

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)



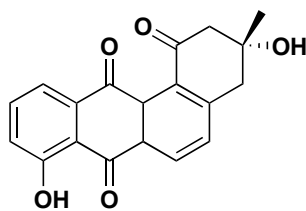
Thiele
(1899)



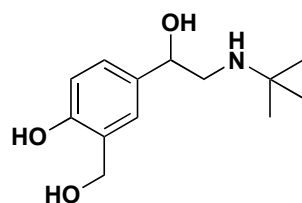
Kekule
(1865)

-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.

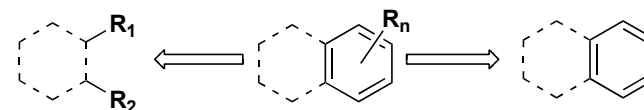


Tetrangomycin



Salbutamol

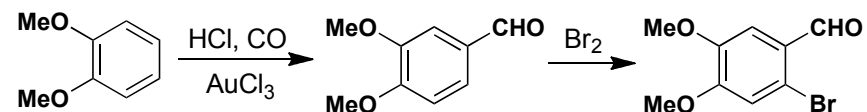
Synthesis of Benzenoids: Substitution versus Synthesis



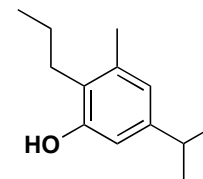
The key choice in the retrosynthesis of a benzenoid is whether to use substitution chemistry or synthesis to prepare the substituted aromatic

General Guidelines:

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



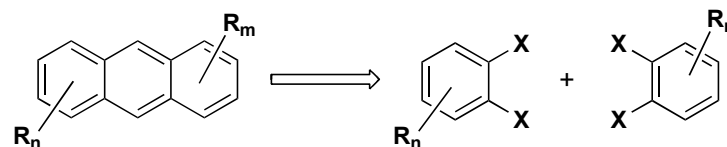
Polyalkyl substituted benzenes can be challenging to prepare by substitution methods and often need to be synthesized



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

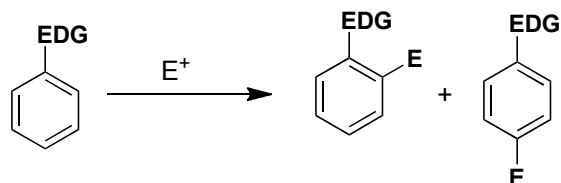
Most substituted naphthalenes are more easily synthesized than substituted

Fused polycyclic aromatics can be synthesized in a highly convergent manner

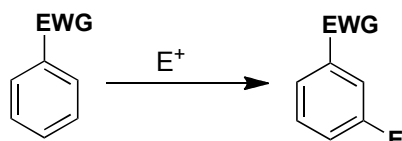


Substitution Methods on Benzenes

Electrophillic Substitution

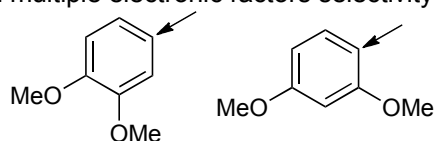


- Sterics favor para but mixtures are usually seen
- Polysubstitution is common

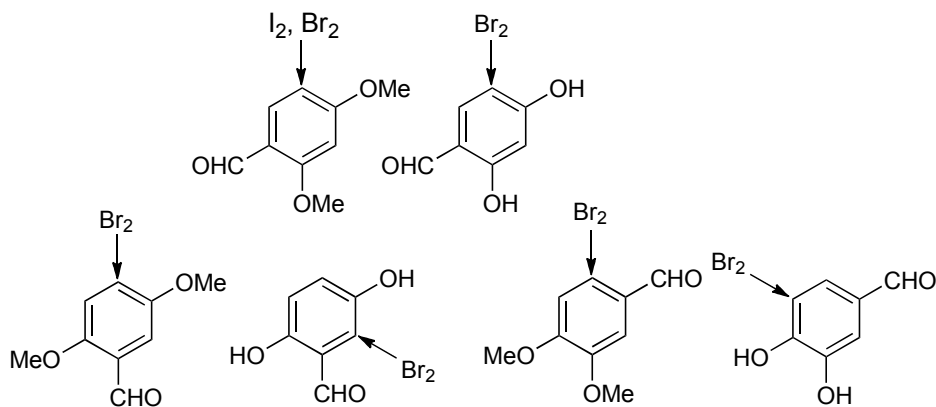


In general selective, reduced polysubstitution

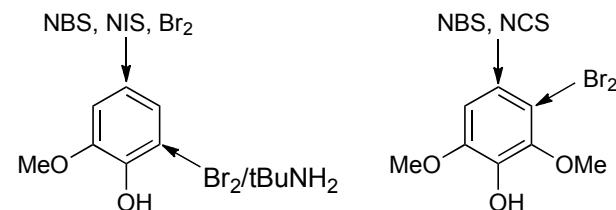
In systems with multiple electronic factors selectivity is very common



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



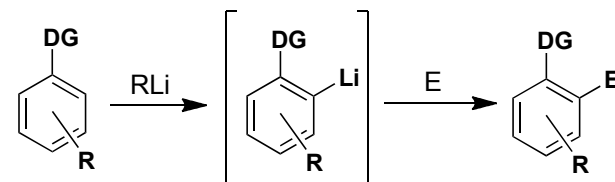
Selectivity can even be governed by reagents and conditions



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

Directed Metalation

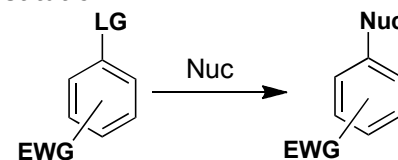
See: Directed Metalation: A Survival Guide (Krawczuk, 2008)



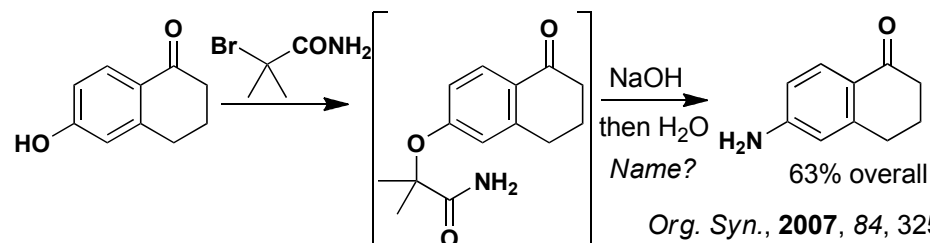
DG= SO_2R , SOR , $CONR_2$, $CONHR$, CO_2H , MOM , OAr , CN , etc.

