Persistent Radicals in Total Synthesis

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Overview

- **Introduction to carbon-centered radical chemistry**

  Terminology and history pertinent to understanding

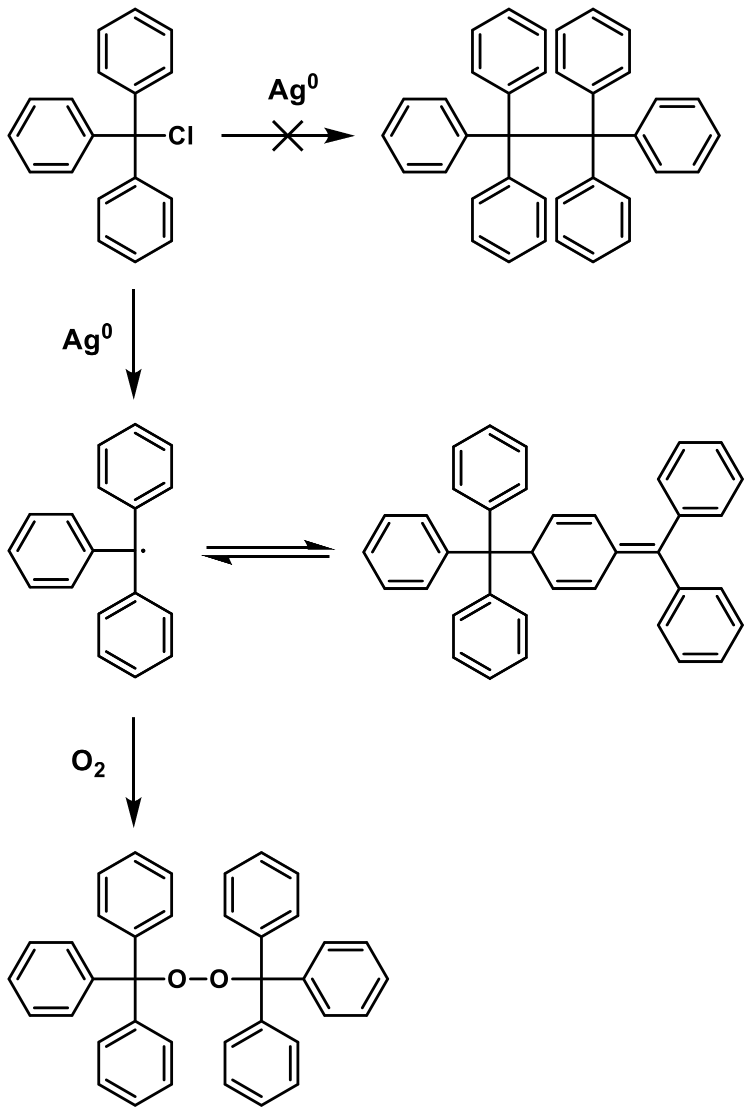
- **Persistent radical effect**

  Kinetic reasoning for why hetero-coupling is major product

- **Specific examples of modern use of radicals in total synthesis**

  Examples contain a key step where persistent or stabilized radicals are important for selectivity

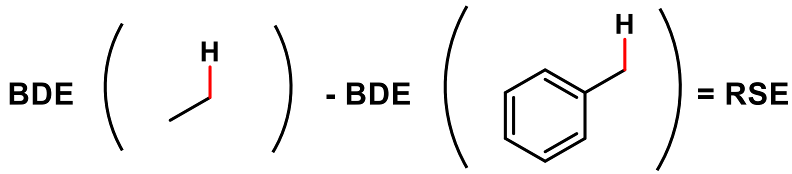
Gomberg's Triphenylmethyl Radical



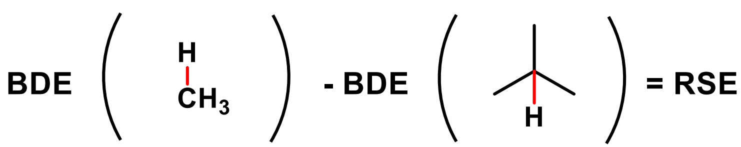
- Discovered during failed Wurtz coupling
- First example of isolation of a radical intermediate
- In the presence of oxygen a peroxide is readily formed
- In the absence of oxygen this radical can persist for several days

