

The Most Important yet Forgotten Organic Transformations

Group Meeting

April 28th, 2010

Benjamin D. Horning

Thank You Contributors!

Thank you very much to everyone who contributed to this group meeting.
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Jeremy Robertson
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Ei-Ichi Negishi
Brian Connell
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The Most Important yet Forgotten Organic Transformations

- Ignoring the important criterion (subjective), where do we find forgotten reactions?

  Baran group meetings: http://www.scripps.edu/chem/baran/html/meetingschedule.html

  http://www.monomerchem.com/display4.html

  http://www.organic-chemistry.org/namedreactions/

  The Merck Index contains a named reactions section

  1950s Chemische Berichte

  http://orgchem.chem.uconn.edu/namereact/named.html

  http://www.ecompound.com/

  http://www.chempensoftware.com/organicreactions.htm

  http://en.wikipedia.org/wiki/List_of_organic_reactions

- How do we break free of the confines of our "Americanized" view of chemistry?

  A French text on named reactions, available online:
  Réactions Organiques Classées par Auteurs
  http://www.infotheque.info/cache/9085/www.refer.mg/cours/alcene/index.html

  A German named reactions book from the 1960's (available in our library):
  Namenreaktionen der organischen Chamie. English (Organic name reactions; a contribution to the terminology of organic chemistry, biochemistry and theoretical organic chemistry. New York, Wiley, 1964
  By Helmut Krauch and Werner Kunz
  (Lots of overlap with the Merck Index named reactions section)

The Most Important yet Forgotten Organic Transformations

- First, some definitions

important - adjective - of much or great significance or consequence

forgotten - past participle of forget - to cease or fail to remember; be unable to recall

- The general consensus is that there are no important yet forgotten organic transformations; If they are important, they are important because they are being used.

  - The most important yet forgotten problems in organic synthesis
  - Things people should know about that they generally don't
  - The reactions that could or should be more important were they not forgotten

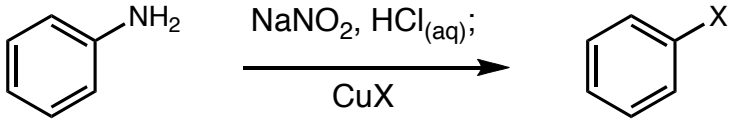
- The control of "relative face selectivity." For example, the exo-selective Diels-Alder reaction

- Direct, catalyzed fluorination, chlorination, and hydroxylation into organic molecules via C-H activation, including diastereo- and enantioselective processes at sp_3-hybridized stereocenter

The Most Historically Important yet Forgotten Reactions

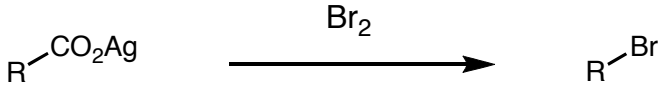
The Sandmeyer reaction

Sandmeyer, T. *Ber.* **1884**, *17*, 1633-1635.



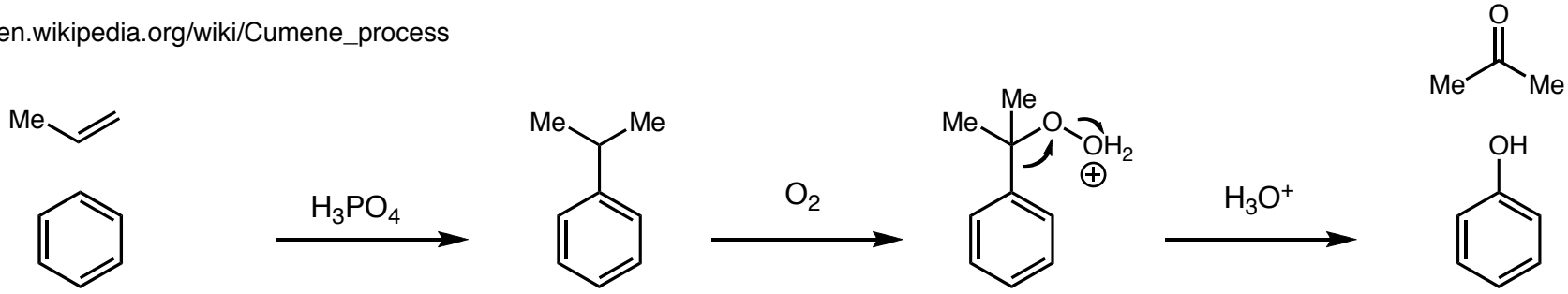
The Hunsdiecker reaction

Hunsdiecker, H.; Hunsdiecker, C. *Ber.* **1942**, *75*, 291-297.



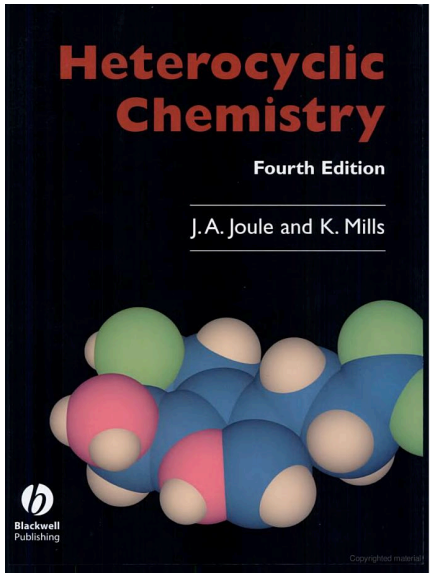
The Cumene process

http://en.wikipedia.org/wiki/Cumene_process



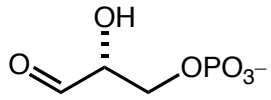
Things People Should Know About that they Generally Don't

- Heterocycle Chemistry



- The Calvin Cycle by which mother nature makes all her organic compounds

$3CO_2 + 9\ ATP + 6NADPH \rightarrow GAP + 9\ ADP + 8P_i + 6NADP^+$

GAP = 

- Other biochemical reactions, such as reactions of thioesters and thiolate/disulfide interchange

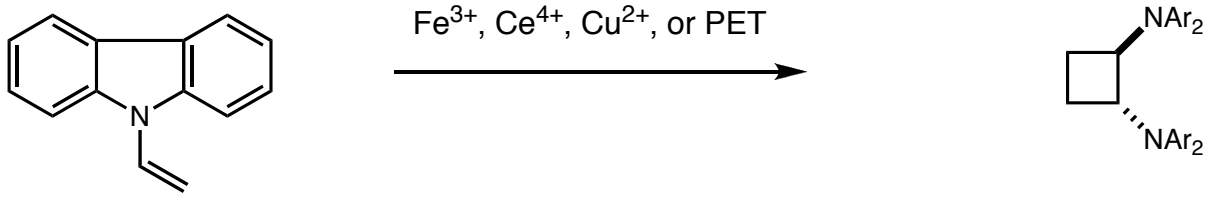
Native Chemical Ligation: Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science*, **1994**, *266*, 776-779.

Tonight's Topics

- Radical-cation sigmatropic rearrangements
- Enantioselective photodeconjugation of enoates
- Arene/olefin photocycloaddition
- Trichlorosilane/tertiary amine combination and the Benkeser reaction
- Willgerodt/Kindler reaction
- Burton trifluoromethylation
- Matteson alkylation and the Zweifel Olefin synthesis
- Berman's NO chemistry

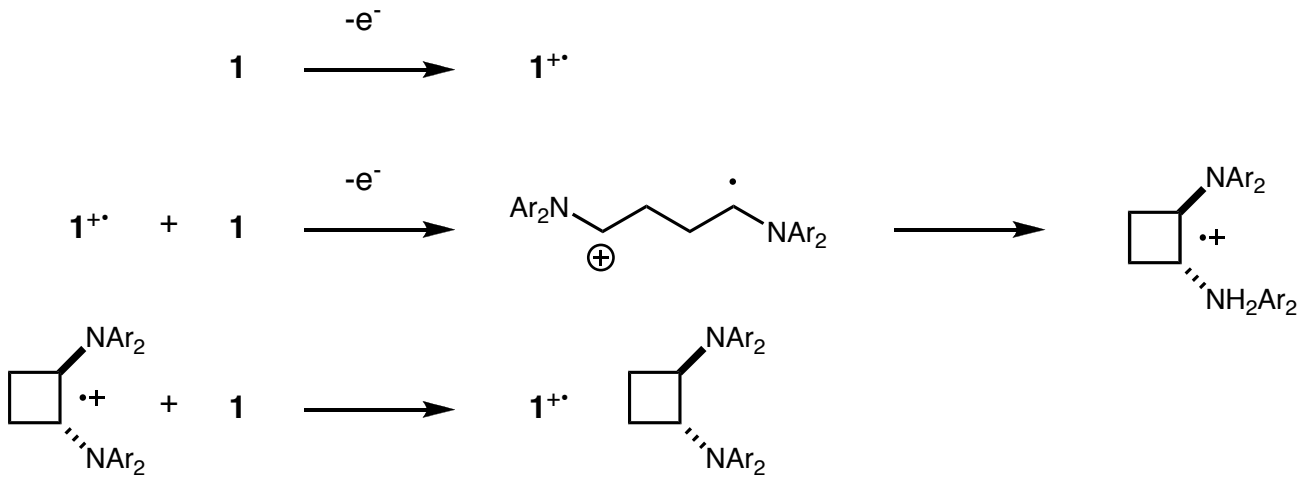
Radical Cation Pericyclic Reactions

■ Oxidative conditions were shown to yield the homodimerization of vinyl carbazole **1**



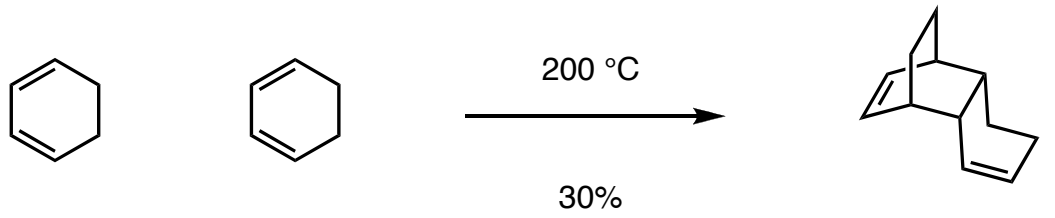
1

Initial discovery: Ledwith, A. *Acc. Chem. Res.* **1972**, *5*, 133-139.
Further utilization: Bauld, N. L. *et al. Acc. Chem. Res.* **1987**, *20*, 371-378.
Bauld, N. L. *Tetrahedron*, **1989**, *45* (17), 5307-5363.

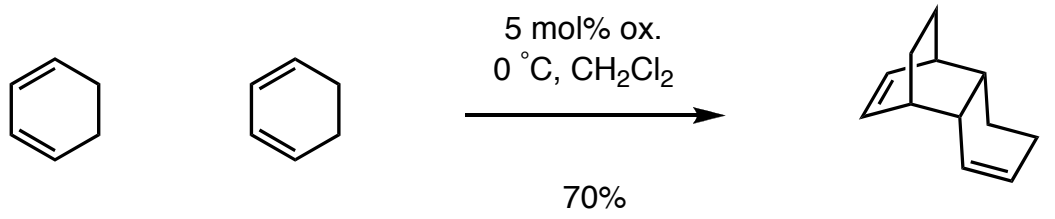


Radical Cation Pericyclic Reactions

- A useful improvement to diene dimerization



4:1 endo:exo

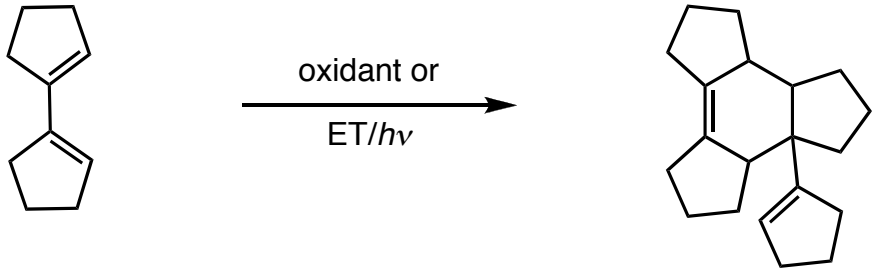


5:1 endo:exo

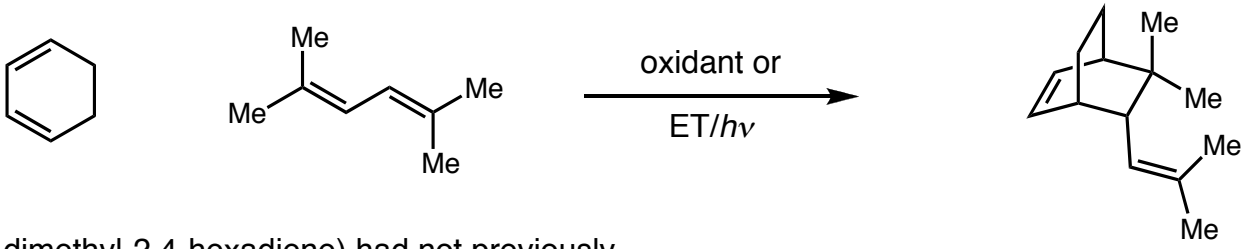
ox. = $Ar_3N^{+\bullet}SbCl_6^-$
an "aminium" salt

