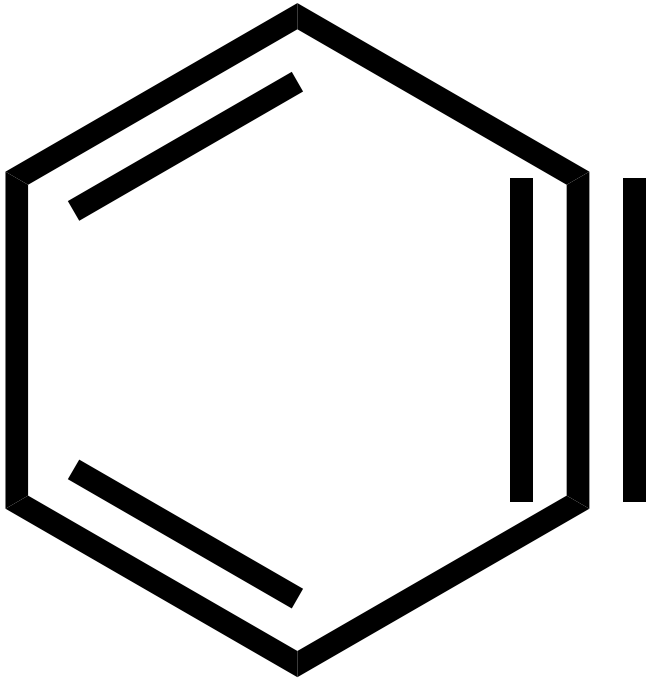
Benzyne: History, Generation, and Reactivity



Eric R. Welin

MacMillan Group Meeting

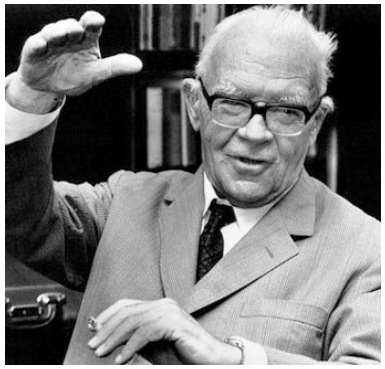
September 18, 2013

Benzyne: History, Generation, and Reactivity

- part 1: history and structure

John D. Roberts

Caltech

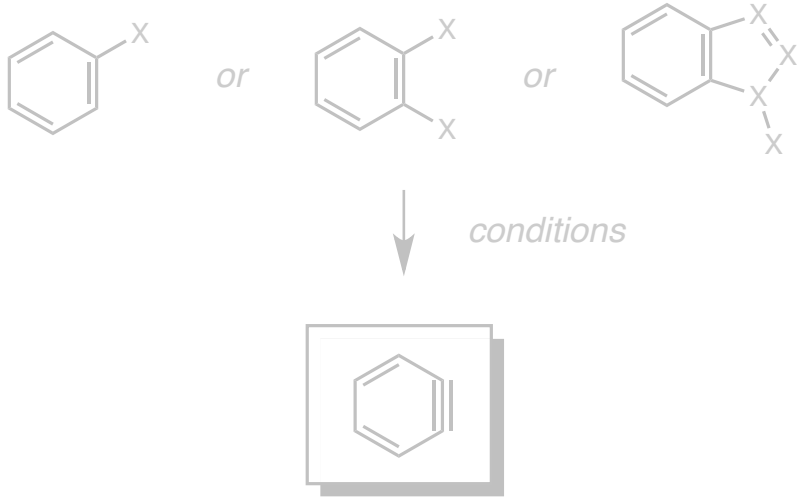


Georg Wittig (Nobel 1979)

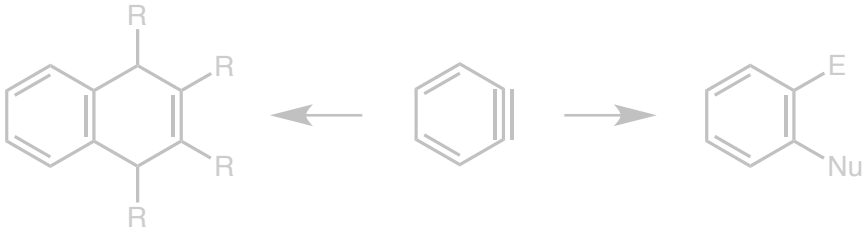
University of Freiburg

University of Tübingen

- part 2: generation



- part 3: reactivity



For very useful reviews see:

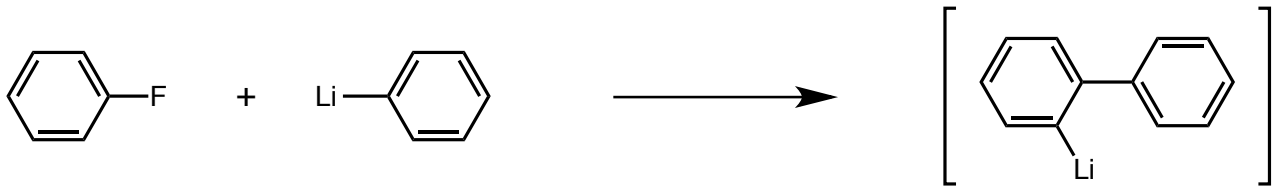
Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701

Tadross, P. M.; Stoltz, B. M.; *Chem. Rev.* **2012**, *112*, 3550

Halobenzenes and Strong Bases Provide Unexpected Results

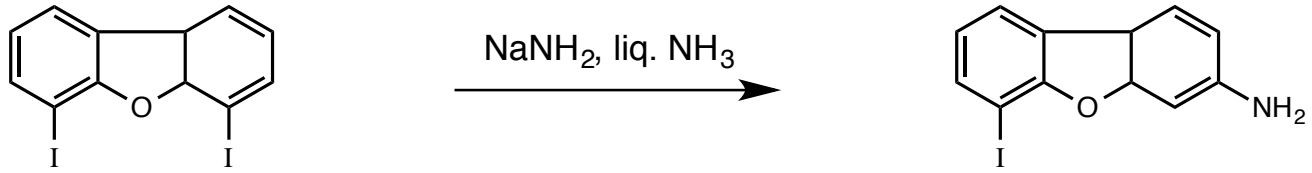
multiple reports from 1940's displayed bizarre reactivity

- 1940: Wittig *et al.*



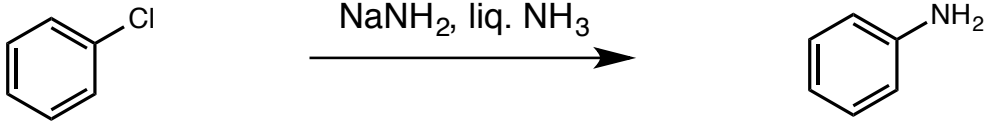
Wittig, G.; Pieper, G.; Fuhrmann, G. *Ber. dtsch. Chem. Ges. A/B*, **1940**, *73*, 1193

- 1945: Gilman *et al.*



Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* **1945**, *67*, 349

- 1946: Bergstrom *et al.*

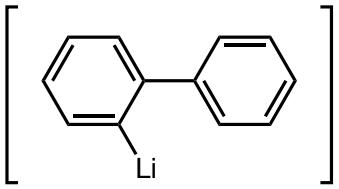


Bergstrom, F. W.; Horning, C. H. *J. Org. Chem.* **1946**, *11*, 334

Wittig's Explanation: A Zwitterionic Species

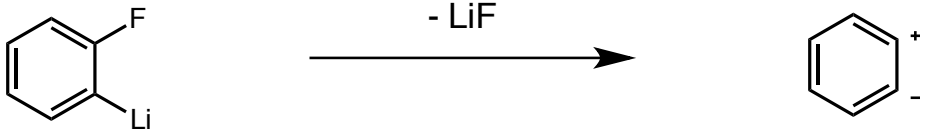
multiple reports from 1940's displayed bizarre reactivity

- product distributions and strong bases implied the presence of carbanions



- reactivity with nucleophiles implied presence of carbocations

- Wittig: Zwitterion structure appears to explain structure

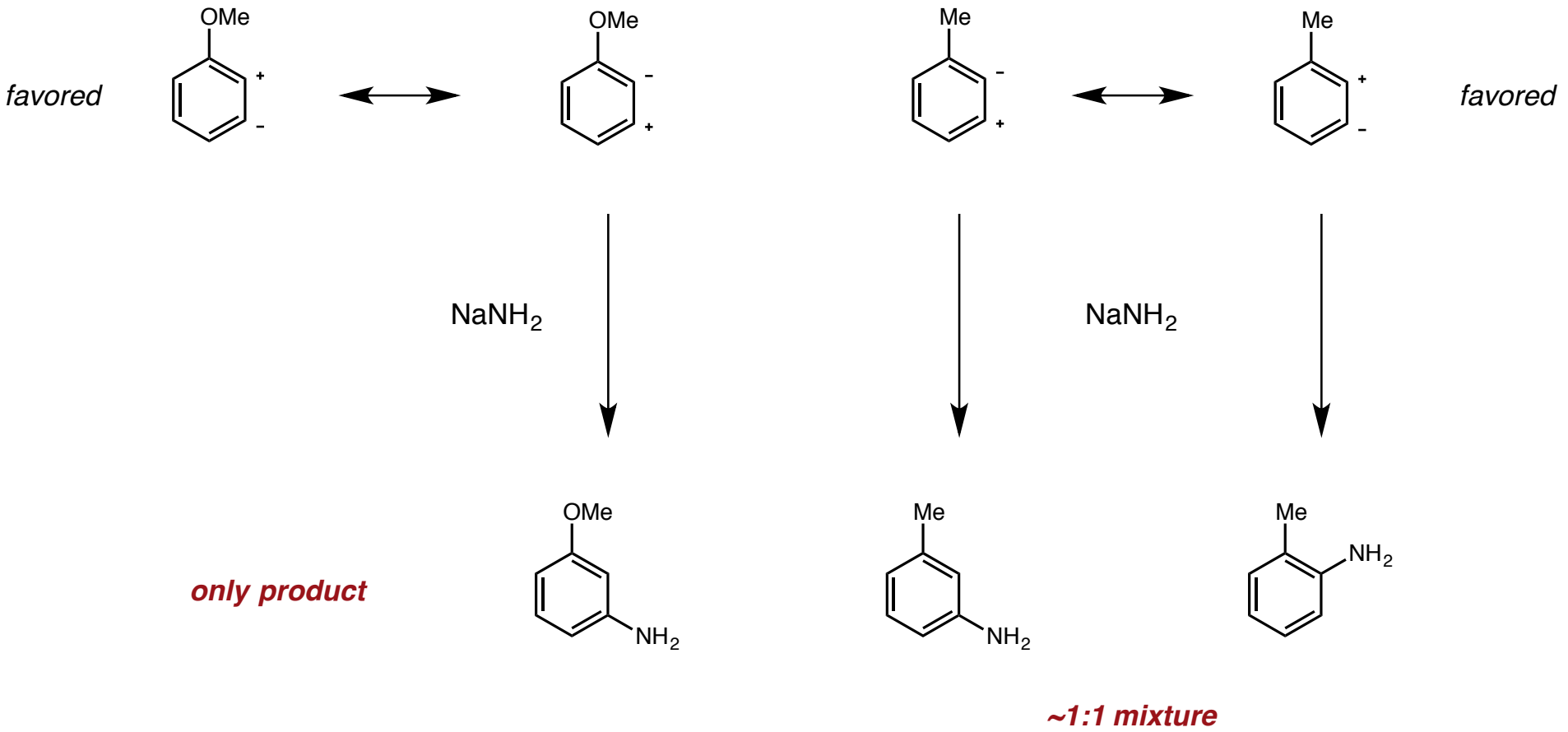


Wittig, G. *Naturwissenschaften*, **1942**, *30*, 696
Wittig, G. *Angew. Chem.* **1954**, *66*, 10

