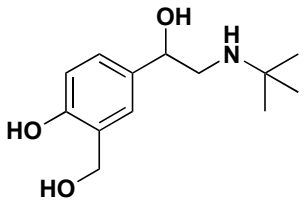
Claus (1867) Dewar (1867) Ladenburg (1869) Thiele (1899) Kekule (1865)

-The structure of benzene was firmly established with X-Ray crystallography by Kathleen Lonsdale in 1929

-Benzenoids are ubiquitous and found in all classes of natural products, pharmaceuticals, materials, etc.

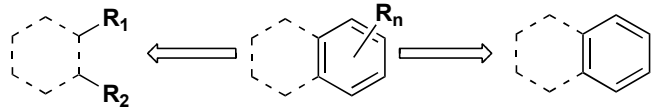


Tetrangomycin



Salbutamol

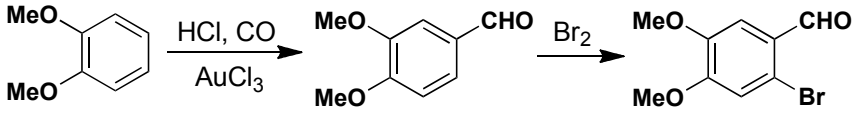
Synthesis of Benzenoids: Substitution versus Synthesis



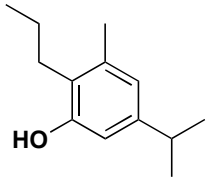
The key choice in the retrosynthesis of a benzenoid is whether to use substitution chemistry or synthesis to prepare the substituted aromatic

General Guidelines:

In the synthesis of simple to moderately substituted benzene derivatives (<4 substituents), venerable substitution methods are generally used



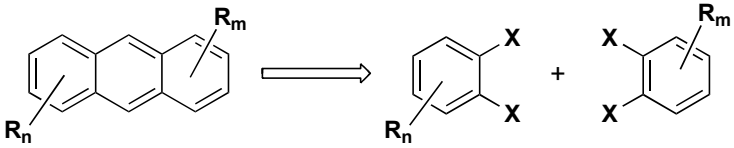
Polyalkyl substituted benzenes can be challenging to prepare by substitution methods and often need to be synthesized



Alkyl or Aryl fused benzene rings are efficiently synthesized via a variety of methods

Most substituted naphthalenes are more easily synthesized than substituted

Fused polycyclic aromatics can be synthesized in a highly convergent manner



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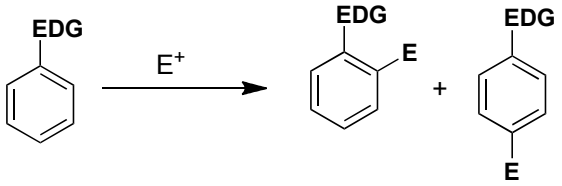
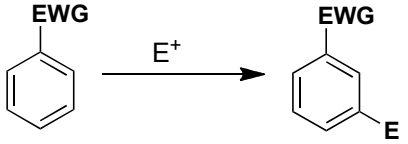
Substitution Methods on Benzenes

Electrophillic Substitution

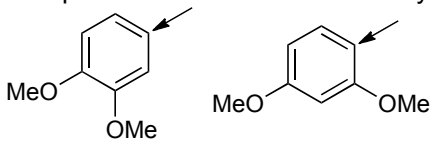


-Sterics favor para but mixtures are usually seen
-Polysubstitution is common

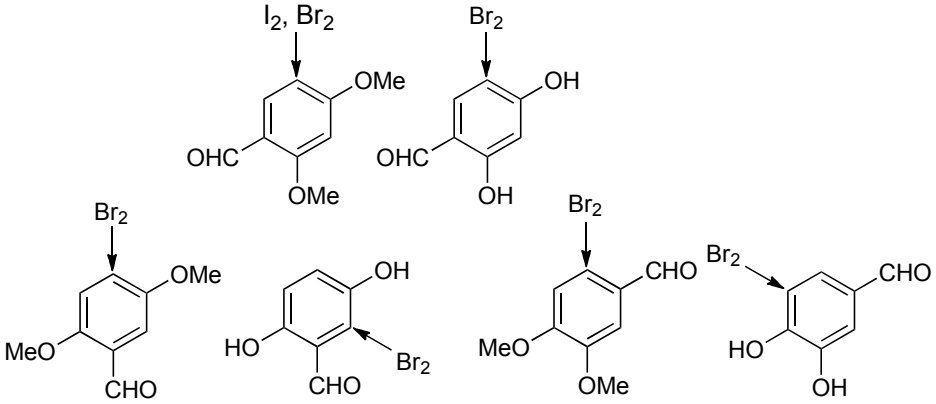


In general selective, reduced polysubstitution

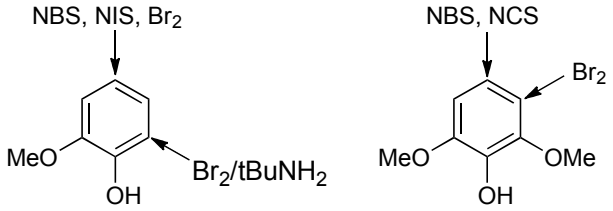
In systems with multiple electronic factors selectivity is very common



Highly substituted benzenes give highly selective reactions, but the selectivity is largely empirical



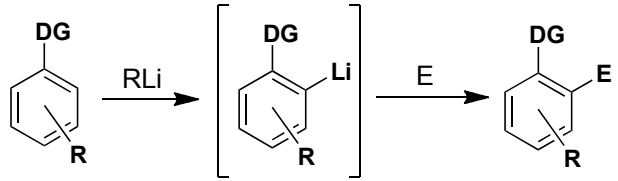
Selectivity can even be governed by reagents and conditions



Electrophillic substitution methods are mose useful (selective) on systems containing a number of electronically active groups

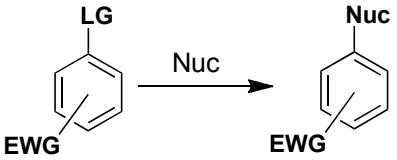
Directed Metalation

See: Directed Metalation: A Survival Guide (Krawczuk, 2008)

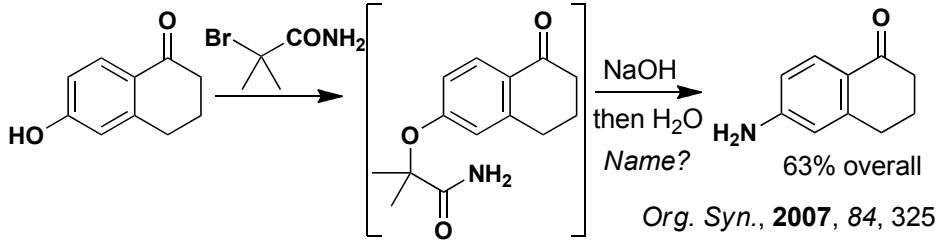


DG=SO_2R, SOR, $CONR_2$, CONHR, CO_2H, MOM, OAr, CN, etc.
E=RCHO, RCOR', RX, CO_2, TMSCl, Ac_2O, RNCO, X_2

Nucleophillic Substitution



-Generally requires one or more electron withdrawing groups on the arene
-Intramolecular case proceeds under much milder conditions



63% overall

Org. Syn., **2007**, *84*, 325

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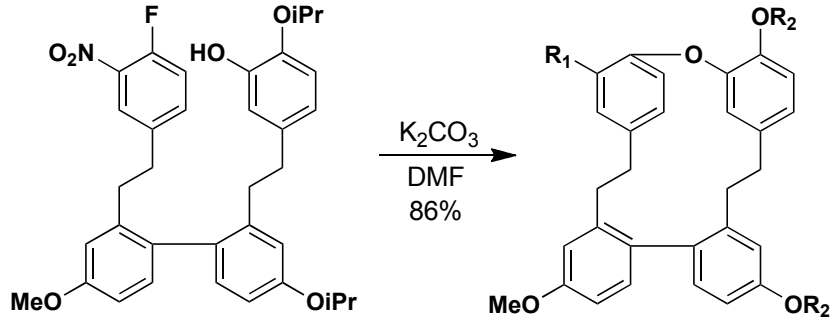
Nucleophillic Substitution (cont.)



