Radical Reactions (Part 1)

Lecture Notes

Key Reviews:

Cascade Cyclizations
K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 2006, 45, 7134.

Barton Decarboxylation
D. H. R. Barton and co-workers, Aust. J. Chem. 1995, 48, 407.

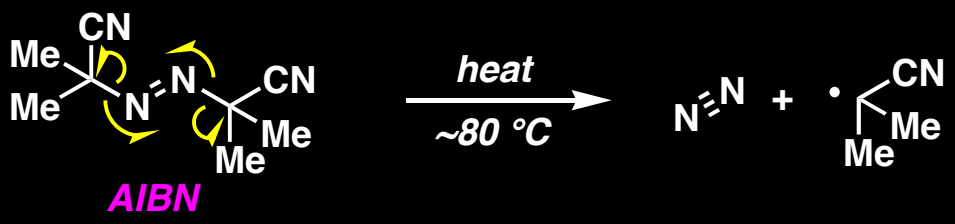
Barton Nitrite Ester Reduction
G. Majetich, K. Wheless, Tetrahedron 1995, 51, 7095.

Barton-McCombie Deoxygenation
W. Hartwig, Tetrahedron 1983, 39, 2609.

Manganese-based Oxidative Cyclizations
B. B. Snider, Chem. Rev. 1996, 96, 339.

Radicals: How Do I Make Them?

Most common method: heating a catalytic amount of AIBN and n-Bu_3SnH



AIBN

B. Giese, B. Kopping, Tetrahedron Lett. 1989, 30, 681.

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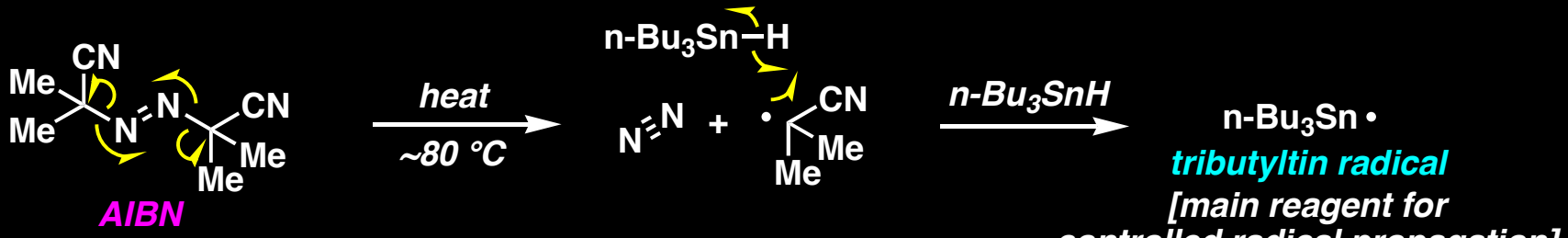

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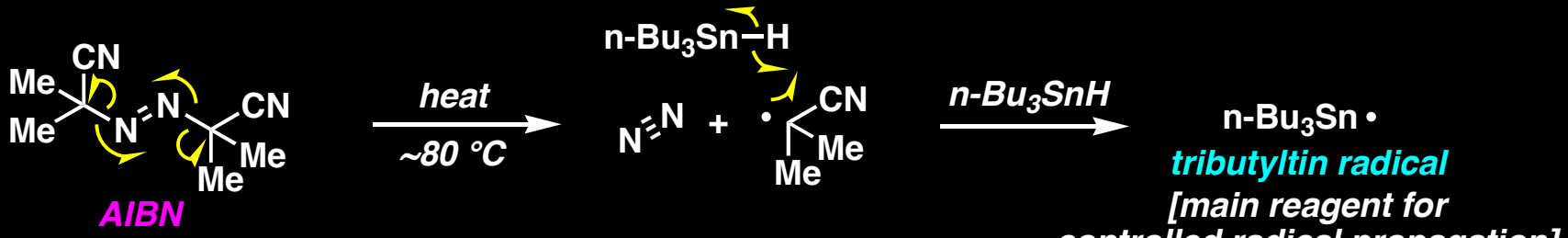

Other metal hydrides that are potential initiators:

$nBu_3Sn–H$	$(Me_3Si)_3Si–H$	$nBu_3Ge–H$	$Et_3Si–H$
74 kcal/mol	*79 kcal/mol*	*84 kcal/mol*	*90 kcal/mol* *[not really a viable source of radical]*

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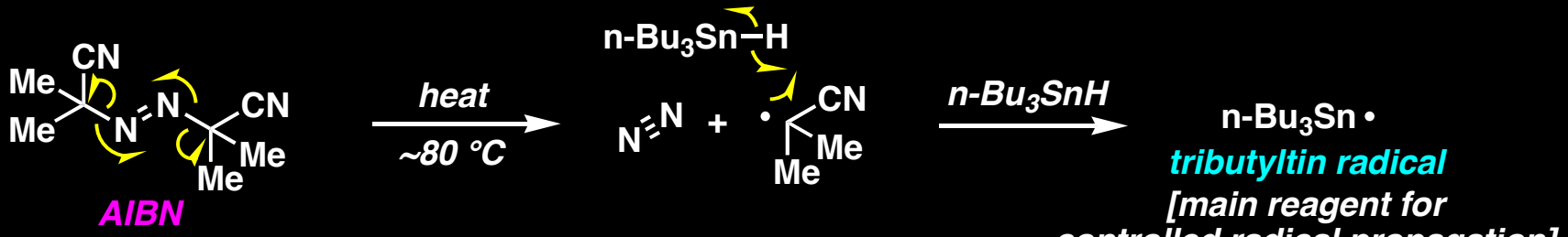

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Lower temperature radicals: Et_3B and n-Bu_3SnH with adventitious oxygen will form the tributyltin radical at ambient temperature.

B. Giese, B. Kopping, Tetrahedron Lett. 1989, 30, 681.

Radicals: How Do I Make Them?

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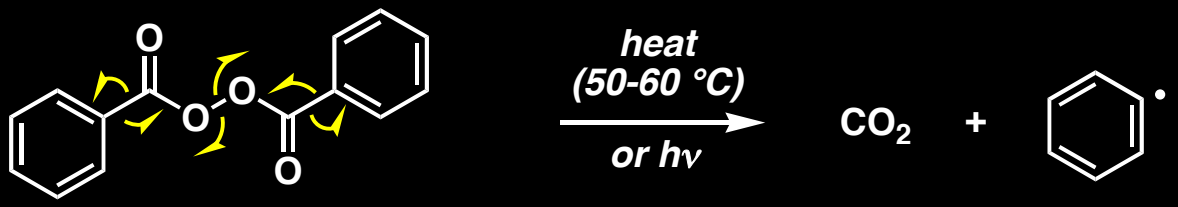

benzoyl peroxide

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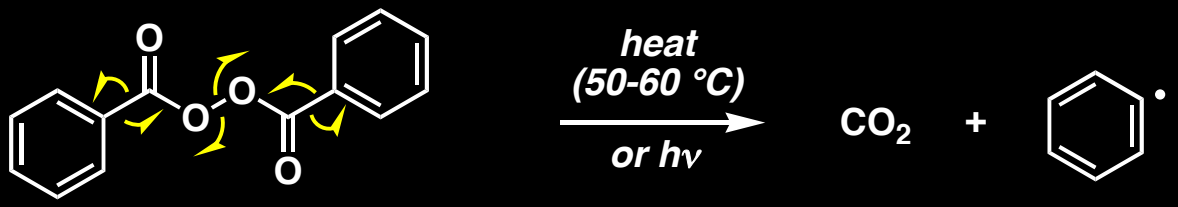

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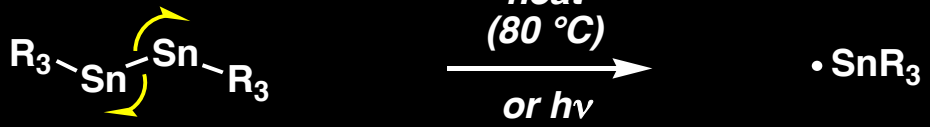

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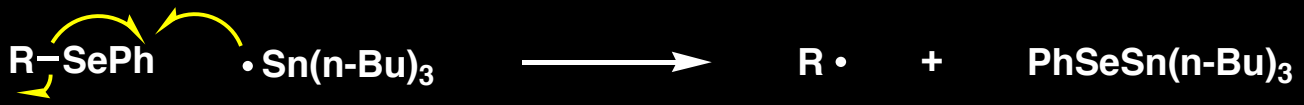

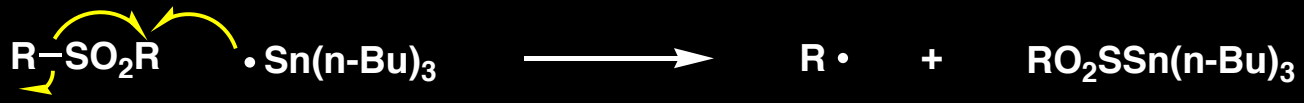

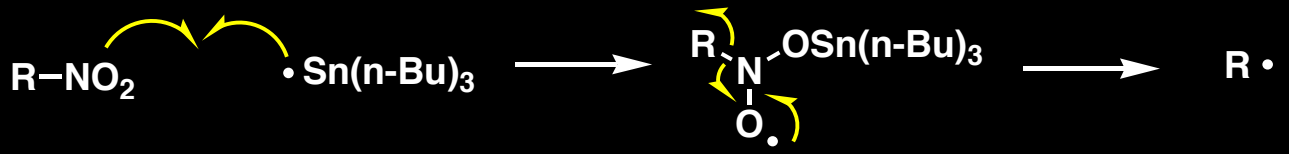

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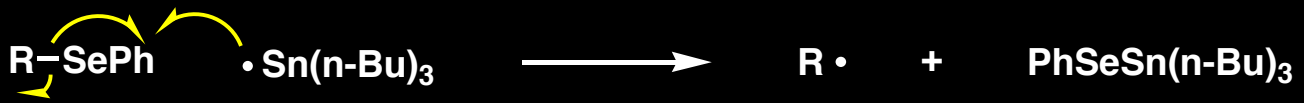

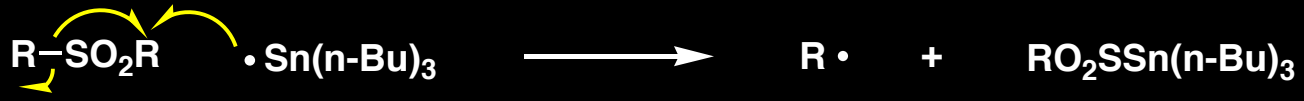

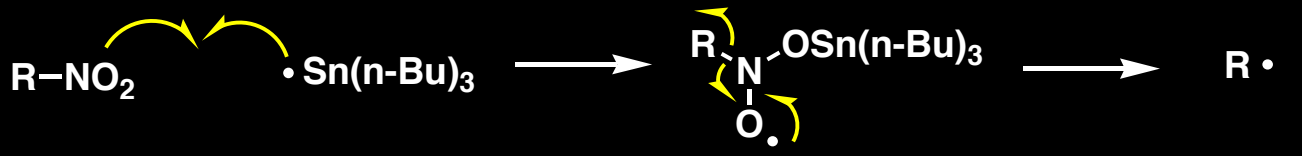

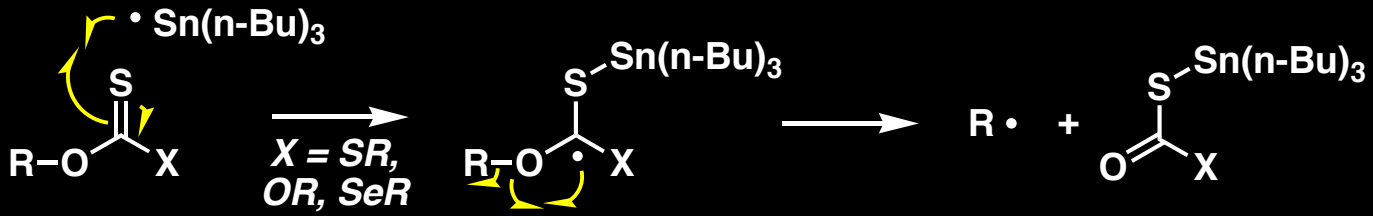

Radical Reactions: Background and General Considerations

Reactivity and Regioselectivity:

	$H_3C\cdot$	$H_3CH_2C\cdot$	$H_3COH_2C\cdot$	$(H_3C)_2\dot{C}H$	$(H_3C)_3C\cdot$
k_{rel}	*1*	*1*	*2.7*	*4.8*	*24*

Alkyl radicals are considered to be "nucleophilic" species

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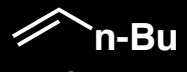
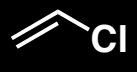
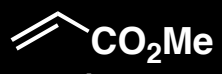
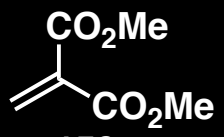
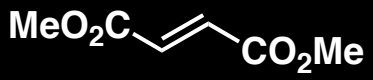
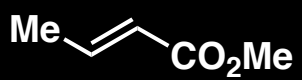
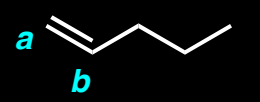
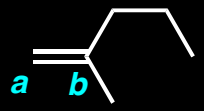
					
k_{rel}	*1*	*8.4*	*84*	*3000*	*8500*

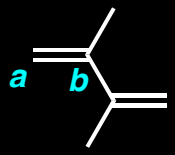
				
k_{rel}	*1*	*150*	*5*	*0.01*

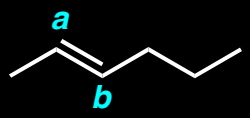
Radical Reactions: Background and General Considerations

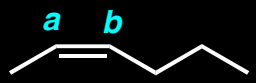
Reactivity and Regioselectivity:

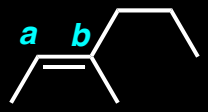


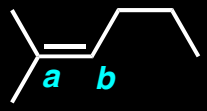






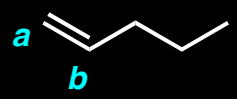
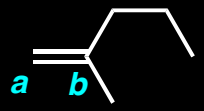
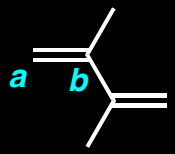
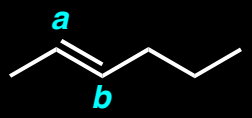
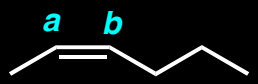
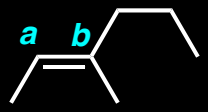
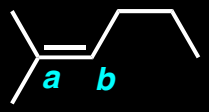






Radical Reactions: Background and General Considerations

Reactivity and Regioselectivity:

	A	B
	>95	<5
	>95	<5
	>95	<5
	50	50
	50	50
	>95	<5
	<5	>95

Radical Reactions: Background and General Considerations

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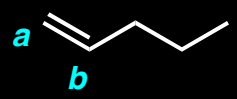
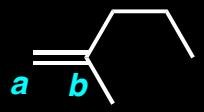
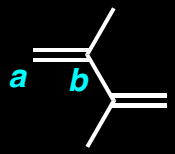
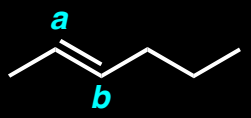
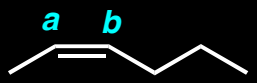
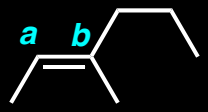
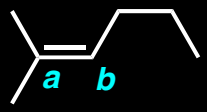
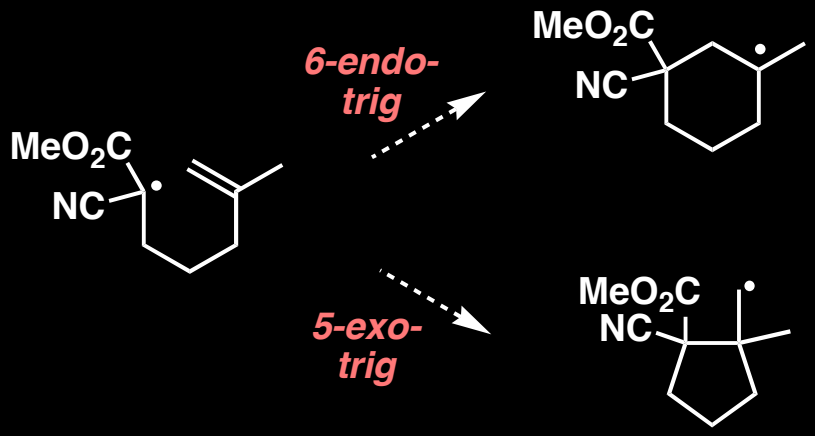
	>95	<5
	>95	<5
	>95	<5
	50	50
	50	50
	>95	<5
	<5	>95

In every case, the addition product leads to the most stable radical intermediate prior to final quench

Note: Intramolecular cases are different!

Radical Reactions: Background and General Considerations

Intramolecular Cyclizations: Regioselectivity with Stabilized Radicals



Julia and co-workers, Compt. Red. 1960, 251, 1030.

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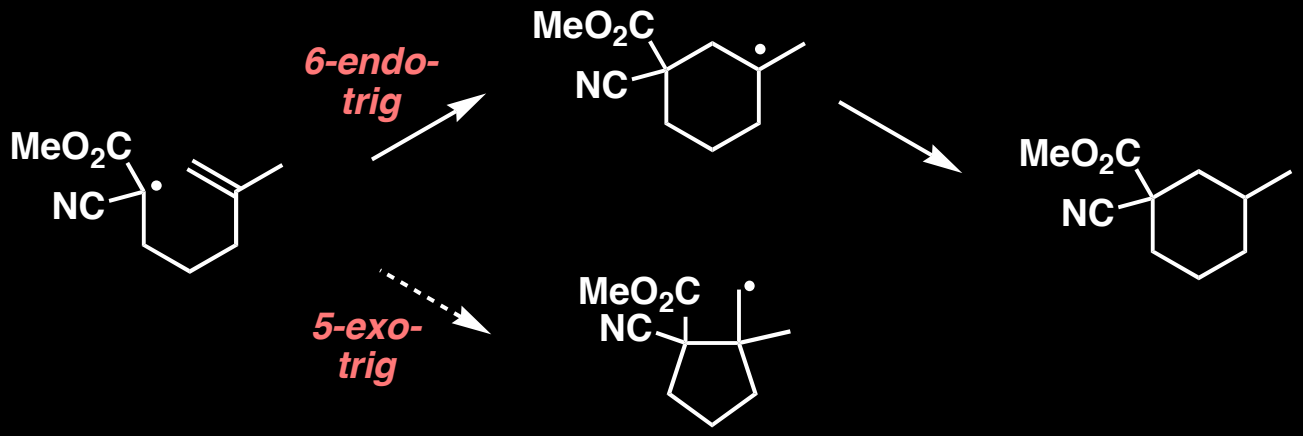

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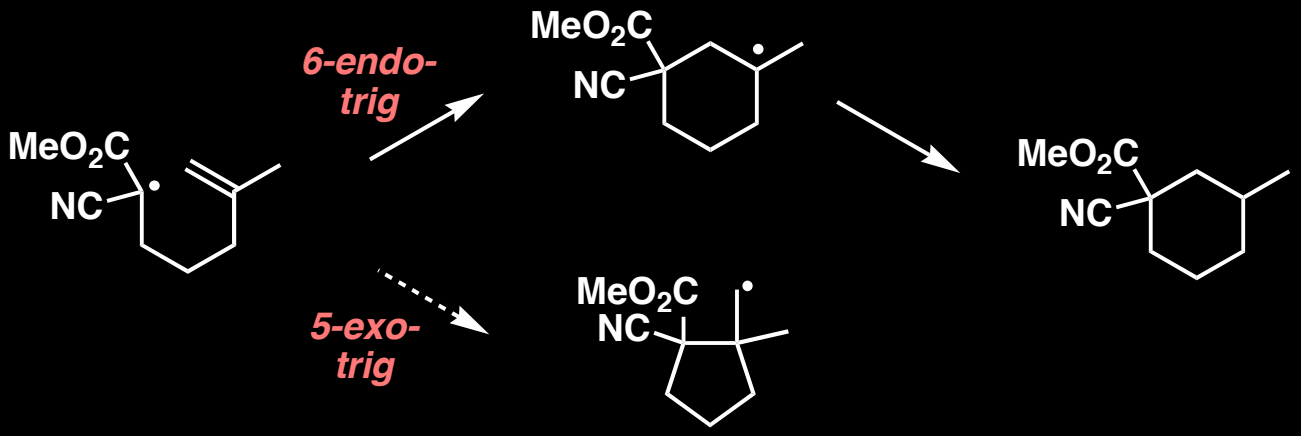

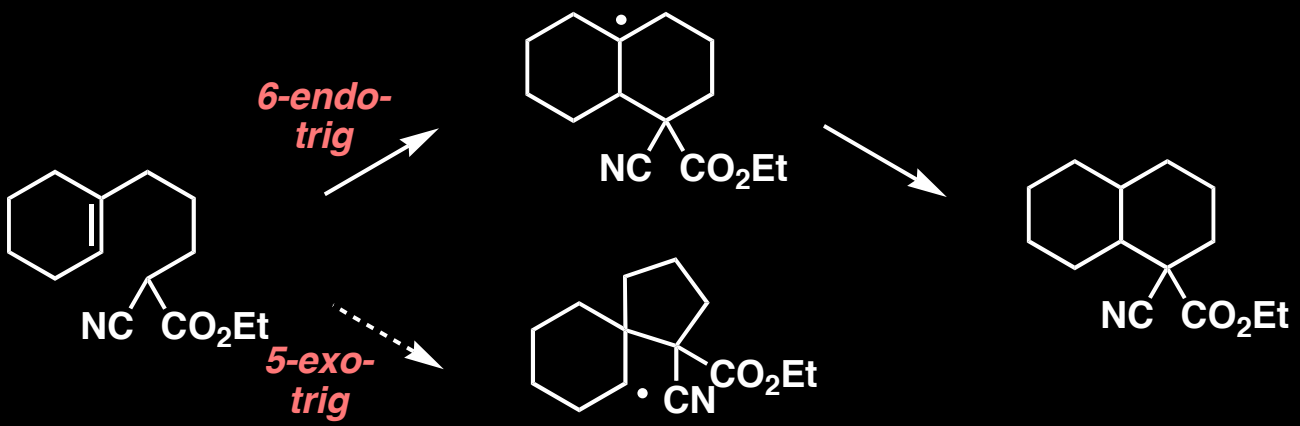

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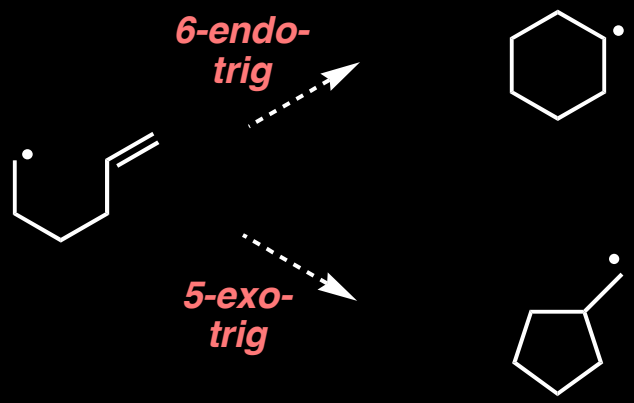
Radical Reactions: Background and General Considerations