E= $RCHO$, $RCOR'$, RX , CO_2 , $TMSCl$, Ac_2O , $RNCO$, X_2

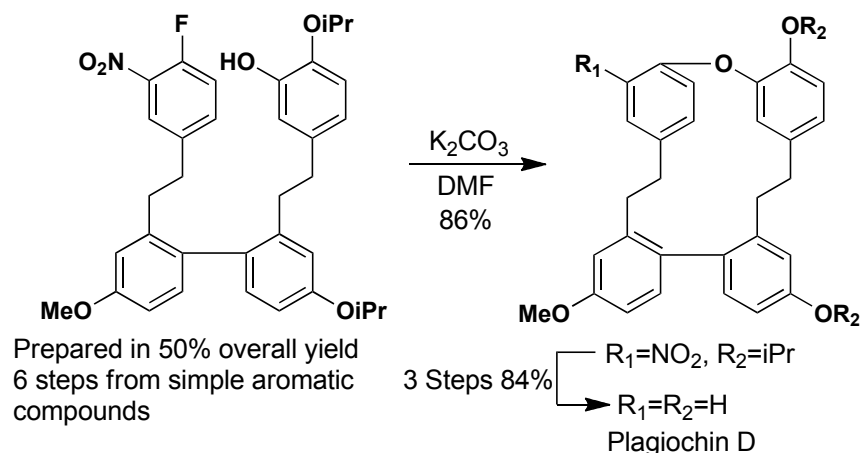
Nucleophilic Substitution



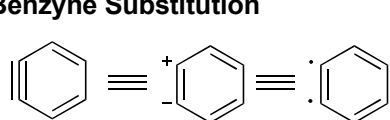
- Generally requires one or more electron withdrawing groups on the arene
- Intramolecular case proceeds under much milder conditions



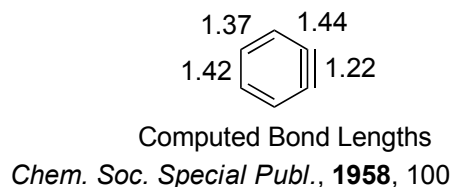
Nucleophilic Substitution (cont.)



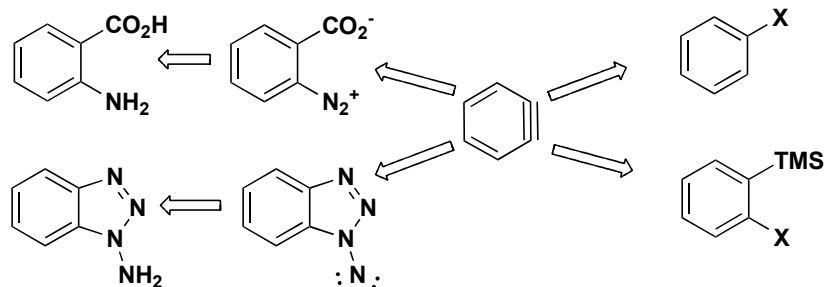
Benzyne Substitution



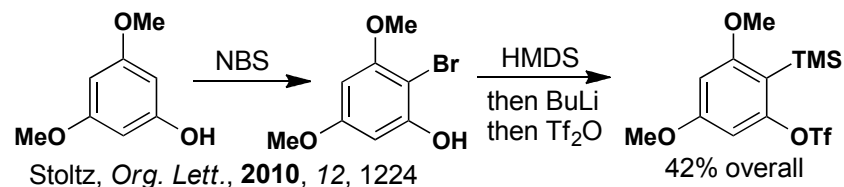
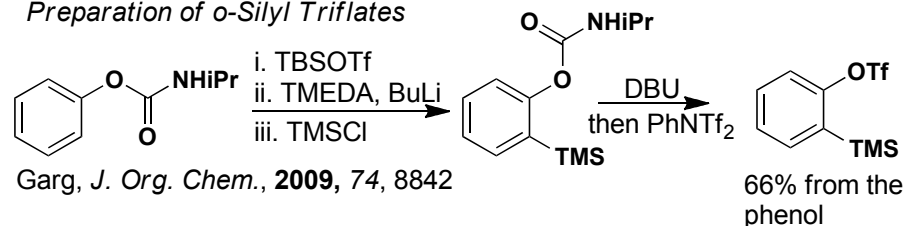
The significant distortion
inherent arynes makes them
highly powerful electrophiles



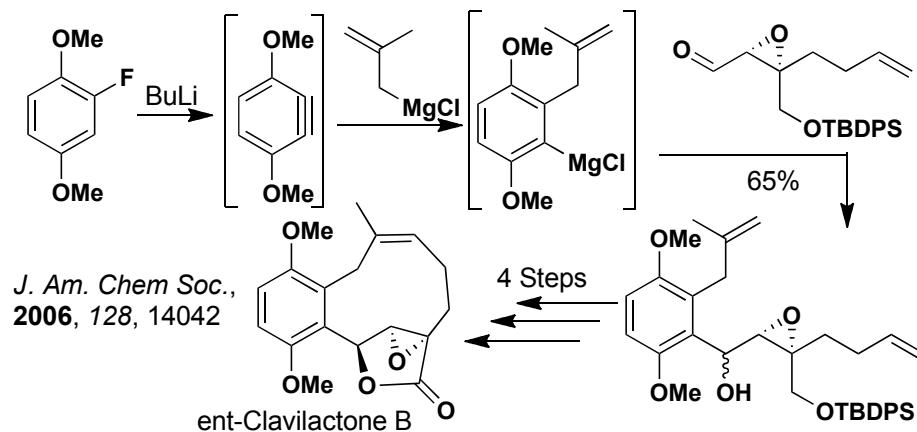
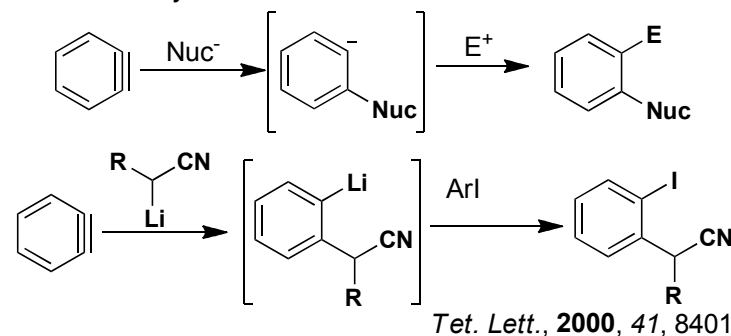
Benzyne can be generated from several different starting materials



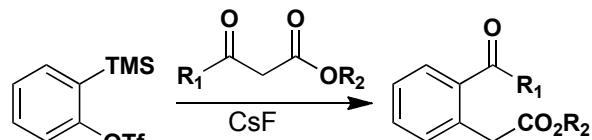
Preparation of *o*-Silyl Triflates



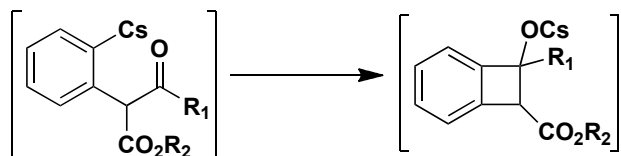
Substitutions on arynes



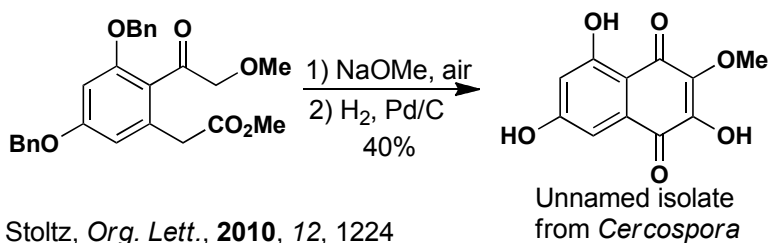
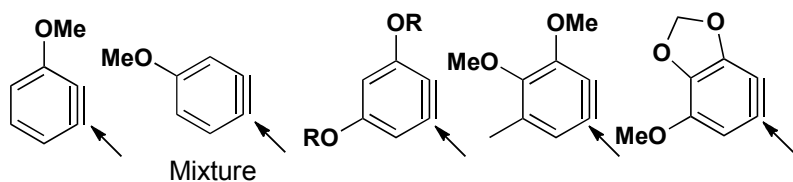
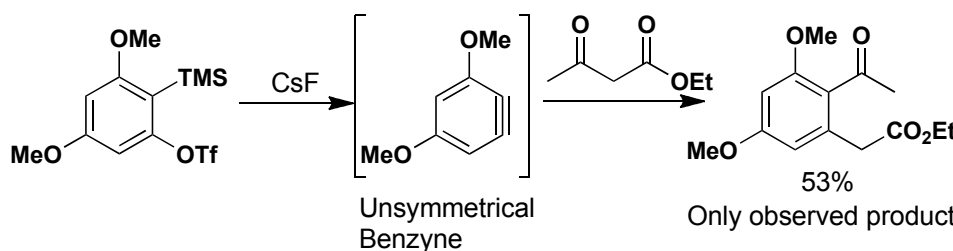
Benzyne Substitution (cont.)



