Radical Reactions (Part 2)

Lecture Notes

Key Reviews:

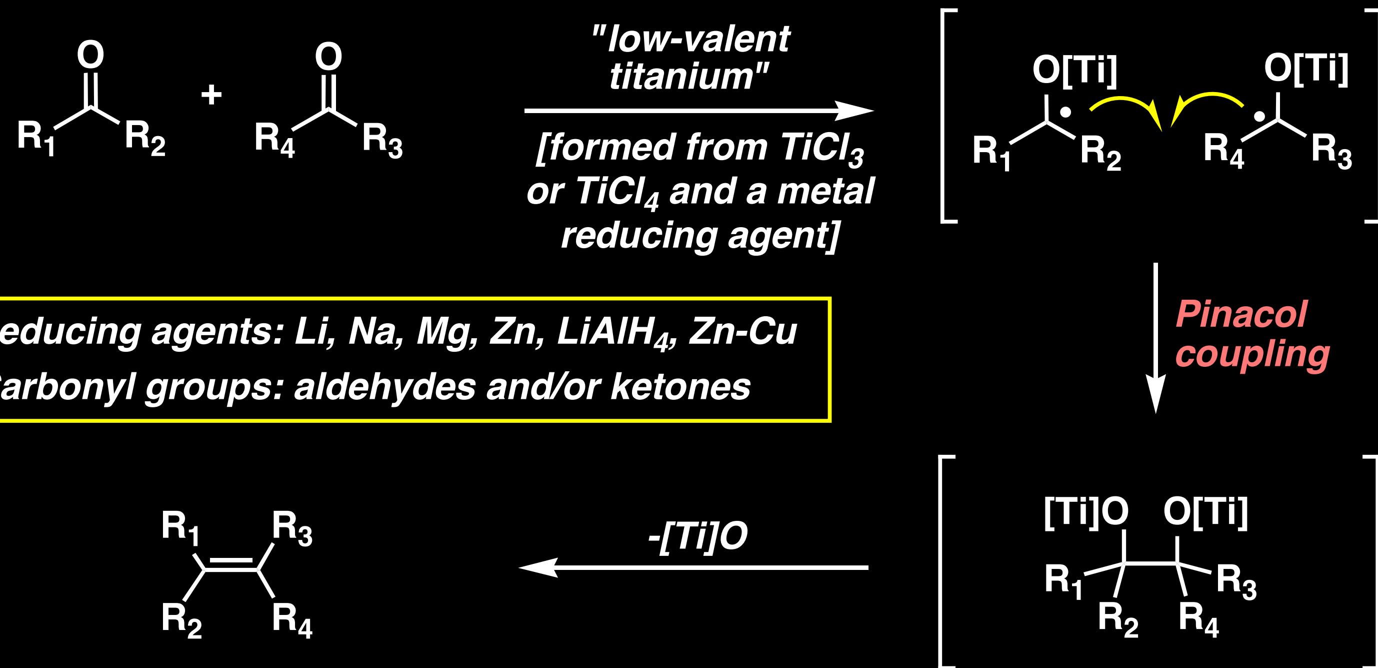
McMurry Reductive Coupling
J. E. McMurry, Chem. Rev. 1989, 89, 1513.

Samarium Diiodide-Mediated Reactions
H. B. Kagan, Tetrahedron 2003, 59, 10351.
A. Krief, A.-M. Laval, Chem. Rev. 1999, 99, 745-777
G. A. Molander, C. R. Harris, Tetrahedron 1998, 54, 3321-3354.

Acyloin Condensation
J. J. Bloomfield and co-workers, Org. React. 1976, 23, 259.

Dissolving Metal Reductions
P. W. Rabideau, Z. Marcinow, Org. React. 1976, 23, 259.

The McMurry Reductive Coupling Reaction: Background and General Considerations



Reducing agents: Li, Na, Mg, Zn, $LiAlH_4$, Zn-Cu

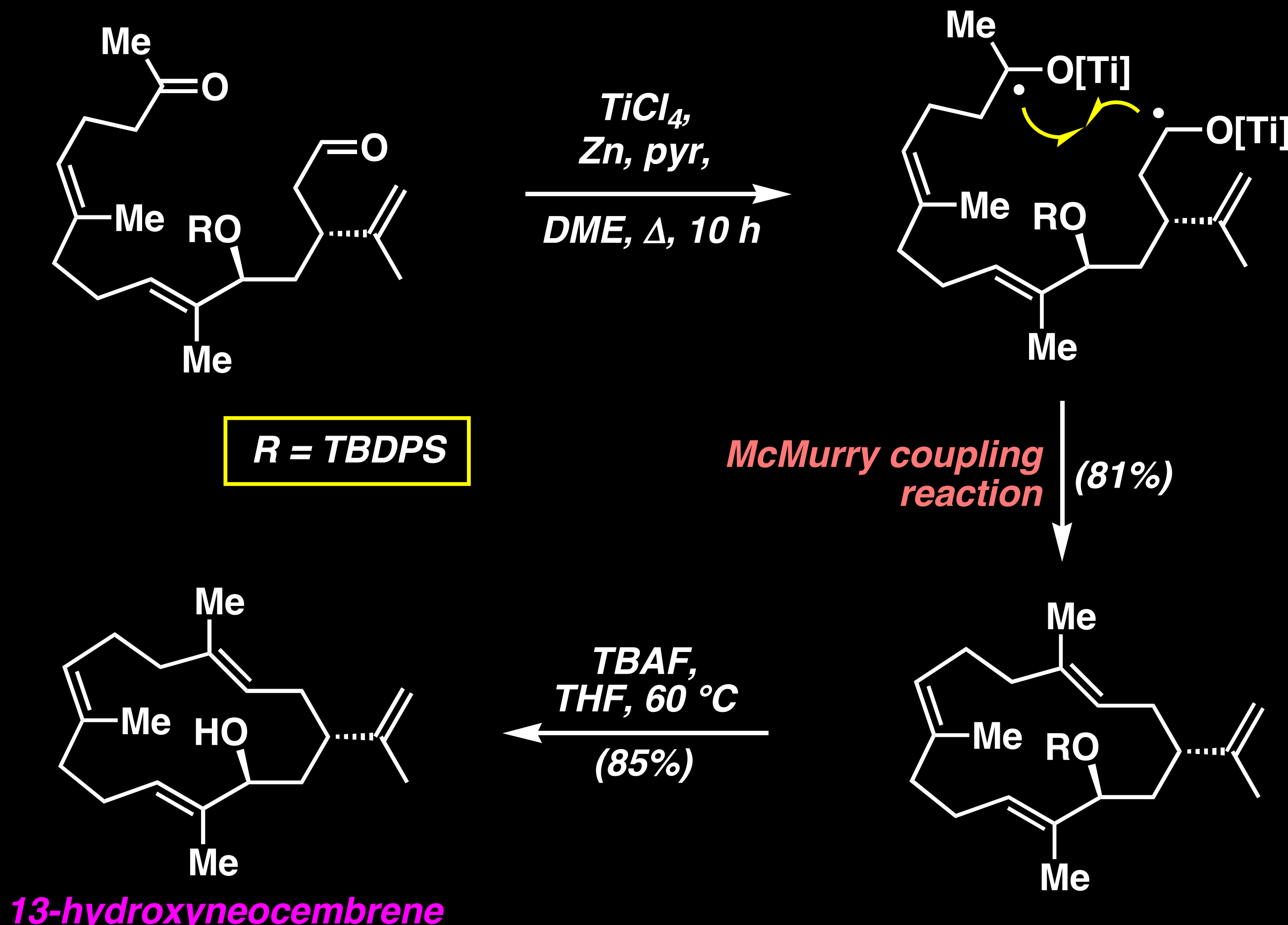
Carbonyl groups: aldehydes and/or ketones

Exact mechanism is unknown because active reagent not entirely known, but involves two key steps: pinacol coupling and deoxygenation to the alkene

Specific intermediates involved depend on the structure of the carbonyl substrate and the exact reaction conditions, making generalizations difficult and yields hard to reproduce

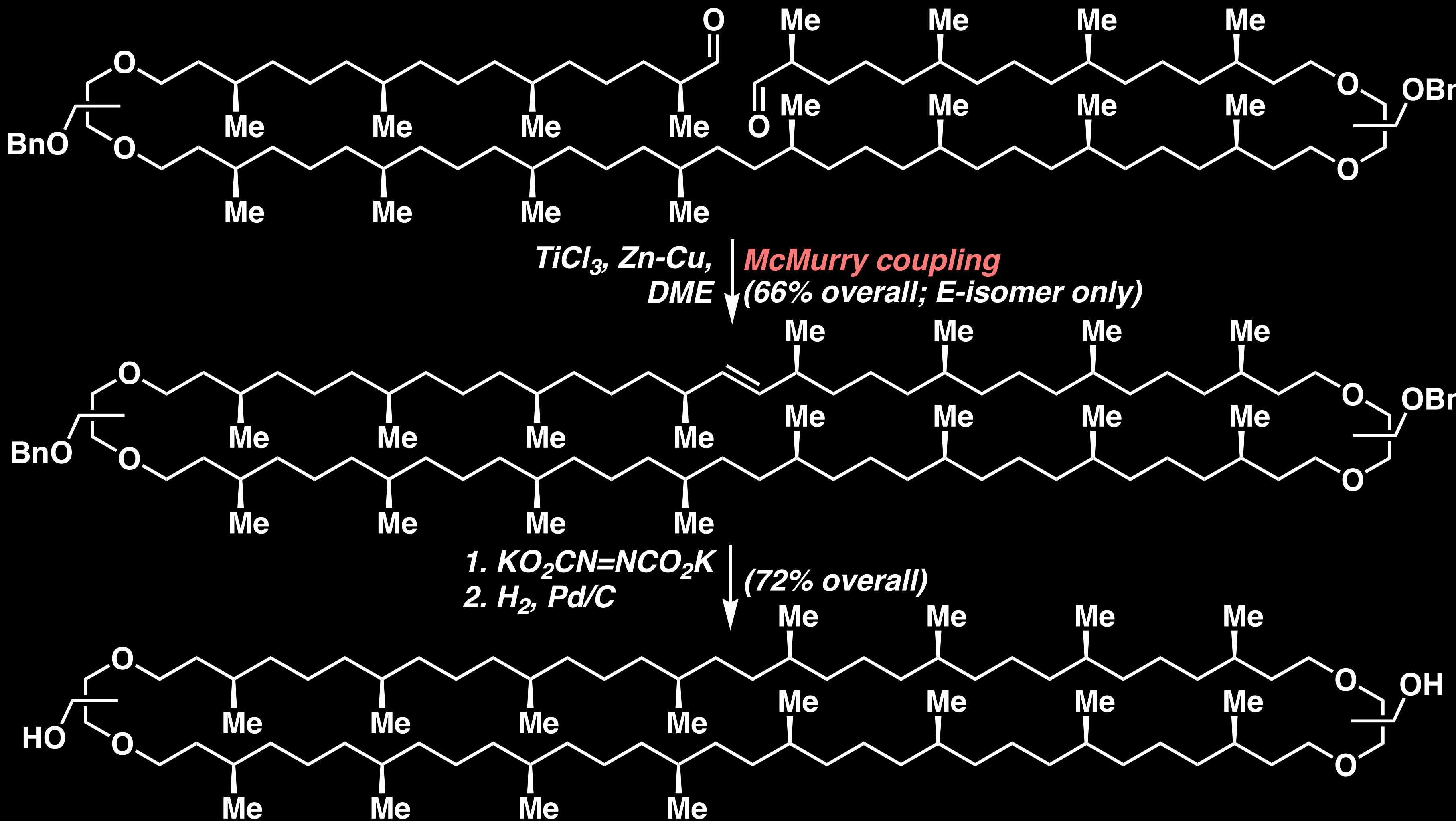
J. E. McMurry, M. P. Fleming, J. Am. Chem. Soc. 1974, 96, 4708.
For a review, see: J. E. McMurry, Chem. Rev. 1989, 89, 1513.

The McMurry Reductive Coupling Reaction: Applications in Synthesis



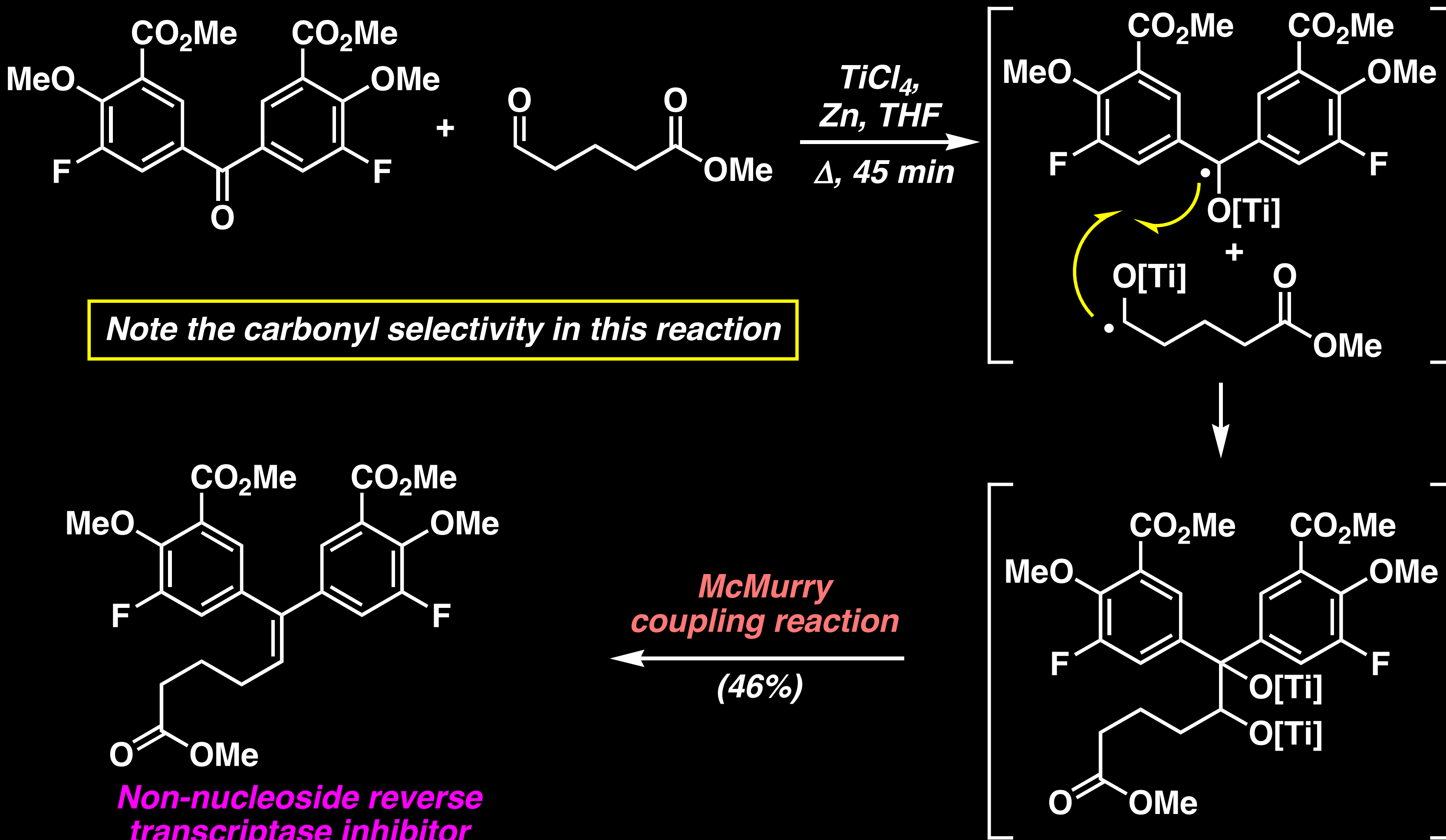
M. Cushman and co-workers, J. Med. Chem. 1999, 42, 4861.

The McMurry Reductive Coupling Reaction: Applications in Synthesis



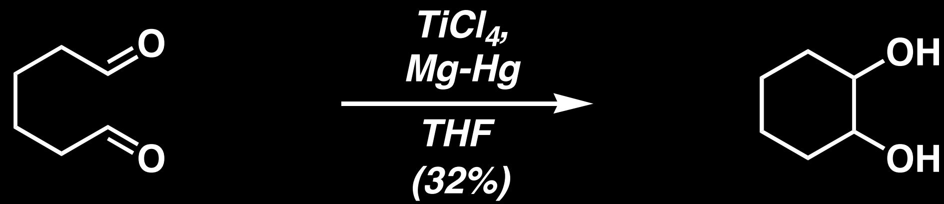
K. Kakinuma and co-workers, J. Org. Chem. 1998, 63, 2689.

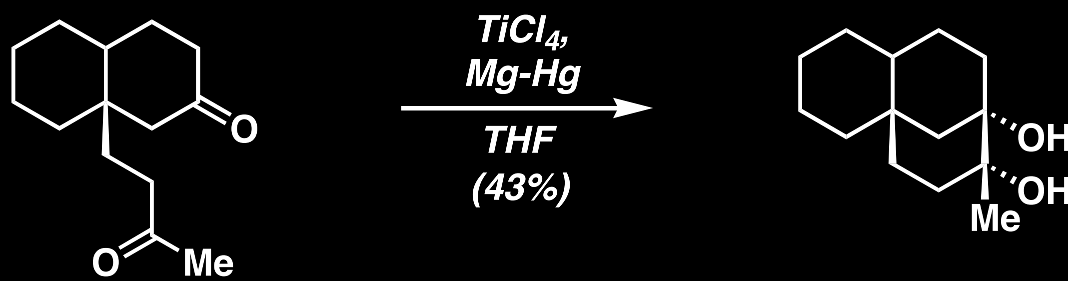
The McMurry Reductive Coupling Reaction: Applications in Synthesis



M. Cushman and co-workers, J. Med. Chem. 1999, 42, 4861.

The McMurry Reductive Coupling Reaction: A Way to Stop at the Diol Product





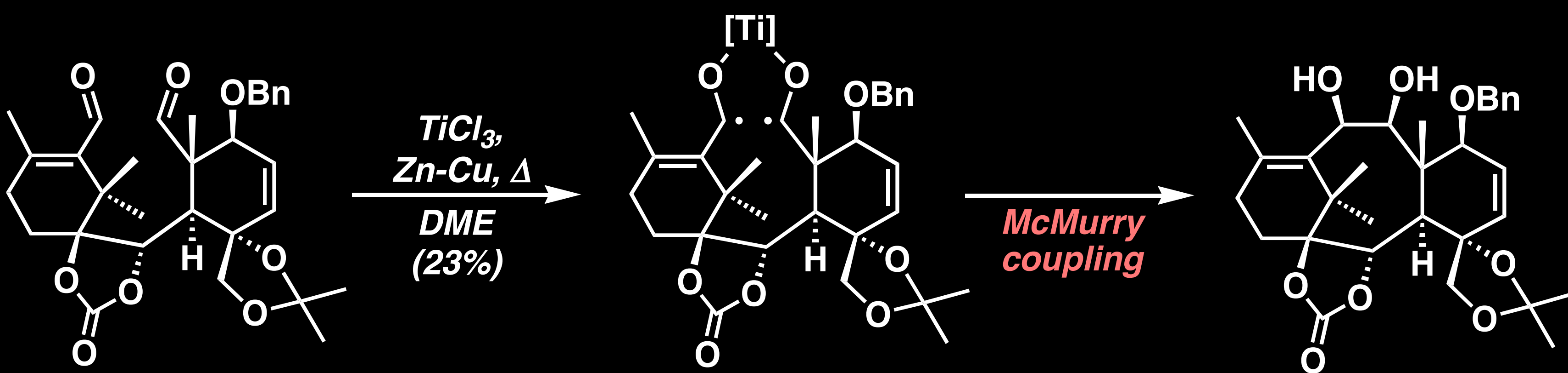
Syn-disposed alcohol results from this reaction;
likely the result of titanium chelation of the reaction intermediates

The only other way to get diol products is in ring systems where the final elimination would impart a great deal of ring strain, an example of which is coming up!

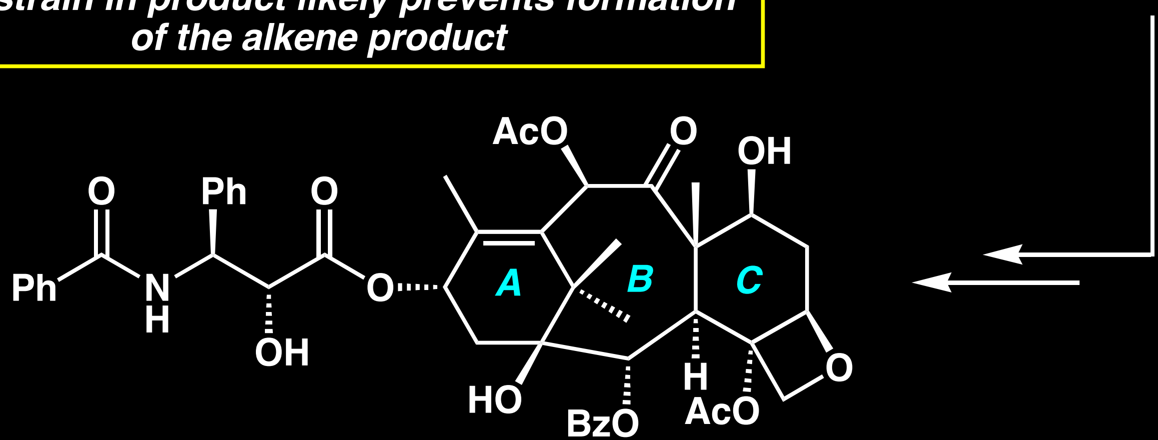
A ring closure of two carbonyls to a diol product is also known as a pinacol cyclization

E. J. Corey, R. D. Danheiser, J. Org. Chem. 1976, 41, 260.

The McMurry Reductive Coupling Reaction: Applications in Synthesis

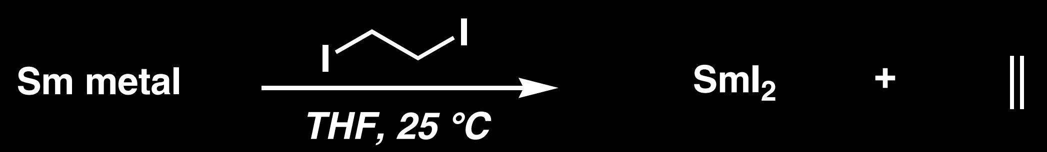


Ring strain in product likely prevents formation of the alkene product



K.C. Nicolaou, Z. Yang, J.J. Liu, H. Ueno, P.G. Nantermet, R.K. Guy, C.F. Claiborne, J. Renaud, E.A. Couladouros, K. Palvannan, E.J. Sorensen, Nature 1994, 367, 630.