Radical Cation Pericyclic Reactions

- Sterically encumbered dienes react well



oxidant - 50%
PET - 70%



oxidant - 40%

"(2,5-dimethyl-2,4-hexadiene) had not previously been induced to participate in a Diels-Alder addition as either the dienic or dienophilic component"

ox. = $Ar_3N^{+\bullet}SbCl_6^-$
an "aminium" salt

Radical Cation Pericyclic Reactions

Some terminology

1987

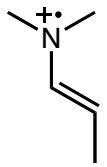
catical = cation radical

caticophile = neutral component which is the reaction partner of the catical

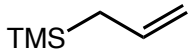
caticogen = neutral component which generates the catical

2007

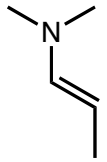
SOMO



SOMO-phile

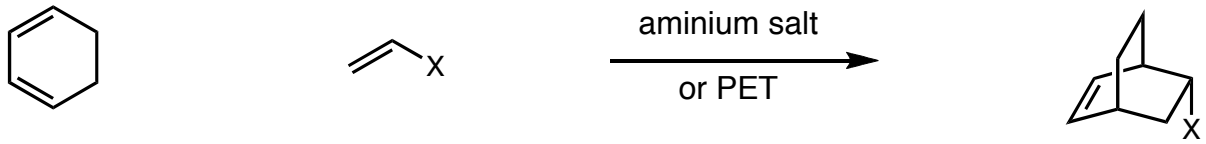


enamine



Radical Cation Pericyclic Reactions

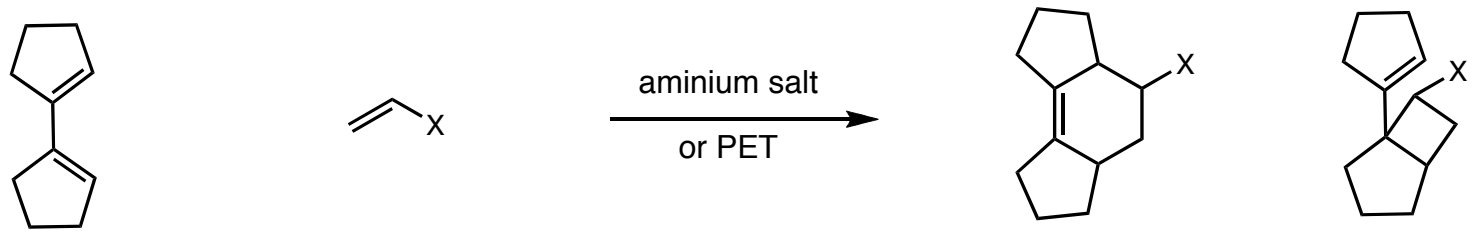
- Diels-Alders beyond diene homo- and heterodimerization



X = SPh, OPh

X = SPh	68%
OPh	75%

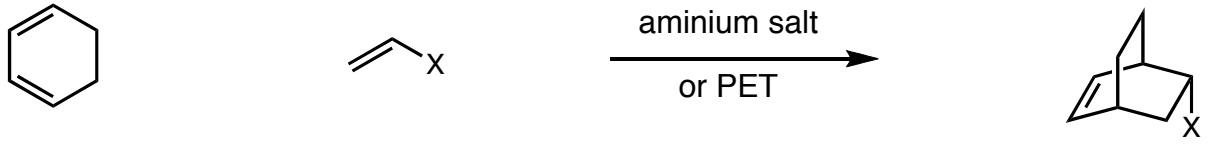
- Acyclic dienes preferentially yield cyclobutanation products



X =			
	NAcMe	0	100
	OEt	2	98
	OCH_2CH_2Cl	3	97
	OPh	18	82
	SPh	31	69

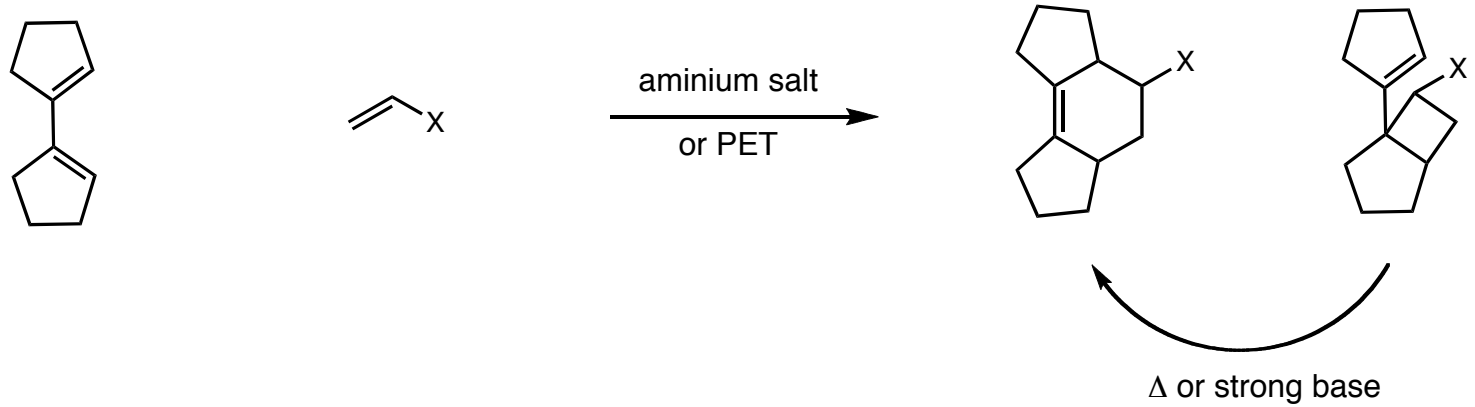
Radical Cation Pericyclic Reactions

- Diels-Alders beyond diene homo- and heterodimerization



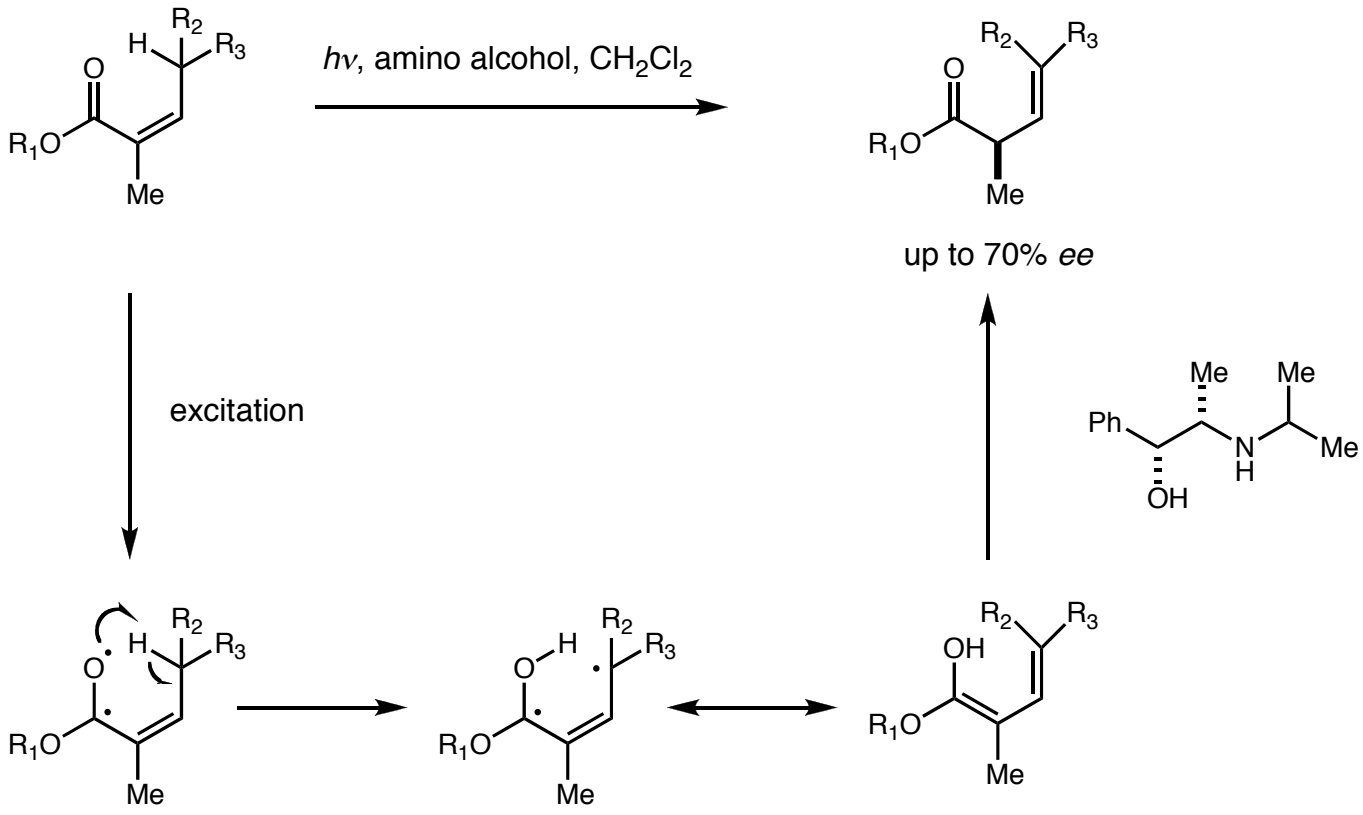
X = SPh 68%
OPh 75%

- Acyclic dienes preferentially yield cyclobutanation products



Enantioselective Photodeconugation of Enoates

- Norrish type II rearrangement/protonation leads to enantioenriched β-χ unsaturated esters



Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 9263-9272.

Enantioselective Photodeconugation of Enoates

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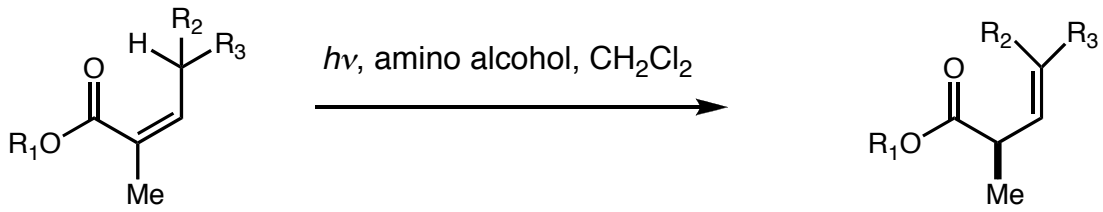
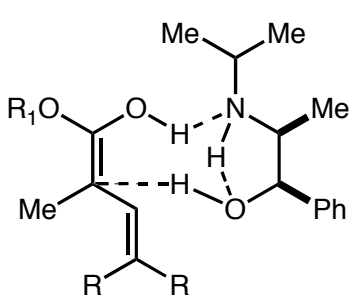
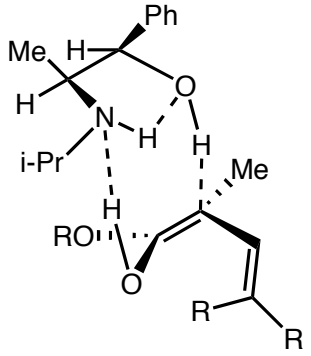