M. Gomberg, *J. Am. Chem. Soc.*, 1900, **22**, 757–771

Radical Stabilization



98 kcal/mol - 85 kcal/mol = 13 kcal/mol (RSE)



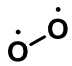
104 kcal/mol - 93 kcal/mol = 11 kcal/mol (RSE)

- Radicals are stabilized by overlap of the SOMO with adjacent Pi orbitals
- Radicals are stabilized, to a lesser extent, by hyperconjugation or orbital overlap with adjacent C-H and C-C bonds
- The extent to which a radical is stabilized can be estimated by radical stabilization energy (RSE)
- These are thermodynamic qualities inherent to the electronic structure of the molecule

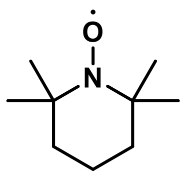
$$\boldsymbol{RSE = BDE(C - H\ bond\ of\ unstabilized\ structure) - BDE(C - H\ bond\ of\ stabilized\ structure)}$$

K. U. Ingold, D. Griller., *Acc. Chem. Res.*, 1976, **9**, 13–19
C. R. J. Stephenson, D. A. Pratt., et. al., *Chem. Soc. Rev.* 2018, **47**, 7851-7866
S. W. Benson, D. M. Golden. *Chem. Rev.* 1968, **69**, 125-134

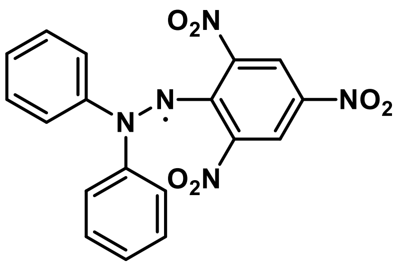
Stable Radicals



Oxygen



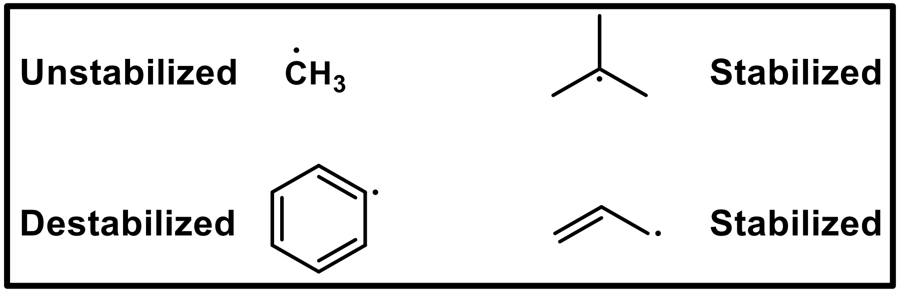
(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)
oxidation catalyst, polymerization mediator

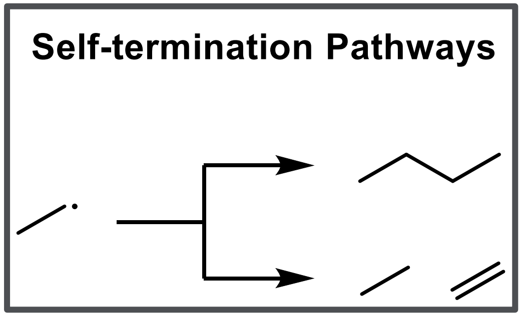


2,2-diphenyl-1-picrylhydrazyl
hydrogen acceptor, measurement of anti-oxidant activity of other compounds

- The word “stable” should only be used to describe species which can be isolated and treated like a common reagent.
- Radicals are typically unstable species and there are very few examples of radicals that fit the above definition

