

Arynes and Cyclohexynes

2012. 6. 19.

Hyung Min Chi

Group Meeting Presentation

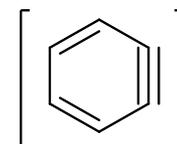
Outline

- Benzyne
 - Characteristic features of benzyne and its formation
 - Representative reactions
 - Applications in synthesis
- Hetarynes
 - Computational interpretation
 - General features and preparation
 - Applications in synthesis
- Cyclohexynes
 - Formation of cyclohexynes
 - Representative reactions
 - Applications in synthesis of natural product compounds

Arynes? Benzynes? Hetarynes?

- Arynes

- An uncharged intermediate from an aromatic system by removal of two ortho-substituents



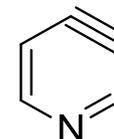
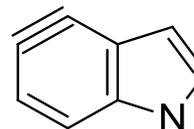
- Benzyne

- Simplest form of aryne is benzynes (1,2-didehydrobenzene)
- Initial suggestion of “benzyne” as intermediate (1942, Wittig)

Wittig, G., *Naturwissenschaften*, **1942**, 30, 46-47, 696.

- Hetarynes

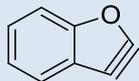
- *ortho*-Dehydroaromatic compounds with heteroatoms in the ring (Heterocyclic arynes)
- Indolynes, pyridynes



Kauffmann, T., *Angew. Chem. int. Ed.* **1965**, 4, 543.

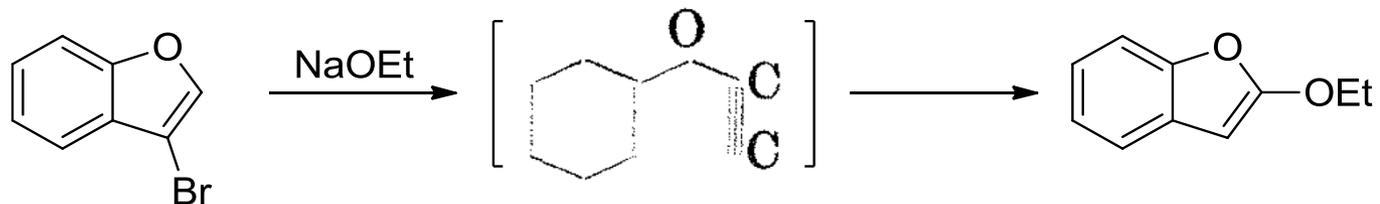
Seminal reports of Arynes

Stoermer & Kahlert:
2,3-didehydrobenzofuran



1902

- Formation of 2-ethoxybenzofuran from 3-bromobenzofuran



- First suggestion of aryne
- no direct evidence

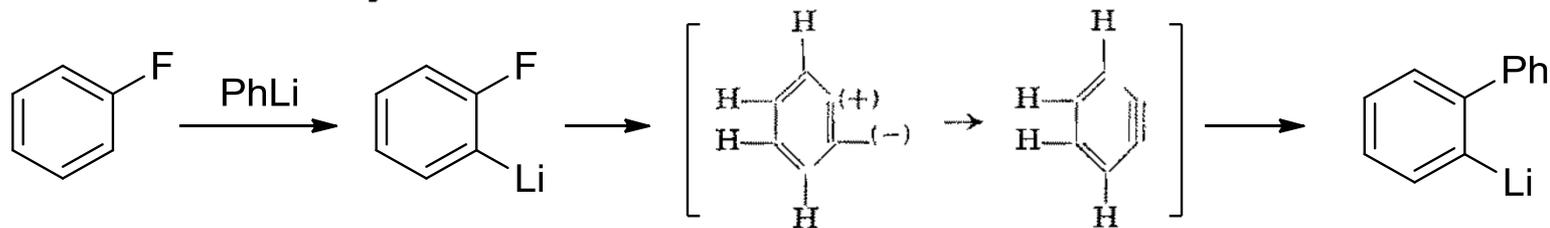
Seminal reports of Arynes

Wittig:
benzyne



1942

- Benzyne (“Dehydrobenzol”) as intermediate



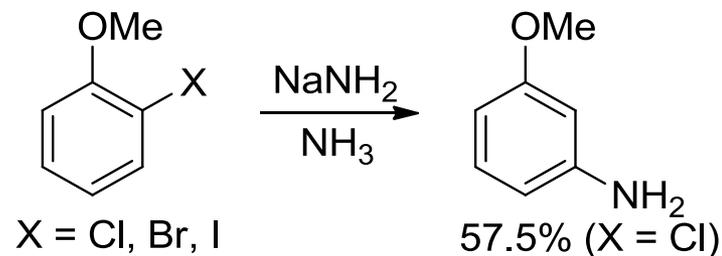
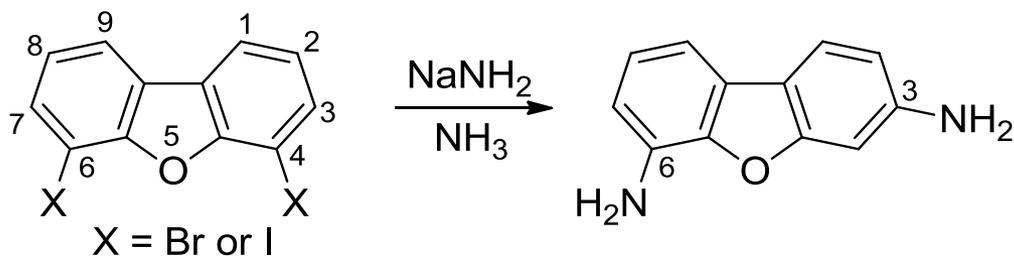
- First suggestion of benzyne
- no direct evidence
- Zwitterionic intermediate

Seminal reports of Arynes

Gilman:
rearrangement

1945

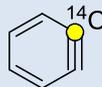
• Rearrangement



- 3,6-diaminodibenzofuran from amination of 4,6-Diiododibenzofuran
- *o*-Haloanisole gave *m*-anisidine

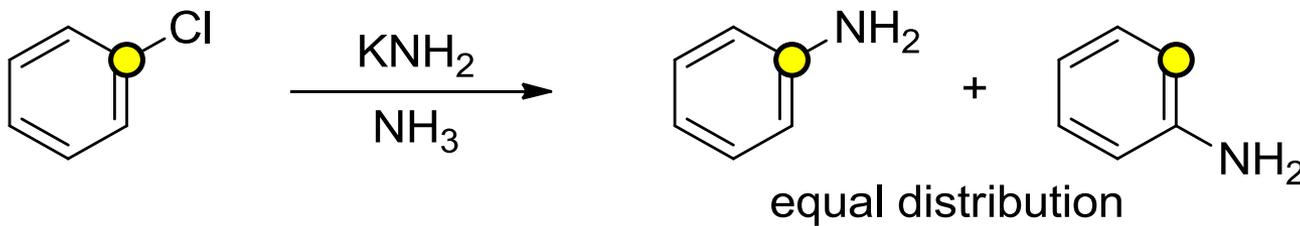
Seminal reports of Arynes

Roberts:
definitive evidence



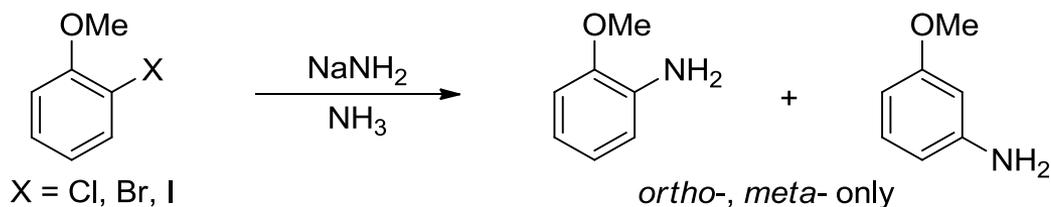
1953

- ^{14}C Labeling experiment

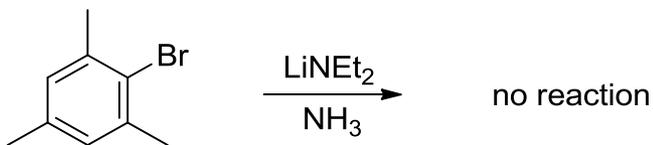


Roberts' experiments: Observations

- 1) "The reactions are very rapid even with chlorobenzene at -33 °C."
- 2) "The entering amino group has never found farther than one carbon away from the position occupied by the leaving halogen." (Gilman, 1945)



- 3) "The starting halides and resulting anilines are not isomerized under the reaction conditions [in liquid ammonia, w/o NaNH_2]." (Vaughan, 1951)
- 4) "No reaction occurs in the benzene series with halides where a hydrogen is not attached to the position adjacent to that occupied by the leaving halogen." (Vaughan, 1951)



J. Am. Chem. Soc. 1945, 67, 349–351.

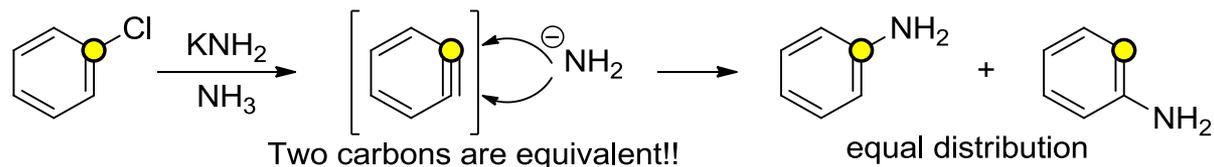
C. W. Vaughan B.S. Thesis, MIT, 1951.

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

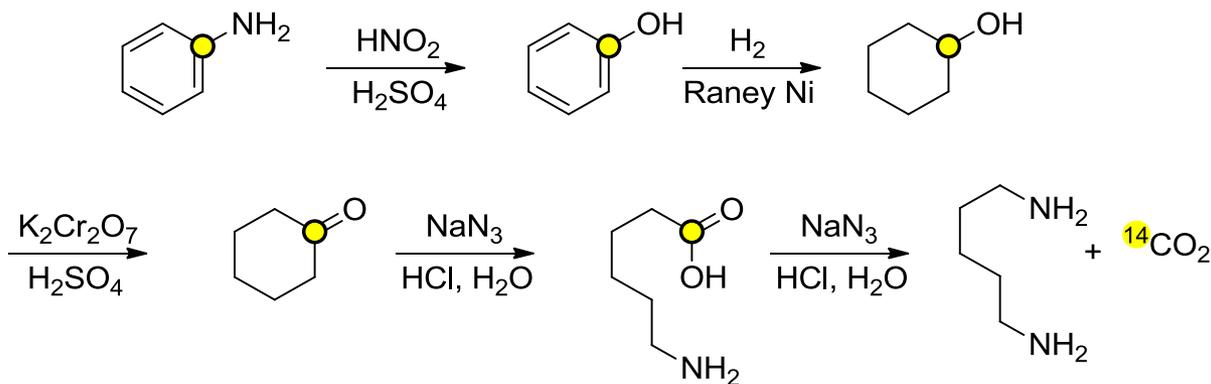
J. D. Roberts, H. E. Simmons Jr., L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.* **1956**, 78, 611.

