UNIVERSITÄT BERN

A Comprehensive History of Arynes in Natural Product Total Synthesis

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Topic Review
31st January 2013
Benjamin Wyler

Outline

A. Introduction
   - History and Structure
   - Reactivity towards Nuclephiles/Electrophiles
   - Methods for the Generation of Benzynes

B. Type of Benzyne Transformation
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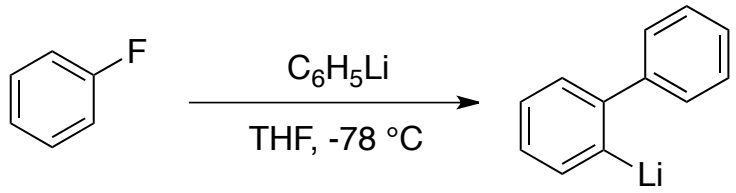
   - Multicomponent Reacitons
   - Bond-Insertion Reactions
   - [4 + 2]-Aryne Cycloadditions
   - [2 + 2]-Aryne Cycloadditions
   - Metal-Catalyzed Aryne Reaction

C. Concluding Remarks

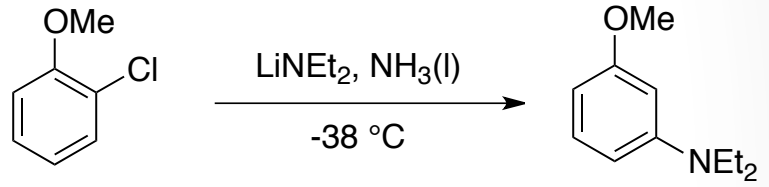
History and Structure

Unusual Rearrangements of Substituted Benzenes

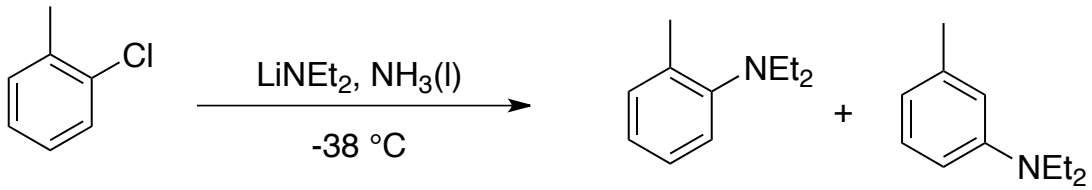
Gilman, Wittig, and Roberts observed strange behavior in reaction of halobenzenes in the 1940s and 1950s



G. Wittig *Naturwissenschafter* **1942**, *30*, 696.



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

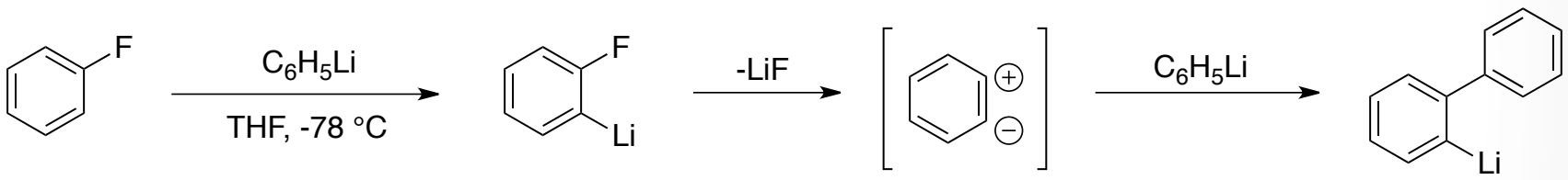


J. D. Roberts, H. E. Simmons Jr., L. A. Carlsmith, C.W. Vaughan *J. Am. Chem. Soc.* **1953**, *75*, 3290.

History and Structure

Wittig's Explanation (*Naturwissenschafter* **1942**)

….close, but no cigar…

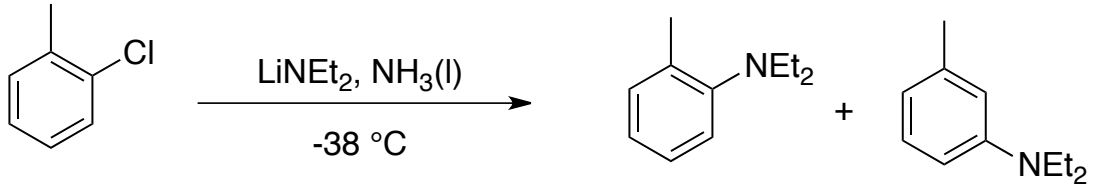


G. Wittig *Naturwissenschafter* **1942**, *30*, 696.

History and Structure

Roberts' Counter Proposal (*JACS* **1953**)

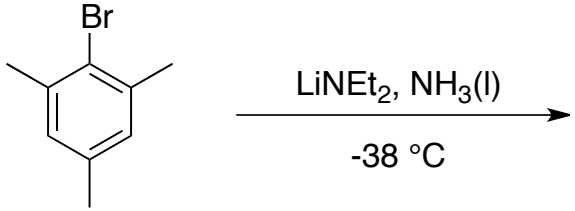
- The entering amino group is never more than one carbon away from the position occupied by the leaving halogen



no p-aminotoluene formed!

- No isomerization of neither the starting halide nor the resulting anilines under reaction conditions

- No reaction occurs when there is no hydrogen adjacent to the leaving halogen

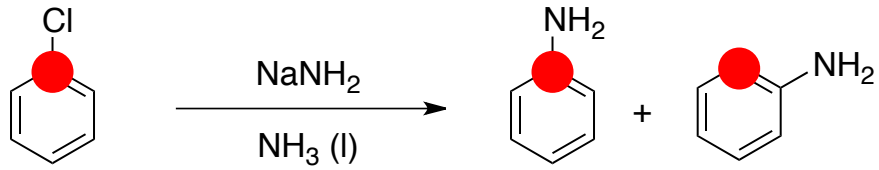


no reaction

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

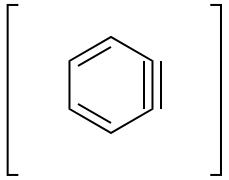
History and Structure

^{14}C Labeling Experiment (Roberts *et al. JACS* **1953**)



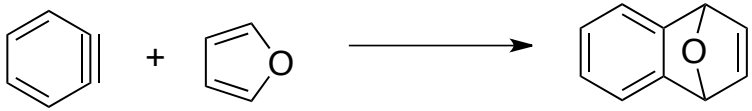
Nearly 1:1 ratio!

Roberts' Proposed Intermediate:



"These facts as well as the orientation data for various substituents can be accomodated by an elimination-addition mechanism involving at least transitory existence of an electrically neutral "benzyne" intermediate."

Wittig finds that benzyne can participate in Diels-Alder reactions as dienophile:

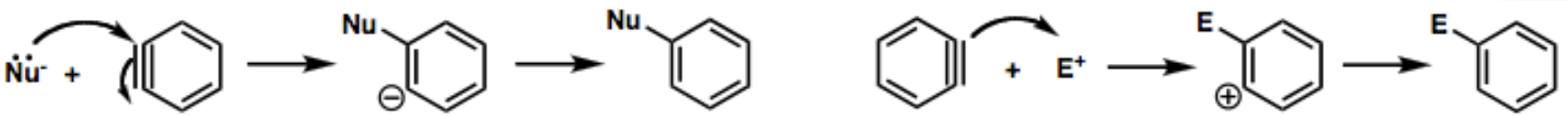


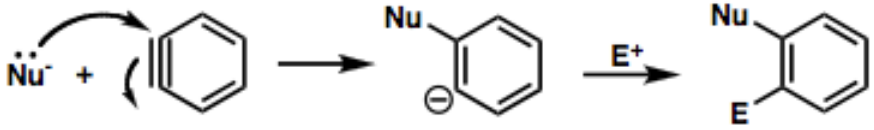
G. Wittig, L. Pohmer, *Angew. Chem.* **1955**, *67 (13)*, 348.

Reactivity towards Nucleophiles/ Electrophiles

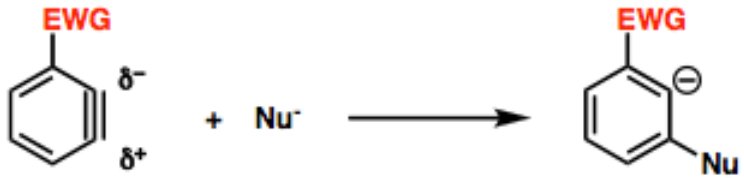
- Polar Reactions of Benzyne

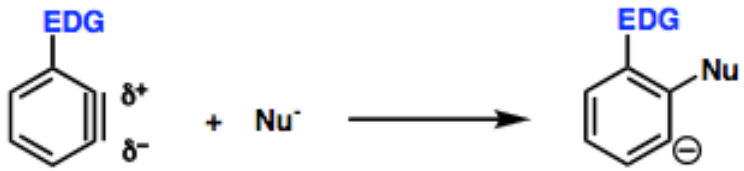
  Benzyne react as both nucleophile and electrophile



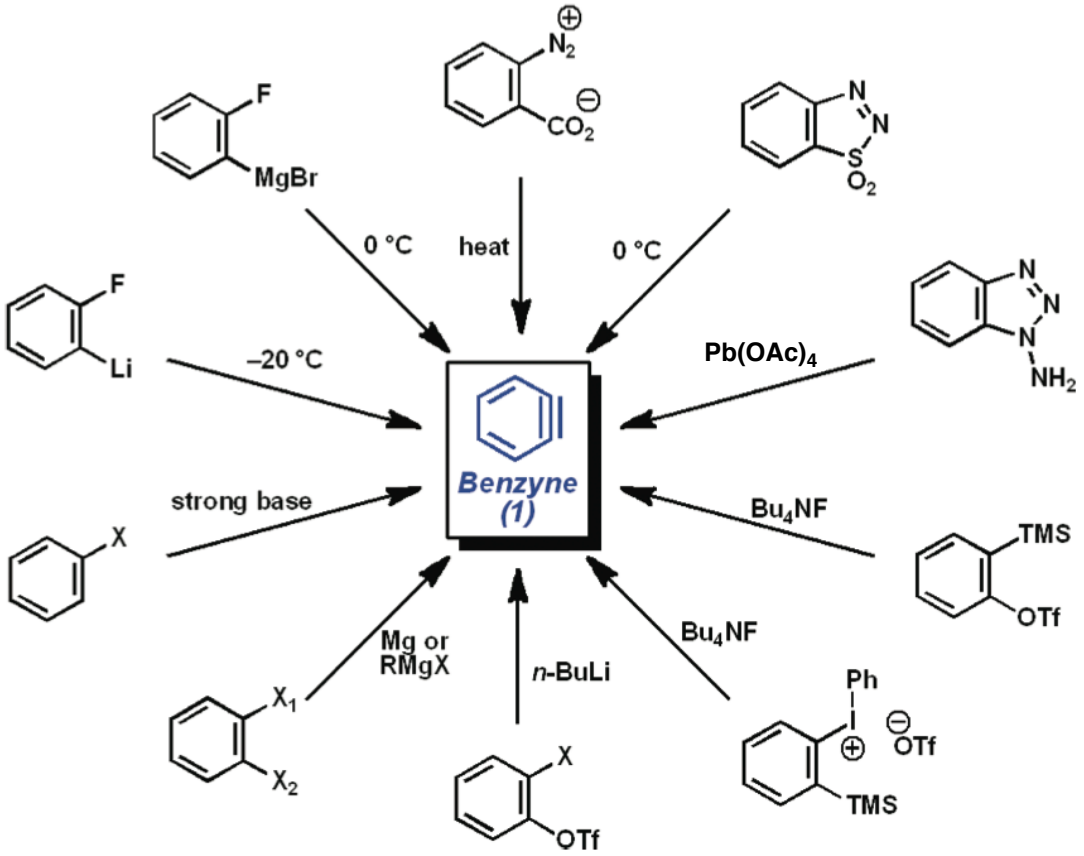


- Regiochemistry of Nucleophilic Additions to Benzyne





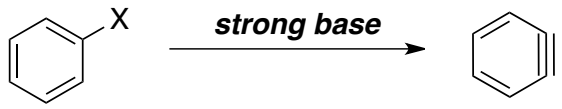
Methods for the Generation of Benzynes



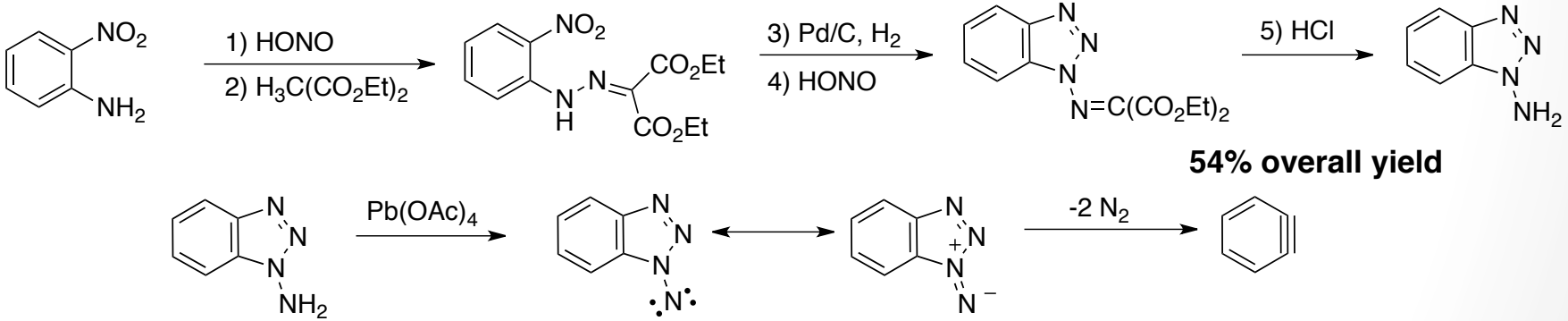
Iodonium Triflate: T. Kitamura, M. Yamane, *J. Chem. Soc., Chem. Commun.* **1995**, 983. Silyl Triflate: Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211. Benztriazole: C. D. Campbell, C. W. Rees, *J. Chem. Soc. (C)* **1969**, 742. Halo Triflate: T. Matsumoto, T. Hosoya, M. Katsuki, 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 *Synth., Coll. Vol. V,* 60, **1971**.

Methods for the Generation of Benzynes

- Aryl halide
  - Can be treated with strong bases to remove an aromatic proton and generate benzyne via elimination



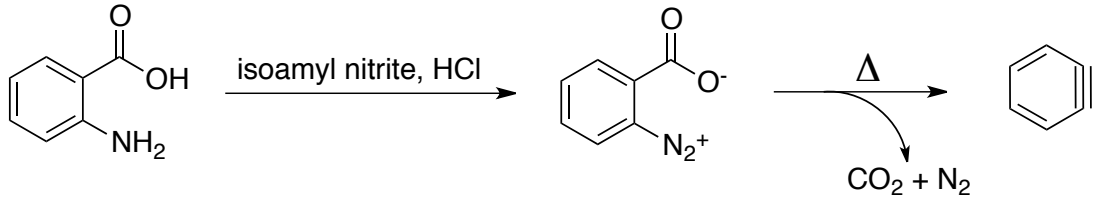
- Benztriazol
  - Oxidative removal of amino-hydrogens would leave to nitrene species, which might be expected to fragment to benzyne and two molecules of nitrogen



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

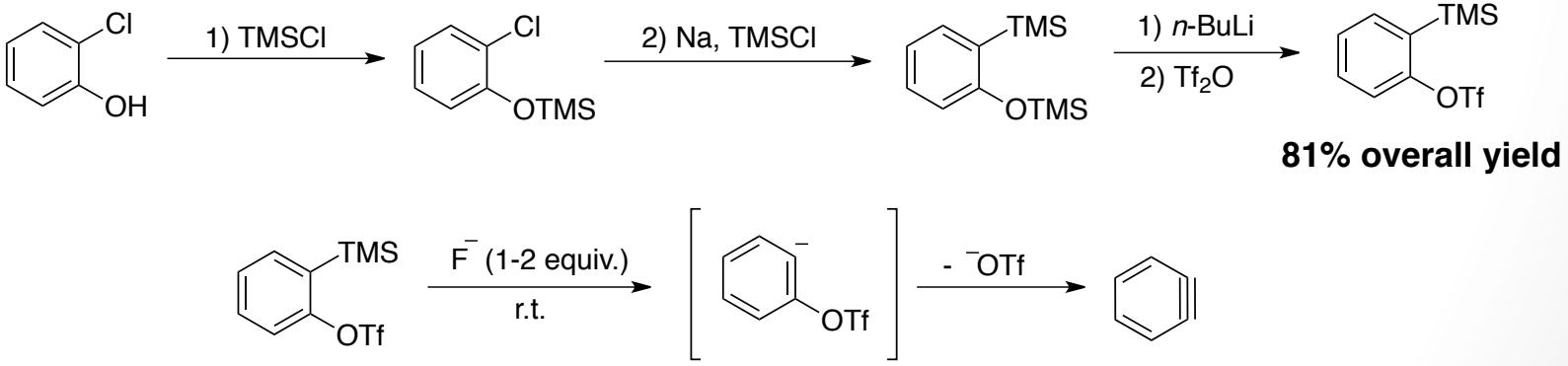
Methods for the Generation of Benzynes

- Diazonium Carboxylate
  - Arenediazonium-2-carboxylate can be transformed by heat to benzyne (– but explosive nature of diazonium!)