Transient Radicals

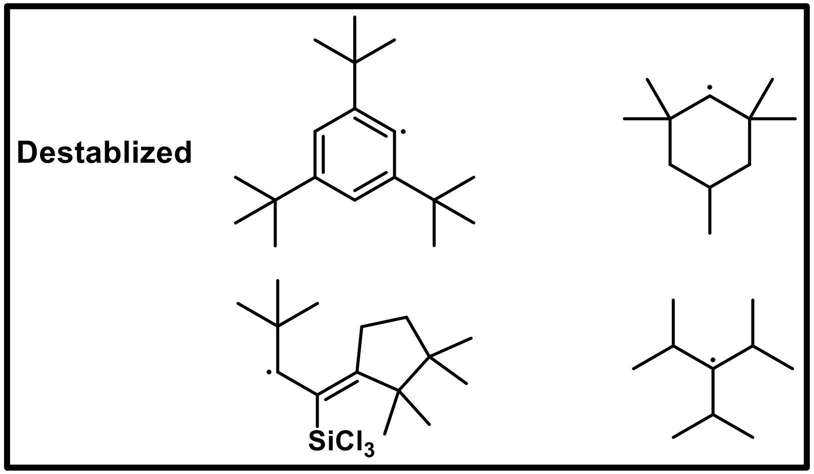




- Undergo bimolecular self-reactions at rates similar to methyl radical
- Immediately terminate
- Difficult to observe in solution

K. U. Ingold, D. Griller., *Acc. Chem. Res.*, 1976, **9**, 13–19

Persistent Radicals

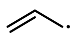
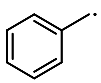
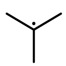
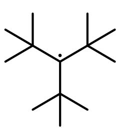
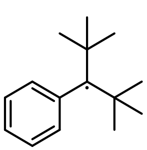


$$P^{\bullet} \quad P^{\bullet} \rightleftharpoons P\text{—}P$$

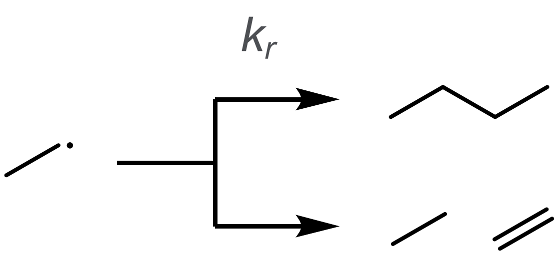
- Lifetime is considerably longer than the methyl radical
- Dimerization tends to be slow and reversible
- Observable in solution
- Steric bulk is the primary factor in determination of persistence

K. U. Ingold, D. Griller., *Acc. Chem. Res.*, 1976, **9**, 13–19

Kinetic and Thermodynamic Character of Radicals

Radical	k_r ($M^{-1}s^{-1}$)	$t_{1/2}$ (s)	RSE (kcal/mol)
$\dot{C}H_3$	1.1×10^{10}	9.1×10^{-6}	0.0
	8.5×10^{9}	1.2×10^{-5}	10
	2.3×10^{9}	4.3×10^{-5}	13
	8.1×10^{9}	1.2×10^{-5}	11
	2×10^{2}	5.0×10^{2}	9
	n/a	days	11

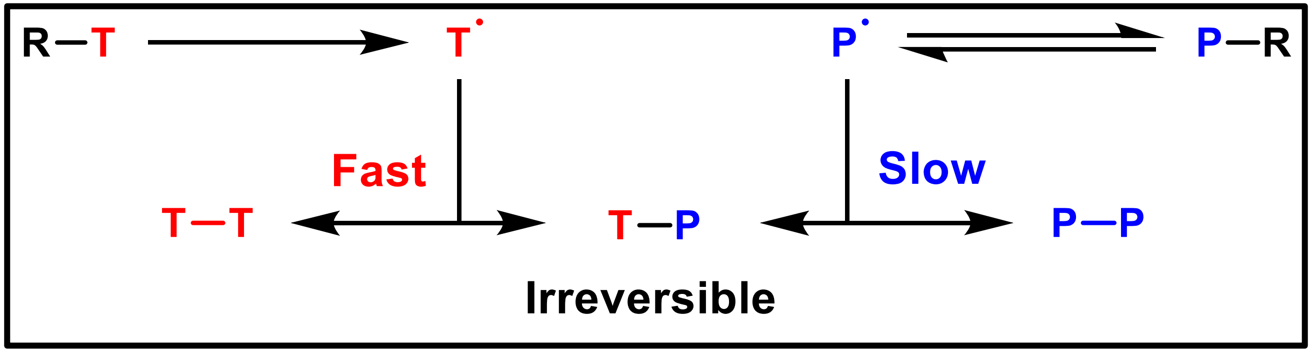
Self-termination Pathways



[radical] = 1×10^{-5} M

C. R. J. Stephenson, D. A. Pratt., et. al., *Chem. Soc. Rev.* **2018**, 47, 7851-7866
S. W. Benson, D. M. Golden., *Chem. Rev.* **1968**, 69, 125-134
G. B. Ellison, S. J. Blanksby. *Acc. Chem. Res.* **2003**, 36, 255-263