Roberts' experiments: ^{14}C Labeling

- “Benzyne” Intermediate serves well with the observations.
- If benzyne was involved, then equal amounts of aniline A, B should be formed

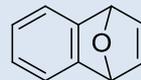


- Does not “prove” benzyne mechanism, but strongly indicates that C1 and C2 are equivalent in the intermediate.
- Degradation of [^{14}C]1-aniline



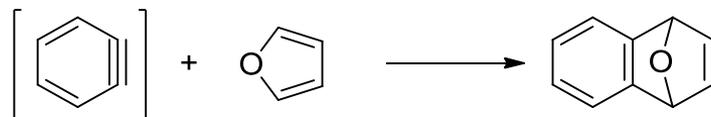
Wittig and Huisgen's experiments

Wittig; Huisgen:
supporting reports



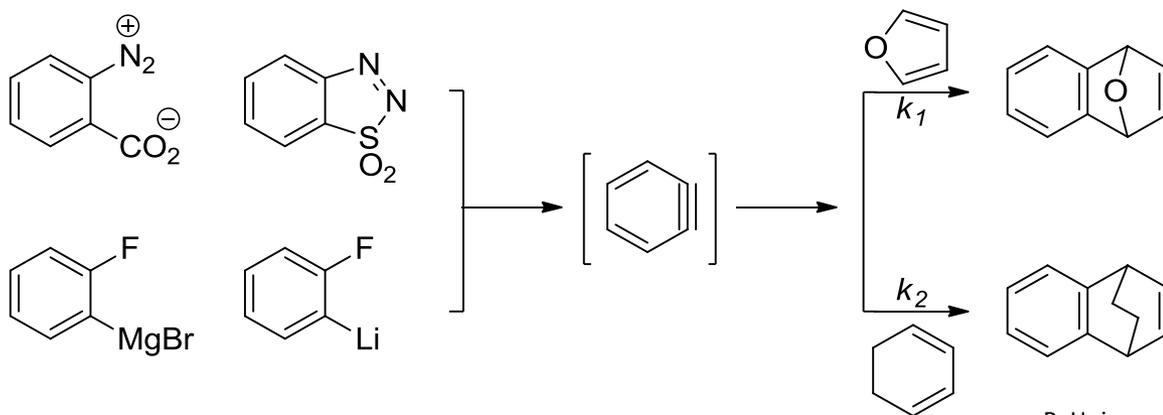
~1960

- Capture of benzyne as dienophile in [4+2] cycloaddition



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

- Competing reactions of benzynes from different preparations
 - k_1 (with furan) / k_2 (cyclohexadiene) = constant



R. Huisgen, R. Knorr, *Tetrahedron Lett.* **1963**, 1017

Efforts made for Spectroscopic Characterization

- Gas-phase microwave spectroscopy

Brown, JACS 1986, 108, 1296-1297.

- UV/Vis

Schweig, Chem. Phys. Lett. 1990, 170, 187-192.

- FT-IR

- Cryogenic Ar matrix trapping (77K)
- [behind story]

Radziszewski, JACS 1992, 114, 52-57.
ACIE 2003, 42, 502-528 [ref. 16]

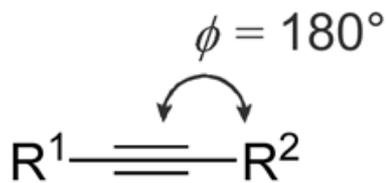
- Solid-state ^{13}C dipolar NMR spectrum at 20 K
 - Triple bond length of o-benzyne

J. Am. Chem. Soc. **1996**, 118, 846-852

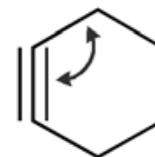
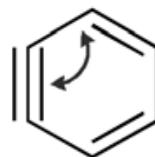
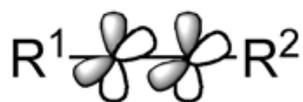
- Guest incarceration in molecular container

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

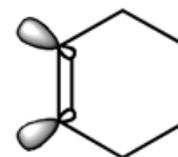
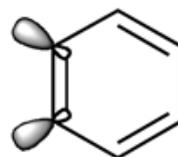
Characteristic feature of Benzynes



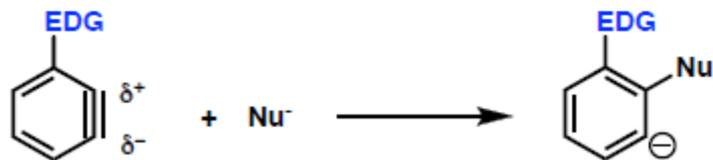
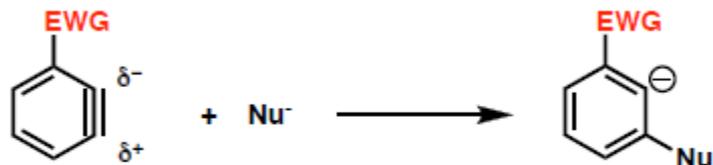
nucleophilic