SmI_2:
An Incredibly Useful One Electron Reductant



Commercially available, but best synthesized prior to use

Addition of the 1,2-diiodoethane must be slow (often added over 20 minutes) and exactly one equivalent. Otherwise, SmI_3 (a yellow-green solid) is formed instead.
SmI_2 in THF solution is a beautiful deep blue color.

For reviews, see: H. B. Kagan, Tetrahedron 2003, 59, 10351.
G. A. Molander, C. R. Harris, Tetrahedron 1998, 54, 3321.

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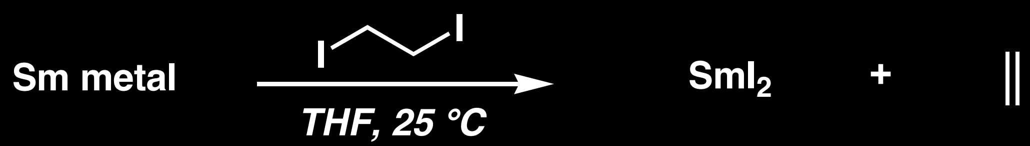

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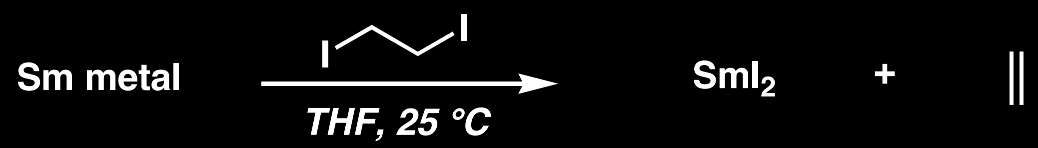


Commercially available, but best synthesized prior to use

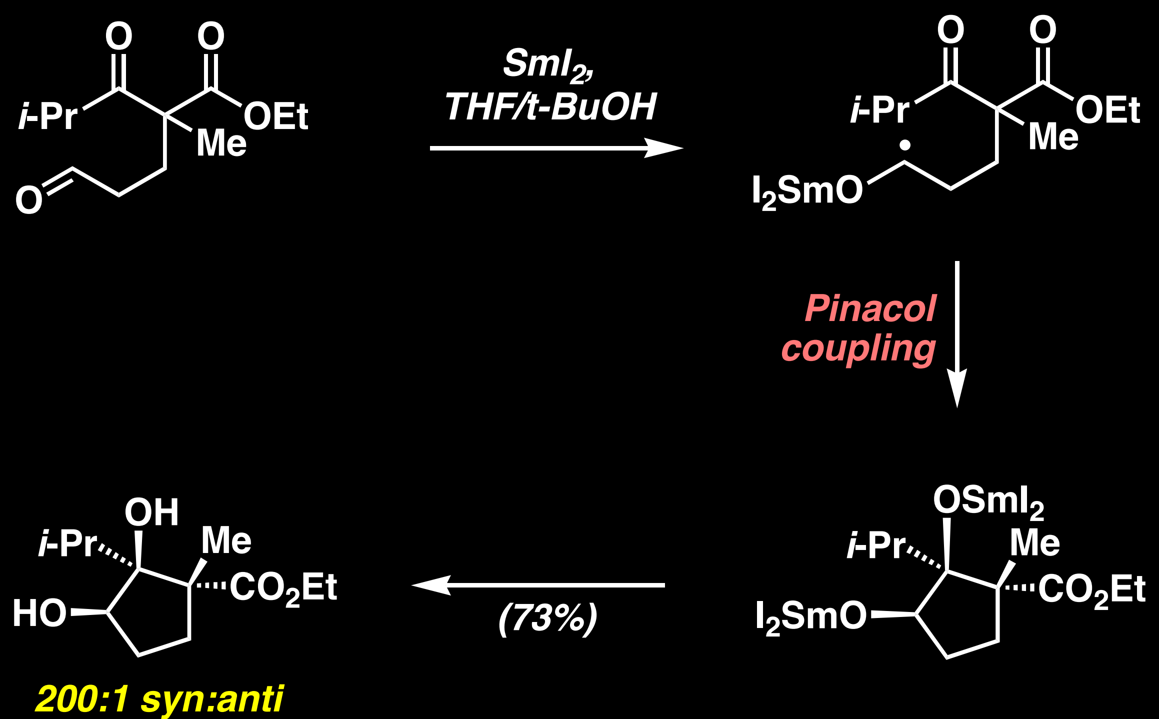
Addition of the 1,2-diiodoethane must be slow (often added over 20 minutes) and exactly one equivalent. Otherwise, SmI_3 (a yellow-green solid) is formed instead. SmI_2 in THF solution is a beautiful deep blue color.

Co-additives can greatly enhance the reducing power of SmI_2, and studies have shown that four equivalents of additive per equivalent of SmI_2 is best.

HMPA = gives a deep purple solution upon complexation
H_2O = gives a blood red solution upon complexation
DMPU = gives a light purple solution upon complexation

For reviews, see: H. B. Kagan, Tetrahedron 2003, 59, 10351.
G. A. Molander, C. R. Harris, Tetrahedron 1998, 54, 3321.

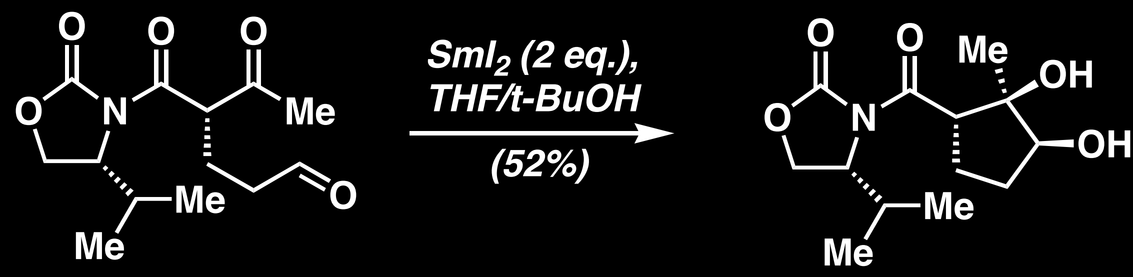
SmI_2:
Picanol Coupling Reactions



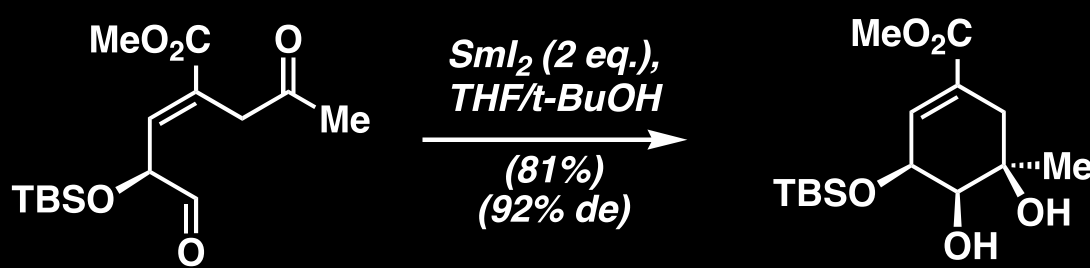
Usually view mechanism as generation of a single ketyl radical, and then attack onto the remaining, and most active, carbonyl group. Samarium complexation with the ketone acceptor for the ketyl radical is the responsible factor for exceedingly high syn diol selectivity.

G. A. Molander and co-workers, J. Org. Chem. 1988, 53, 2132.

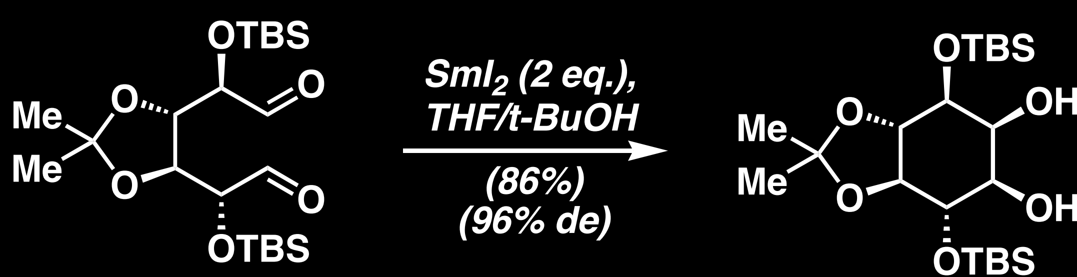
SmI_2:
Picanol Coupling Reactions



J. Org. Chem.
1988, 53, 2132.

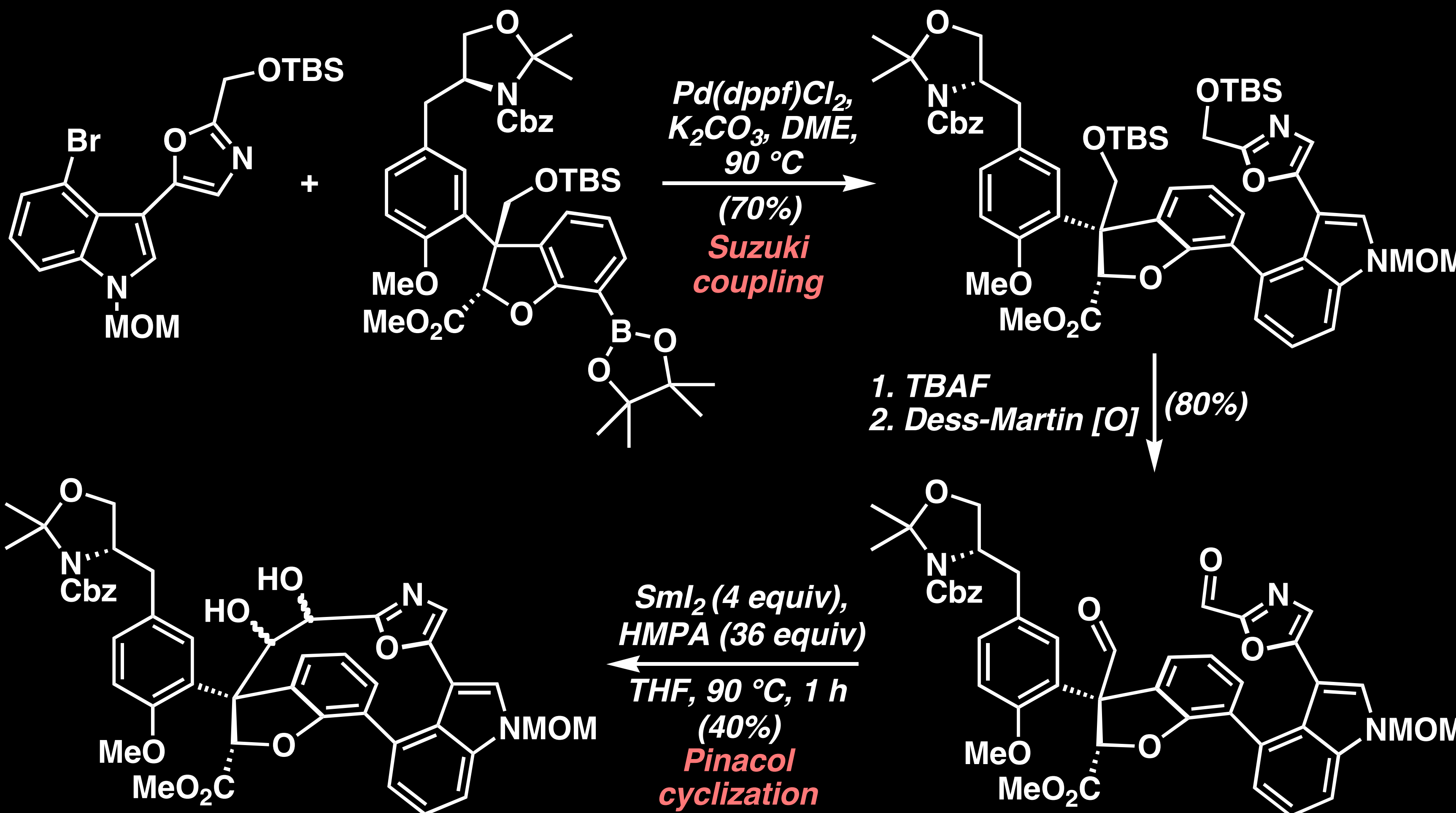


Tetrahedron Lett.
1991, 32, 1125.



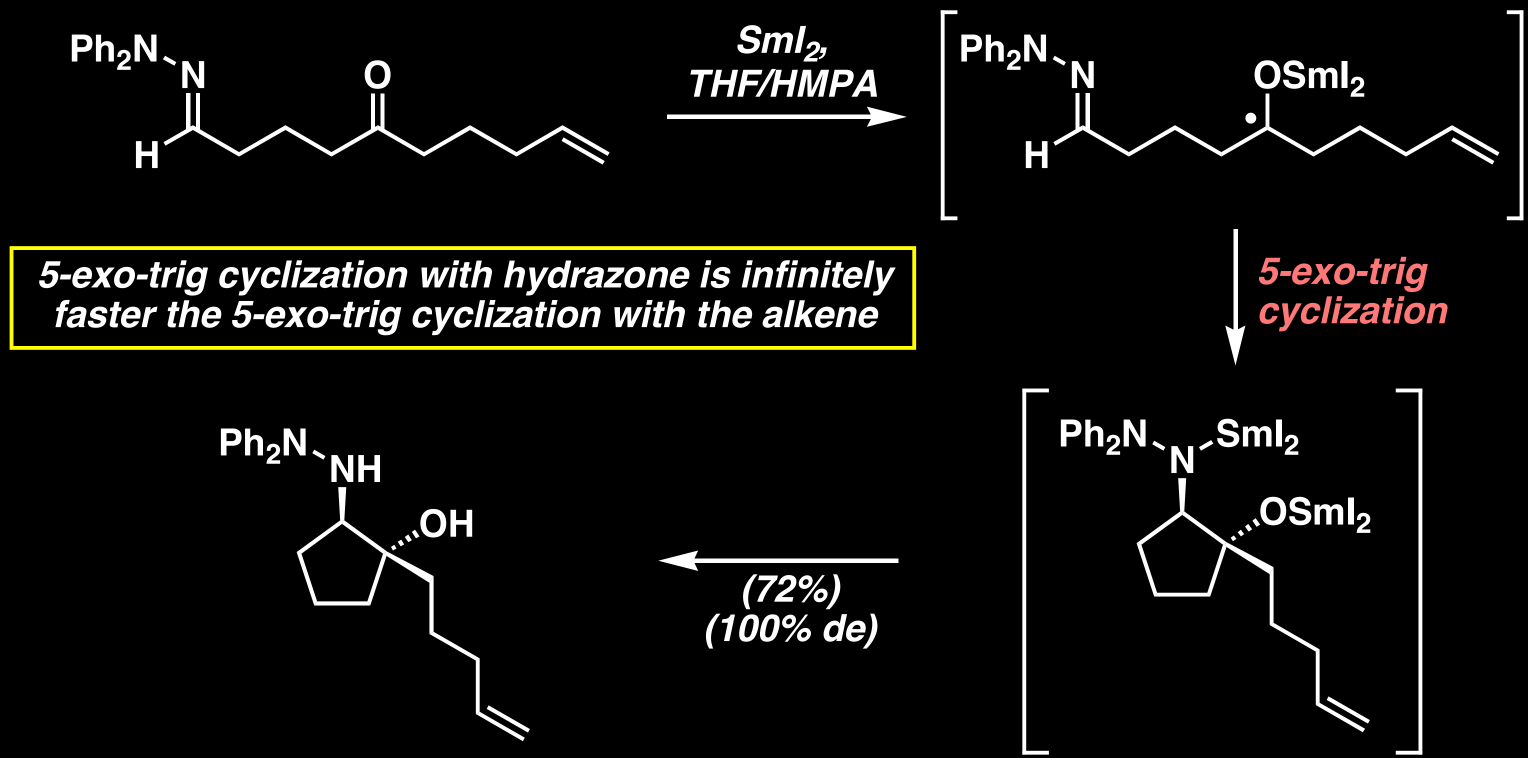
Tetrahedron Lett.
1994, 35, 2969

SmI_2-induced Pinacol Coupling: Application to the Original Structure of Diazonamide A



K. C. Nicolaou, S. A. Snyder, unpublished results

SmI_2:
Hetero Pinacol Coupling Reactions

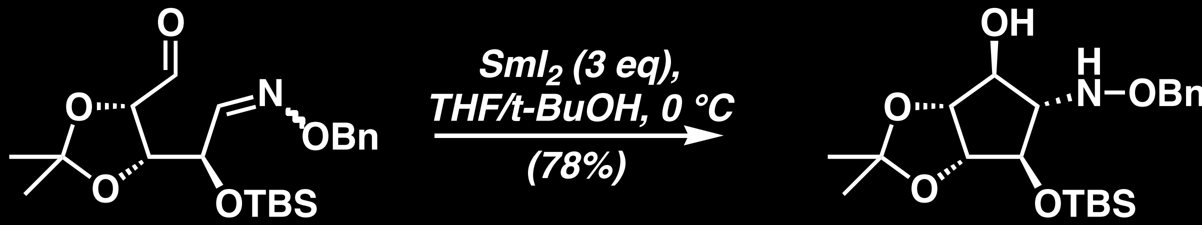


Unlike pinacol couplings, hetero pinacol couplings typically give rise to trans products (in terms of the 1,2-aminoalcohol functionality)

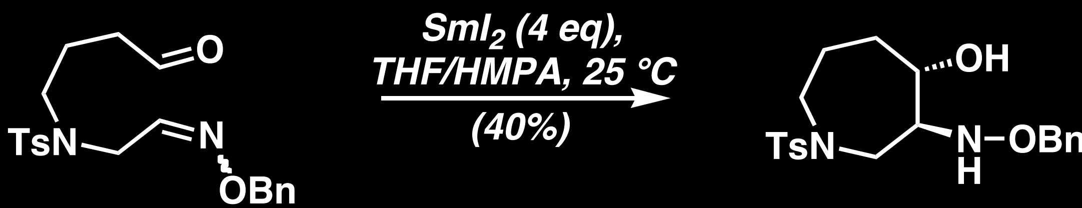
A. G. Fallis and co-workers, J. Am. Chem. Soc. 1994, 116, 7447.
A. G. Fallis and co-workers, J. Org. Chem. 1994, 59, 6514.

Hetero Pinacol Couplings Induced by SmI_2

Intramolecular hetero pinacol couplings:



J.L. Chiara, et al.
J. Org. Chem. 1995
60, 6010-6011.



T. Skrydstrup, et al.
J. Org. Chem. 2000
65, 5382-5390.

For reviews, see: A. Krief, A.-M. Laval, Chem. Rev. 1999, 99, 745-777
G. A. Molander, C. R. Harris, Tetrahedron 1998, 54, 3321-3354.