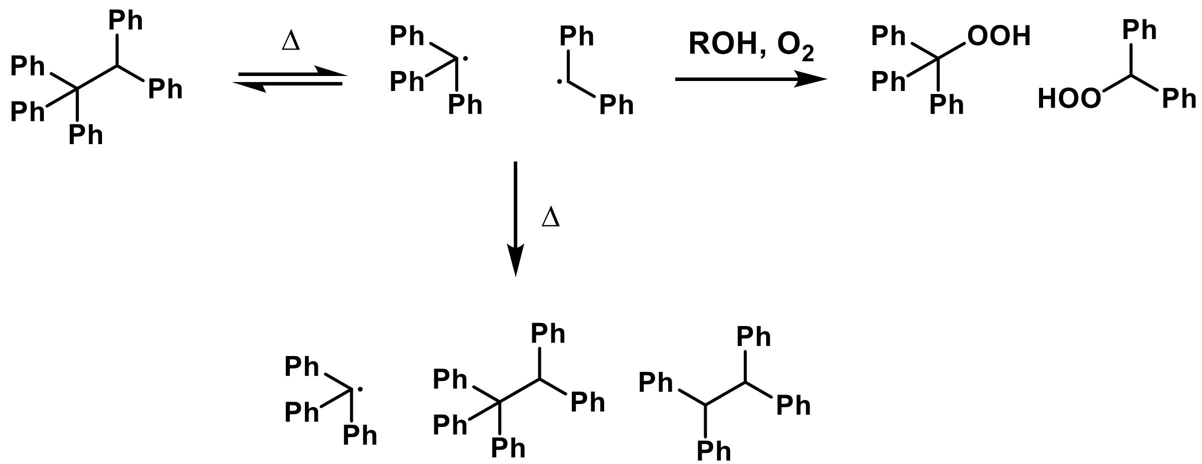
Persistent Radical Effect



- Transient and persistent radicals must be formed at nearly the same rate
- Transient radical is short lived and rate of termination is fast
- This causes a build-up of persistent radical
- The cross-product is the major product

H. Fischer, *Chem. Rev.* 2001, **101**, 3581−3610

Bachmann's Observation of Persistent Radical Effect

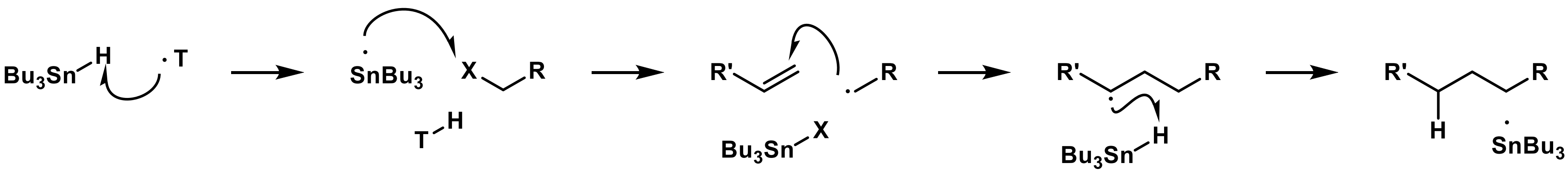


- In the presence of oxygen and hydrogen source, peroxides form
- In absence of oxygen, dimerization of diphenylmethane occurs
- This causes a build-up of persistent radical triphenylmethyl radical
- Solution takes on the color of triphenylmethyl radical and shifts equilibrium to pentaphenylethane