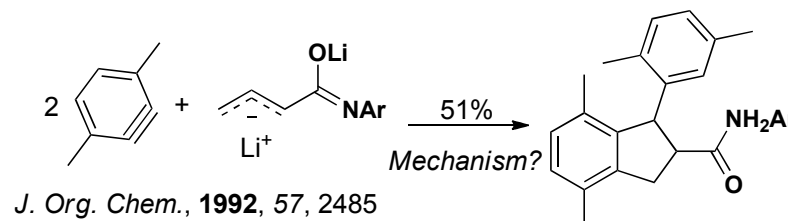
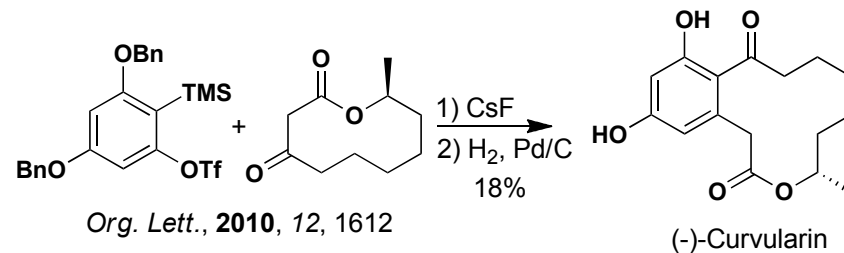
Various cyclic and acyclic ketoesters work
50-90% yield



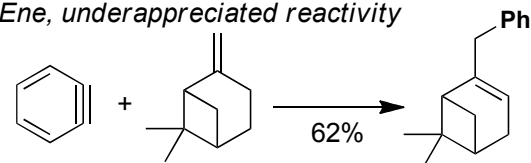
Stoltz, *J. Am. Chem. Soc.*, **2005**, 127, 5340



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

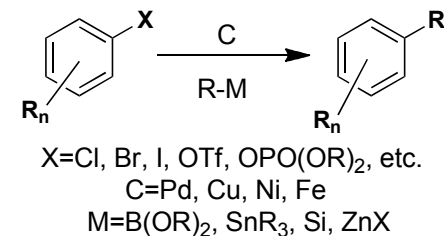


Benzyne Ene, underappreciated reactivity



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

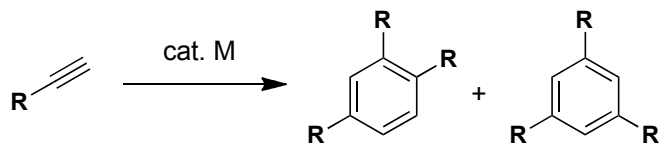
Cross Coupling Reactions



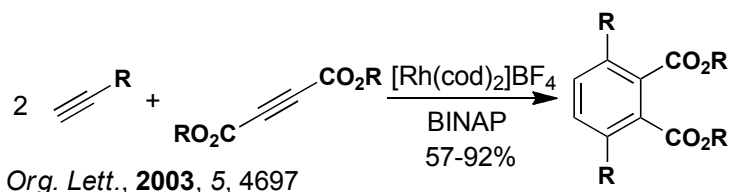
- Useful for modular syntheses
- Useful for substituted biary compounds
- Not generally useful when one coupling partner is simple (phenyl, tolyl, etc)
- When planning it can be compared with some substitution methods (benzyne)
- Simple or easily accessible aromatics can be incorporated in synthesis

Synthesis of Isolated Benzene Rings

[2+2+2] Cycloaddition

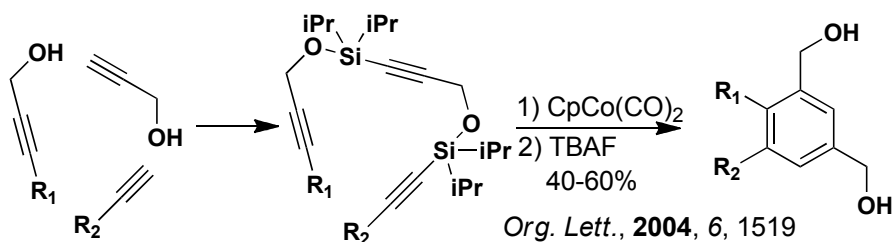


In most cases the intermolecular trimerization is problematic and mixtures of regioisomers is common