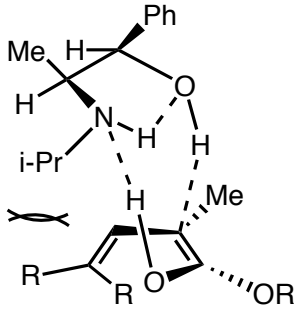
up to 70% *ee*



proposed transition state



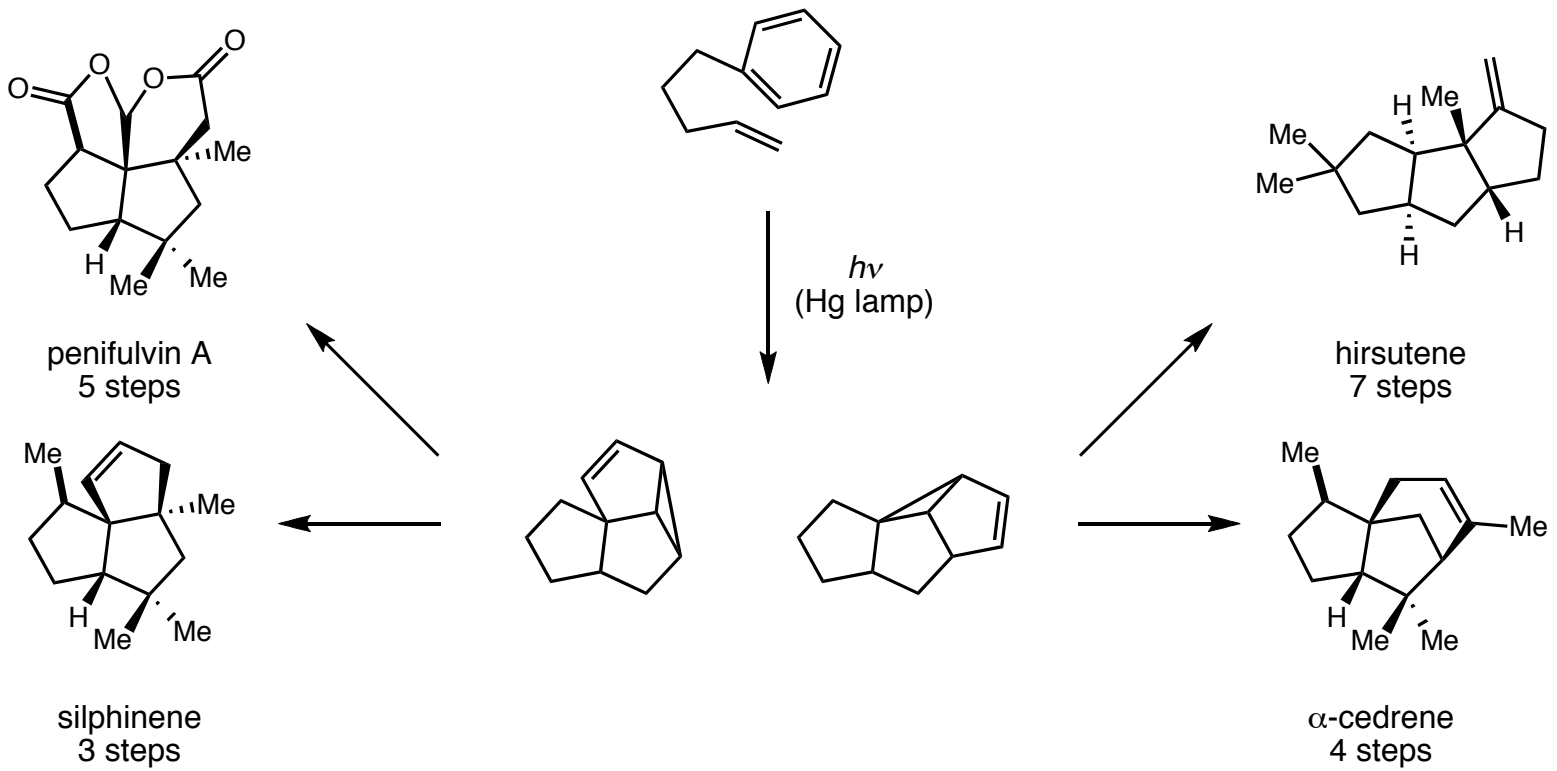
favored



disfavored

Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 9263-9272.

Intramolecular Arene-Olefin Photocycloaddition



(Intermolecular) Discovery: Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066-2067.
Bryce-Smith, D.; Gilbert, A.; Orger, B .H. *Chem. Commun.* **1966**, 512.

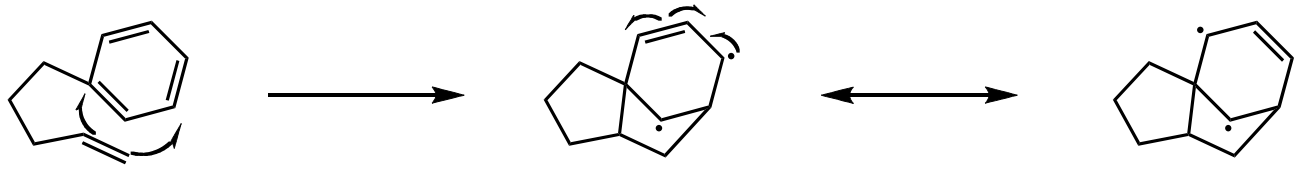
Intramolecular variant: Morrison, H.; Ferree, W. *J. Chem Soc., Chem. Commun.* **1969**, 268.
Ferree, W.; Grutzner, J.; Morrison, H. *J. Am. Chem. Soc.* **1971**, *93*, 5502-5512.

Histurene: Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983-3986.
Cedrene: Wedner, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688-690.
Silphinene: Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625-2628.
Penifulvins: Gaich, T.; Mulzer, J. *J. Am. Chem. Soc.* **2009**, *131*, 452-453.
Gaich, T.; Mulzer, J. *Org. Lett.* ASAP.

Review of arene-olefin photocycloaddition in total synthesis: Russell, A. T.; Chappell, D. *Org. Biomol. Chem.* **2006**, *4*, 4409-4430.

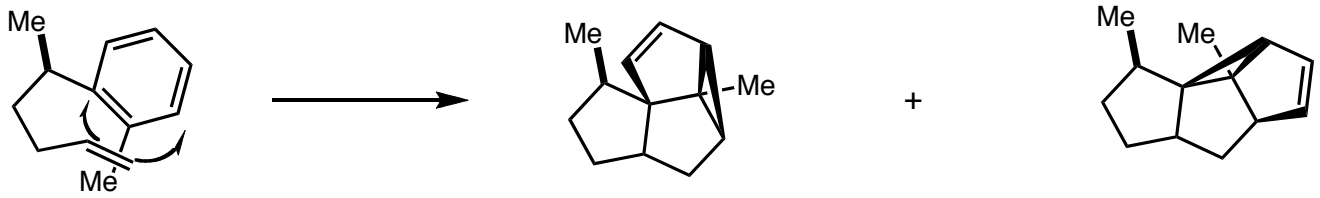
Intramolecular Arene-Olefin Photocycloaddition

- Photoexcitation of a bichromophoric arene-olefin leads to exciplex formation/cyclization



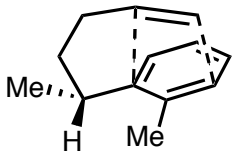
an exciplex

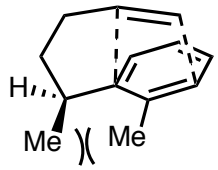
- The presence of a benzylic stereocenter serves to impart diastereoselectivity



Intramolecular Arene-Olefin Photocycloaddition

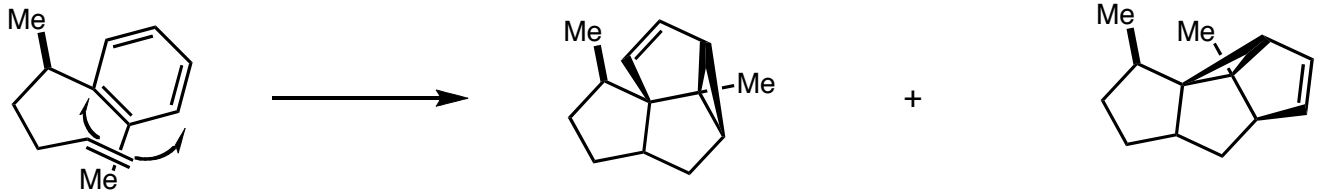
- Model for diastereoselectivity





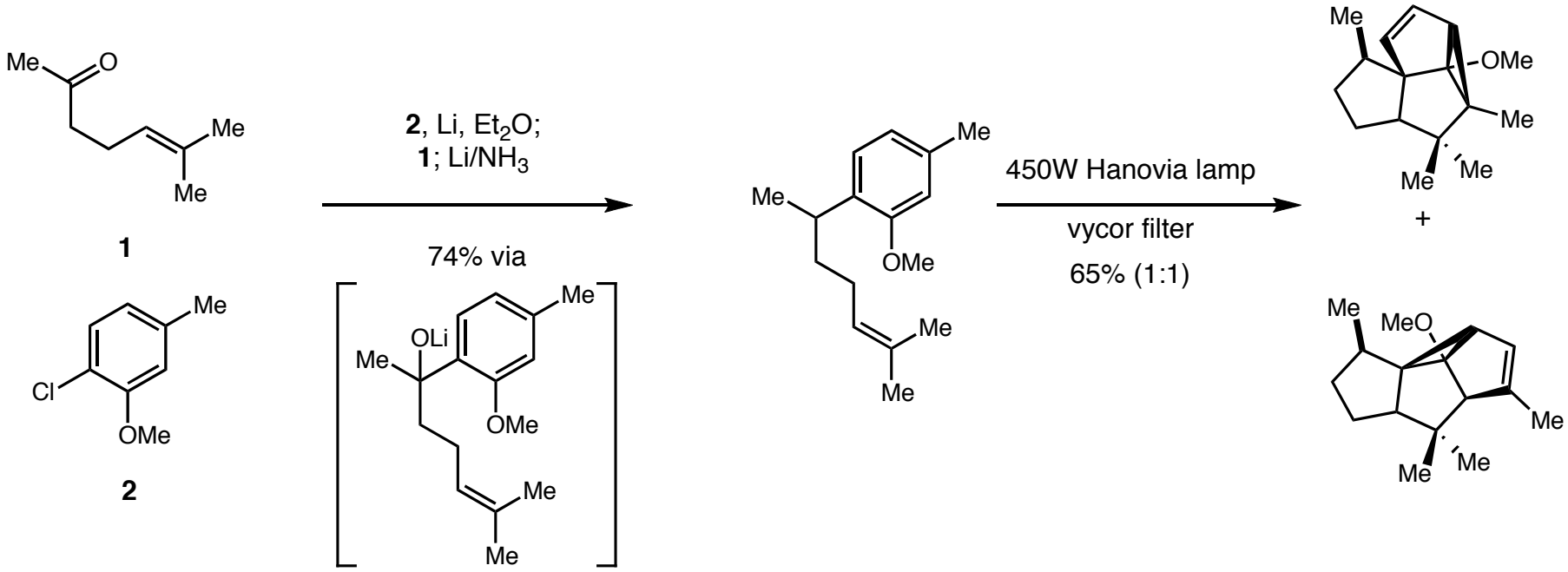
single diastereomer observed for each regioisomer

- The presence of a benzylic stereocenter serves to impart diastereoselectivity



Intramolecular Arene-Olefin Photocycloaddition

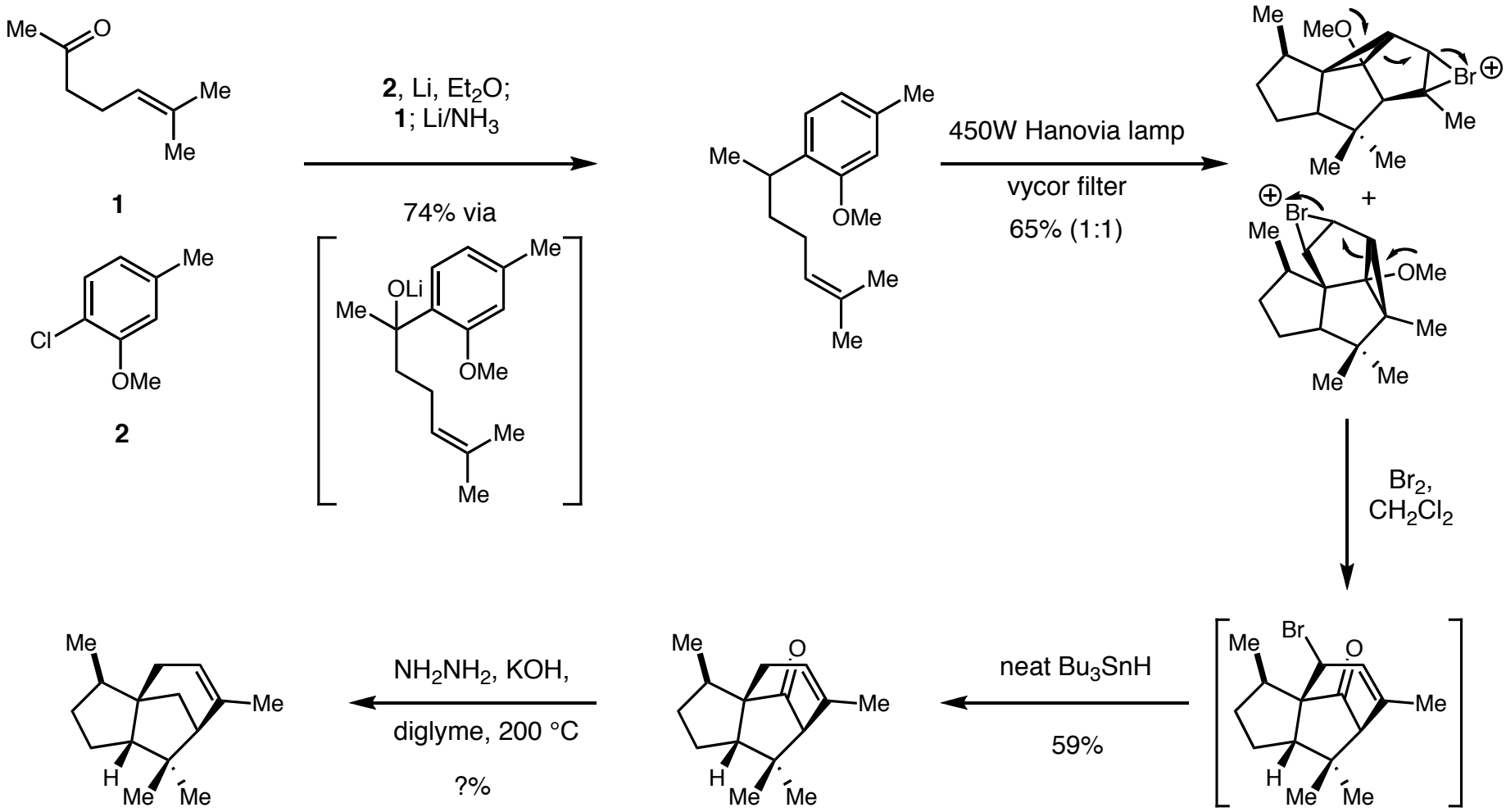
■ Cyclized products can be advanced to a variety of terpenoid natural products



Hall alkylation: Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271-275.