Intramolecular Cyclizations: Regioselectivity with Non-stabilized Radicals



J. P. Beckwith and co-workers, J. Chem. Soc., Chem. Commun. 1974, 474.
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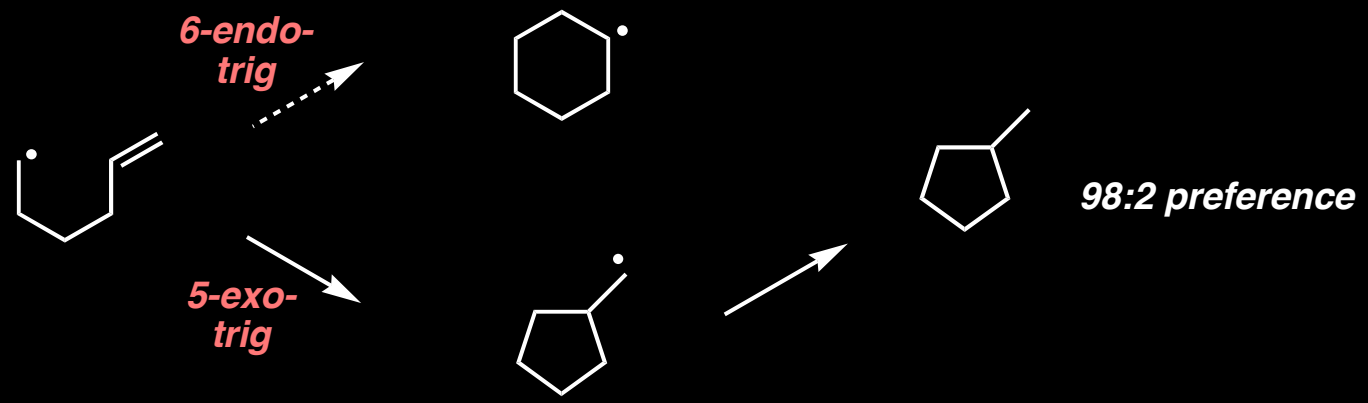
Radical Reactions: Background and General Considerations

Intramolecular Cyclizations: Regioselectivity with Non-stabilized Radicals



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Radical Reactions: Background and General Considerations

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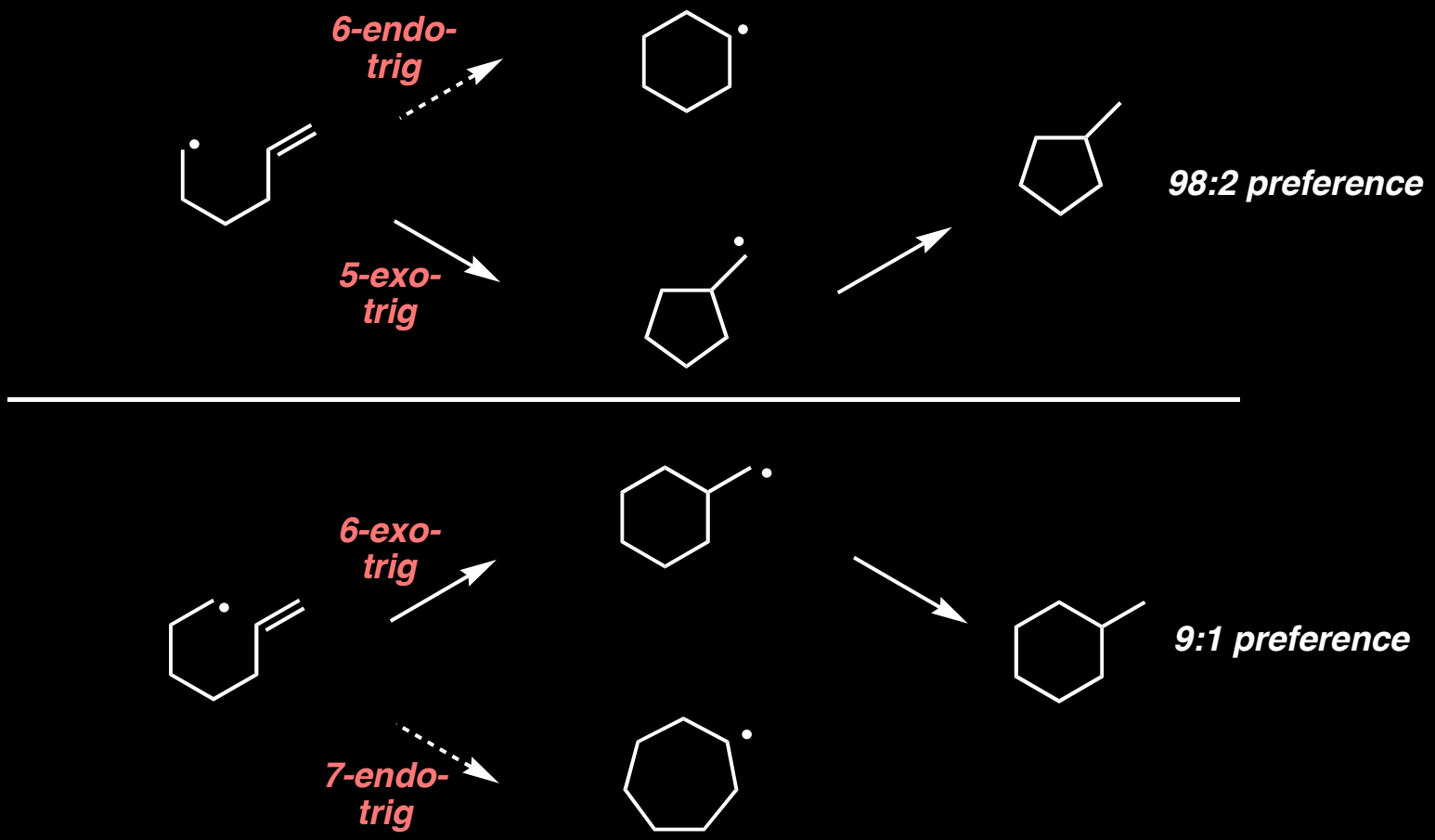

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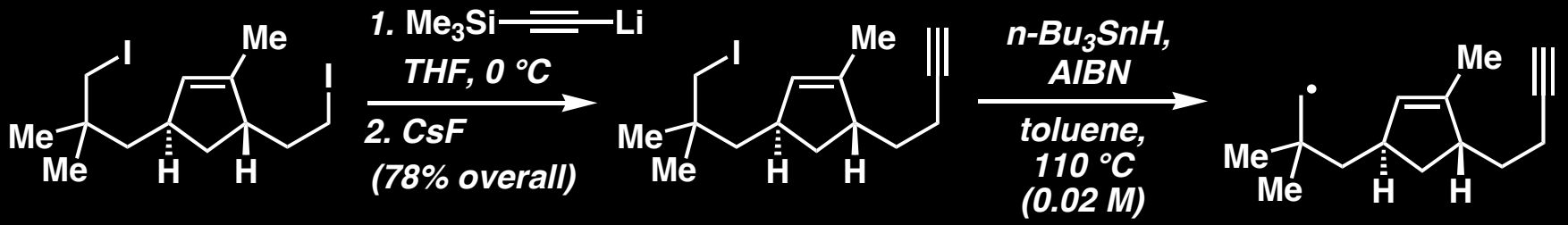
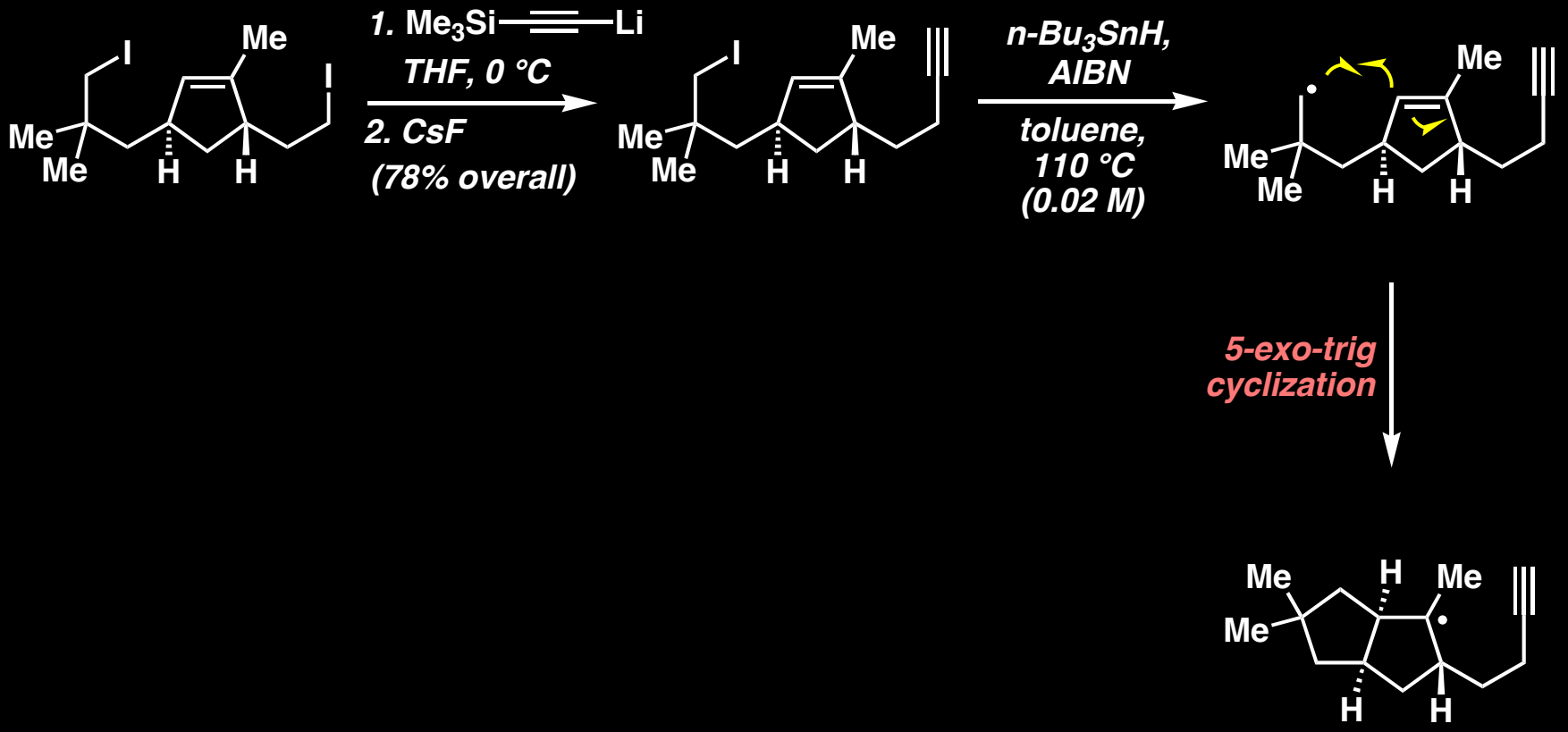
Radical-based Cascade Cyclizations: Curran's Total Synthesis of Hirsutene



D. P. Curran and co-workers, J. Am. Chem. Soc. 1985, 107, 1448.
D. P. Curran and co-workers, Tetrahedron 1985, 41, 3943.

Radical-based Cascade Cyclizations: Curran's Total Synthesis of Hirsutene



D. P. Curran and co-workers, J. Am. Chem. Soc. 1985, 107, 1448.
D. P. Curran and co-workers, Tetrahedron 1985, 41, 3943.

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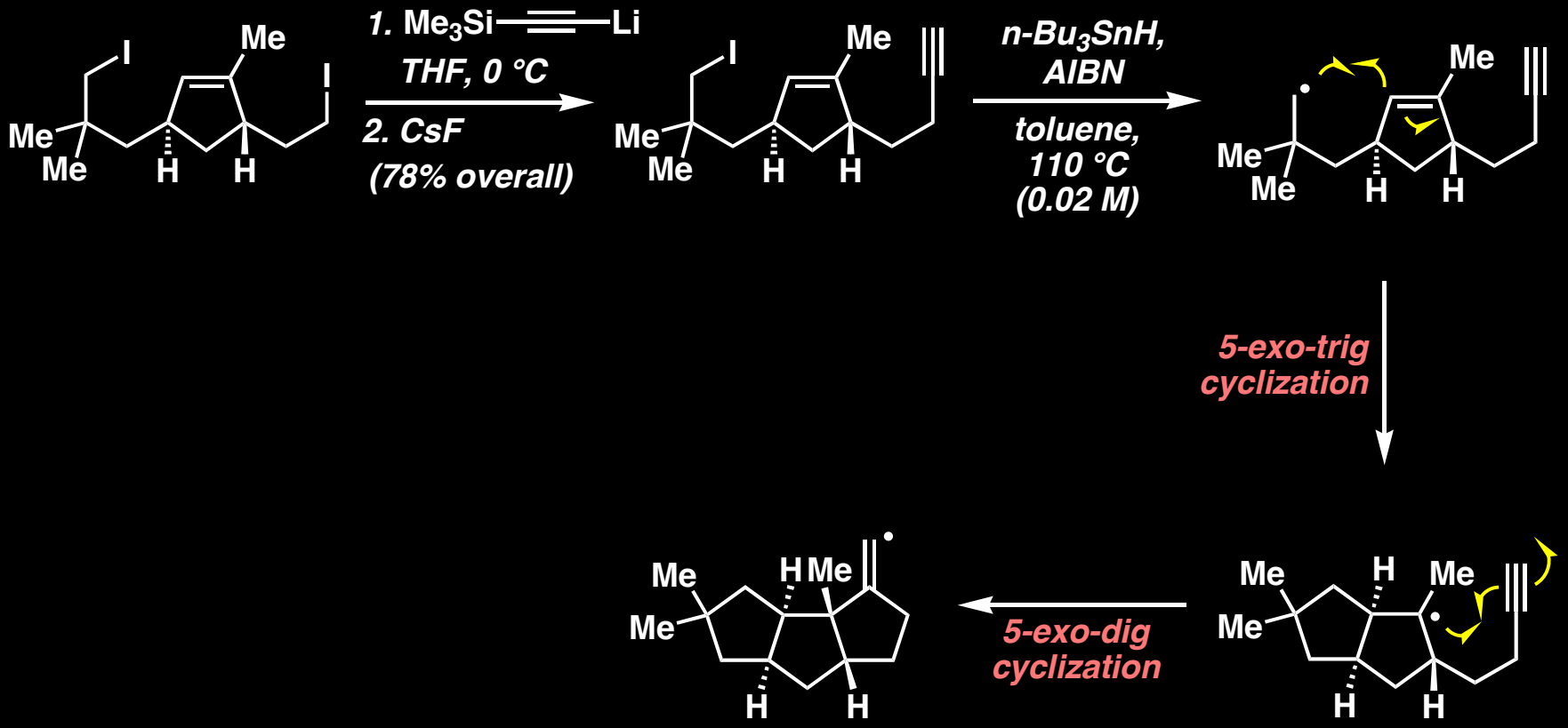

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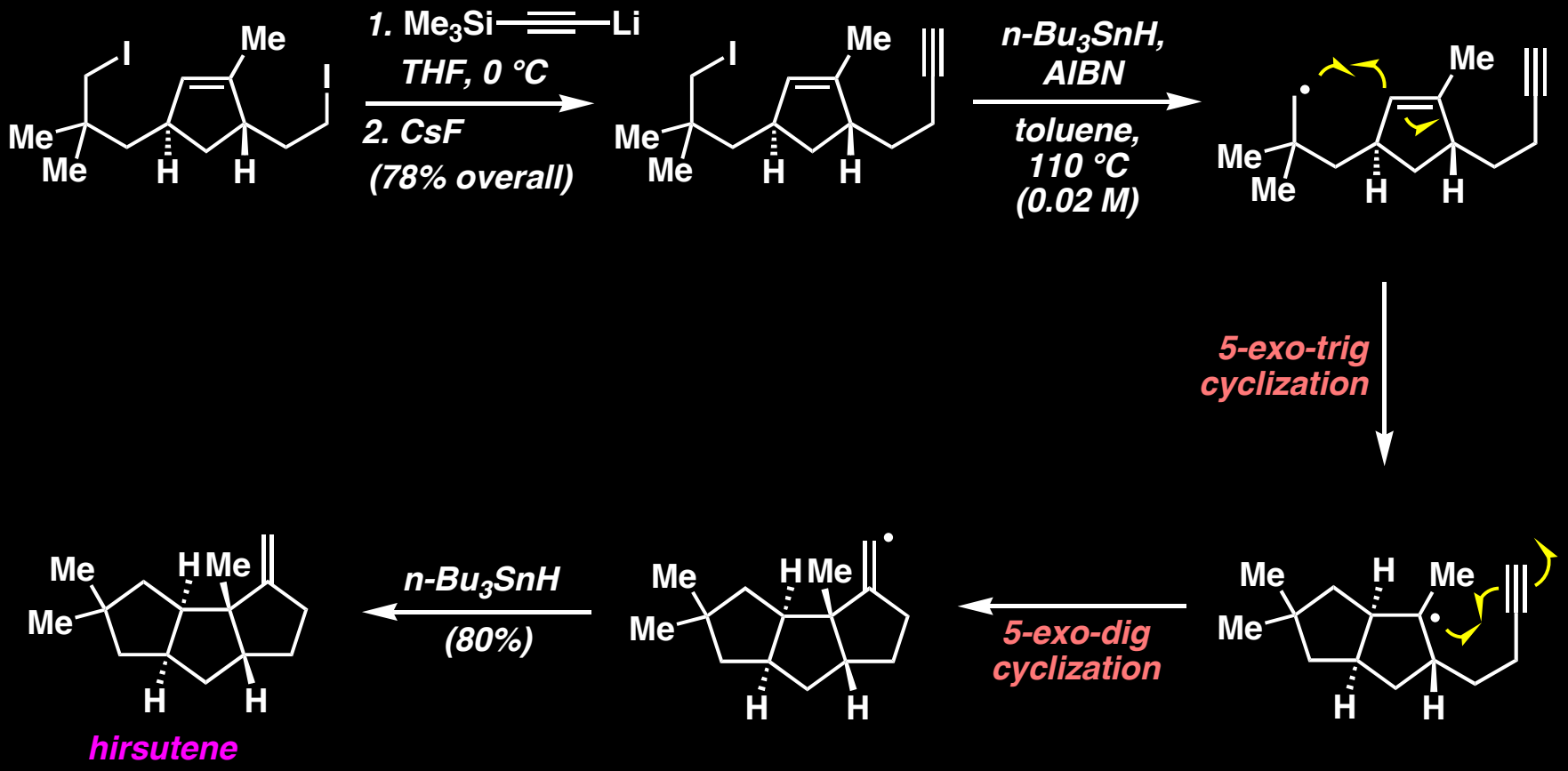
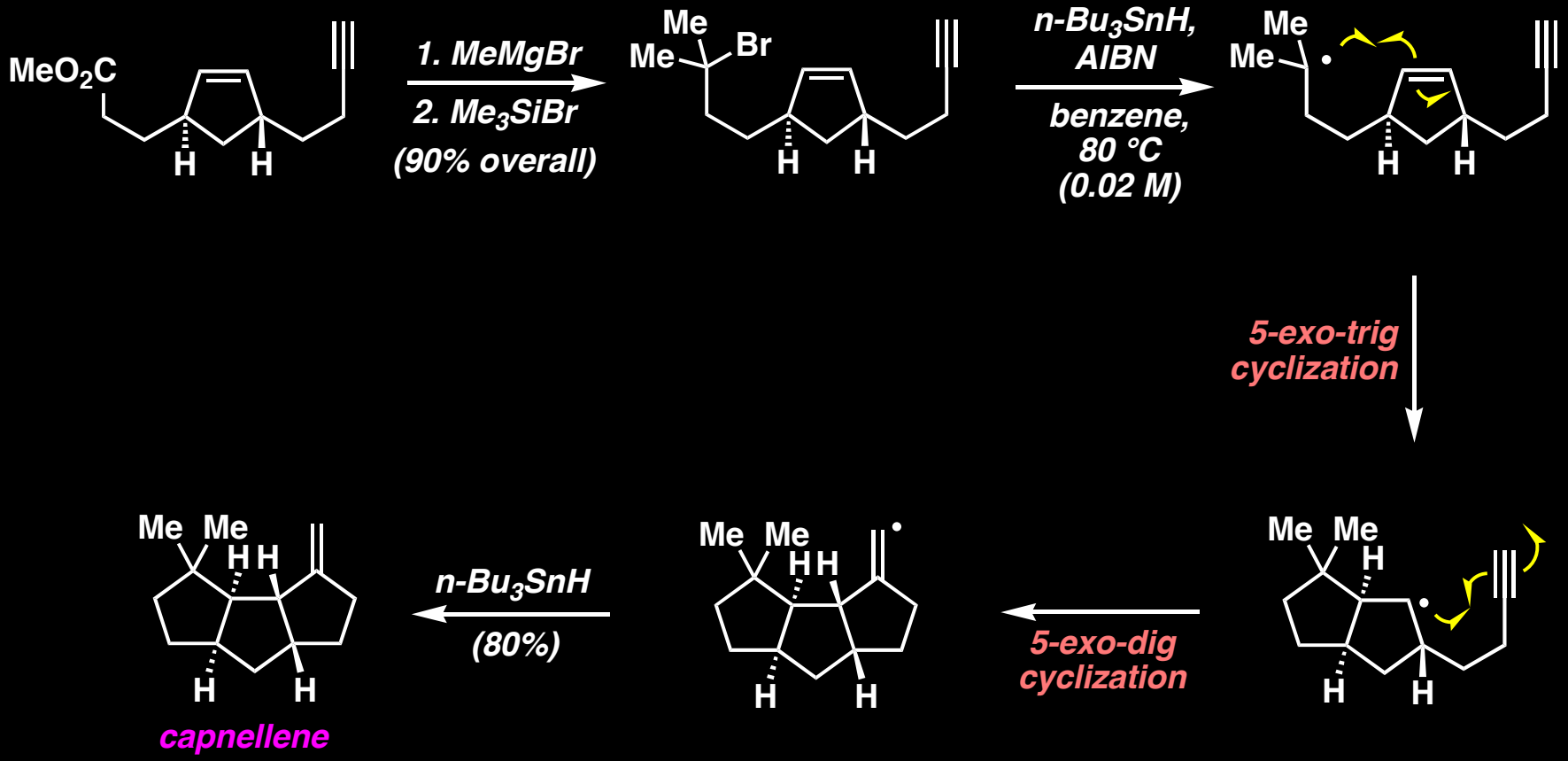
D. P. Curran and co-workers, Tetrahedron 1985, 41, 3943.

Radical-based Cascade Cyclizations: Curran's Total Synthesis of Hirsutene



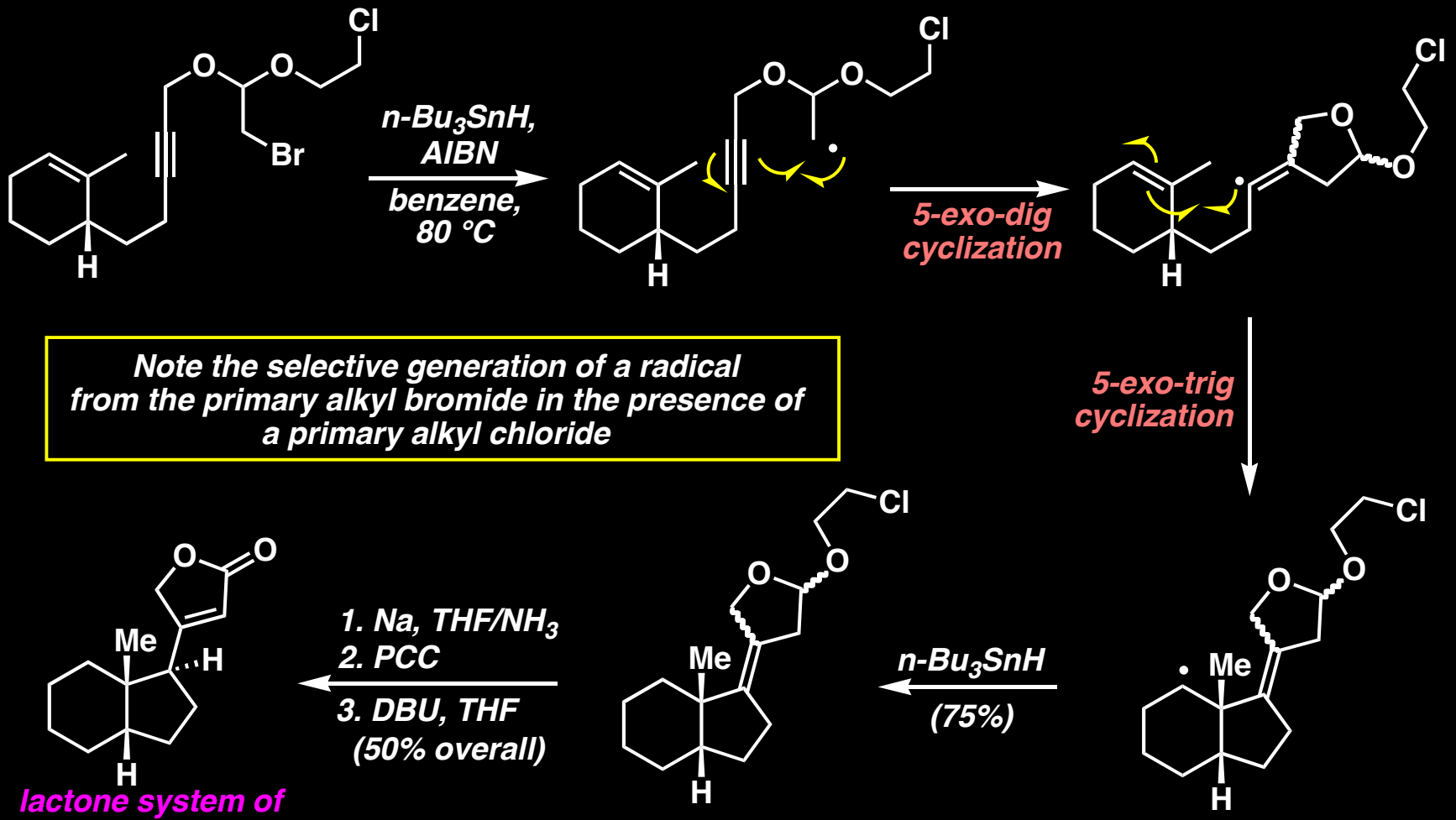
D. P. Curran and co-workers, J. Am. Chem. Soc. 1985, 107, 1448.
D. P. Curran and co-workers, Tetrahedron 1985, 41, 3943.