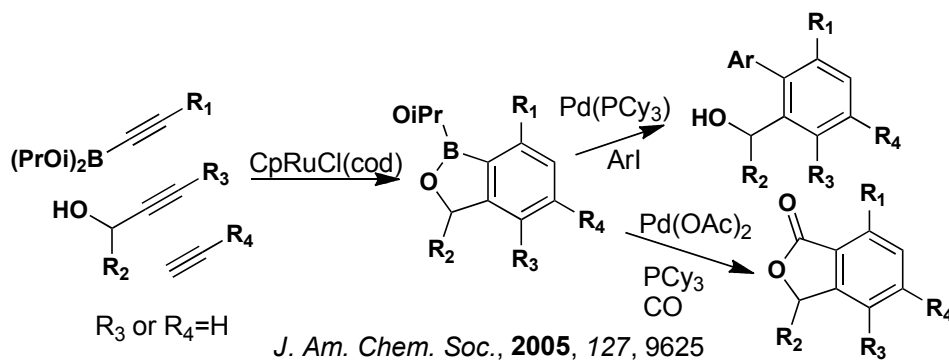


Org. Lett., 2003, 5, 4697

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

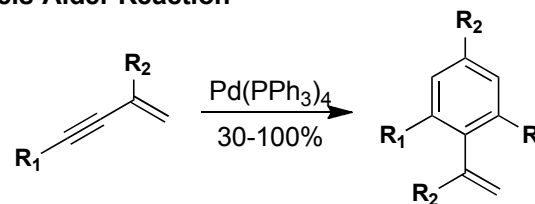


Org. Lett., 2004, 6, 1519

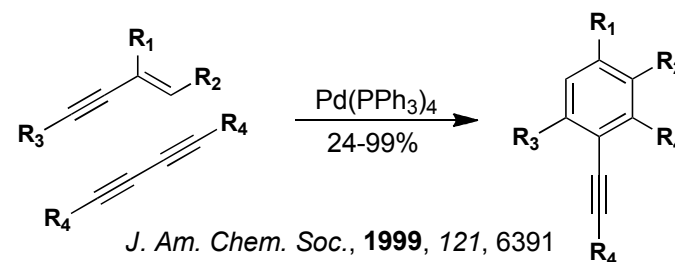


J. Am. Chem. Soc., 2005, 127, 9625

Dehydro-Diels-Alder Reaction

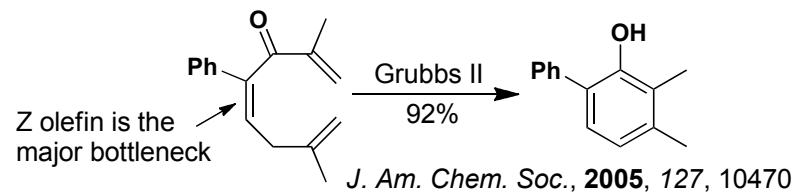


J. Am. Chem. Soc., 1996, 118, 4218
J. Org. Chem., 1998, 63, 7022

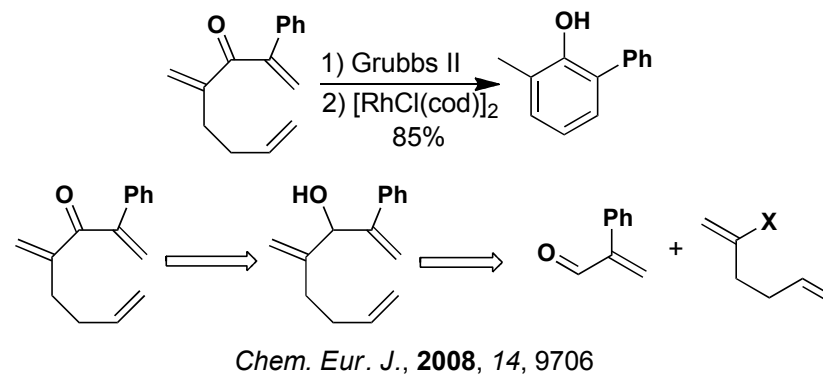


J. Am. Chem. Soc., 1999, 121, 6391

Metathesis

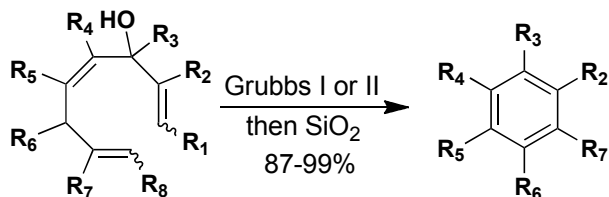
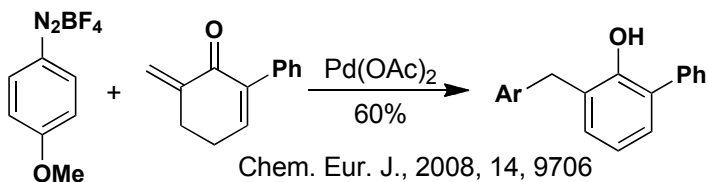


While the reaction is efficient, the synthesis of RCM substrates is not trivial



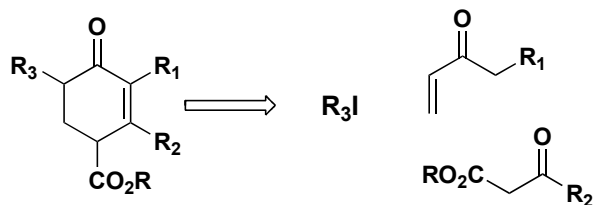
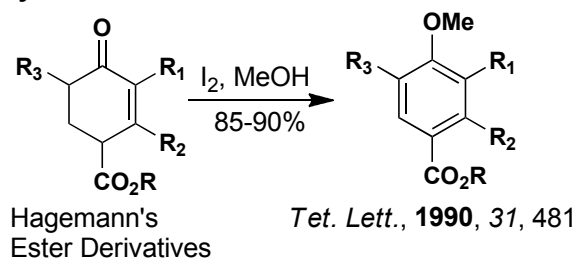
Chem. Eur. J., 2008, 14, 9706

Metathesis (cont.)



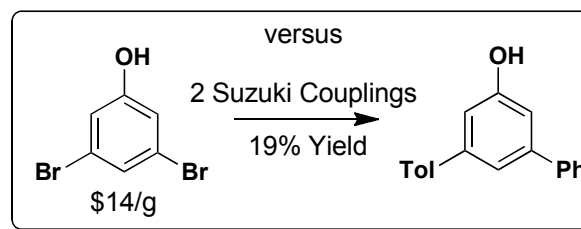
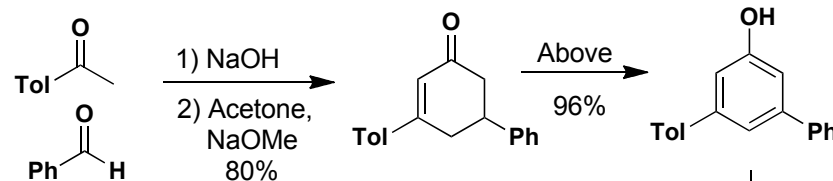
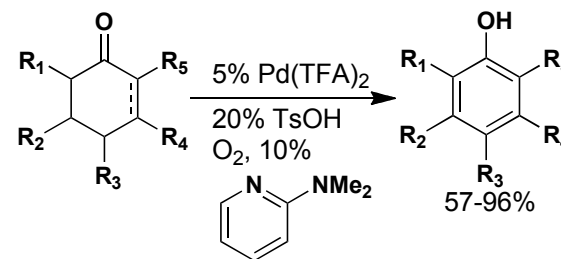
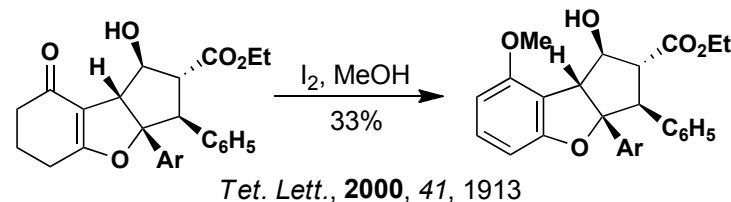
Synthesis of cis olefin is challenging, only tenable systems are fused at R₄ and R₅

Oxidation of Cyclohexenones

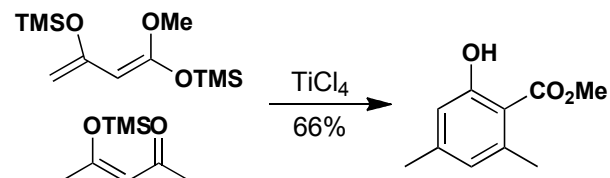


Synthesis and chemistry of Hagemann's Ester: Tet., 2010, 66, 2775

- Synthesis of highly substituted cyclohexenones is very well known
- Extremely useful for polyalkyl phenols and anisoles
- Oxidative aromatization to phenols is also possible with I₂/tBuOH or Pd/C