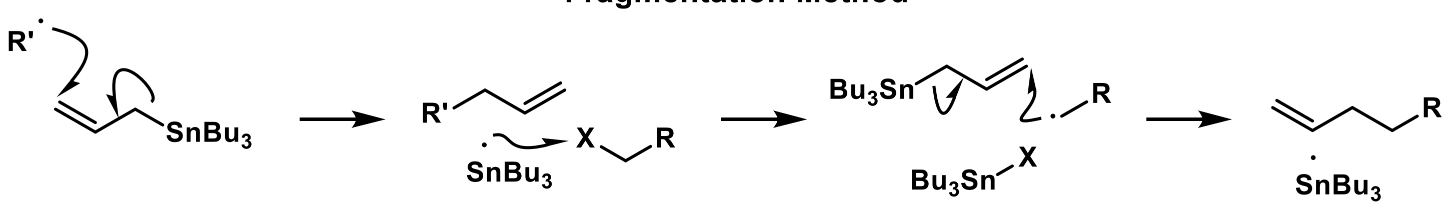
H. Fischer, *Chem. Rev.* 2001, **101**, 3581−3610
W. E. Bachmann, F. Y. Wiselogle. *J. Org. Chem.* 1936, **1**, 354

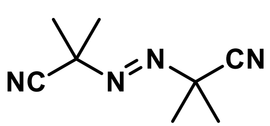
Methods of Generating Carbon-centered Radical

"Tin Hydride Method"