Radical Cyclizations: Curran's Total Synthesis of Capnellene



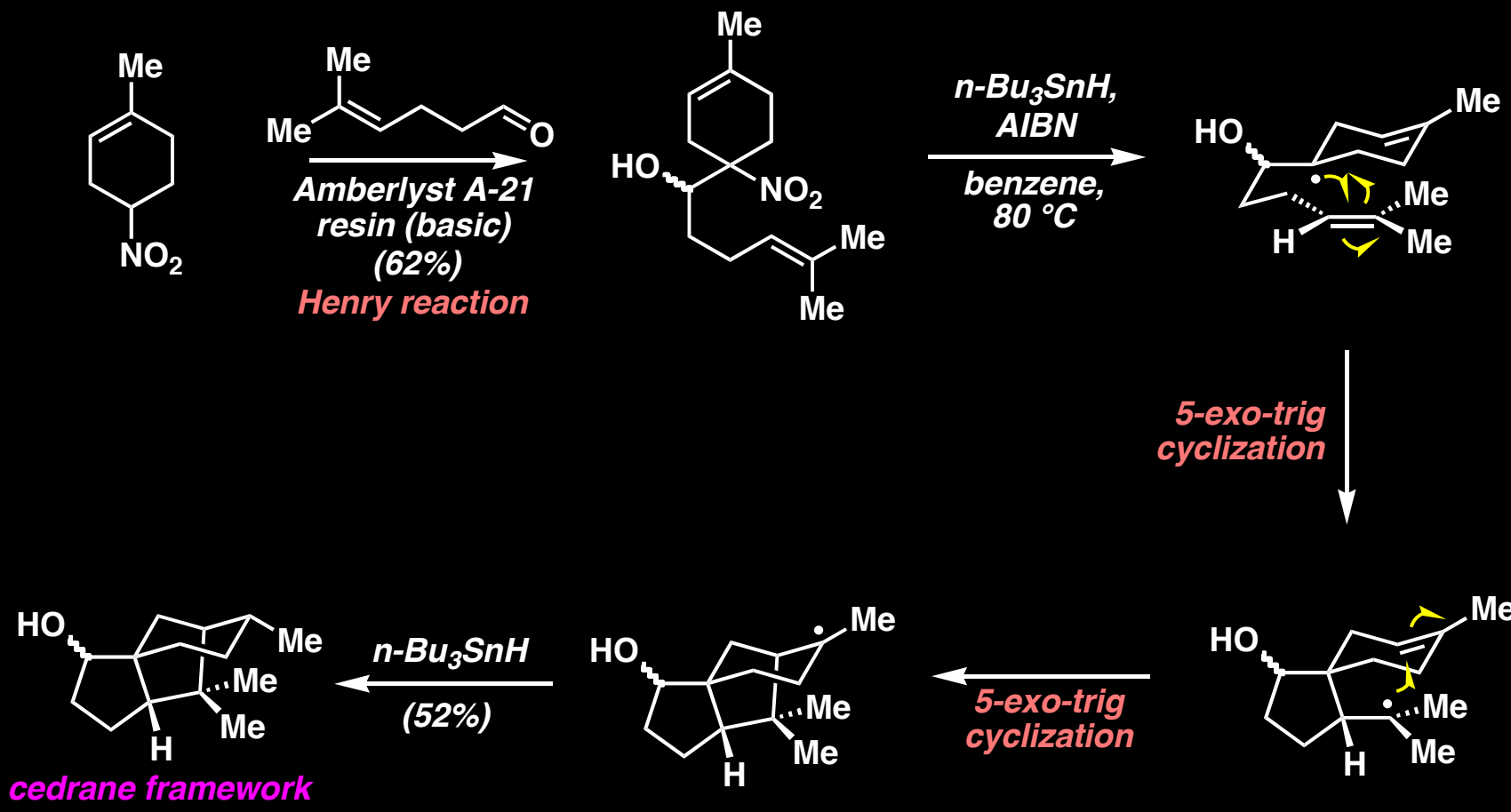
D. P. Curran and co-workers, Tetrahedron Lett. 1985, 26, 4991.

Radical Cyclizations: Stork's Approach to the Cardiac Aglycones



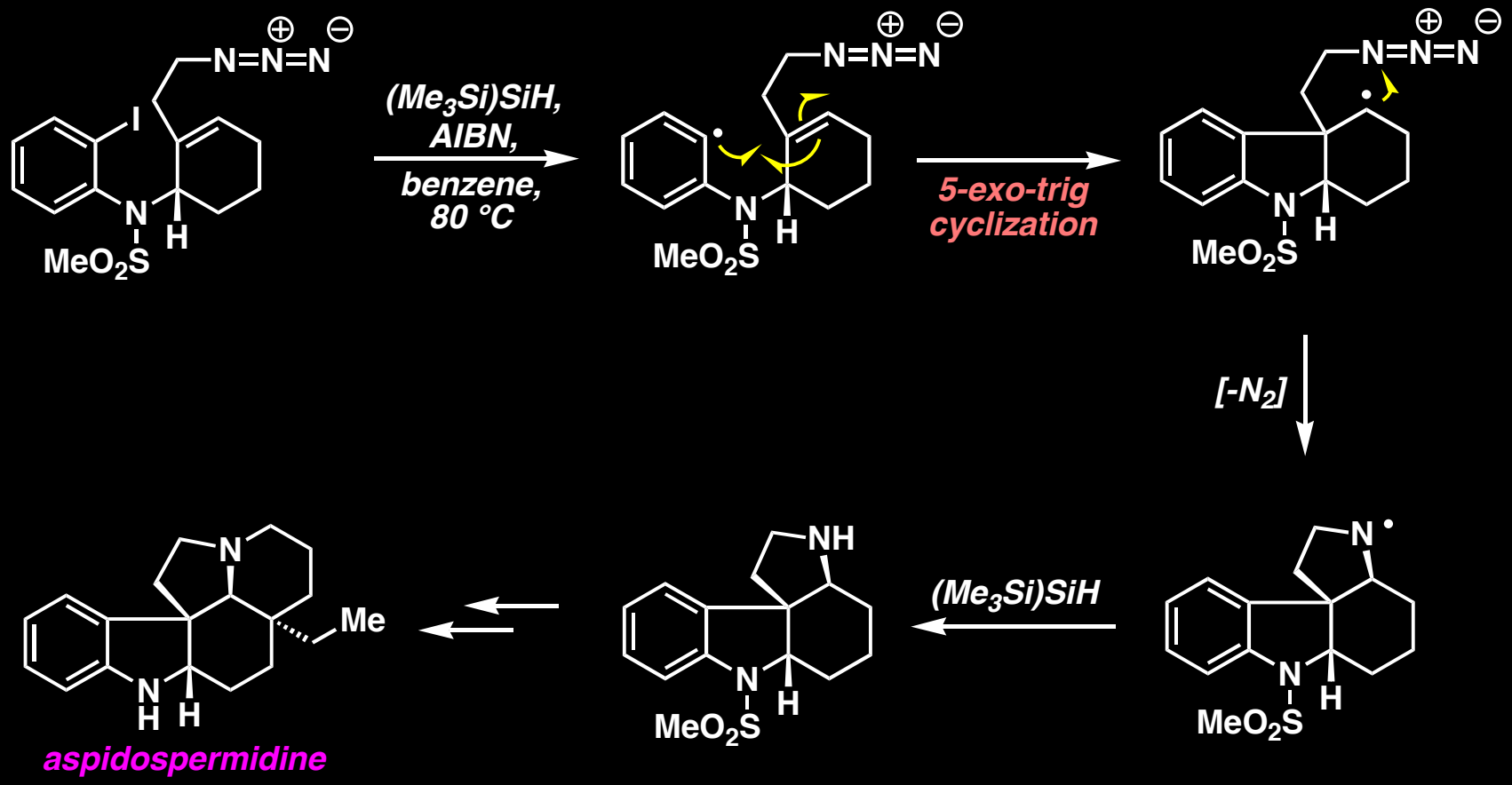
G. Stork and co-workers, J. Am. Chem. Soc. 1983, 105, 3720.
G. Stork and co-workers, J. Am. Chem. Soc. 1983, 105, 3741.

Radical Cyclizations: Chen's Approach to the Cedrane Framework



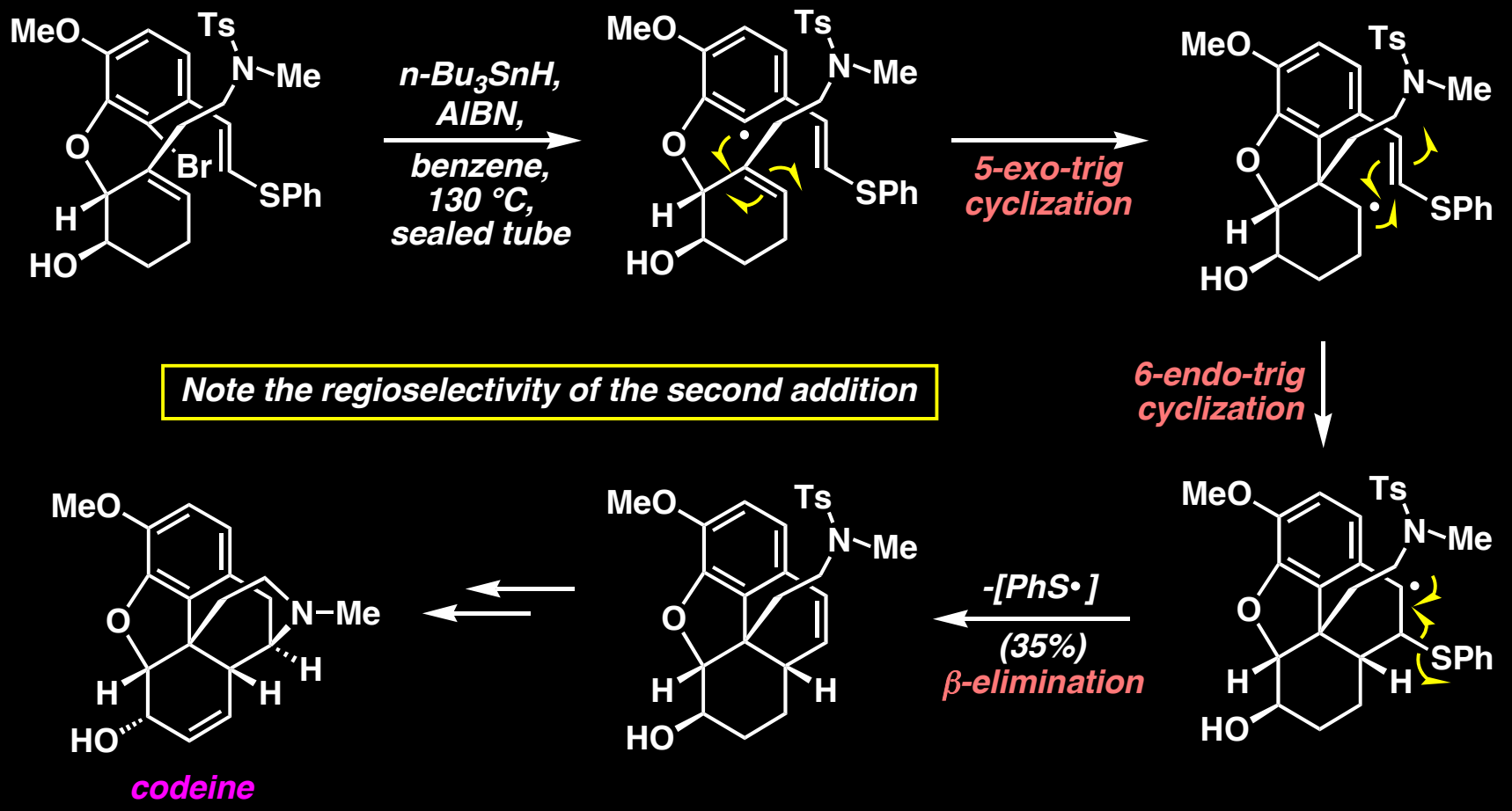
Y. Chen and co-workers, J. Am. Chem. Soc. 1986, 108, 6384.

Radical Cyclizations: Murphy's Approach to the Core Rings of Aspidospermidine



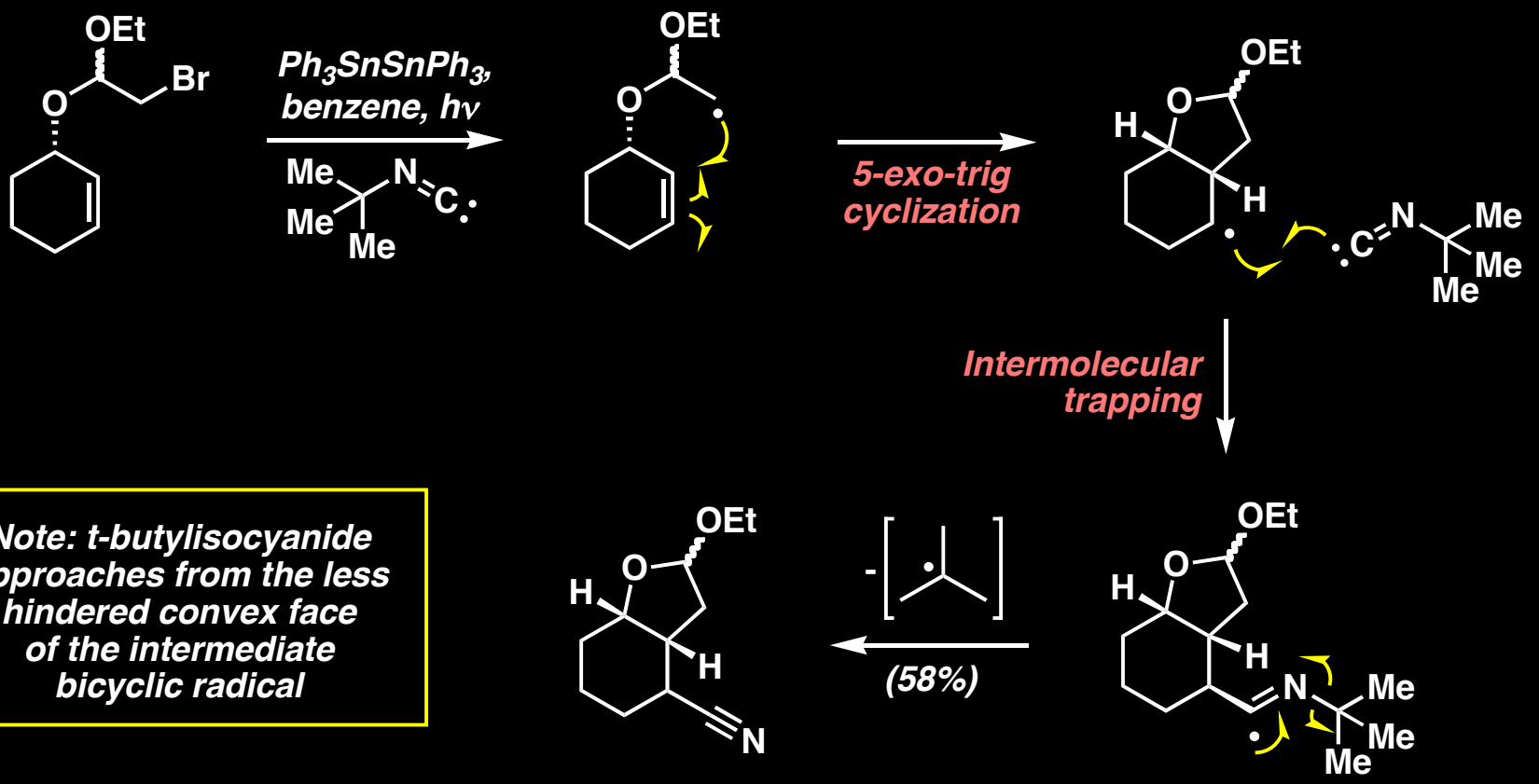
P. J. Murphy and co-workers, J. Chem. Soc., Chem. Commun. 1995, 1409.

Radical Cyclizations: Parker's Approach to Codeine



K. A. Parker and co-workers, J. Am. Chem. Soc. 1992, 114, 9688.

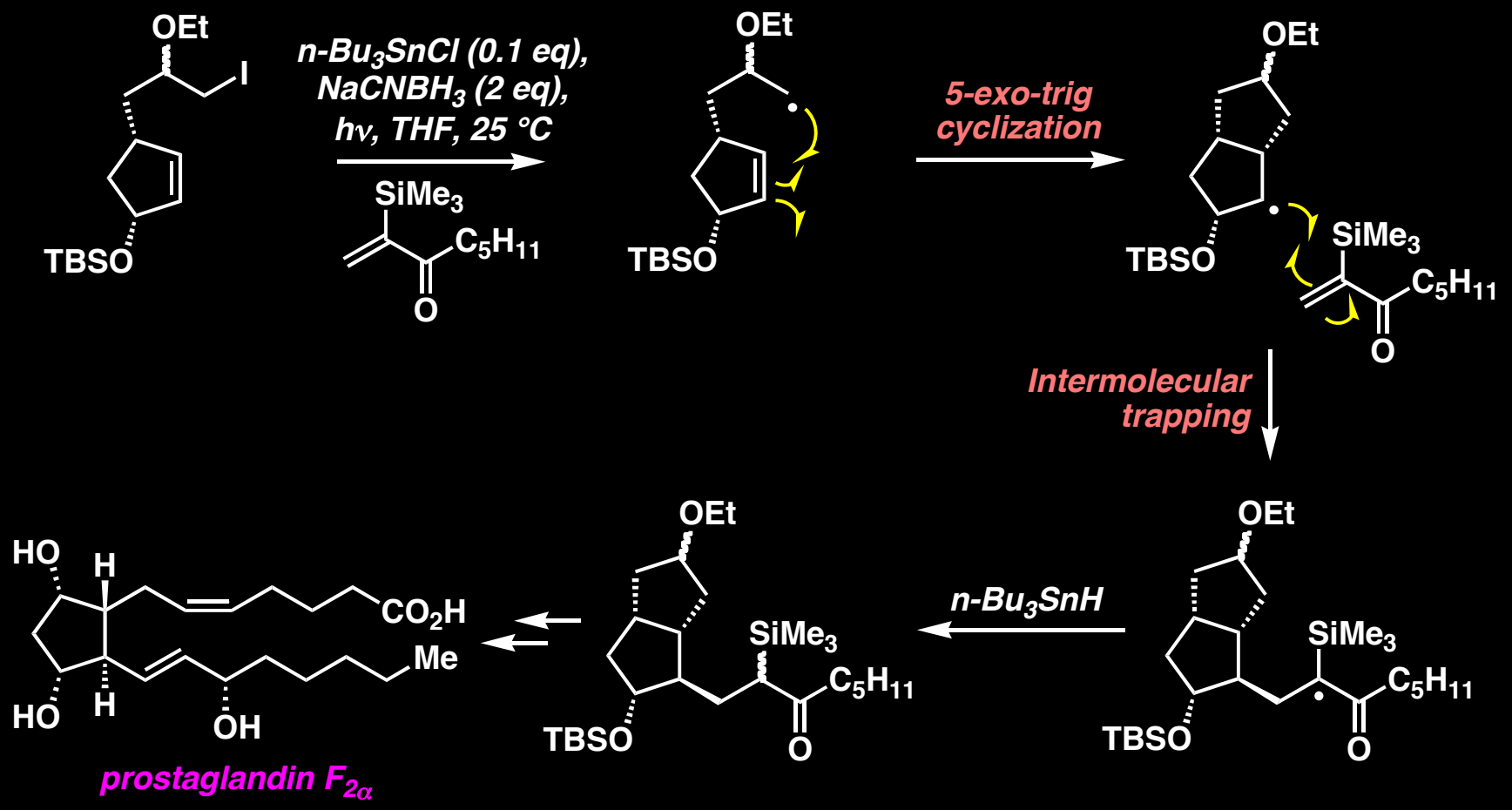
Radical Cyclizations: Stork's Tandem Vicinal Difunctionalization



Note: t-butylisocyanide approaches from the less hindered convex face of the intermediate bicyclic radical

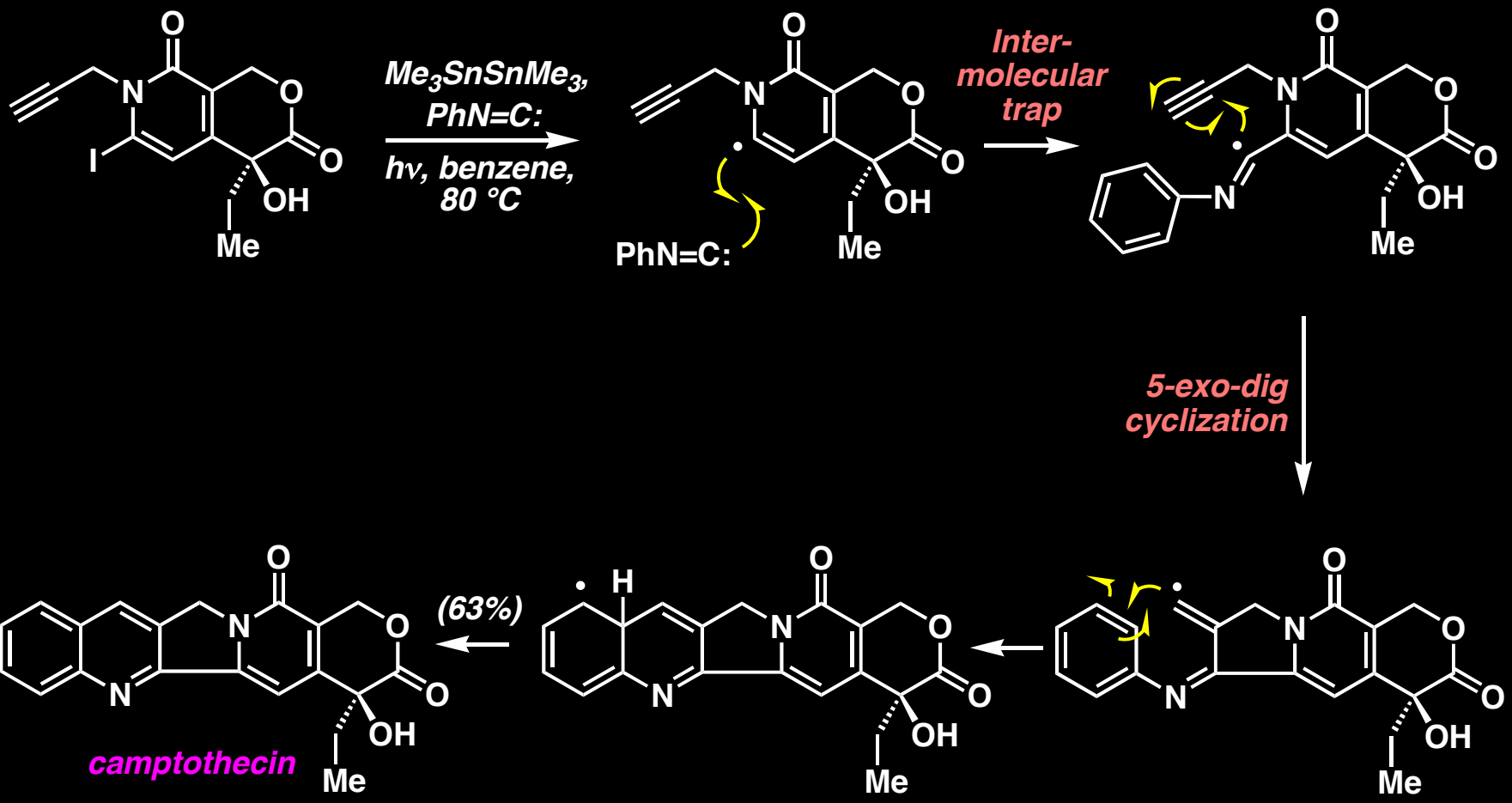
G. Stork and co-workers, J. Am. Chem. Soc. 1983, 105, 6765.