Zwitterion: An Imperfect Explanation

reactivity and selectivity trends call into question the likelihood of a Zwitterion

- problem: Zwitterion fails to explain observed regiochemistry

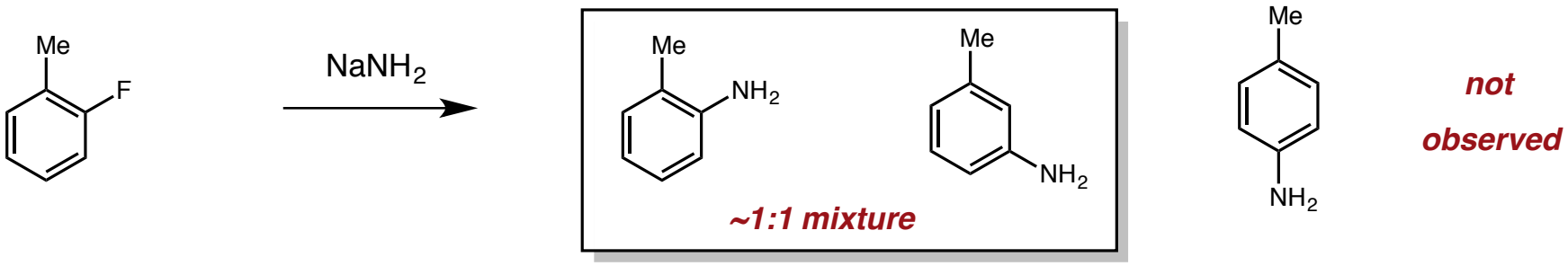


Roberts, J. D.; Simmons Jr., H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290

Zwitterion: An Imperfect Explanation

reactivity and selectivity trends call into question the likelihood of a Zwitterion

- problem: Zwitterion fails to explain observed regiochemistry
- problem: substitution only observed at *ipso* and *ortho* positions to halide

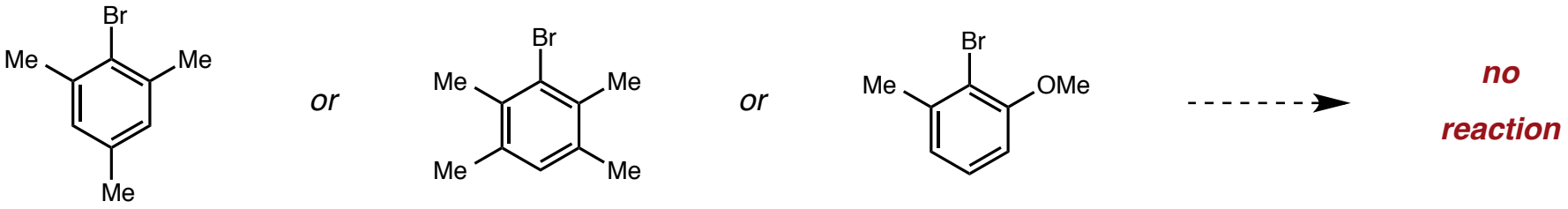


Roberts, J. D.; Simmons Jr., H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290

Zwitterion: An Imperfect Explanation

reactivity and selectivity trends call into question the likelihood of a Zwitterion

- problem: Zwitterion fails to explain observed regiochemistry
- problem: substitution only observed at *ipso* and *ortho* positions to halide
- problem: neither starting material nor product are isomerized under the reaction conditions
- an additional caveat: halides with no *ortho* protons are unreactive



(excluding reactions of *ortho*-dihalides)

Roberts, J. D.; Simmons Jr., H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290

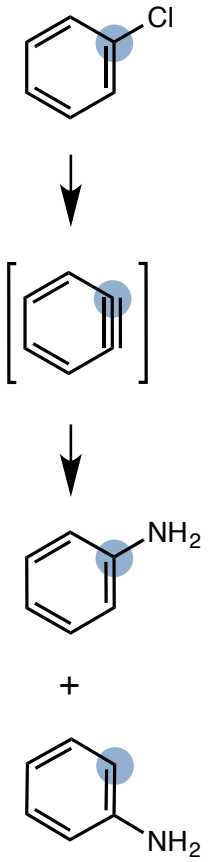
1954: Official Introduction of the Benzyne Concept

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

Sir:

No satisfactory explanation has been published for the rearrangements which often occur in the amination of "non-activated" aryl halides with alkali-metal amides.[2] The pattern of the rearrangements shows a considerable disregard for the influences governing the usual aromatic substitutions and is well illustrated by the products obtained from the amination of the methoxy- and trifluoromethylhalobenzenes. These facts as well as the orientation data for various substituents can be accommodated by an elimination-addition mechanism involving at least transitory existence of an electrically neutral "benzyne" intermediate (II).

J. D. Roberts *et al.* *J. Am. Chem. Soc.* **1953**, *75*, 3290



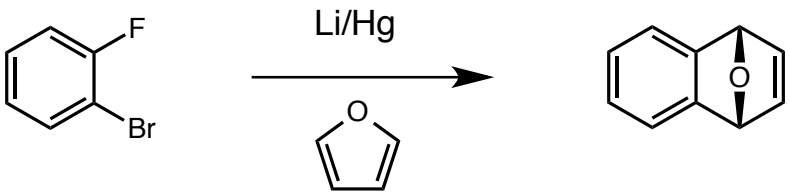
- ^{14}C label shows a 1:1 mixture of products: reaction proceeds through symmetrical intermediate

see also: Huisgen, R.; Rist, H. *Naturwissenschaften,* **1954**, *14,* 358

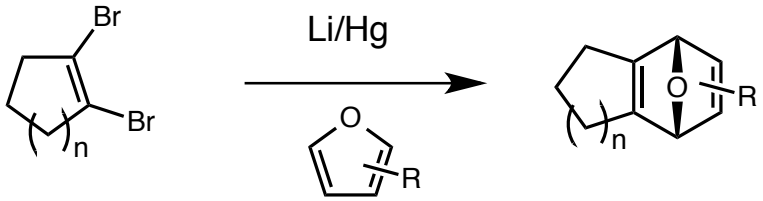
Further Proof of Triple Bond-Containing Structure

over the next decade, evidence for "the benzyne" grows

- 1955: the first benzyne Diels-Alder

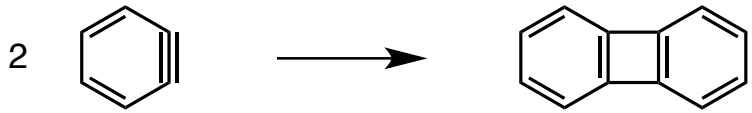


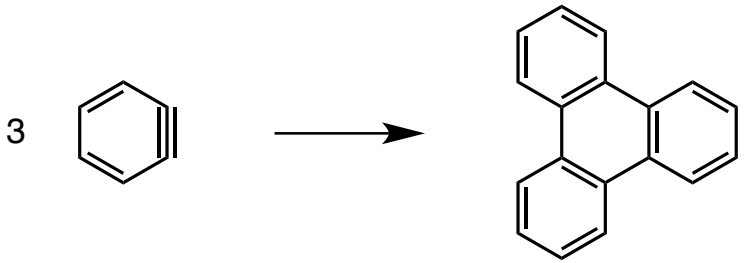
- 1960: aliphatic cycloalkynes postulated



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

- early reports: dimerization and trimerization products always present





Heaney, H. *Chem. Rev.* **1962**, *62*, 81

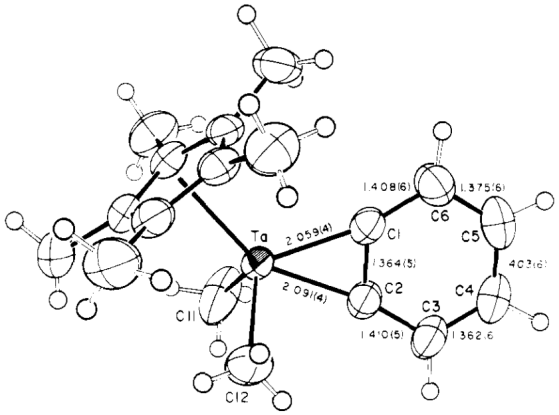
Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348

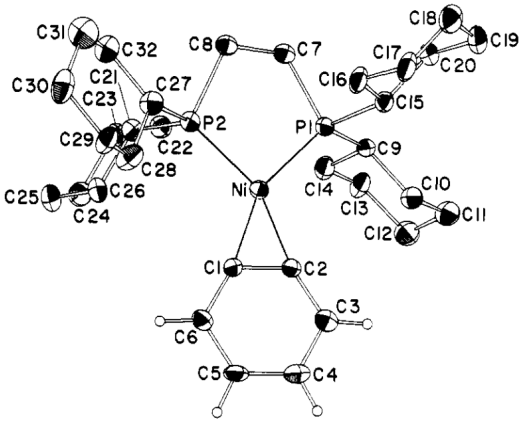
Wittig, G.; Krebs, A.; Pohlke, R. *Angew. Chem.* **1960**, *72*, 324

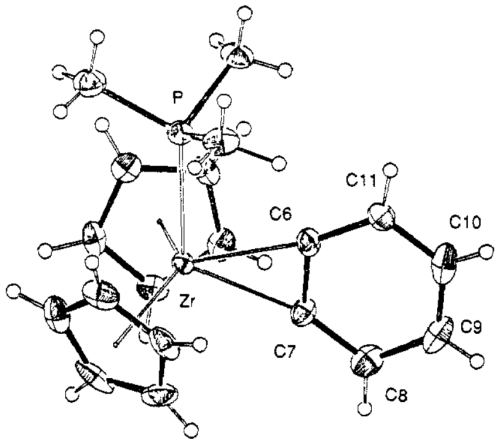
Further Proof of Triple Bond-Containing Structure

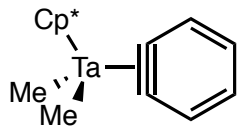
after 25 years, crystal structures are obtained