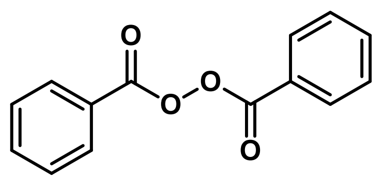
Fragmentation Method



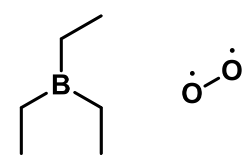


azobisisobutyronitrile

AIBN

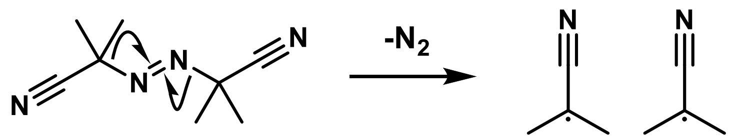


benzoyl peroxide

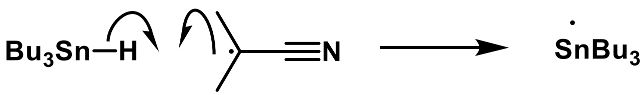


triethylborane/O_2

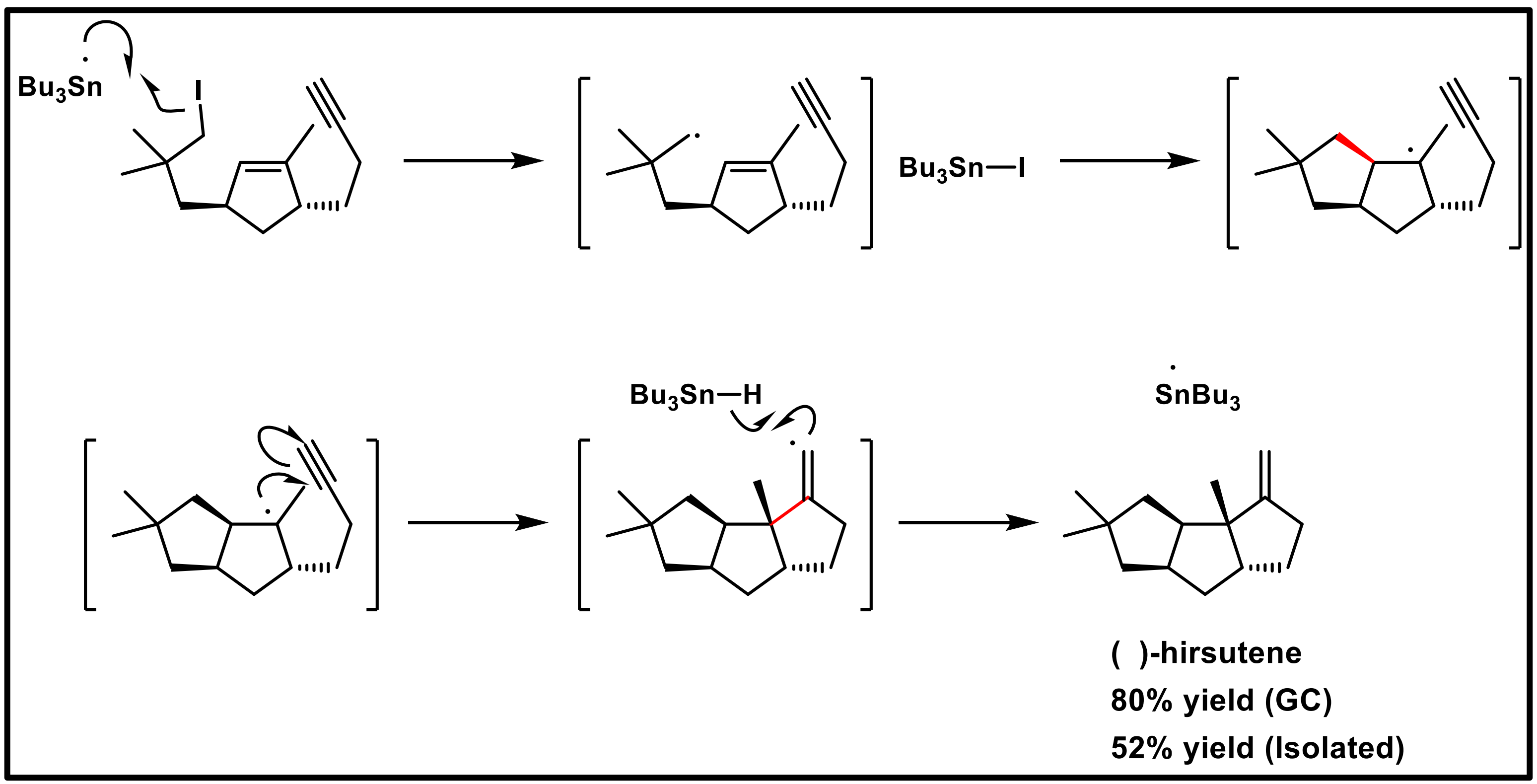
Curran's Synthesis of Hirsutene



Transient Radicals (low concentration)