Radical Cyclizations: Stork's Tandem Vicinal Difunctionalization in Synthesis



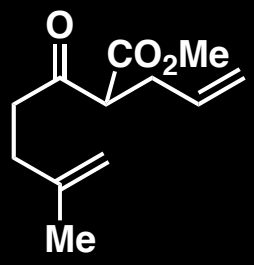
G. Stork and co-workers, J. Am. Chem. Soc. 1986, 108, 6384.

Radical Cyclizations: Curran's Synthesis of Camptothecin



D. P. Curran and co-workers, Angew. Chem. Int. Ed. Engl. 1995, 34, 2683.

Oxidative Free-Radical Cyclizations: $Mn(OAc)_3/Cu(OAc)_2$



B. B. Snider and co-workers, J. Org. Chem. 1987, 52, 5487.

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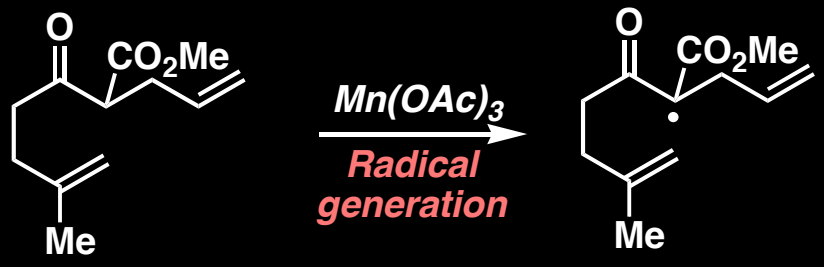

B. B. Snider and co-workers, J. Org. Chem. 1987, 52, 5487.

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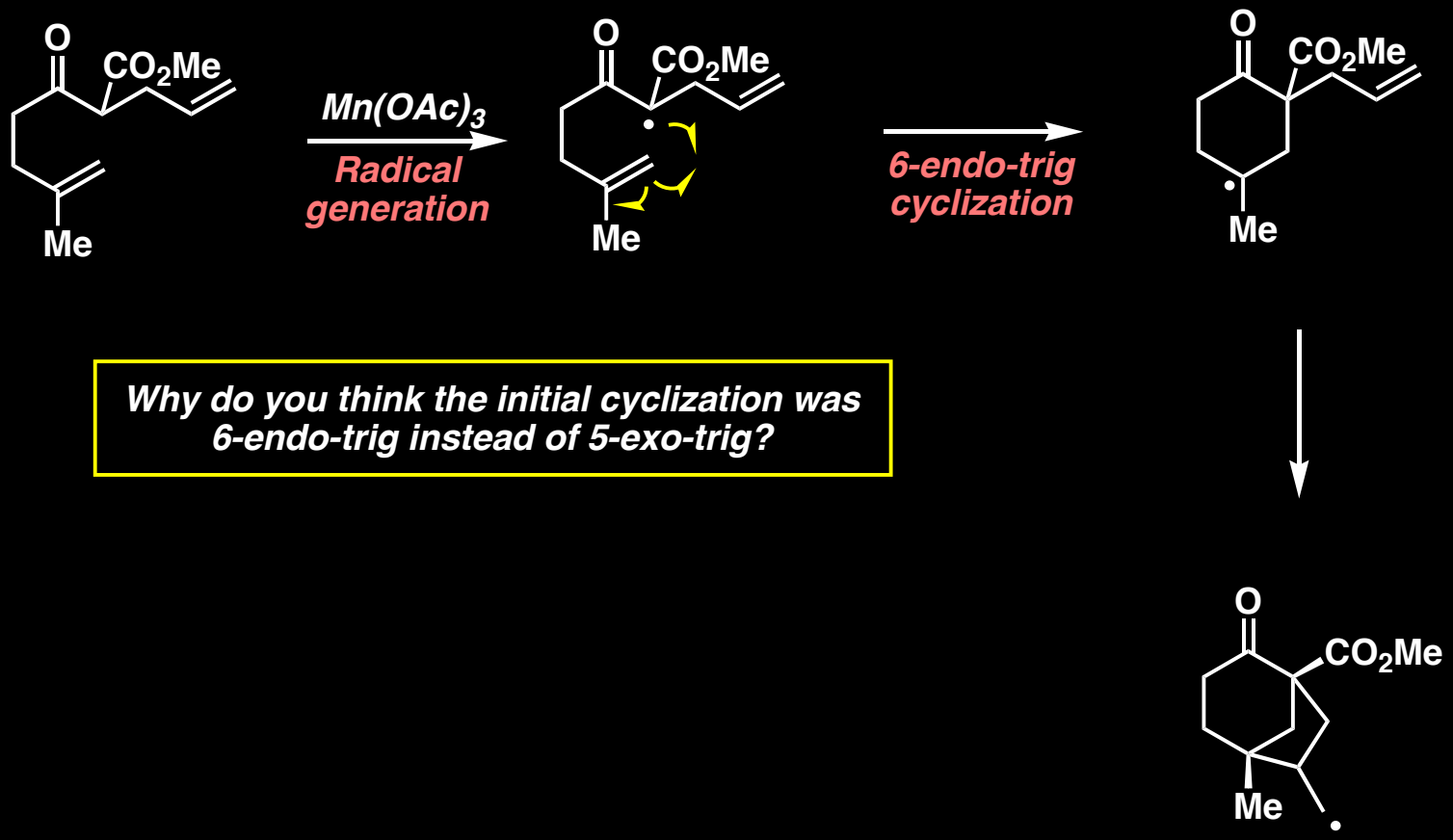
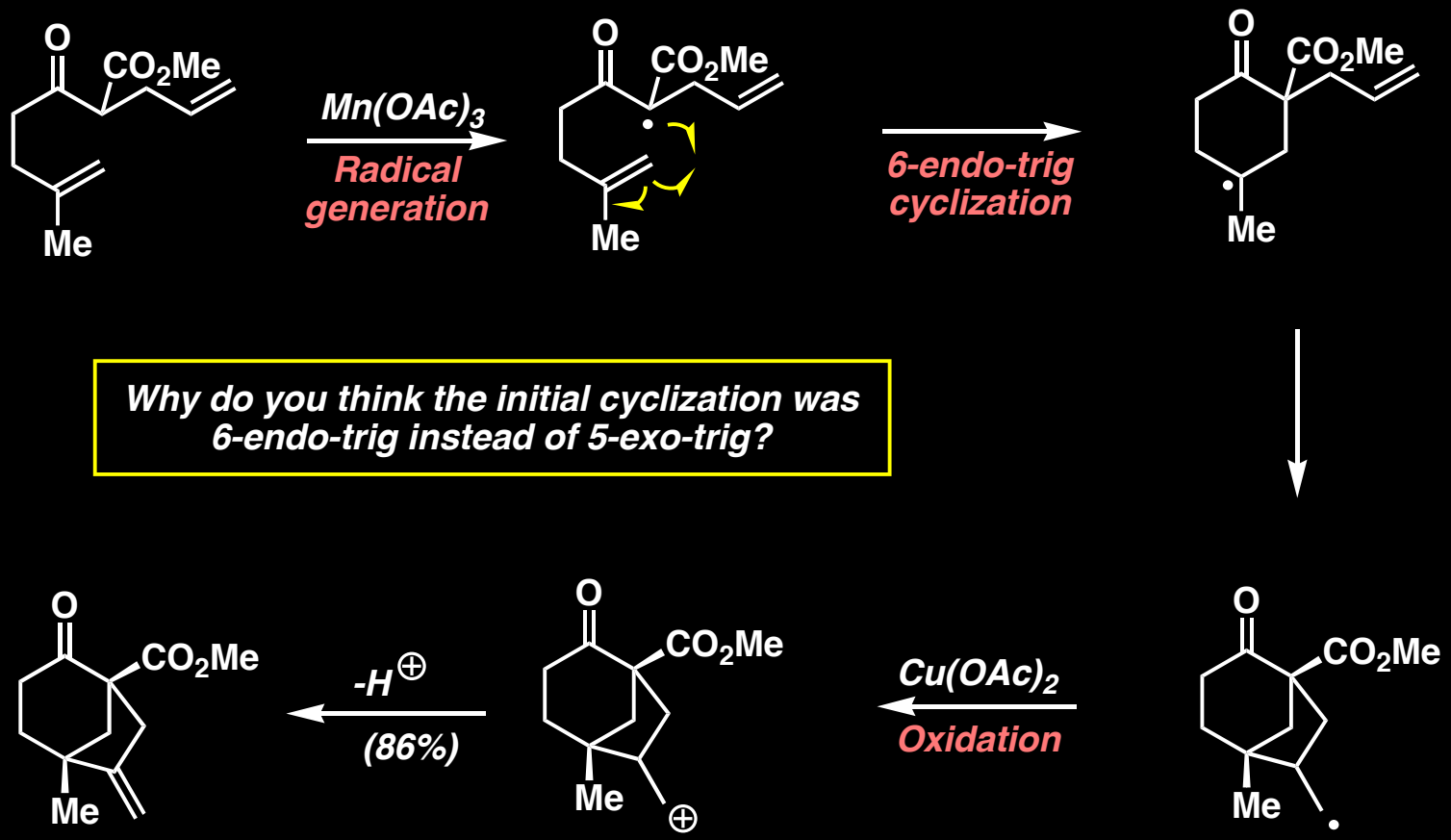


Why do you think the initial cyclization was 6-endo-trig instead of 5-exo-trig?

B. B. Snider and co-workers, J. Org. Chem. 1987, 52, 5487.

Oxidative Free-Radical Cyclizations: $Mn(OAc)_3/Cu(OAc)_2$



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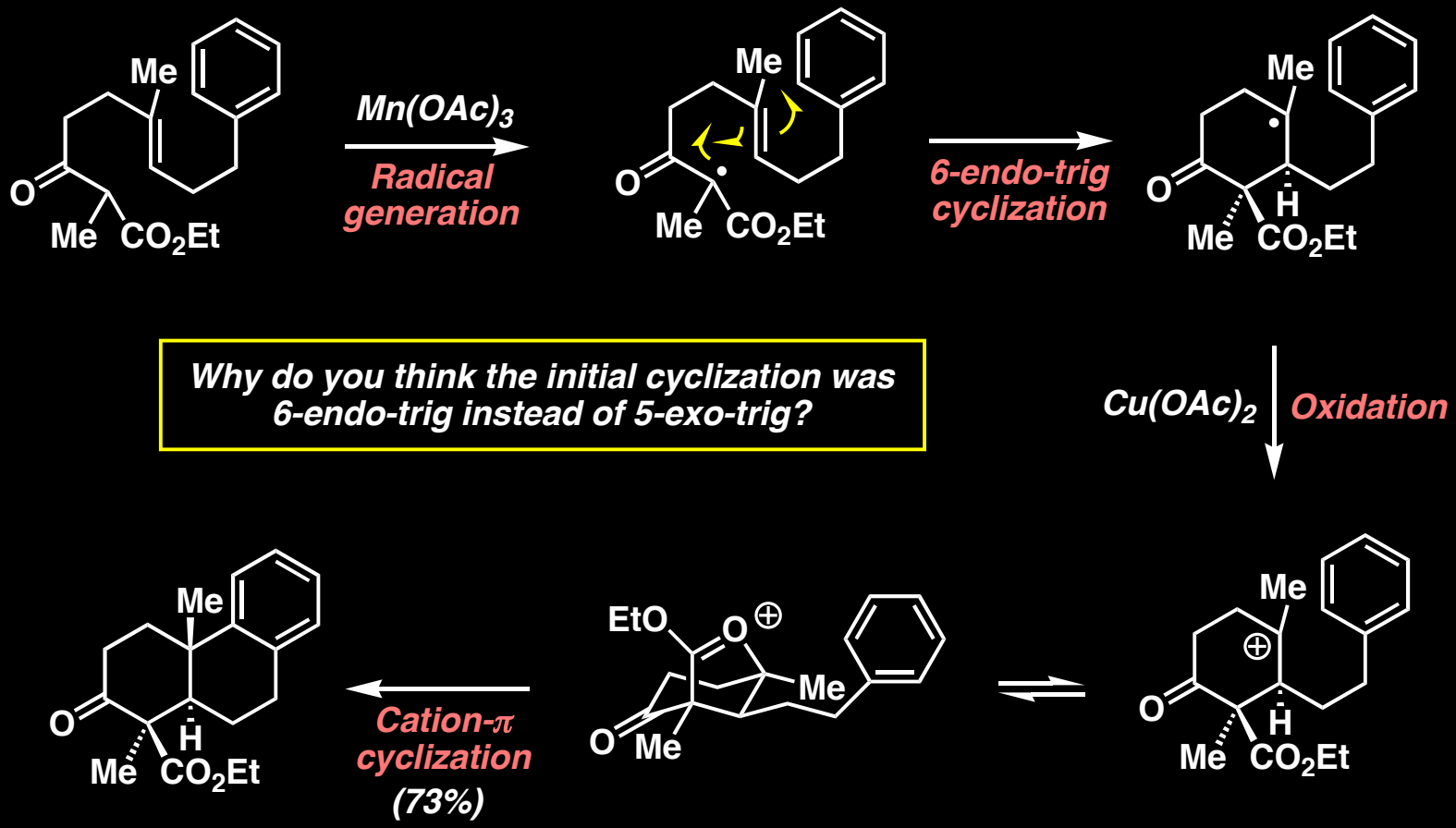
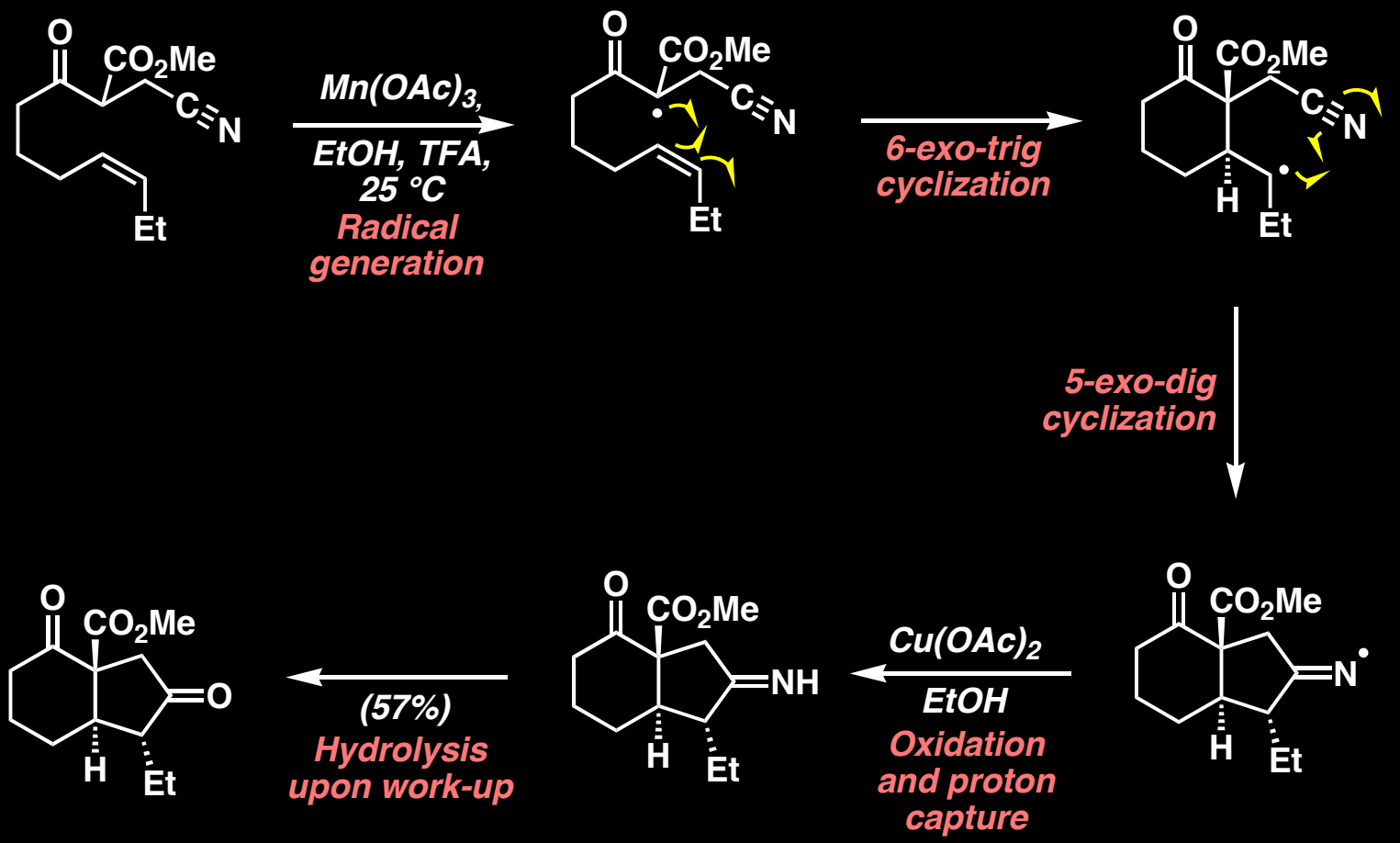


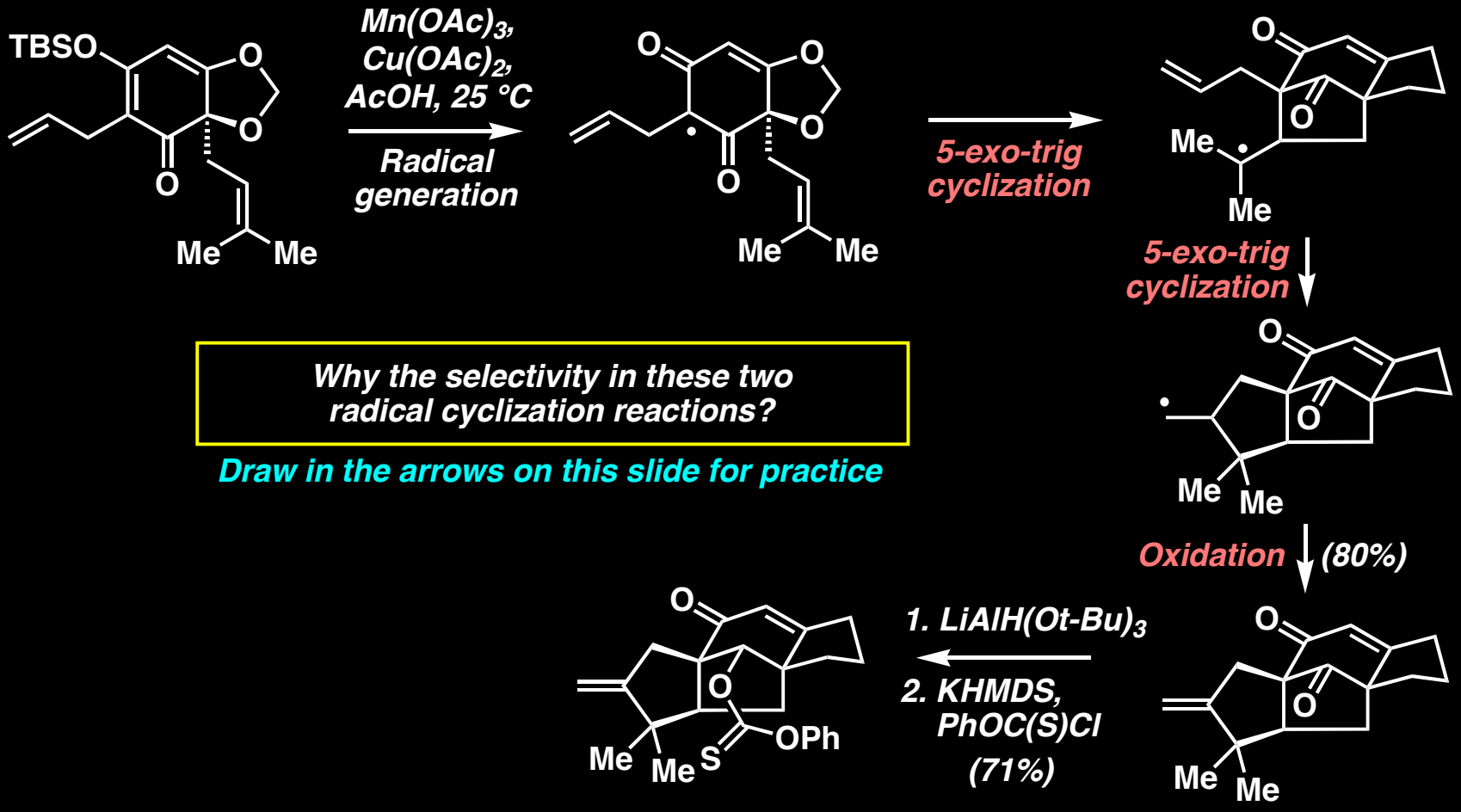
B. B. Snider and co-workers, Tetrahedron Lett. 1987, 28, 841.