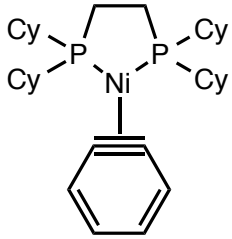
- 1979-1980's: crystal structure of η^2-metal-bound benzyne

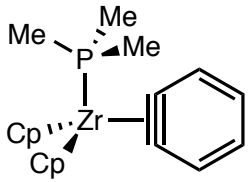












Shrock, 1979

Bennett, 1985

Buchwald, 1986

Buchwald, S. L.; Watson, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 7411

Bennett, M. A.; Hambley, T. W.; Roberts, N. K.; Robertson, G. B. *Organometallics*, **1985**, *4*, 1992

McLain, S. J.; Shrock, R. R.; Sharp, P. R.; Churchill, M. P.; Youngs, W. J. *J. Am. Chem. Soc.* **1979**, *101*, 263

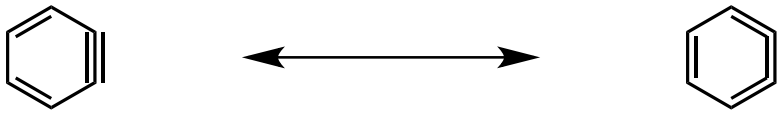
Further Proof of Triple Bond-Containing Structure

spectroscopic advances allow for more rigorous structural evaluation

^{13}C (δ)	70	***95***	***182***	75/214 (terminal/internal)
IR (cm^{-1})	2100	2216	***1846***	***1950***

- ^{13}C NMR and IR data imply significant resonance contributions of both triple-bond and cumulene-type structures:

consistent with ^{13}C data



consistent with IR data

Warmuth, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 1347

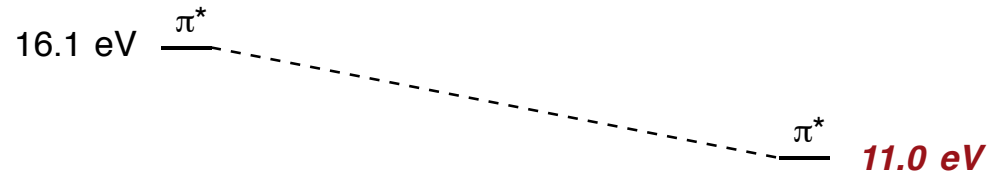
Radziszewski, J. G.; Hess, B. A.; Zahradnik, R. *J. Am. Chem. Soc.* **1992**, *114*, 52

Das, A.; Dash, C.; Celik, M. A.; Yousufuddin, M.; Frenking, G.; Dias, H. V. R. *Organometallics*, **2013**, *32*, 3135

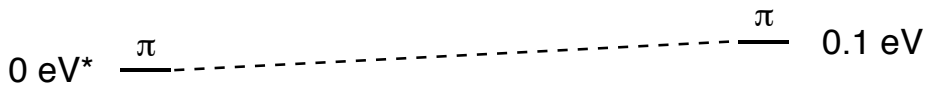
So Why is Benzyne Electrophilic?

why is a highly strained triple bond inherently electrophilic?

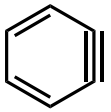
- Hoffman's application of extended Hückel theory sheds light

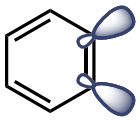


significantly lowered LUMO



slightly raised HOMO





- significant deviation from preferred 180° bond angle results in a low-lying LUMO
- low LUMO explains extreme reactivity towards nucleophiles and dienes

*Arbitrarily reassigned to 0 eV. Actual value = -9.6 eV

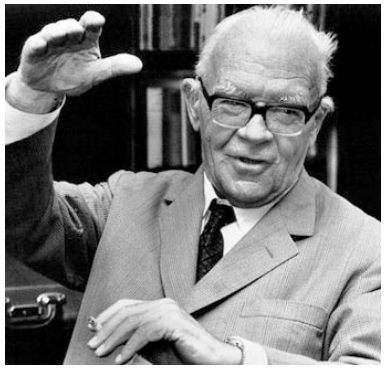
Hoffman, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499

Benzyne: History, Generation, and Reactivity

- part 1: history and structure

John D. Roberts

Caltech

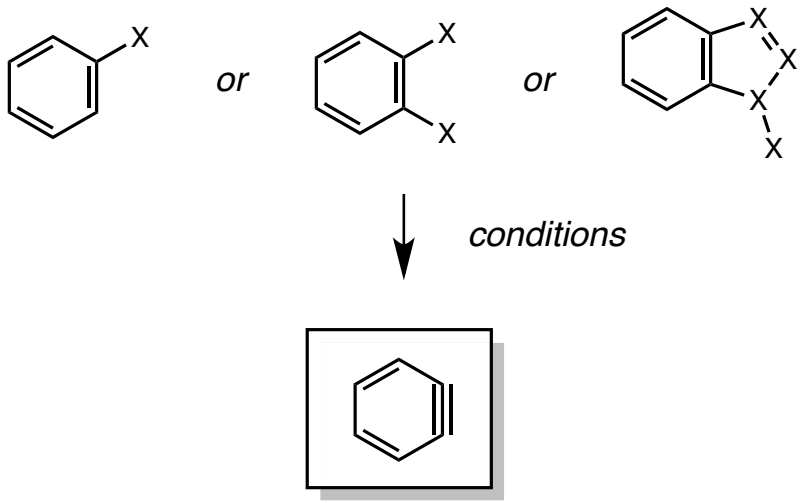


Georg Wittig (Nobel 1979)

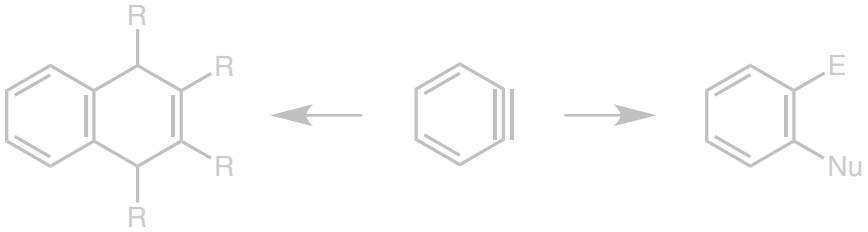
University of Freiburg

University of Tübingen

- part 2: generation



- part 3: reactivity

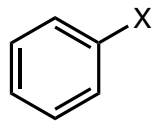


For very useful reviews see:

Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701

Tadross, P. M.; Stoltz, B. M.; *Chem. Rev.* **2012**, *112*, 3550

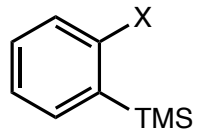
Generation of Aryne Intermediates



X = halogen, OTf

strong base

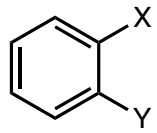
fluoride



X = OTf, I^+Ph

strongly basic conditions

milder conditions



X = Cl, Br, I

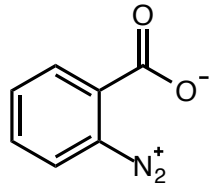
Y = halogen, OTf, I^+Ph

Mg^0, Li^0, Li-Hg

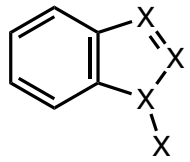
reducing metals

Δ, LG lost as gas

entropy driven



or

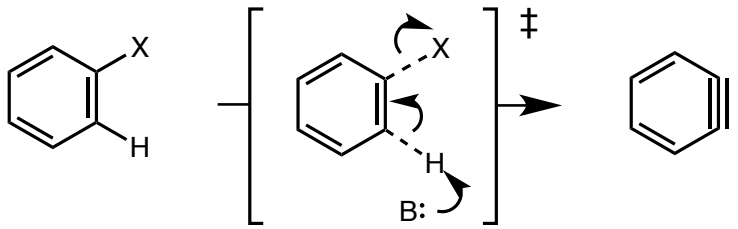


X = N, SO_2

Mono- and o*-Dihalobenzenes as Precursors*

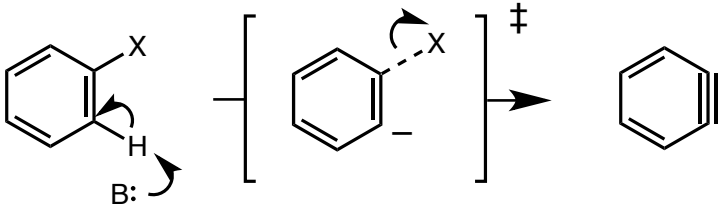
variable trends depending on nature of base and solvent or metal

- protic solvents: concerted mechanism



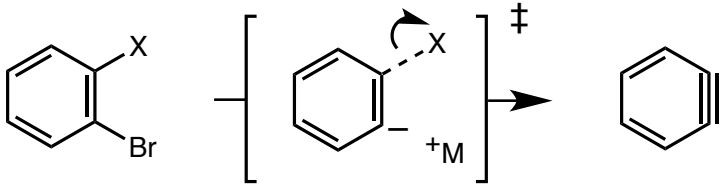
rate: Br > I > Cl > F

- aprotic solvents: stepwise mechanism



rate: F > Cl > Br > I

- dihalides: rate mainly affected by choice of metal



X = F, Cl, Br, I, OTf, I^{+}Ph

rate: Na > Mg > Li >> Cu*

*elimination not observed with *o*-chloro aryl copper intermediates!