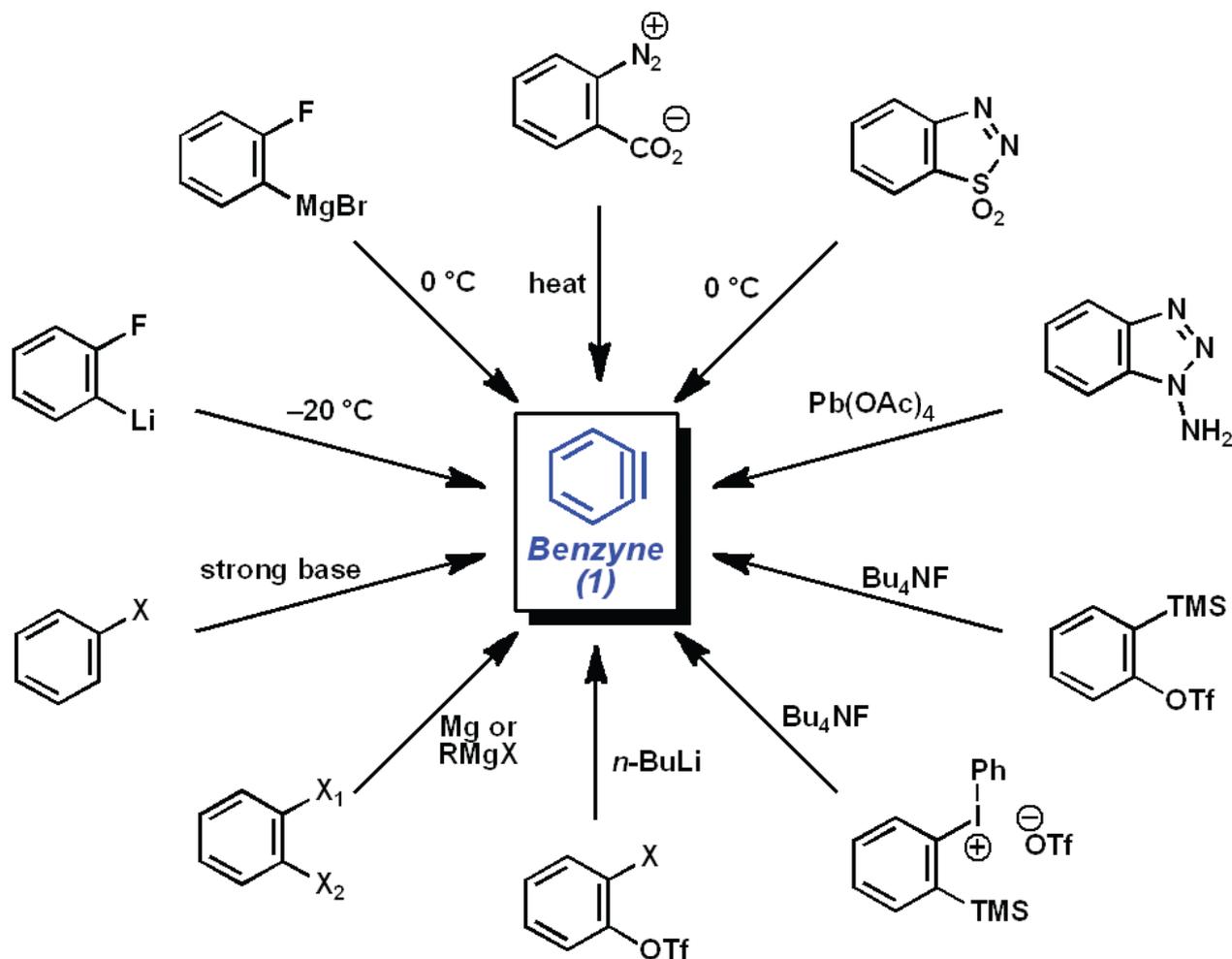
electrophilic



Regiochemistry of Nucleophilic Additions to Benzyne



Generation of Benzyne



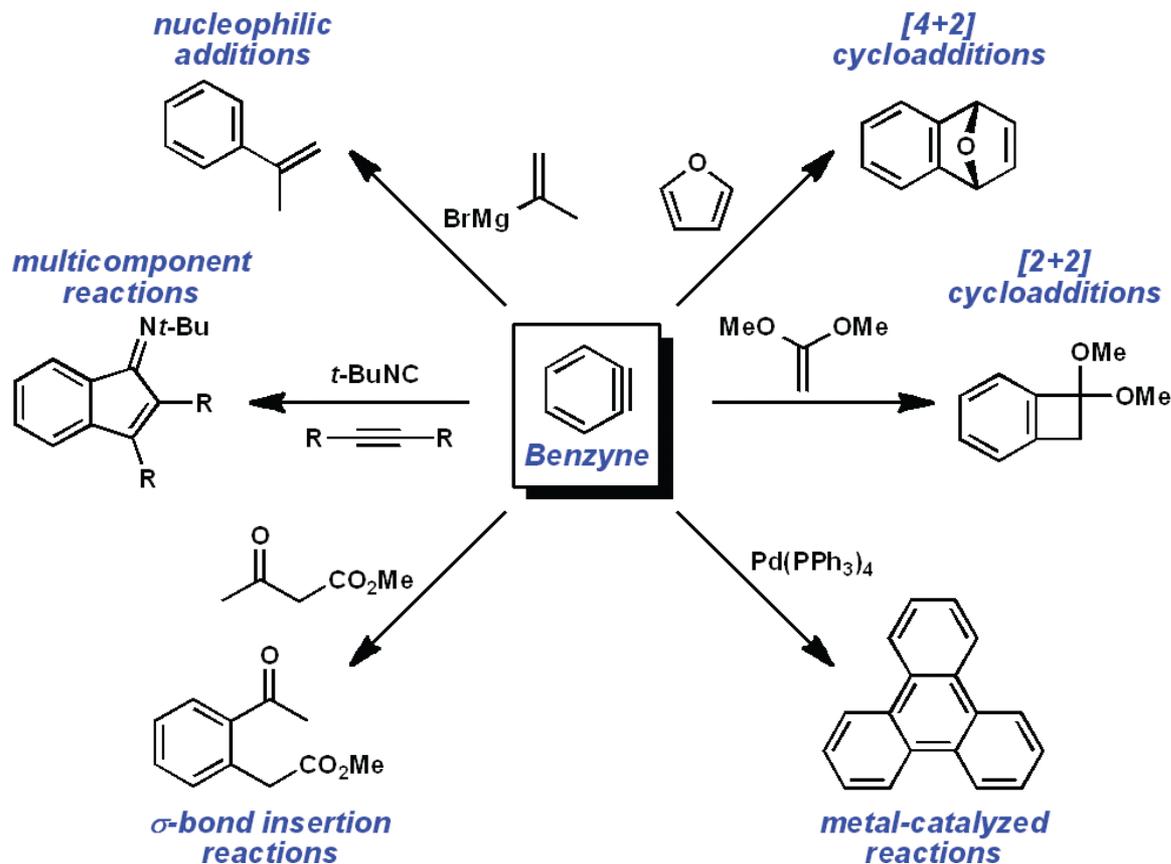
Stoltz, Chem. Rev. ASAP

Iodonium Triflate: T. Kitamura, M. Yamane, *J. Chem. Soc., Chem. Commun.* **1995**, 983. Silyl Triflate: Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

Benzotriazole: C. D. Campbell, C. W. Rees, *J. Chem. Soc. (C)* **1969**, 742. Halo Triflate: T. Matsumoto, T. Hosoya, M. Katsuki, K. Suzuki, *Tet. Lett.* **1991**, 32, 6735.

Diazonium Carboxylate: L. Friedman, F. M. Logullo, *J. Am. Chem. Soc.* **1963**, 85, 1792. Fluoro Magnesium and Fluoro Lithium: R. W. Hoffmann, *Dehydrobenzene and Cycloalkanes*, Academic Press, New York, **1967**. Benzothiadiazol-1,1-dioxide: G. Wittig, R. W. Hoffmann, *Org. Synth., Coll. Vol. V*, 60, **1971**.

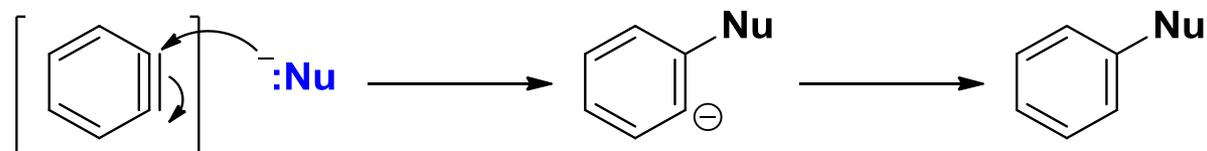
Representative Reactions of Benzyne



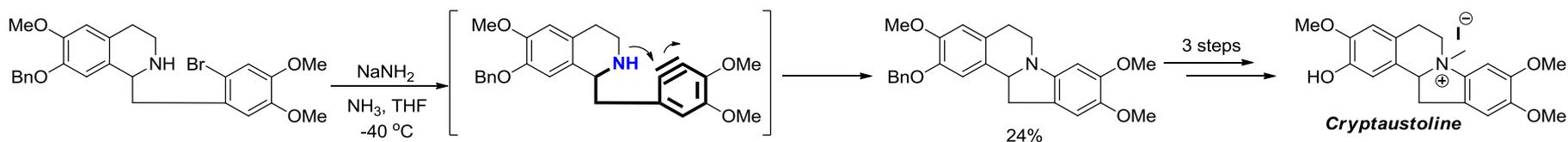
Stoltz, Chem. Rev. *Asap*

Liu, Z.; Larock, R. C. *Org. Lett.* 2003, 5, 4673. Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* 2011, 50, 4488. Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* 2005, 127, 5340. Wittig, G.; Pohmer, L. *Chem. Ber.* 1956, 89, 1334. Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* 1982, 47, 2393. Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* 1998, 37, 2659

Nucleophilic Addition

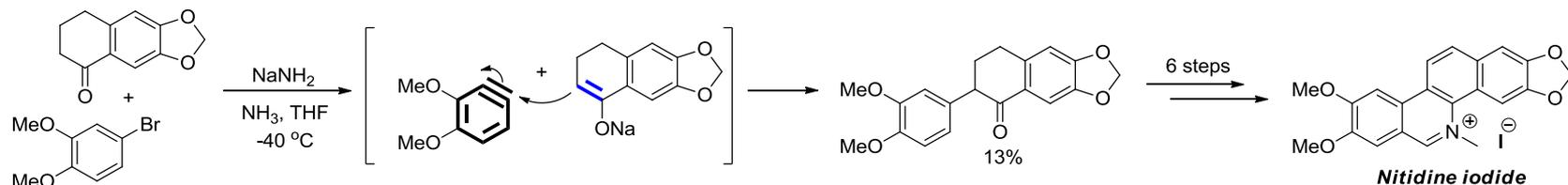


- **Cryptaustoline (Kametani, 1967)**



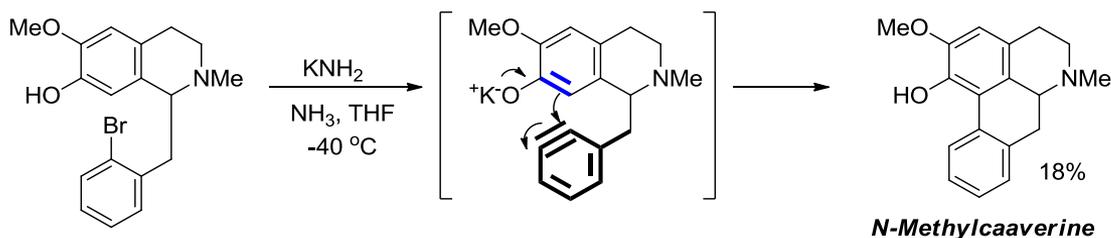
Kametani, T.; Ogasawara, K. J. Chem. Soc., C 1967, 2208.

- **Nitidine iodide (Kametani, 1973)**



Kametani, T.; Kigasawa, K.; Hiiragi, M.; Kusama, O. J. Heterocycl. Chem. 1973, 10, 31.

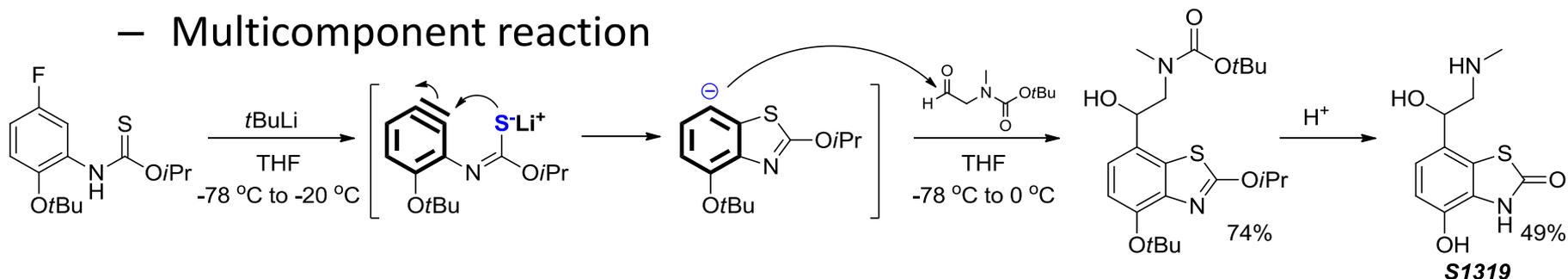
- **N-Methylcaaverine (Kessar, 1975)**



Kessar, S. V.; Batra, S.; Nadir, U. K.; Gandhi, S. S. Indian J. Chem. 1975, 13, 1109.

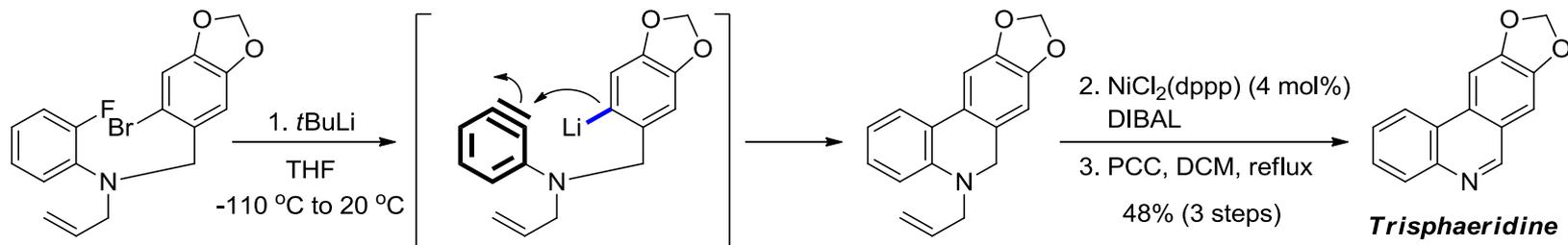
Nucleophilic Addition

- S1319 (Fairhurst, 2005)
 - Use of tBuLi, Thiocarbamate
 - Multicomponent reaction



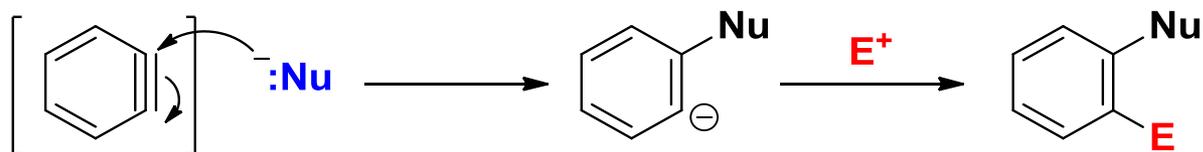
Fairhurst, R. A.; Janus, D.; Lawrence, A. *Org. Lett.* 2005, 7, 4697.