Oxidative Free-Radical Cyclizations: $Mn(OAc)_3/Cu(OAc)_2$



B. B. Snider and co-workers, J. Org. Chem. 1992, 57, 322.

Oxidative Free-Radical Cyclizations: $Mn(OAc)_3/Cu(OAc)_2$ Combined With Deoxygenation

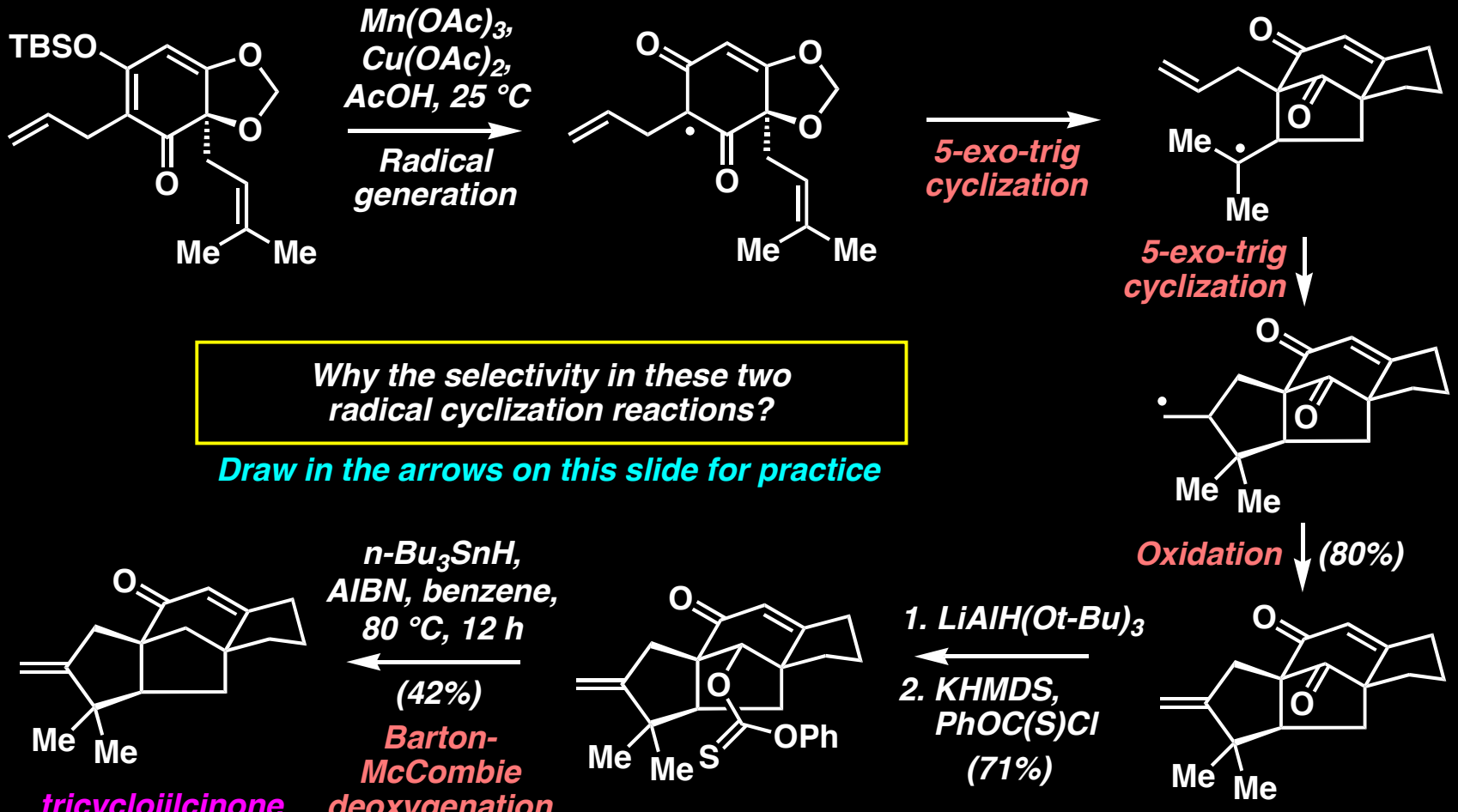


Why the selectivity in these two radical cyclization reactions?

Draw in the arrows on this slide for practice

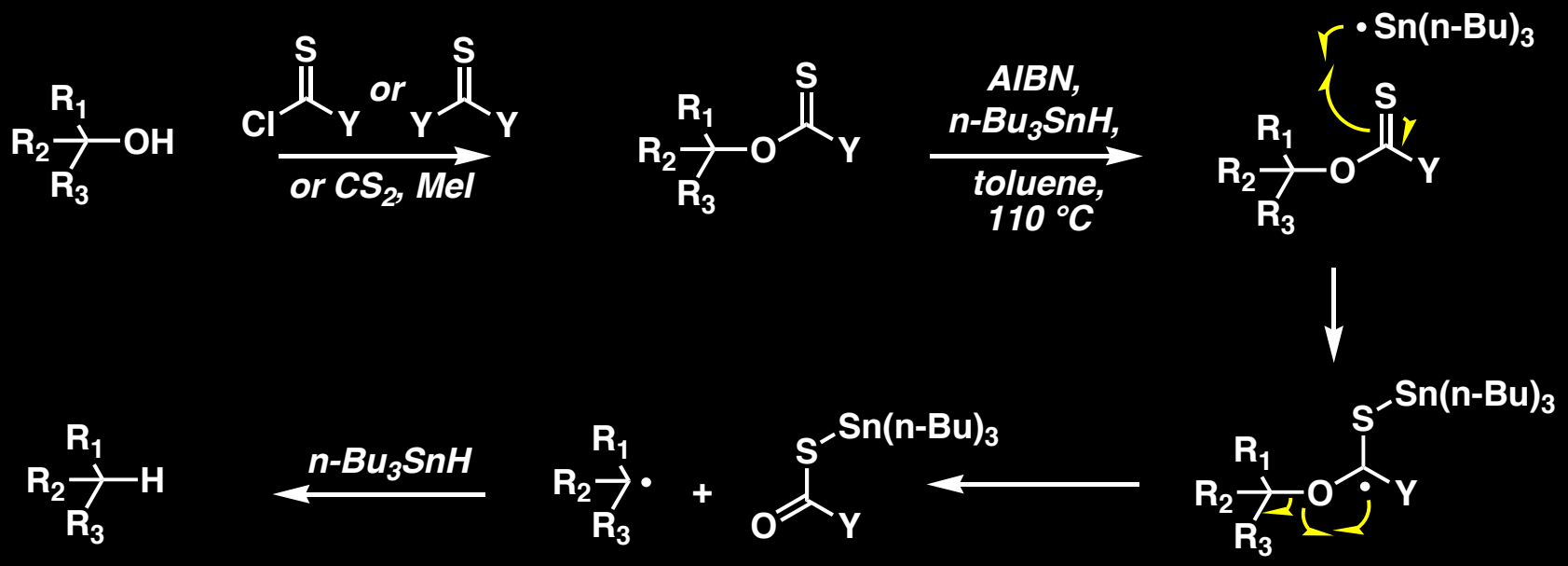
S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 2000, 122, 6160.

Oxidative Free-Radical Cyclizations: $Mn(OAc)_3/Cu(OAc)_2$ Combined With Deoxygenation



S. J. Danishefsky and co-workers, J. Am. Chem. Soc. 2000, 122, 6160.

Barton-McCombie Deoxygenation: Background and General Considerations



D. H. R. Barton, S. W. McCombie, J. Chem. Soc., Perkin Trans. 1 1975, 1574.

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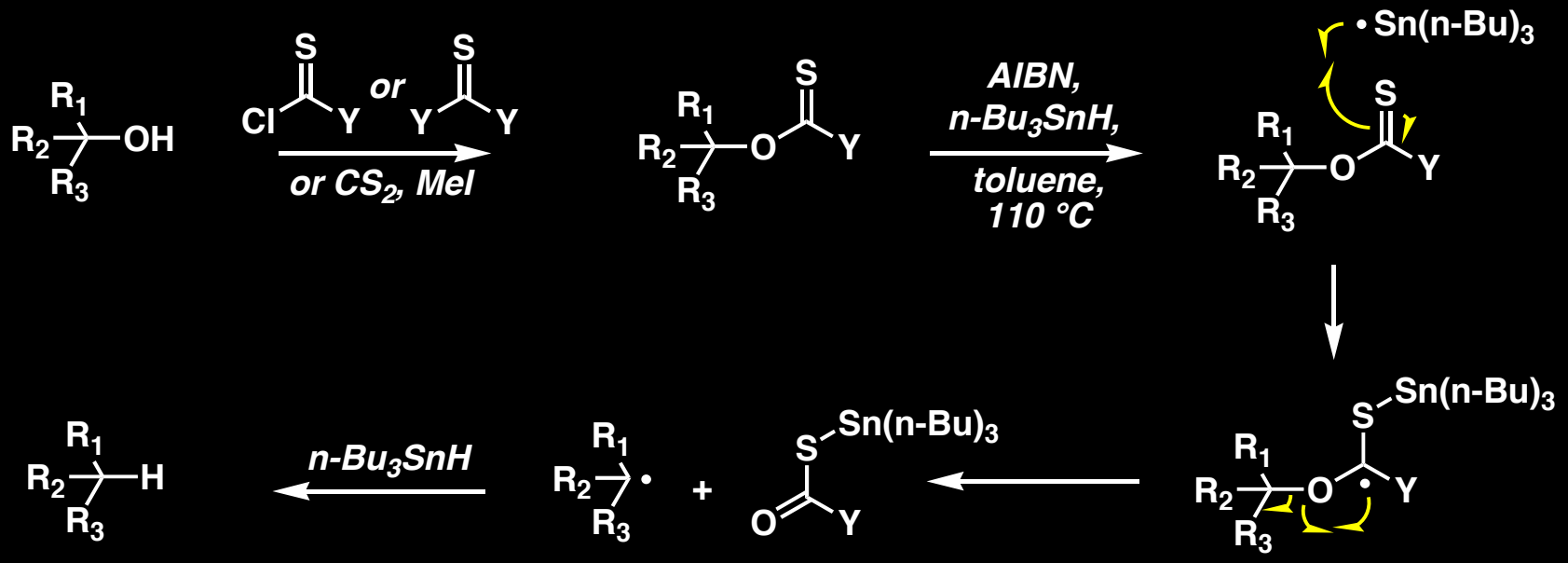
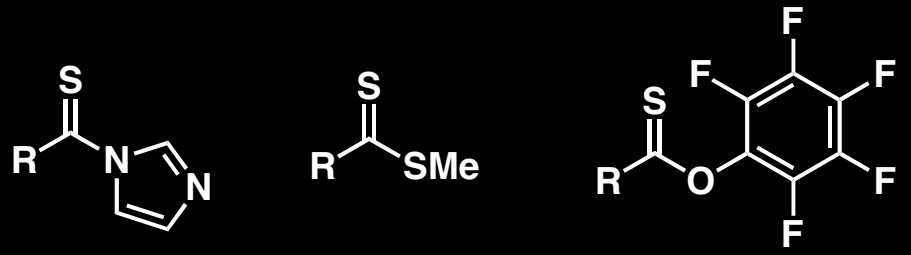




Typical deoxygenation substrates

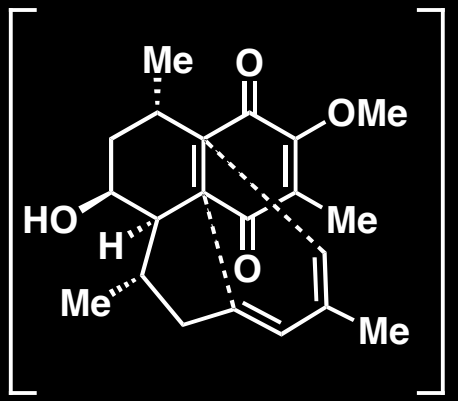
Method works well for most hydroxyl groups, including highly hindered secondary and tertiary alcohols.

D. H. R. Barton, S. W. McCombie, J. Chem. Soc., Perkin Trans. 1 1975, 1574.

Barton-McCombie Deoxygenation: Application in a Total Synthesis of Colombiasin A

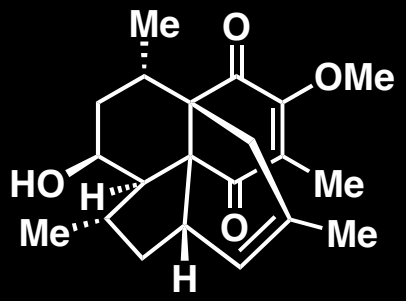
toluene, 180 °C

Cheletropic elimination of SO_2



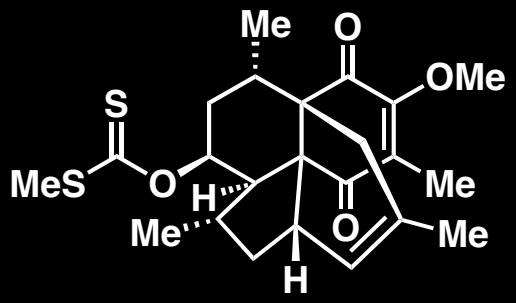
Diels-Alder reaction

(89%)
(100% endo)



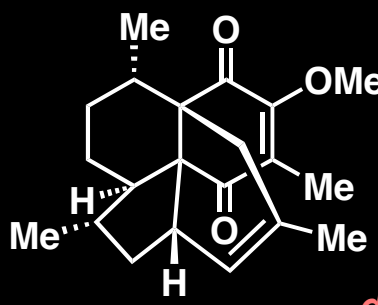
The xanthate ester was the only intermediate that could be successfully attached to this hindered secondary alcohol

NaH, CS_2, MeI *(73%)*



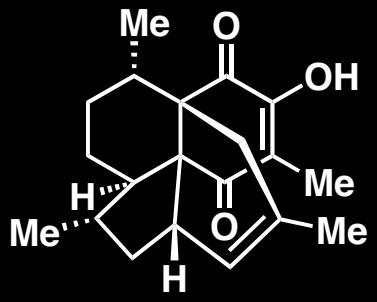
AIBN, $n\text{-}Bu_3SnH$, 110 °C, 30 min

Barton deoxygenation



BBr_3, cis-cyclooctene, CH_2Cl_2, -78 °C, 20 min

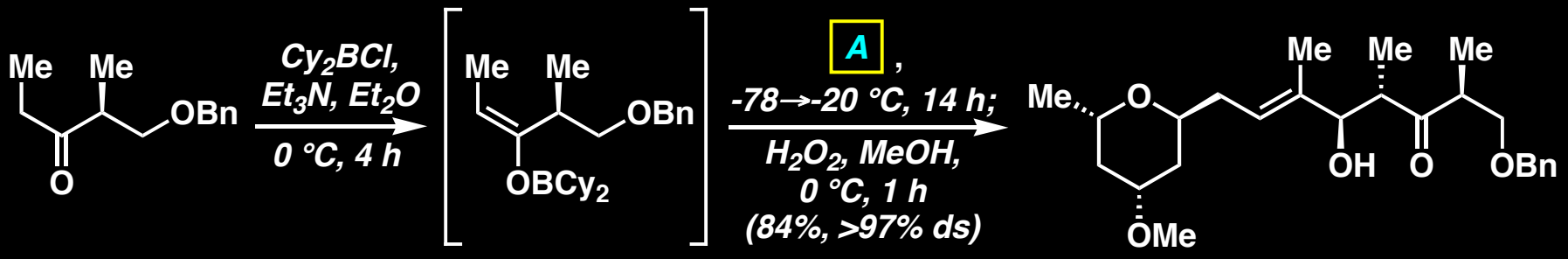
(43% based on 70% conversion)

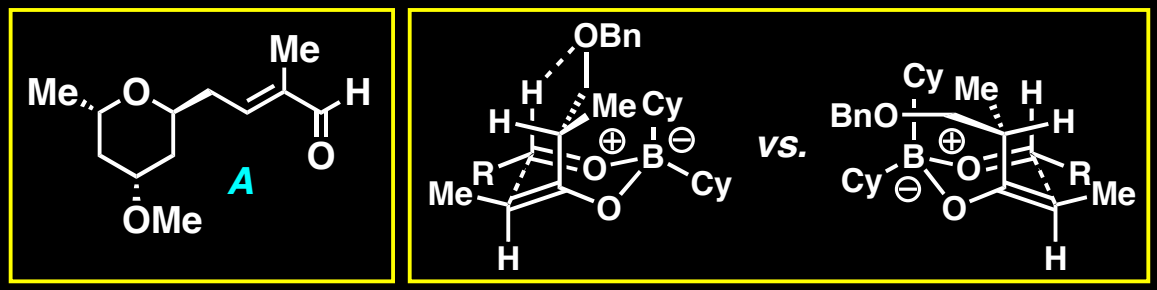


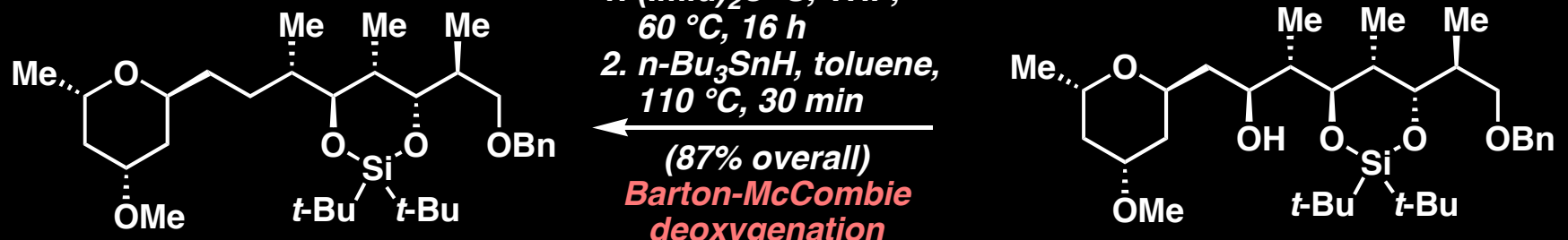
(–)-colombiasin A

K. C. Nicolaou and co-workers, Angew. Chem. Int. Ed. 2001, 40, 2482.

Barton-McCombie Deoxygenation: Application in a Total Synthesis of Swinholide A

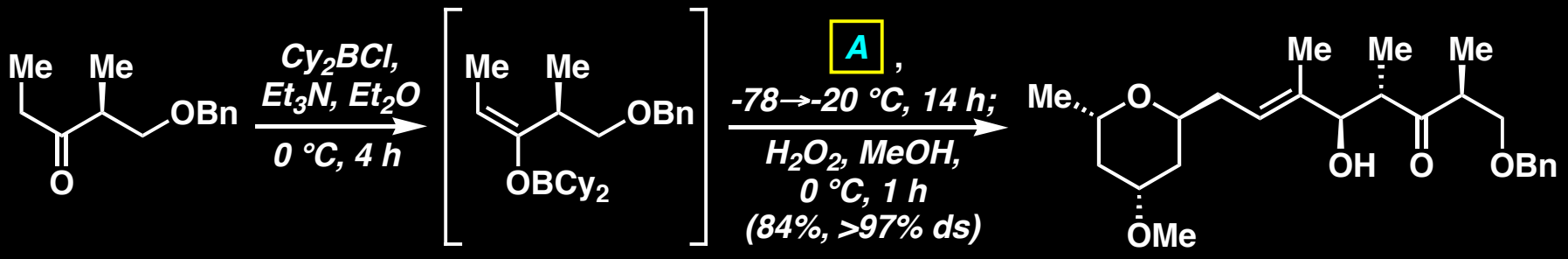


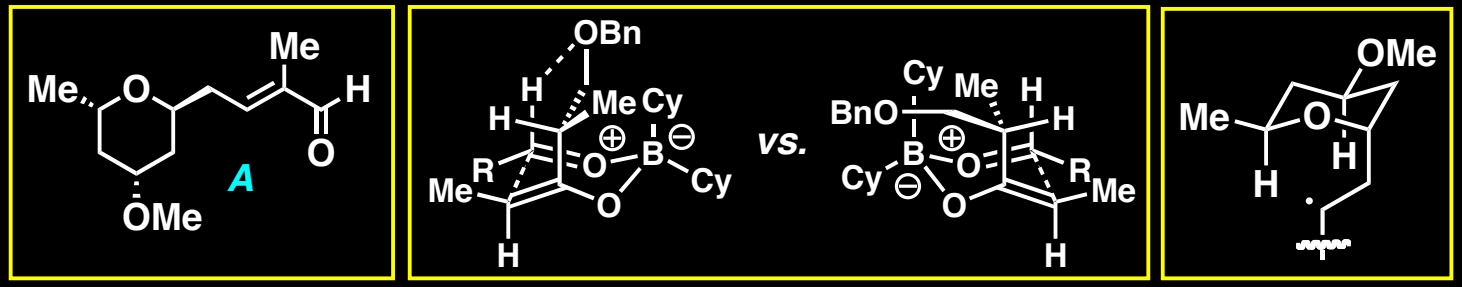


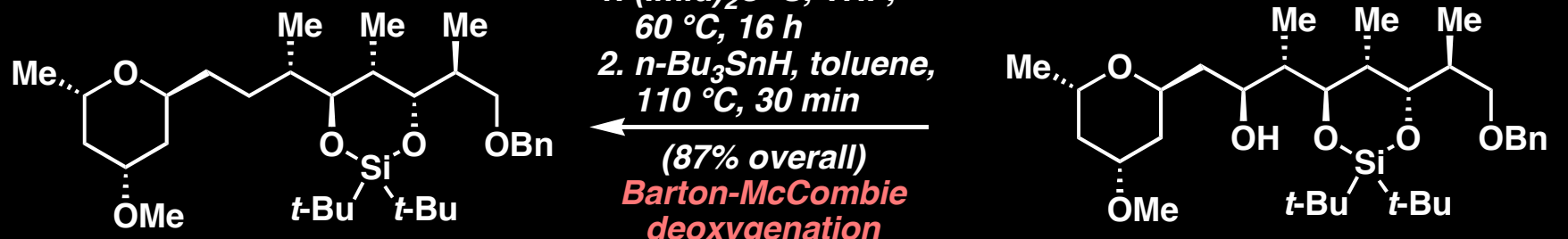


I. Paterson and co-workers, J. Am. Chem. Soc. 1994, 116, 9391.
I. Paterson and co-workers, Tetrahedron 1995, 51, 9394.

Barton-McCombie Deoxygenation: Application in a Total Synthesis of Swinholide A

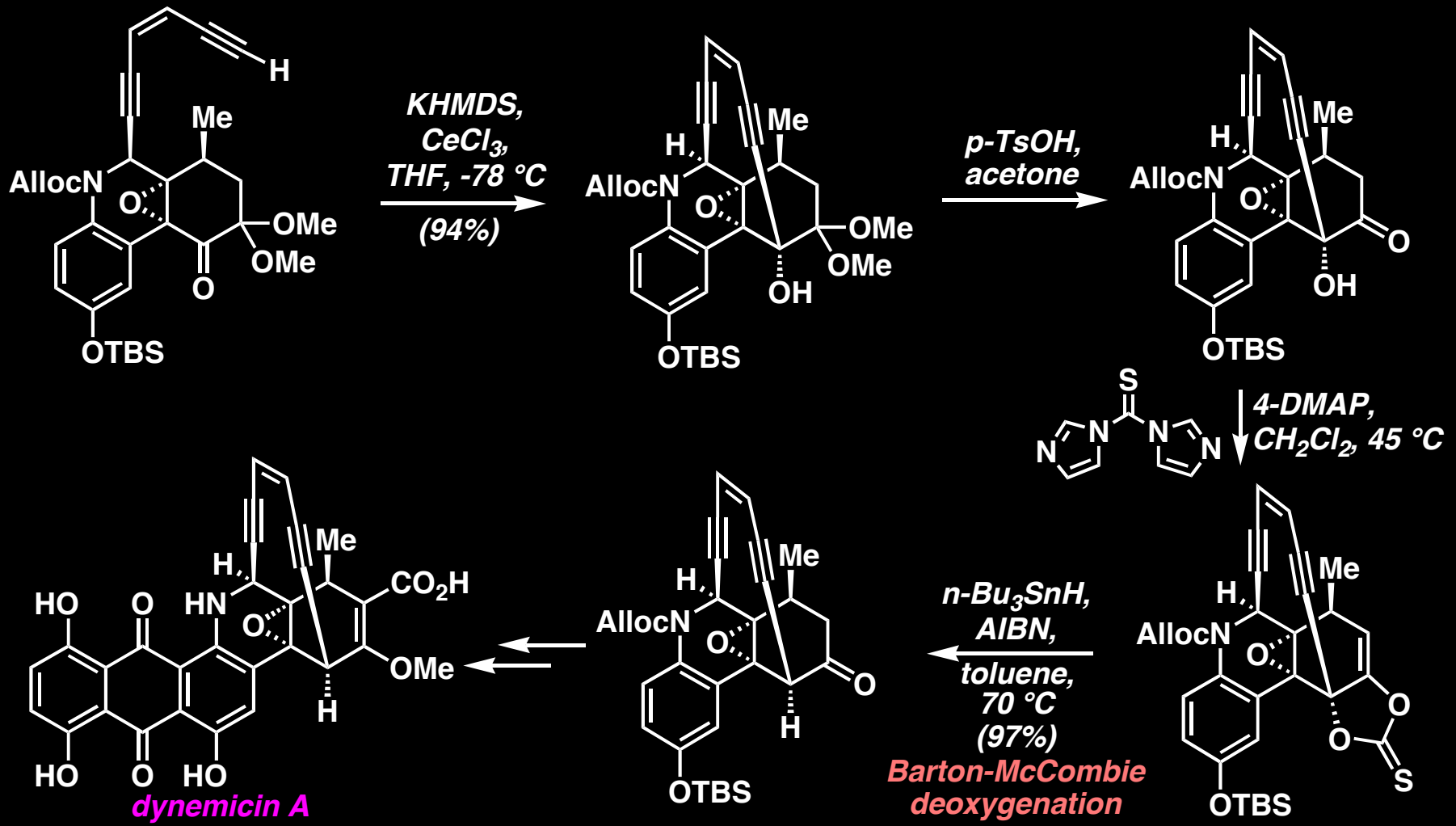






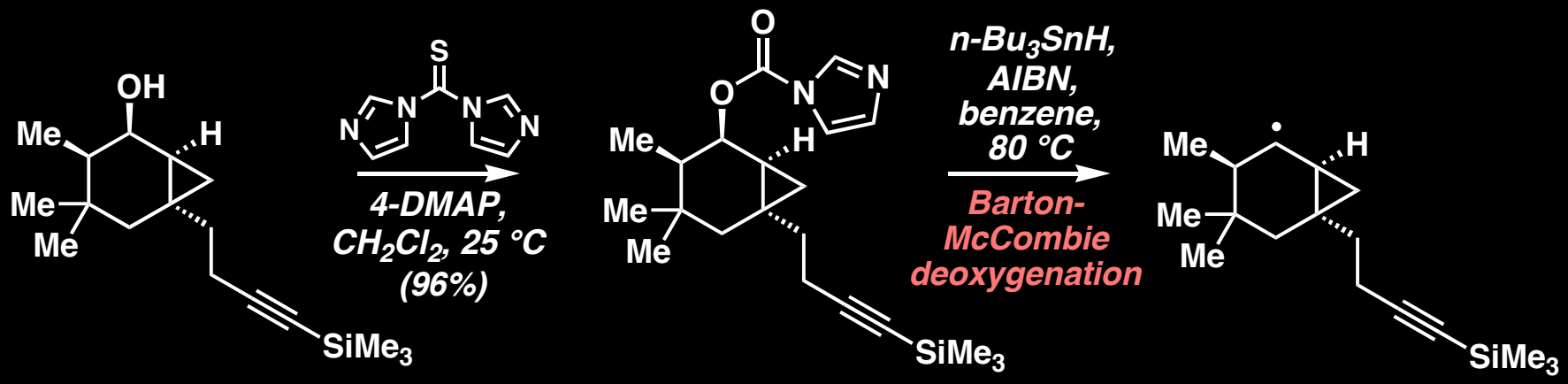
I. Paterson and co-workers, J. Am. Chem. Soc. 1994, 116, 9391.
I. Paterson and co-workers, Tetrahedron 1995, 51, 9394.