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

- Silyl Triflate
  - Mild method (room temperature)

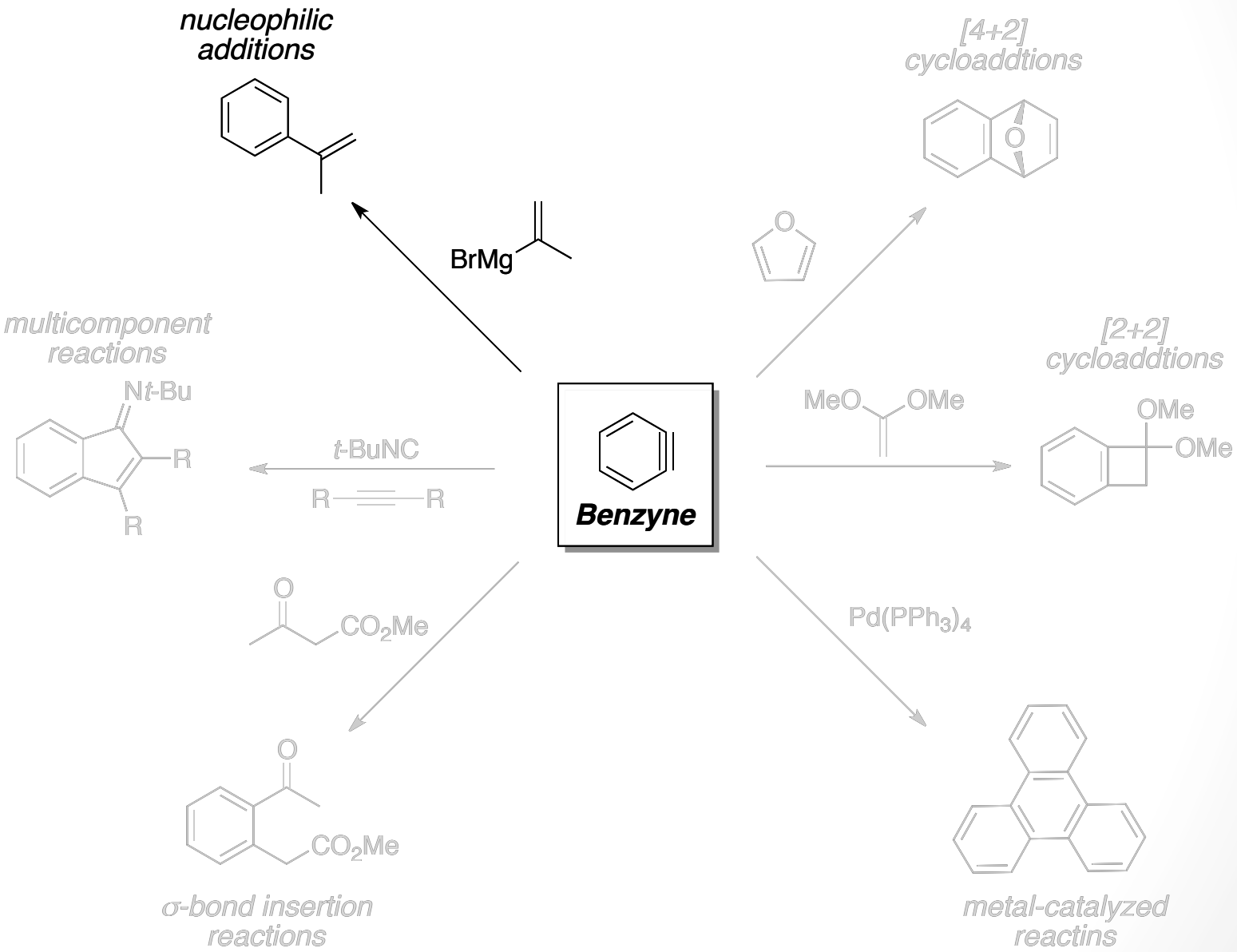


H. Kobayashi *et al. Chem. Lett.* **1983**, 1211.

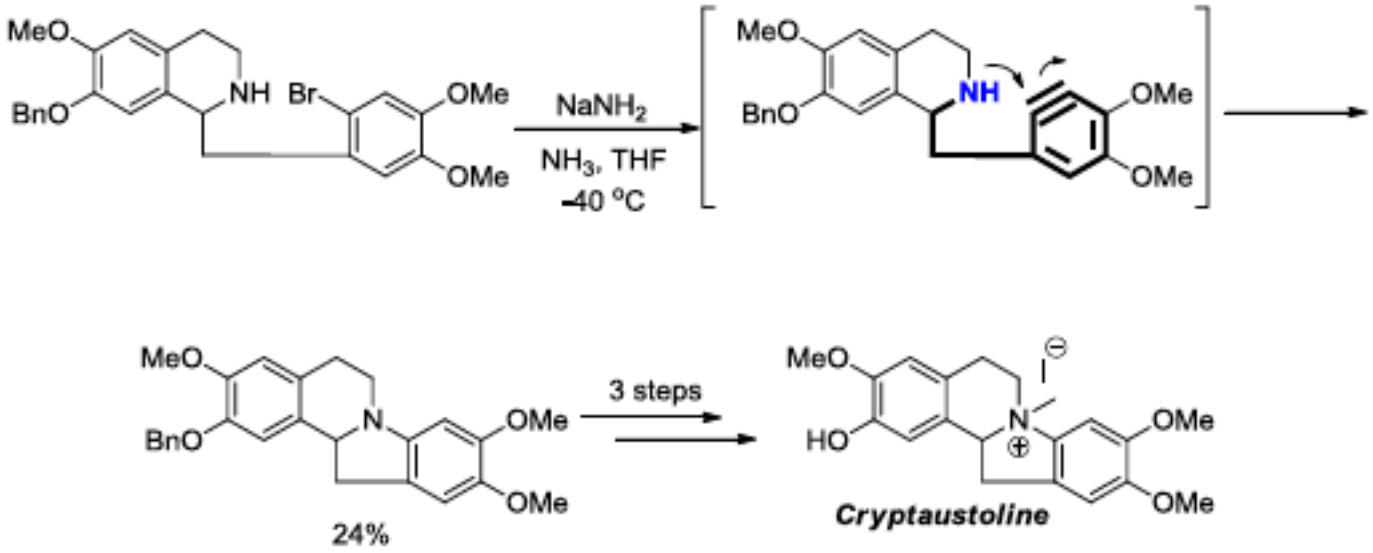
Nucleophilic Additions

Type of Benzyne Transformation

(forms only a single new carbon-carbon or carbon-heteroatom bond to the aryne intermediate)

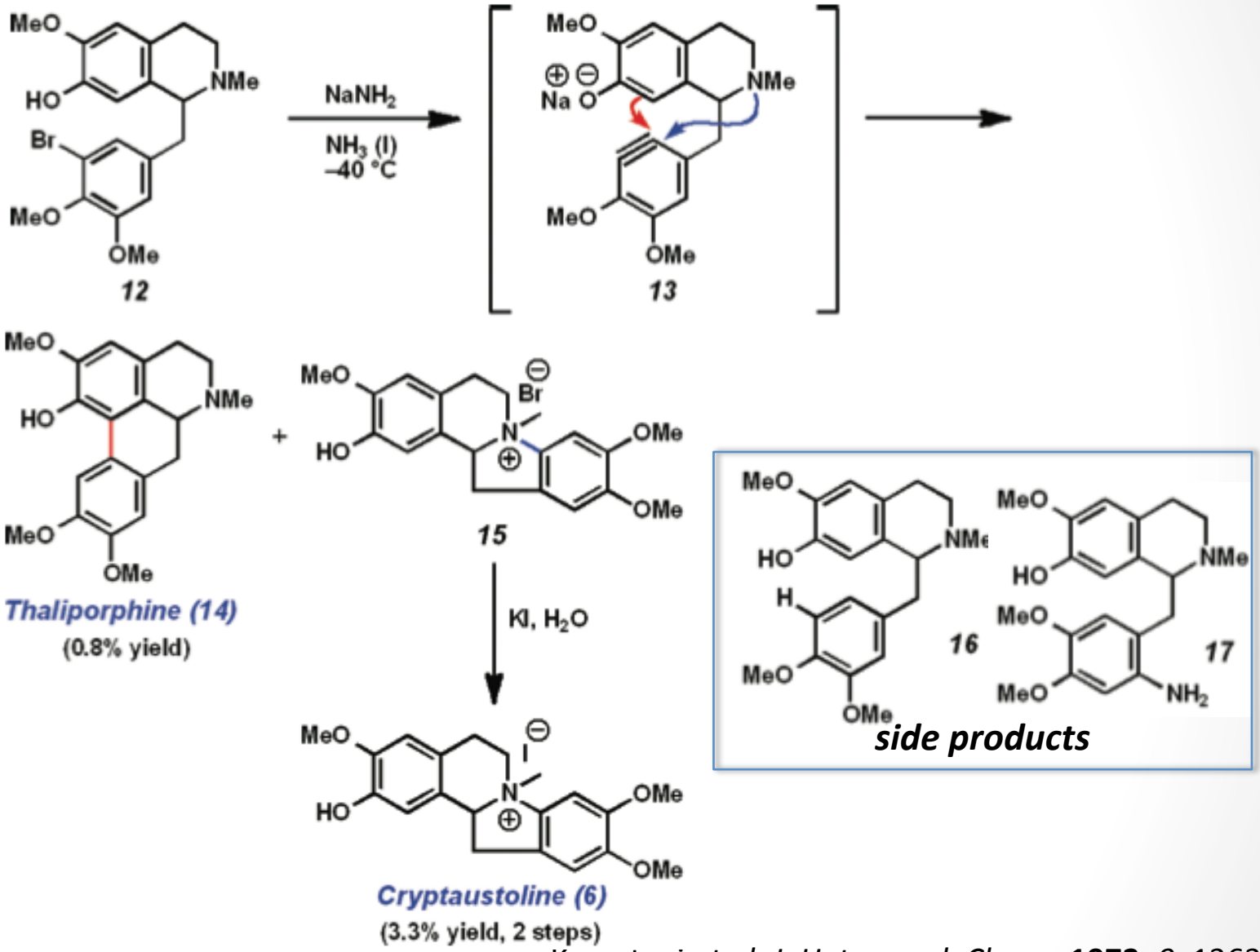


- Cryptaustoline (Kametani, 1967)



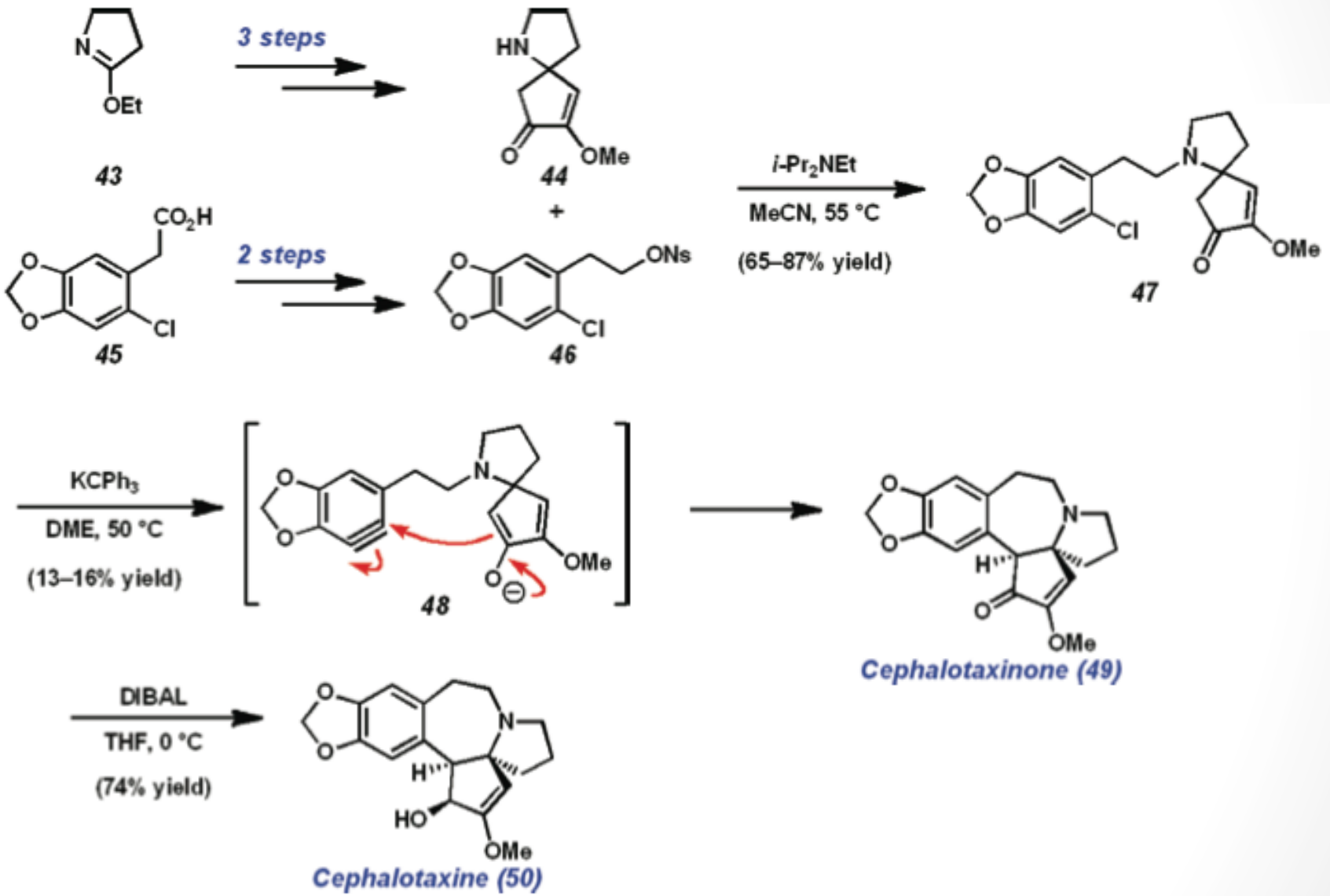
Kametani *et al. J. Chem. Soc., C* **1967,** 2208.