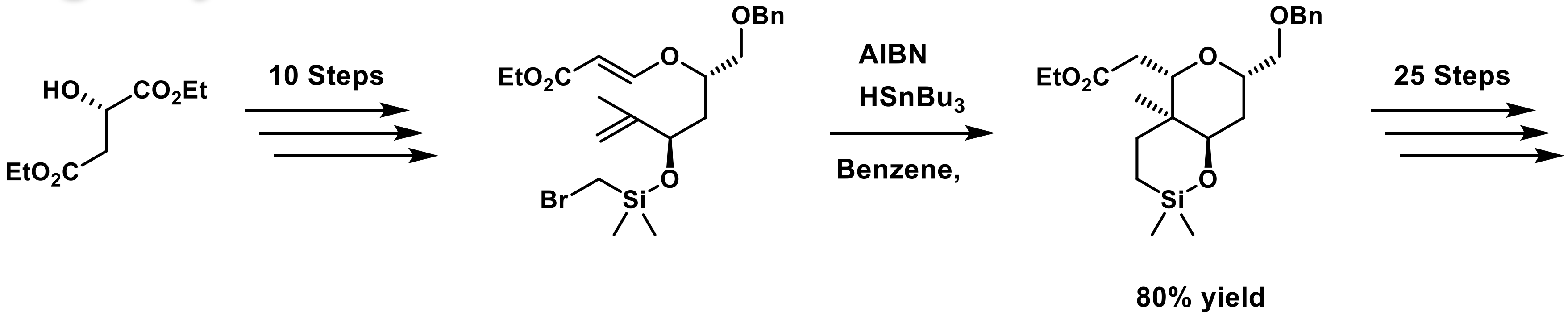


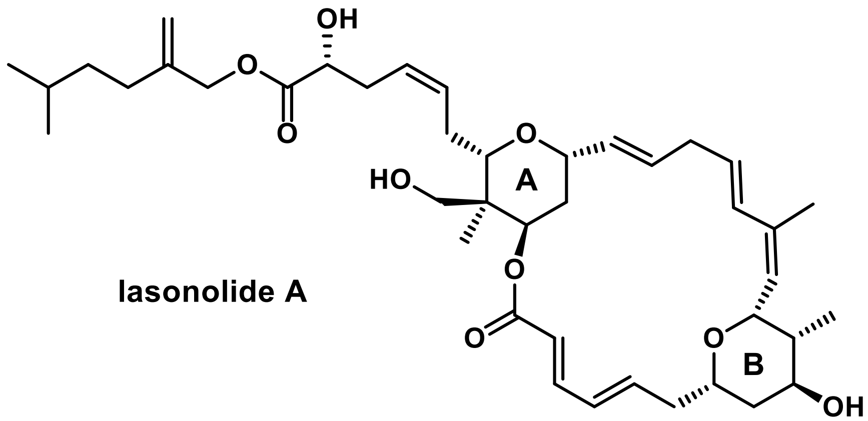
Persistent Radical



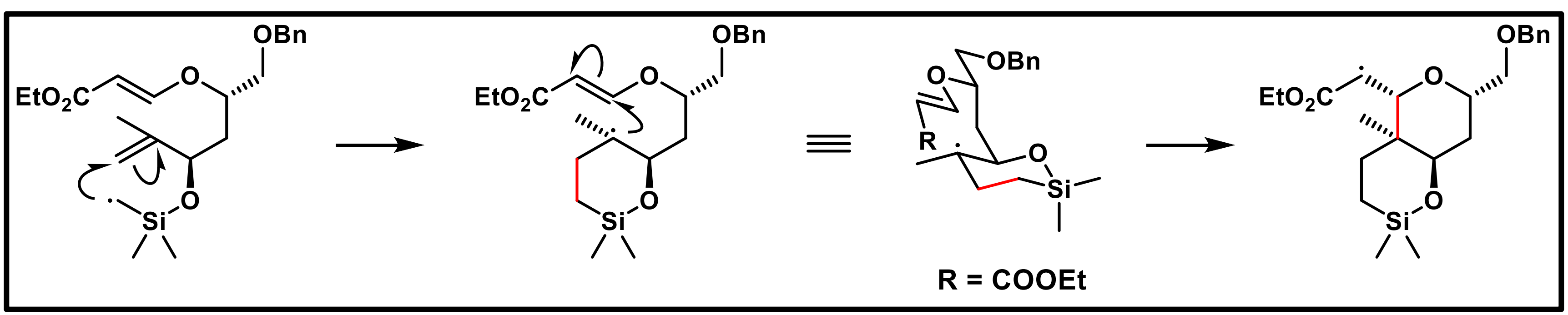
D. P. Curran and D. M. Rakiewicz, *J. Am. Chem. Soc.*, 1985, **107**, 1448–1449