Barton-McCombie Deoxygenation: Application in a Total Synthesis of Dynemicin A



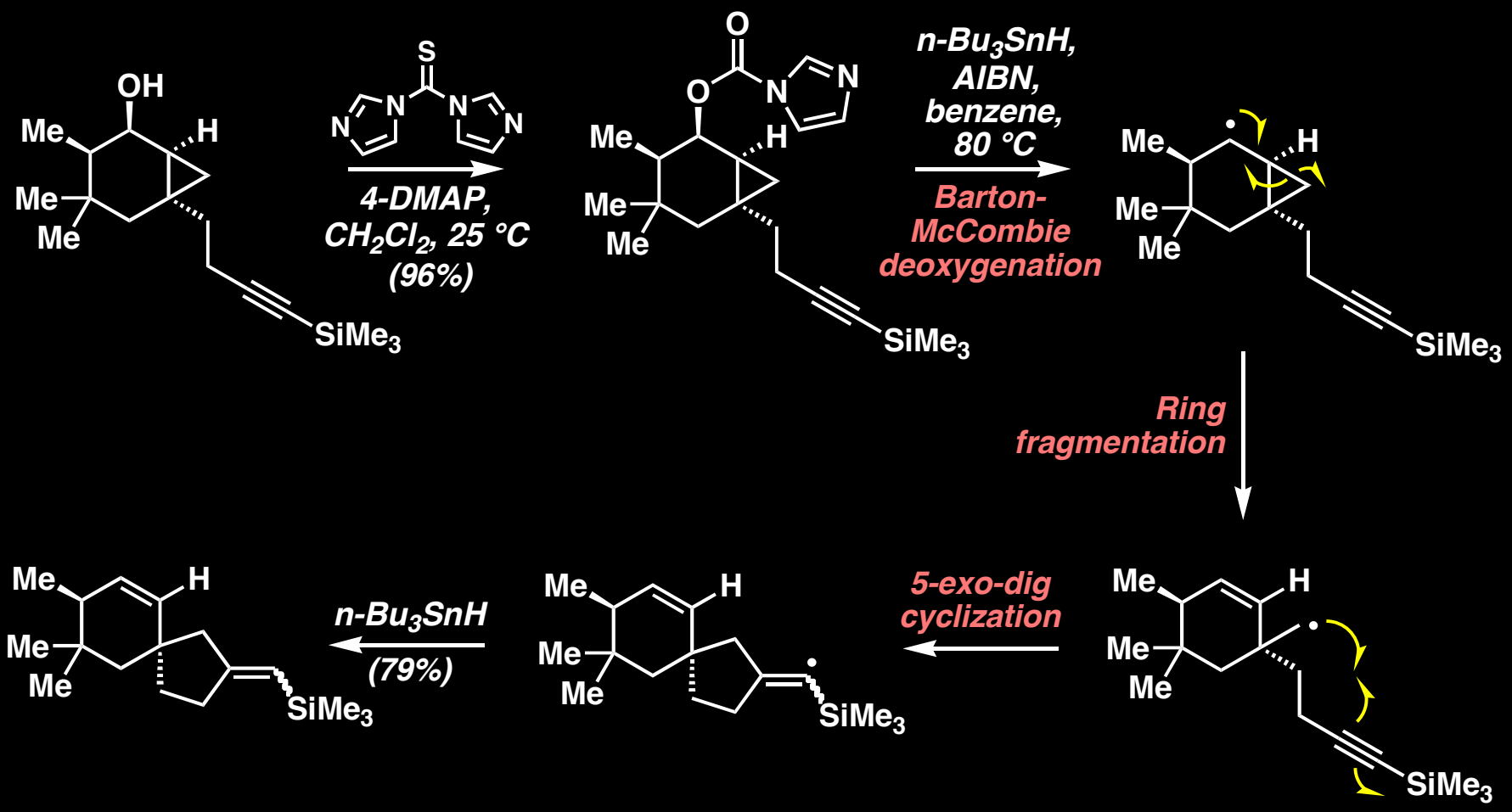
A. G. Myers and co-workers, J. Am. Chem. Soc. 1994, 116, 1670.

Barton-McCombie Deoxygenation: What Can You Do Beyond Removing an Alcohol?



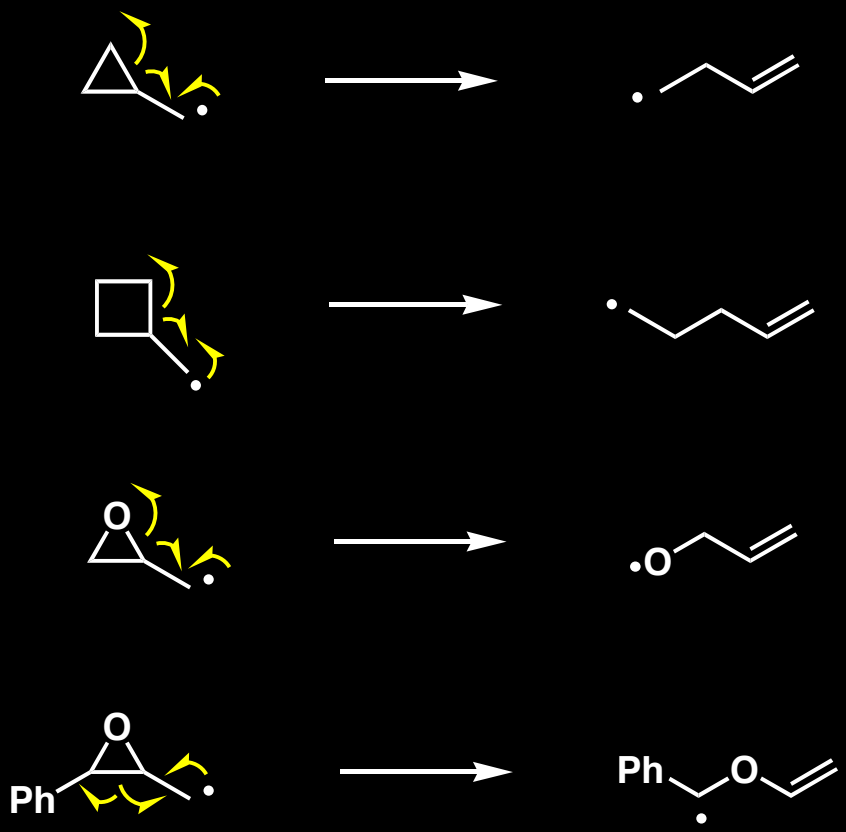
R. Motherwell and co-workers, J. Chem. Soc., Chem. Commun. 1988, 1380.

Barton-McCombie Deoxygenation: What Can You Do Beyond Removing an Alcohol?

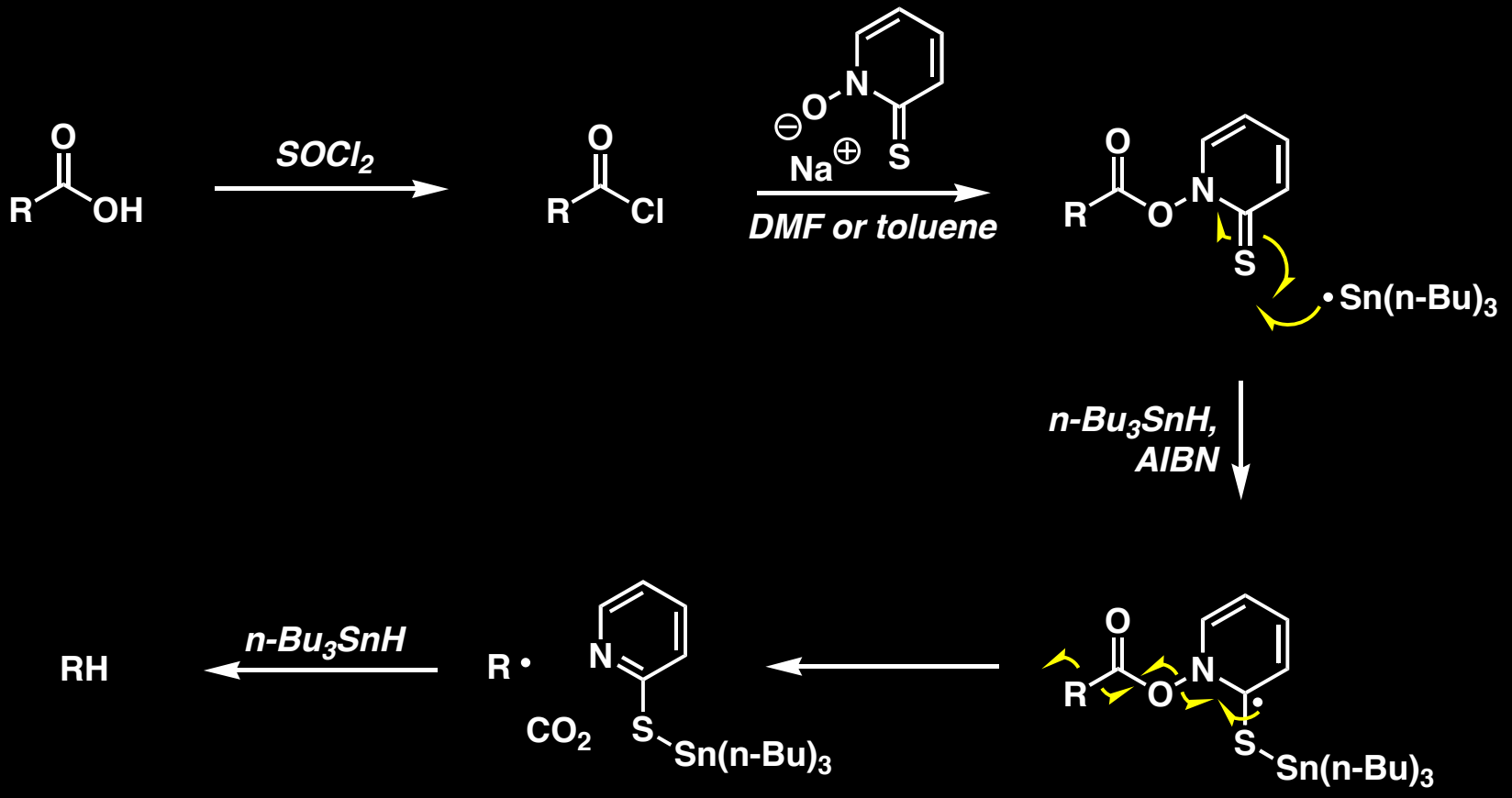


R. Motherwell and co-workers, J. Chem. Soc., Chem. Commun. 1988, 1380.

Radical Rearrangements: Other Possibilities

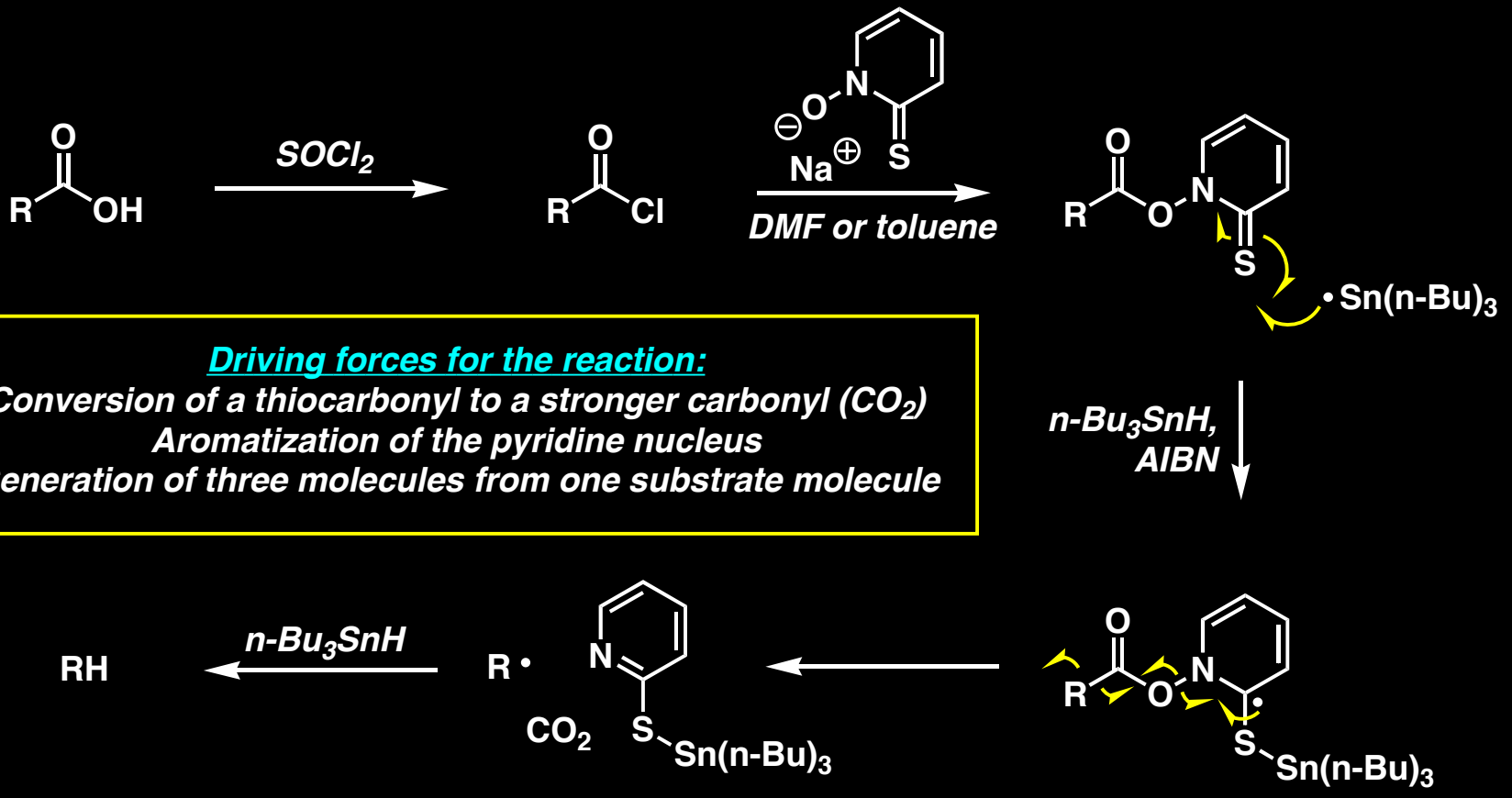


Barton's Thiohydroxamate Esters: Background and General Considerations



D. H. R. Barton and co-workers, J. Chem. Soc., Chem. Commun. 1983, 939.
D. H. R. Barton and co-workers, Tetrahedron 1985, 41, 3901.

Barton's Thiohydroxamate Esters: Background and General Considerations

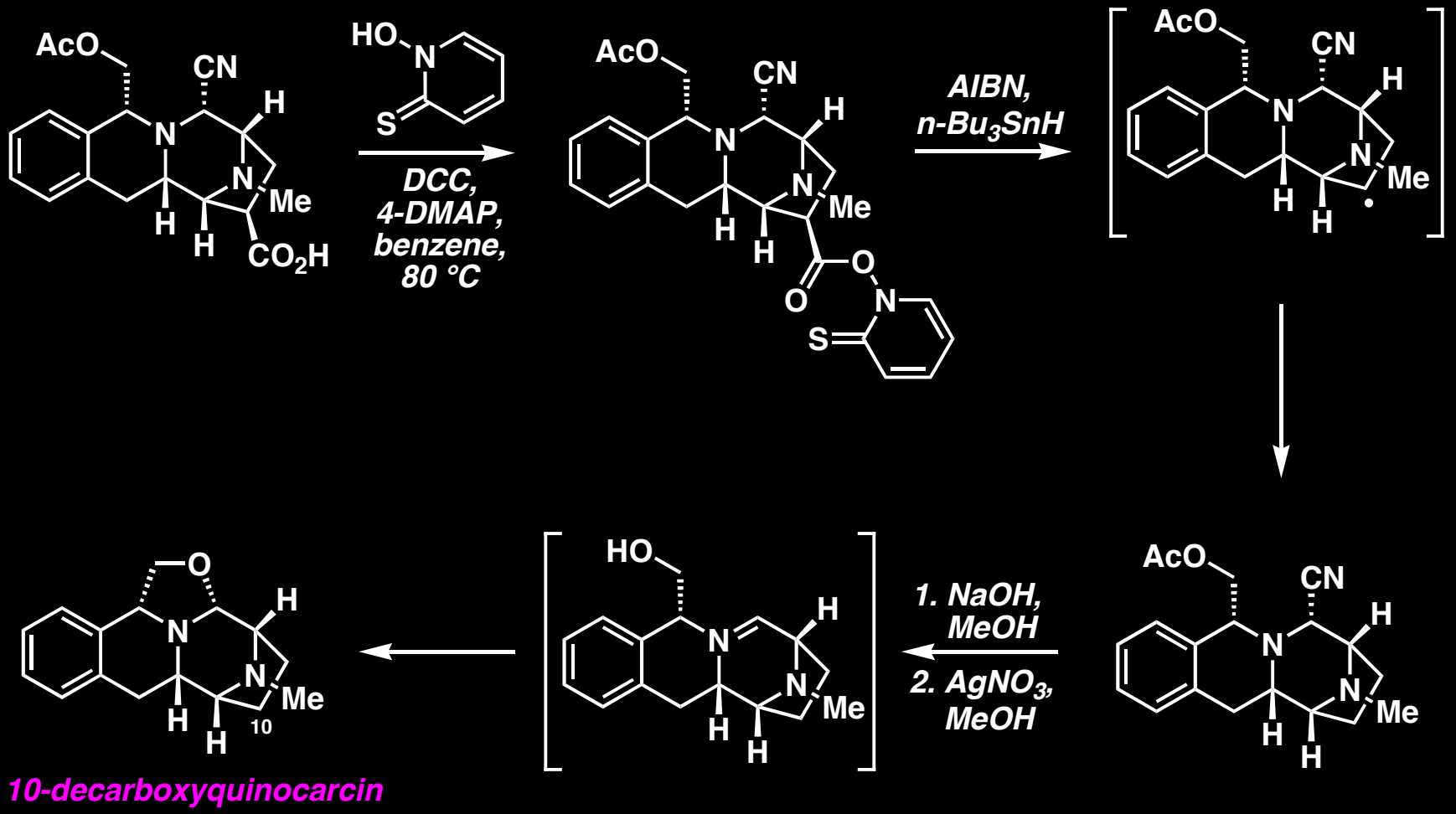


Driving forces for the reaction:

Conversion of a thiocarbonyl to a stronger carbonyl (CO_2)
Aromatization of the pyridine nucleus
Generation of three molecules from one substrate molecule

D. H. R. Barton and co-workers, J. Chem. Soc., Chem. Commun. 1983, 939.
D. H. R. Barton and co-workers, Tetrahedron 1985, 41, 3901.