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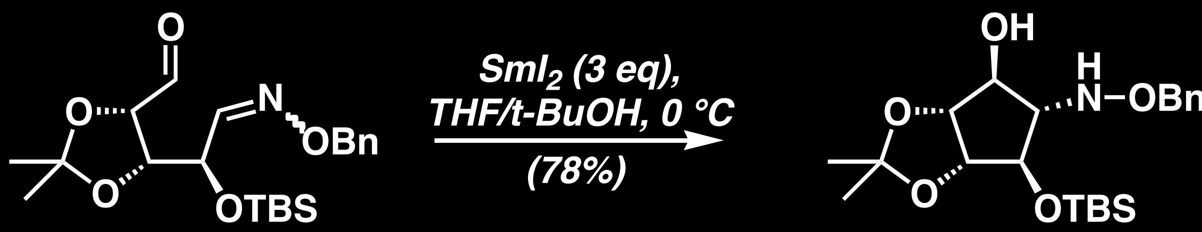

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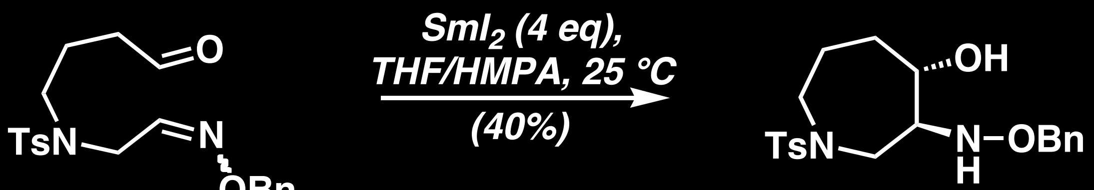
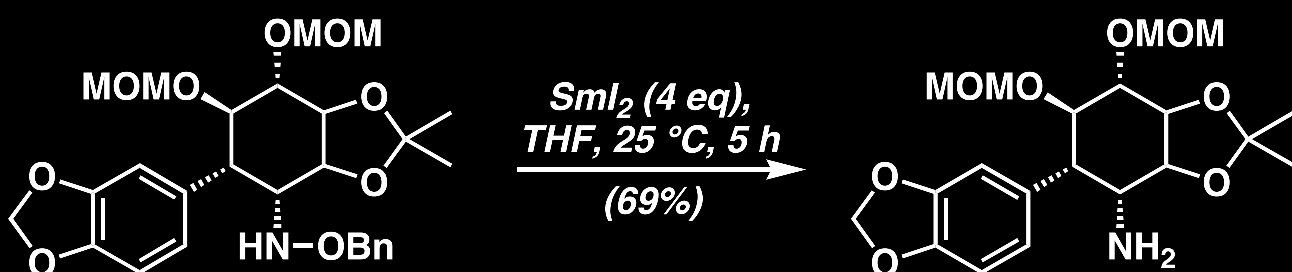


T. Skrydstrup, et al.
J. Org. Chem. 2000
65, 5382-5390.

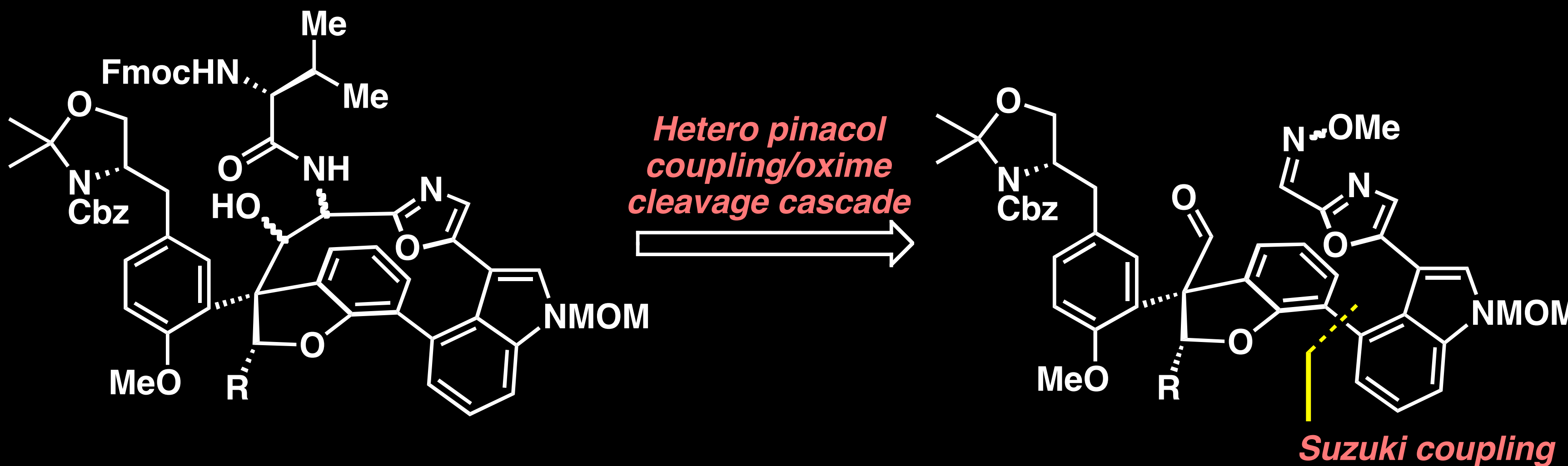
N-O bond cleavage:



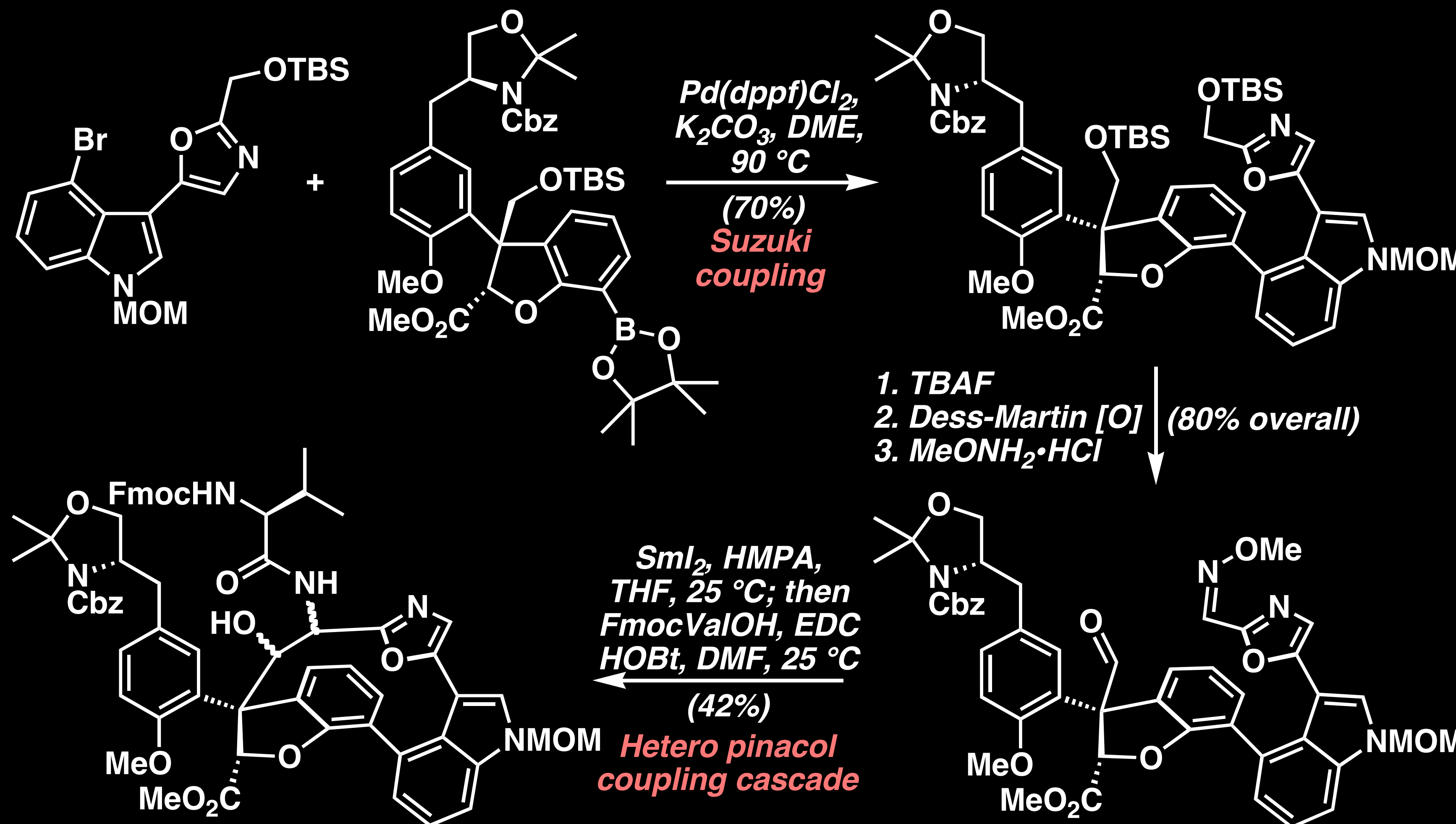
G.E. Keck, et al.
Tetrahedron, 1999
55, 11755-11772.

For reviews, see: A. Krief, A.-M. Laval, Chem. Rev. 1999, 99, 745-777
G. A. Molander, C. R. Harris, Tetrahedron 1998, 54, 3321-3354.

Possible Retrosynthetic Analysis for the Heterocyclic Core of Diazonamide A

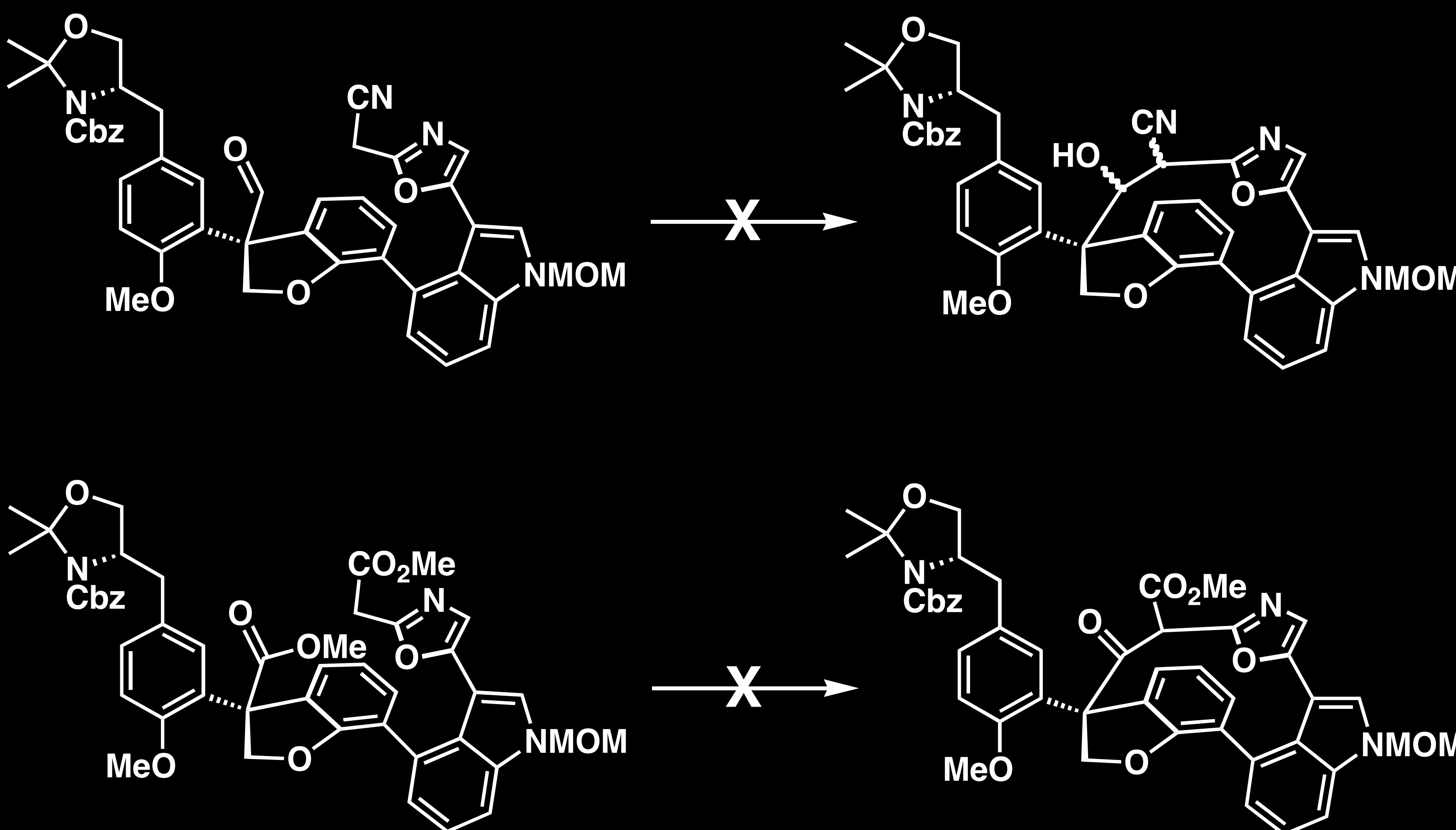


Pinacol Coupling to Generate the Heterocyclic Core of Diazonamide A

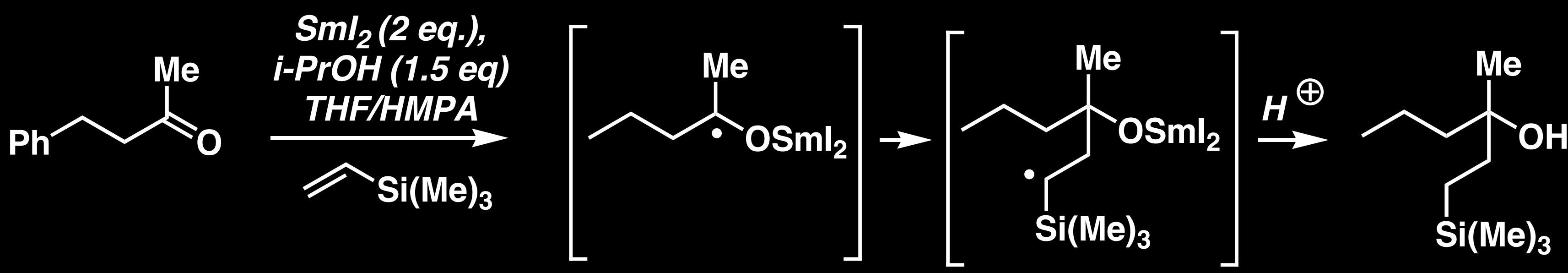


K.C. Nicolaou and co-workers, J. Am. Chem. Soc. 2004, 126, 10174.

Failed Approaches To Generate The Macrocyclic Core of Diazonamide A



SmI_2:
Ketyl-Olefin Coupling Reactions



Must use alkenes that are activated (i.e. electron poor) for intermolecular reactions.

Simple alkenes do not work for these couplings unless in an intramolecular reaction.

K. Inanaga and co-workers, Tetrahedron Lett. 1986, 27, 5763.
K. Inanaga and co-workers, Tetrahedron Lett. 1989, 30, 2837.

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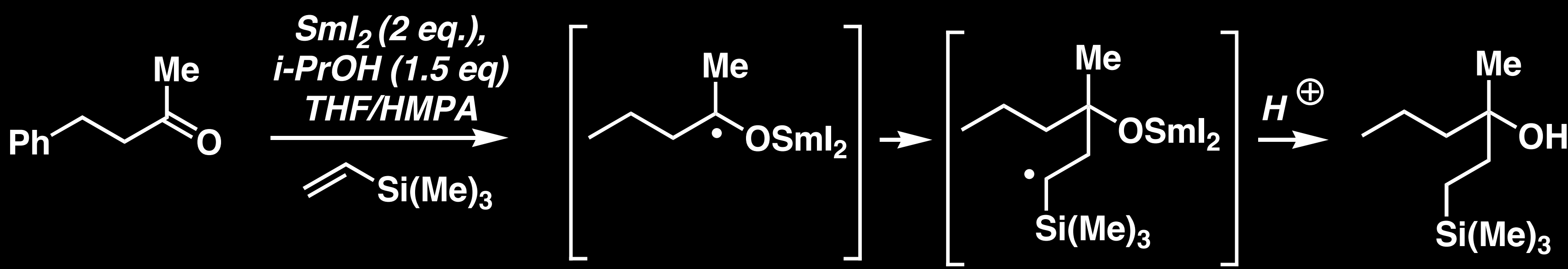

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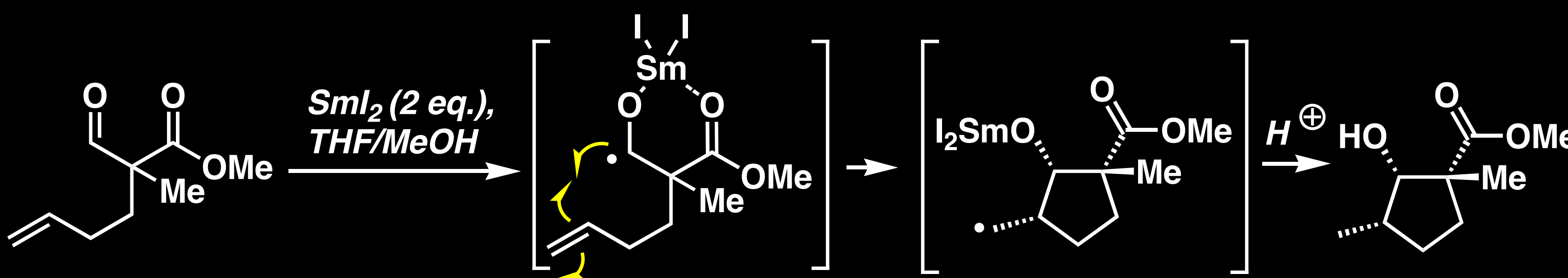

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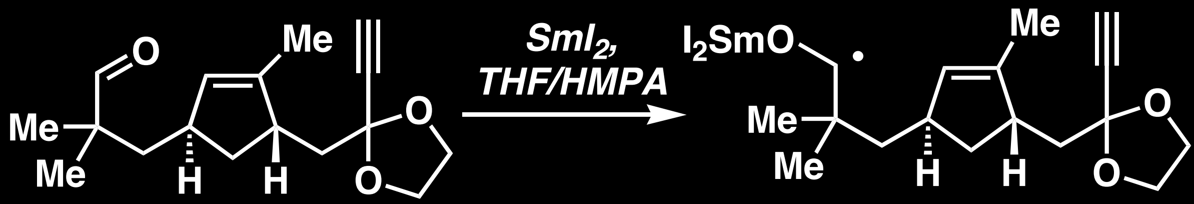

D. P. Curran and co-workers, J. Am. Chem. Soc. 1988, 110, 5064.

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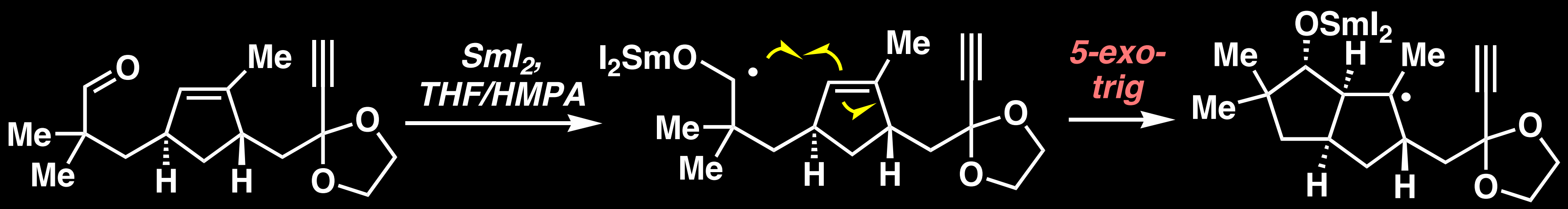

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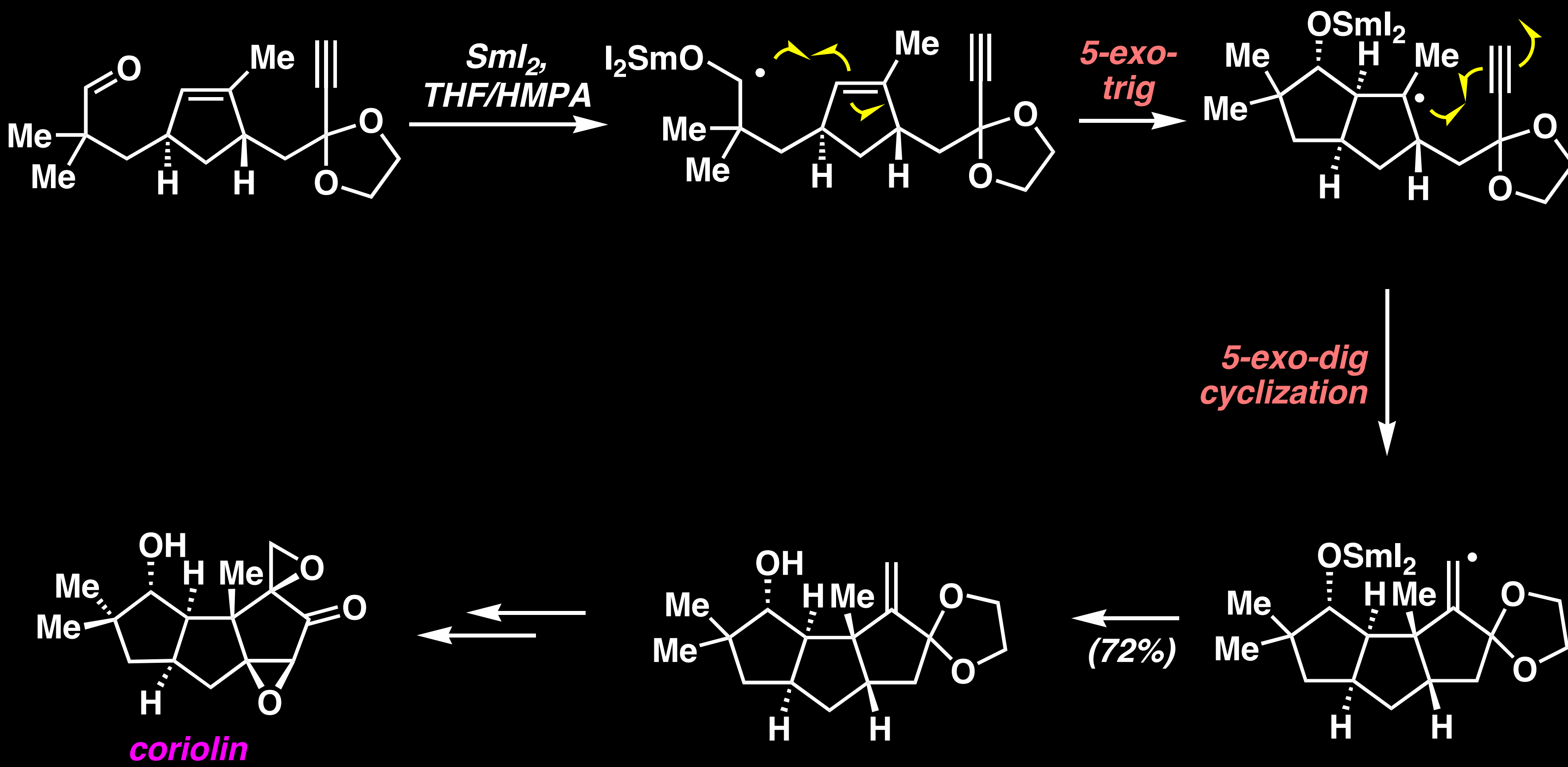