Stahl, Science, 2011, 333, 209

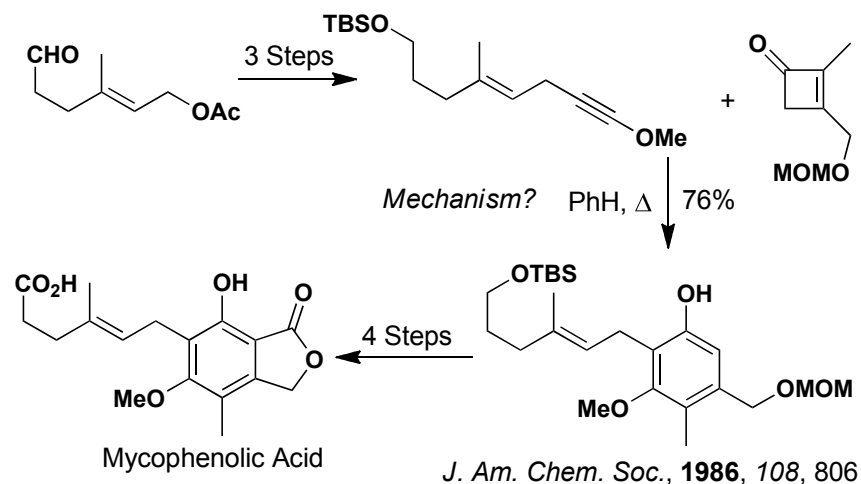


J. Am. Chem. Soc., 1980, 102, 3534

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

Misc. Other Methods

Danheiser Annulation Preview

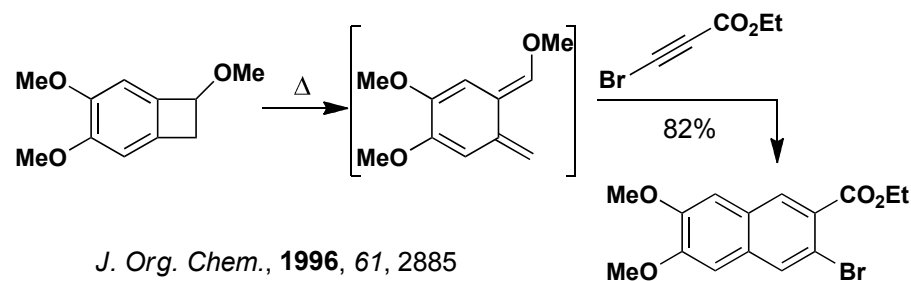


Naphthalenes and higher order fused polyaromatics

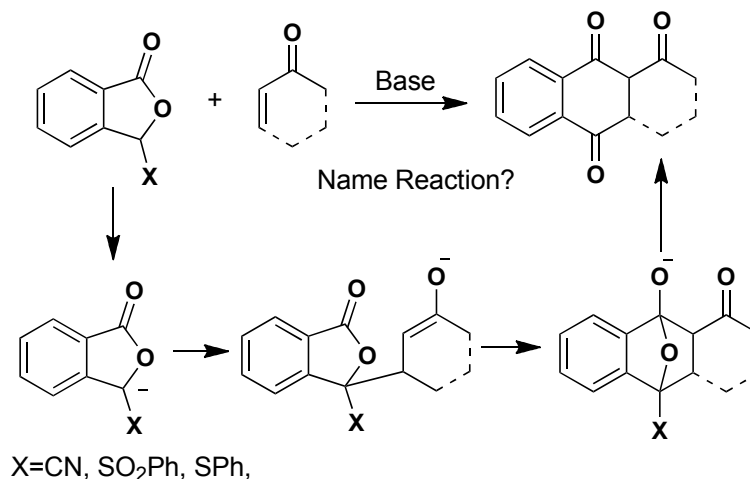
Substitution of Naphthalenes

- Electrophilic 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

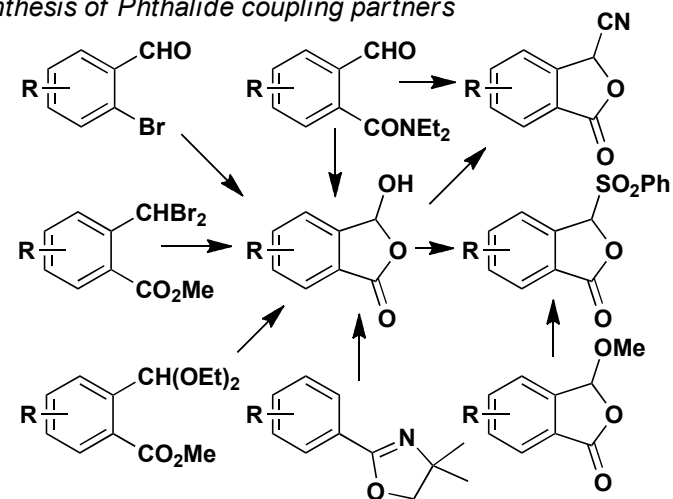
o-Quinodimethanes



Phthalide Annulations



Synthesis of Phthalide coupling partners

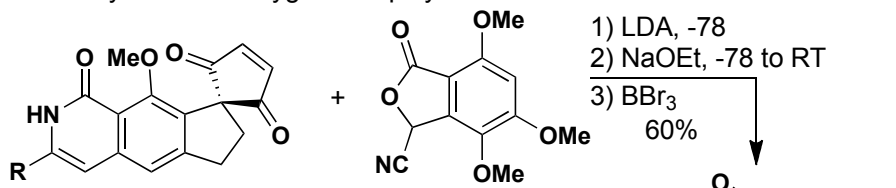


A wide variety of starting materials can be used to quickly synthesize Phthalide donors, allowing for the facile synthesis of highly substituted donors via previously discussed methods

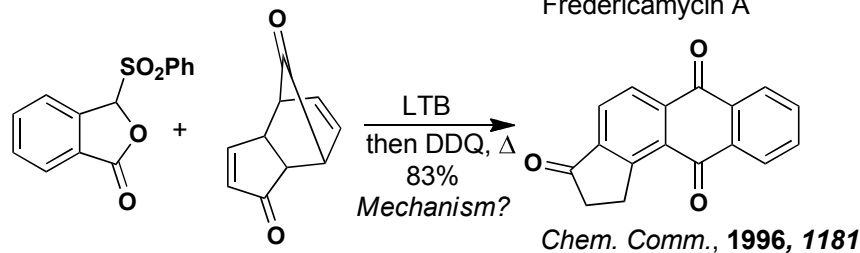
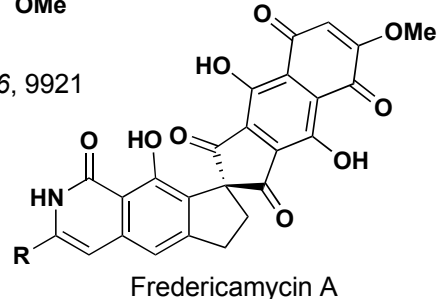
Chem. Rev., **2007**, *107*, 1892

Phthalide Annulations (cont.)