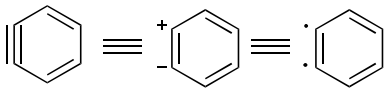
Prepared in 50% overall yield
6 steps from simple aromatic compounds

3 Steps 84% → R_1=NO_2, R_2=iPr → R_1=R_2=H

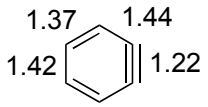
Plagiochin D

Eur. J. Org. Chem., **2011**, 3165-3170

Benzyne Substitution



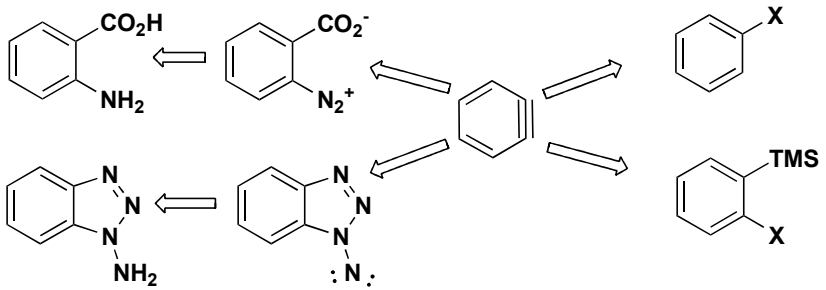
The significant distortion inherent arynes makes them highly powerful electrophiles



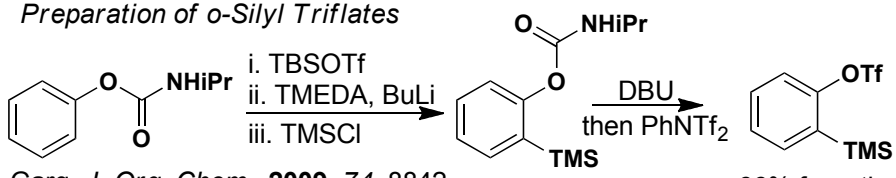
Computed Bond Lengths

Chem. Soc. Special Publ., **1958**, 100

Benzyne can be generated from several different starting materials

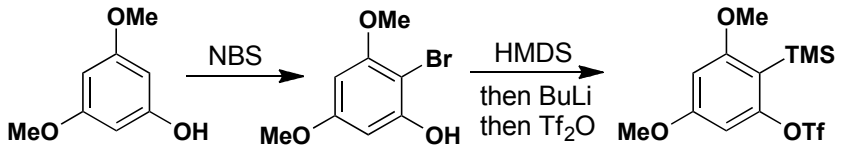


Preparation of o-Silyl Triflates



Garg, *J. Org. Chem.*, **2009,** *74*, 8842

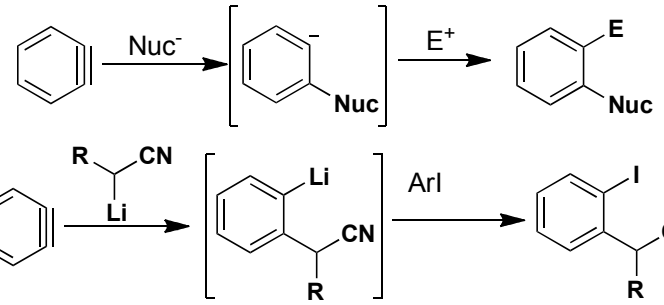
66% from the phenol



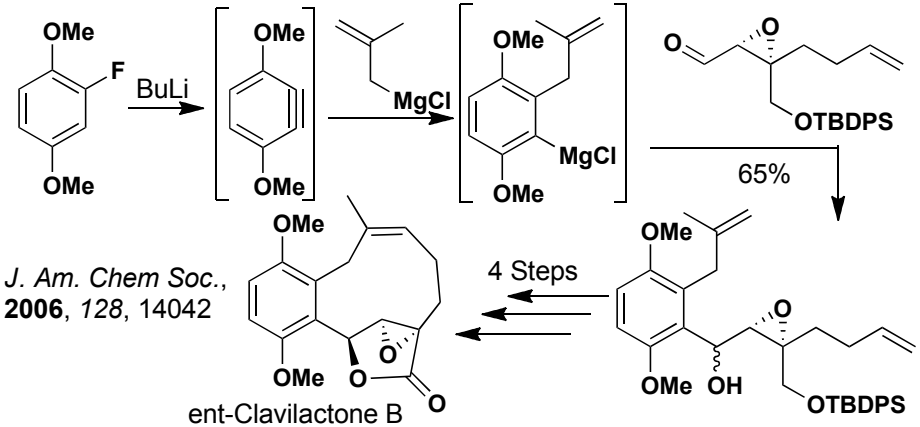
Stoltz, *Org. Lett.*, **2010**, *12*, 1224

42% overall

Substitutions on arynes



Tet. Lett., **2000**, *41*, 8401



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

ent-Clavilactone B

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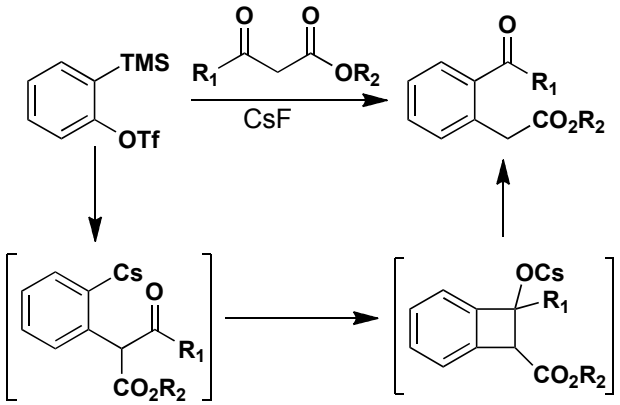
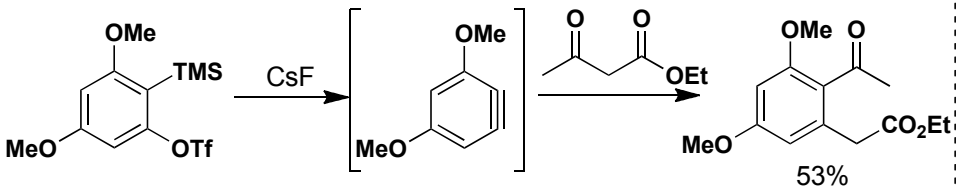
Benzyne Substitution (cont.)