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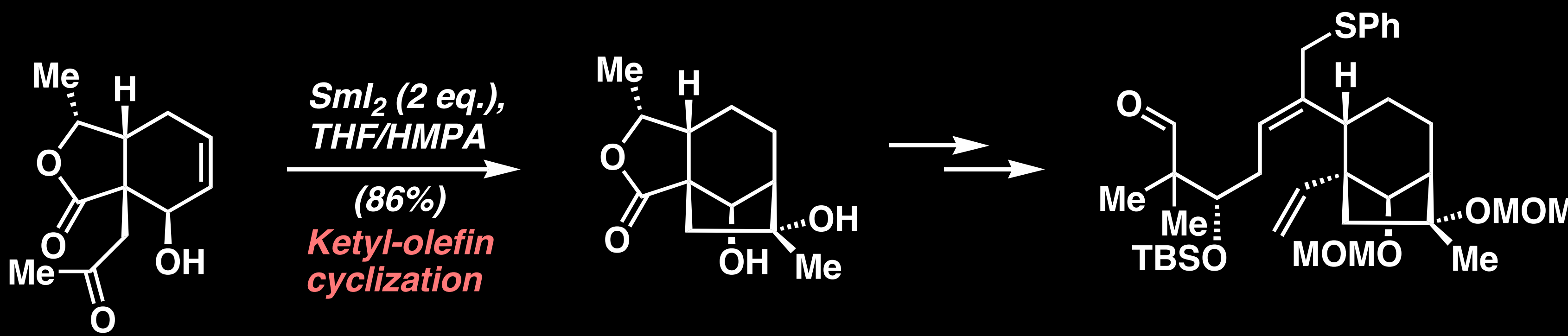
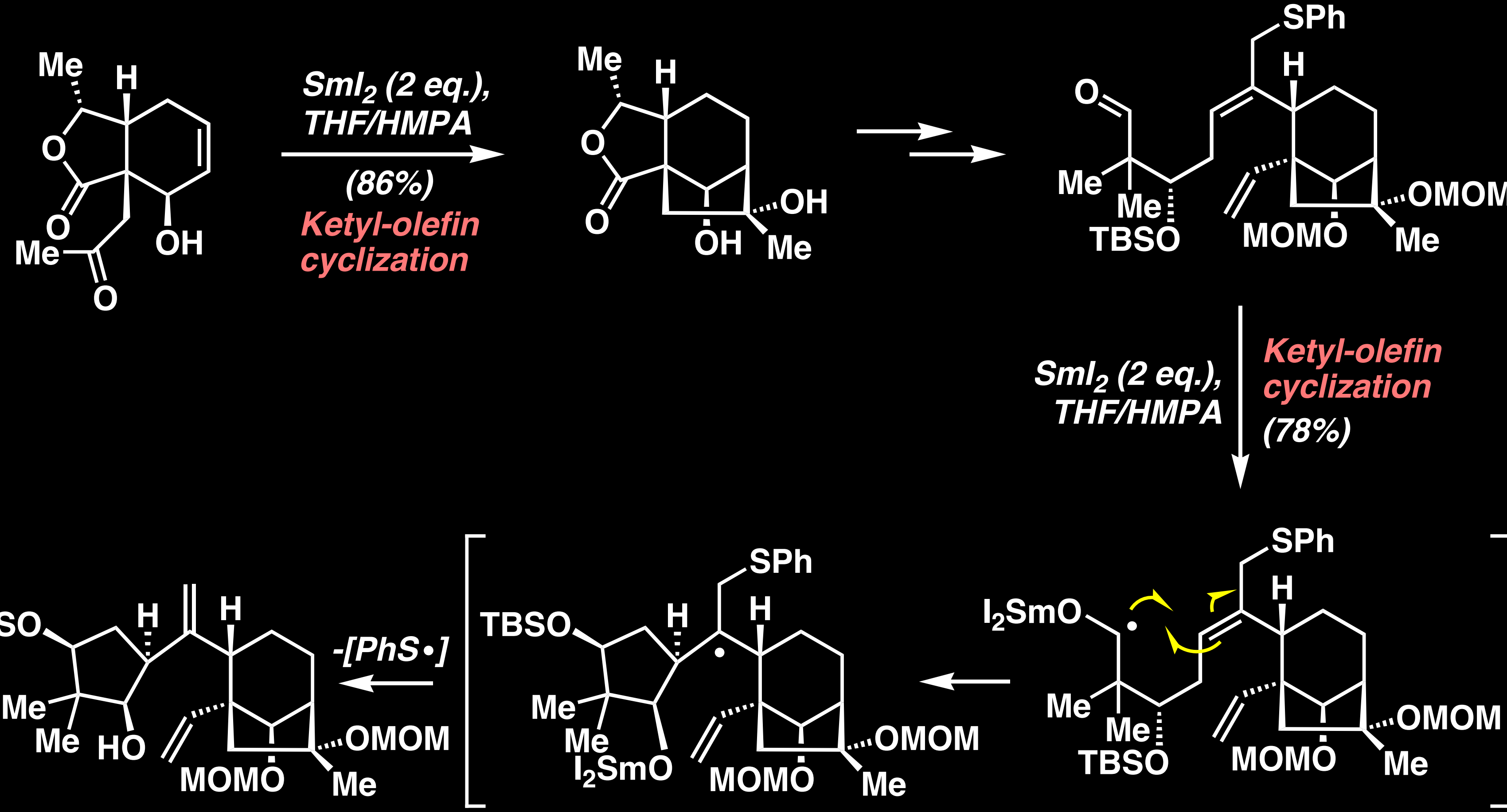
SmI_2: Applications in Synthesis



T. Shirahama and co-workers, J. Org. Chem. 1994, 59, 5532.

SmI_2: Applications in Synthesis



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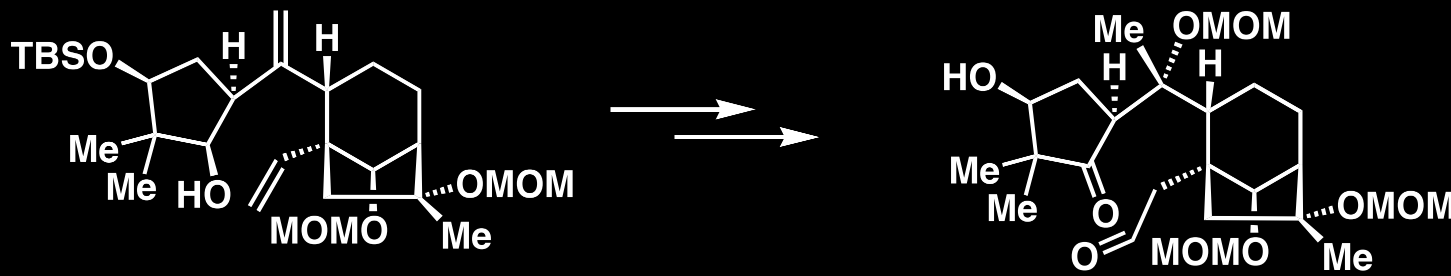

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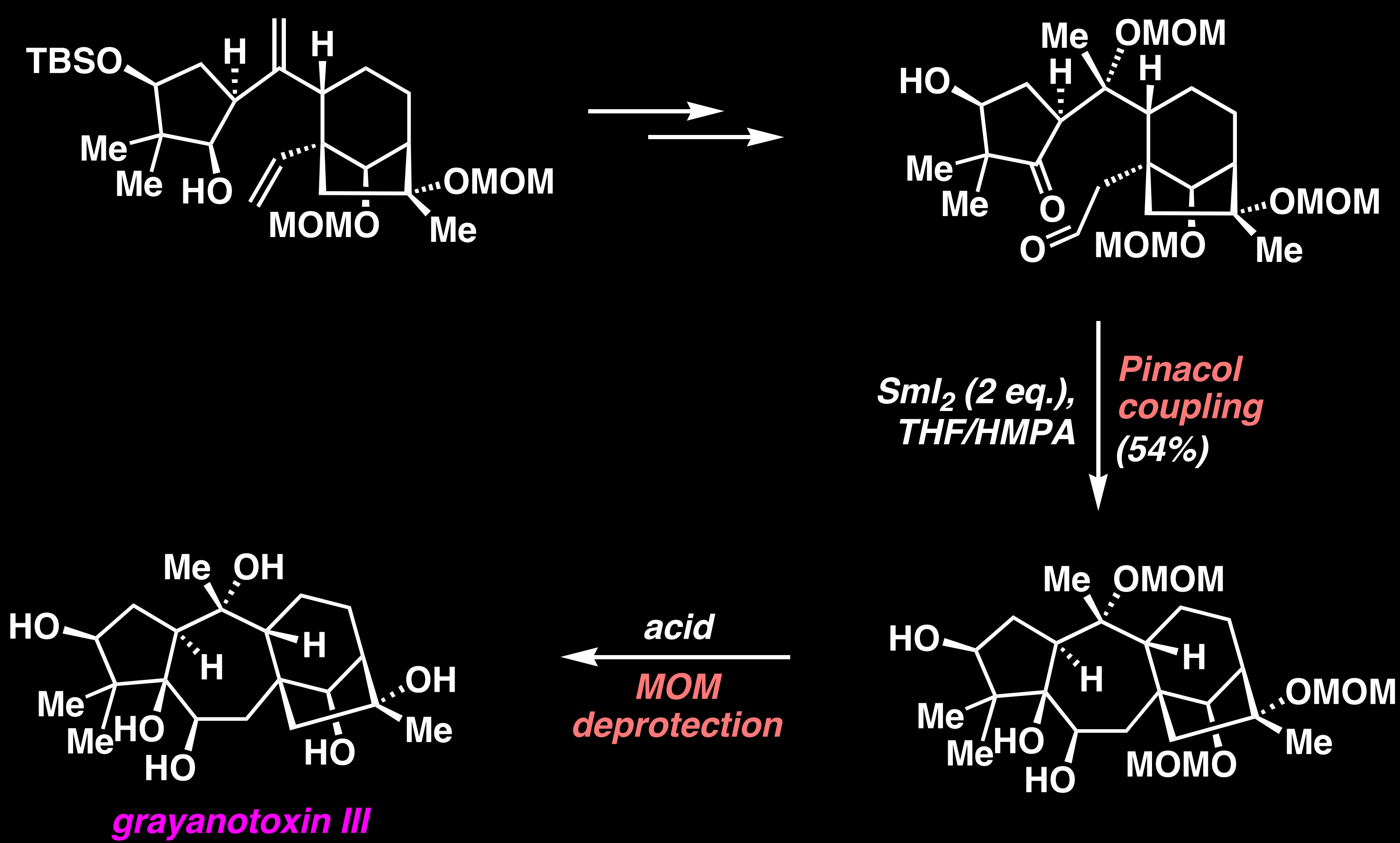

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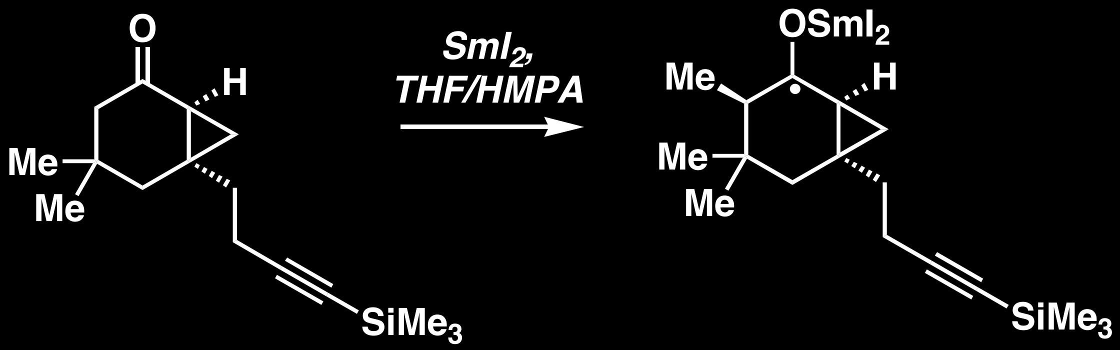

R. Motherwell and co-workers, Tetrahedron Lett. 1991, 32, 6649.

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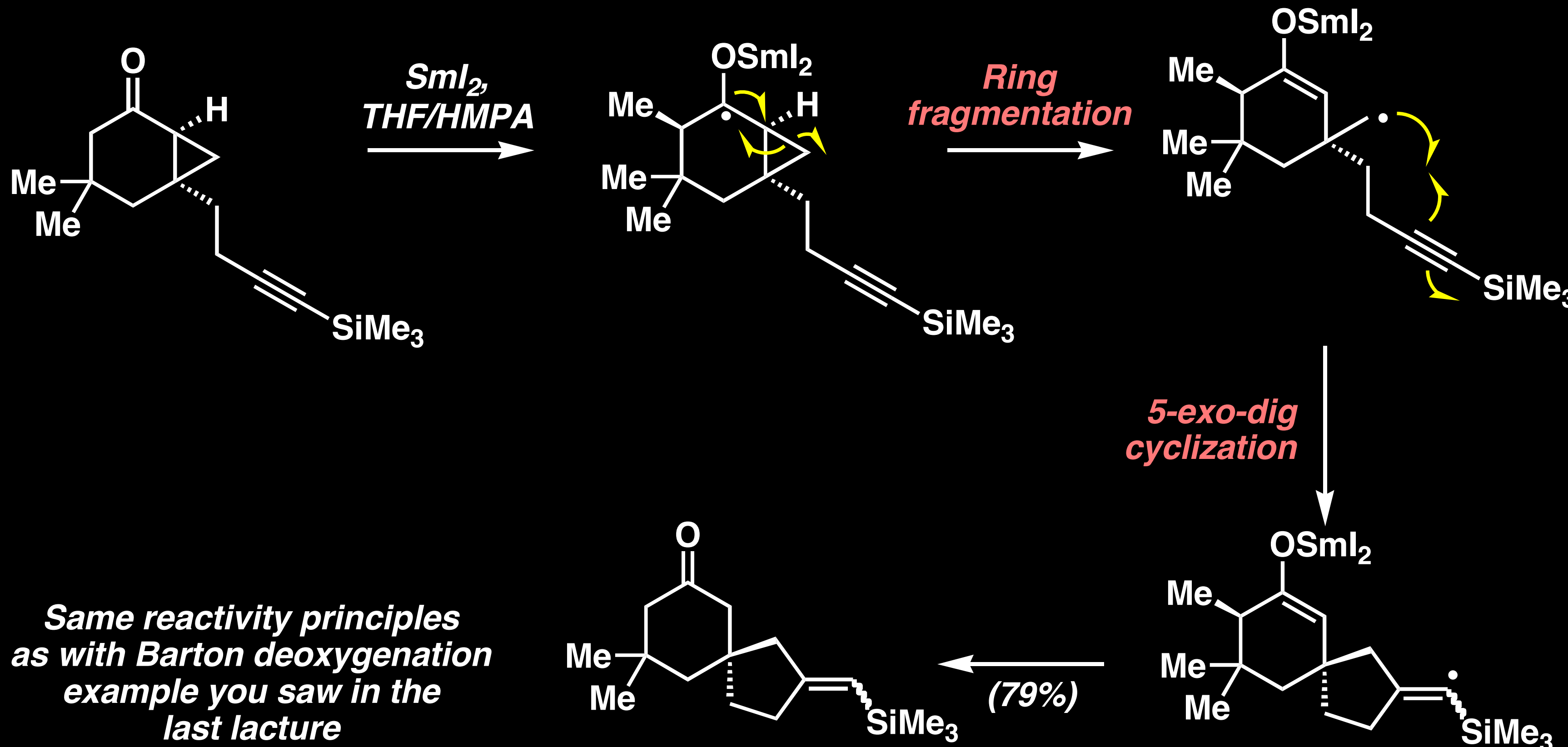
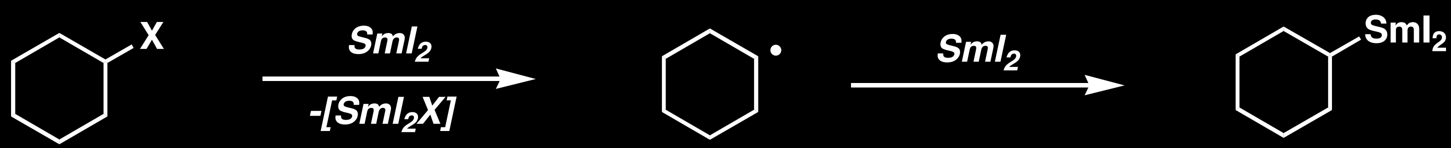


Same reactivity principles as with Barton deoxygenation example you saw in the last lacture

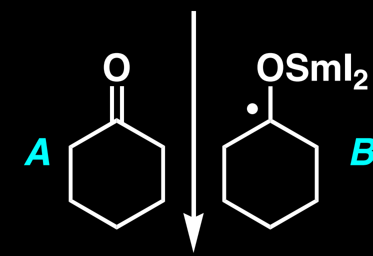
R. Motherwell and co-workers, Tetrahedron Lett. 1991, 32, 6649.

The Kagan-Molander SmI_2-Mediated Coupling Reaction: Background and General Considerations

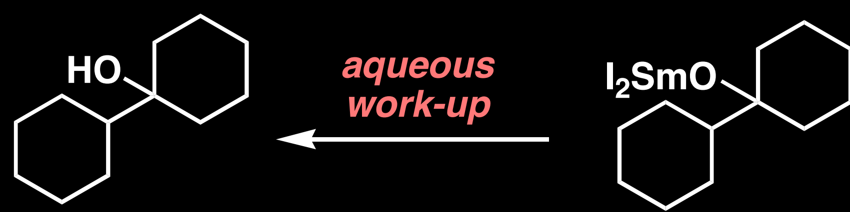


***A**: Add ketone to preformed organosamarium intermediate [samarium Grignard conditions]*

***B**: Ketone in same pot with halide when SmI_2 added [samarium Reformatsky conditions]*



Works well with most halides; exceptions are aryl, vinyl, and tertiary halides.

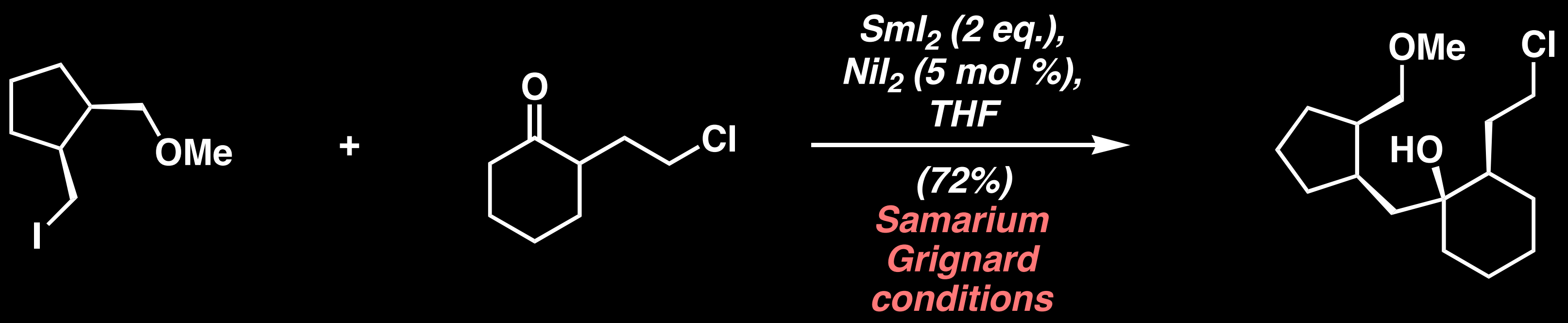


Reactions rates can be greatly accelerated by the addition of Ni(II) or Fe(III) salts.

Addition of HMPA or DMPU as co-solvent to enhance the reducing power of SmI_2 usually helps.

For a review, see: G. A. Molander, C. R. Harris, Chem. Rev. 1996, 96, 307.