- Thalidorphine and Cryptaustoline (Kametani, 1972)



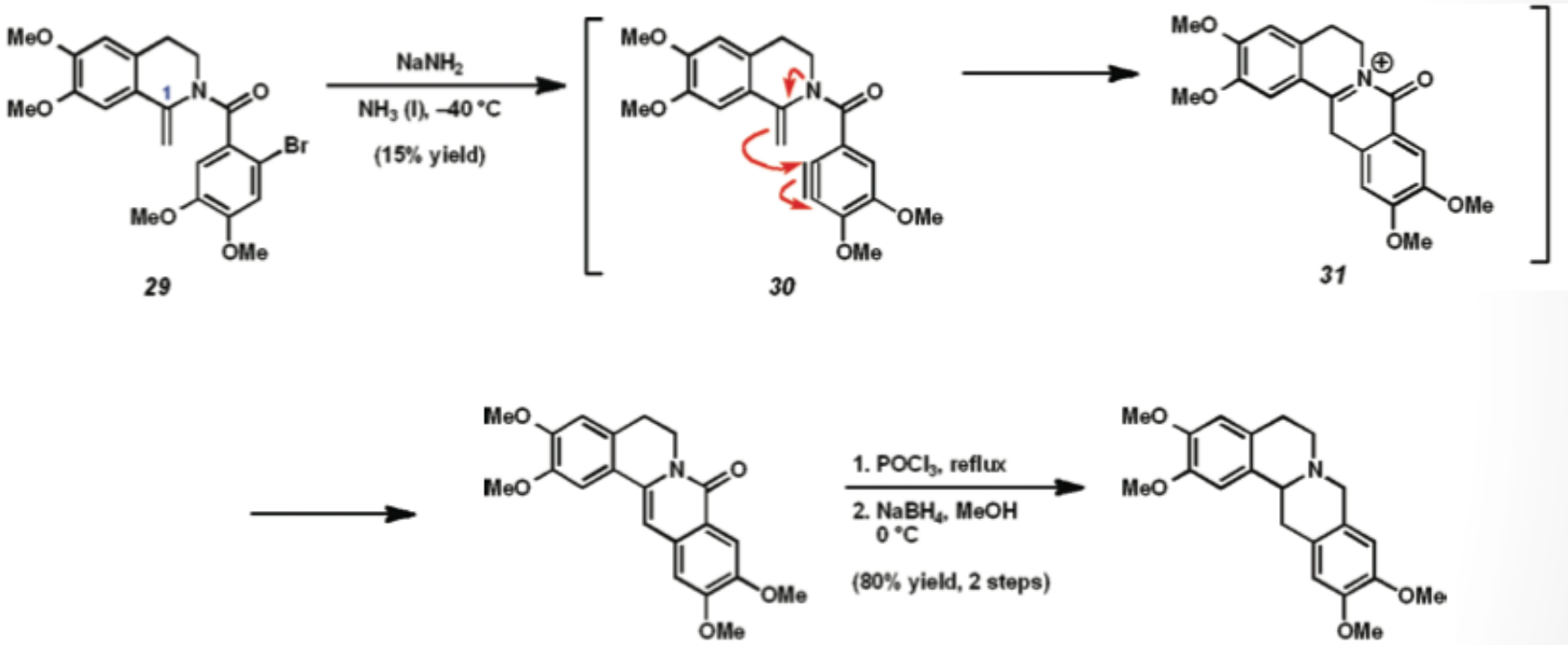
Kametani *et al. J. Heterocycl. Chem.* **1972,** *9,* 1363.
Kametani *et al. J. Chem. Soc., Perkin Trans. 1* **1973**, 1212.

- Cephalotaxinone/Cephalotaxine (Semmelhack, 1972)



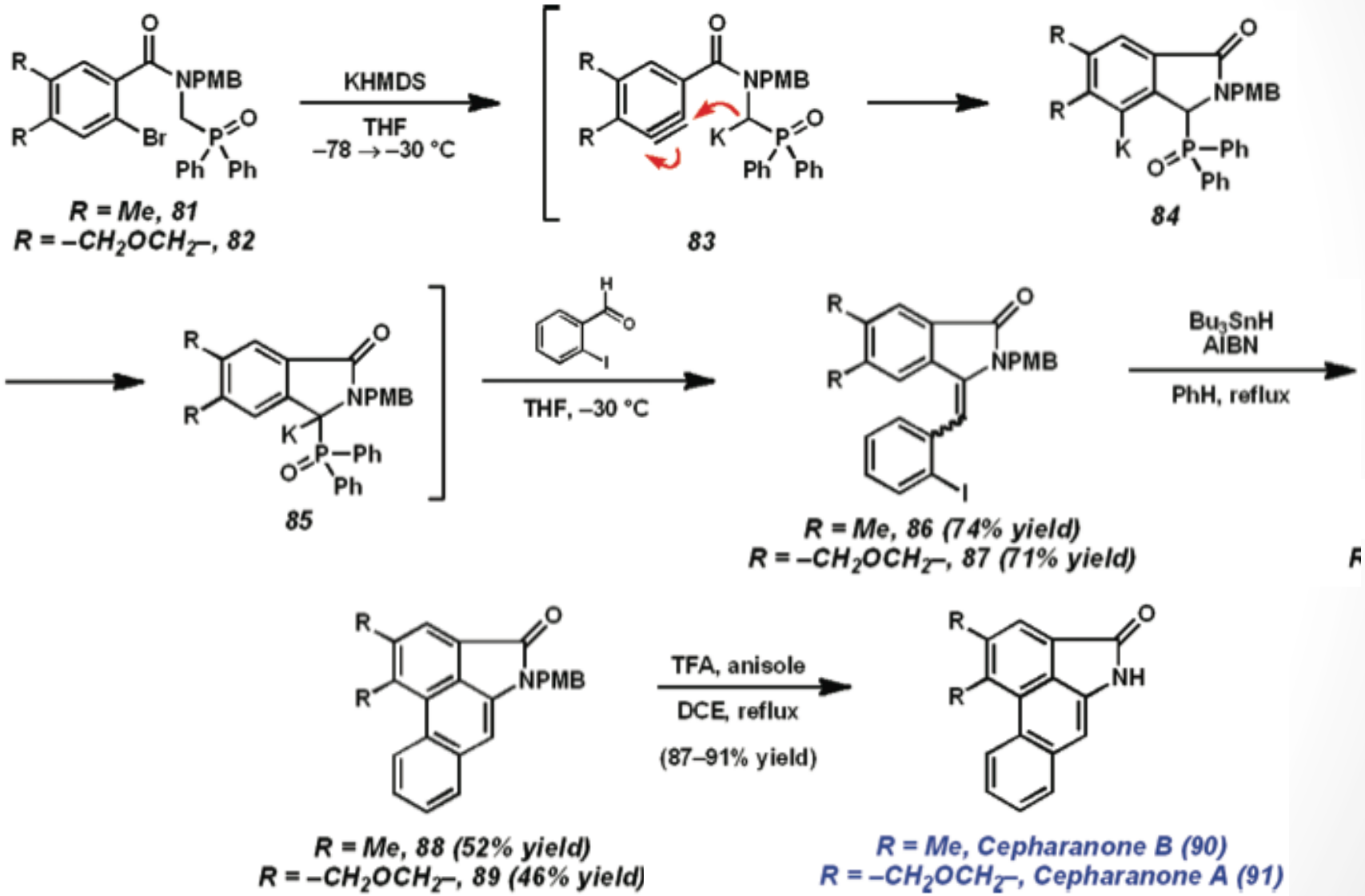
Semmelhack *et al. J. Am. Chem. Soc.* **1972,** *94,* 8629.

- Xylopinine (Kametani, 1977)



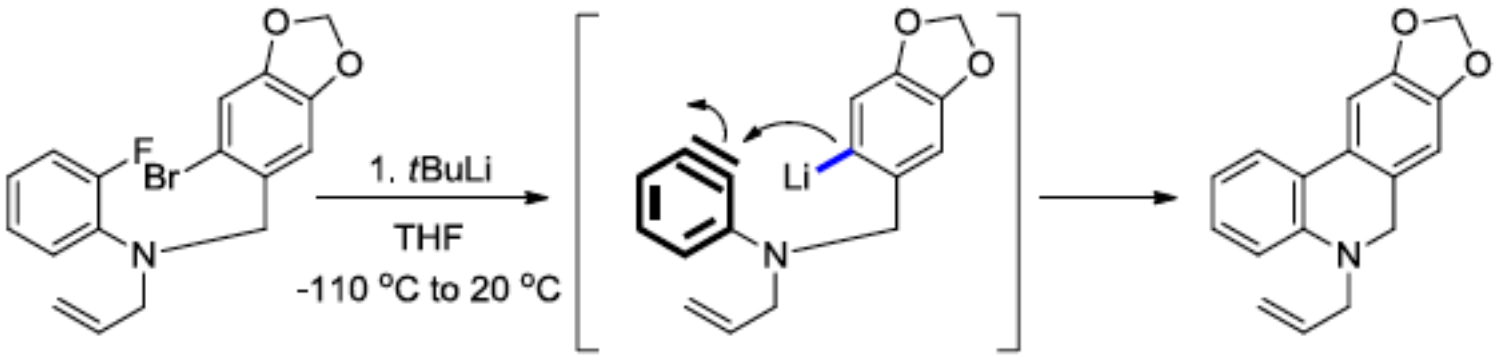
Kametani *et al. J. Chem. Soc., Perkin Trans. 1* **1977**, 1151.

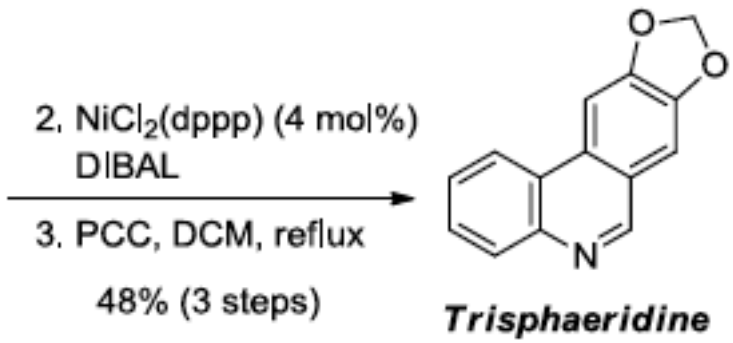
- Cepharanone A/B (Couture, 1997)
  - Tandem aryne cyclization/olefination and radical cyclization



Couture *et al. Synlett* **1997**, 1475.

- Trisphaeridine (Sanz, 2007)
  - Selective benzyne generation



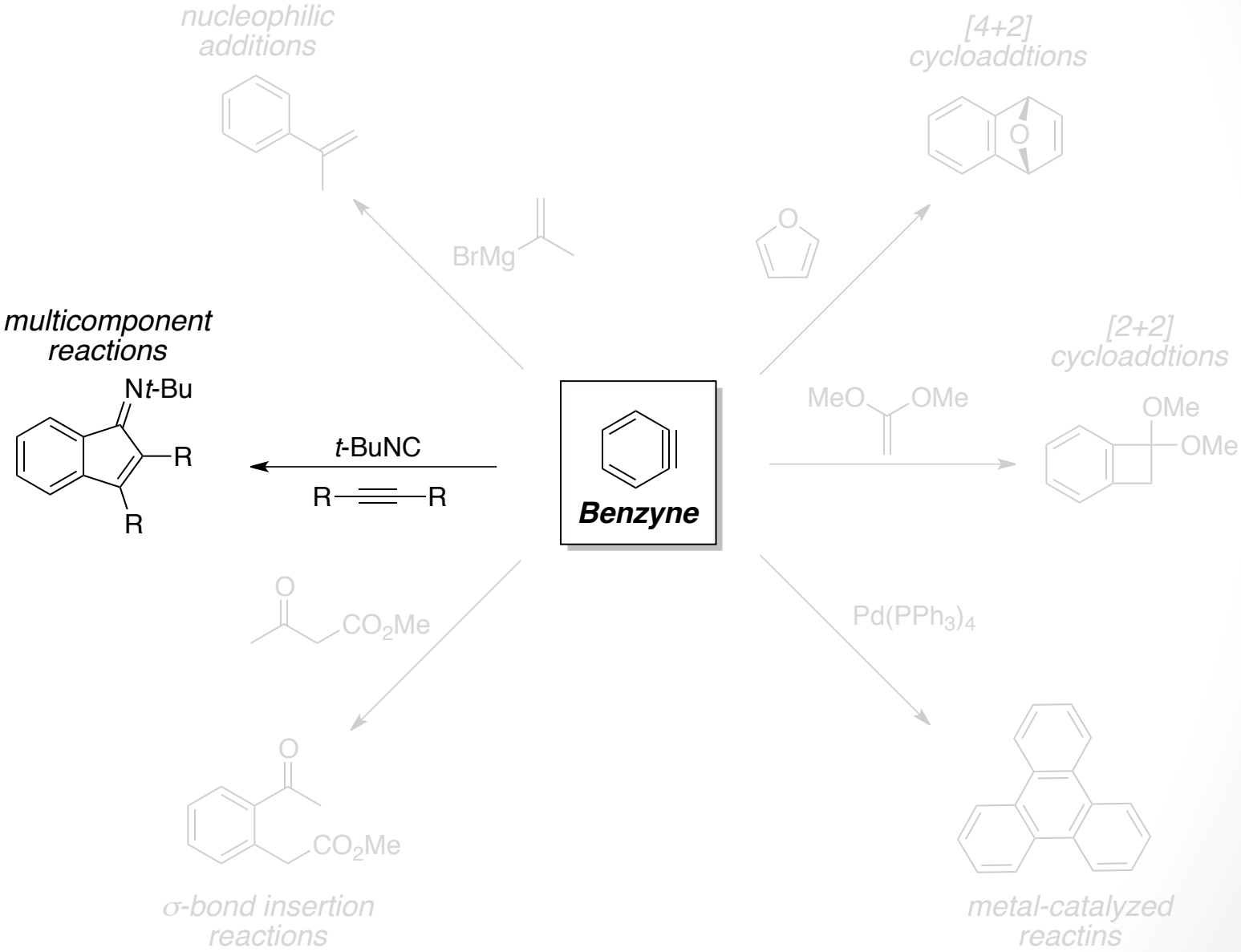


Trisphaeridine

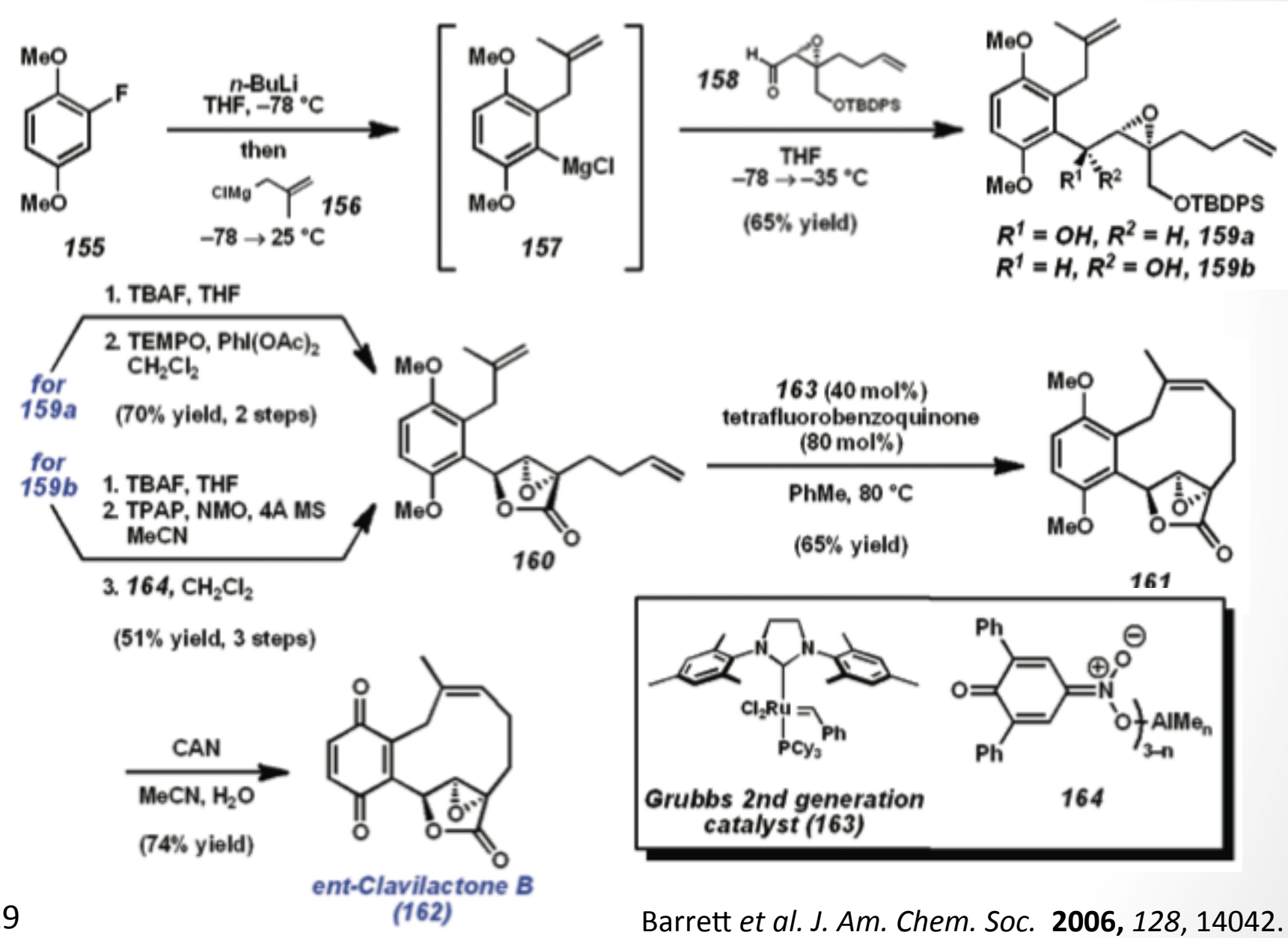
Sanz *et al. Eur. J. Org. Chem.* **2007,** 62.