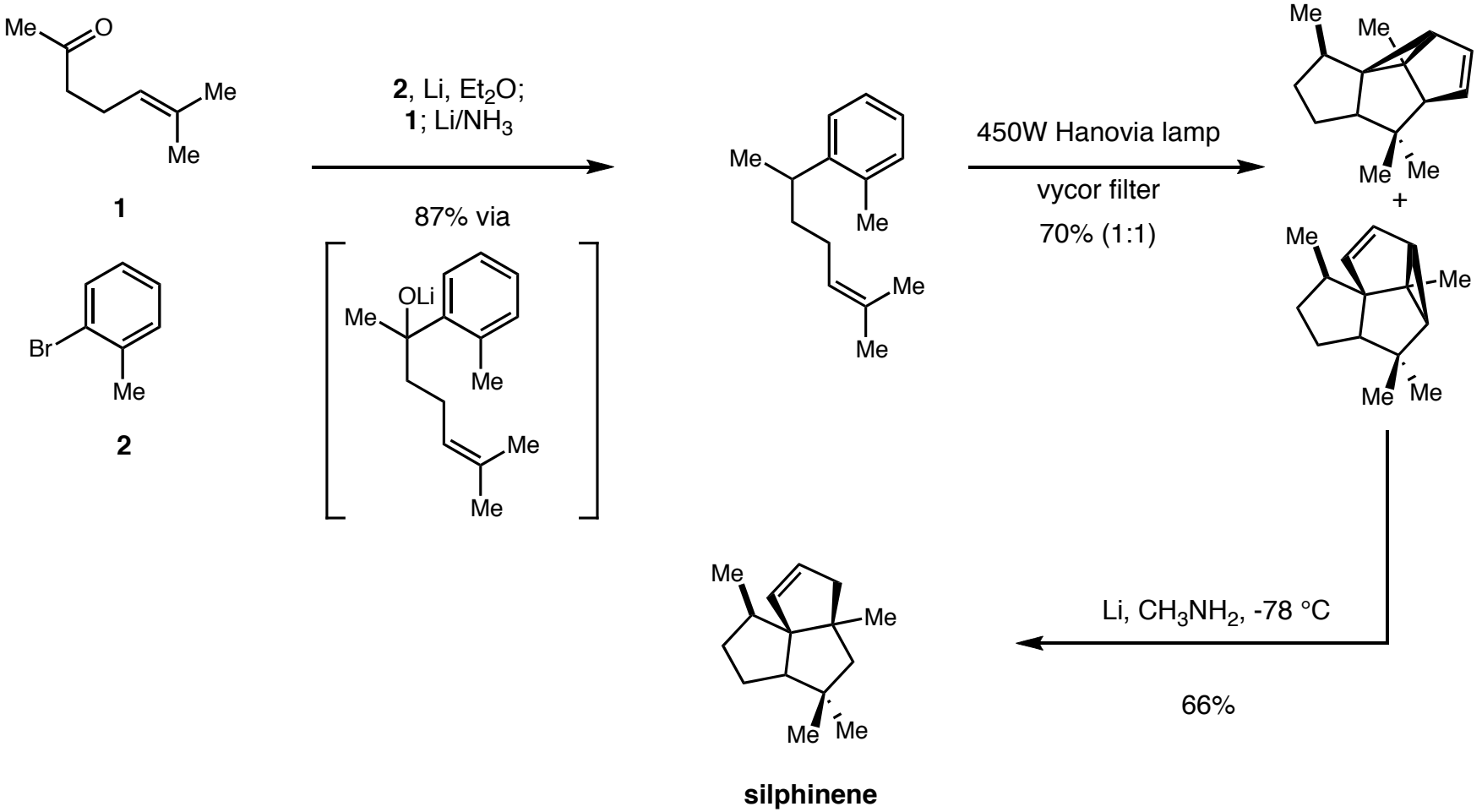
Intramolecular Arene-Olefin Photocycloaddition

■ Cyclized products can be advanced to a variety of terpenoid natural products



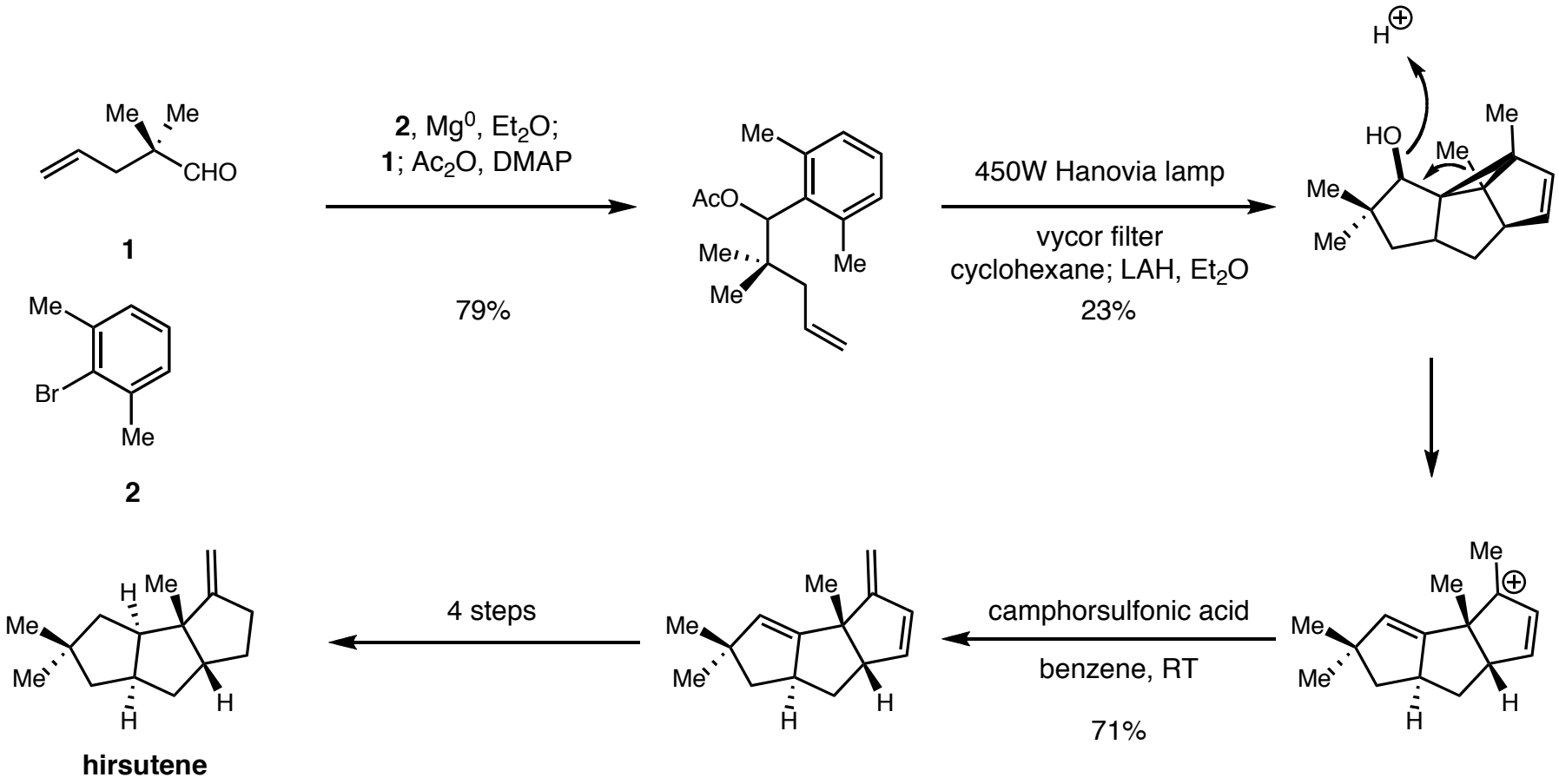
Intramolecular Arene-Olefin Photocycloaddition

- Reductive cleavage leads to a different series of products



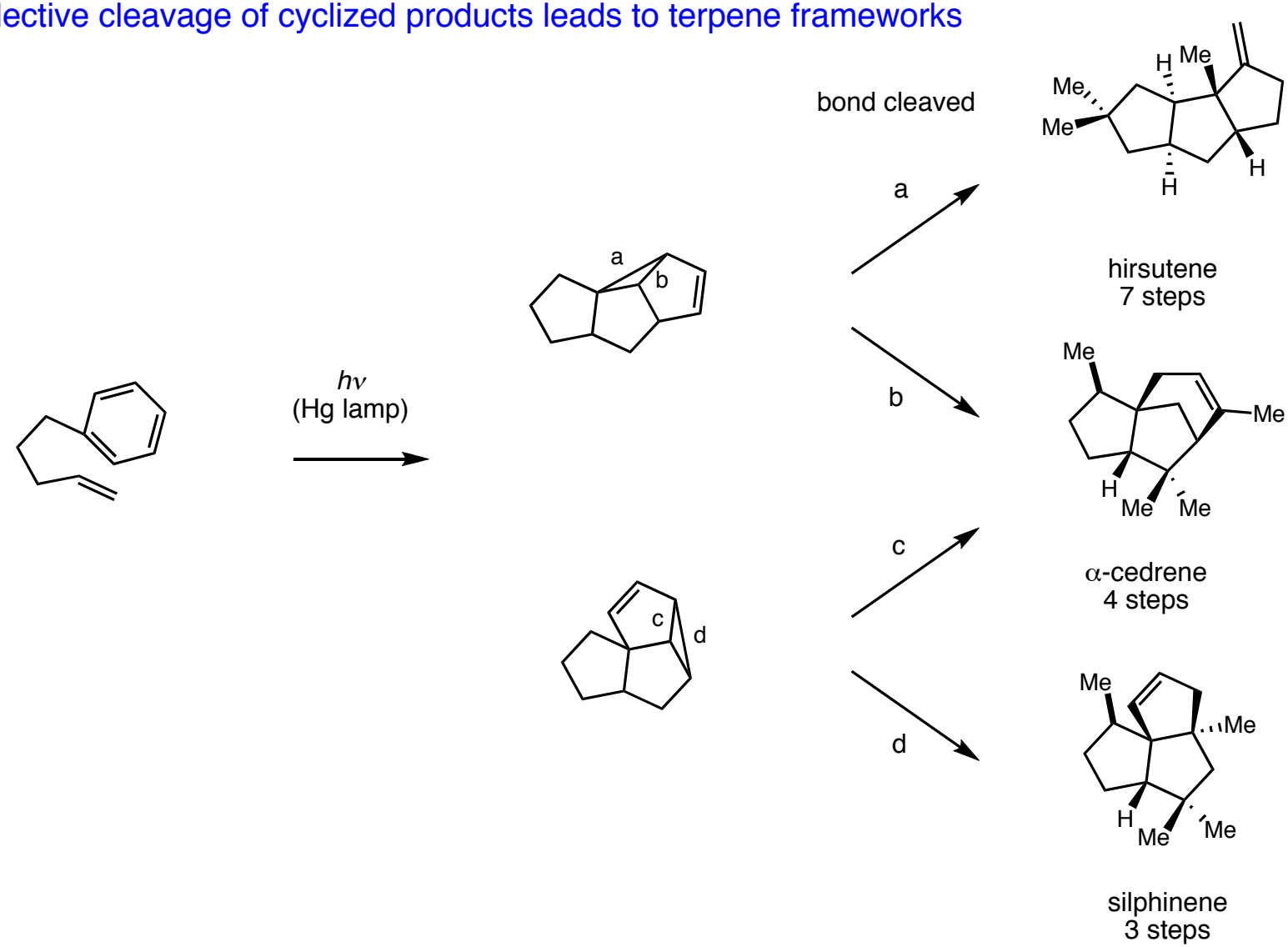
Intramolecular Arene-Olefin Photocycloaddition