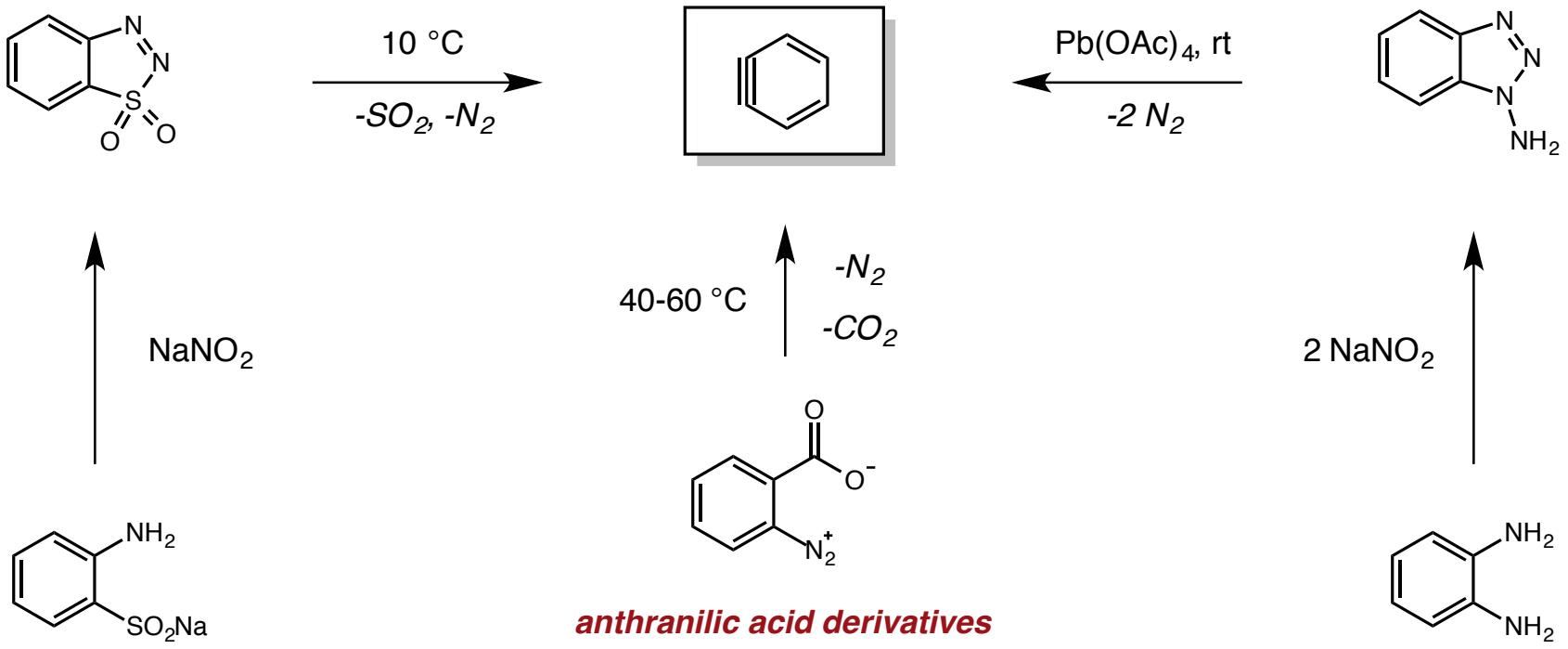
Heaney, H. *Chem. Rev.* **1962**, *62*, 81

Ebert, G. W.; Pfennig, D. R.; Suchan, S. D.; Donovan Jr., T. A. *Tetrahedron Lett.* **1993**, *34*, 2279

Diazotization of o*-Disubstituted Anilines Provides Labile Benzyne Precursors*

mild thermal/oxidative cleavage provides acess to benzyne derivatives

- loss of 2 gas molecules drives benzyne formation under relatively mild conditions



Wittig, G.; Hoffman, R. W. *Ber.* **1962**, *95*, 2718

Wittig, G.; Hoffman, R. W. *Org. Syn.* **1967**, *47*, 4

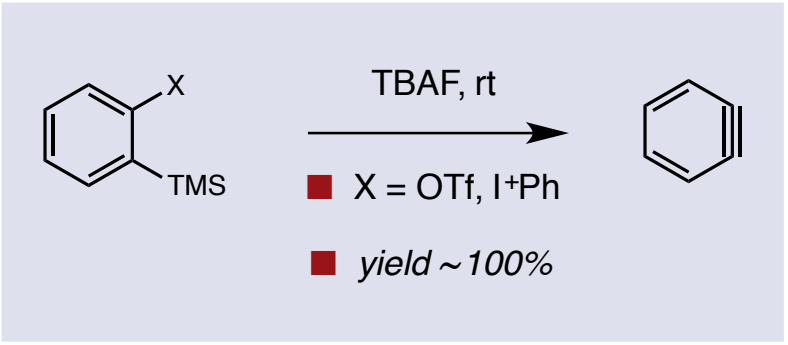
Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C* **1969**, *742*

Stiles, M.; Miller, R. G.; Burckhardt, U. *J. Am. Chem. Soc.* **1963**, *85*, 1792

o-*Triflyl and* o-*Phenyliodonio Silanes as Precursors*

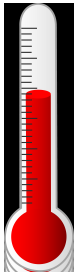
benefits abound with silane precursors bearing ortho *leaving groups*

- avoid use of pyrophoric/ highly reactive bases

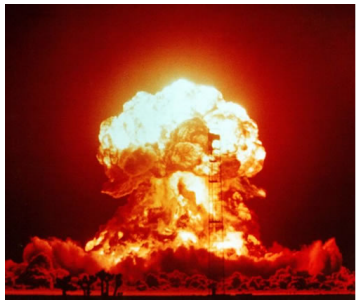


- facile yet controlled at rt

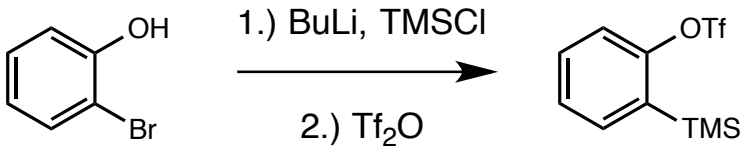
25 °C!



- not shock-sensitive



- easily synthesized



- avoid use of toxic oxidants [$Pb(OAc)_4$]

Himeshima, Y.; Sonada, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211

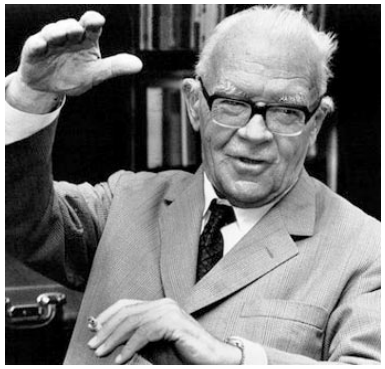
Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983

Benzyne: History, Generation, and Reactivity

- part 1: history and structure

John D. Roberts

Caltech

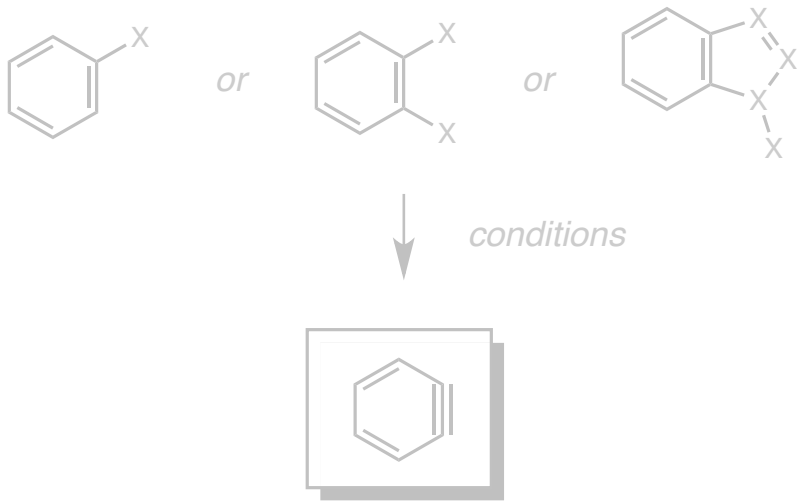


Georg Wittig (Nobel 1979)

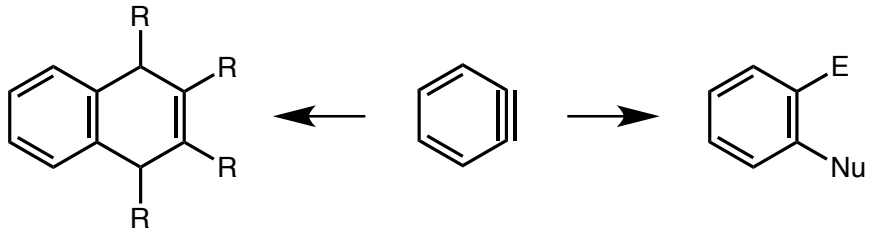
University of Freiburg

University of Tübingen

- part 2: generation



- part 3: reactivity



For very useful reviews see:

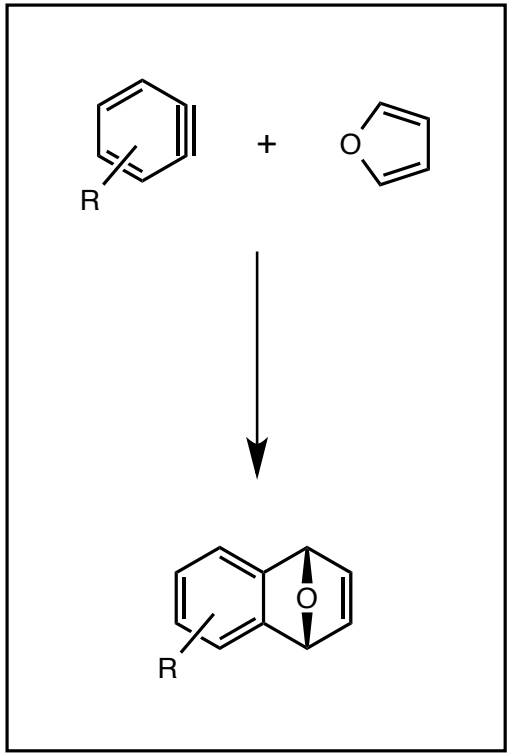
Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701

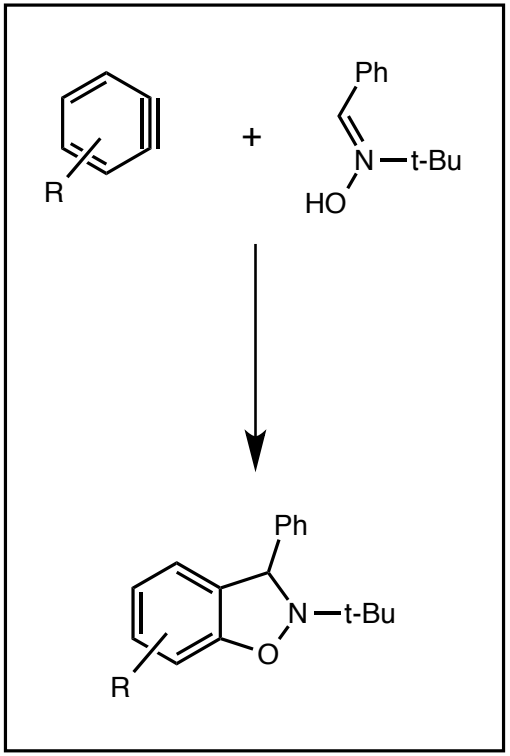
Tadross, P. M.; Stoltz, B. M.; *Chem. Rev.* **2012**, *112*, 3550