Various cyclic and acyclic ketoesters work

50-90% yield

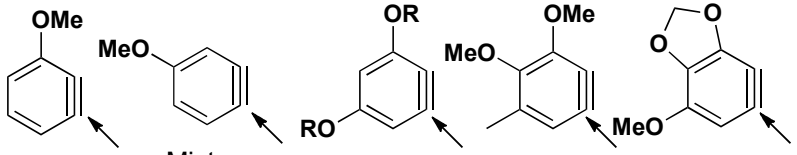
Stoltz, *J. Am. Chem. Soc.*, **2005**, *127*, 5340



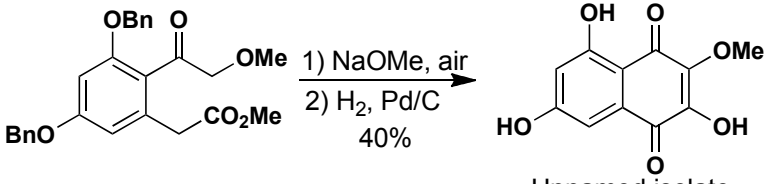
Unsymmetrical Benzyne

53%

Only observed product

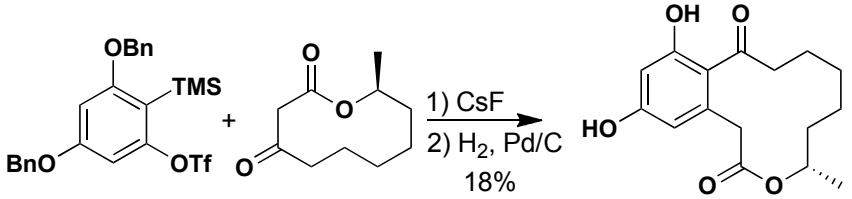


Mixture



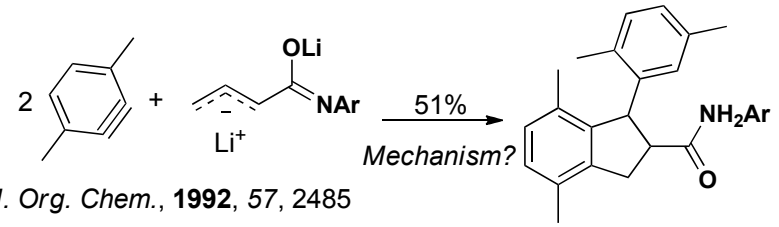
Stoltz, *Org. Lett.*, **2010**, *12*, 1224

Unnamed isolate from *Cercospora*



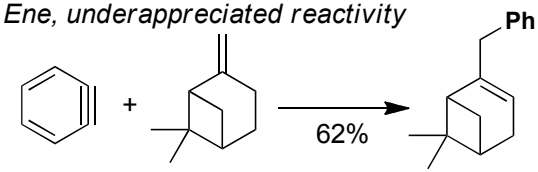
Org. Lett., **2010**, *12*, 1612

(-)-Curvularin



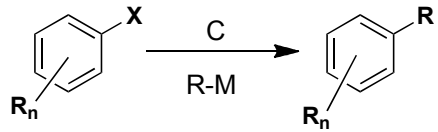
J. Org. Chem., **1992**, *57*, 2485

Benzyne Ene, underappreciated reactivity



J. Am. Chem Soc., **1974**, *96*, 4207

Cross Coupling Reactions



X=Cl, Br, I, OTf, $OPO(OR)_2$, etc.
C=Pd, Cu, Ni, Fe
M=$B(OR)_2$, SnR_3, Si, ZnX

-Useful for modular syntheses
-Useful for substituted biary compounds
-Not generally useful when one coupling partner is simple (phenyl, tolyl, etc)
-When plannaing it can be compared with some substitution methods (benzyne)
-Simple or easily accessable aromatics can be incorporated in synthesis

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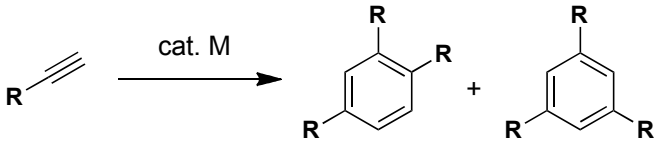
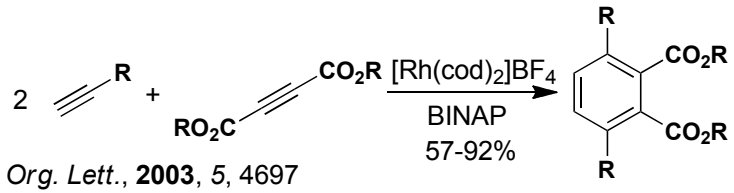
Synthesis of Isolated Benzene Rings

[2+2+2] Cycloaddition

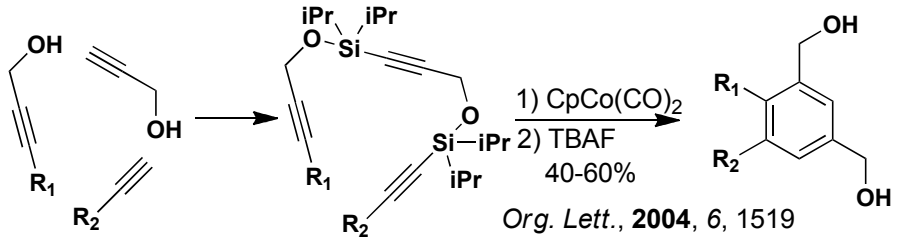


In most cases the intermolecular trimerization is problematic and mixtures of regioisomers is common

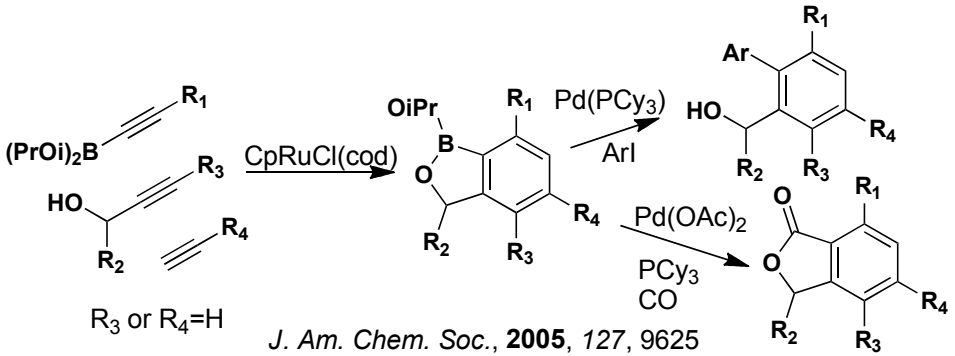


Org. Lett., **2003**, *5*, 4697

Regioselectivity is achieved by using one coupling partner that is significantly less reactive in the initial cyclometalation