- A third mode of cleavage leads to triquinanes



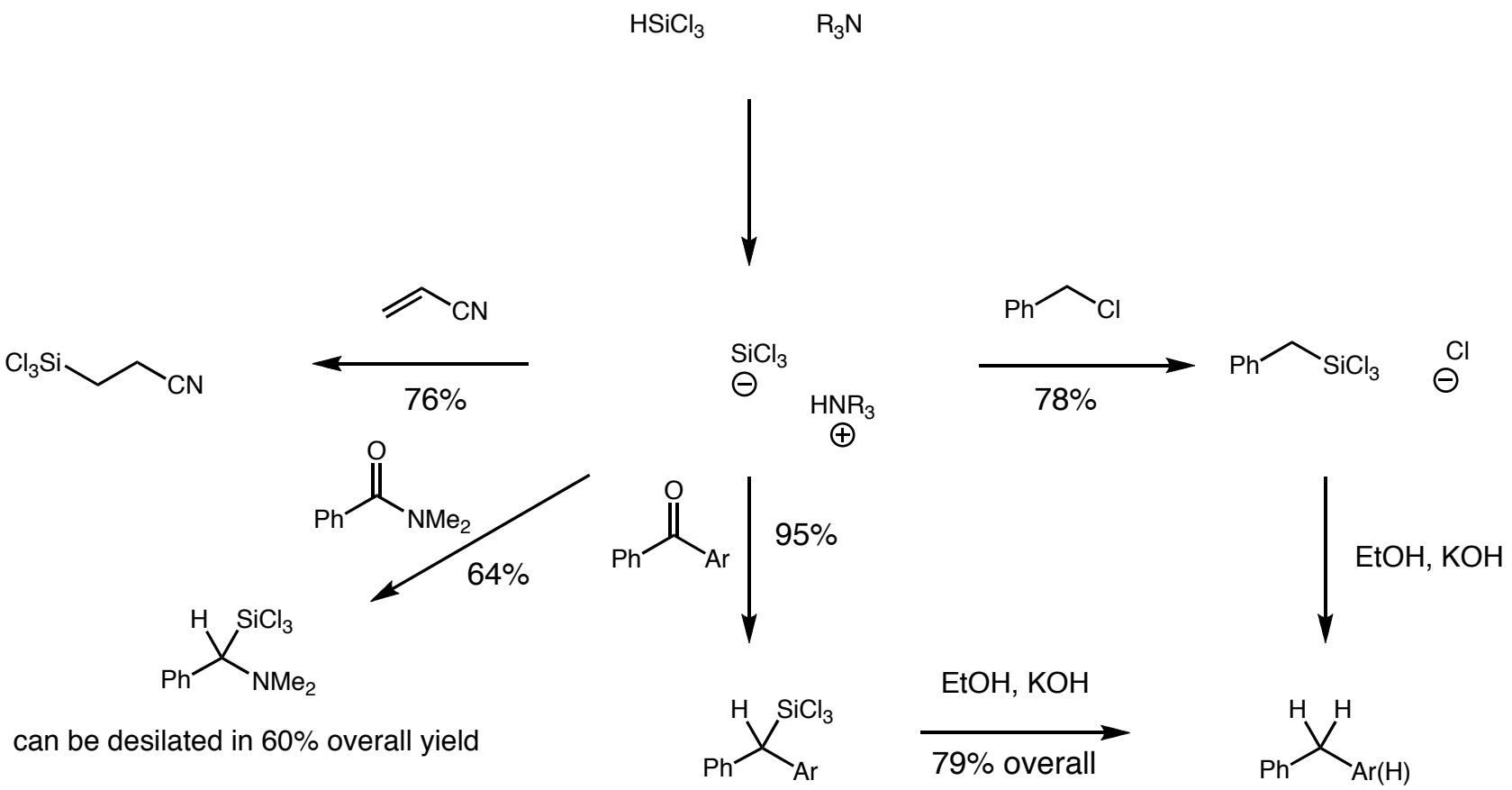
Intramolecular Arene-Olefin Photocycloaddition

- Selective cleavage of cyclized products leads to terpene frameworks



Trichlorosilane-Tertiary Amine Combinations - The Benkeser Reaction

- Trichlorosilane is inexpensive and abundant due to its use in transistor-grade silicon

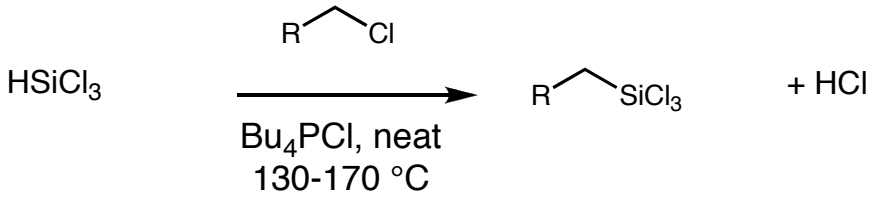


- Unfortunately, these reactions only work with $HSiCl_3$, not even $HMeSiCl_2$ works

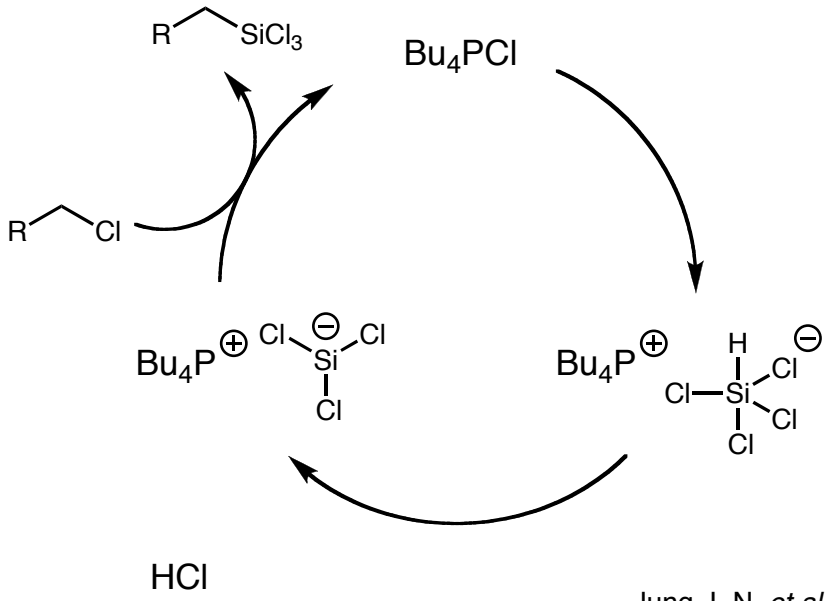
Benkeser, R. B. *Acc. Chem. Res.* **1971**, *4*, 94-100.

Trichlorosilane-Tertiary Amine Combinations - The Benkeser Reaction

- A recent (2001) JACS paper updated this methodology, expanding the nature of the electrophile



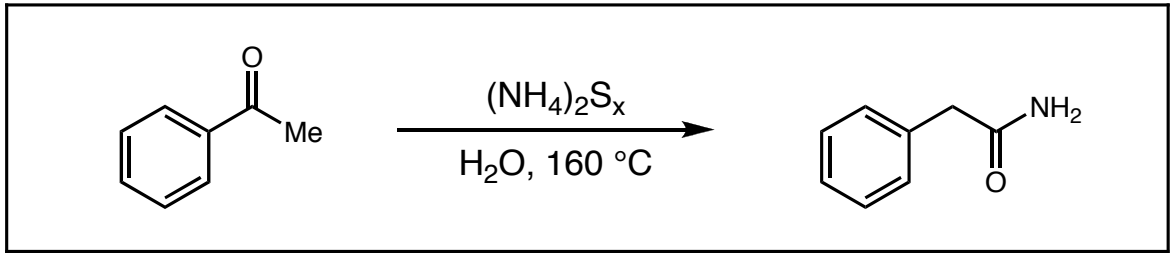
R = benzyl, allyl, alkyl



Jung, I. N. *et al. J. Am. Chem. Soc.* **2001**, *123*, 5584-5585.

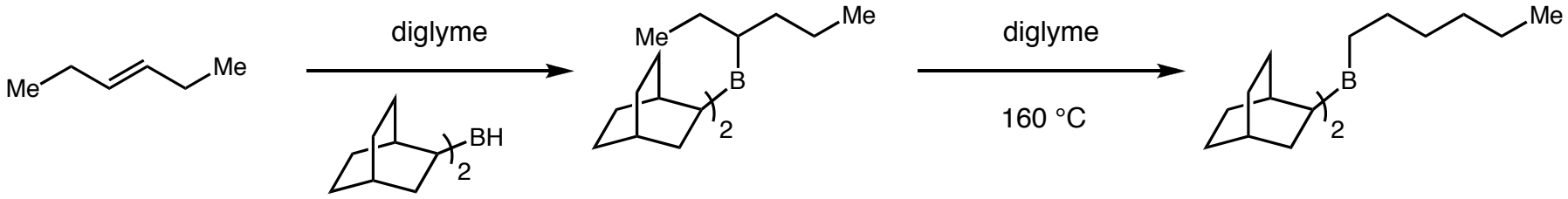
The Willgerodt-Kindler Reaction

- Reaction of aryl alkyl ketones with an amine and sulfur at high temperatures

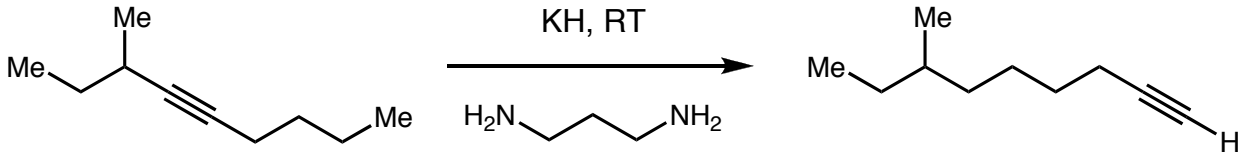


Willgerodt, C. *Ber.* **1887**, *20*, 2467-2470.
Kindler, K. *Ann. Chem.* **1923**, *431*, 187.

- Conceptually related to the (H. C.) Brown borane/olefin isomerization and the (C. A.) Brown acetylene zipper reactions



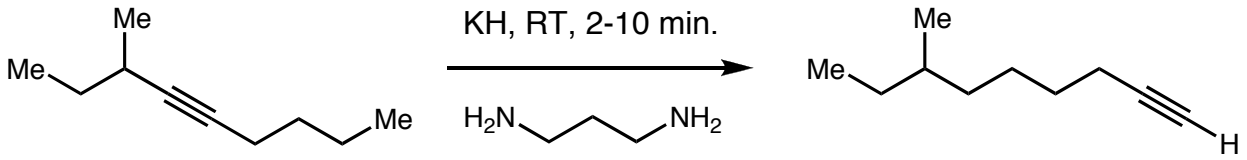
Brown, H. C.; Racherla, U. S. *J. Organometal. Chem.* **1983**, *241*, C37-C40.



Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1974**, *97*, 891-891.

The Willgerodt-Kindler Reaction - Related Contrathermodynamic Isomerizations

■ C. A. Brown's KAPA contribution makes the alkyne zipper synthetically useful

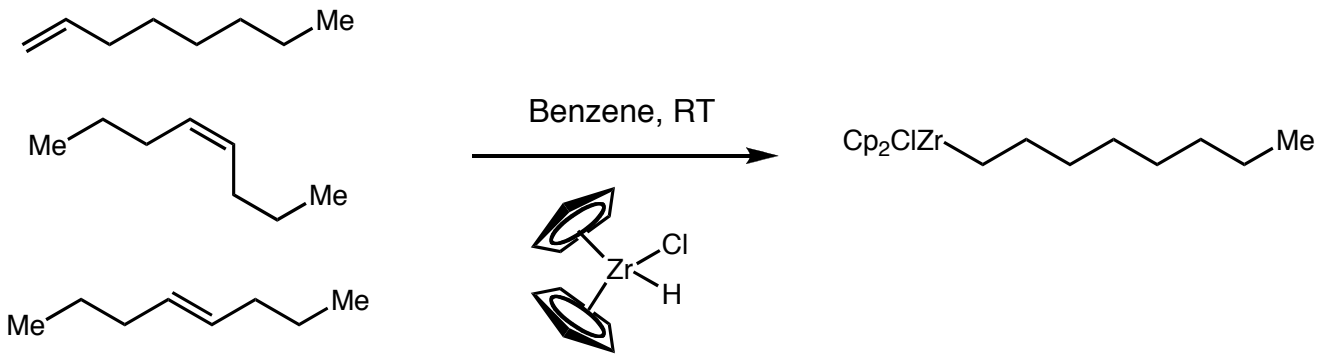


84%

Previous conditions required > 100 °C, longer than 2 hours, and only workd on methyl alkynes

Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1974**, *97*, 891-891.