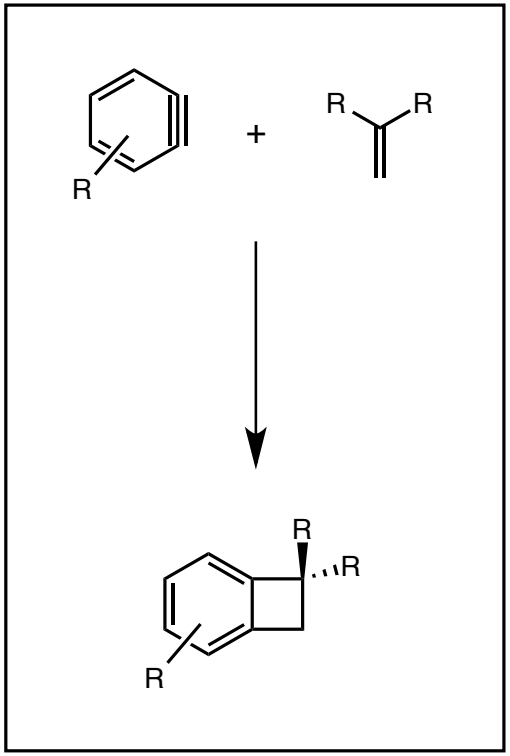
Benzyne Reactivity: Cycloadditions

extremely low LUMO provides high reactivity in a variety of cycloaddition reactions

- [4+2] and Diels-Alder
- [3+2] cycloadditions
- [2+2] cycloadditions







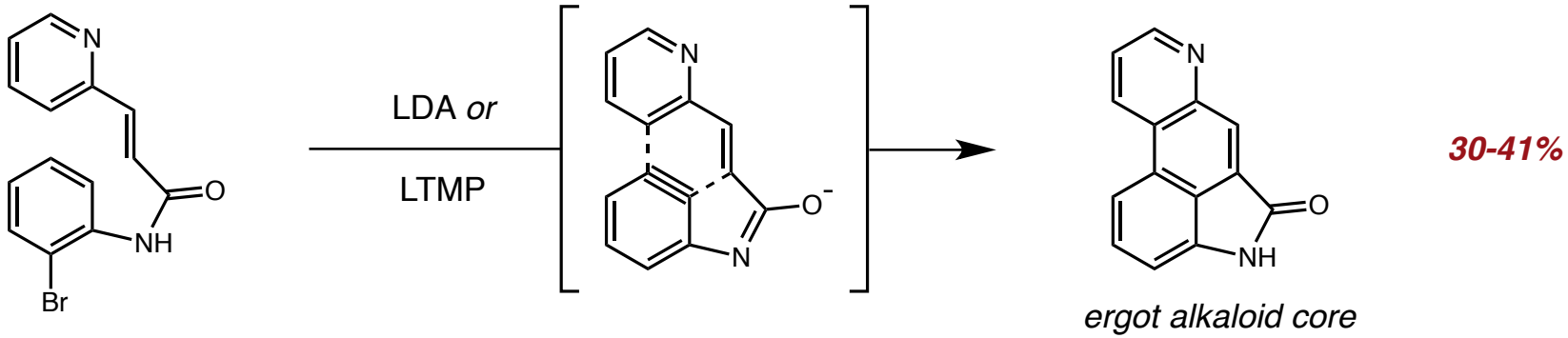
Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701

Tadross, P. M.; Stoltz, B. M.; *Chem. Rev.* **2012**, *112*, 3550

Benzyne Diels-Alder and [4+2] Cycloadditions

literature is flush with intra- and intermolecular annulations

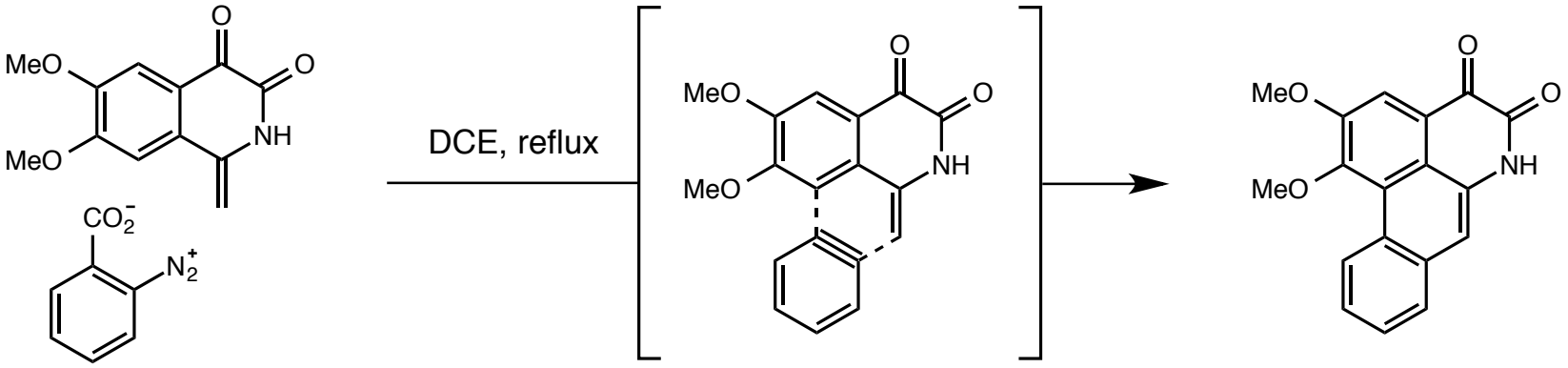
- intramolecular example towards ergot alkaloids



30-41%

ergot alkaloid core

- intermolecular example towards aporphinoids



norcepharadione B, 62%

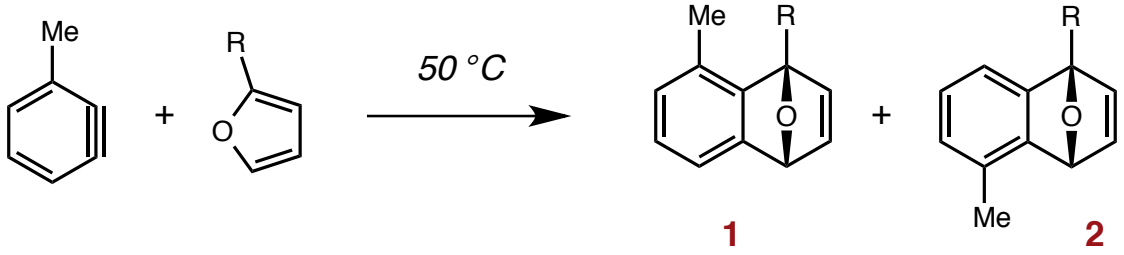
Gómez, B.; Guitián, E.; Castedo, L. *Synlett*, **1992**, 903

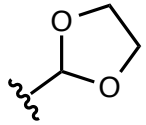
Saá, C.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1985**, *26*, 4559

Benzyne Diels-Alder and [4+2] Cycloadditions

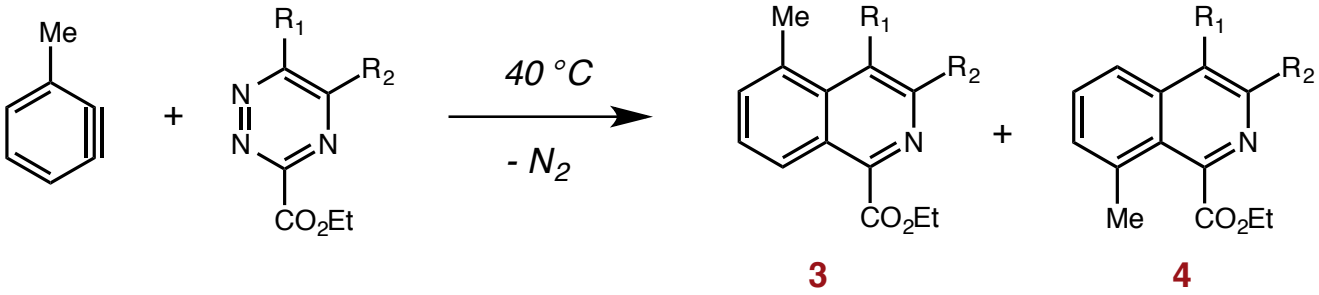
literature is flush with intra- and intermolecular annulations

- non-symmetrical dienes often display little selectivity:



R	1 : 2
Me	42 : 58
t-Bu	36 : 64
CO_2Me	43 : 57
	39 : 61

- less reactive dienes appear to be under steric control



R_1	R_2	3 : 4
CO_2Et	CO_2Et	40 : 60
H	Ph	100 : 0
Ph	Ph	5 : 95

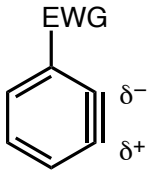
Newman, M. S.; Kannan, R. *J. Org. Chem.* **1976**, *41*, 3356

Gonsalves, A. M. R.; Pihno e Melo, T. M. V. D. *Tetrahedron*, **1992**, *48*, 6821

Can Selectivity be Induced with Benzyne Intermediates?

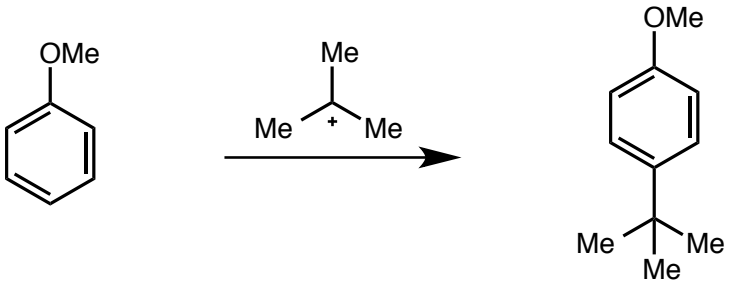
biasing of the aryne intermediate can powerfully affect selectivity

- introduction of polar group at 3-position dramatically influences selectivity



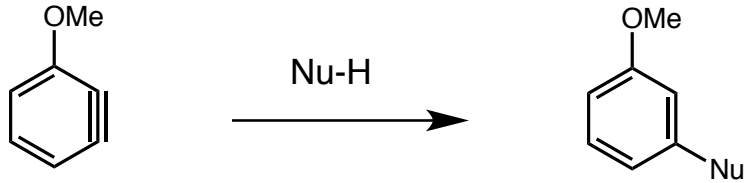
- dipoles arranged to be stabilized by electron withdrawing group
- due to orthogonal nature, typical donating groups are withdrawing!