- Trisphaeridine (Sanz, 2007)
 - Selective benzyne generation



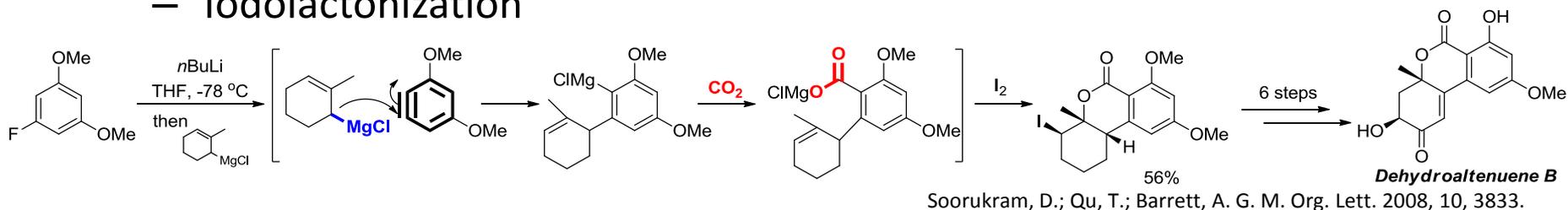
Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *Eur. J. Org. Chem.* 2007, 62.

Multicomponent Reaction



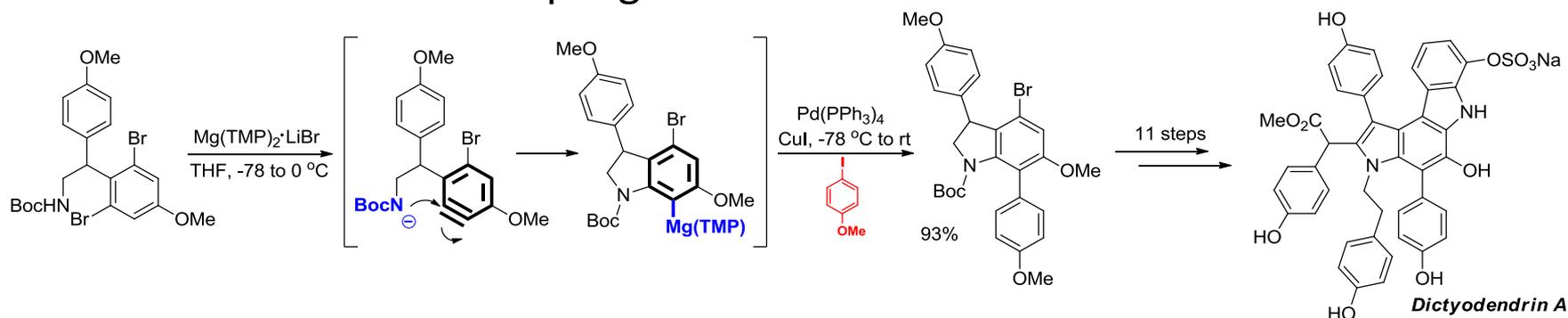
- Dehydroaltenuene B (Barrett, 2008)

- Capture of CO_2 with ArMgX
- Iodolactonization



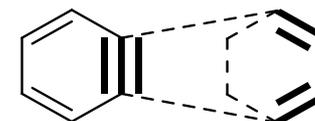
- Dictyodendrins A (Tokuyama, 2010)

- Kumada-Tamao coupling

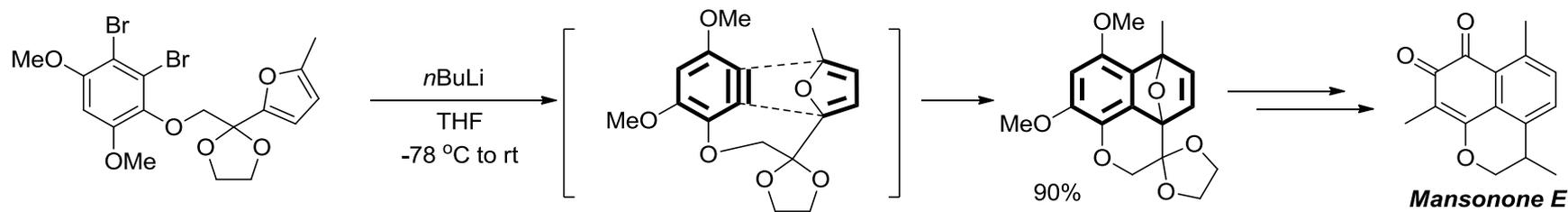


[4+2] Cycloadditions

- Major strategies with arynes
 - Mostly cyclic dienes, especially furans
 - More likely undergoes stepwise process



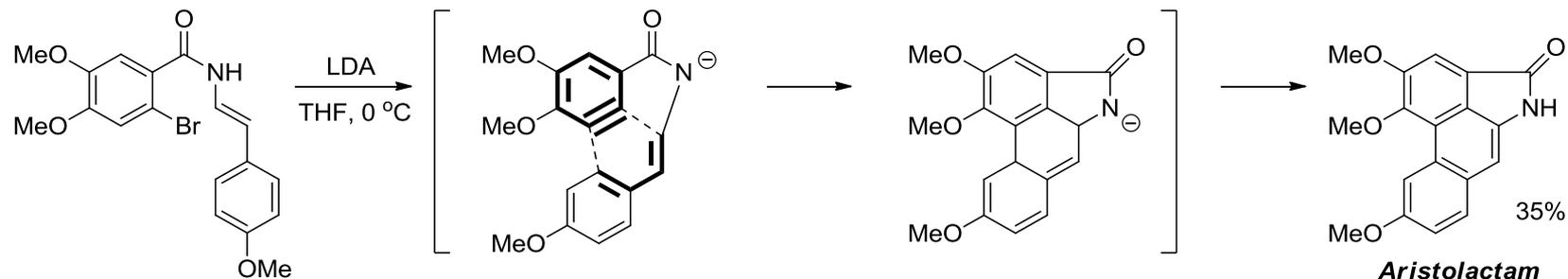
- Mansonone (Best, 1981)**



Best, W. M.; Wege, D. *Tetrahedron Lett.* 1981, 22, 4877.

- Aristolactam (Castedo, 1989)**

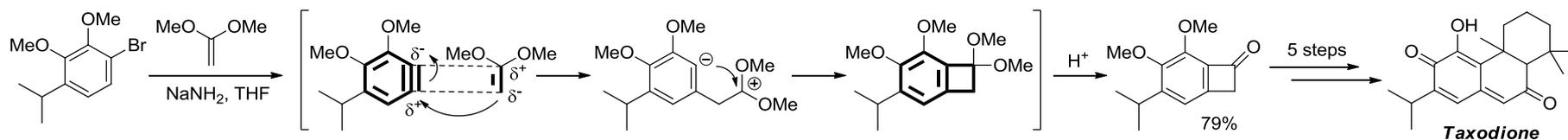
- With pendant styrene



Estévez, J. C.; Estévez, R. J.; Guitián, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* 1989, 30, 5785.

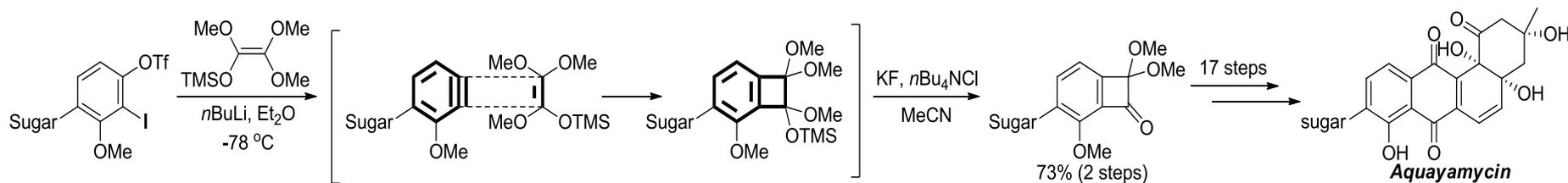
[2+2] Cycloadditions

- Underutilized methods
 - Significant side product formation
 - Thermally forbidden [2+2] => stepwise
 - Easy access to benzocyclobutenones
- Taxodione (Stevens, 1982)



Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* 1982, 47, 2396.

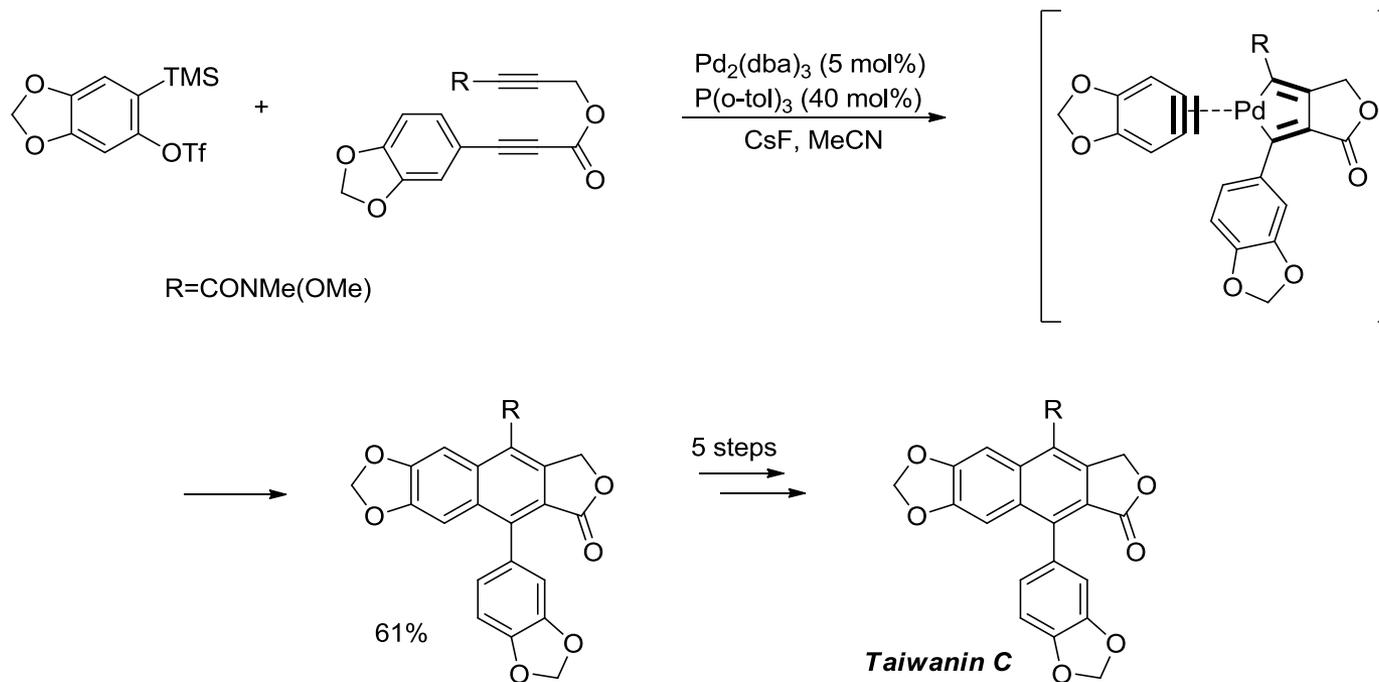
- Aquayamycin (Suzuki, 2000)



Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* 2000, 41, 8383

Metal-catalyzed reactions

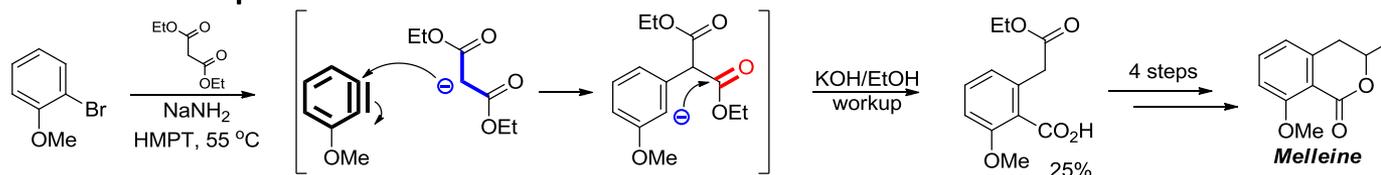
- Taiwanin C (Mori, 2004)
 - Pd-catalyzed [2+2+2]-cycloaddition of aryne and diyne



σ -Bond Insertion

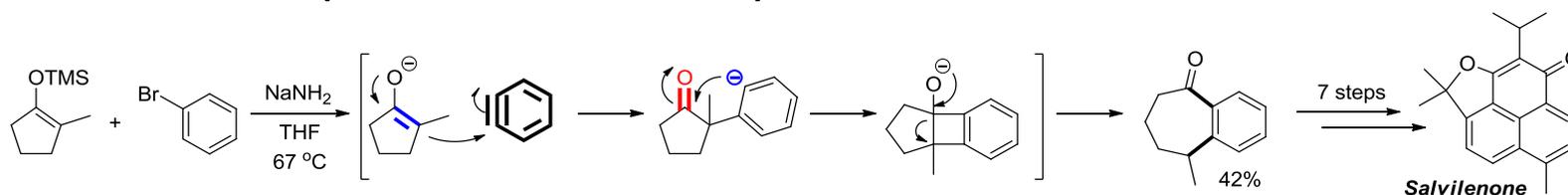
- Melleine (Guyot, 1973)

- Initial report



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

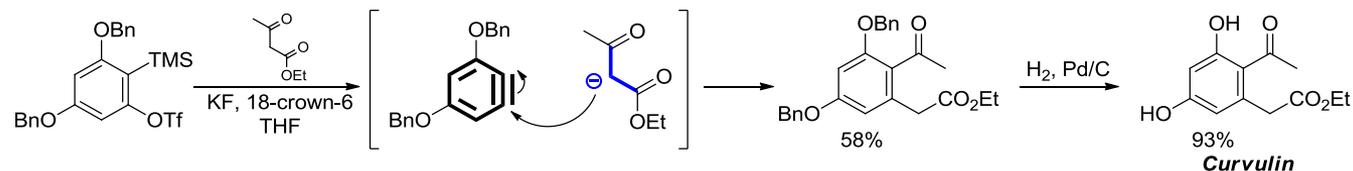
- Salvilenone (Danheiser, 1994)



Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* 1994, 116, 9471.

- Curvulin (Stoltz, 2010)

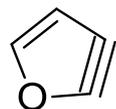
- KF, 18-crown-6



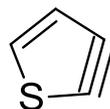
Tadross, P. M.; Gilmore, C. D.; Bugga, P. B.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* 2010, 12, 1224.

Heteroarynes

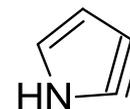
- Heterocyclic ortho-arynes
- Five-membered heterocycles



Didehydrofuran

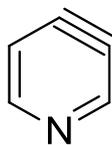


Didehydrothiophene

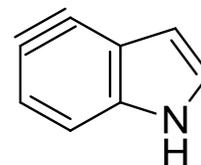


Didehydropyrrol

- Six-membered heterocycles



3,4-Didehydropyridine
"Pyridyne"

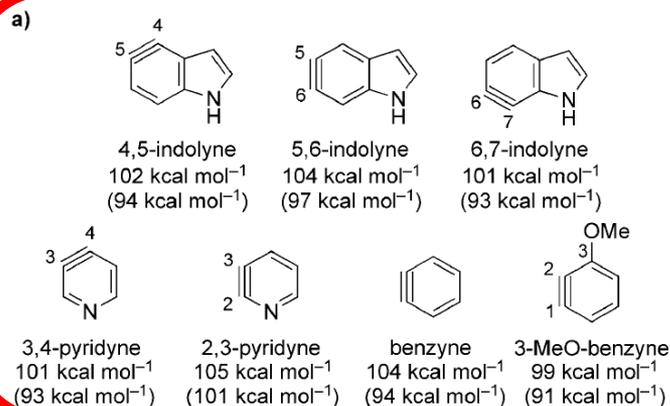


4,5-Didehydroindoline
"Indolyne"

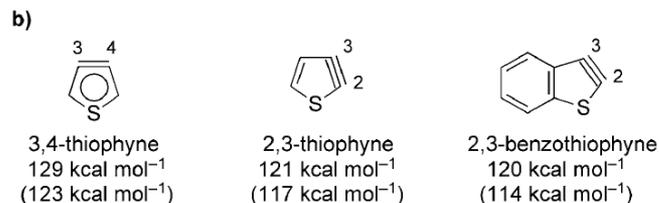
Computational interpretation

- Accessibility

$$\text{energy of dehydrogenation in kcal mol}^{-1} = (\text{energy of aryne} + \text{energy of H}_2) - (\text{energy of parent arene})$$

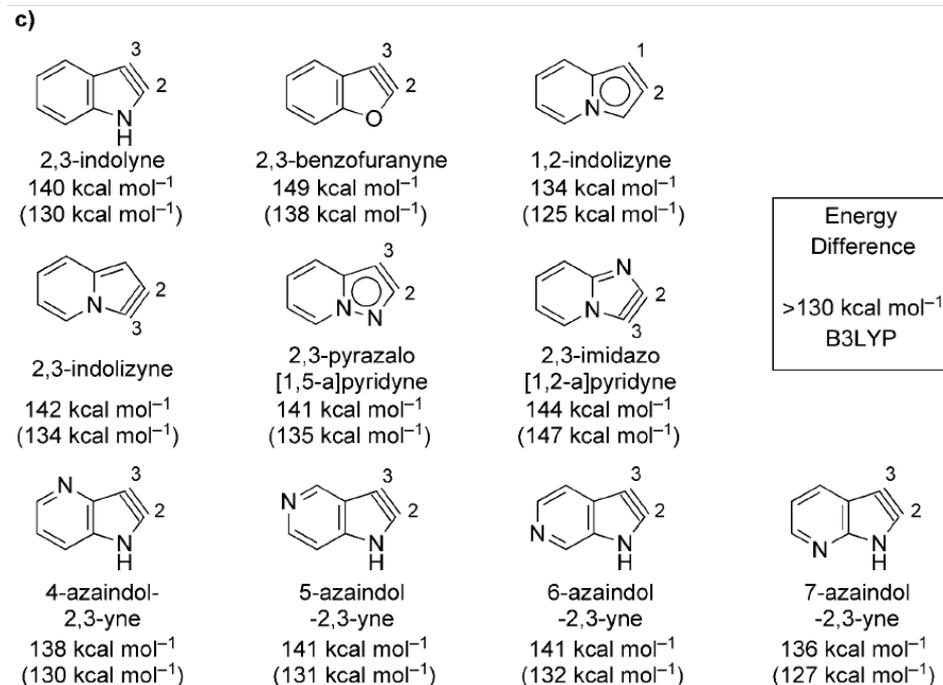


Energy Difference
<115 kcal mol⁻¹
B3LYP



Energy Difference =
115 – 130
kcal mol⁻¹
B3LYP

DFT: B3LYP/6-31G*
(ab initio: MP2/6-311+G**)

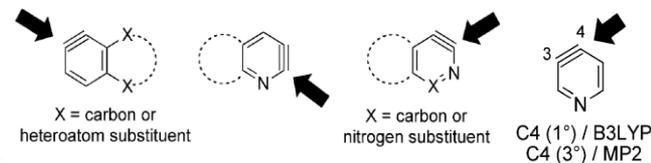


Energy Difference
>130 kcal mol⁻¹
B3LYP

Computational interpretation

- Site-selectivity

- Internal angles of geometry-optimized models
- More linear terminus is most electrophilic
- Angle differences $\geq 4^\circ$: synthetically useful site selectivity



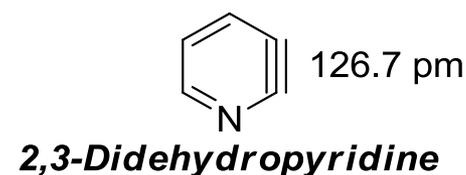
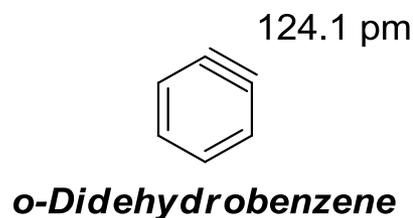
Entry	Site of Attack ^[a] (angle difference)		Hetaryne
	B3LYP	MP2	
1: indolynes	C5 (4°)	C5 (1°)	
	C5 (3°)	C5 (<1°)	
	C6 (17°)	C6 (7°)	
2: benzofuranynes	C5 (7°)	C5 (3°)	
	C5 (2°)	N/A (0°)	
	C6 (20°)	C6 (9°)	
1: pyridynes	C4 (1°)	C4 (3°)	
	C2 (47°)	C2 (34°)	

Entry	Site of Attack ^[a] (angle difference)		Hetaryne
	B3LYP	MP2	
3: benzotriazolynes	C5 (11°)	C5 (4°)	
	C5 (2°)	C5 (1°)	
	C6 (20°)	C6 (9°)	
4: quinolynes	C6 (2°)	C6 (<1°)	
	C7 (1°)	C7 (1°)	
	C7 (2°)	C7 (3°)	