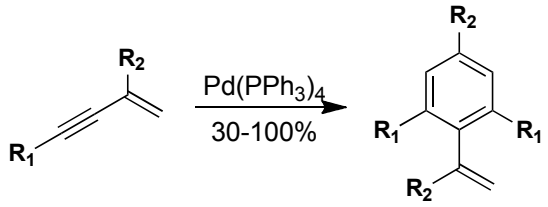
Org. Lett., **2004**, *6*, 1519



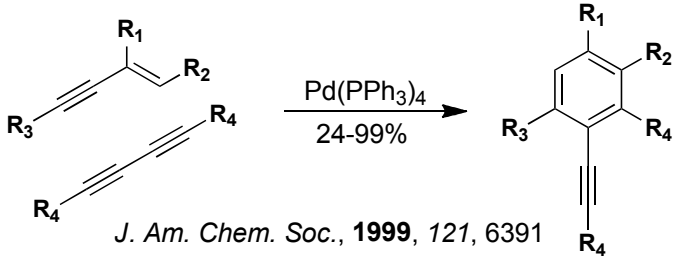
R_3 or R_4=H

J. Am. Chem. Soc., **2005**, *127*, 9625

Dehydro-Diels-Alder Reaction

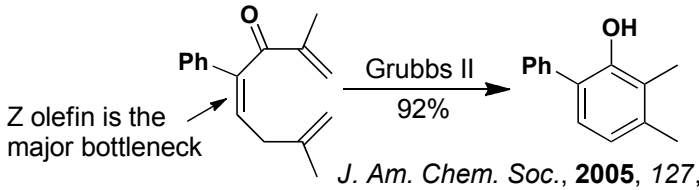


J. Am. Chem. Soc., **1996**, *118*, 4218
J. Org. Chem., **1998**, *63*, 7022



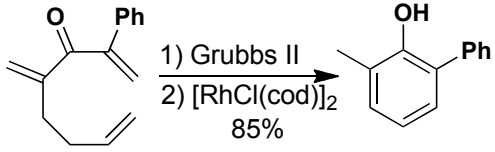
J. Am. Chem. Soc., **1999**, *121*, 6391

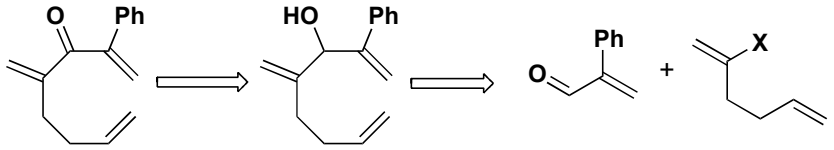
Metathesis



J. Am. Chem. Soc., **2005**, *127*, 10470

While the reaction is efficient, the synthesis of RCM substrates is not trivial





Chem. Eur. J., **2008**, *14*, 9706

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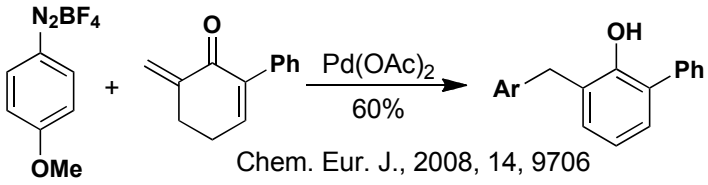
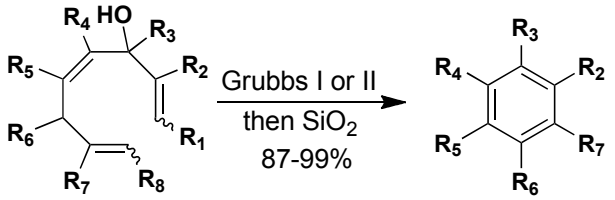
Metathesis (cont.)

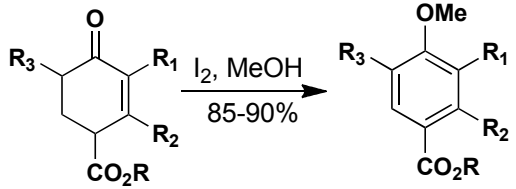


Chem. Eur. J., 2008, 14, 9706



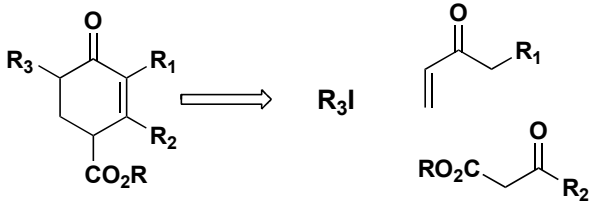
Synthesis of cis olefin is challenging, only tenable systems are fused at R_4 and R_5

Oxidation of Cyclohexenones



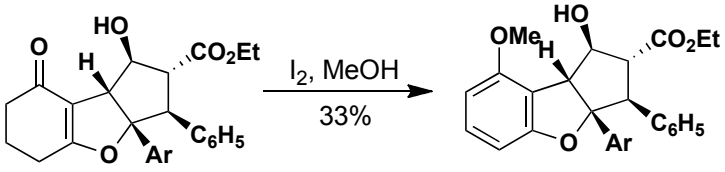
Hagemann's Ester Derivatives

Tet. Lett., **1990**, *31*, 481

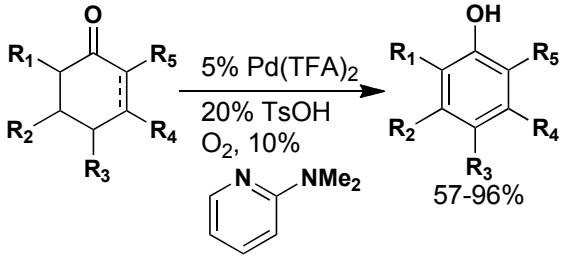


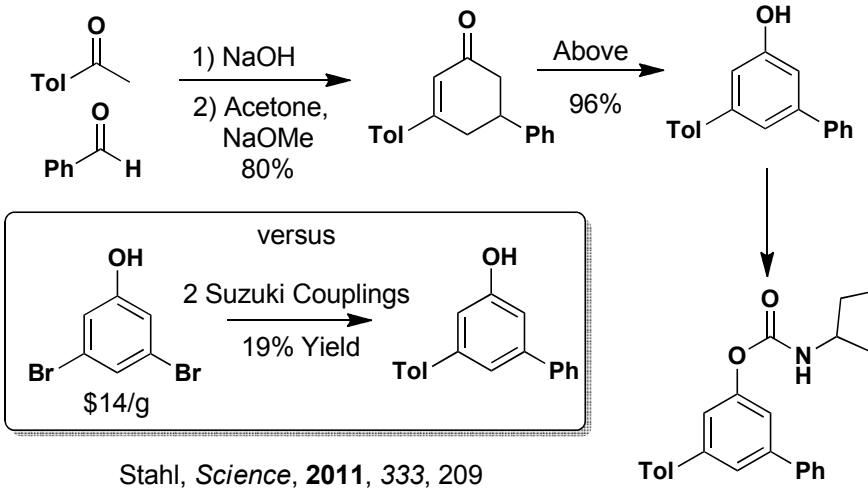
Synthesis and chemistry of Hagemann's Ester: *Tet.*, **2010**, *66*, 2775

-Synthesis of highly substituted cyclohexenones is very well known
-Extremely useful for polyalkyl phenols and anisoles
-Oxidative aromatization to phenols is also possible with I_2/tBuOH or Pd/C

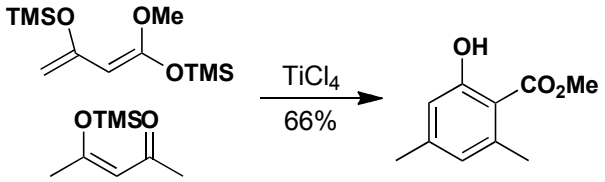


Tet. Lett., **2000**, *41*, 1913





Stahl, *Science*, **2011**, *333*, 209



J. Am. Chem. Soc., **1980**, *102*, 3534

See Also: Poly(B-carbonyl)s (Michaudel, 2011)