Multicomponent Reactions

(three or more components are united in such a way that two new bonds to the aryne are formed in a single operation)

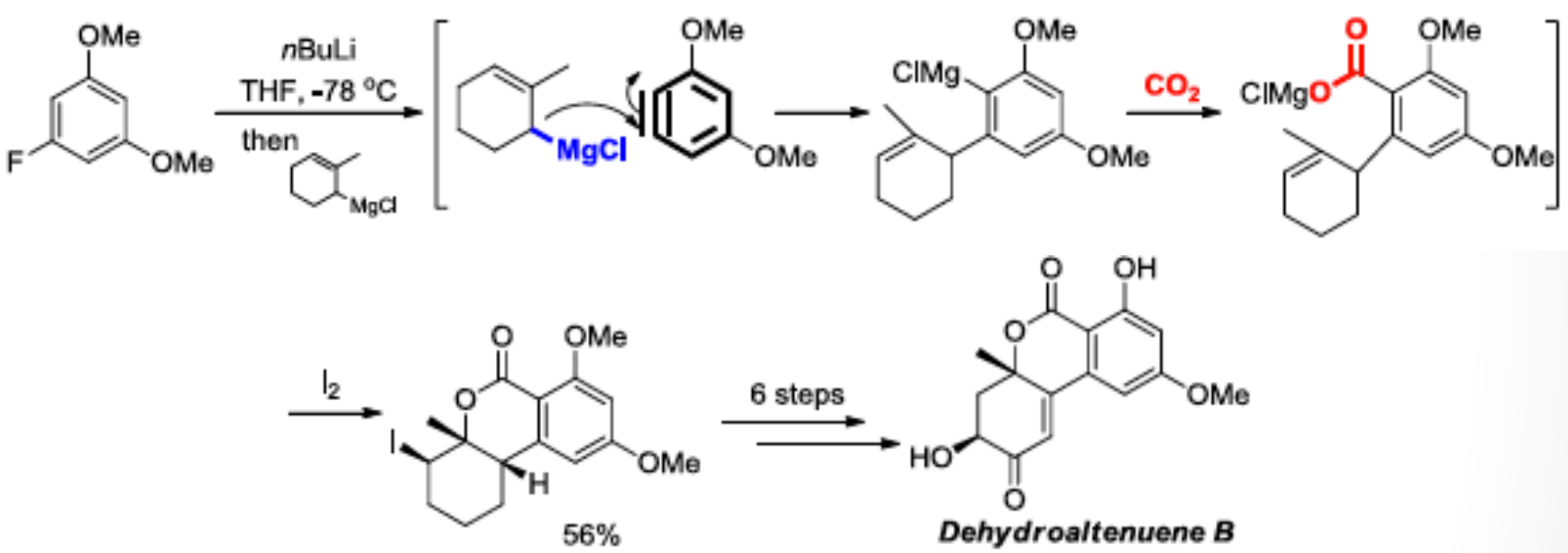


- *ent*-Clavilactone B (Barrett, 2006)



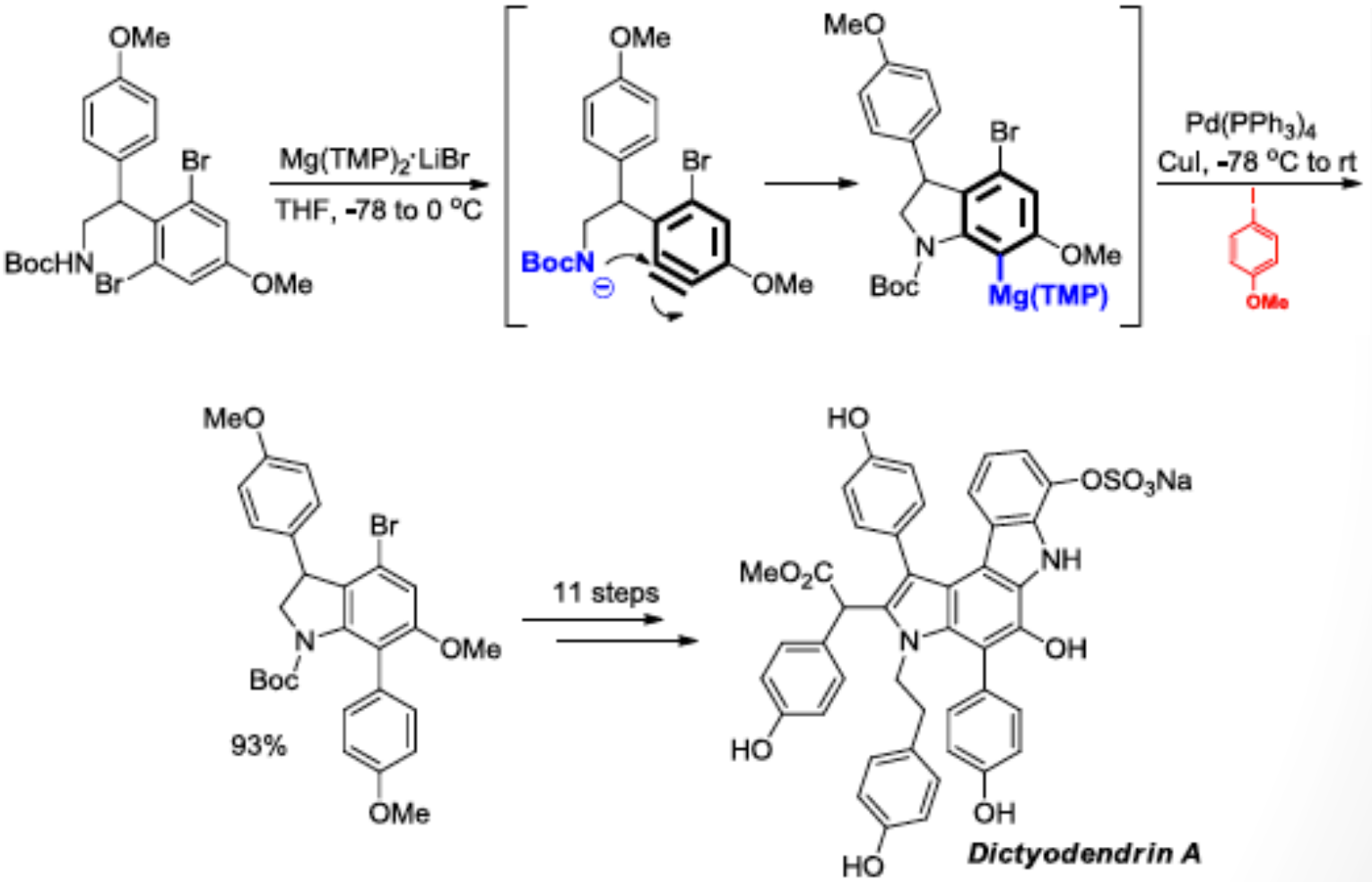
Barrett *et al. J. Am. Chem. Soc.* **2006,** *128*, 14042.

- Dehydroaltenuene (Barrett, 2008)
  - Capture of CO_2 with ArMgX
  - Iodolactonization



Barrett *et al. Org Lett.* **2008,** *10*, 3833.

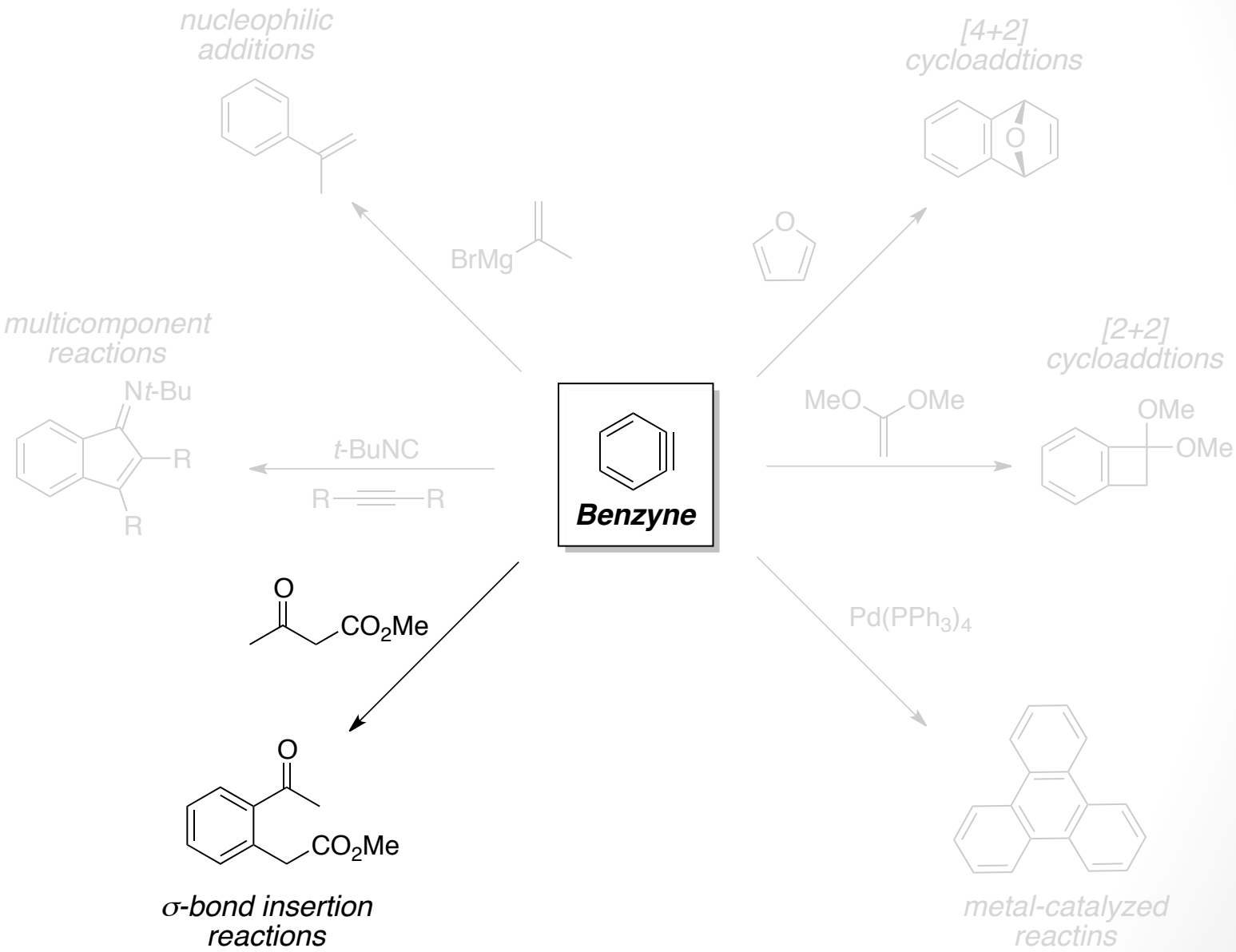
- Dictyodendrin A (Tokuyama, 2010)
  - Kumada Tamao Coupling



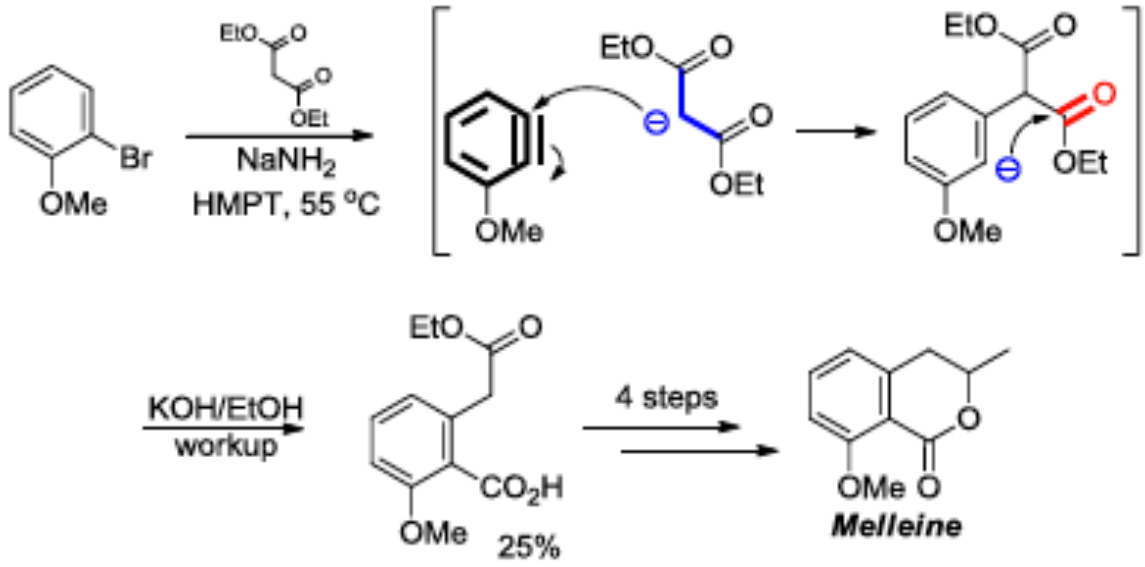
Tokuyama *et al. Angew. Chem., Int. Ed.* **2010,** *49*, 5925.