The Kagan-Molander SmI_2-Mediated Coupling Reaction: Applications in Synthesis



G. A. Molander and co-workers, Org. Lett. 2001, 3, 2257.

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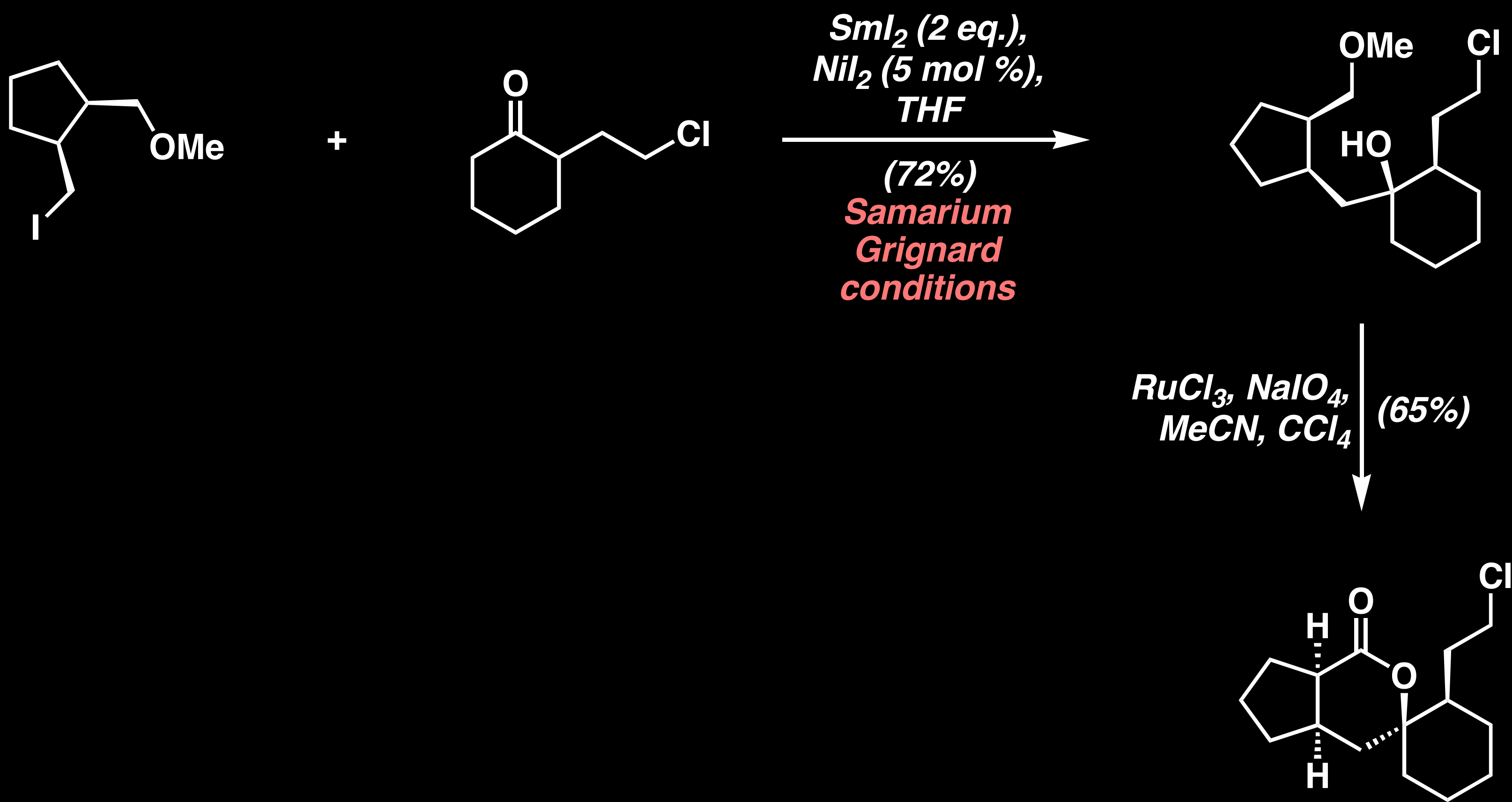

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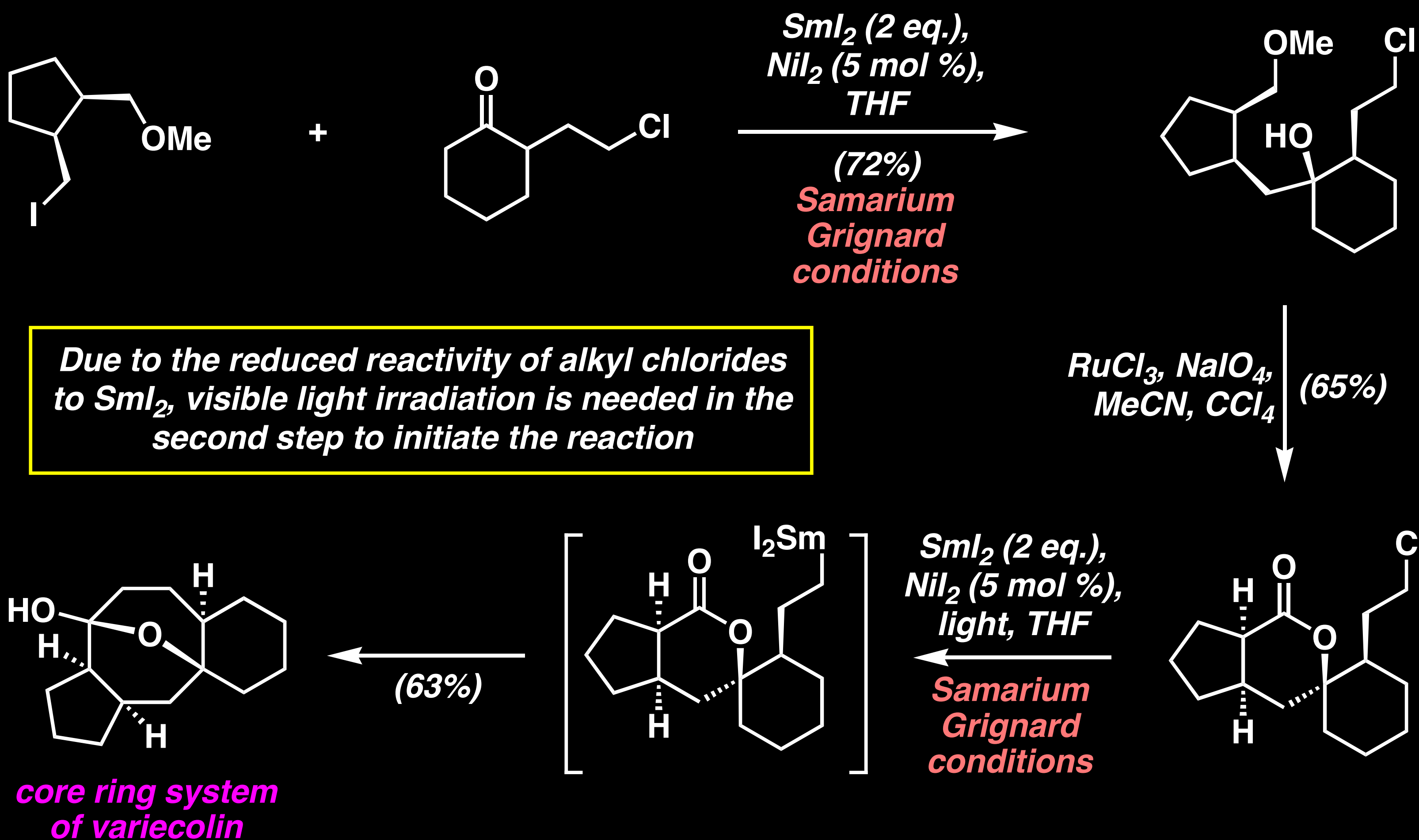

G. A. Molander and co-workers, Org. Lett. 2001, 3, 2257.

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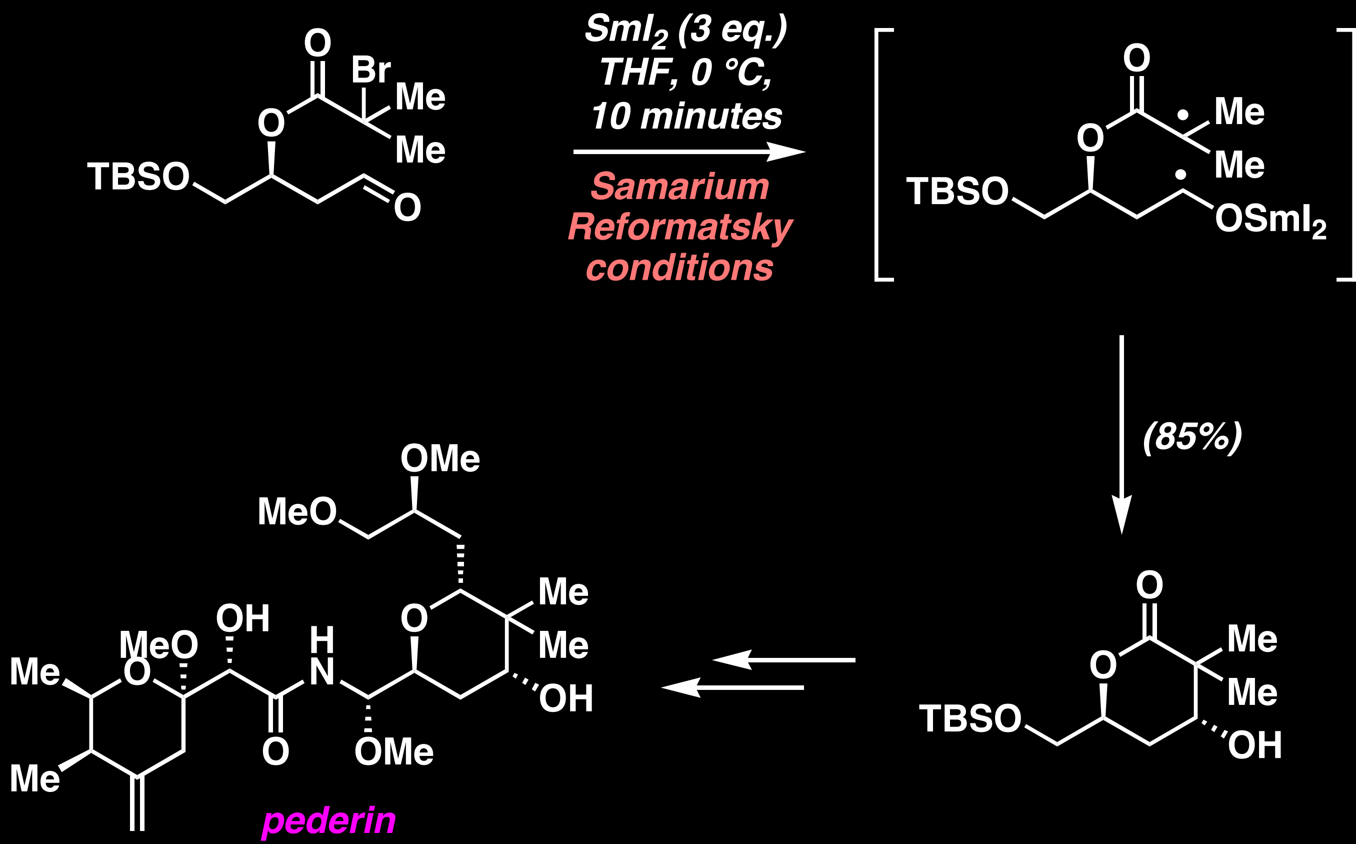
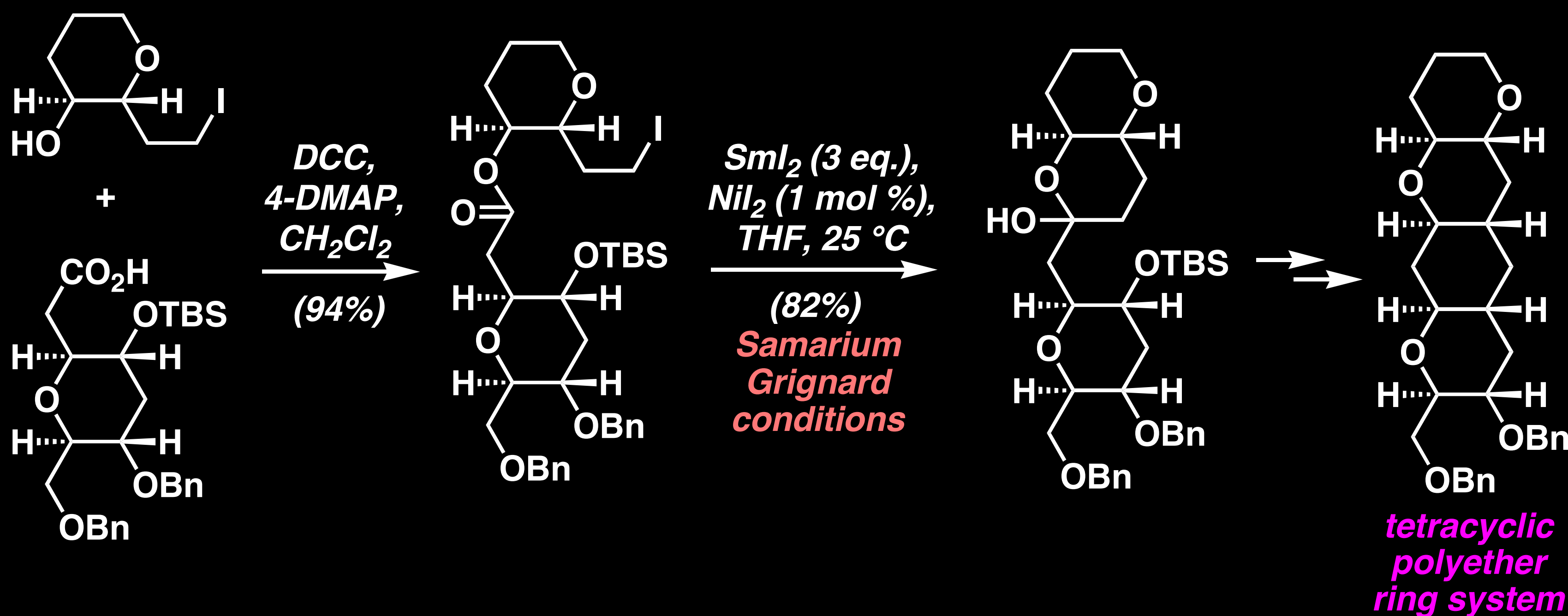


T. Nakata and co-workers, Tetrahedron 2002, 58, 6359.

The Kagan-Molander SmI_2-Mediated Coupling Reaction: Applications in Synthesis



T. Nakata and co-workers, Tetrahedron Lett. 2003, 44, 5259.

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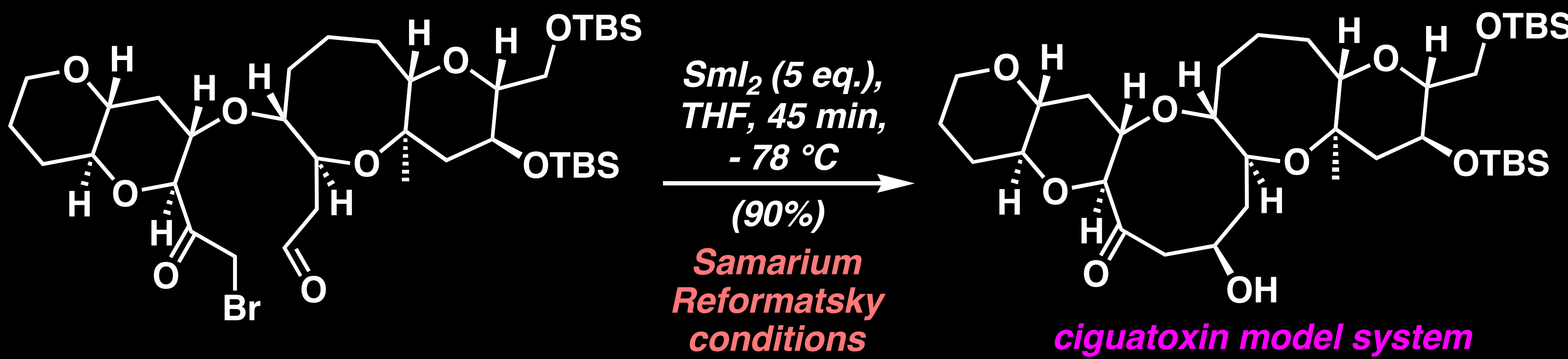
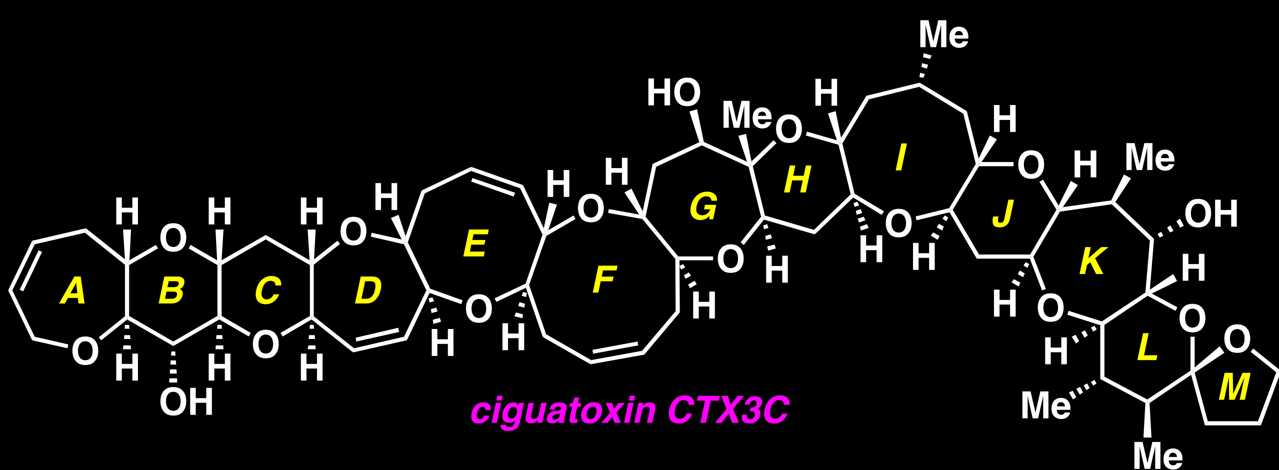
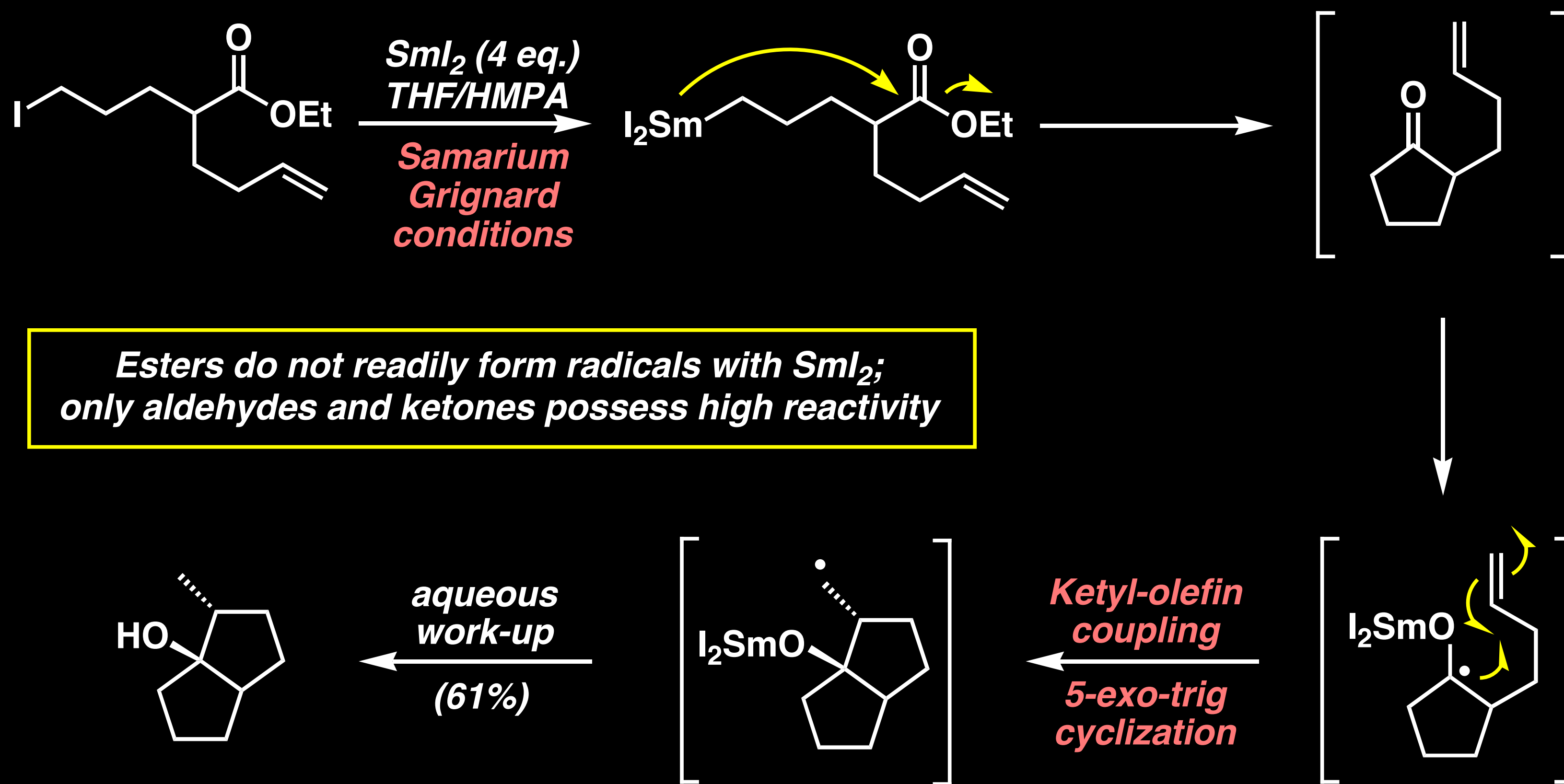