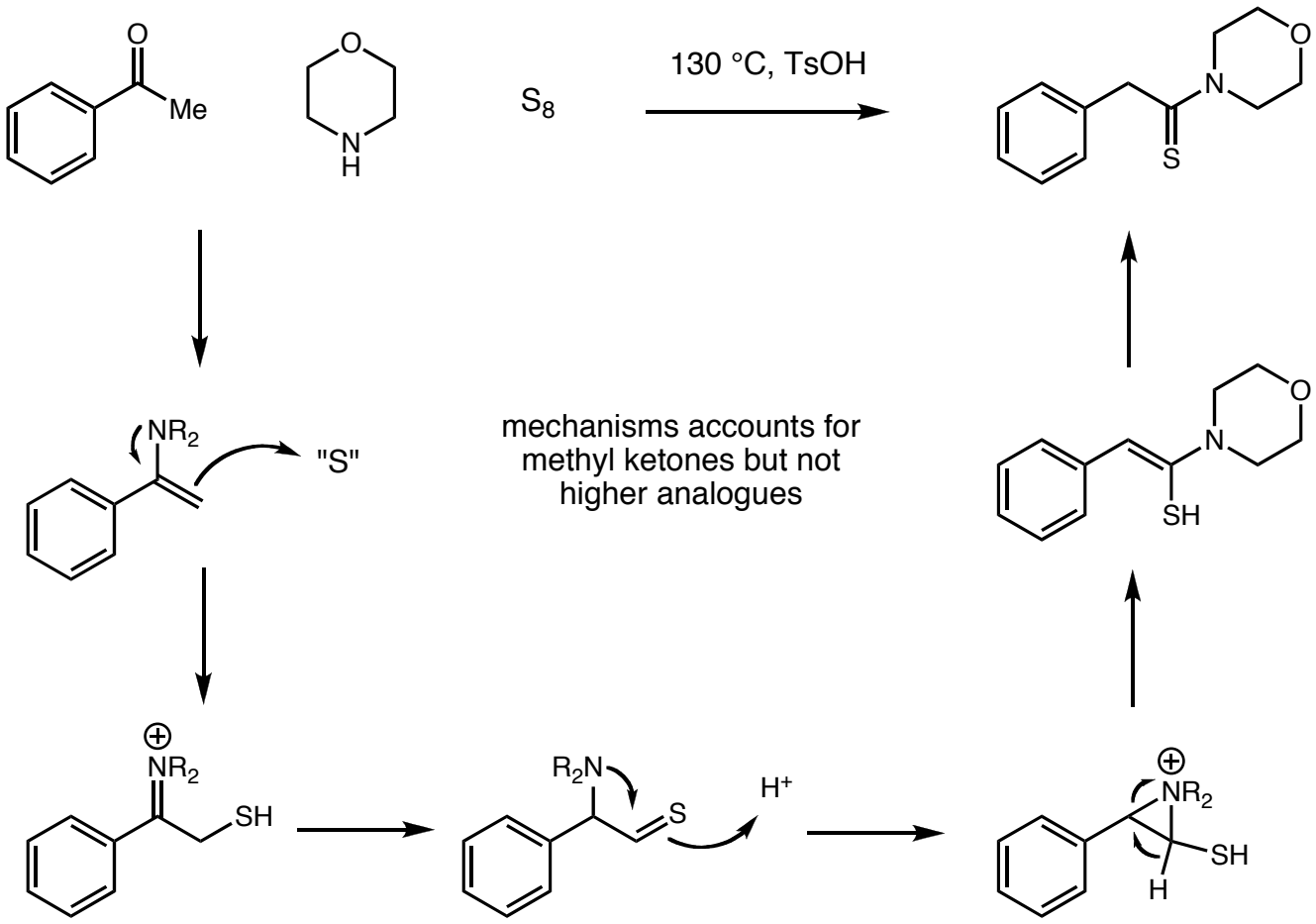
■ J. Schwartz's hydrozirconation isomerization trumps H. C. Brown's hydroboration isomerization



Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115-8116.

The Willgerodt-Kindler Reaction - Mechanism

- At high temperatures, many mechanistic oddities are possible



Carmack, M., *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.

The Willgerodt-Kindler Reaction - Mechanism

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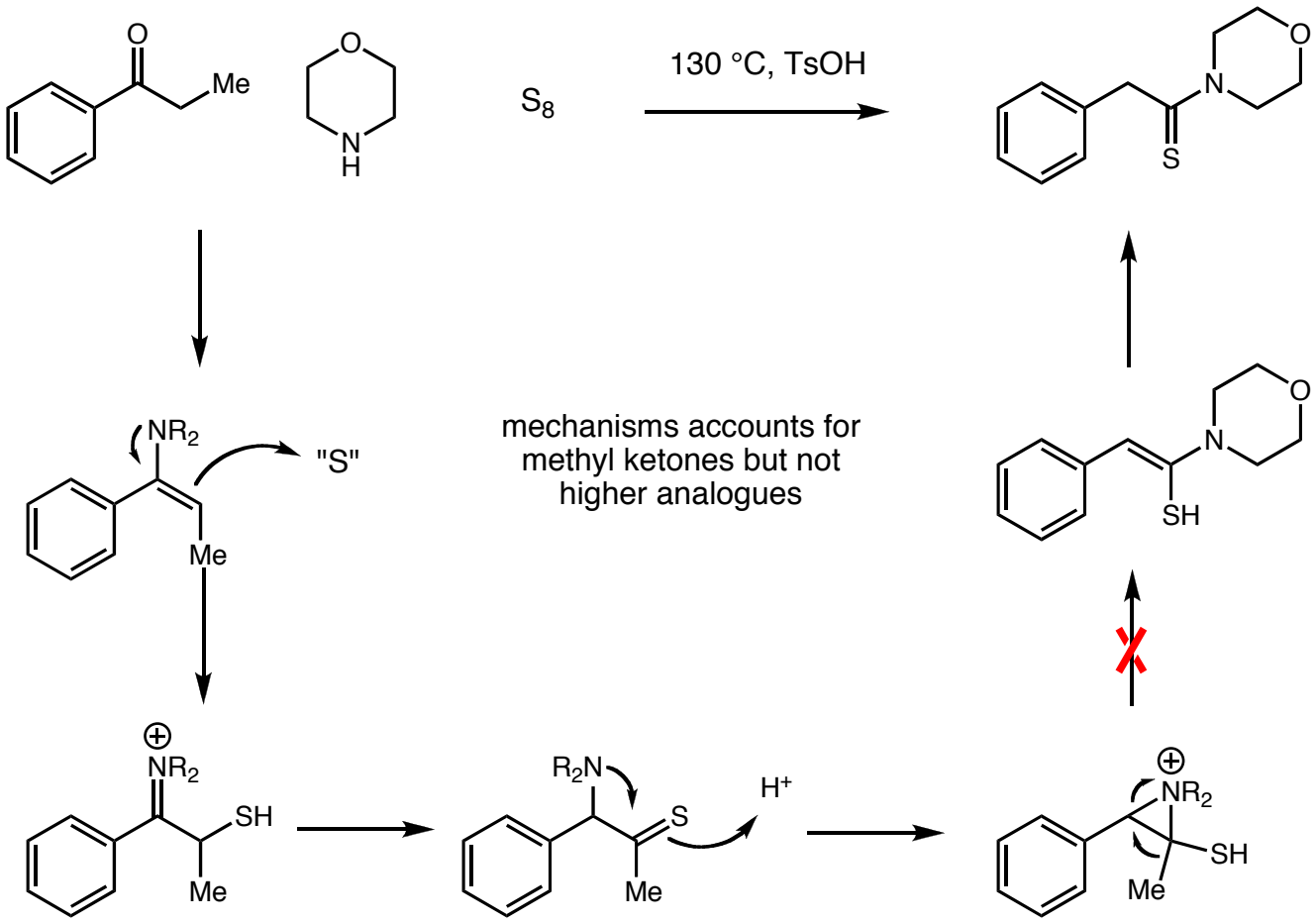
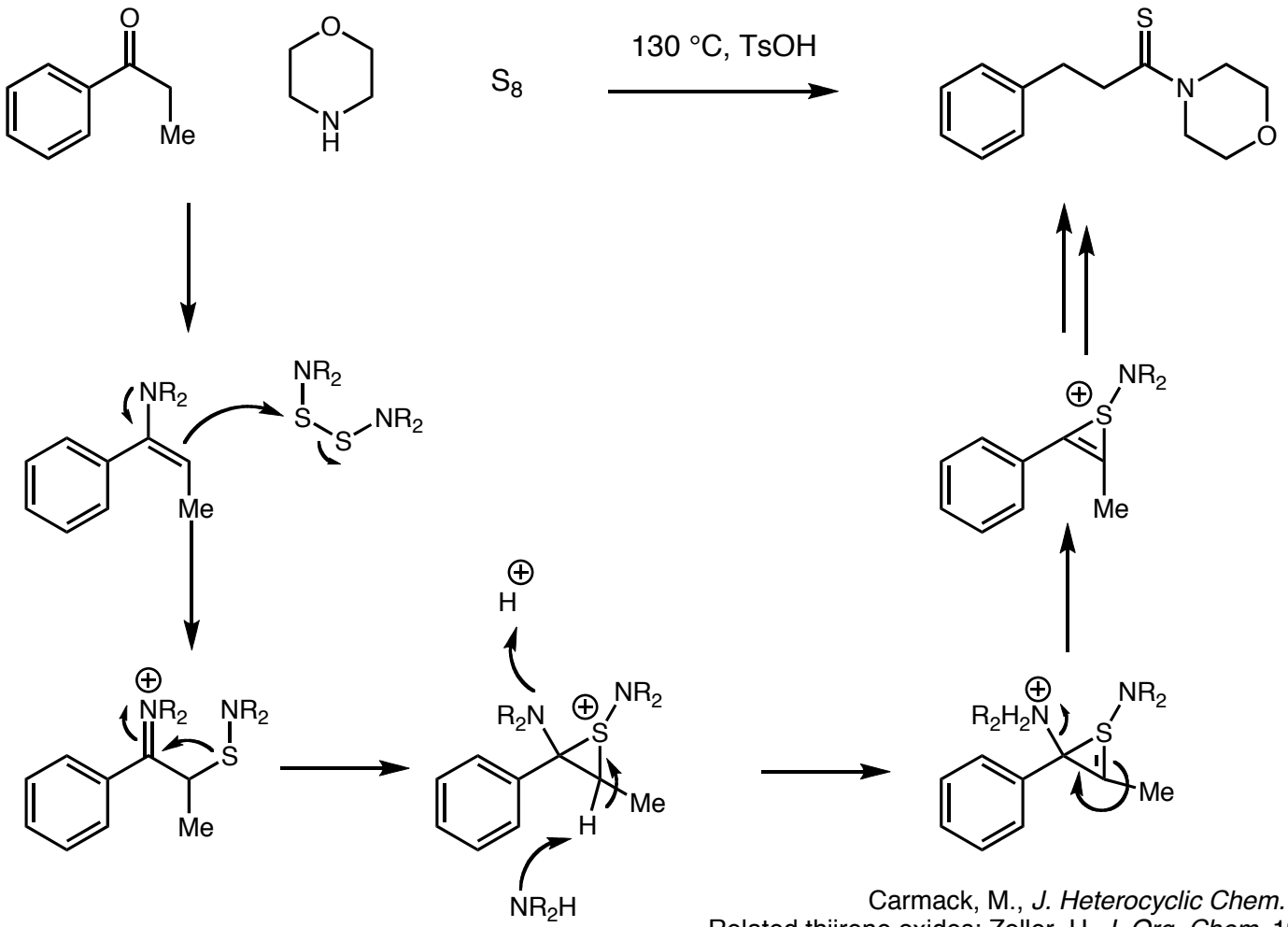


Carmack, M., *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.