σ–Bond Insertion Reactions

(first reported in the context of total synthesis, whereas generalized methods were not disclose until 2005)

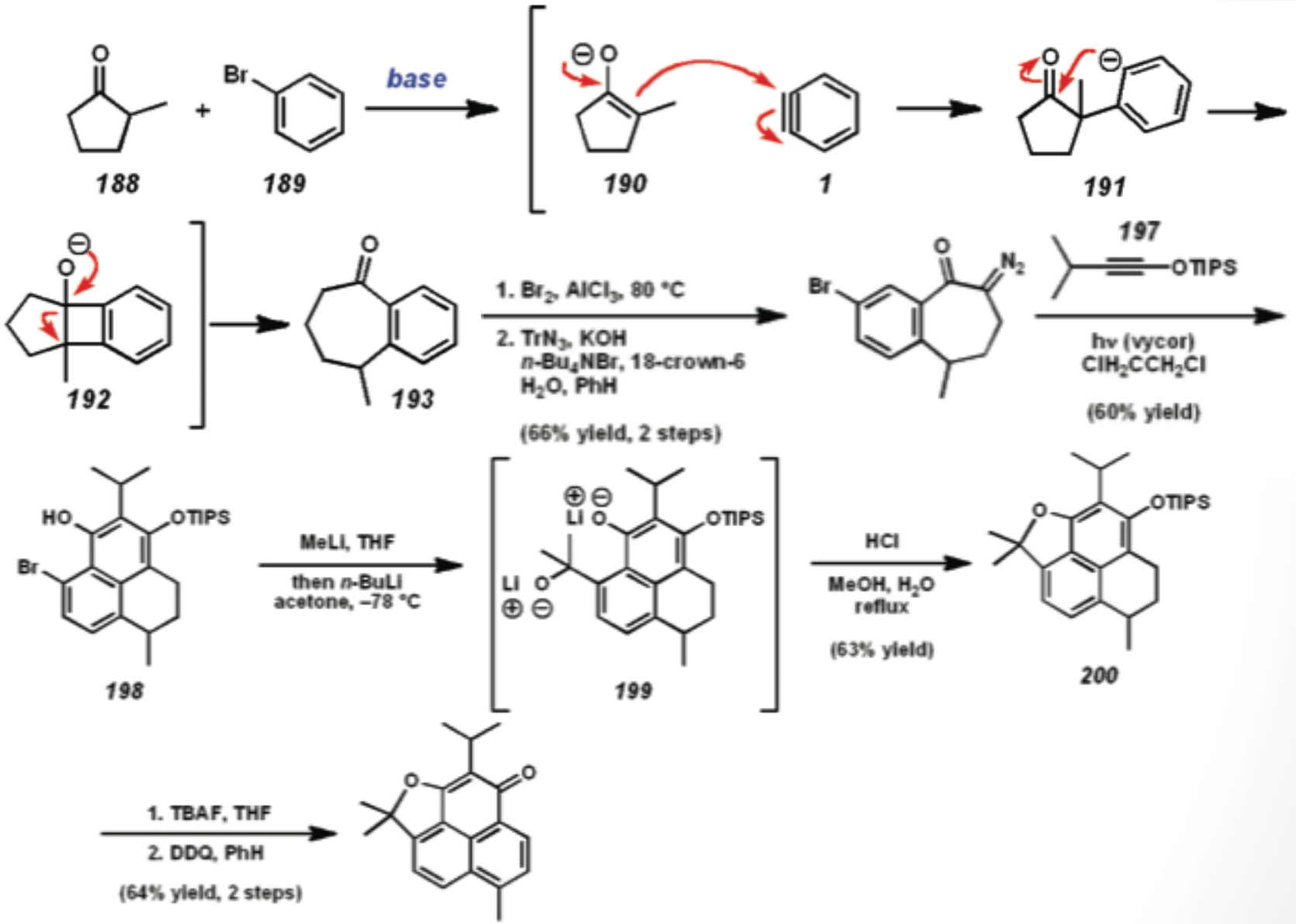


- Melleine (Guyot, 1973)
  - Initial report



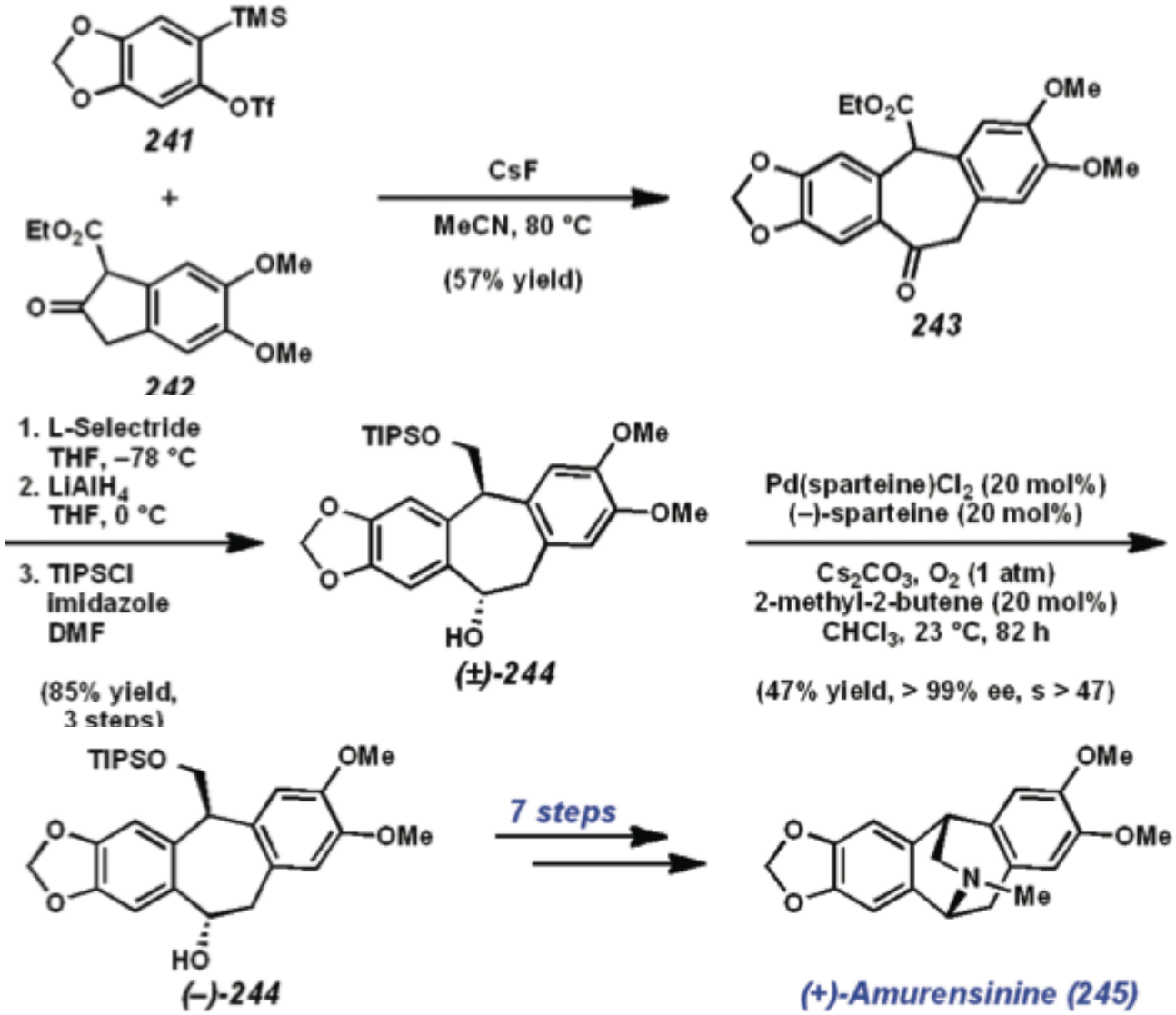
M. Guyot, D. Mohlo *Tetrahedron Lett.* **1973,** *14*, 3433.

- Salvilenone (Danheiser, 1994)



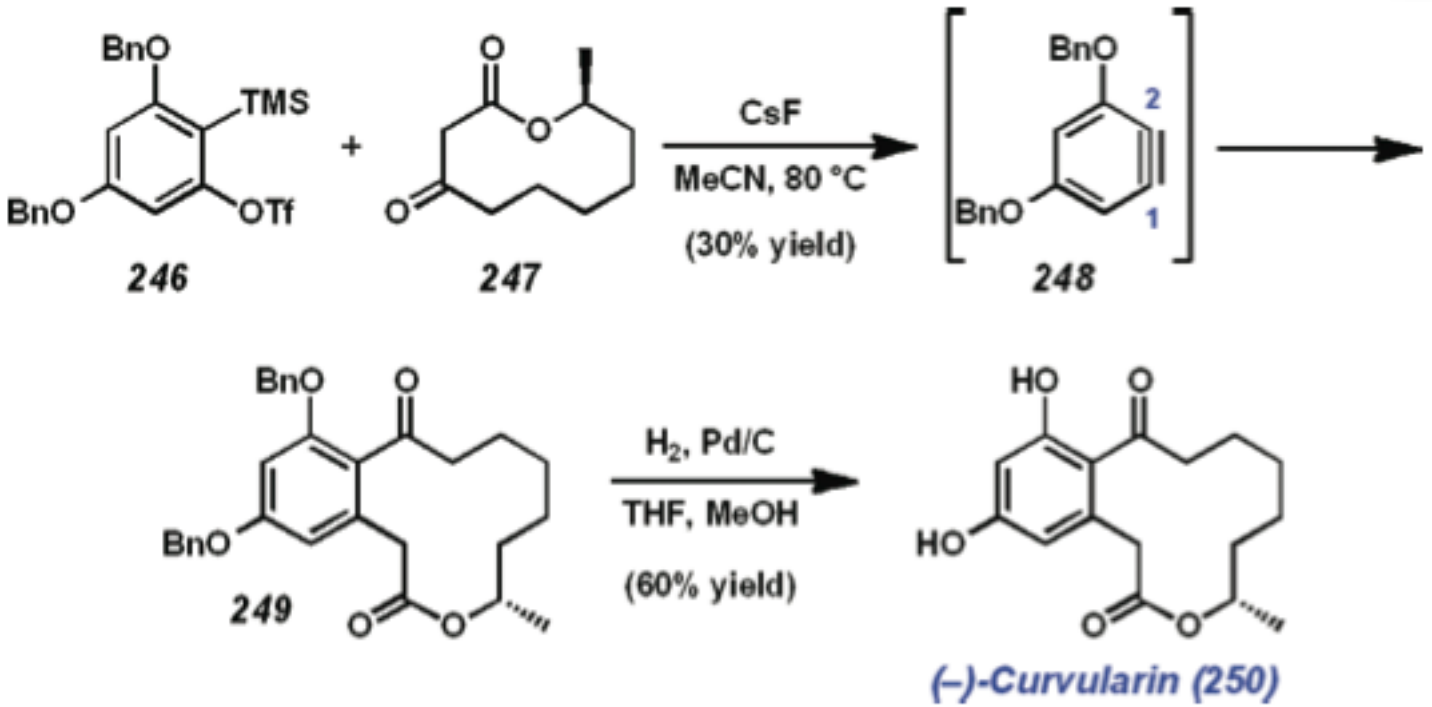
R. L. Danheiser *et al. J. Am. Chem. Soc.* **1994,** *116*, 9471.

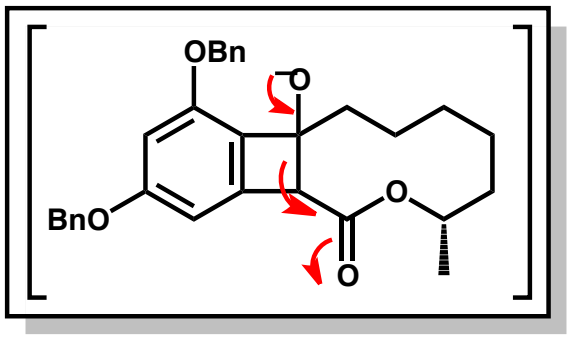
- (+)-Amurensinine (Stoltz, 2006)
  - Acylalkylation of a sesamol-derived aryne with benzannulated beta-ketoester



B. Stoltz *et al. J. Am. Chem. Soc.* **2006,** *128*, 11752.
B. Stoltz *et al. J. Am. Chem. Soc.* **2001**, *123*, 7725.

- Curvularin (Stoltz, 2009)