- Friedel-Crafts chemistry:



OMe is activating as EDG

- benzyne chemistry:

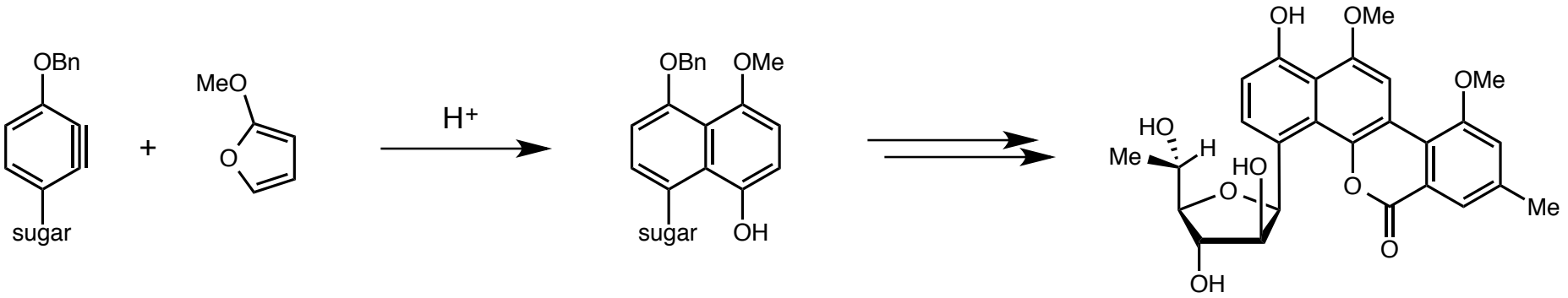


OMe is activating as EWG

Applications in Total Synthesis

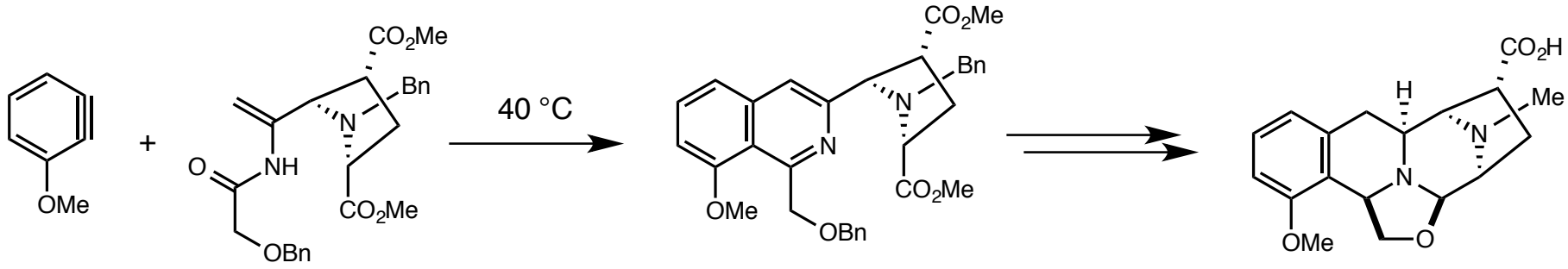
high selectivity achieved with 3-methoxy arynes

- Suzuki *et al.*, 1992:



94%, 9 : 1 regioselectivity ***(+)-gilvocarcin M***

- Stoltz *et al.*, 2008:



60%, single isomer ***(–)-quinocarcin***

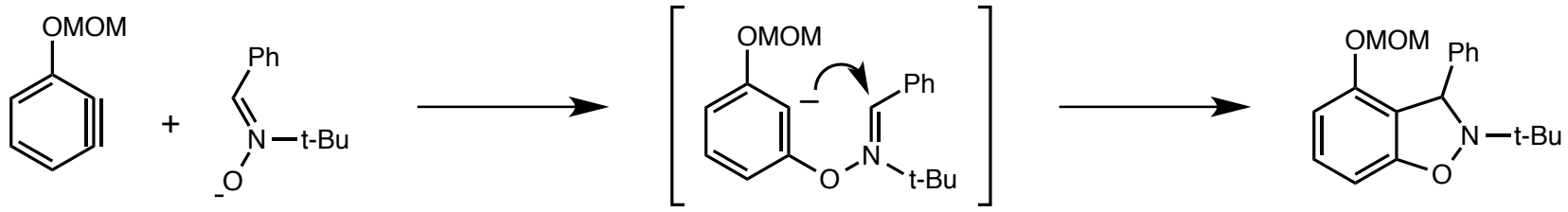
Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270

Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568

[2+2] and [3+2] Cycloadditions

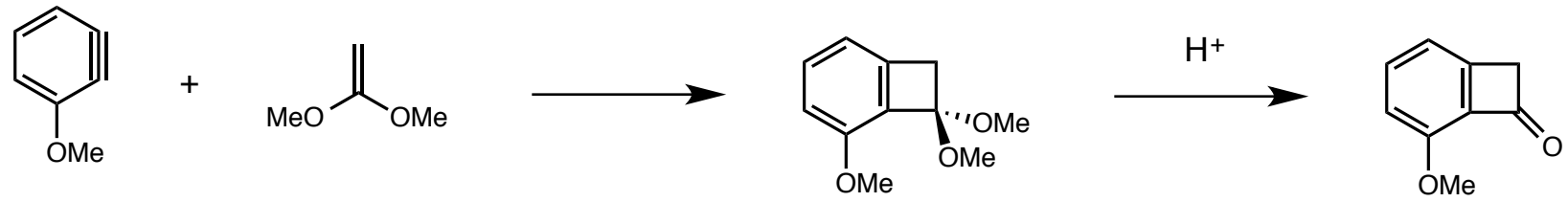
high selectivity achieved with 3-methoxy arynes

- stepwise [3+2] cycloadditions proceed with same regiochemistry:



80%, > 20 : 1 rr

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



76%, single regioisomer

Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393

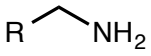
Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett*, **1993**, *843*

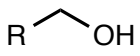
Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377

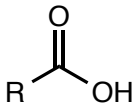
Nucleophilic Attack on Arynes

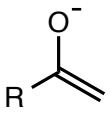
the most common reactivity of arynes

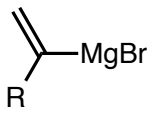
- nearly any nucleophile will react with benzyne:

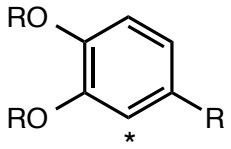




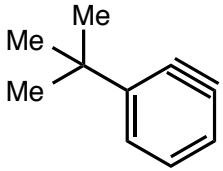


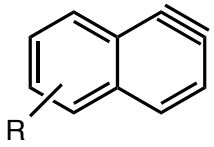


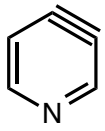




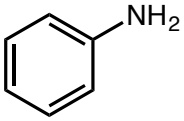
- nature of the aryne has little effect on reactivity:

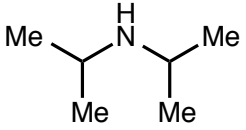


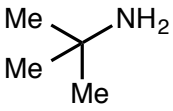


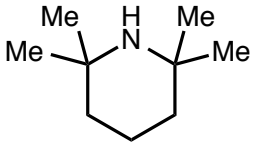


- even sterically-hindered and electronically-deactivated nucleophiles are highly reactive:





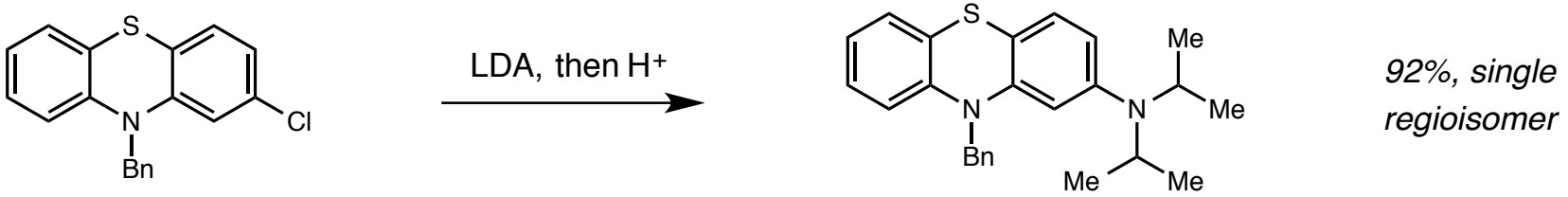




Nucleophilic Attack on Arynes: Selectivity Trends

high selectivity sometimes observed in bicyclic systems

- again, adjacent EWG will dictate selectivity:



92%, single regioisomer

- theory provides a predictive model based on bond angle distortion:

- very distorted; very high selectivity
- very little distortion; no selectivity
- slightly distorted; very high selectivity
- very distorted; very high selectivity

smaller bond angle has more s-character (δ^-); larger bond angle has more p character (δ^+)

Self, J. L.; Khanapure, S. P.; Biehl, E. R. *Heterocycles*, **1991**, *32*, 311

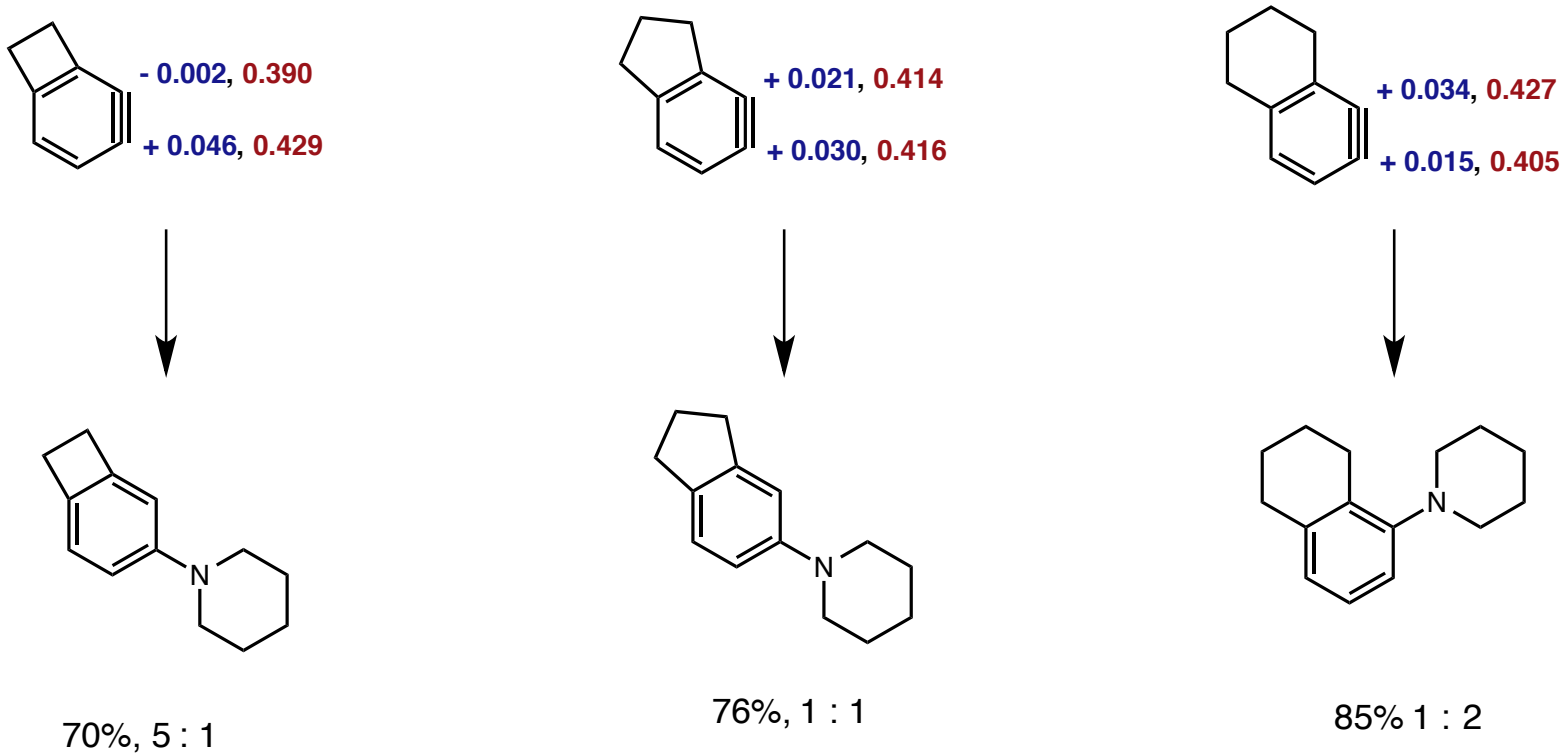
Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96

Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk. K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267

Effect of Ring Strain on Regioselectivity

- calculation of charge and LUMO coefficients matches predictions of bond angle strain with selectivity trends

DFT calculated charge, LUMO coefficient

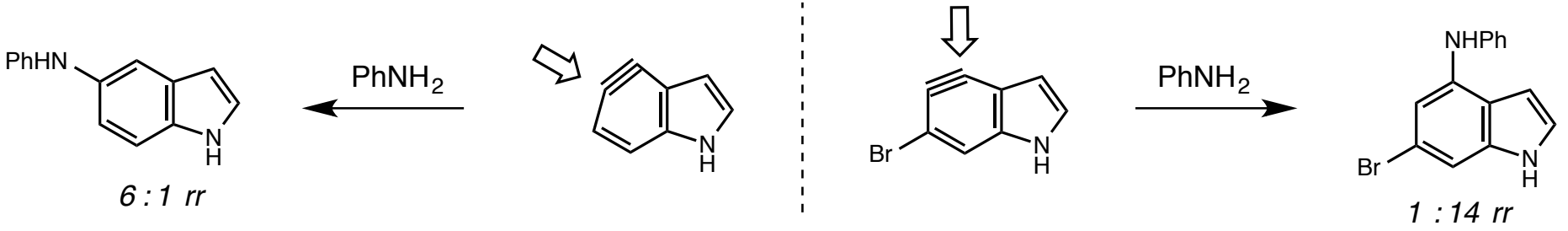


Suzuki, K. *et al. Org. Lett.* **2003**, *5*, 3551

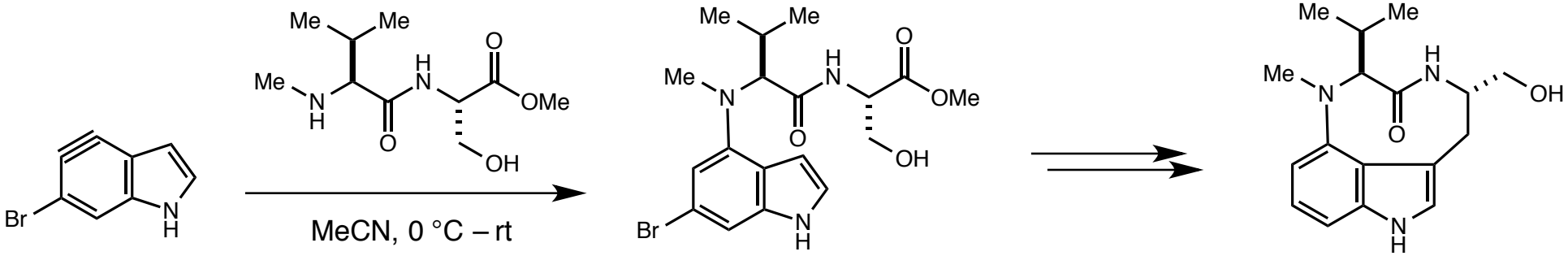
Nucleophilic Attack on Arynes: Selectivity Trends

can inherent selectivity be reversed?

- indroduction of bromide to indole strongly influences site of nucleophilic attack



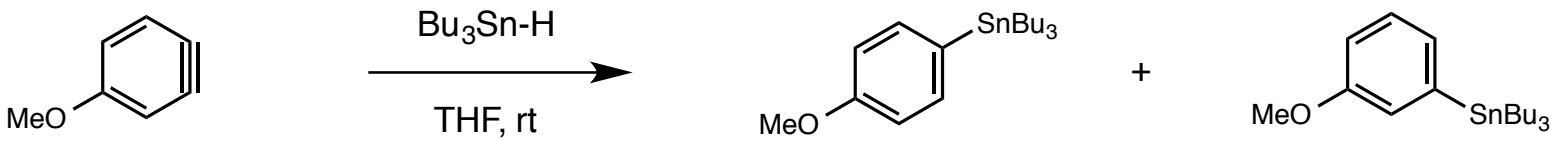
- application to the total synthesis of indolactam V



Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832

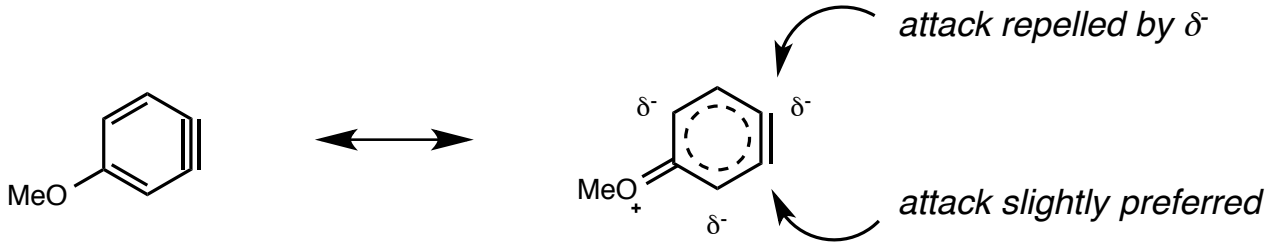
More Distal Polar Group Results in Greatly Diminished Selectivity

- recent example: 4-methoxybenzyne provides products in only a 1.5 : 1 ratio



80%, 42 : 58 regiomeric ratio

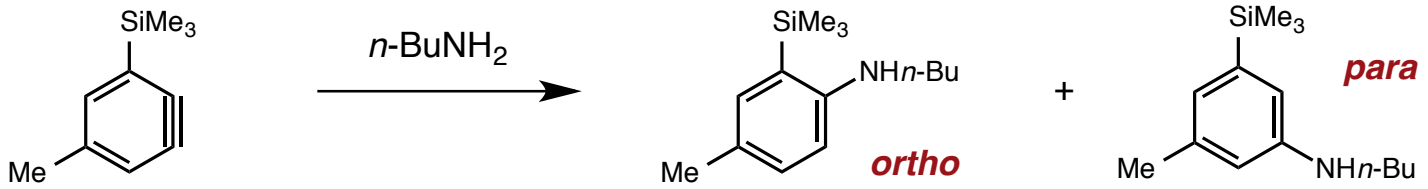
- possible cause: electrostatic repulsion of electron rich π-system



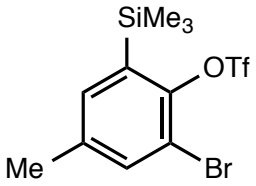
Lakshmi, B. V.; Wefelscheid, U. K.; Kazmaier, U. *Synlett* **2011**, *345*

Reversing Selectivity: Formation of ate-Complex

- introduction of silyl group produces *meta*-product, likely due to non-bonding interactions

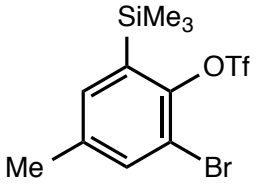


- method of generation and presence of fluoride strongly influences selectivity:



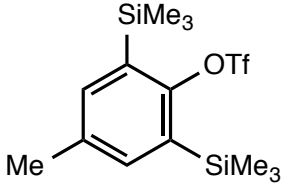
and BuLi

1 : 50 ***o : p***



and BuLi
+ 2 equiv. TBAT

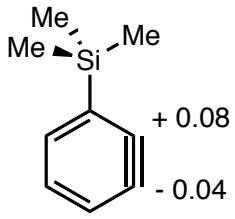
1: 1.2 ***o : p***

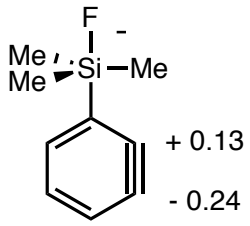


and TBAF

8 : 1 ***o : p***

- DFT predicts significantly increased charges in ate-complex



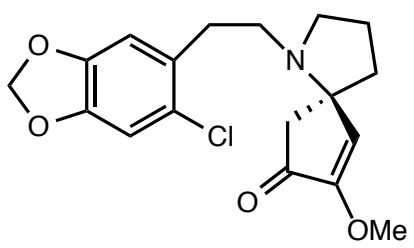


Akai, S *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 5674

Nucleophilic Attack on Arynes by Enolates

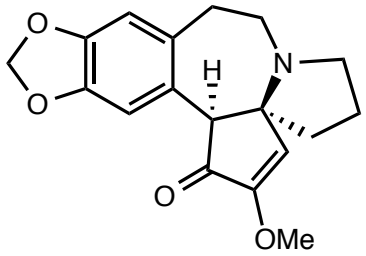
notable appearances in natural product synthesis

- first report: Semmelhack, 1972



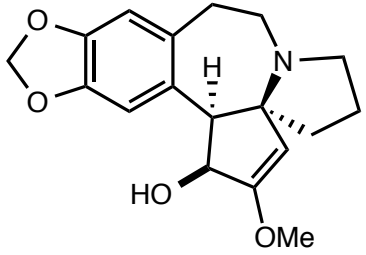
$KCPh_3$, DME

50 °C, 13-16%



cepholotaxinone

DIBAL-H
quant.