Pyridynes

- Stability

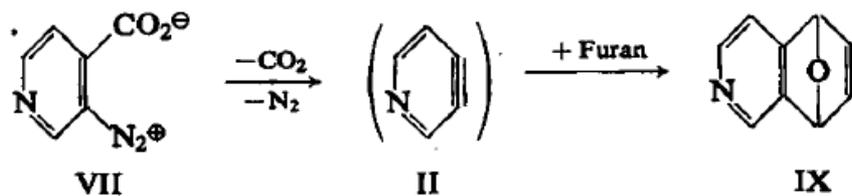
- 3,4-Pyridyne is significantly more stable than the 2,3-isomer
- Triple C-C bond length



Garg, ACIE 2012, 51, 2758

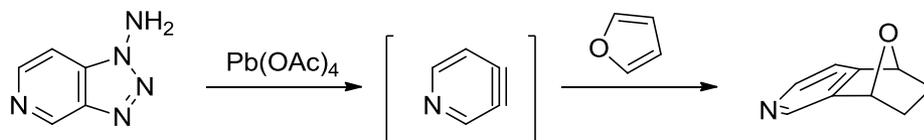
- Generation

- Diazonium carboxylate (Kauffmann, 1966)



T. Kauffmann and F.-P. Boettcher, *Chem. Ber.*, 1962,95,949

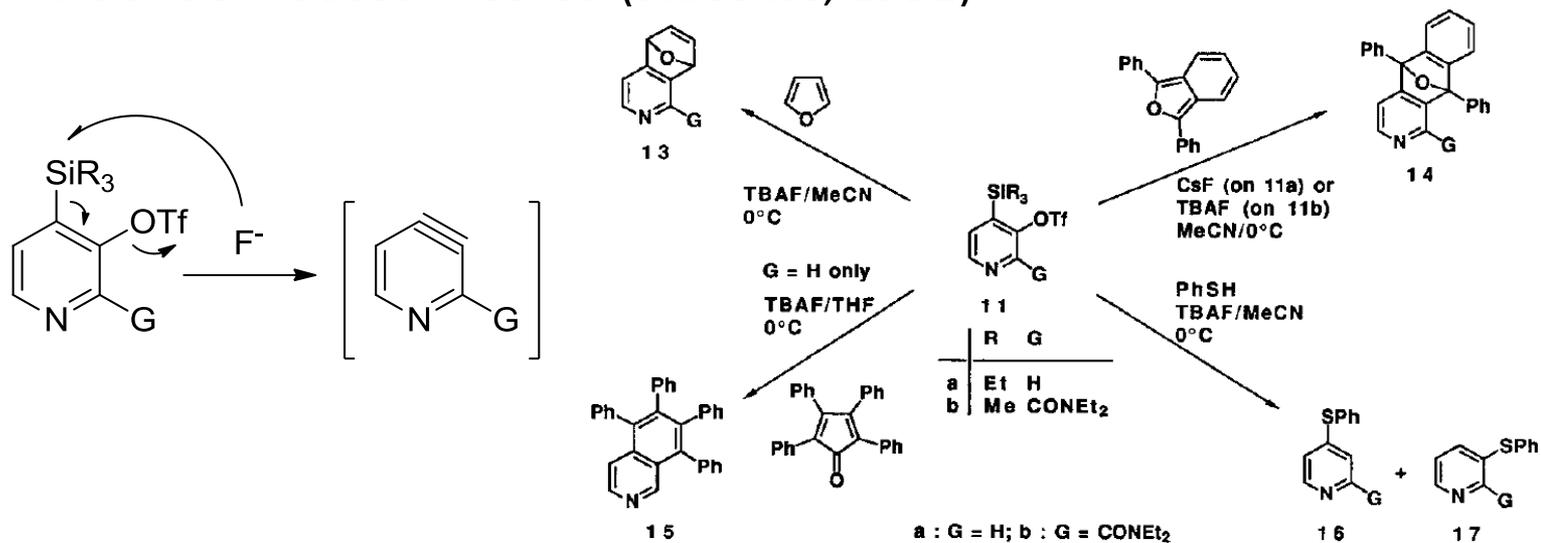
- Oxidative degradation (Sasaki, 1971)



T. Sasaki, K. Kanematsu, and M. Uchide, *Bull. Chem. Soc. Japan*, 1971,44, 858

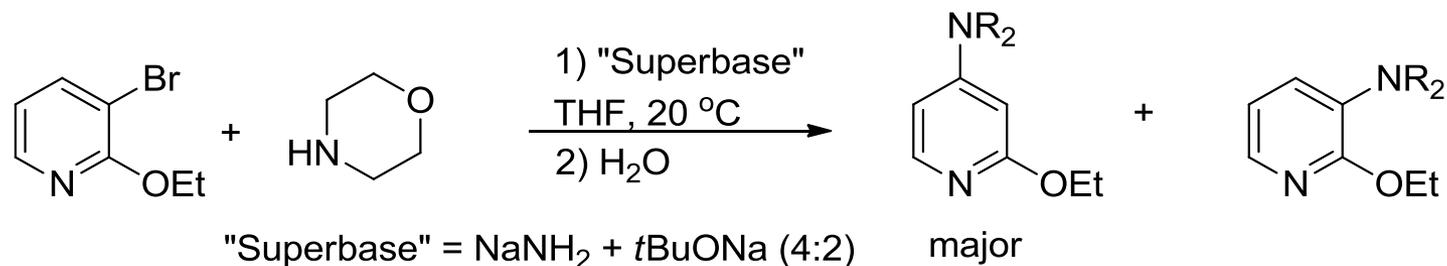
Pyridynes

- Fluoride-induced method (Snieckus, 1992)



M. Tsukazaki, V. Snieckus, *Heterocycles* 1992, 33, 533.

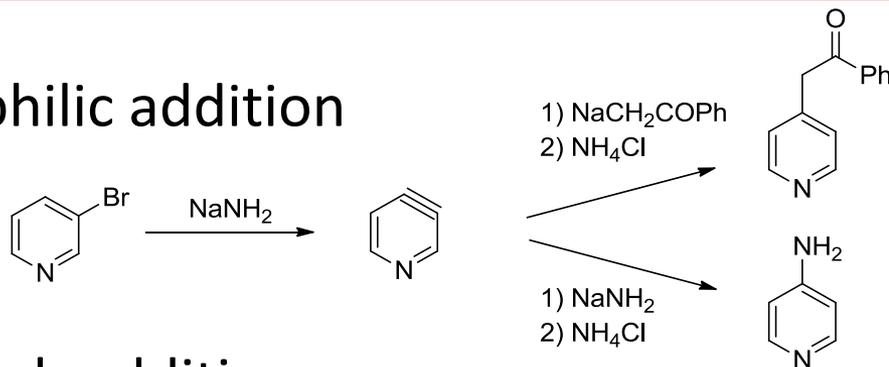
- Super-base (Caubere, 1997)



Caubere, *Heterocycles* 1997, 45, 2113.

Representative Reactions of Pyridynes

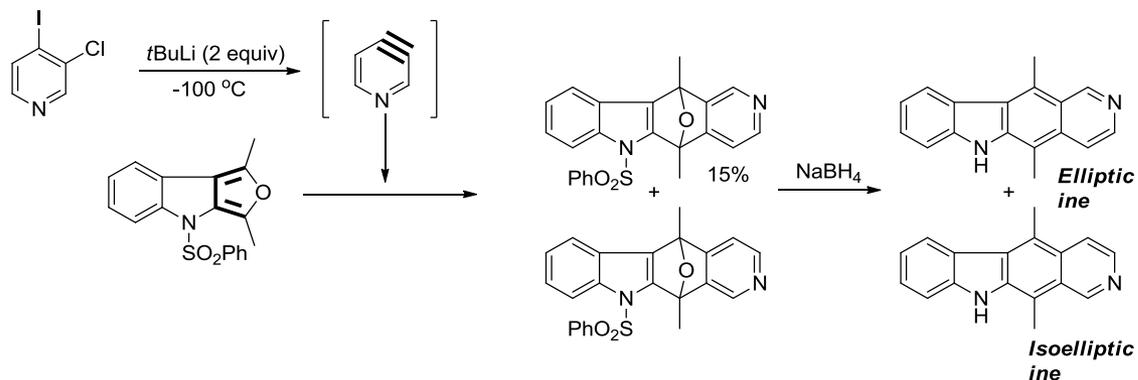
- Nucleophilic addition



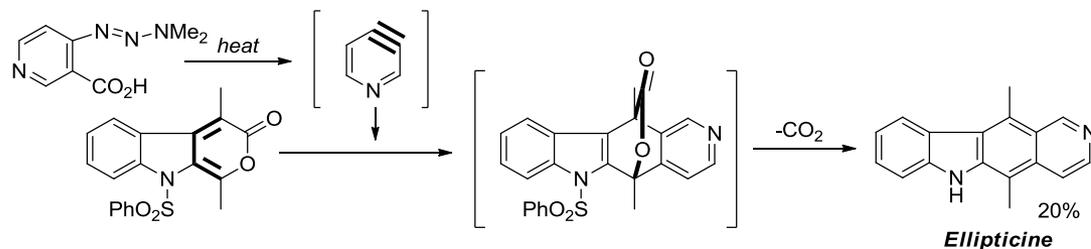
Levine, Science 1955, 121, 780.

- [4+2] Cycloaddition

- Synthesis of ellipticine and isoellipticine



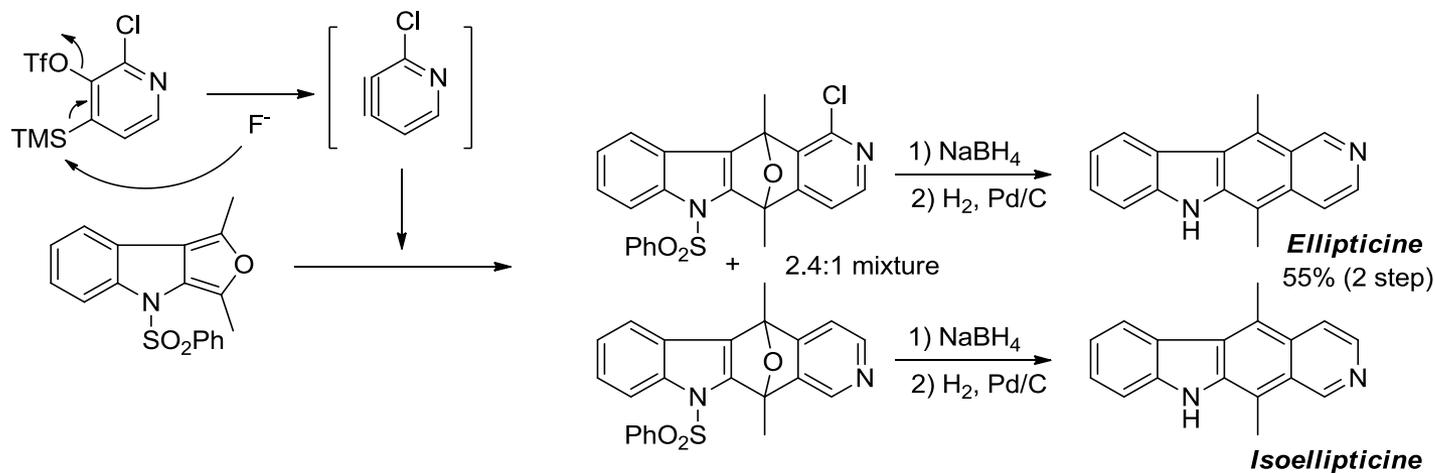
Gribble JOC, 1984, 49,4518.