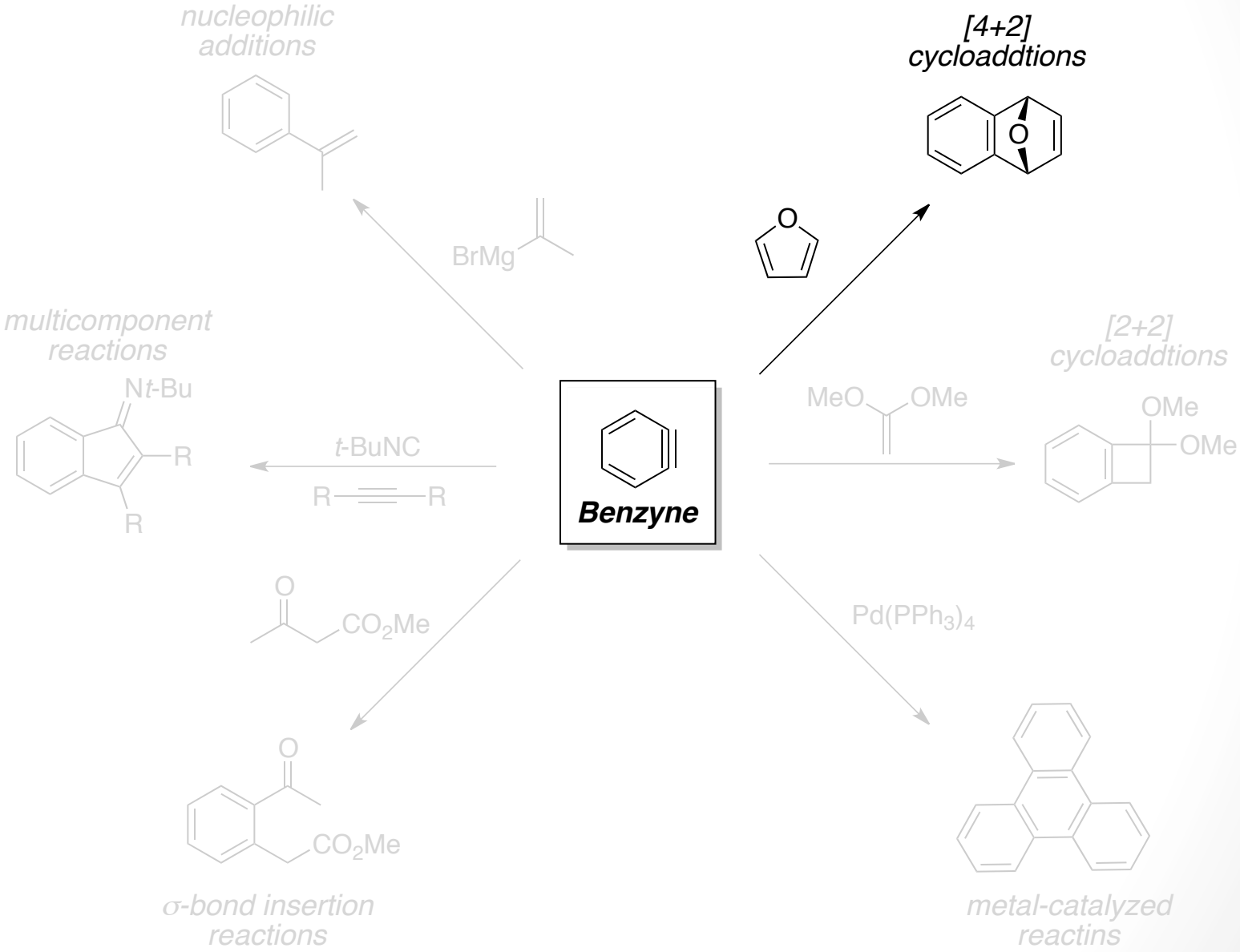




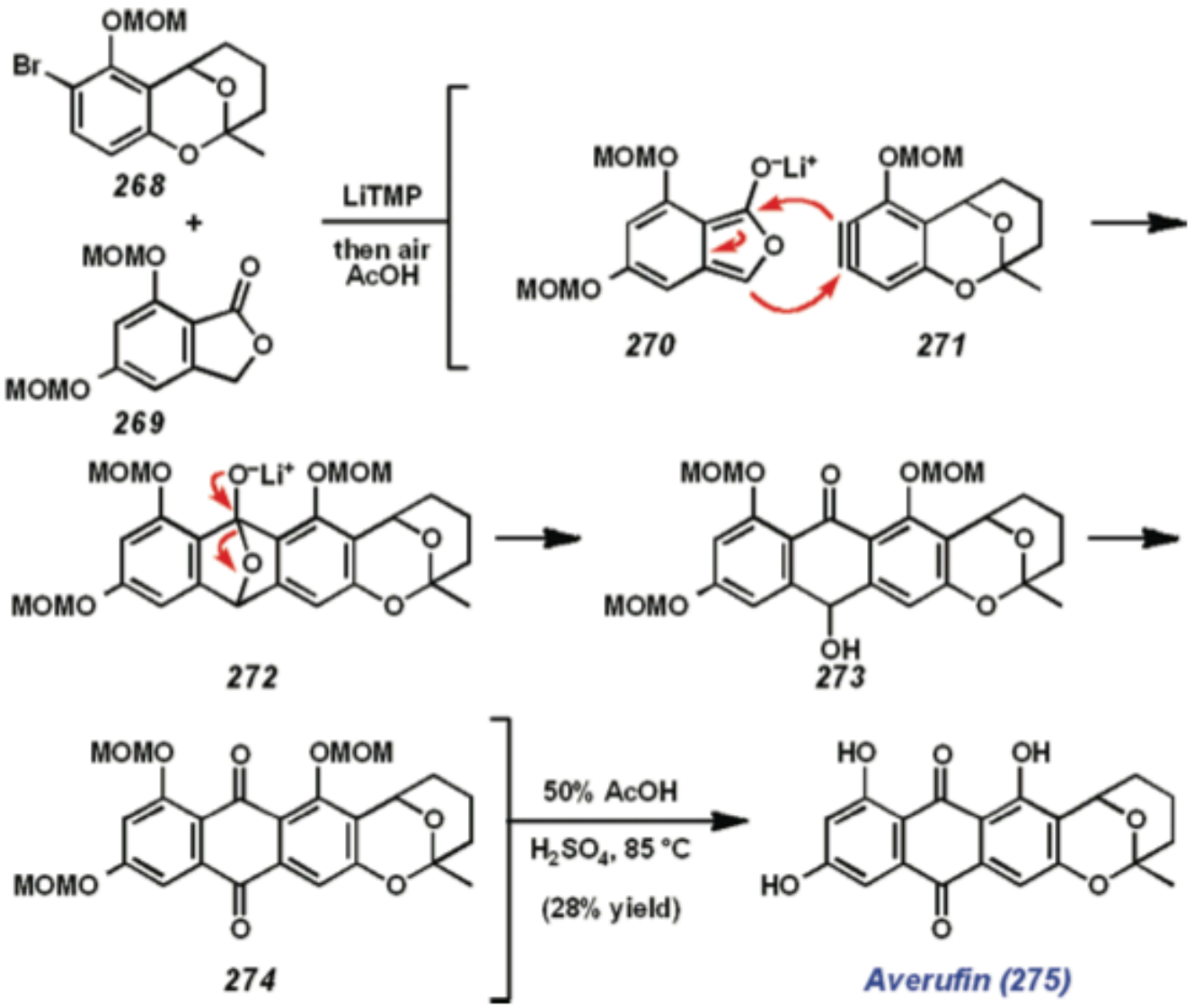
B. Stoltz *et al. Org. Lett.* **2009,** *12*, 1612.

[4+2]-Cycloadditions

(constrained dienes, mostly furans are required)

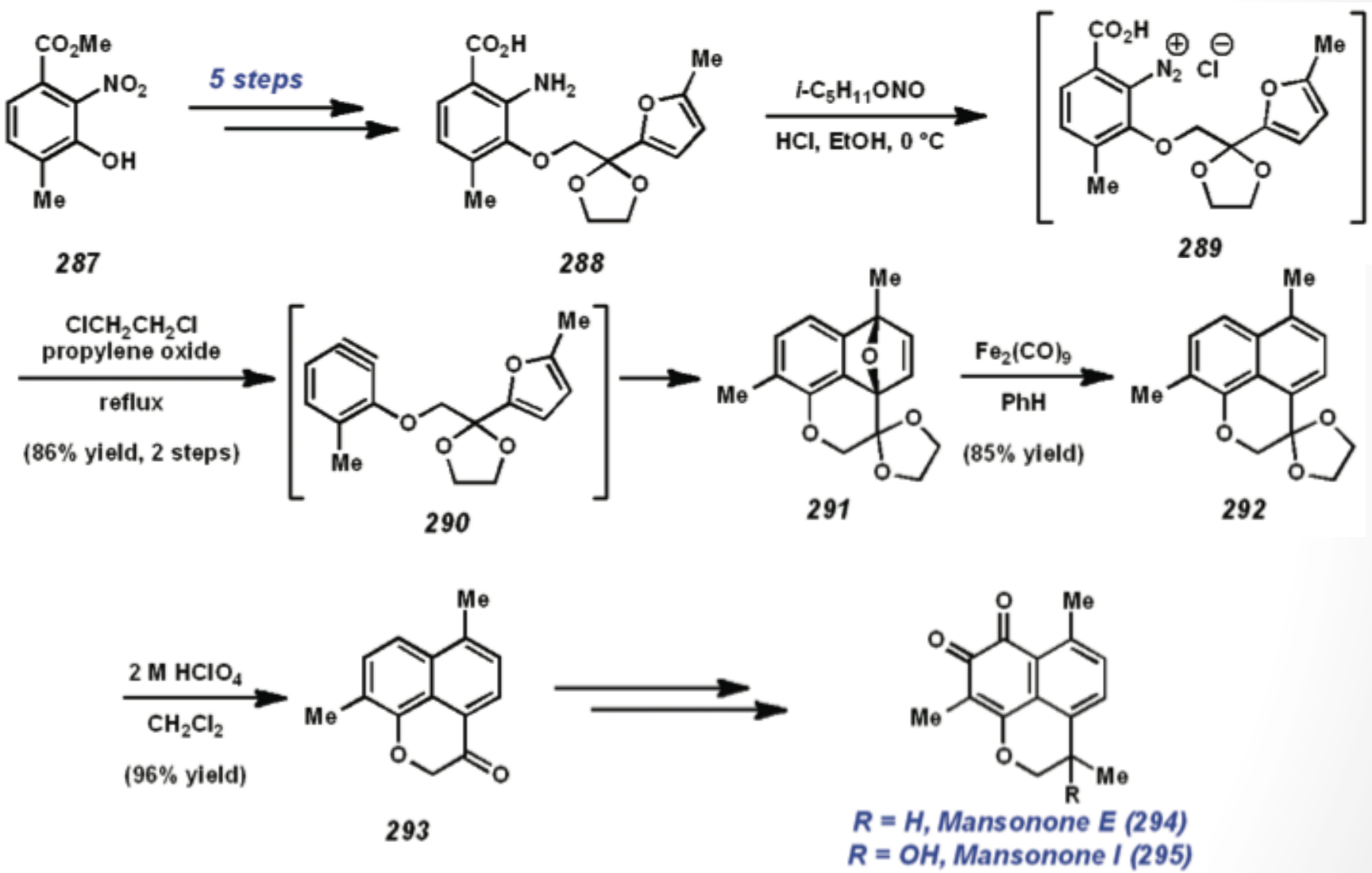


- Averufin (Townsend, 1981)
  - [4+2]-Cycloaddition of a benzannulated lactone and an aryl bromide



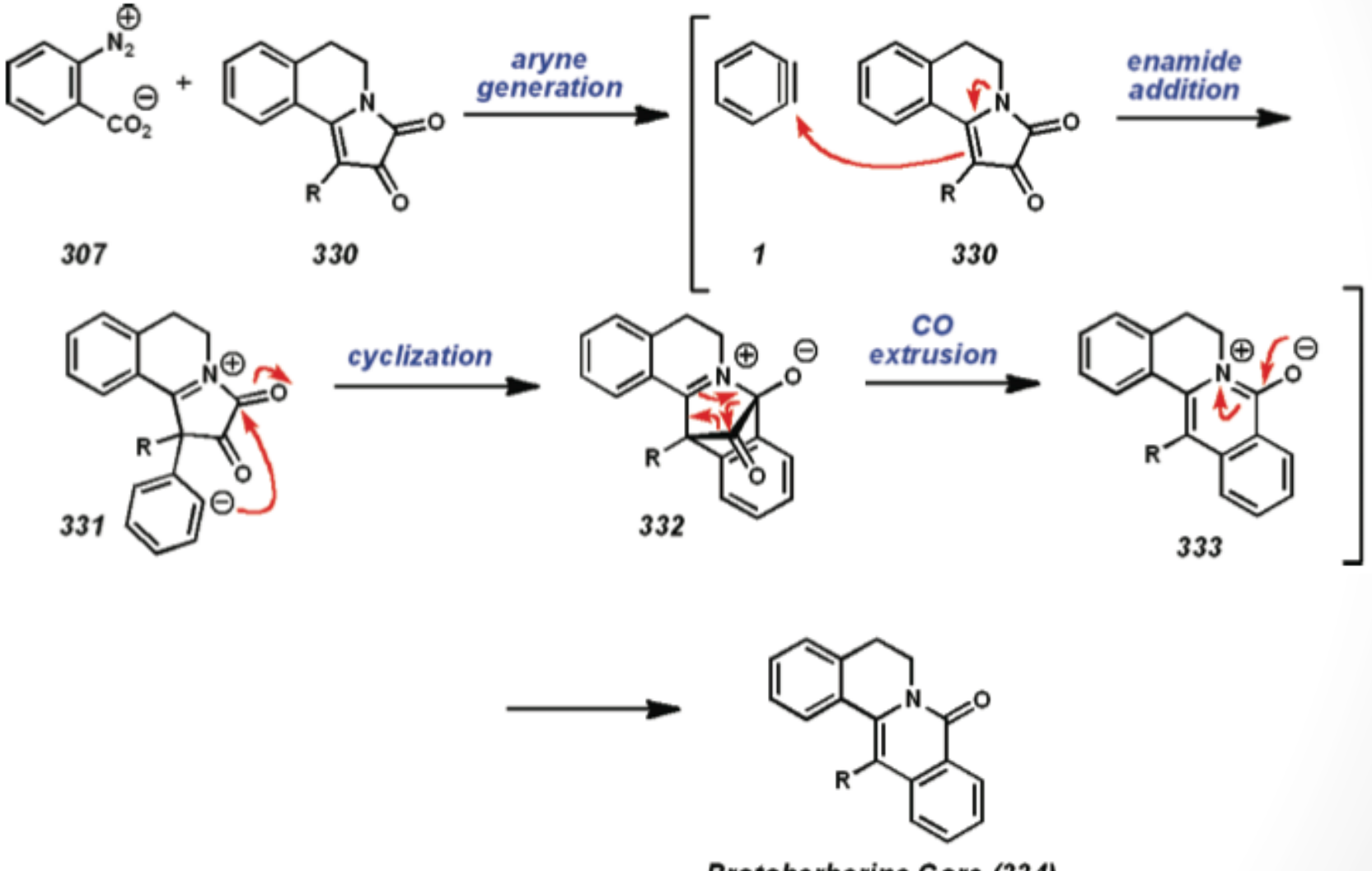
Townsend *et al. J. Am. Chem. Soc.* **1981,** *103*, 6885.

- Mansonone E/I (Best and Wege, 1981/1986)
  - Intramolecular [4+2]-cycloaddtion



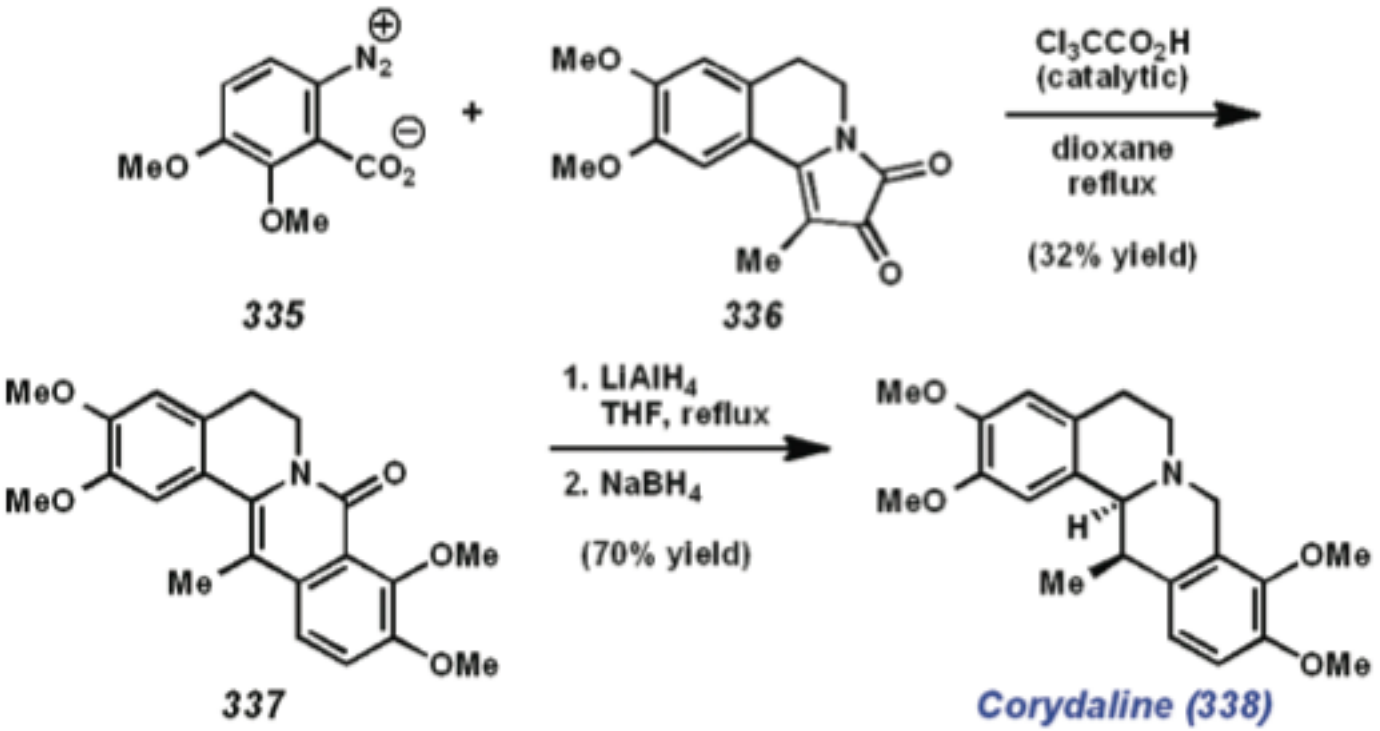
W. M. Best, D, Wege *Tetrahedron Lett.* **1981,** *22*, 4877.
W. M. Best, D, Wege *Austr. J. Chem.* **1986,** *39*, 647.