cepholotaxine

cephalotaxinone = 6 steps

cephalotaxine = 7 steps

also represents the first use of arynes

in natural product synthesis

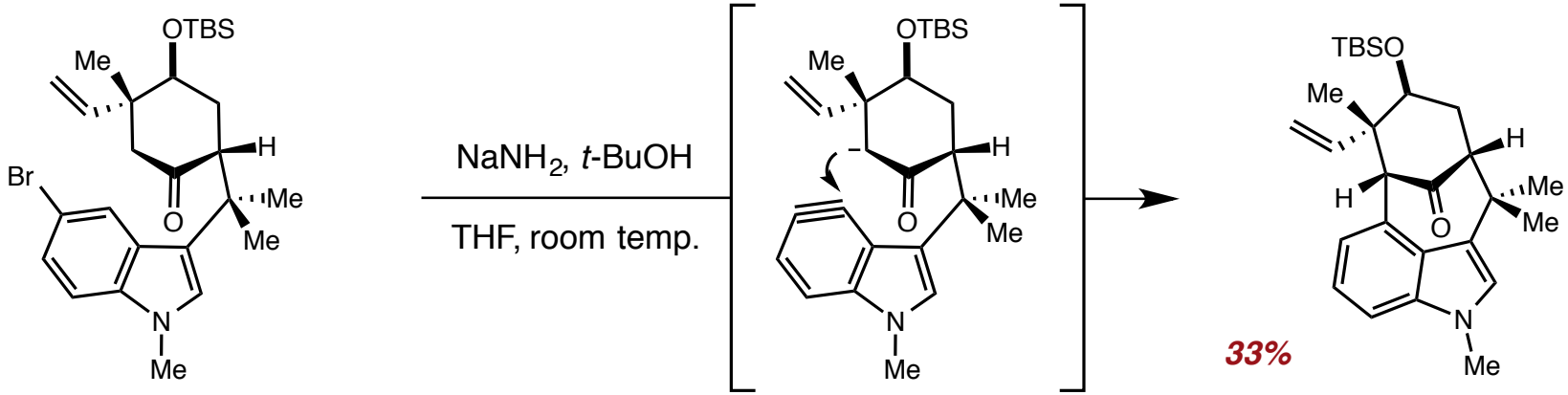
Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629

Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507

Nucleophilic Attack on Arynes by Enolates

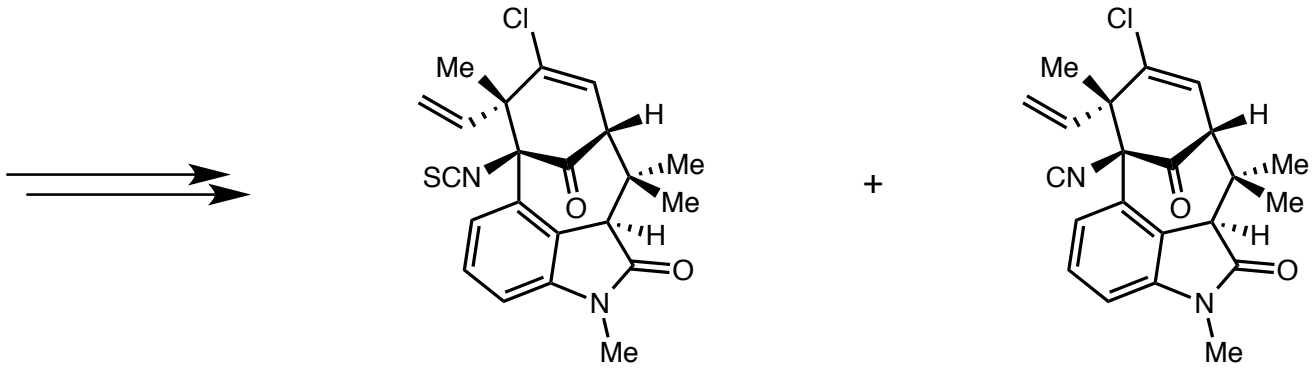
notable appearances in natural product synthesis

- 2011: Garg's synthesis of welwitindolinones



from S-carvone

33%



(–)-N-methylwelwitindolinone C isothiocyanate

(–)-N-methylwelwitindolinone C isonitrile

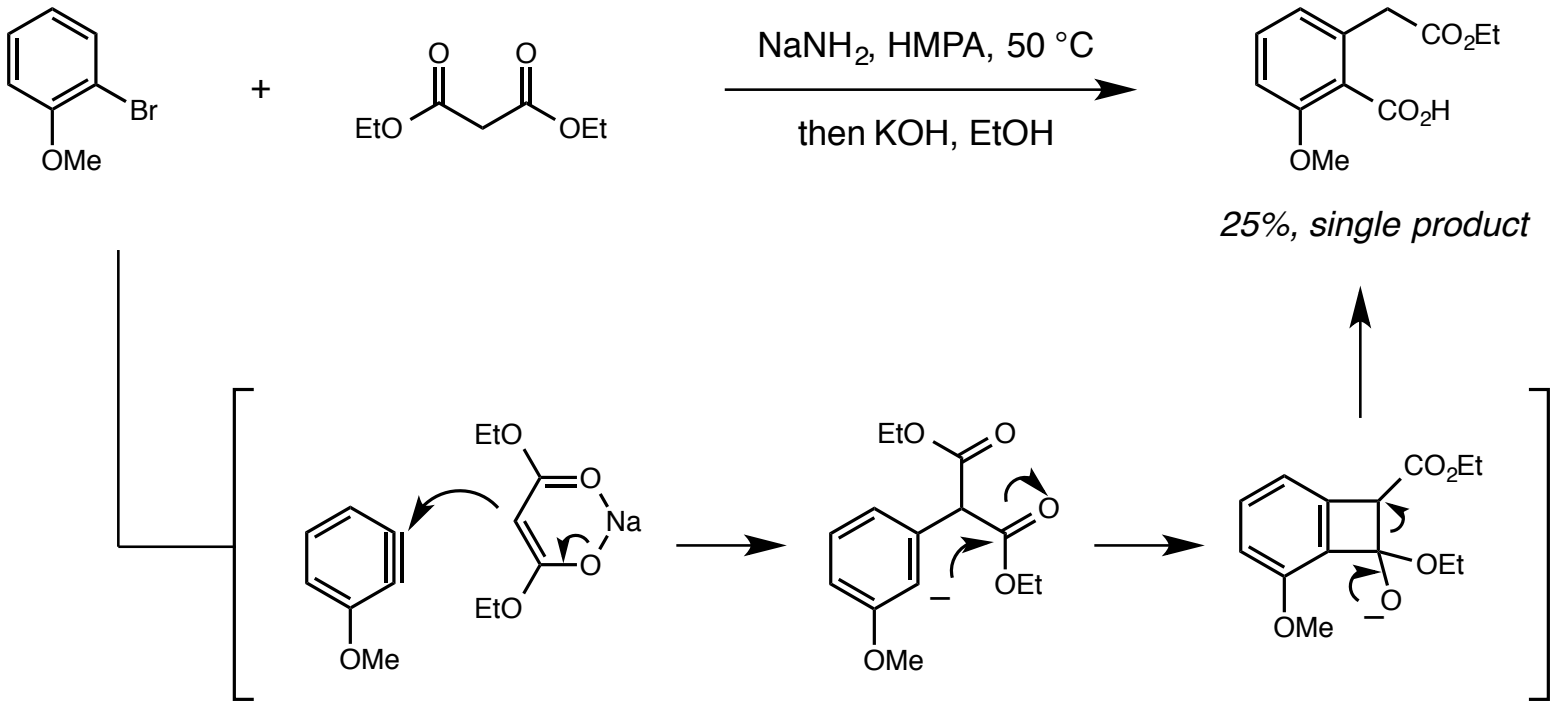
Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *133*, 15797

Quasdorf, K. W.; Huters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *134*, 1396

Nucleophilic Attack on Arynes by Enolates

notable appearances in natural product synthesis

- interesting products are delivered with malonate nucleophiles:



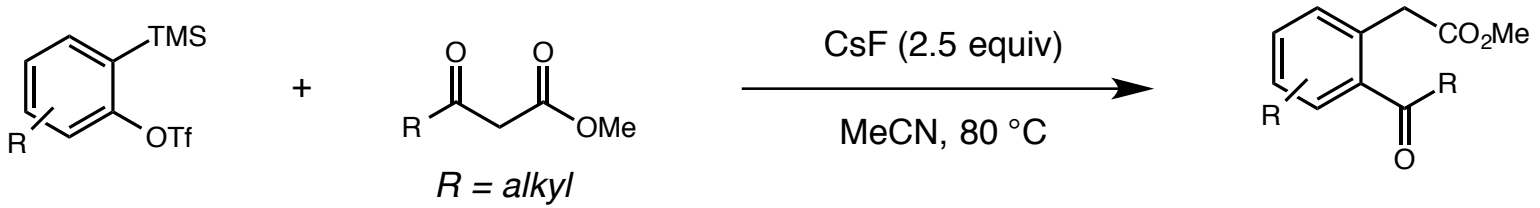
- retro-Dieckmann fragmentation provides products of formal σ-bond insertion

Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, *14*, 3433

Nucleophilic Attack on Arynes by β-Dicarbonyls

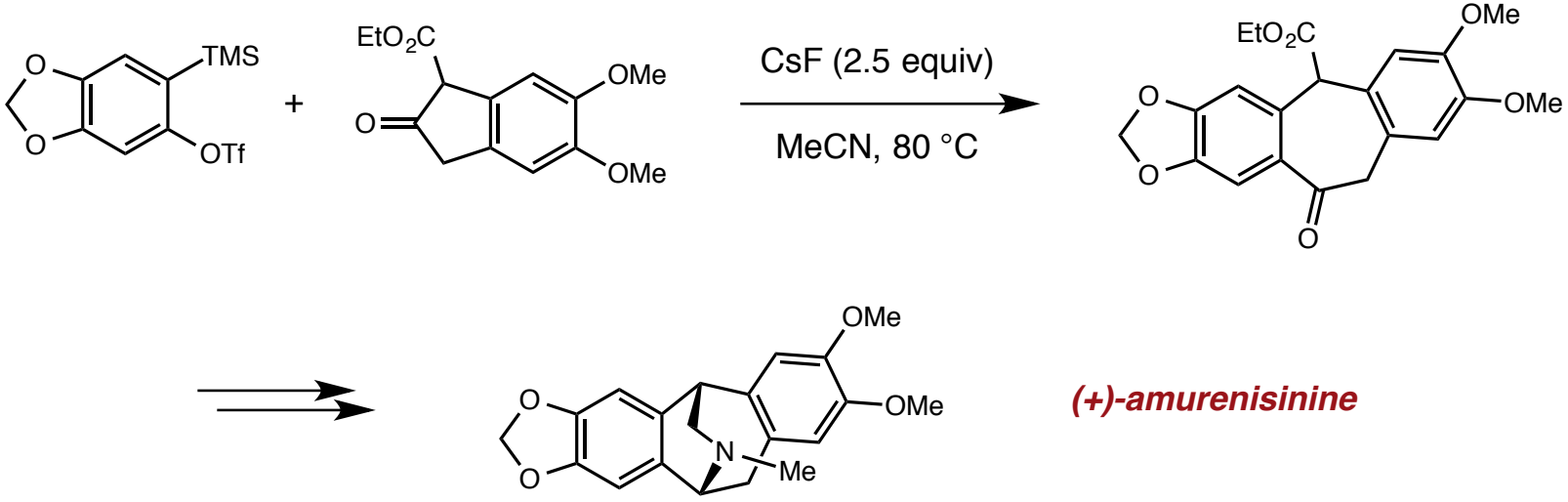
notable appearances in natural product synthesis

- Tambar and Stoltz optimize with β-keto esters and *o*-silyl triflates



53-99% yield

- application: total synthesis of (+)-amurensinine



(+)-amurenisinine

Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340

Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 161

Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752