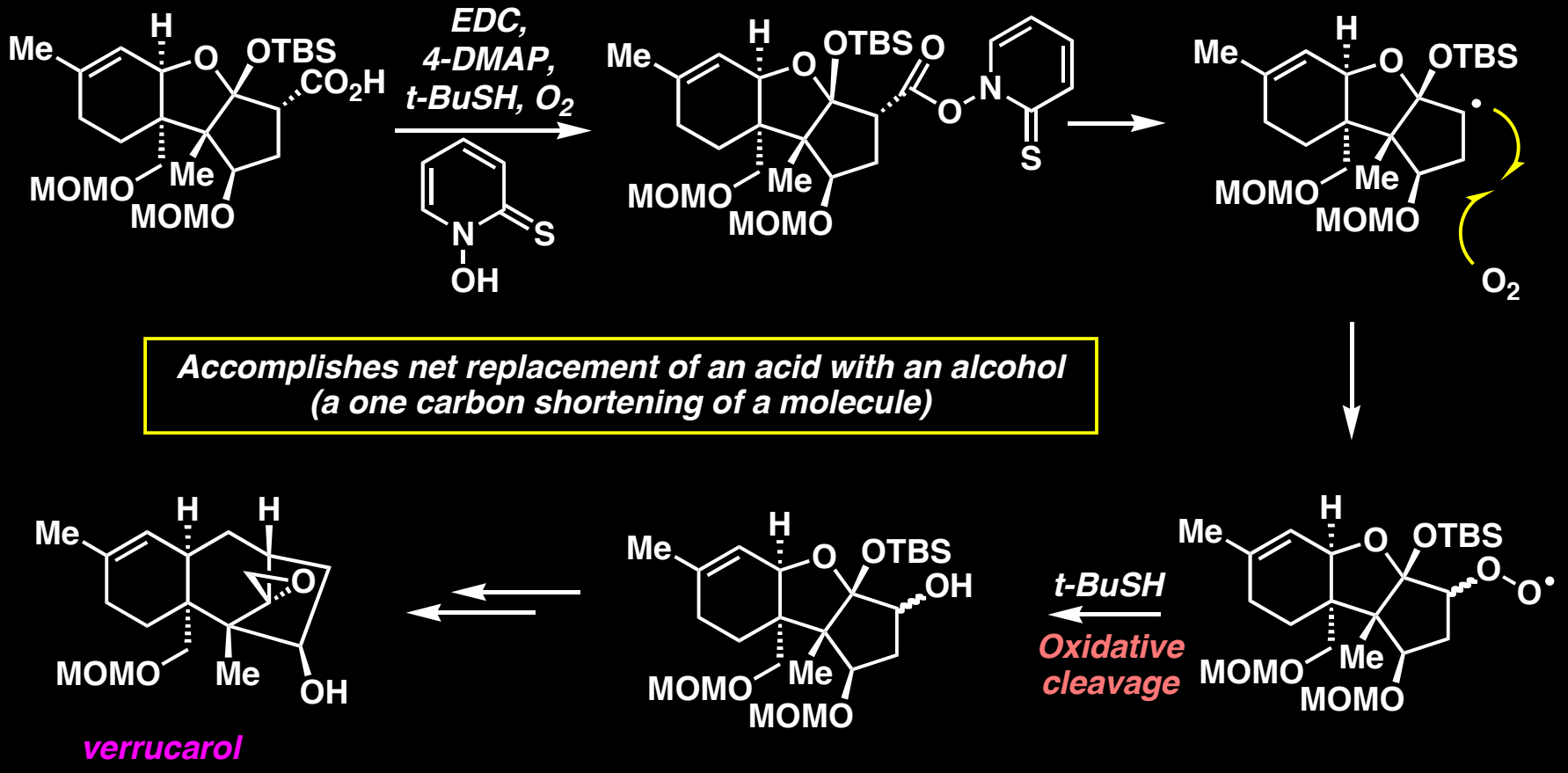
Barton's Thiohydroxamate Esters: Application in Total Synthesis



10-decarboxyquinocarcin

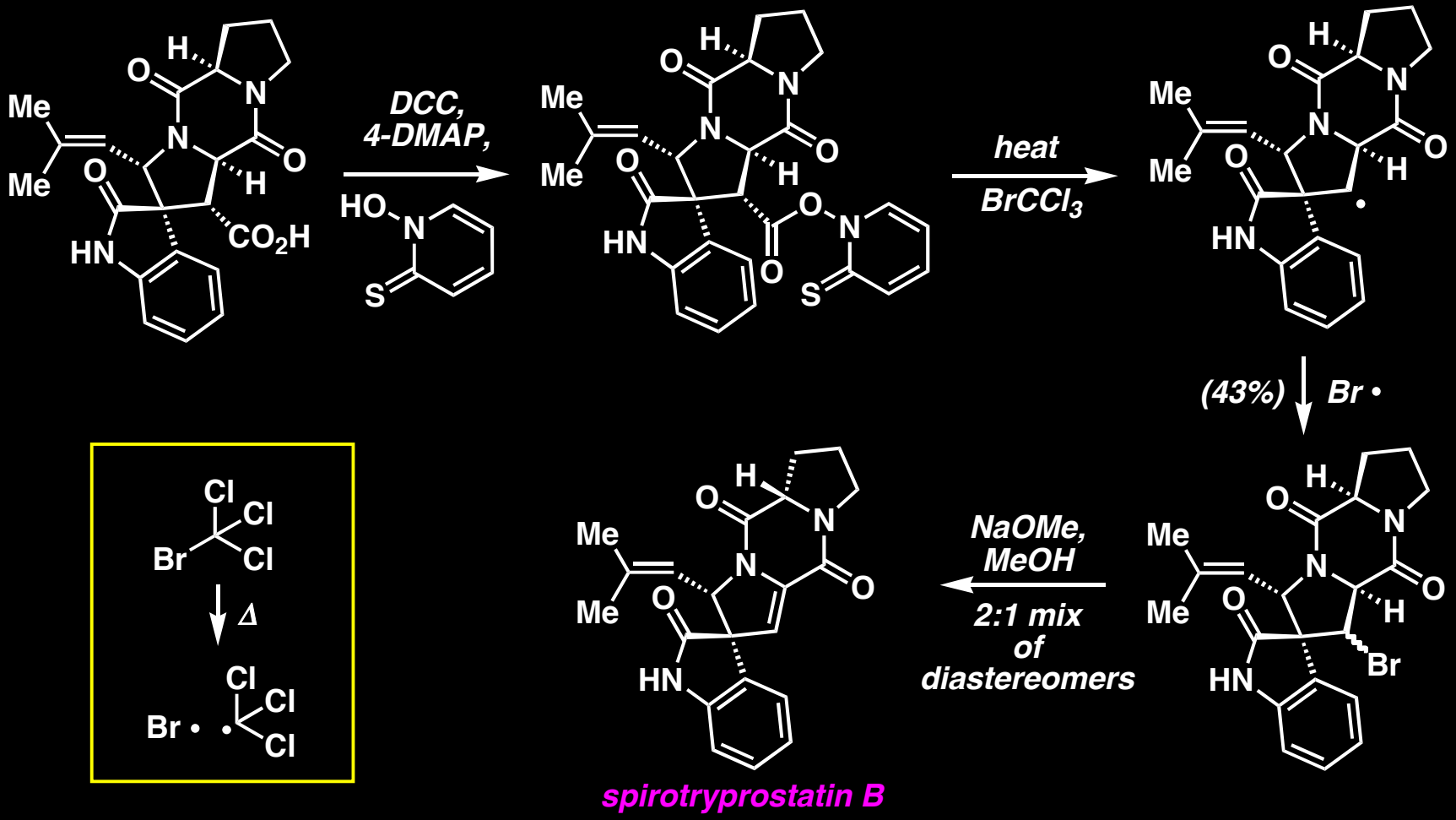
S. Terashima and co-workers, Tetrahedron 1994, 50, 6259.

Barton's Thiohydroxamate Esters: Application in Total Synthesis



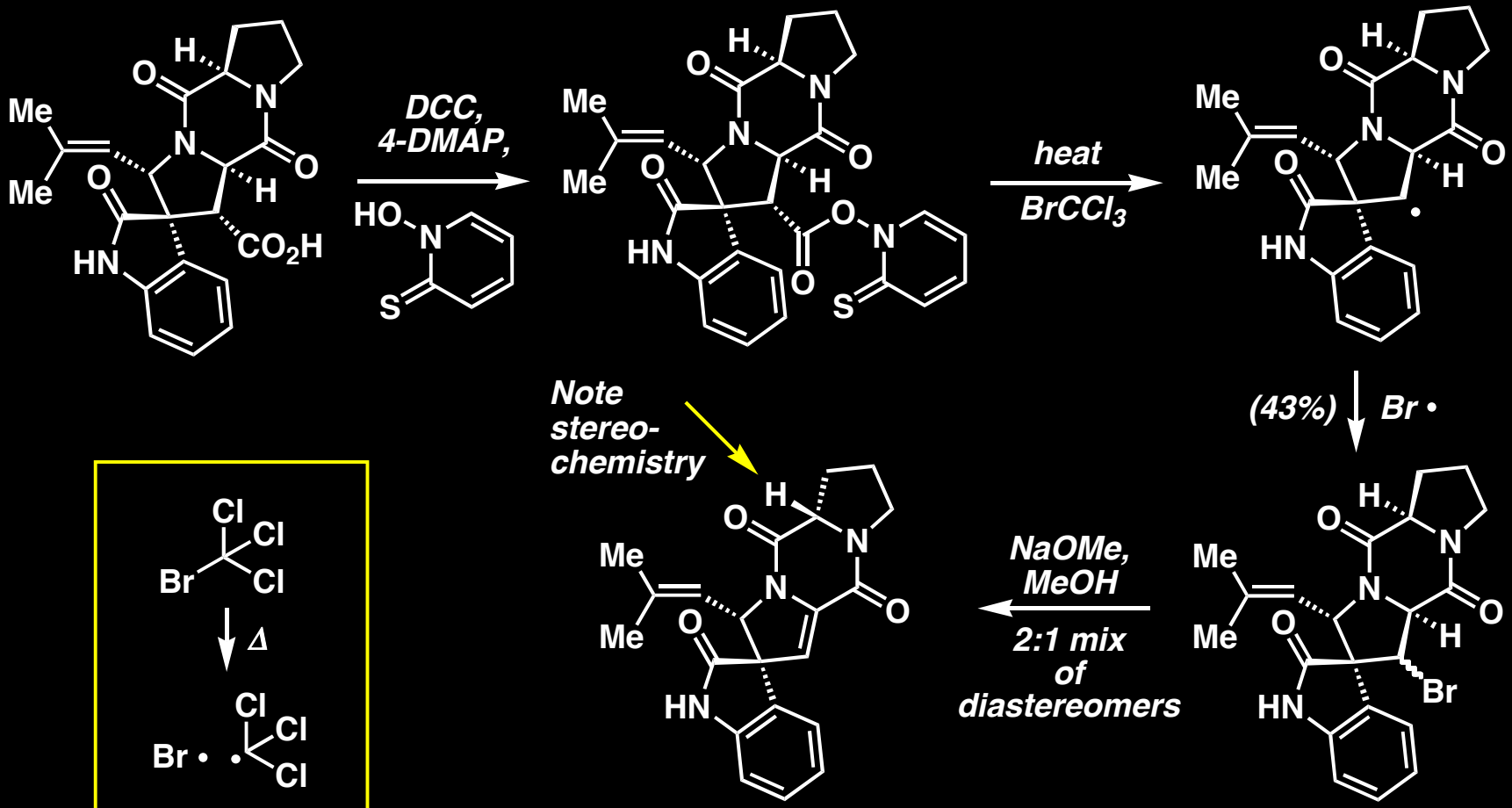
K. Tadano and co-workers, J. Org. Chem. 1998, 63, 2679.

Barton's Thiohydroxamate Esters: Really the Hunsdiecker Reaction



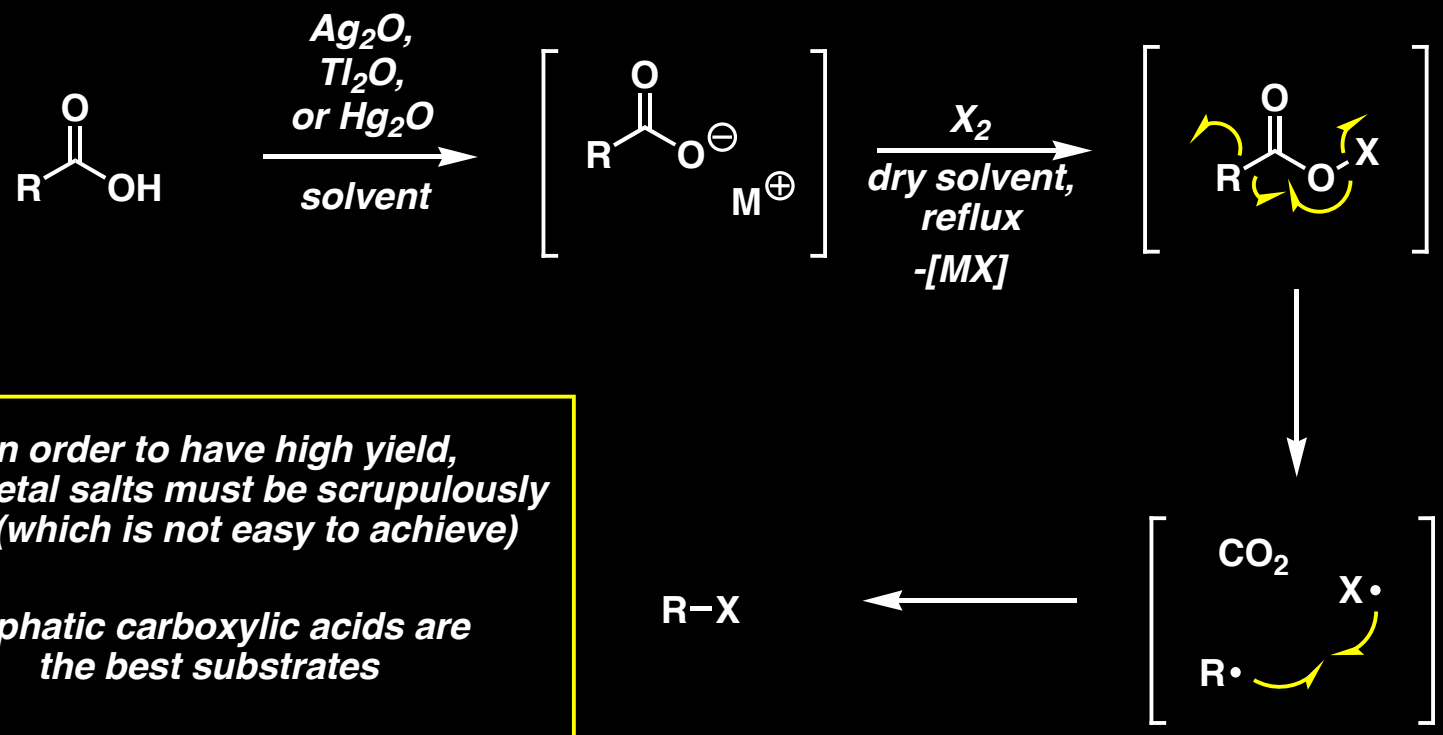
R. M. Williams and co-workers, J. Am. Chem. Soc. 2000, 122, 5666.

Barton's Thiohydroxamate Esters: Really the Hunsdiecker Reaction



R. M. Williams and co-workers, J. Am. Chem. Soc. 2000, 122, 5666.

The Hunsdiecker Reaction (Halodecarboxylation): Background and General Considerations



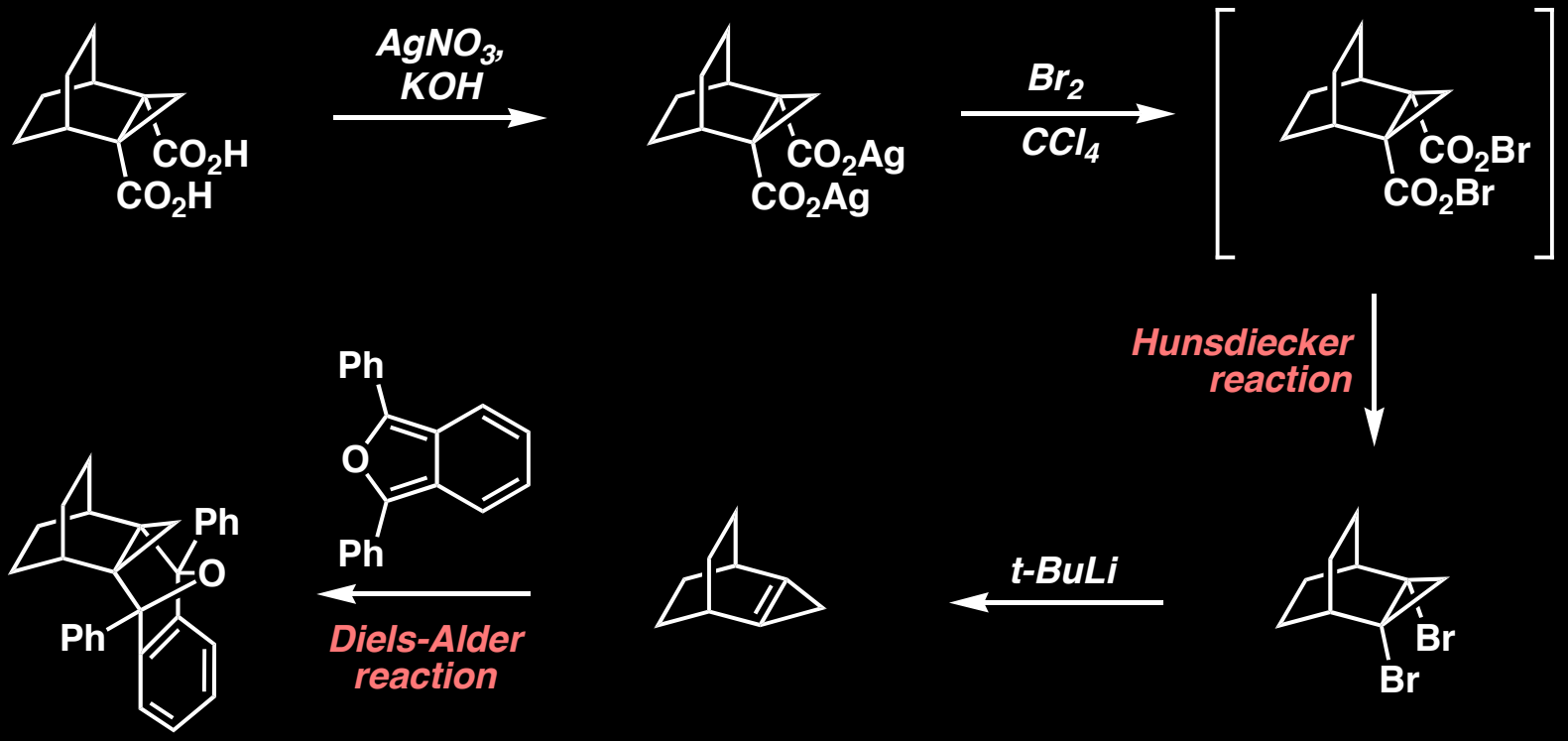
In order to have high yield, the metal salts must be scrupulously dry (which is not easy to achieve)

Aliphatic carboxylic acids are the best substrates

Electron-deficient aromatic acids can also work

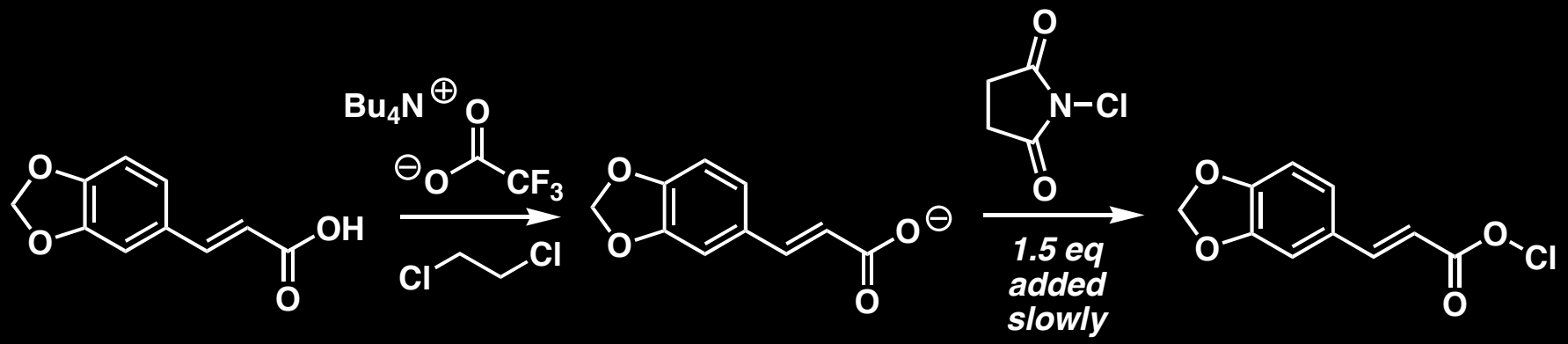
H. Hunsdiecker and co-workers, Ber. 1942, 75B, 291.

The Hunsdiecker Reaction: Use of Classical Reaction Conditions



P. J. Chenier, D. A. Southard, J. Org. Chem. 1990, 55, 4333.

The Hunsdiecker Reaction: Modified Conditions for Vinyl Halide Synthesis



Works for all halides, but fastest halodecarboxylation occurs with NBS.

Must use 1,2-dichloroethane as solvent

Requires adjacent electron rich systems

S. Roy and co-workers, Tetrahedron 2000, 56, 1369.

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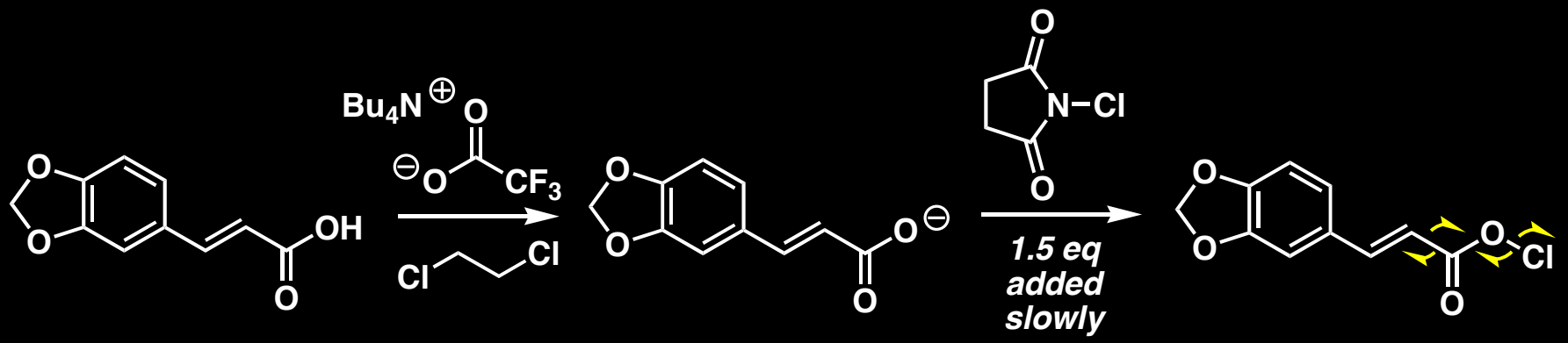