- Protoberberine Alkaloids (Castedo, 1986)
  - Tandem [4+2]-cycloaddition/CO extrusion approach
  - Benzyne from diazonium carboxylate



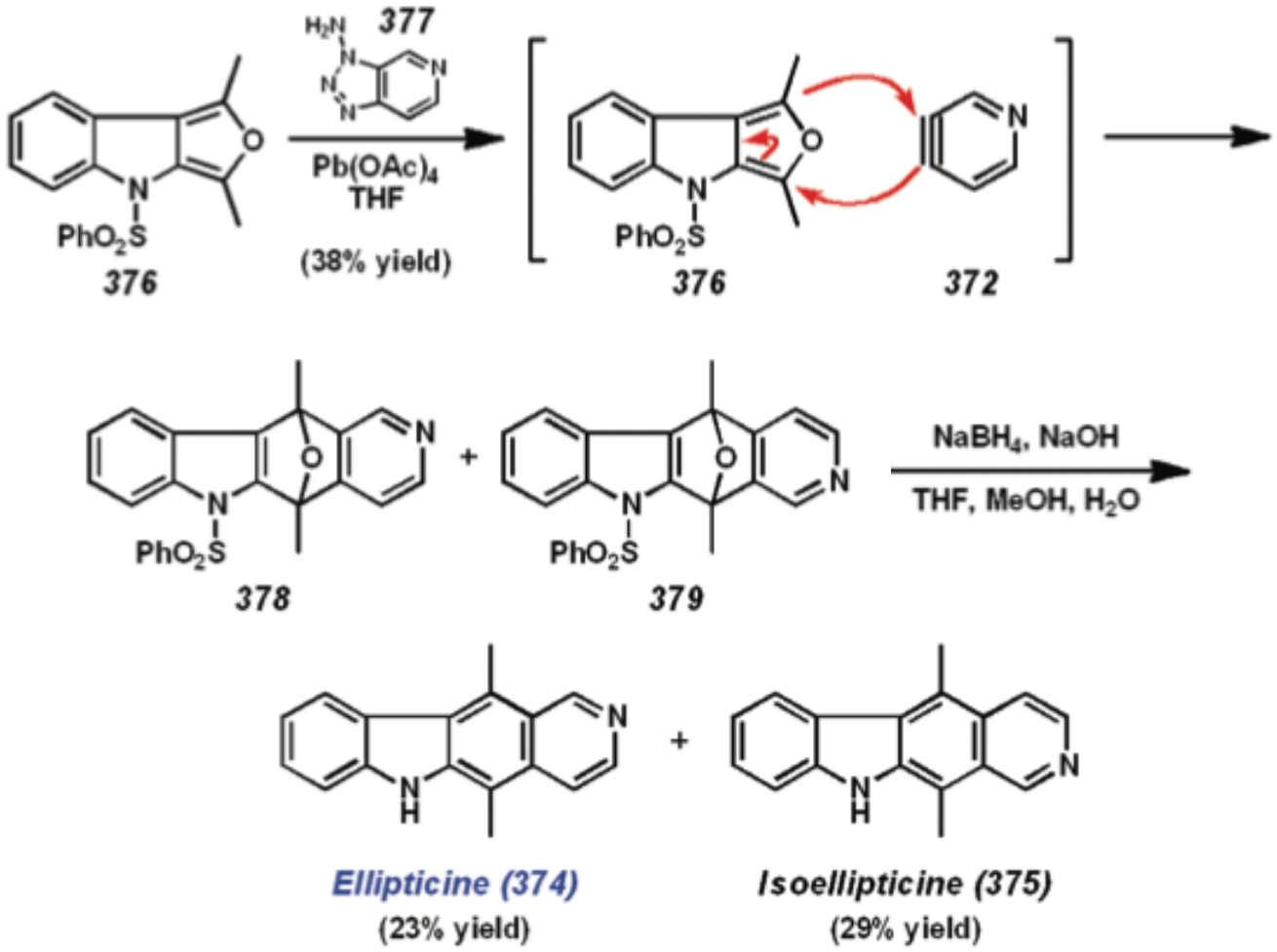
L. Castedo *et al. J. Org. Chem.* **1986,** *51*, 2781.

- Corydaline (Castedo, 1986)
  - Tandem [4+2]-cycloaddition/CO extrusion approach



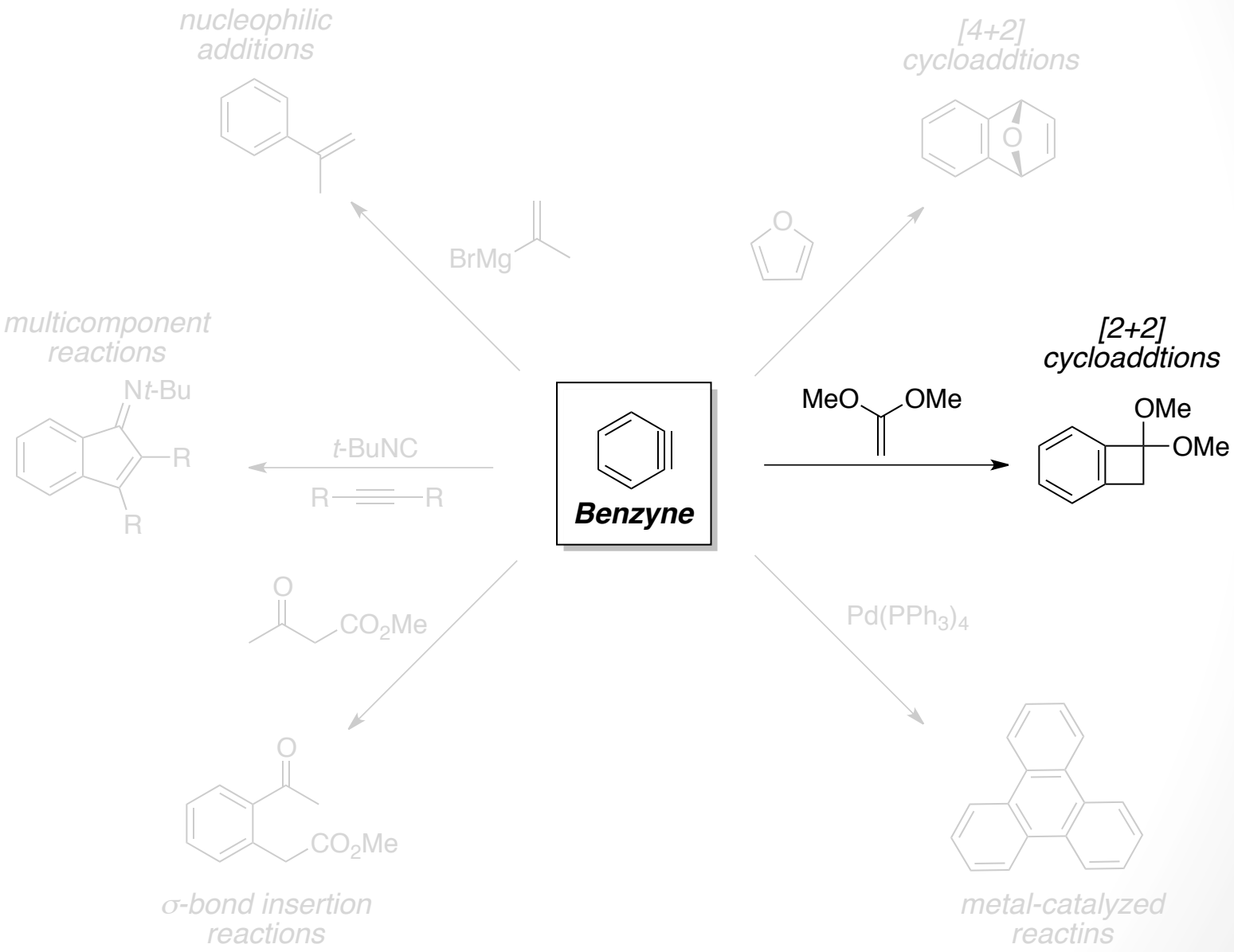
L. Castedo *et al. J. Org. Chem.* **1986,** *51*, 2781.

- Ellipticine (Gribble, 1984)
  - Pyridyne from benztriazole

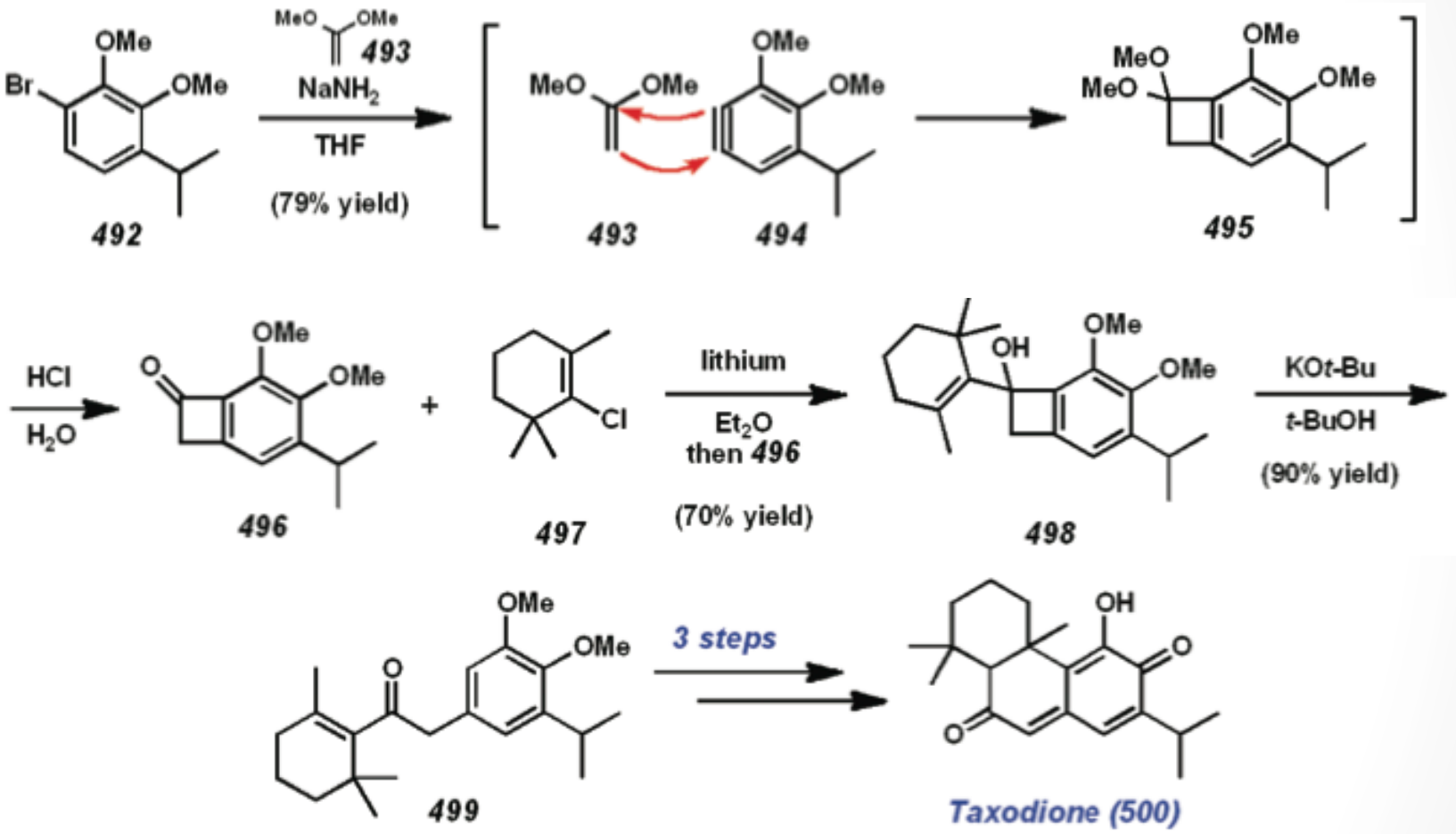


G. W. Gribble *et al. J. Org. Chem.* **1984**, *49,* 4518.

[2+2]-Cycloadditions

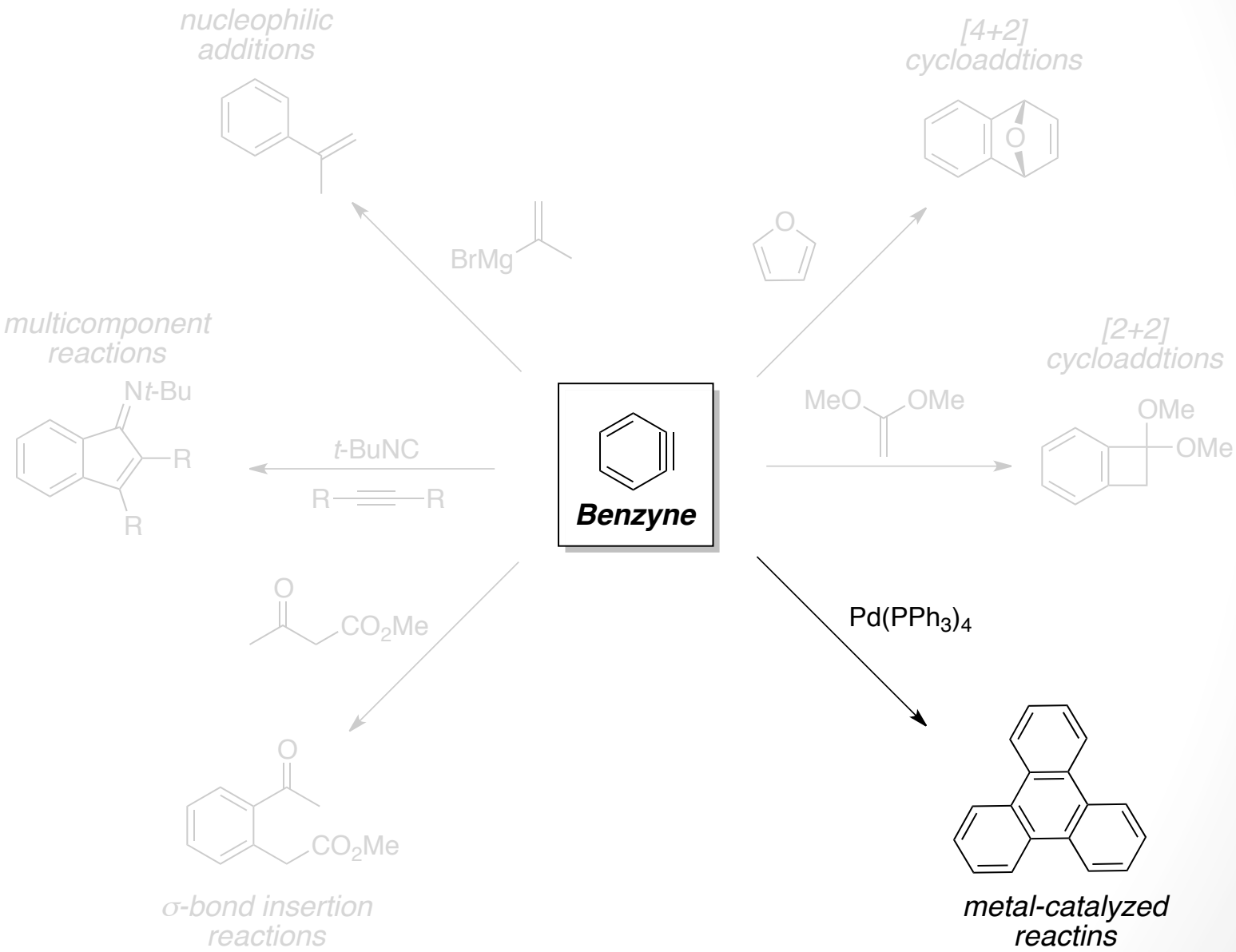


- Taxodione (Stevens, 1982)
  - [2+2]-Cycloaddition between an aryne and a ketene acetal