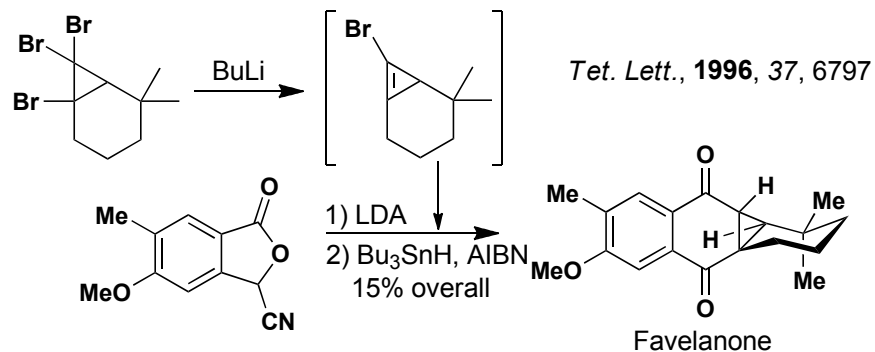
Hauser annulations are extremely useful for the convergent synthesis of oxygenated poly aromatics



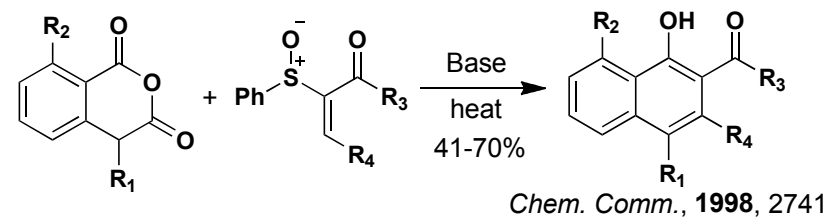
Bach, *J. Am. Chem. Soc.*, **1994**, 116, 9921



Unlikely Acceptor

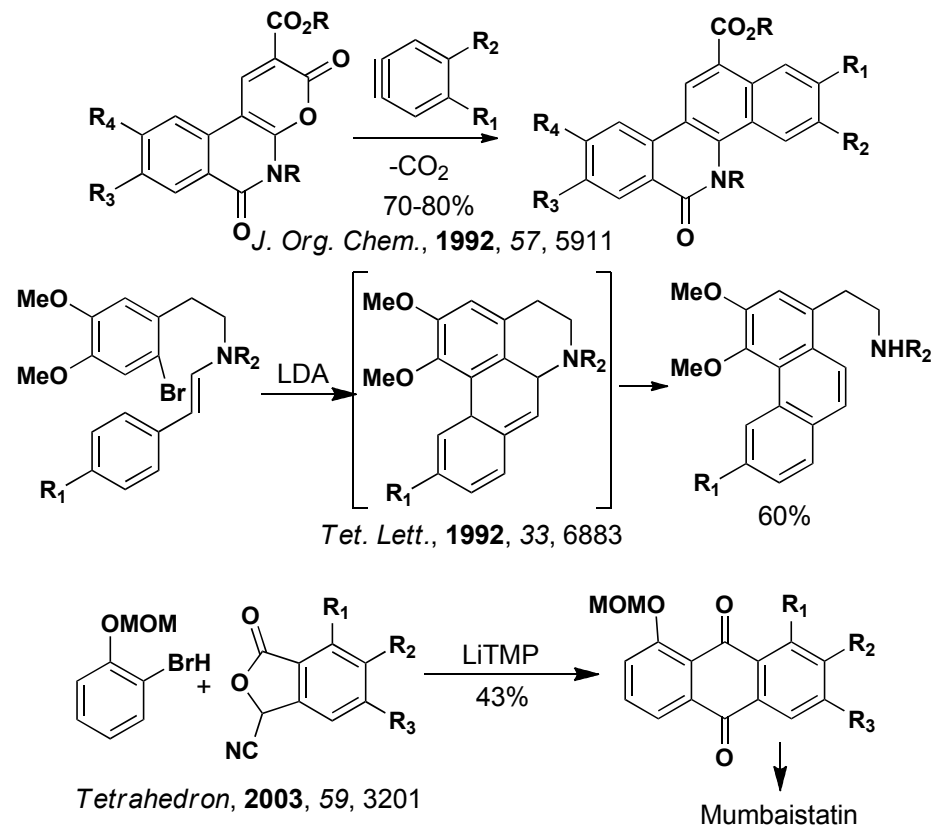


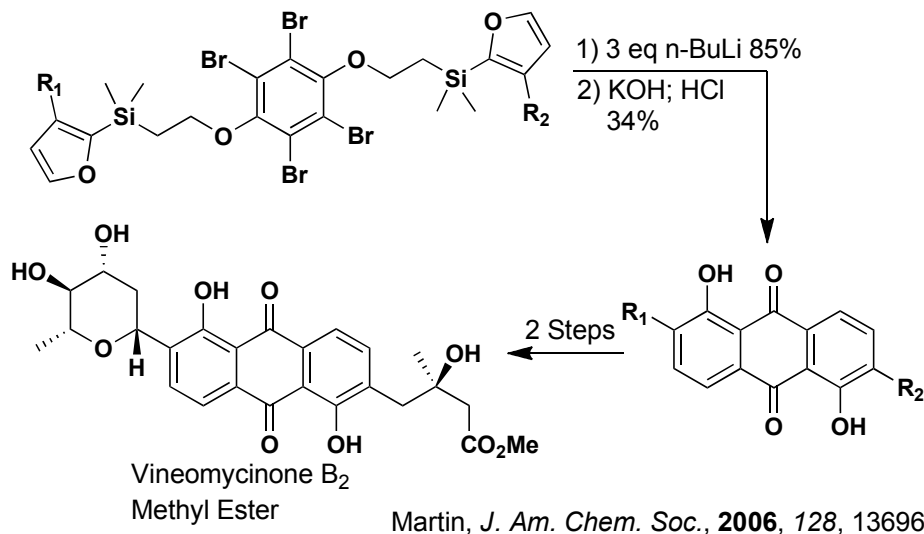
Modified Hauser Reactions



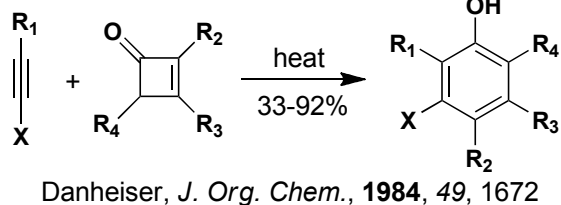
Benzyne Cycloadditions

In addition to being powerful electrophiles arynes are very powerful dieneophiles

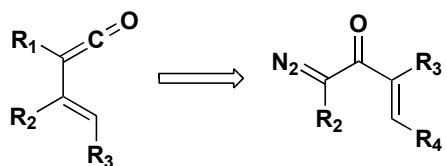




Danheiser Benzannulation and Related Reactions

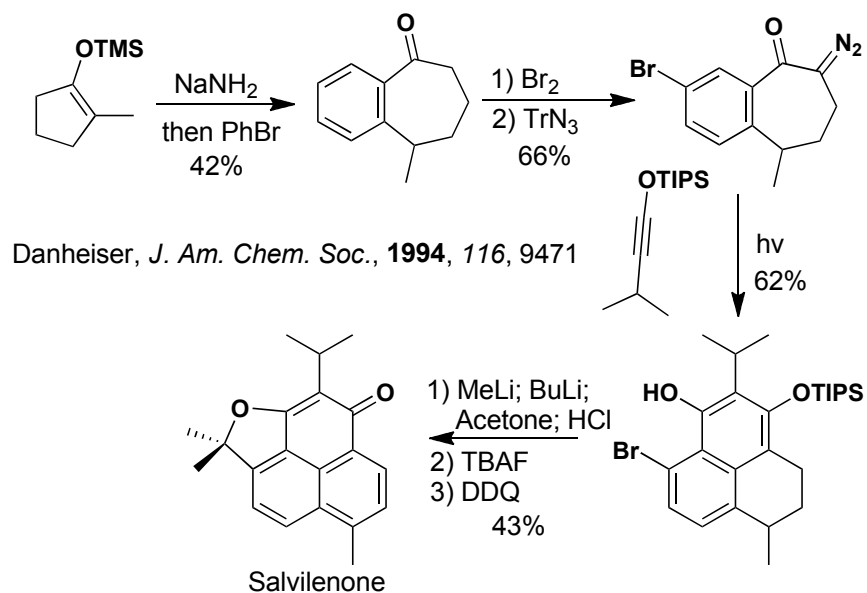


- Lack of general methods for many heterosubstituted alkynes is a significant drawback
- Cyclobutenones are non-trivial to synthesize