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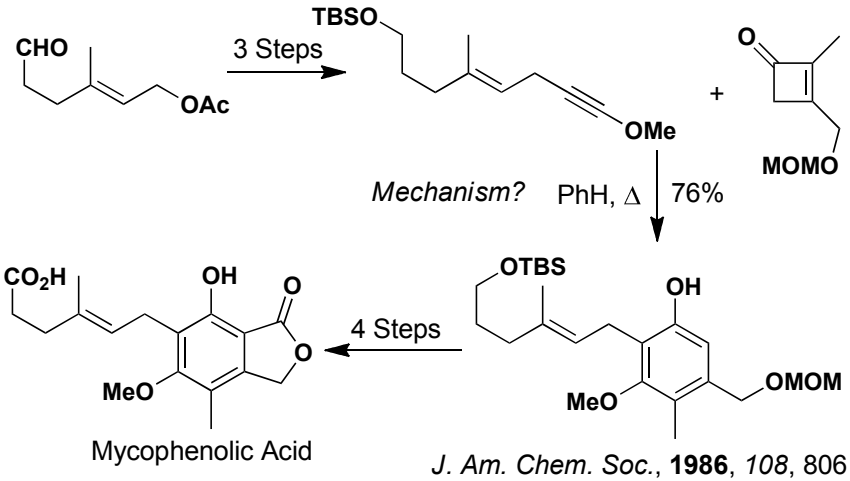
Misc. Other Methods

Danheiser Annulation Preview



Mycophenolic Acid

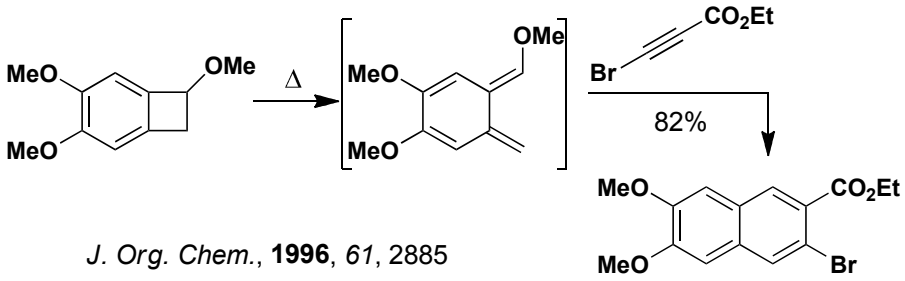
J. Am. Chem. Soc., **1986**, *108*, 806

Naphthalenes and higher order fused polyaromatics

Substitution of Naphthalenes

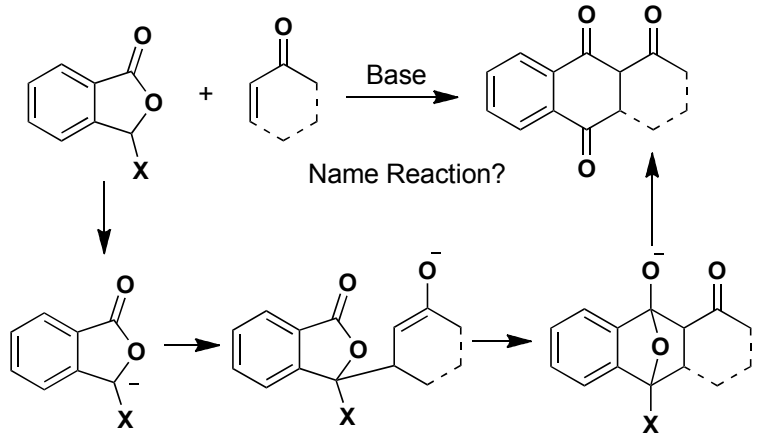
-Electrophillic Substitution, Directed Metalation, S_nAr, etc can be used to prepare moderately functionalized Naphthalenes
-Chemistry is very similar to that of benzenes
-In most cases naphthalenes bearing 4 or more substituents are synthesized because of regiochemical issues

o-Quinodimethanes



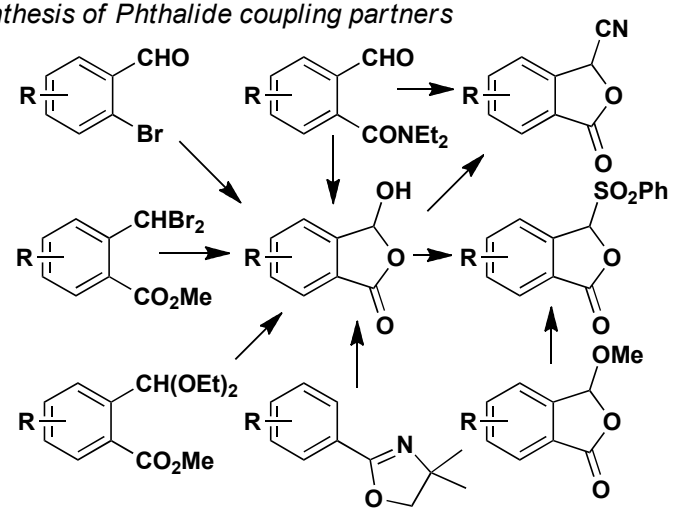
J. Org. Chem., **1996**, *61*, 2885

Phthalide Annulations



X=CN, SO_2Ph, SPh,

Synthesis of Phthalide coupling partners



A wide variety of starting materials can be used to quickly synthesize Phthalide donors, allowing for the facile synthesis of highly substituted donors via previously discussed methods

Chem. Rev., **2007**, *107*, 1892

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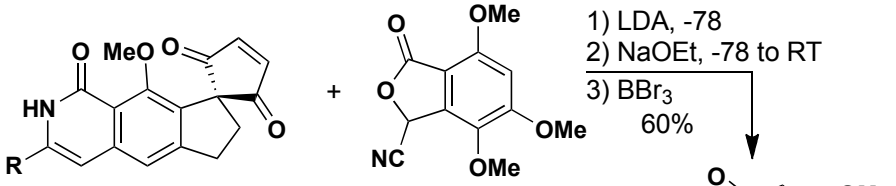
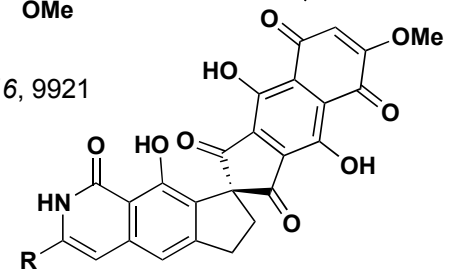
Phthalide Annulations (cont.)