M. Sasaki and co-workers, J. Org. Chem. 1999, 64, 9416.

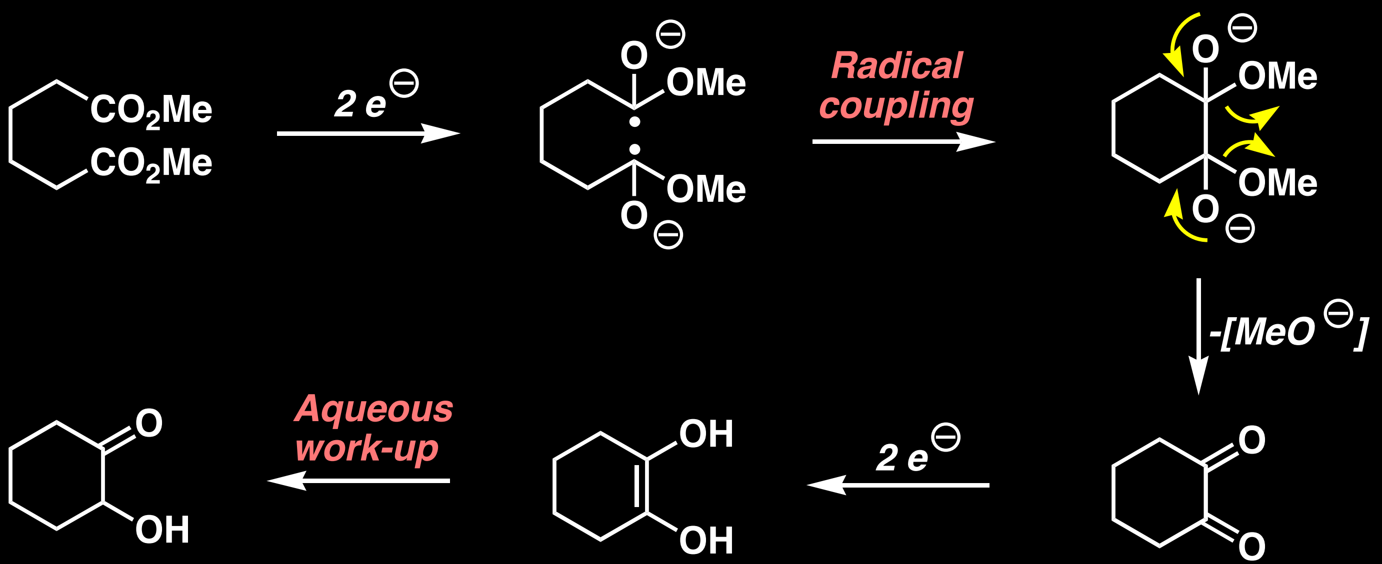
SmI_2:
Ketyl-Olefin Coupling Reactions



Esters do not readily form radicals with SmI_2;
only aldehydes and ketones possess high reactivity

The Acyloin Condensation: Background and General Considerations

One possible mechanism



Note: acyloin derives its name from the older literature as a shorthand notation for α-hydroxy ketones

J. C. Sheehan and co-workers, J. Am. Chem. Soc. 1950, 72, 3376.

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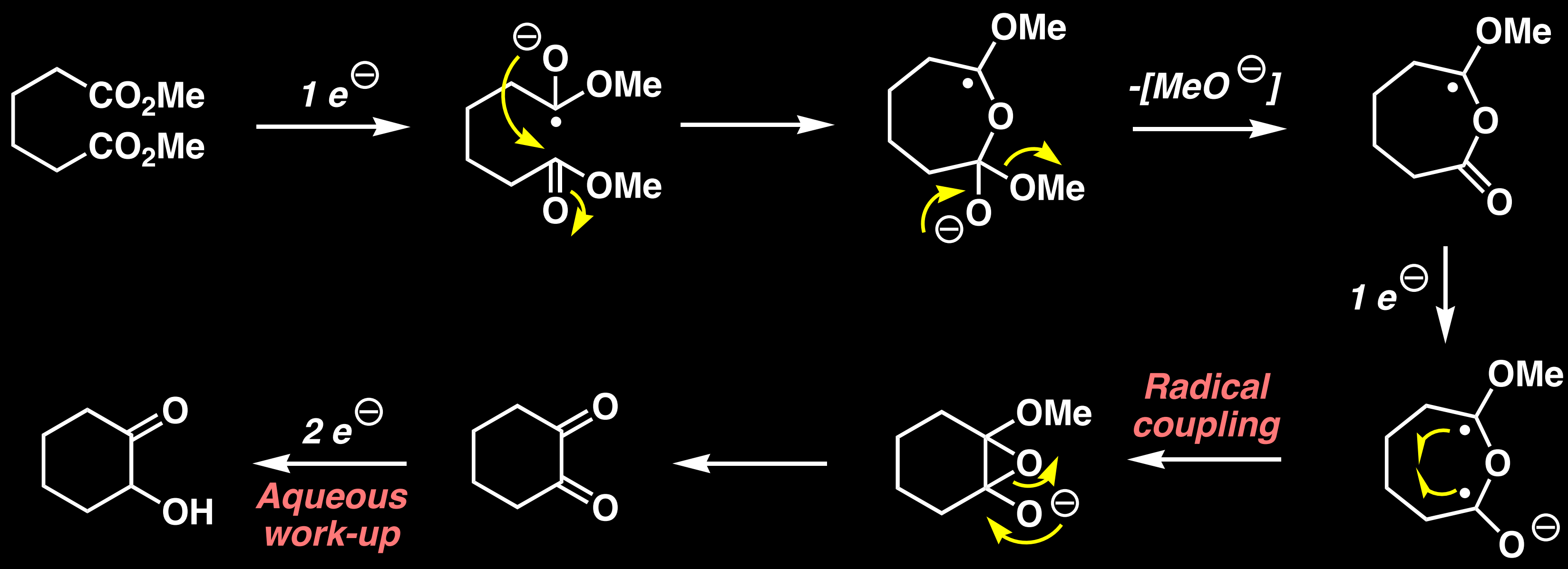

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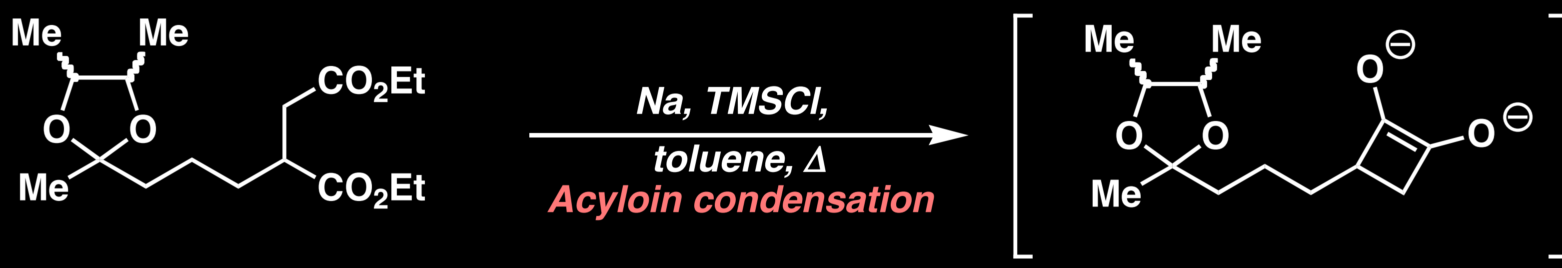
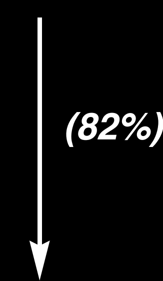
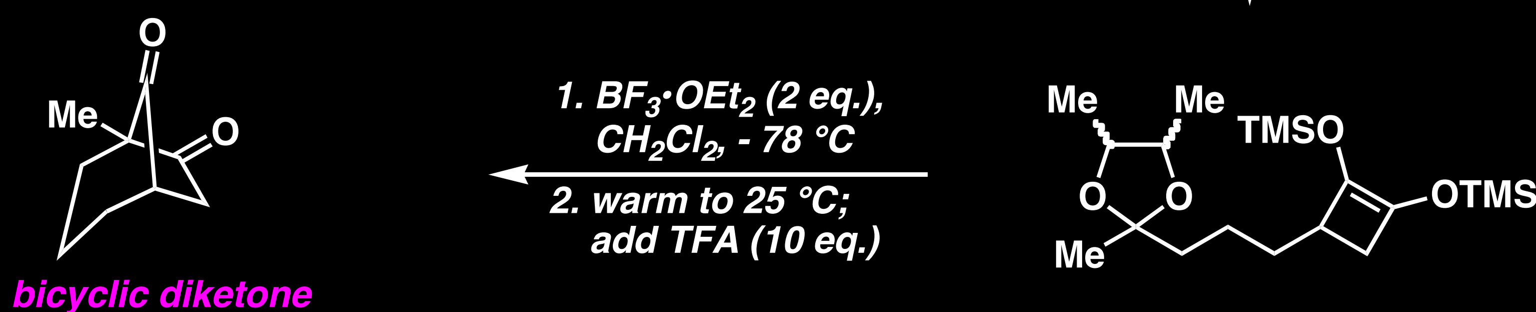
The Acyloin Condensation: Applications in Synthesis





Note: the addition of TMSCl is often done to prevent any base-catalyzed side-reactions such as β-elimination, Claisen, or Dieckmann-type condensations; this simple change greatly expands the scope of this reaction.



A. N. Blanchard, D. J. Burnell, Tetrahedron Lett. 2001, 42, 4779.

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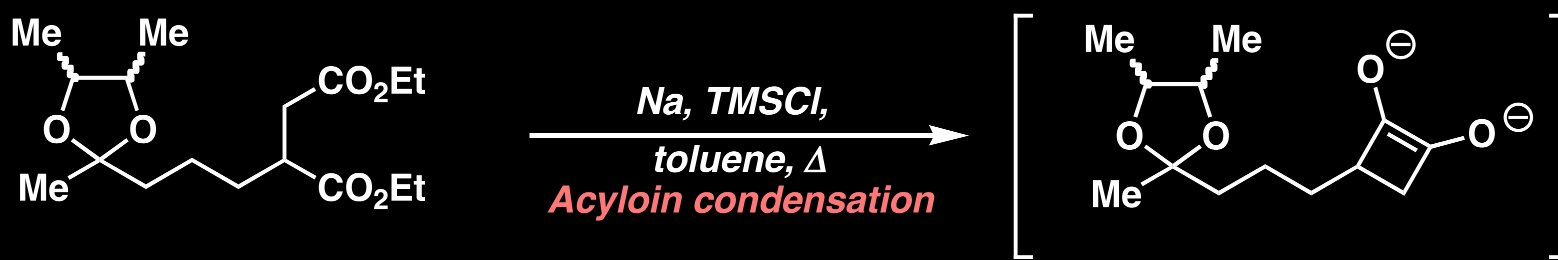

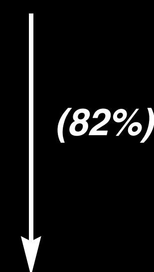

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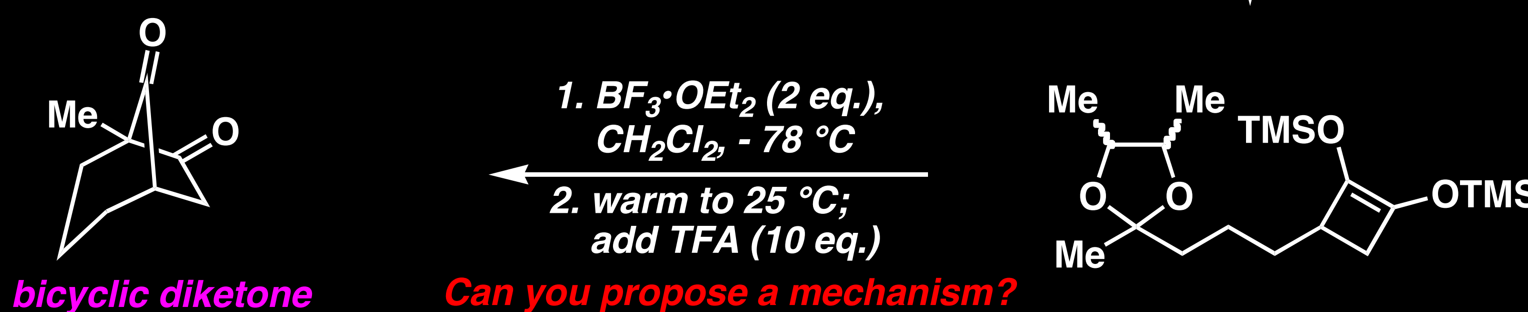

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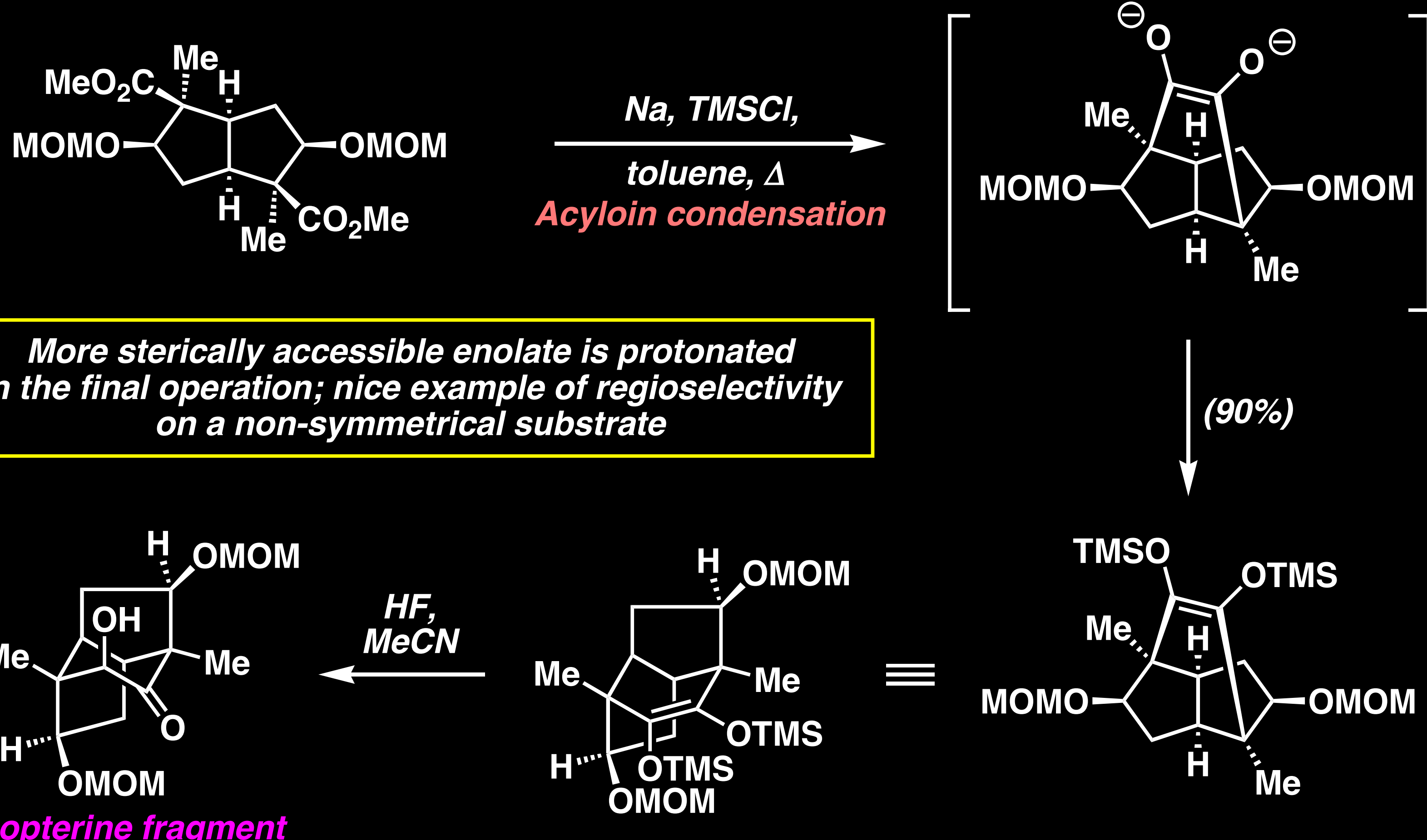
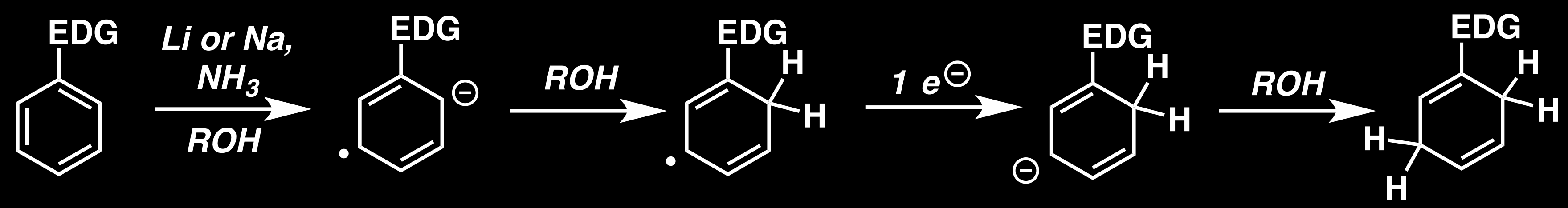


More sterically accessible enolate is protonated in the final operation; nice example of regioselectivity on a non-symmetrical substrate

S. M. Sieburth, E. D. Santos, Tetrahedron Lett. 1994, 35, 8127.

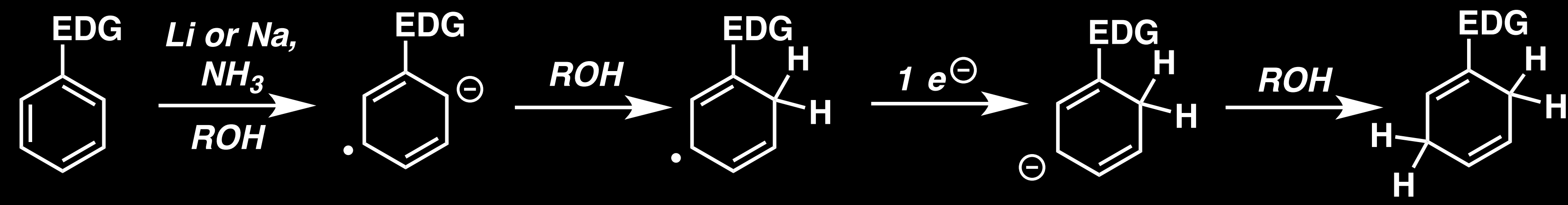
Birch Reduction:
Background and General Considerations



EDG = alkyl, OR, NR_2

H. E. Zimmerman, P. A. Wang, J. Am. Chem. Soc. 1993, 115, 2205.

Birch Reduction: Background and General Considerations



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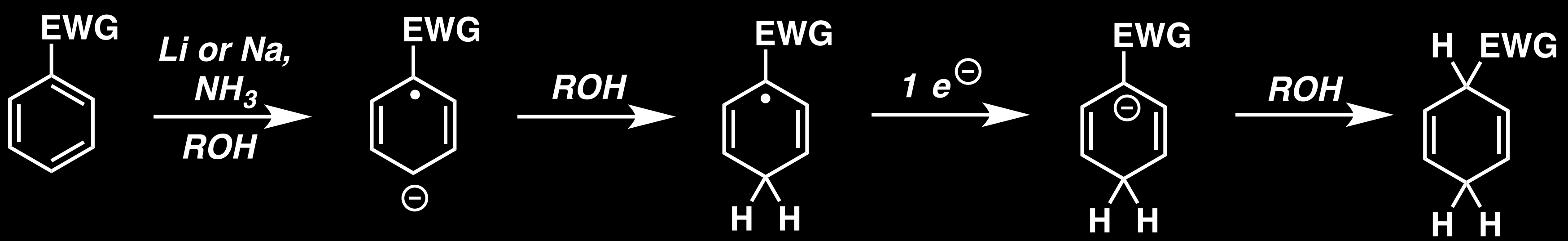

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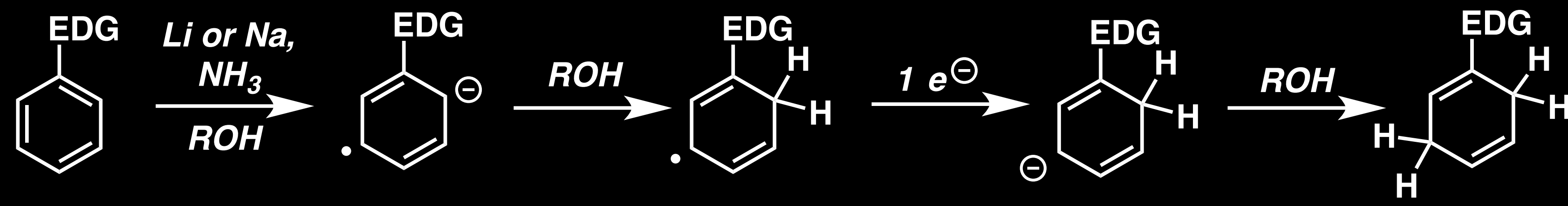
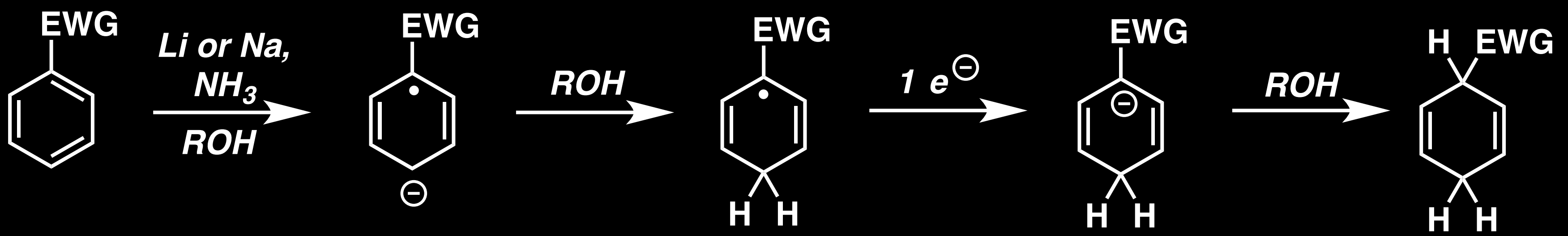


EDG = alkyl, OR, NR_2

Protonation of the radical anion is determined by the site of maximum electron density



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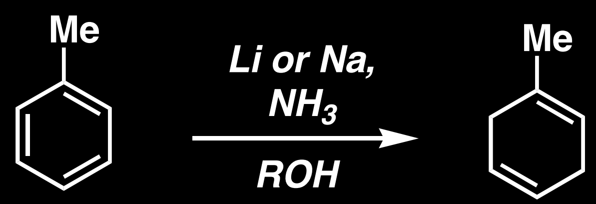
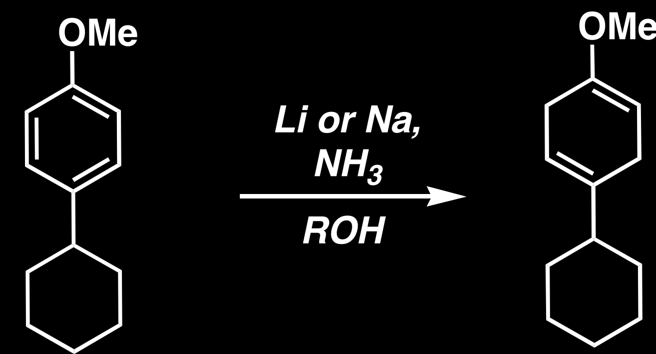
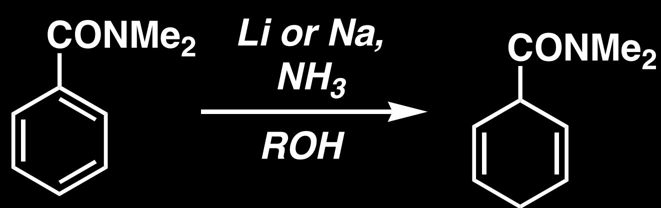
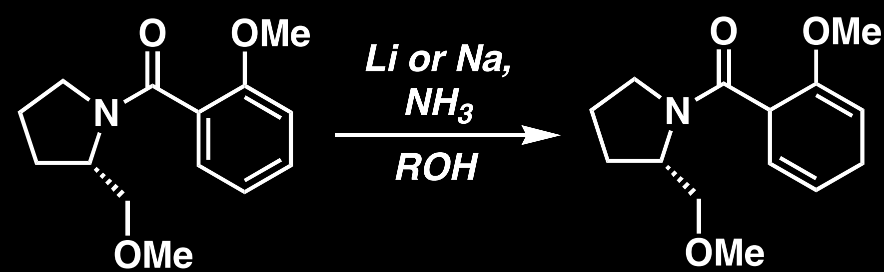
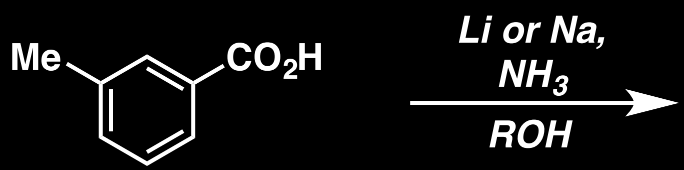








Birch Reduction:
Background and General Considerations



For any disubstituted system, the groups must reinforce each other for effective Birch reduction. All the examples on this and the previous slide are reinfocing in terms of the regioselectivity of Birch reduction.