Moody, J Chem Soc Chem Commun, 1984, 926.

Representative Reactions of Pyridynes

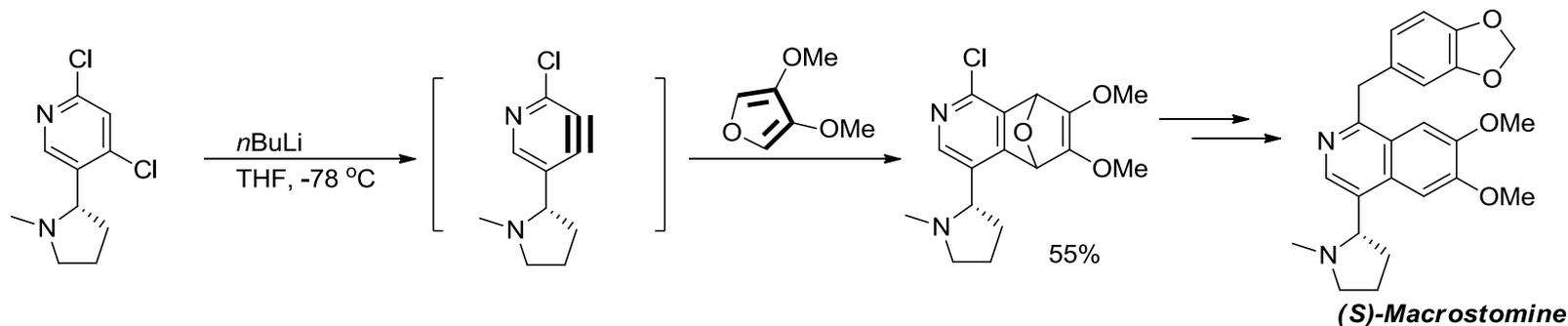
– Polar control with chlorine substitution



Guitian, Synlett 1998, 157.

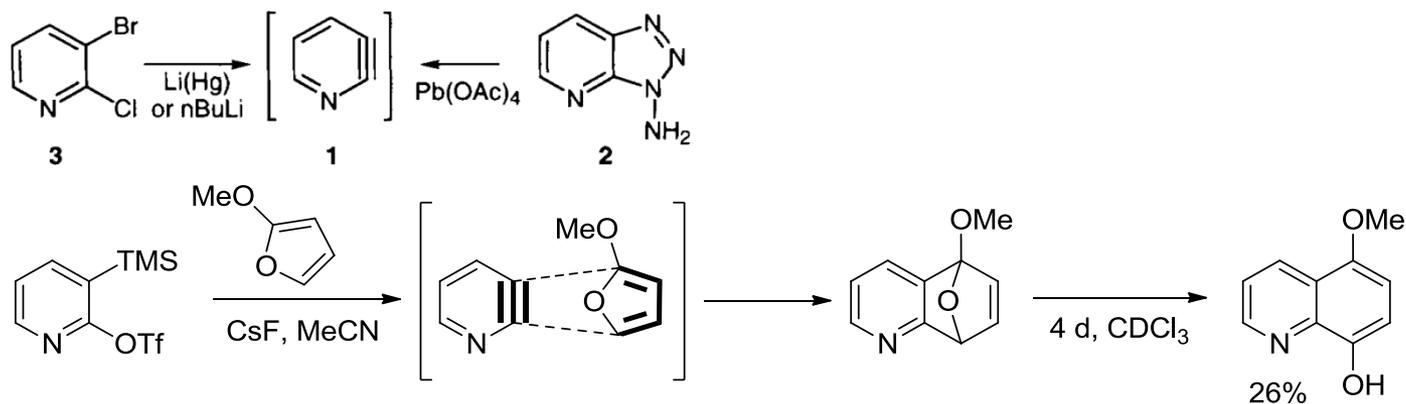
Representative Reactions of Pyridynes

– (S)-Macrostomine



D. L. Comins, Org Lett 2010, 12, 4513.

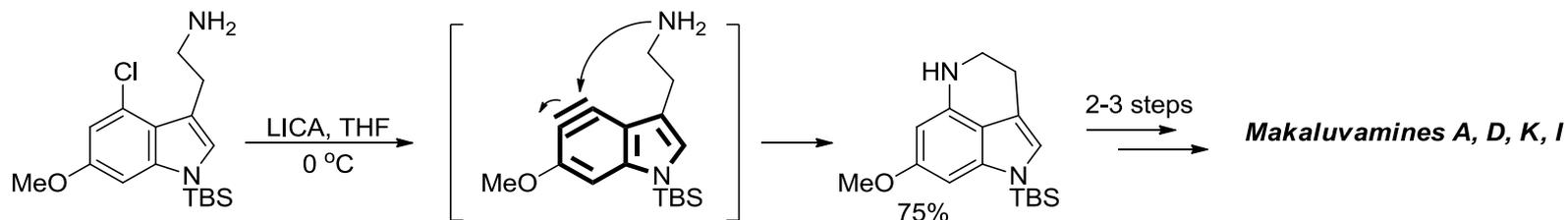
• 2,3-Pyridynes



M. A. Walters, Synth. Commun. 1997, 27, 3573.

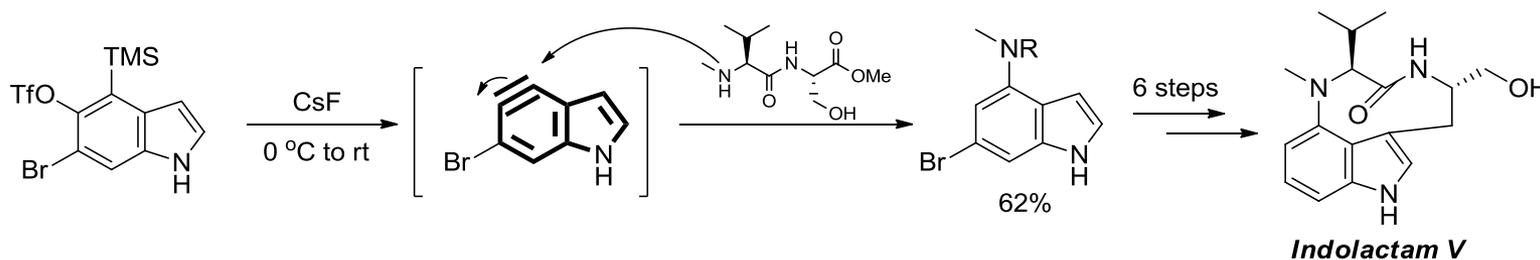
Representative Reactions of Indolynes

- Nucleophilic addition
 - Makaluvamines (Iwao, 1998)



Iwao, M.; Motoi, O.; Fukuda, T.; Ishibashi, F. *Tetrahedron* 1998, 54, 8999.

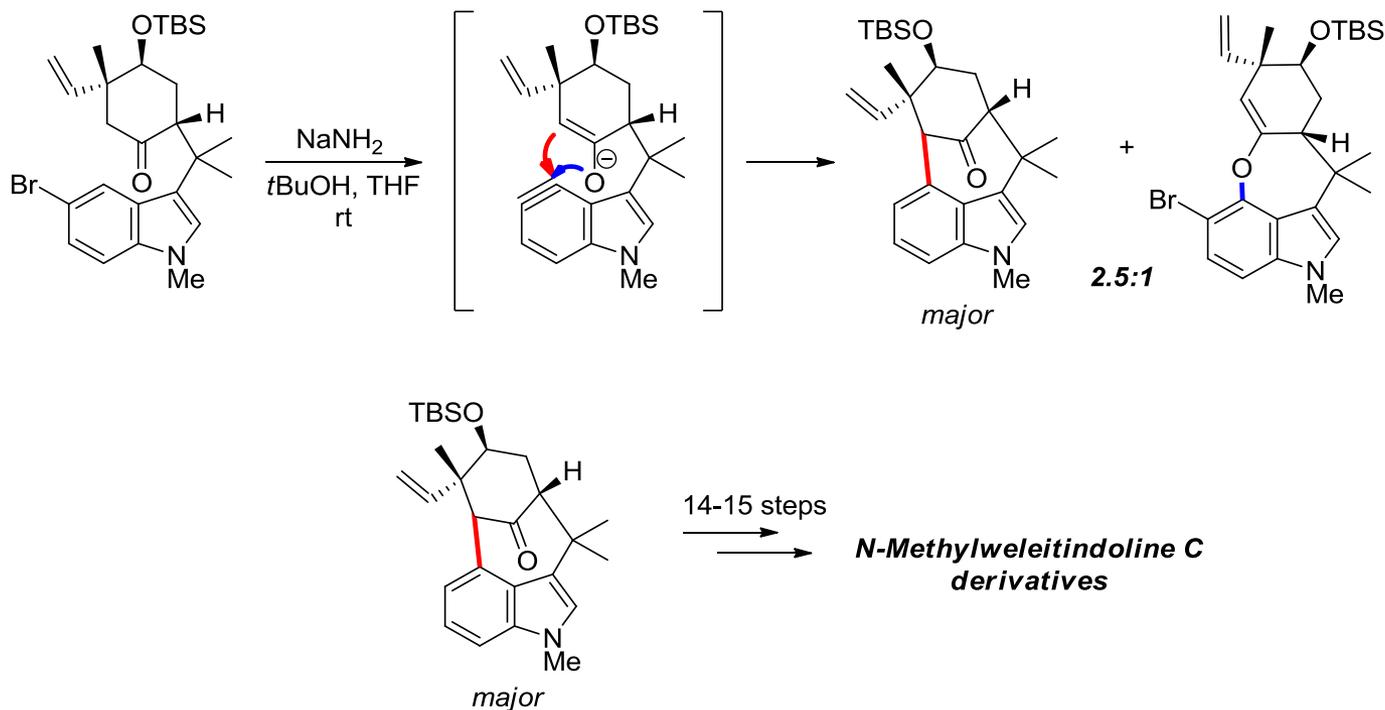
- Indolactam V (Garg, 2011)