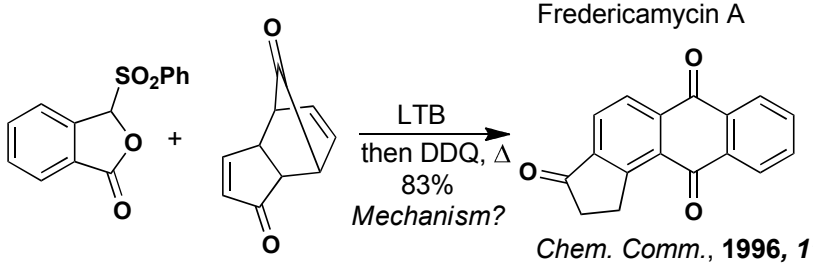
Hauser annulations are extremely useful for the convergent synthesis of oxygenated poly aromatics



Bach, *J. Am. Chem. Soc.*, **1994**, *116*, 9921

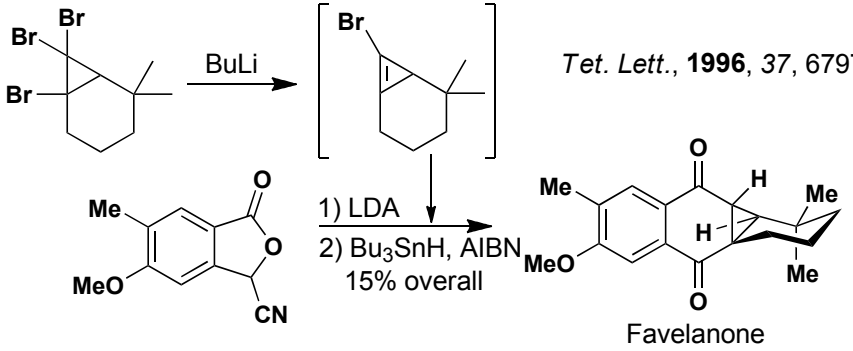


Fredericamycin A



Chem. Comm., **1996**, ***1181***

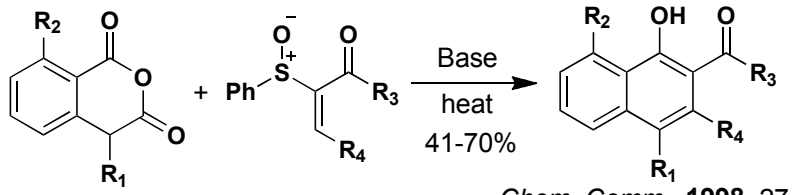
Unlikely Acceptor



Tet. Lett., **1996**, *37*, 6797

Favelanone

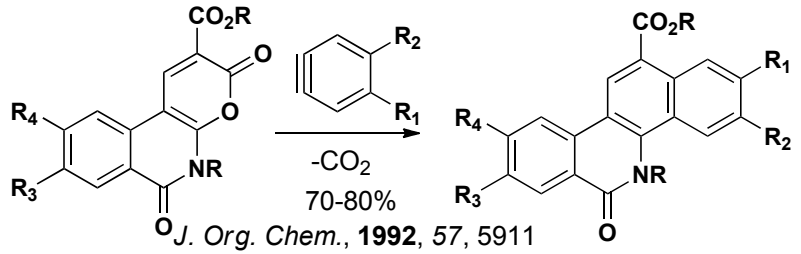
Modified Hauser Reactions



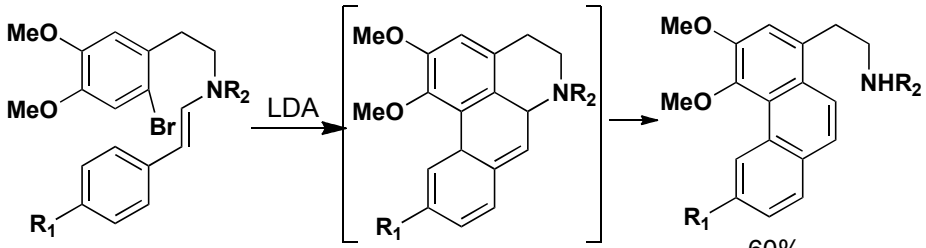
Chem. Comm., **1998**, 2741

Benzyne Cycloadditions

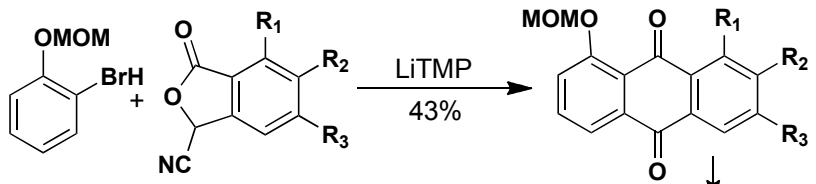
In addition to being powerful electrophiles arynes are very powerful dieneophiles



J. Org. Chem., **1992**, *57*, 5911



Tet. Lett., **1992**, *33*, 6883



Tetrahedron, **2003**, *59*, 3201

Mumbaistatin

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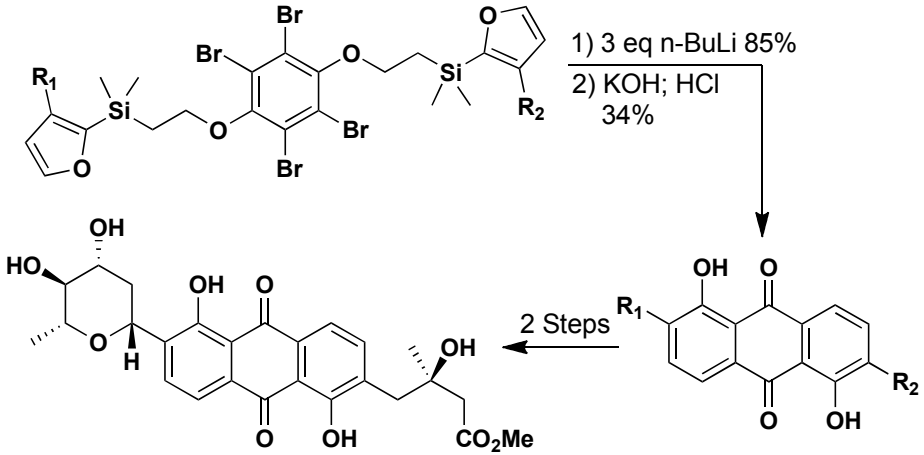
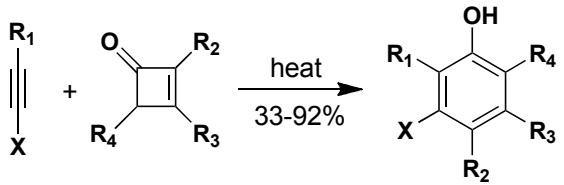


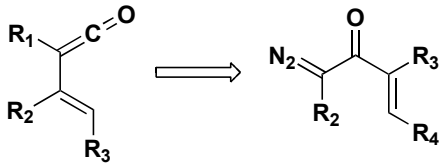
Martin, *J. Am. Chem. Soc.*, **2006**, *128*, 13696

Danheiser Benzannulation and Related Reactions



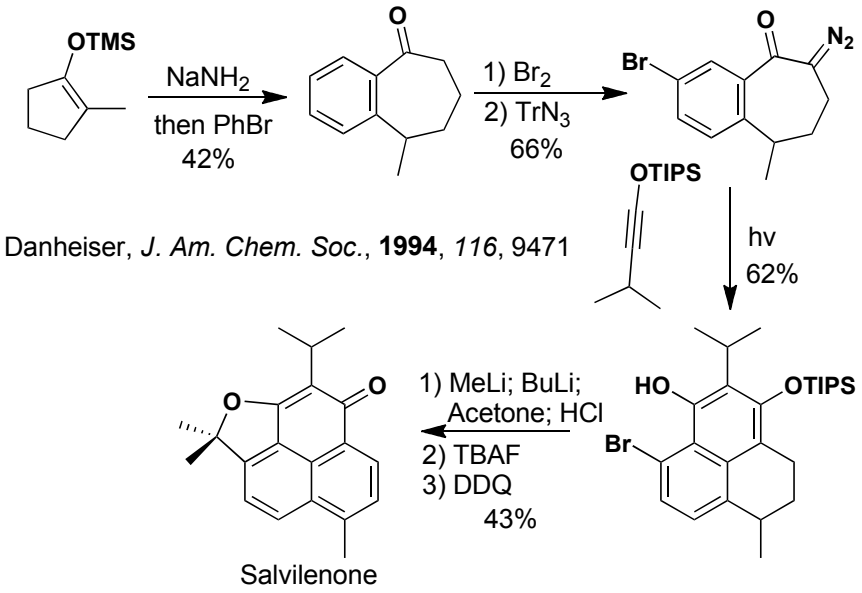
Danheiser, *J. Org. Chem.*, **1984**, *49*, 1672