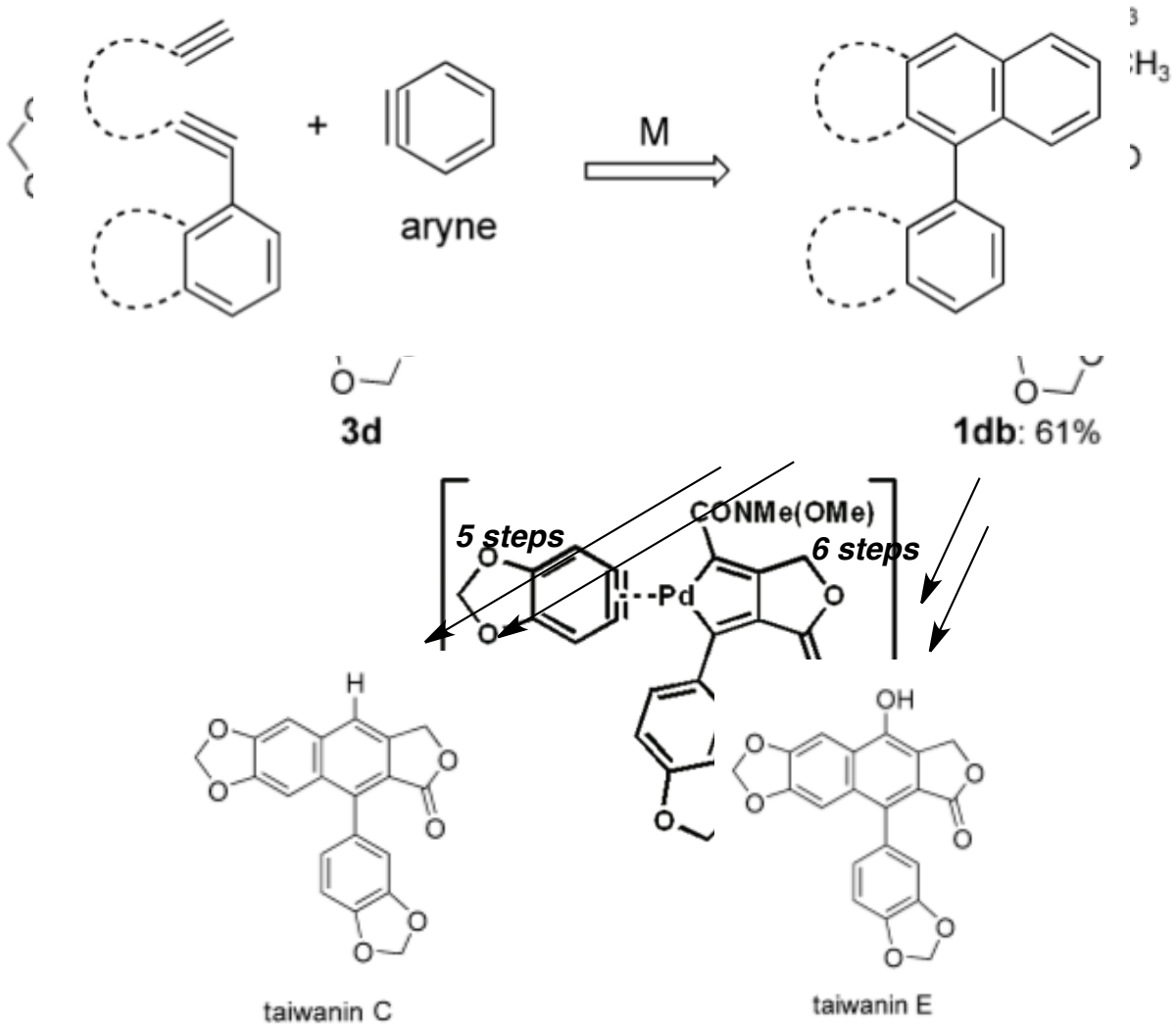


R. V. Stevens *et al. J. Org. Chem.* **1982,** *47*, 2396.

Metal-Catalyzed Reactions



- Taiwanin C/E (Mori, 2004)
  - Pd-catalyzed [2+2+2]-cocyclization of an aryne and diyne

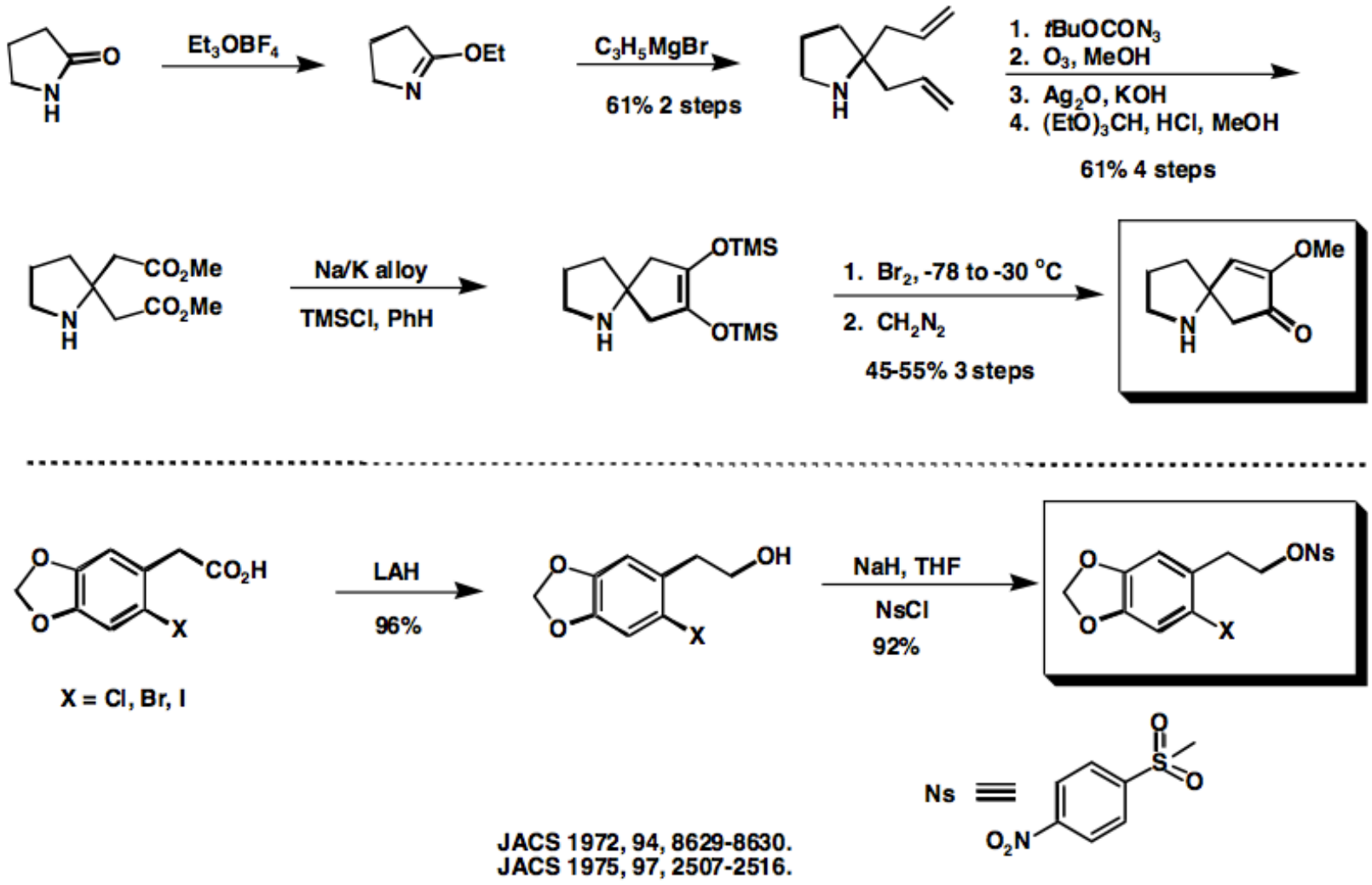


Mori *et al. Angew. Chem., Int. Ed.* **2004,** *43*, 2436.

Conclusion

- To date, **75 individual natural products** have been prepared using arynes to generate key synthetic intermediates.
- Mostly **aryl halides** are used as **benzyne precursors** (→ harsh conditions are required).
- ***o*-Silyl aryl triflates** as aryne precursors has allowed generation of the reactive intermediates under almost **neutral conditions**.
- **[4+2]-aryne cycloadditions** require **constrained dienes**, most commonly **furans**. The use of acyclic dienes in natural product synthesis is still a considerable challenge and represents an underexplored area of aryne methodology.
- Rapid preparation of **1,2-disubstituted arenes** (→ multi-component reactions)

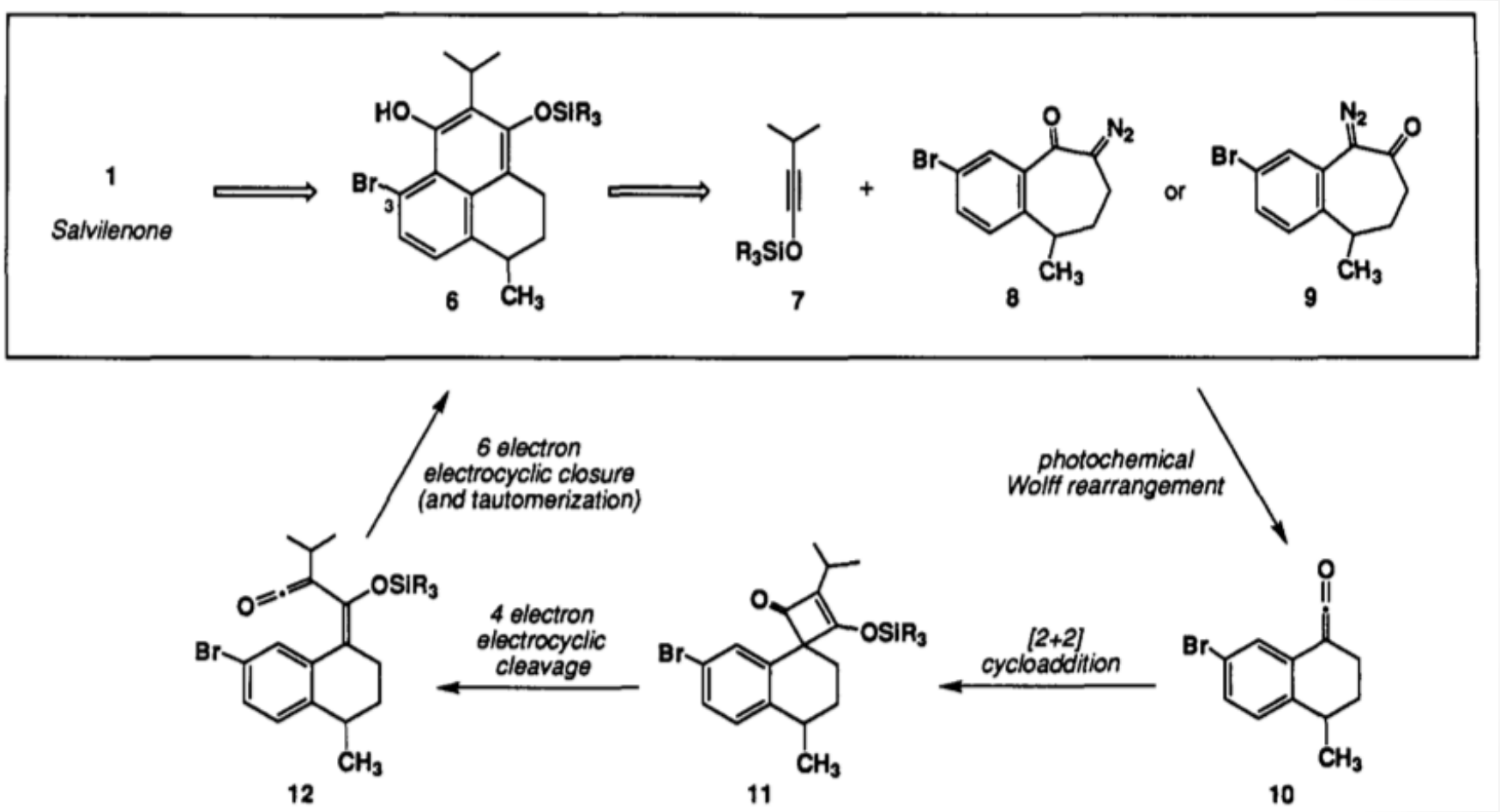
- Cephalotaxinone/Cephalotaxine (Semmelhack, 1972)



JACS 1972, 94, 8629-8630.
JACS 1975, 97, 2507-2516.

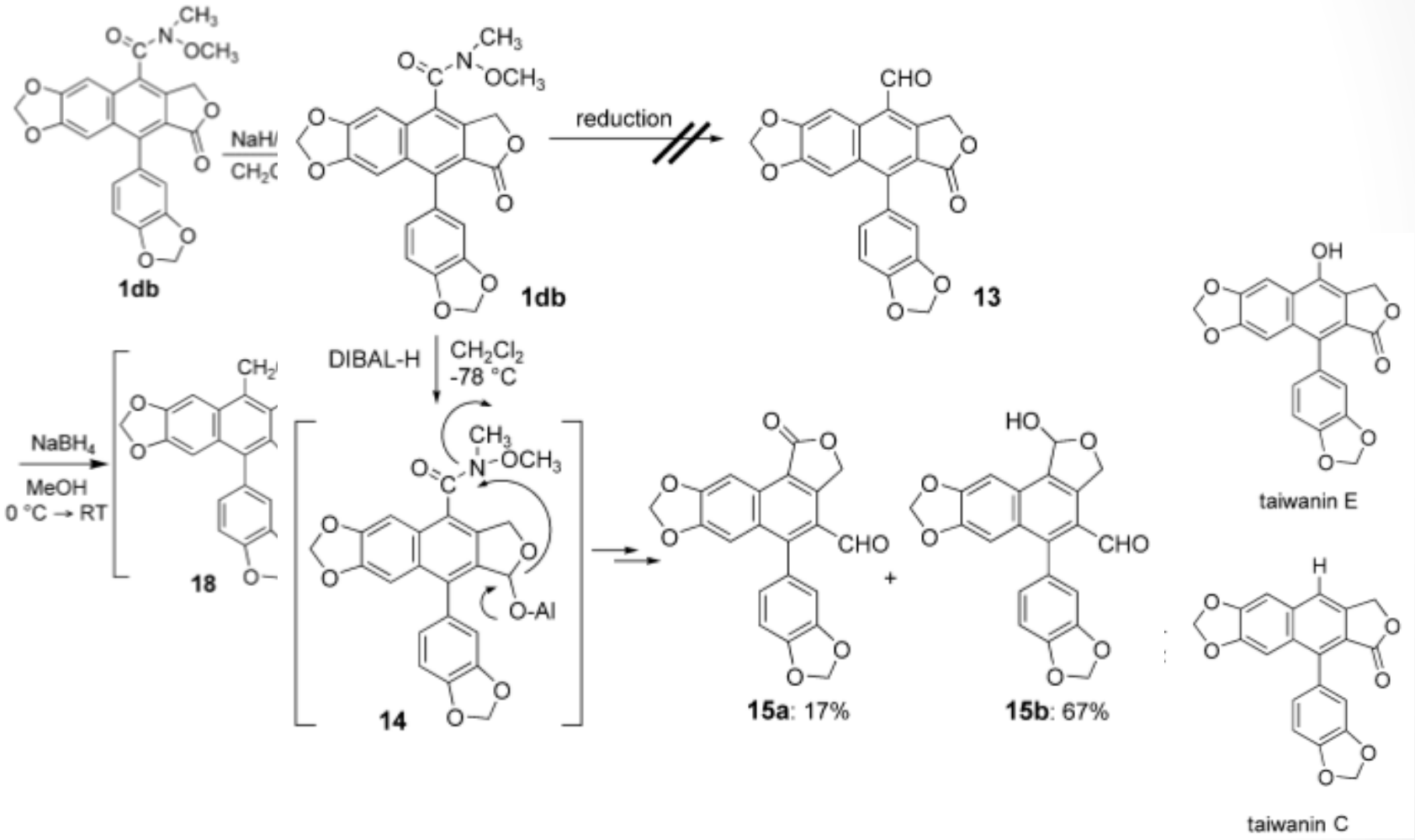
Semmelhack *et al. J. Am. Chem. Soc.* **1972,** *94,* 8629.

- Salvilenone (Danheiser, 1994)



R. L. Danheiser *et al. J. Am. Chem. Soc.* **1994,** *116*, 9471.

- Taiwanin C/E (Mori, 2004)
  - Pd-catalyzed [2+2+2]-cocyclization of an aryne and diyne



Mori *et al. Angew. Chem., Int. Ed.* **2004,** *43*, 2436.