The Willgerodt-Kindler Reaction - Mechanism

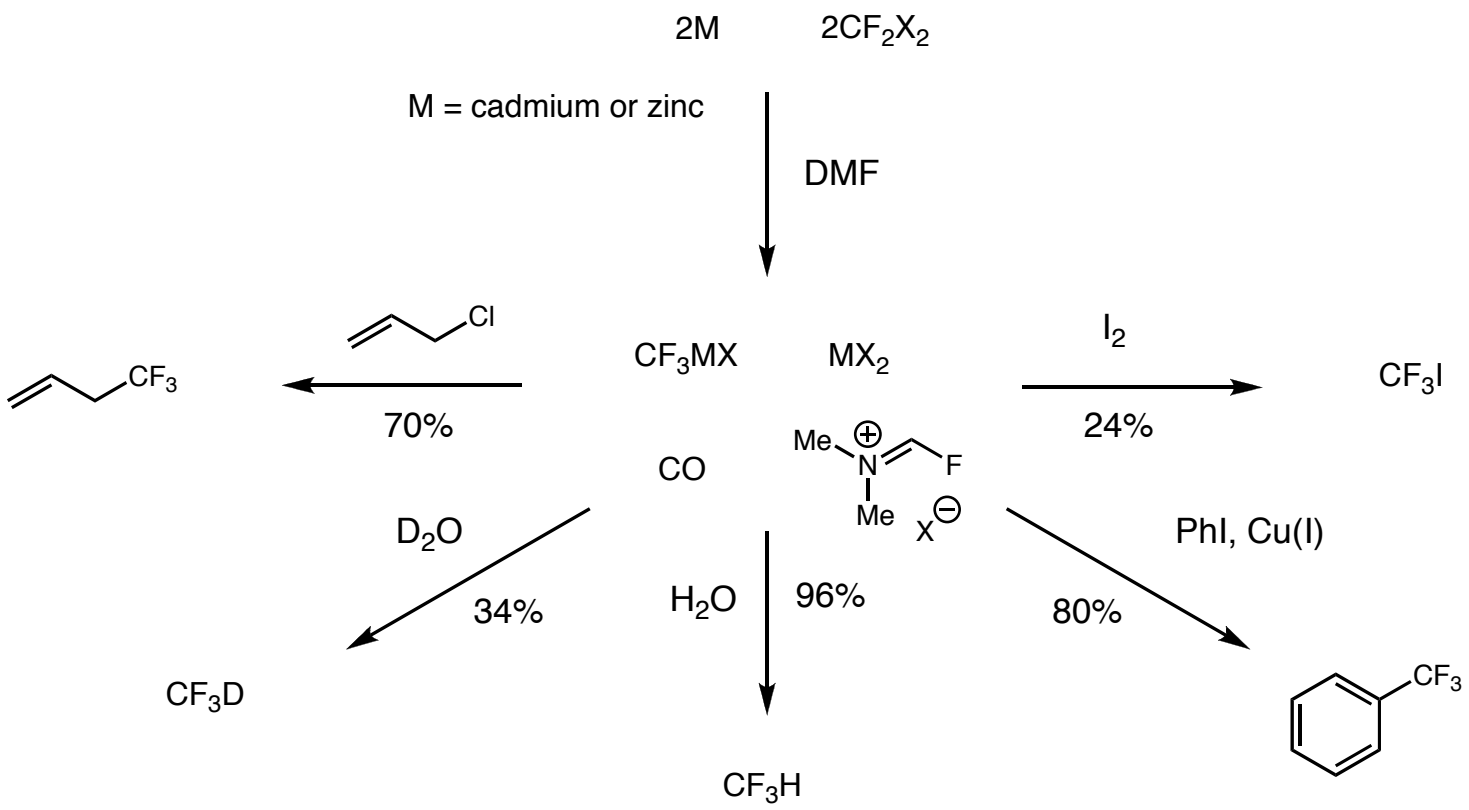
- In order to walk the carbonyl along the chain, a new mechanistic proposal was needed



Carmack, M., *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.
Related thiirene oxides: Zoller, U. *J. Org. Chem.* 1**985**, *50* , 1107–1110.

Burton Trifluoromethyl Organometallics

- Preparation of trifluoromethyl organometallics via reduction of CF_2X_2



Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014-5015.
Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 832-834.

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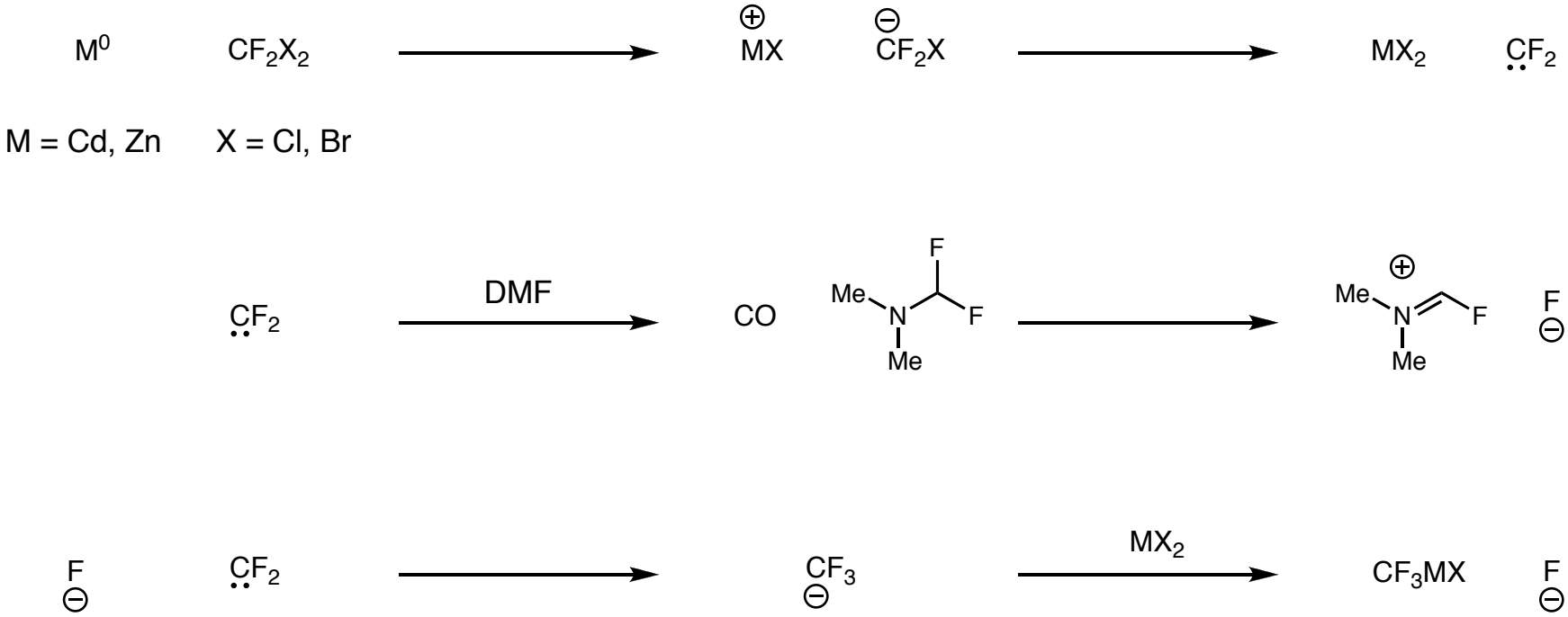

Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014-5015.
Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 832-834.

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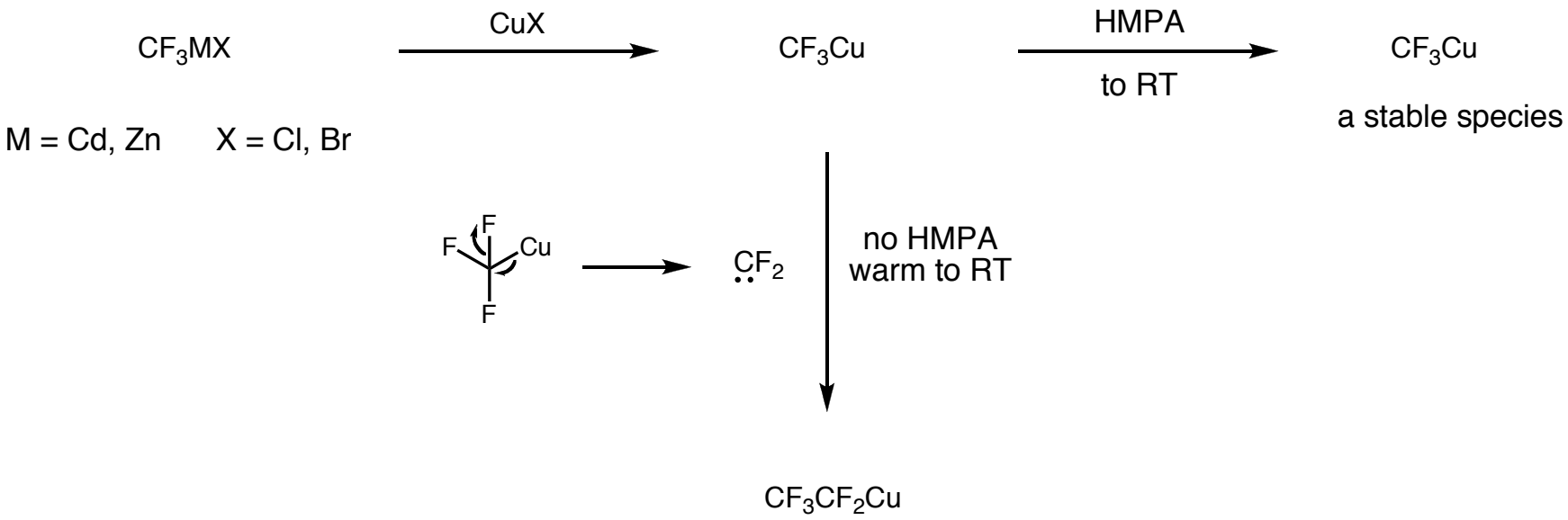
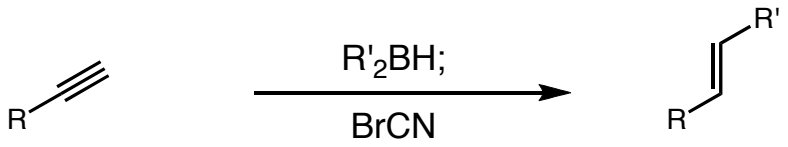


Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014-5015.
Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 832-834.

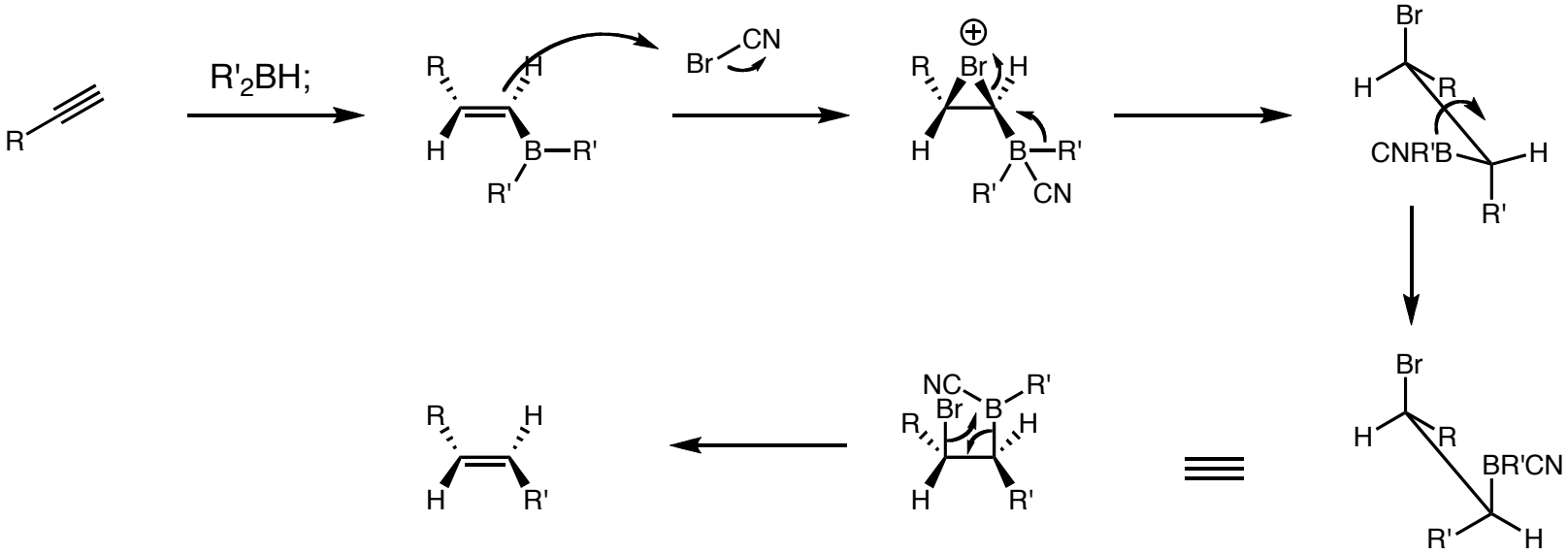
The Zweifel Olefin Synthesis

- Hydroboration of an alkyne leads to a vinyl borane, which can undergo net reductive elimination



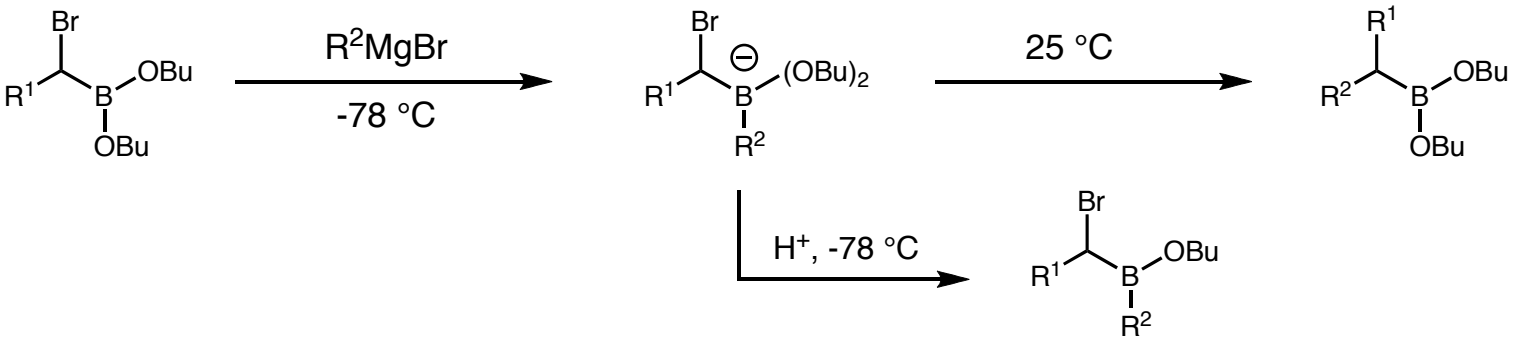
Zweifel, G.; Fisher, R. P.; Snow, J. T.; Whitney, C. C. *J. Am. Chem. Soc.* **1972**, *94*, 6560-6571.