S. M. Bronner, K. B. Bahnck, N. K. Garg, *Org. Lett.* 2009, 11, 1007.

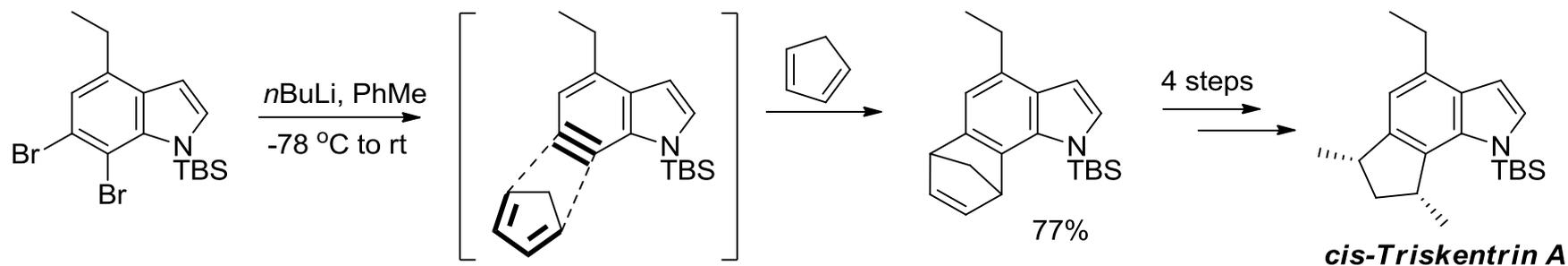
Representative Reactions of Indolynes

- Nucleophilic addition
 - Welwitindolinone (Garg, 2011)



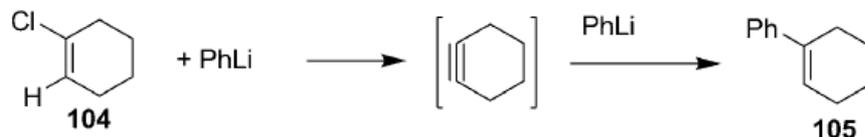
Representative Reactions of Indolynes

- [4+2] Cycloadditions
 - Trikentron A (Buszek, 2009)

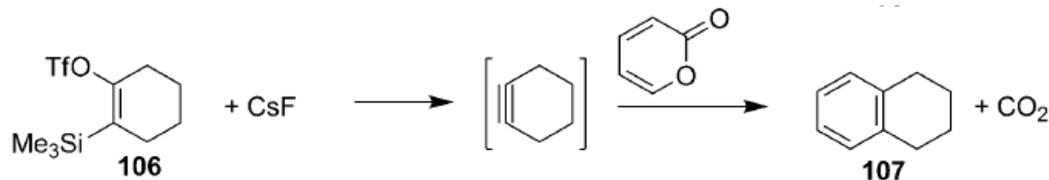


Formation of Cyclohexyne

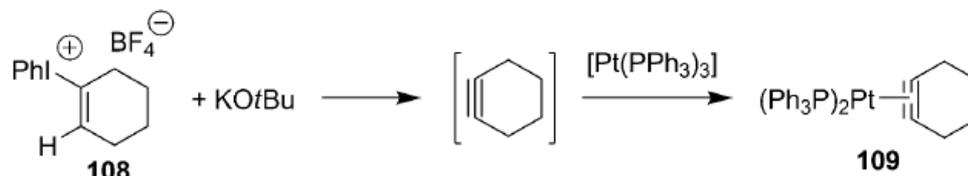
- Scardiglia & Roberts



- Guitian (Kobayashi's method for aryne generation)

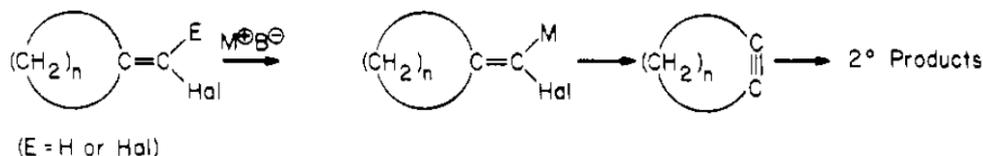


- Fujita

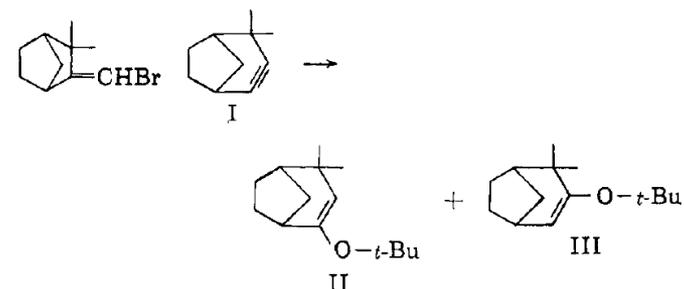


Carreira, ACIE 2012, 51, 3766

- Other approaches (rearrangements)



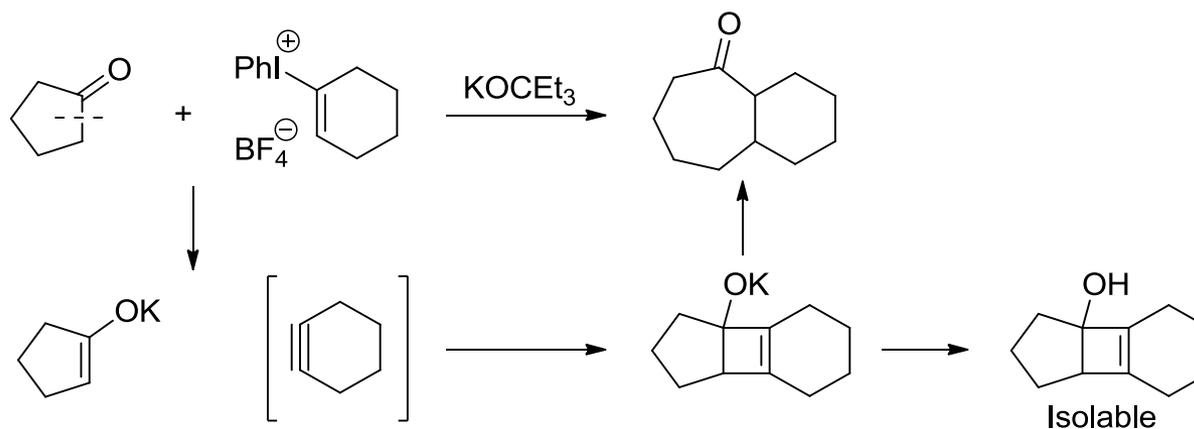
Gilbert, *J. Am. Chem. Soc.* **1983**, *105*, 665-667



Erickson, *JACS* 1965, *87*, 1142.

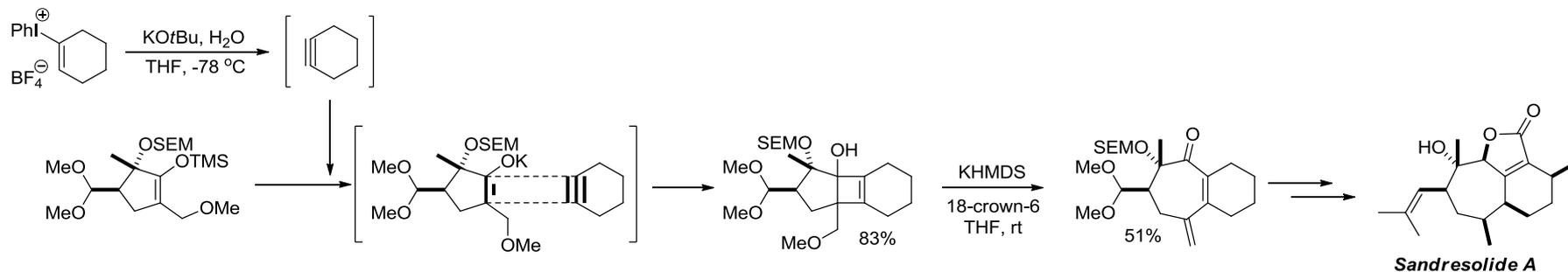
Reaction of Cyclohexynes

- Ring insertion reactions (Cycloinsertion reactions)
 - [2+2] cycloaddition – cyclobutene cleavage
 - Fujita's cyclohexyne precursor



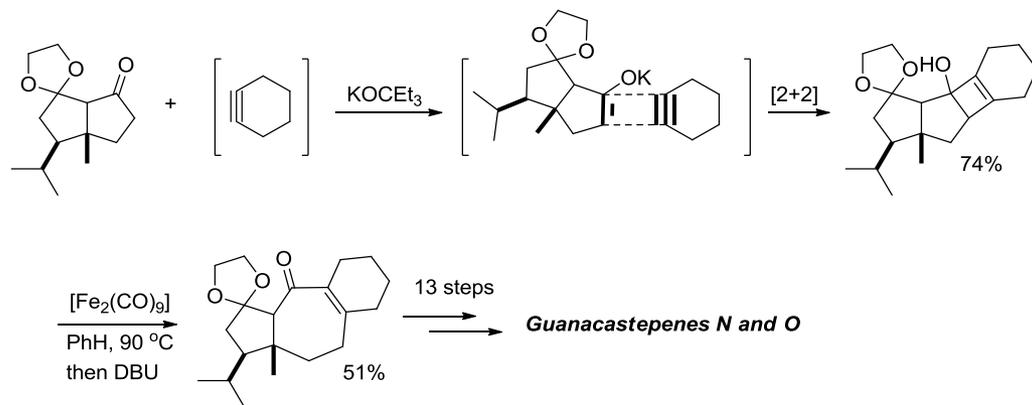
Ring insertion Reactions of Cyclohexynes

- Sandresolide A



C. M. Gampe, S. Boulos, E. M. Carreira, *Angew. Chem. Int. Ed.* 2010, 49, 4092 – 4095.

- Guanacastepenes N, O



C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.* 2011, 50, 2962.

Conclusion

- Arynes are highly reactive intermediates which undergoes polar and pericyclic reactions
- Hetarynes show lower reactivity than benzyne
- In contrast to aryne chemistry, cyclohexyne has yet more to discover
- σ -bond insertions give new options for synthetic routes
- Better control of regiochemistry in aryne reactions is needed