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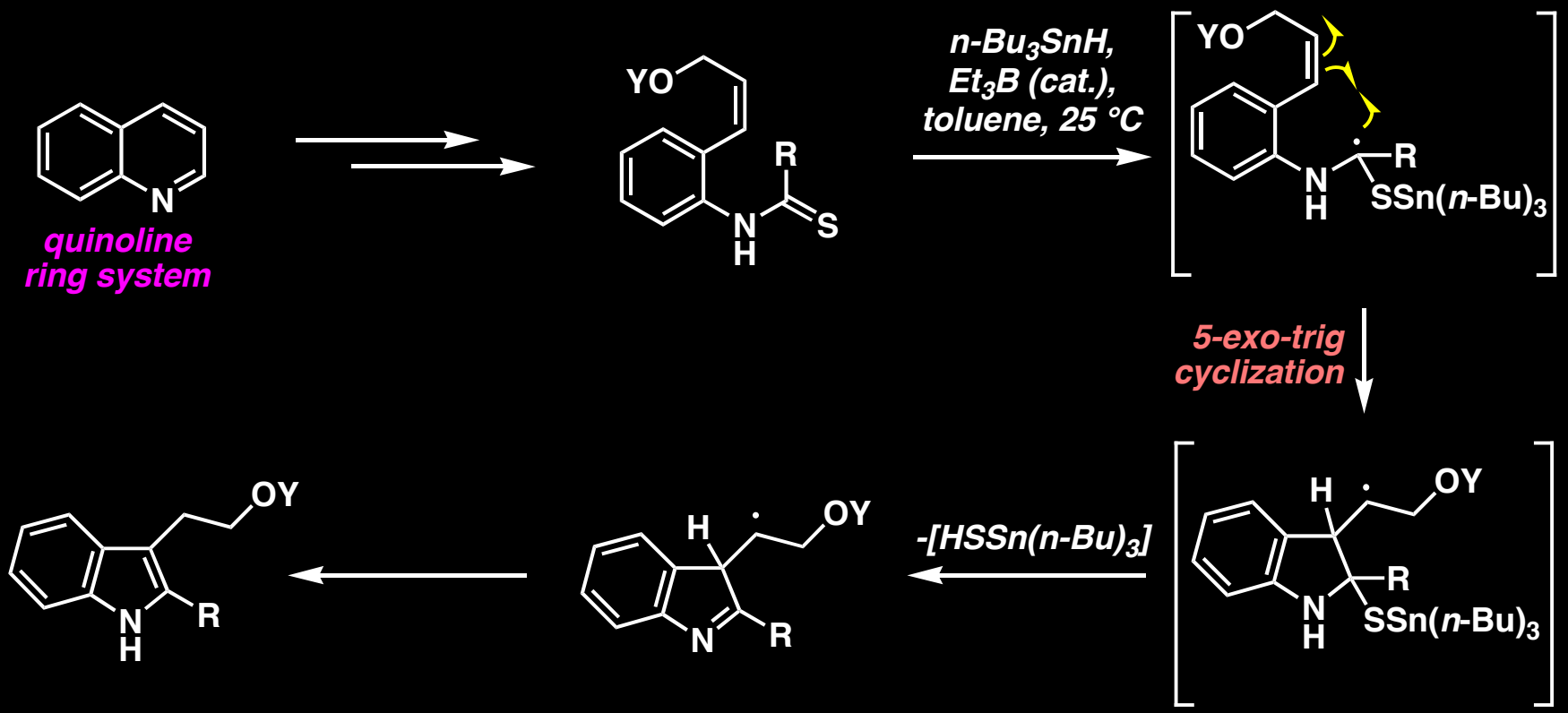
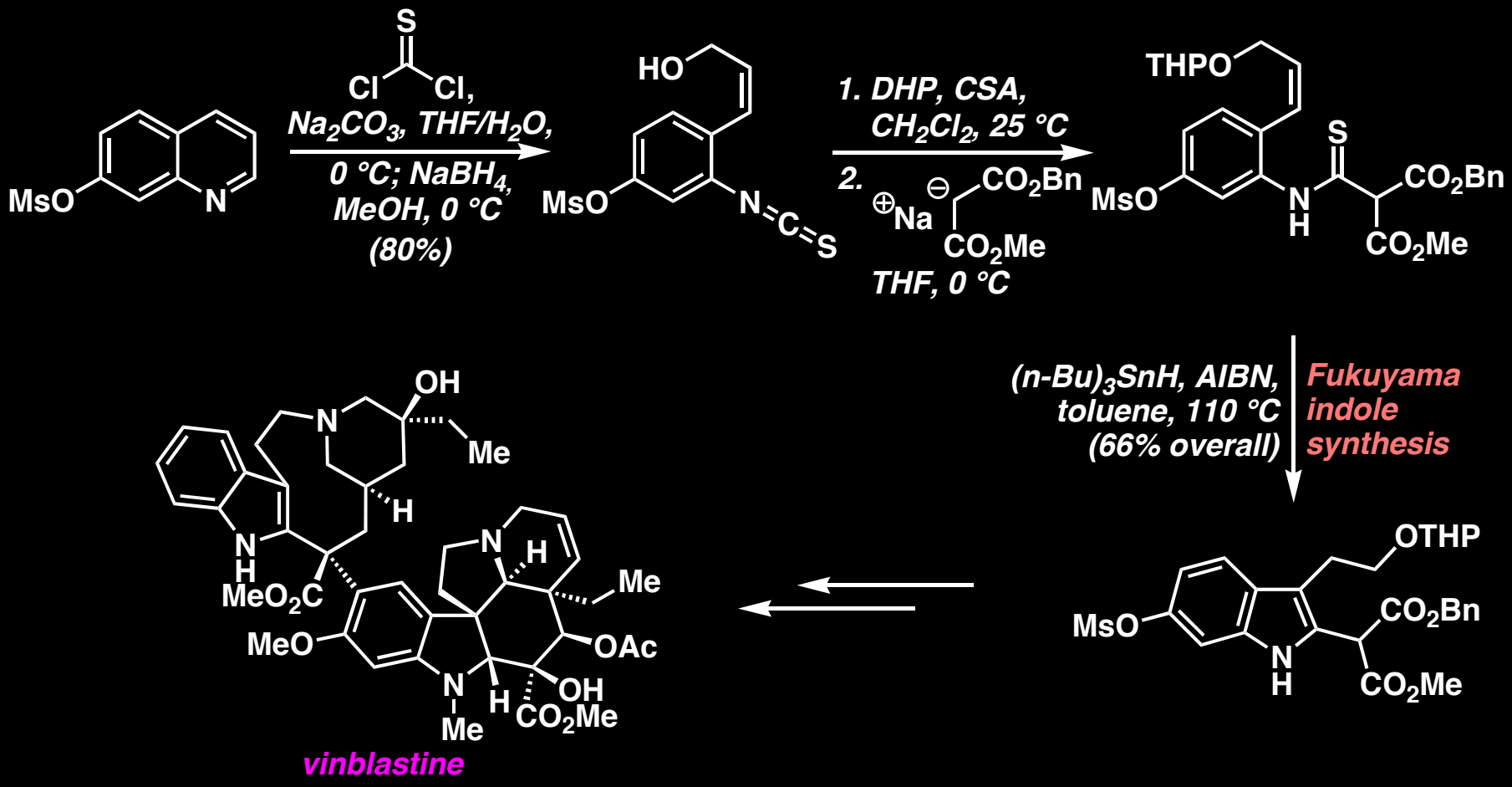
Fukuyama's Indole Synthesis: A Clever Use of a Thiocarbonyl in Radical Chemistry



T. Fukuyama and co-workers, J. Am. Chem. Soc. 1999, 121, 3791.

Fukuyama's Indole Synthesis: Application in the Total Synthesis of Vinblastine



T. Fukuyama and co-workers, J. Am. Chem. Soc. 2002, 124, 2137.

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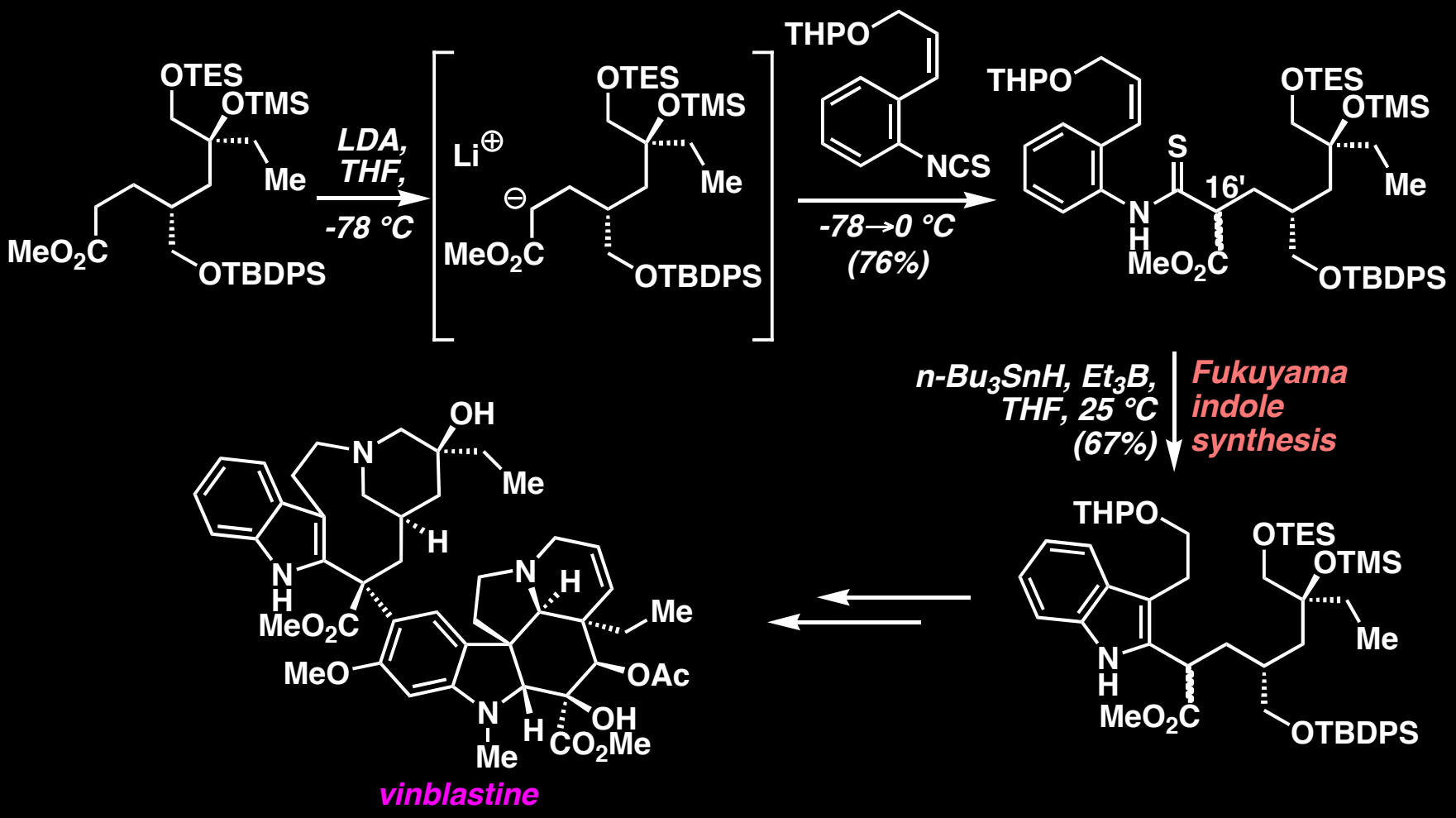
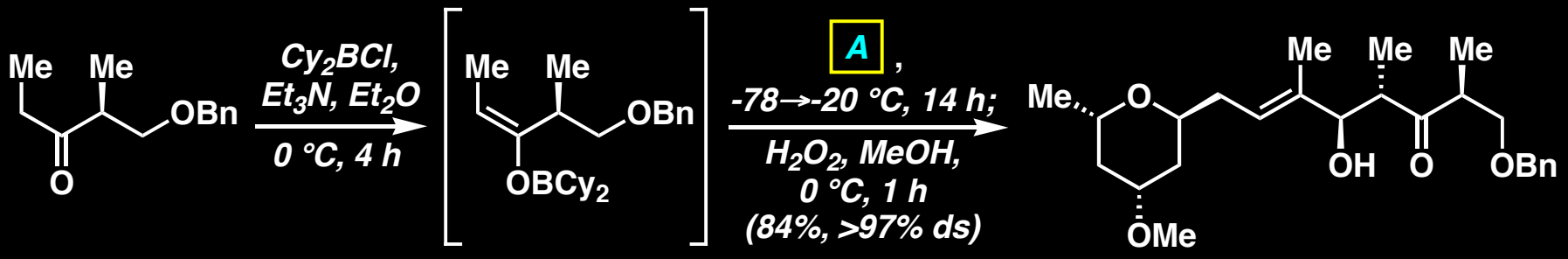
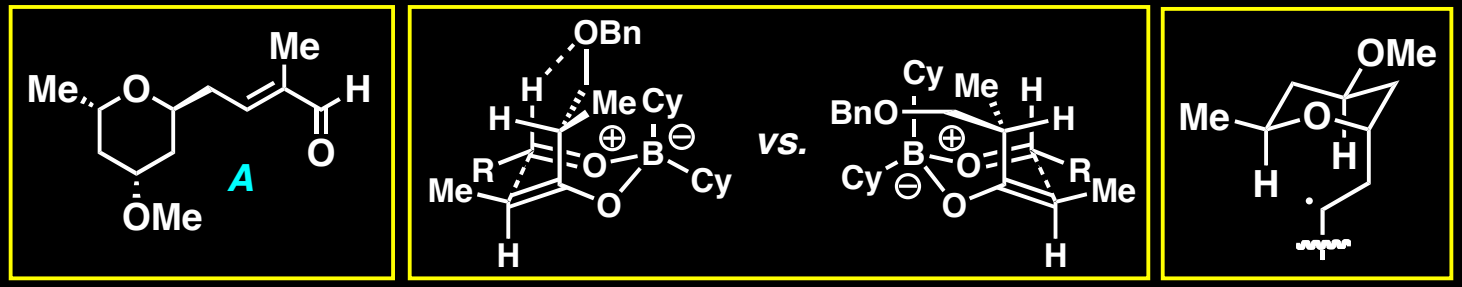
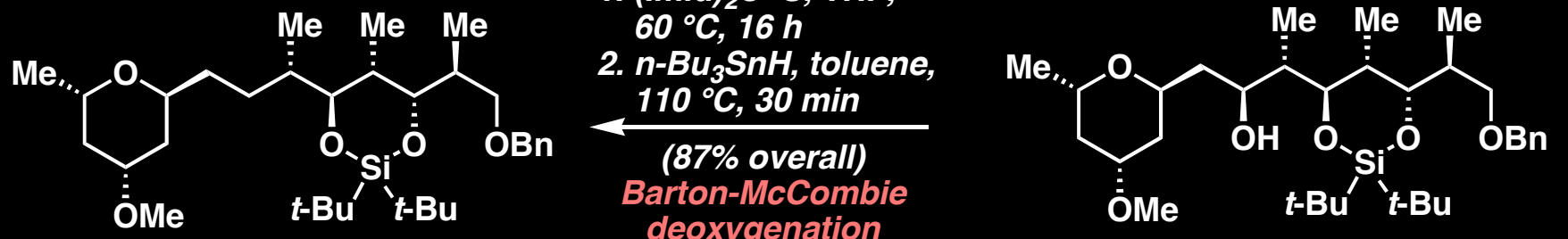


T. Fukuyama and co-workers, J. Am. Chem. Soc. 2002, 124, 2137.

Barton-McCombie Deoxygenation: Application in a Total Synthesis of Swinholide A

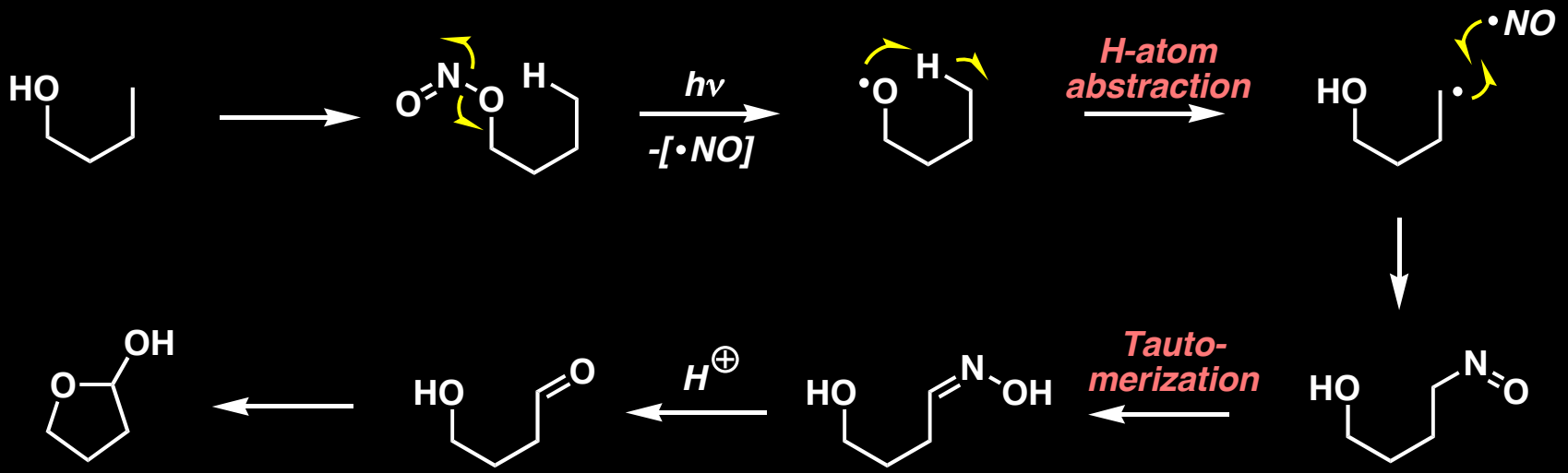






I. Paterson and co-workers, J. Am. Chem. Soc. 1994, 116, 9391.
I. Paterson and co-workers, Tetrahedron 1995, 51, 9394.

The Barton Reaction: Photolysis of Nitrite Esters



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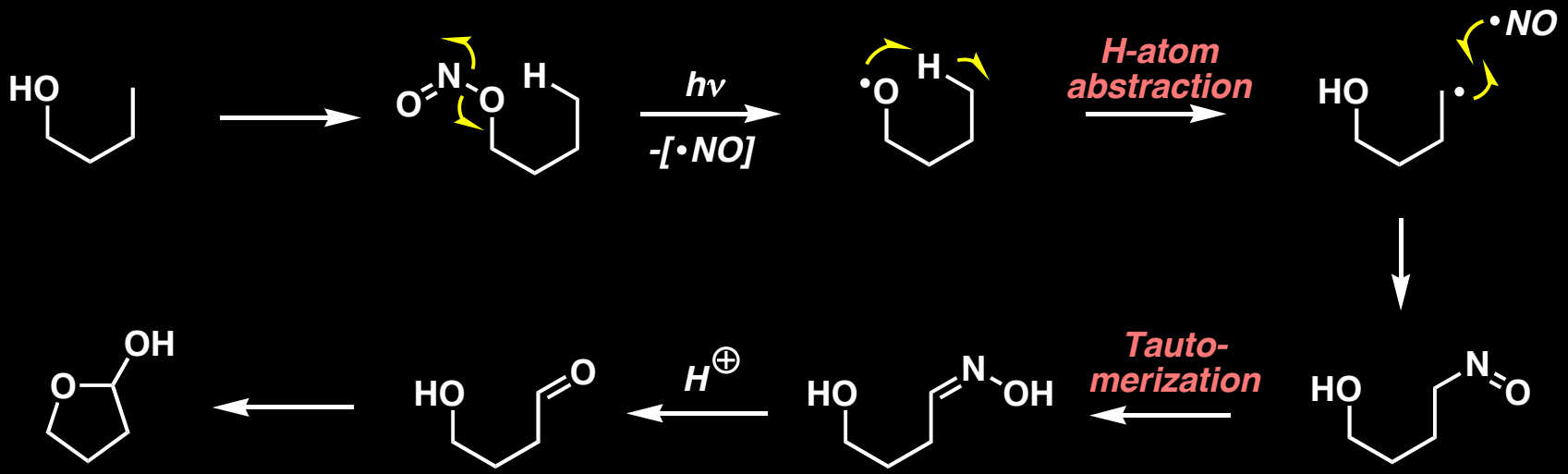

The high reactivity of heteroatom-centered radicals can be exploited to accomplish the formidable task of functionalizing unactivated hydrocarbons.

This reaction is one of the first examples of a field more broadly defined today as C-H activation

D. H. R. Barton and co-workers, J. Am. Chem. Soc. 1960, 82, 2640.

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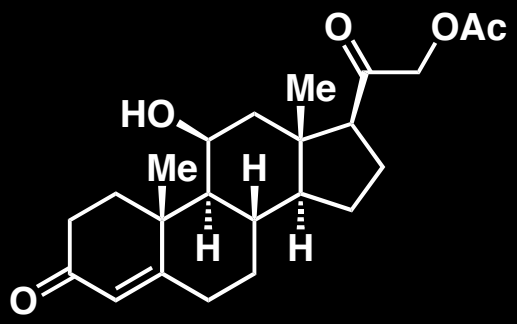
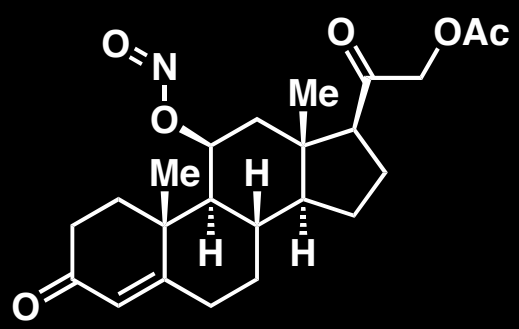


corticosterone acetate

ClNO

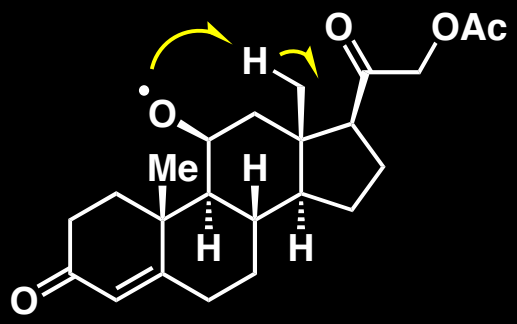
pyridine, 25 °C



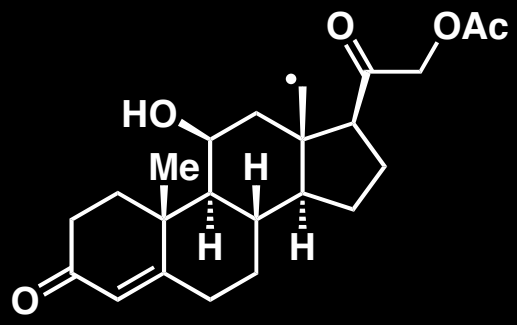
hν, toluene, 32 °C
-[•NO]

Nitrite ester photolysis

Note the regioselectivity of hydrogen atom abstraction from two possible methyl groups



H-atom abstraction



D. H. R. Barton and co-workers, J. Am. Chem. Soc. 1961, 83, 4083.

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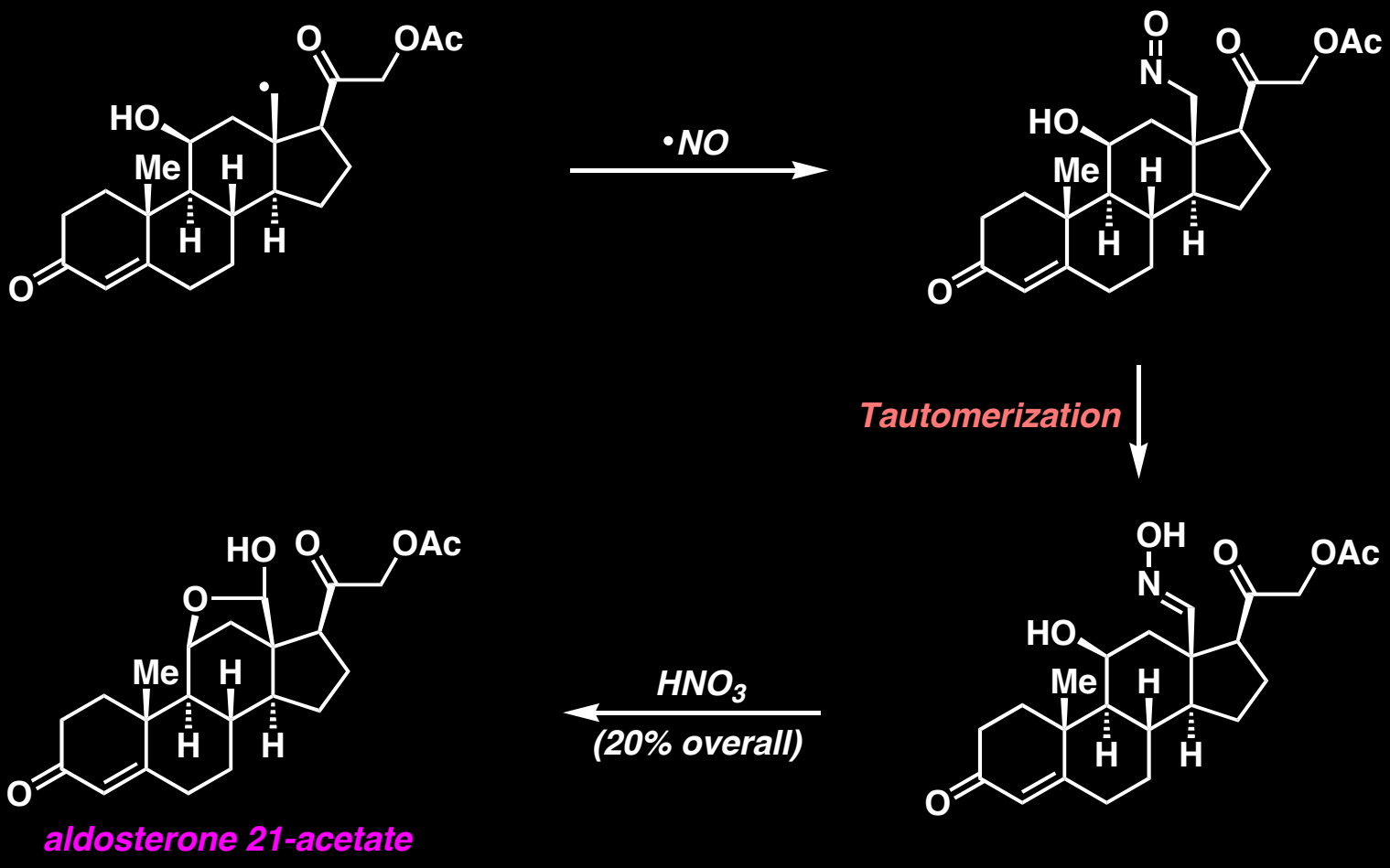

D. H. R. Barton and co-workers, J. Am. Chem. Soc. 1961, 83, 408