For early examples of this effect, see:
H. E. Zimmerman, P. A. Wang, J. Am. Chem. Soc. 1993, 115, 2205.

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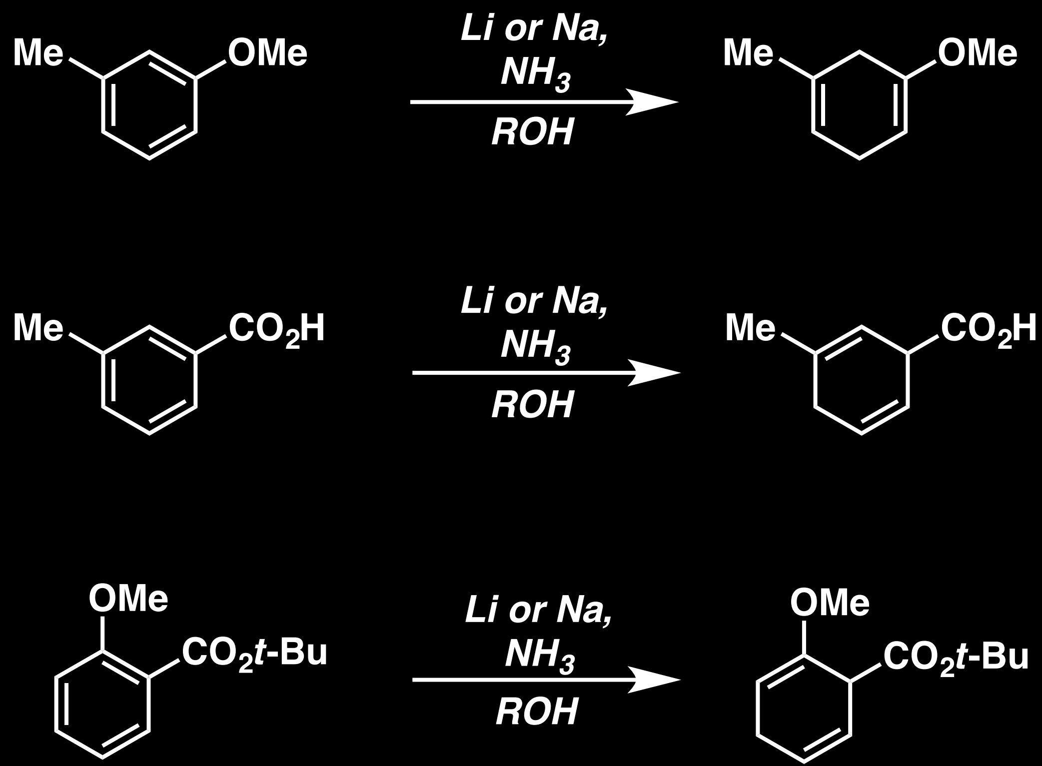
Background and General Considerations



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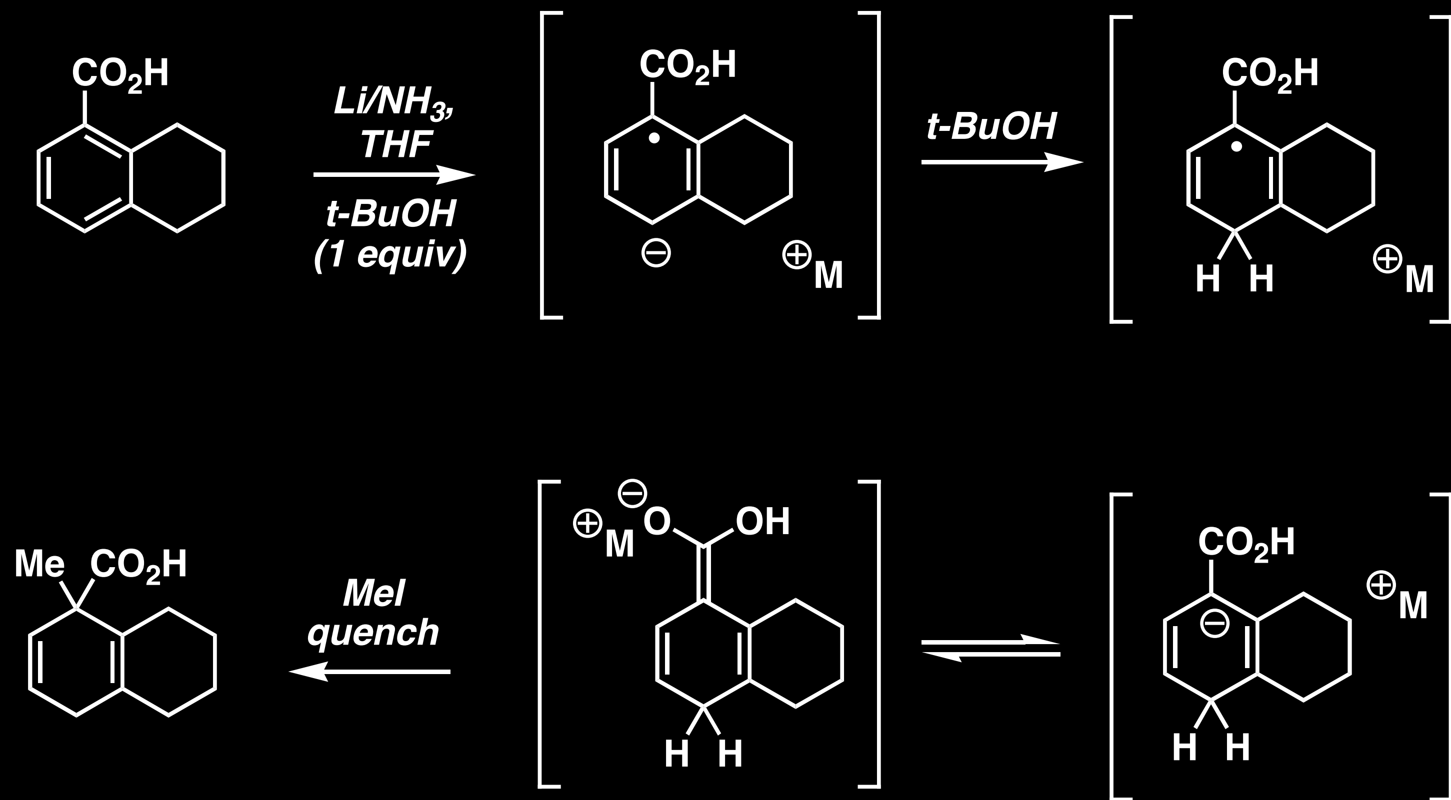
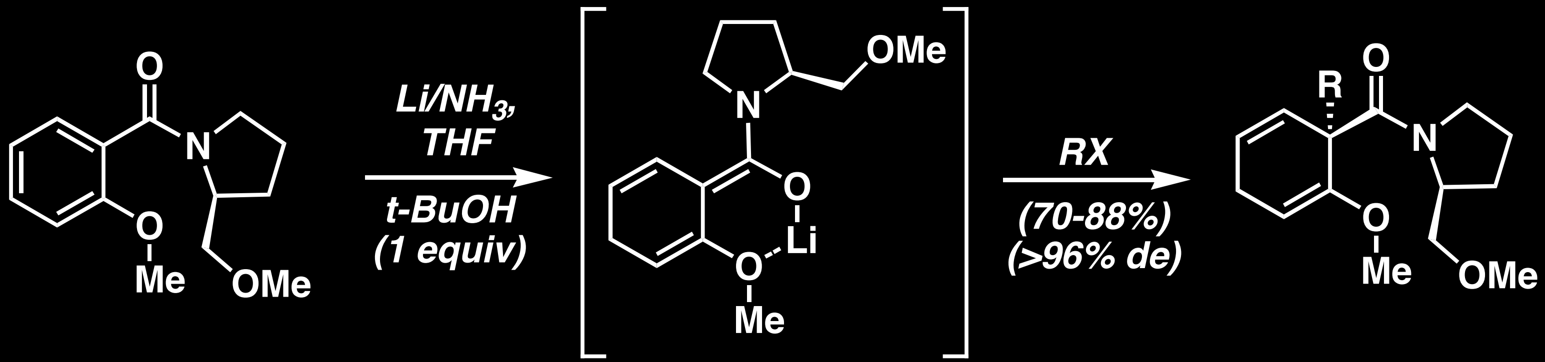
Birch Reduction:
What Other Products Can You Get?



With controlled use of 1 equivalent of a proton source, several alkylating agents can be added to give quaternary carbons and products that cannot aromatize.

Birch Reduction:
What Other Products Can You Get?



For reviews, see: A. G. Schultz, Acc. Chem. Res. 1990, 23, 207.
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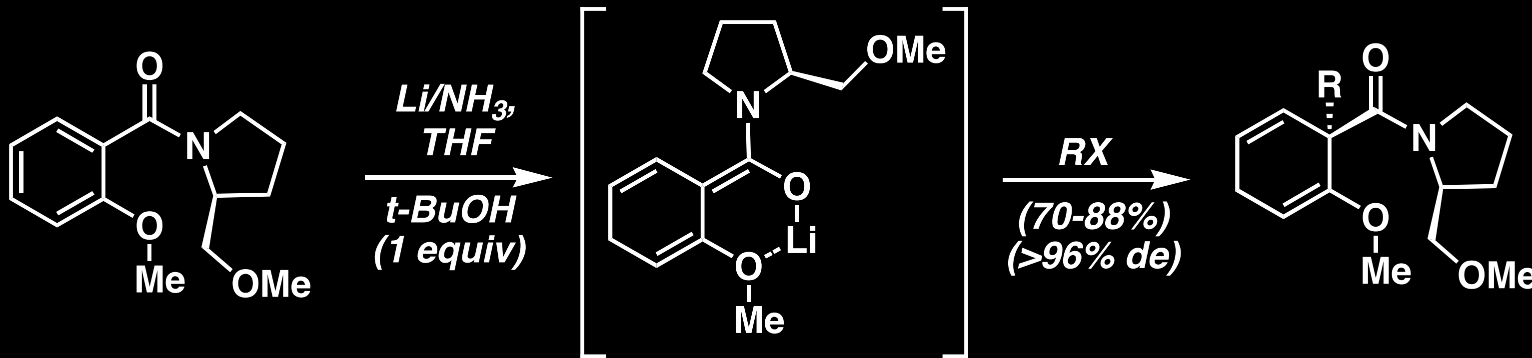

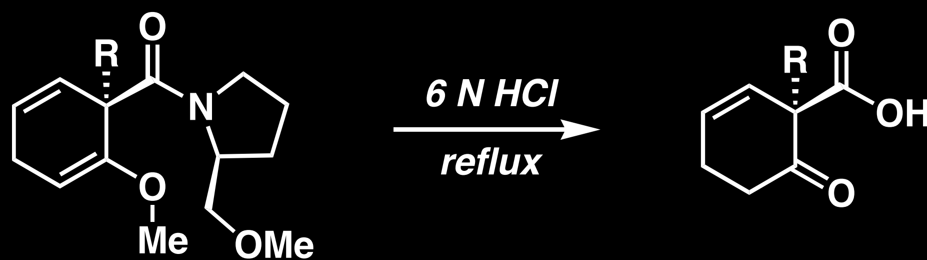

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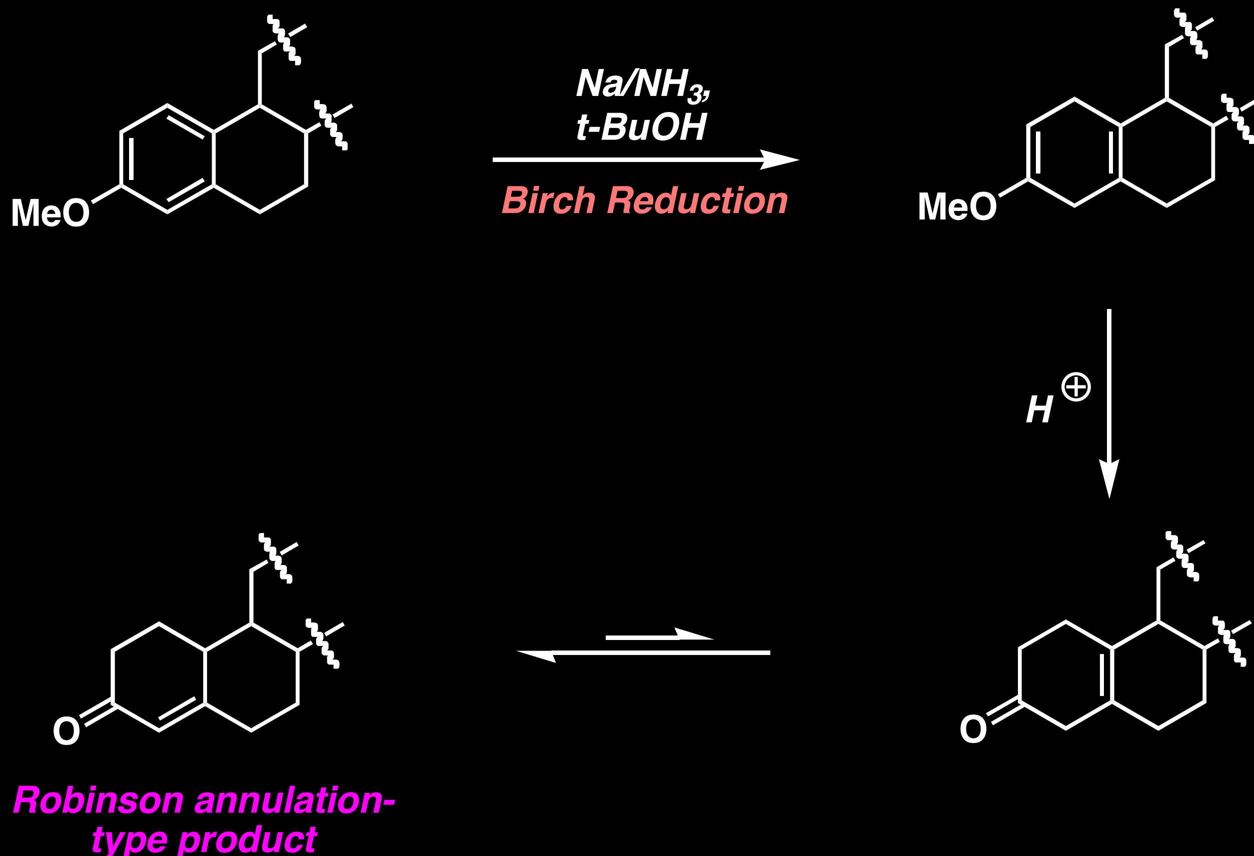
Birch Reduction: What Can You Do With the Reaction Products?



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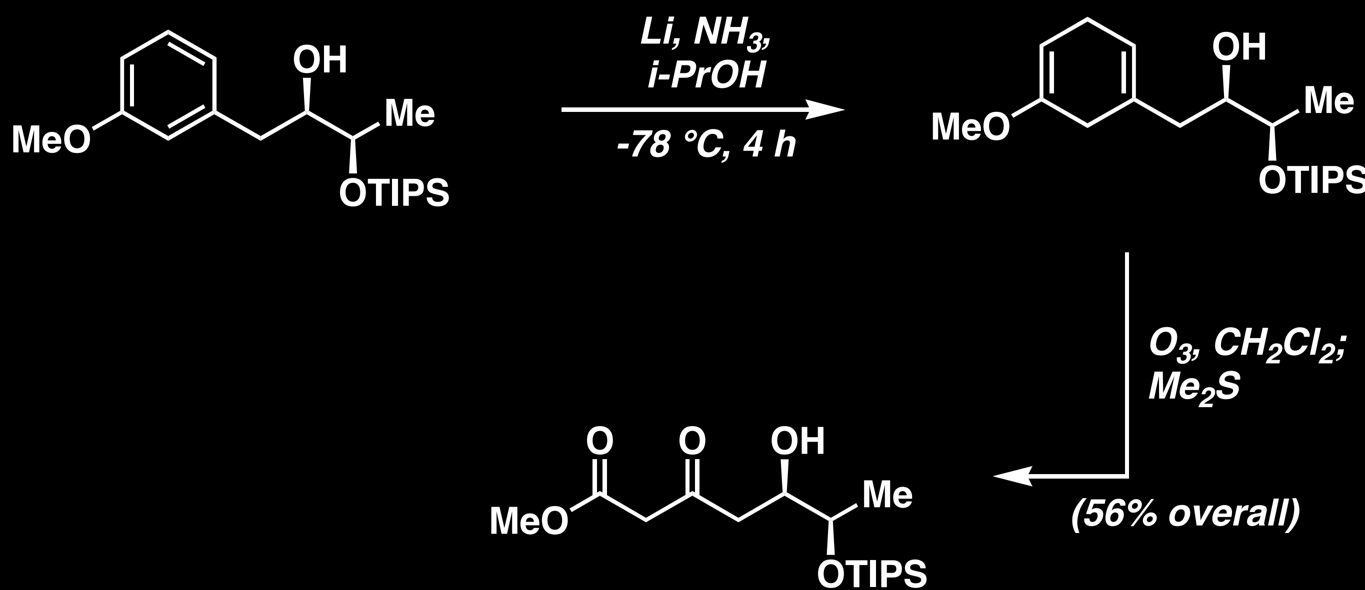

D. A. Evans and co-workers, *J. Org. Chem.* 1991, 56, 741.

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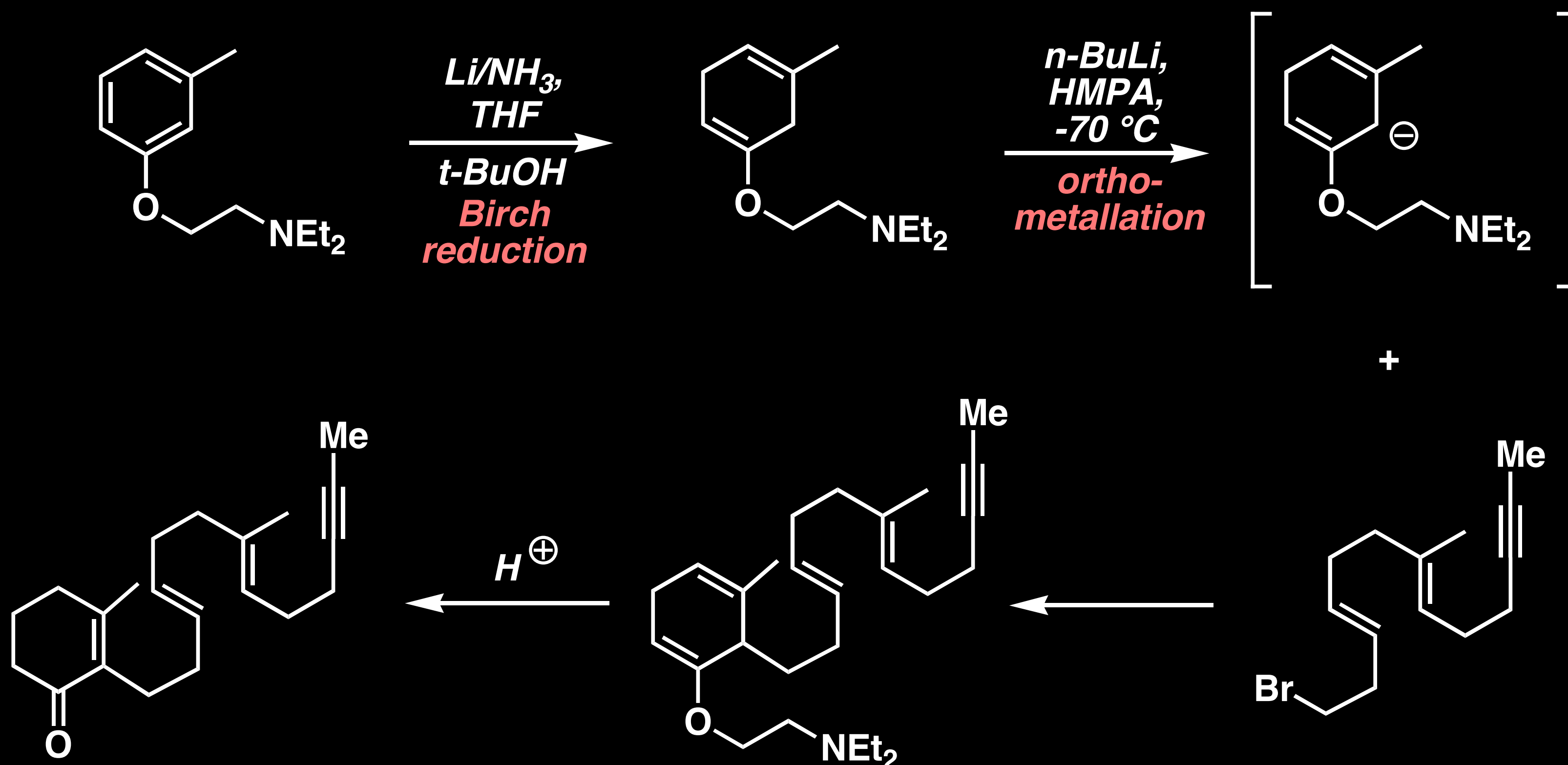