-Lack of general methods for many heterosubstituted alkynes is a significant drawback
-Cyclobutenones are non-trivial to synthesize



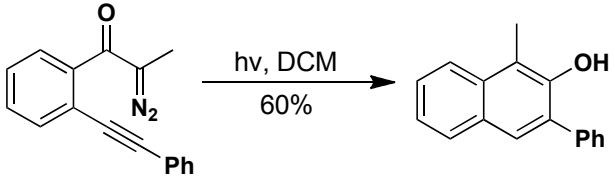
Key intermediate is also available from a photochemical Wolff Rearrangement

Danheiser, *J. Am. Chem. Soc.*, **1990**, *112*, 3093



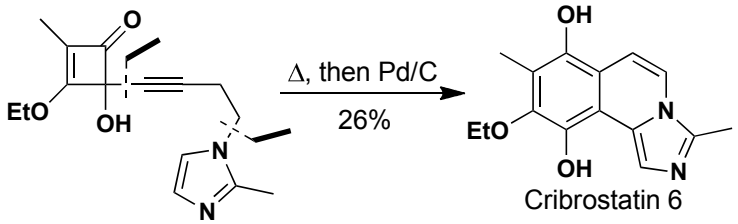
Danheiser, *J. Am. Chem. Soc.*, **1994**, *116*, 9471

Normal alkynes can be used in both inter and intramolecular cases



Padwa, *Tet. Lett.*, **1991**, *32*, 5923

It is likely a diradical mechanism in these cases



Martin, *Angew. Chem. Int. Ed.*, **2009**, *48*, 2569

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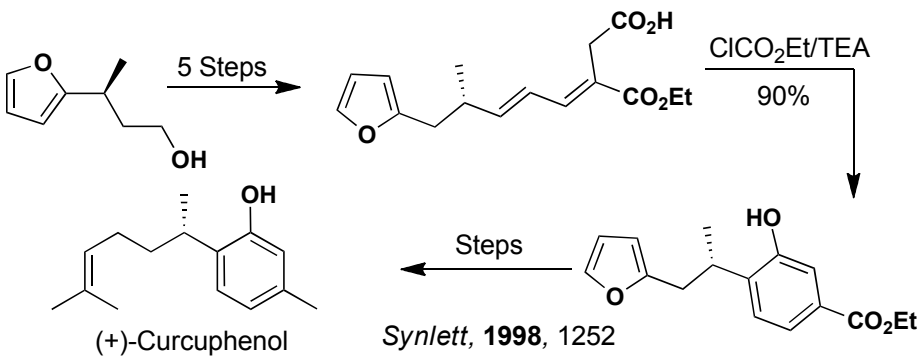
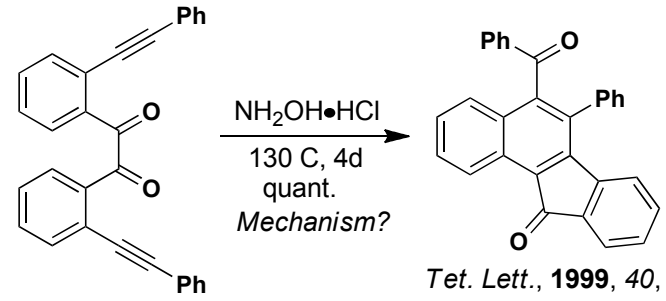


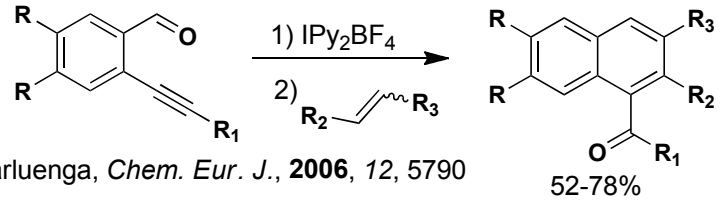
(+)-Curcuphenol

Synlett, **1998**, 1252

Acid Mediated Ring Closures

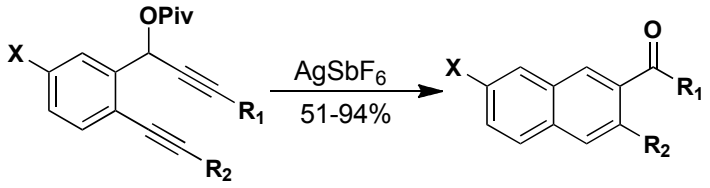


Tet. Lett., **1999**, *40*, 7457



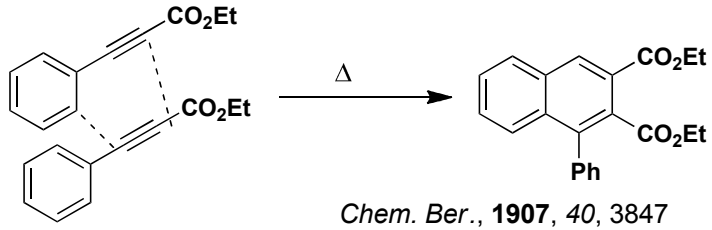
Barluenga, *Chem. Eur. J.*, **2006**, *12*, 5790

52-78%



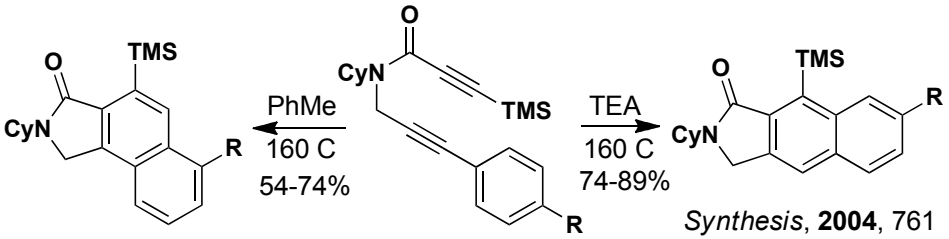
Toste, *J. Am. Chem. Soc.*, **2006**, *128*, 7436

Dehydro-Diels-Alder



Chem. Ber., **1907**, *40*, 3847

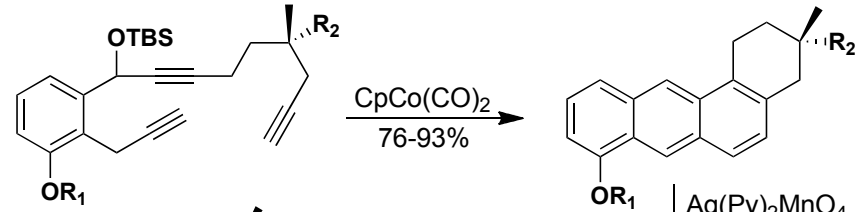
-Reaction can be done inter or intramolecularly (tether)
-In general the yields and regioselectivities are modest