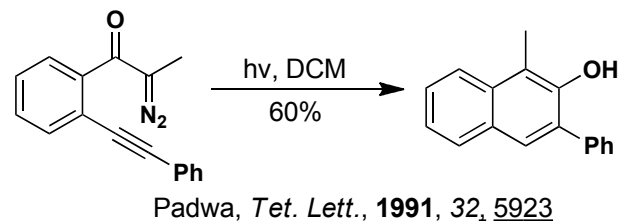


Key intermediate is also available from a photochemical Wolff Rearrangement

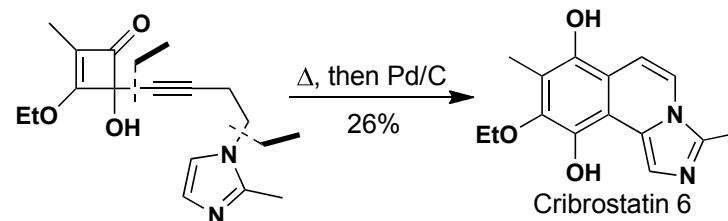
Danheiser, *J. Am. Chem. Soc.*, **1990**, *112*, 3093

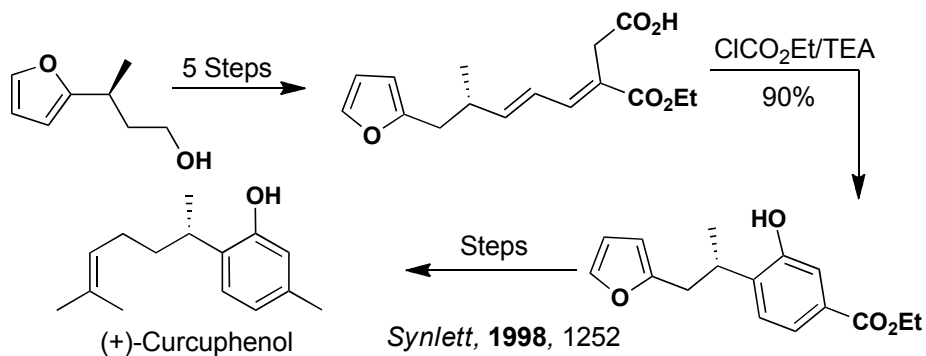


Normal alkynes can be used in both inter and intramolecular cases

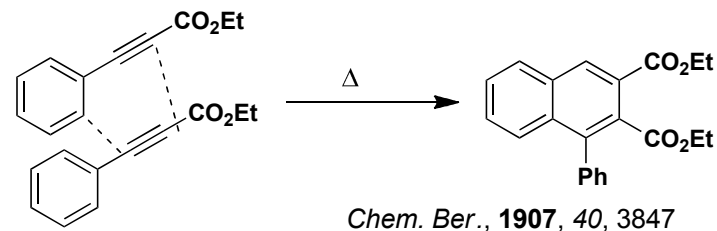


It is likely a diradical mechanism in these cases



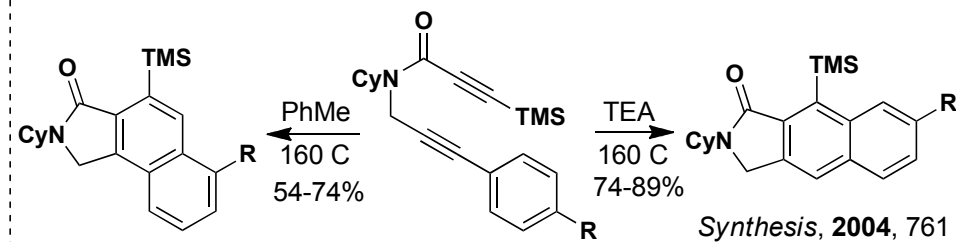
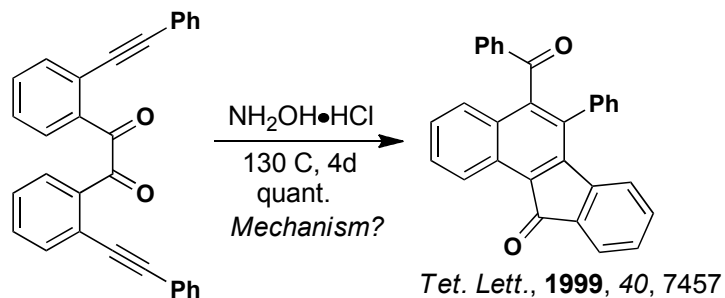


Dehydro-Diels-Alder

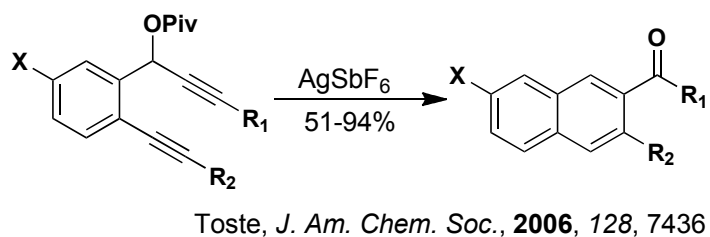
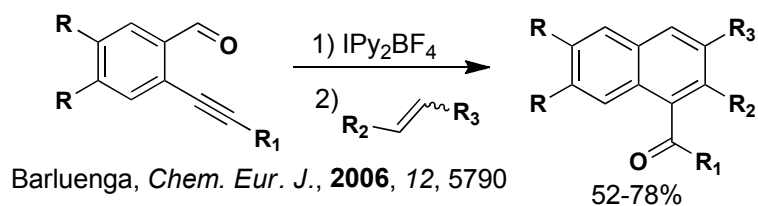


-Reaction can be done inter or intramolecularly (tether)
-In general the yields and regioselectivities are modest