J. K. Sutherland and co-workers, *J. Chem. Soc., Chem. Commun.* 1978, 852.

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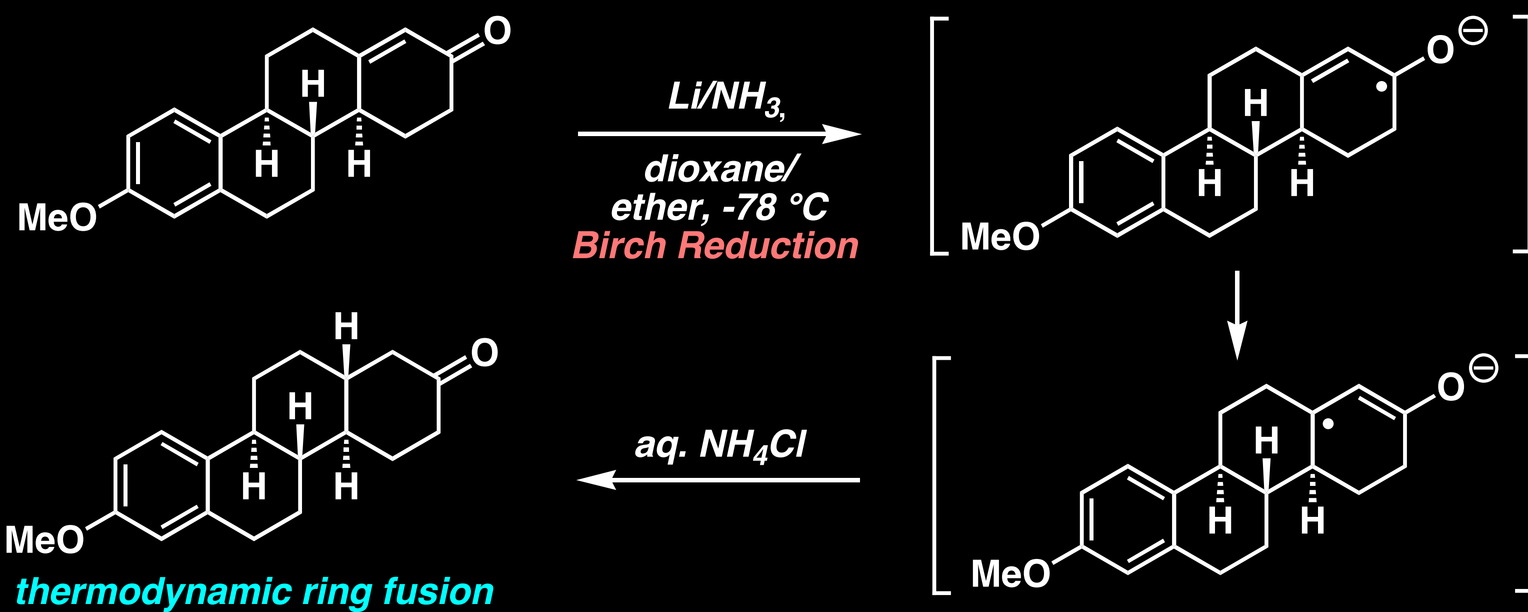

W. S. Johnson and co-workers, J. Org. Chem. 1963, 28, 1856.

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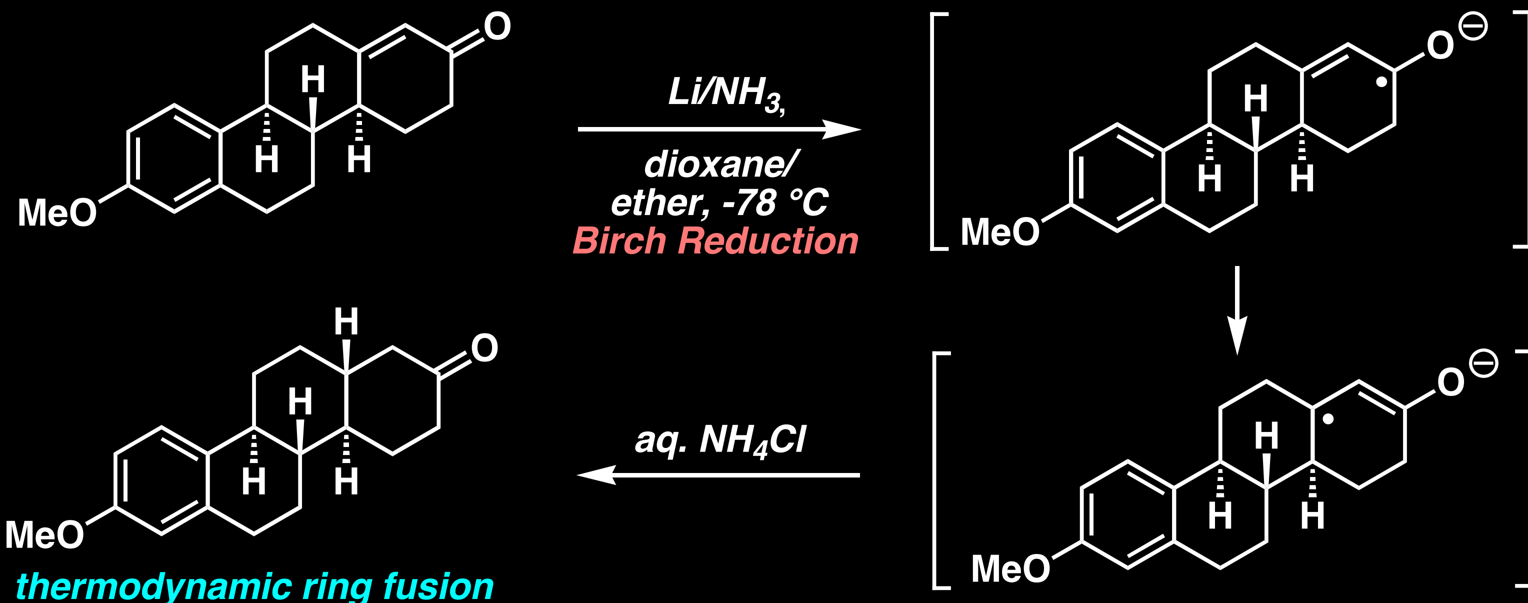

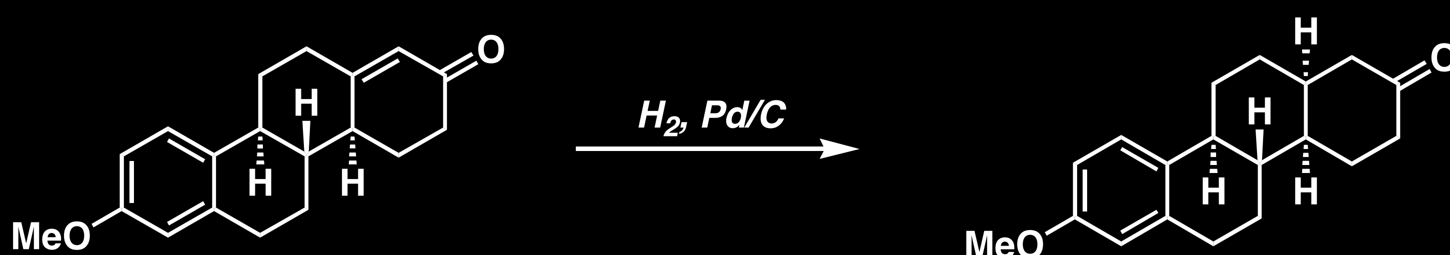

less stable cis-fusion

W. S. Johnson and co-workers, *J. Org. Chem.* **1963**, *28*, 1856.

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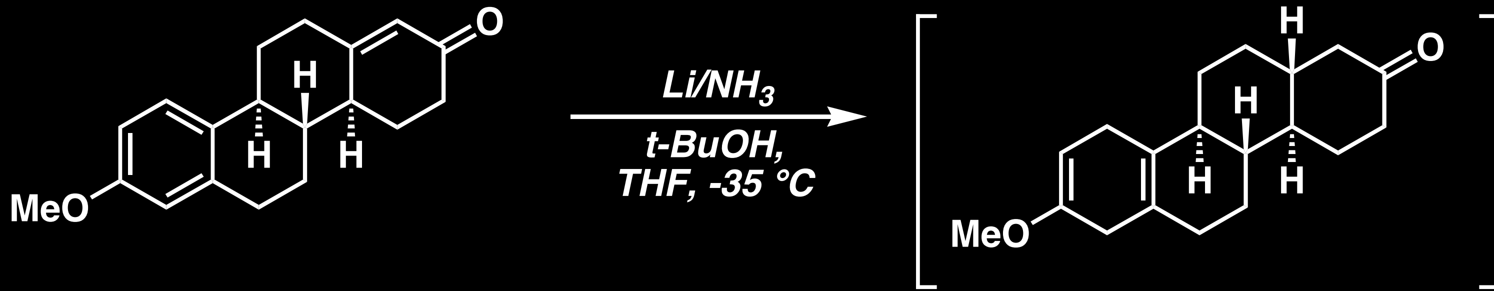
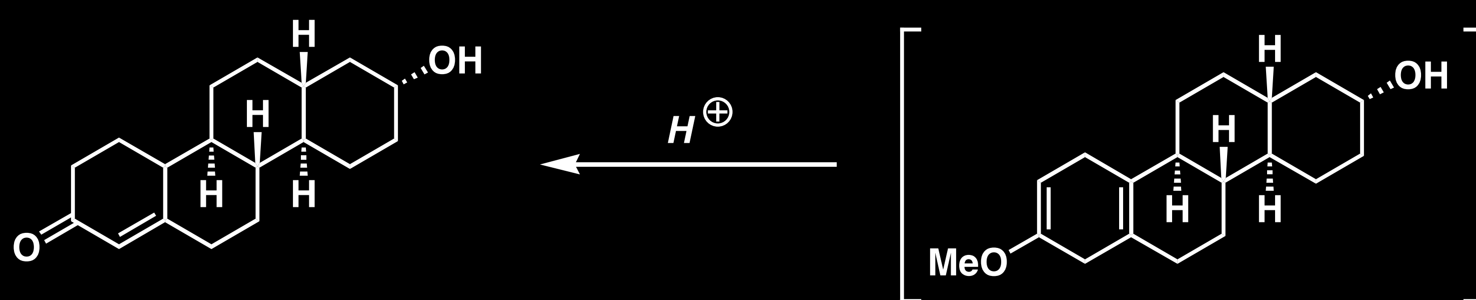
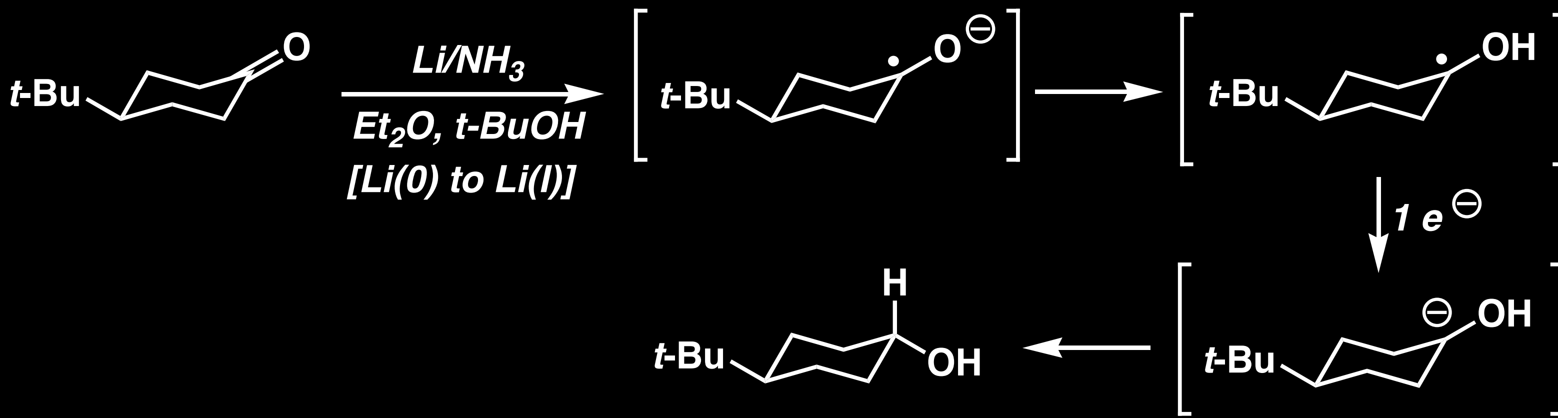


- t-BuOH protonates enone reduction intermediate in situ
- Equatorial alcohol is most stable
- Higher temperature of reaction ensures that Birch reduction happens as well



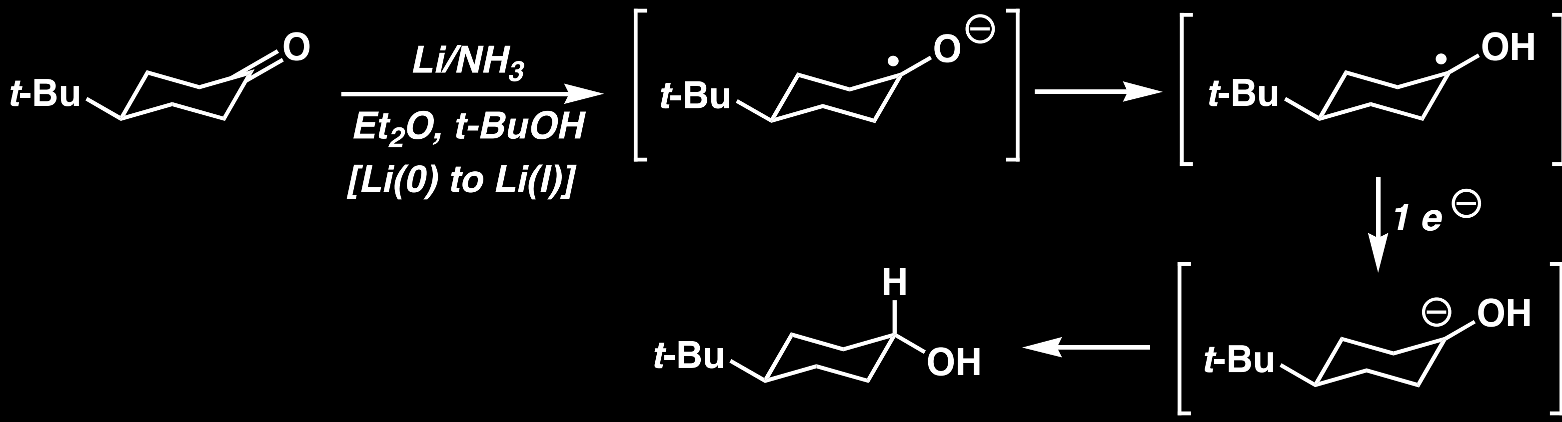
W. S. Johnson and co-workers, J. Org. Chem. 1963, 28, 1856.

Dissolving Metal Reduction: What Can You Do With the Reaction Products



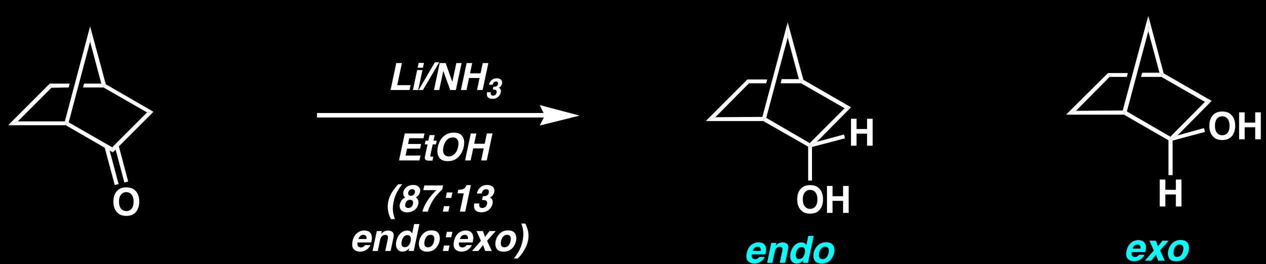
***Rule*: Dissolving metal reduction gives the thermodynamically most stable product**

Dissolving Metal Reduction:
What Can You Do With the Reaction Products

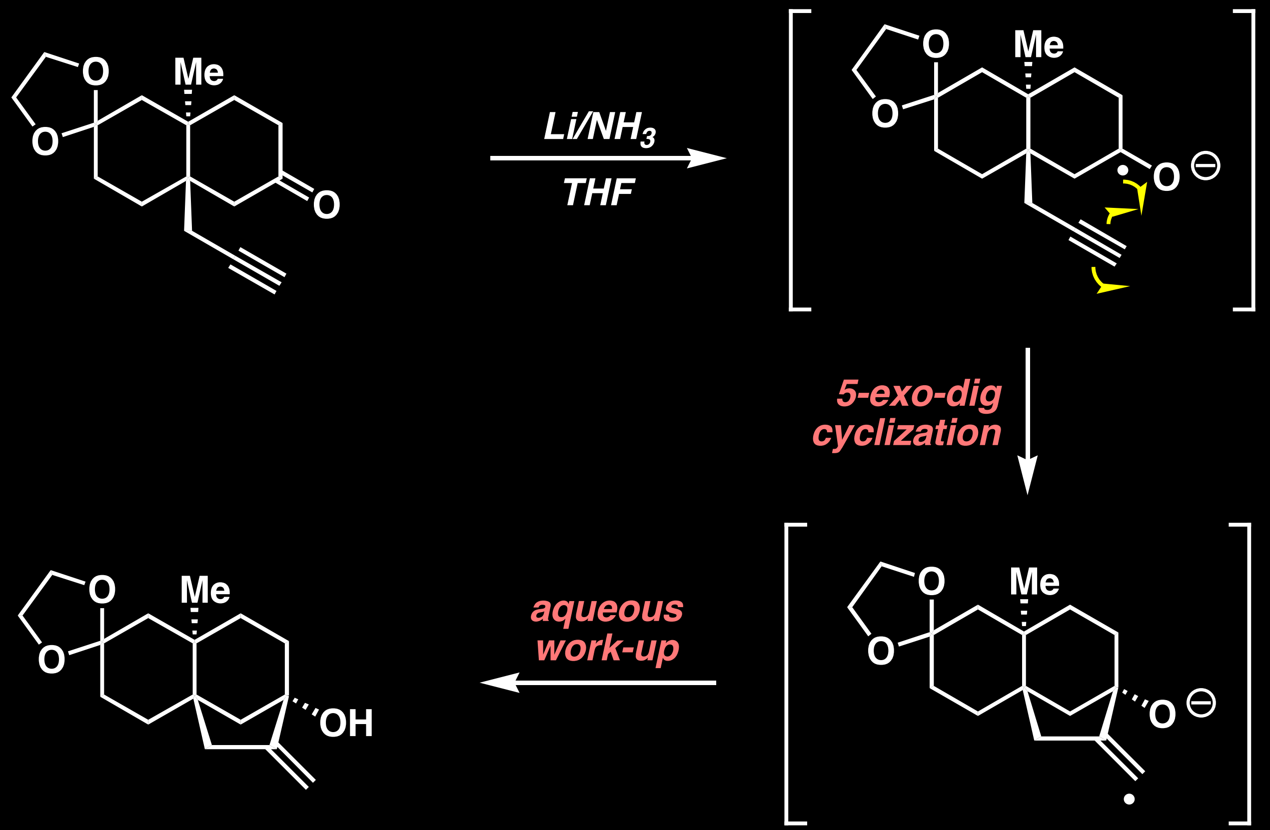


Rule: *Dissolving metal reduction gives the thermodynamically most stable product*

Exception: *Strained or sterically hindered ketones*



Dissolving Metal Reduction: Other Synthetic Opportunities



G. Stork and co-workers, J. Am. Chem. Soc. 1979, 101, 7107.