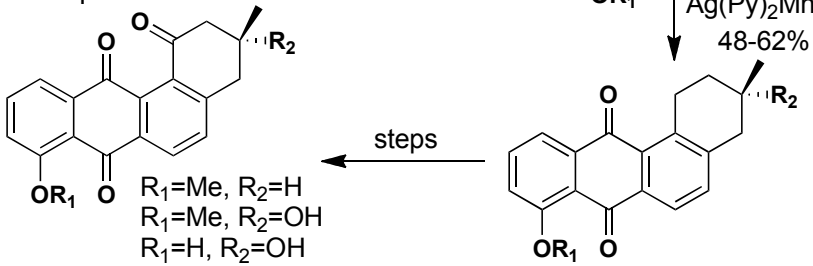


Synthesis, **2004**, 761

Mechanism is complex, involves isomerization versus reopening/reclosing of the initial intermediate

[2+2+2] Cycloaddition





Angucyclinone Antibiotics

Chem. Eur. J., **2010**, *16*, 8805

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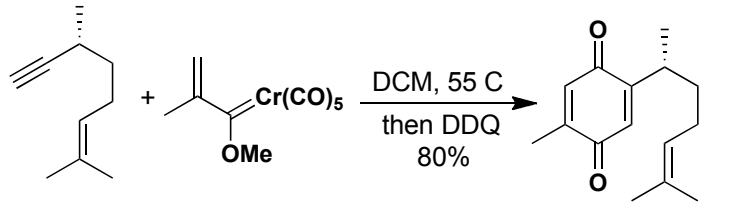
Chromium Carbene

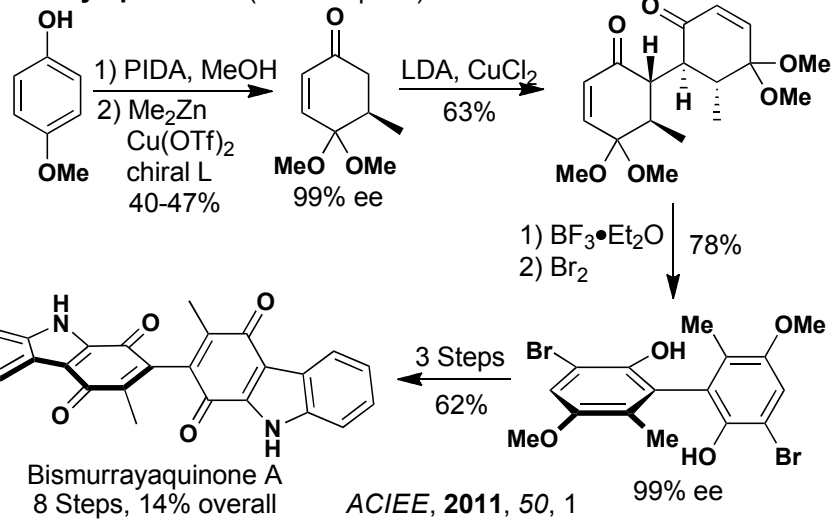


J. Org. Chem., **2005**, *70*, 3745

(-)-curcuquinone

Selected Total Syntheses

Bismurrayaquinone A (R. Thompson)

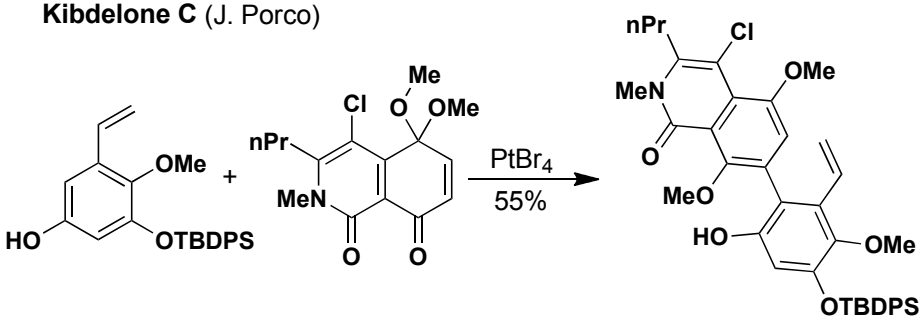


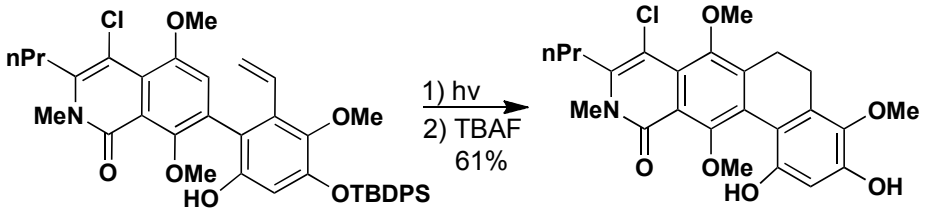
Bismurrayaquinone A
8 Steps, 14% overall

ACIEE, **2011**, *50*, 1

99% ee

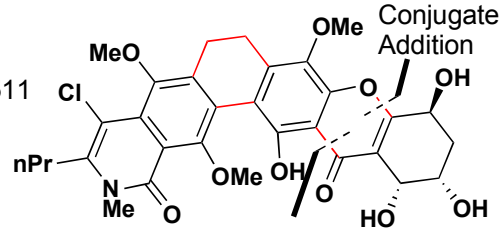
Kibdelone C (J. Porco)





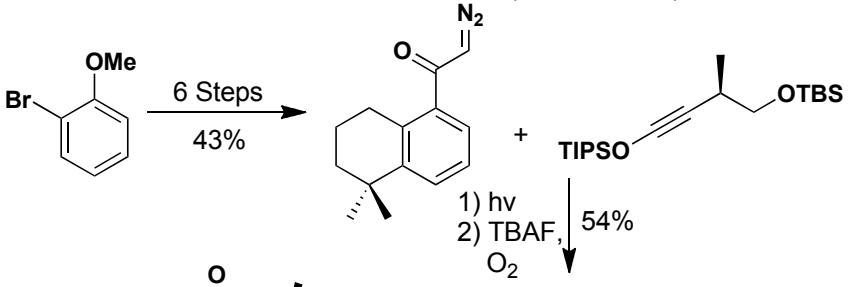
Steps

Angew. Chem. Int. Ed., **2011**, *50*, 2511
J. Am. Chem. Soc., **2011**, *133*, 9952



Kibdelone C Friedel-Crafts

Fused Dan Shen Diterpenoid Quinones (R. Danheiser)



-Cryptotanshinone
-Tanshinone IIA (Δ1,2

J. Org. Chem., **1995**, *60*, 8341

Neocryptotanshinone
8 Steps 23% Overall

Further Reading

General:
Tet., **2003**, *59*, 7
Chem. Rev., **2000**, *100*, 2901

o-Quinonedimethanes:
Chem. Rev., **1999**, *99*, 3199
Tet., **2001**, *57*, 625

Electrocyclization:
Chem. Eur. J., **2007**, *13*, 6782

Arynes:
Tet., **2003**, *59*, 701
Chem. Rev., **1962**, *62*, 81

Metathesis:
Chem. Rev., **2009**, *109*, 3743

Dehydro-Diels-Alder
Chem. Rev., **2008**, *108*, 2051

Hauser Annulation
Chem. Rev., **2007**, *107*, 1892

Oxidative Aromatization
Molecules, **2009**, *14*, 5308