- Hydroboration, alkyl migration and B-X elimination are all stereospecific

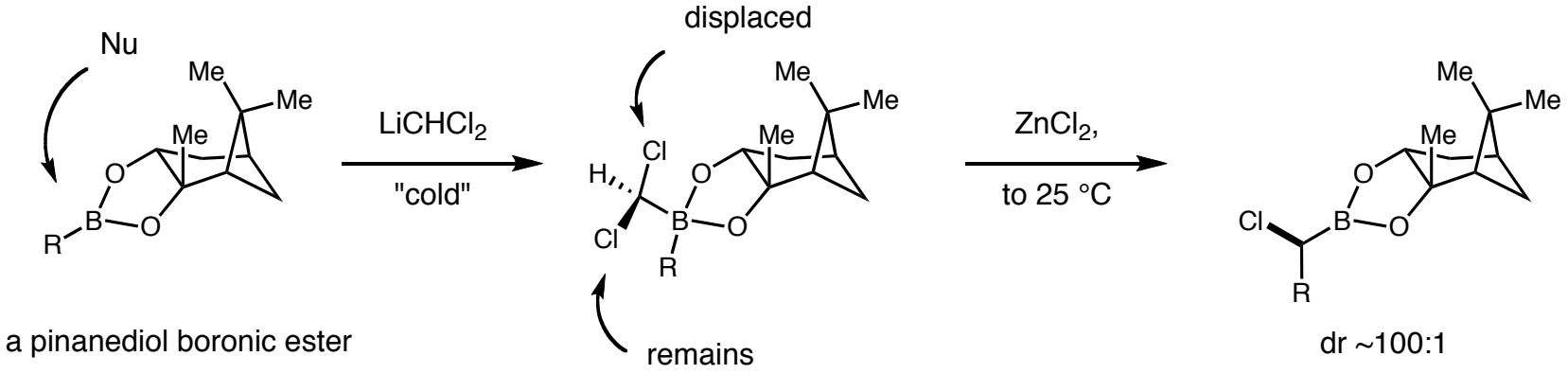


The Matteson Alkylation

- Addition of alkyl lithium and grignard reagents to α-halo boronic esters leads to net displacement



- Very high levels (>1000:1) of diastereoselection can be achieved with chiral boronic esters



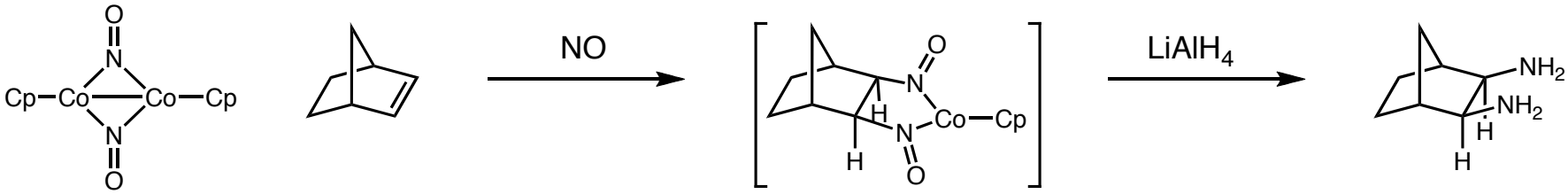
a pinanediol boronic ester

dr ~100:1

Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555-10607.

Bergman Chemistry Involving $(CoCpNO)_2$

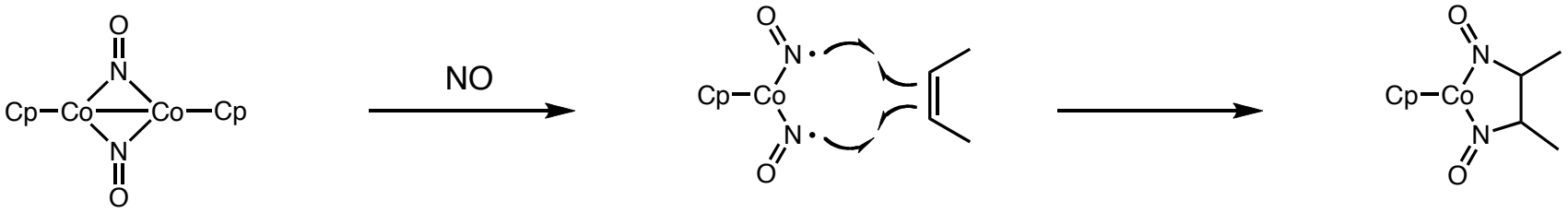
- So much CO chemistry (hydroformylation) is know, why is there so little NO chemistry?



Brunner's dimer

Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5676-5677.
Weiner, W. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 3922-3929.
Becker, P. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 2985-2995.
Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787-796.
Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777-3779.

- The reaction is proposed to proceed via $CpCo(NO)_2$



Brunner's dimer

- An interesting case of a metal's ligands interacting with an olefin, rather than the metal itself (another exmple is osmium tetroxide)

Bergman Chemistry Involving $(CoCpNO)_2$

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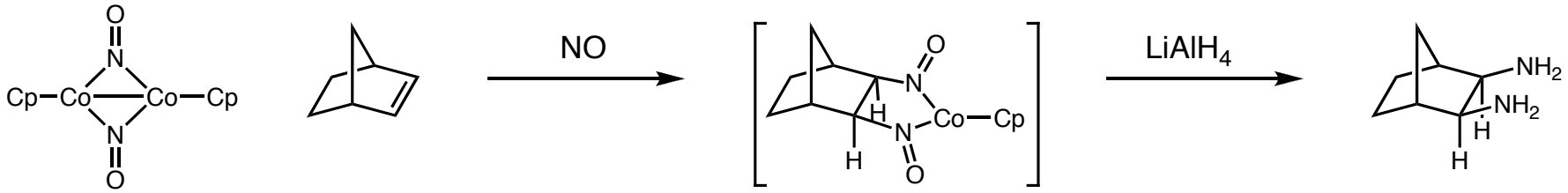

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Weiner, W. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 3922-3929.
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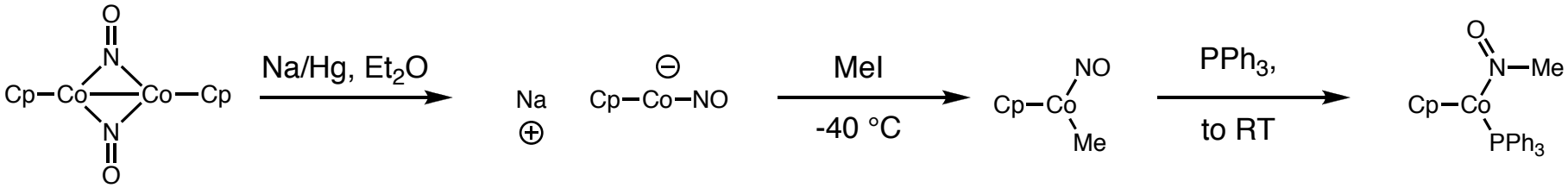
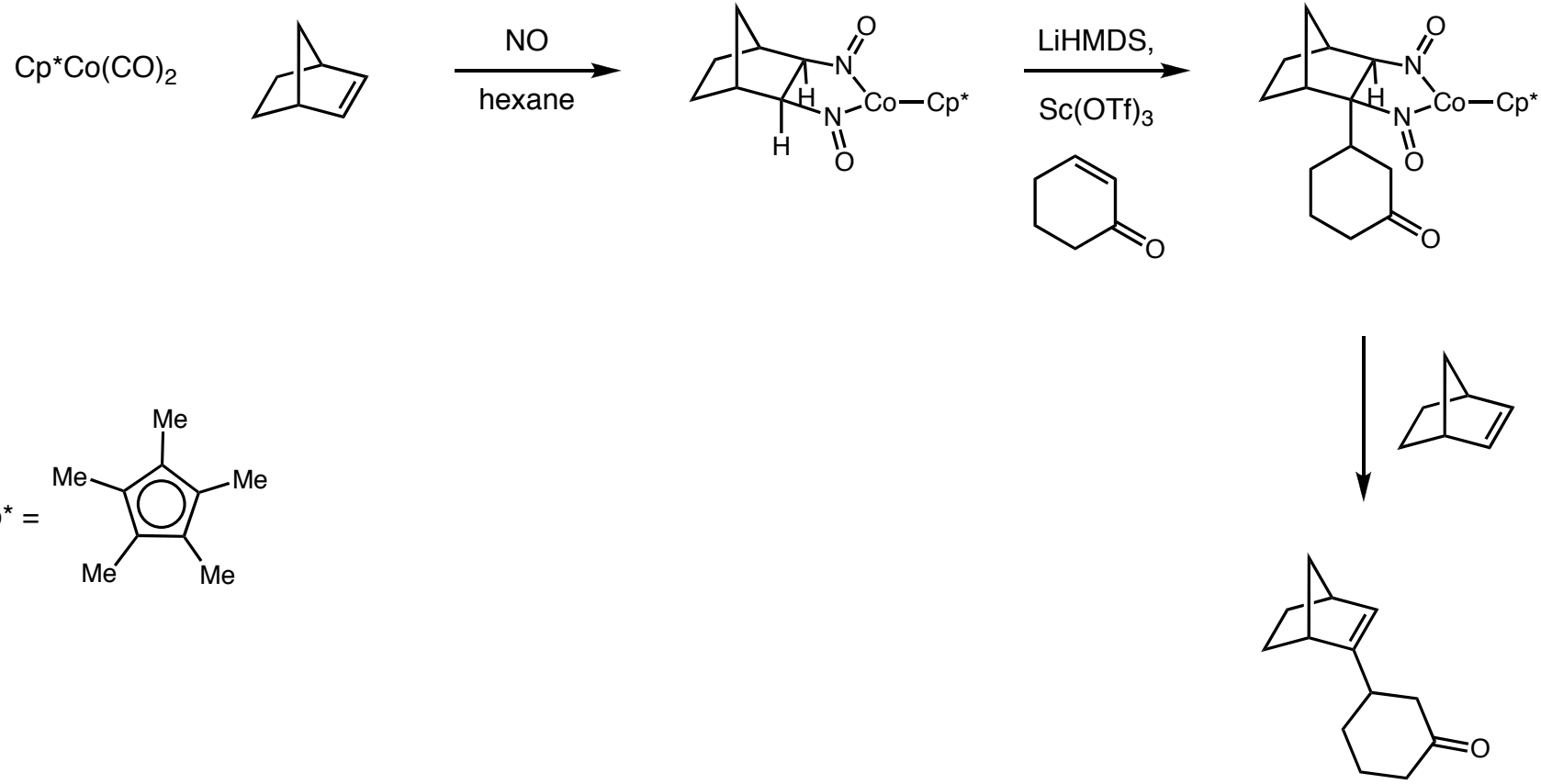
Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787-796.
Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777-3779.

- NO can undergo migratory insertion analogous to CO



Bergman Chemistry Involving $(CoCpNO)_2$

- Recently, the groups of Bergman and Toste looked at some new chemistry involving nitrosoalkanes



Schomaker, J. M.; Boyd, W. C.; Stewart, I. C.; Toste, F. D.; Bergman, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3777-3779.