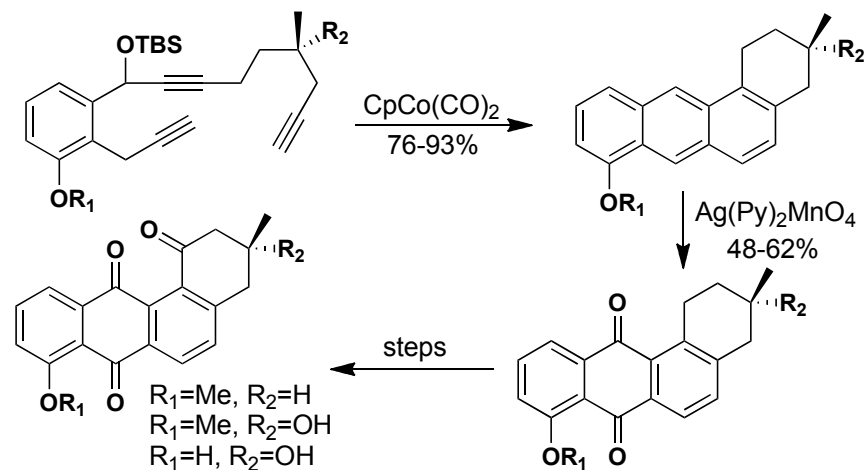
Acid Mediated Ring Closures



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



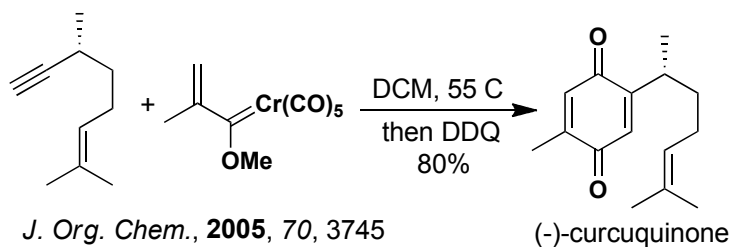
[2+2+2] Cycloaddition



Angucyclinone Antibiotics

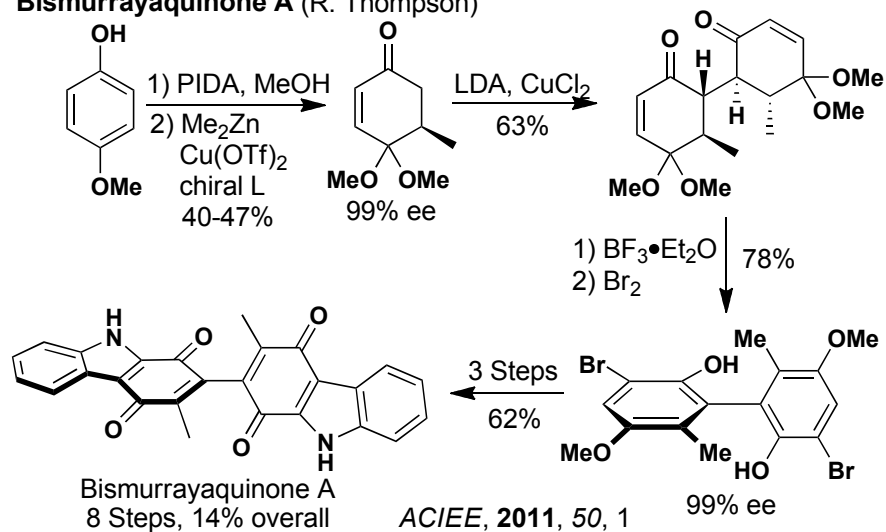
Chem. Eur. J., **2010**, 16, 8805

Chromium Carbene

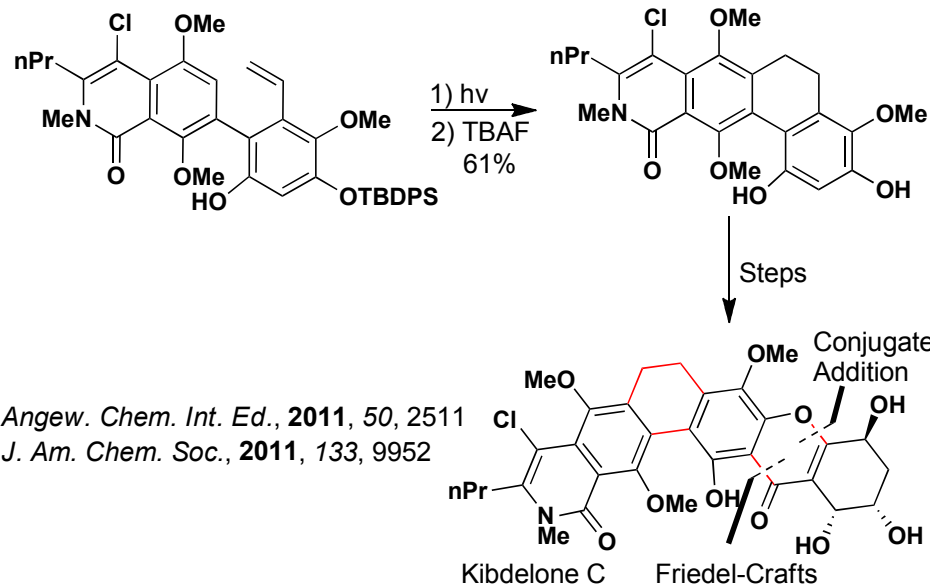
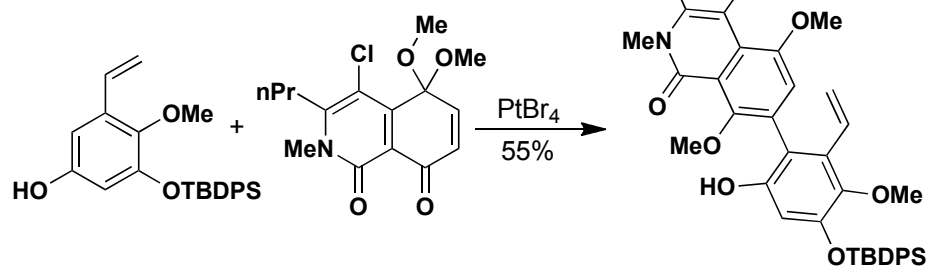


Selected Total Syntheses

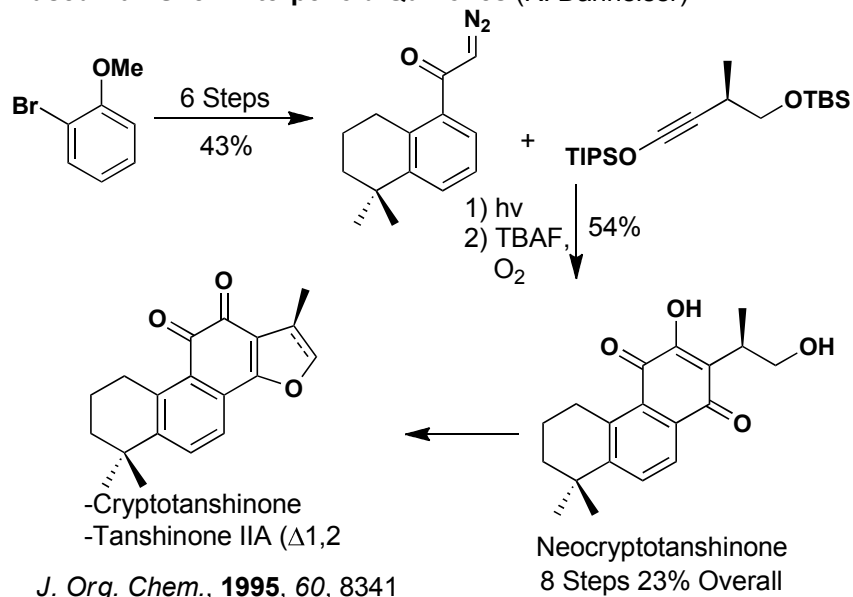
Bismurrayaquinone A (R. Thompson)



Kibdelone C (J. Porco)



Fused Dan Shen Diterpenoid Quinones (R. Danheiser)



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