Song's Synthesis of Lasonolide A



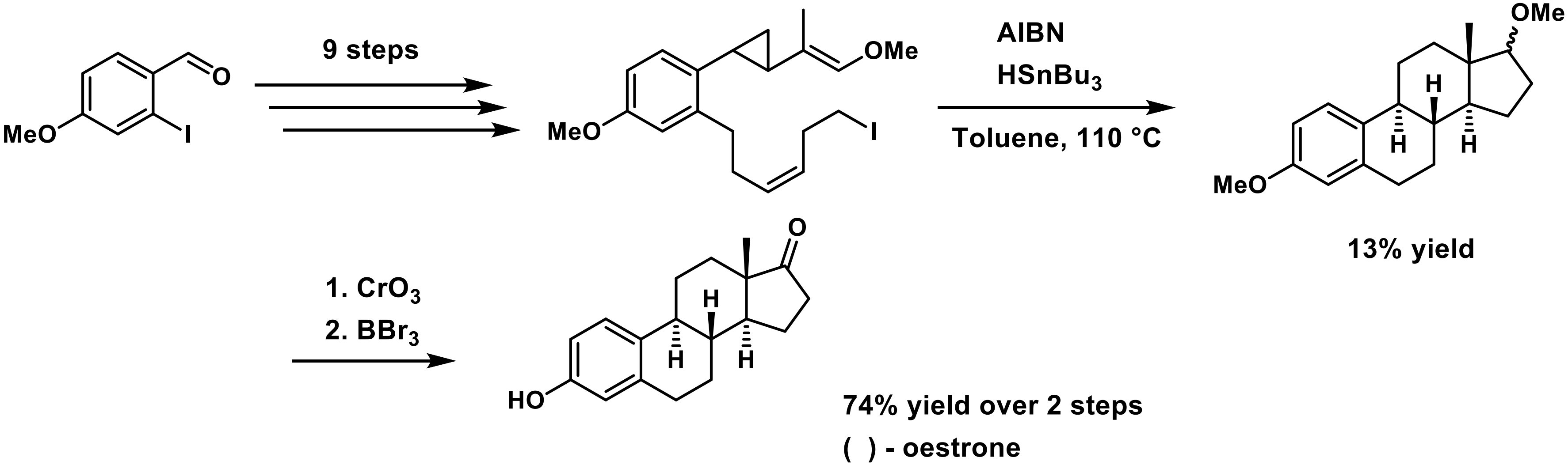


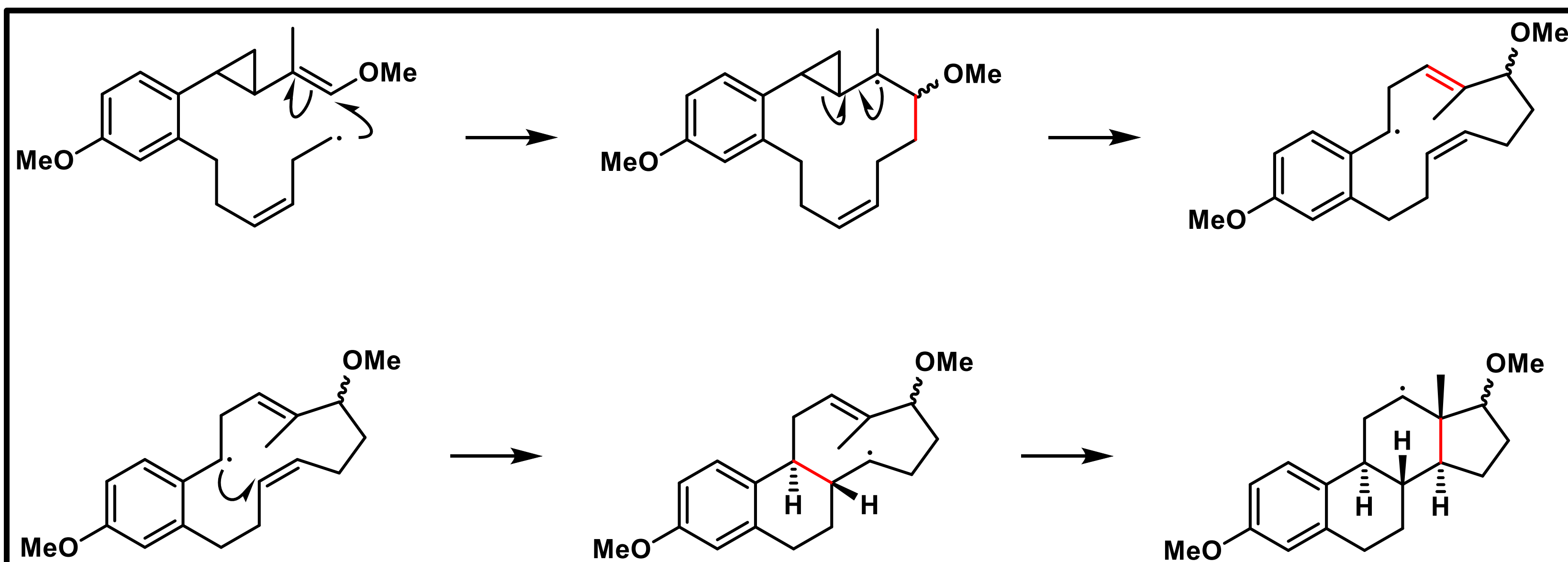
lasonolide A



H. Y. Song, et al., *J. Org. Chem.*, 2003, **68**, 8080–8087

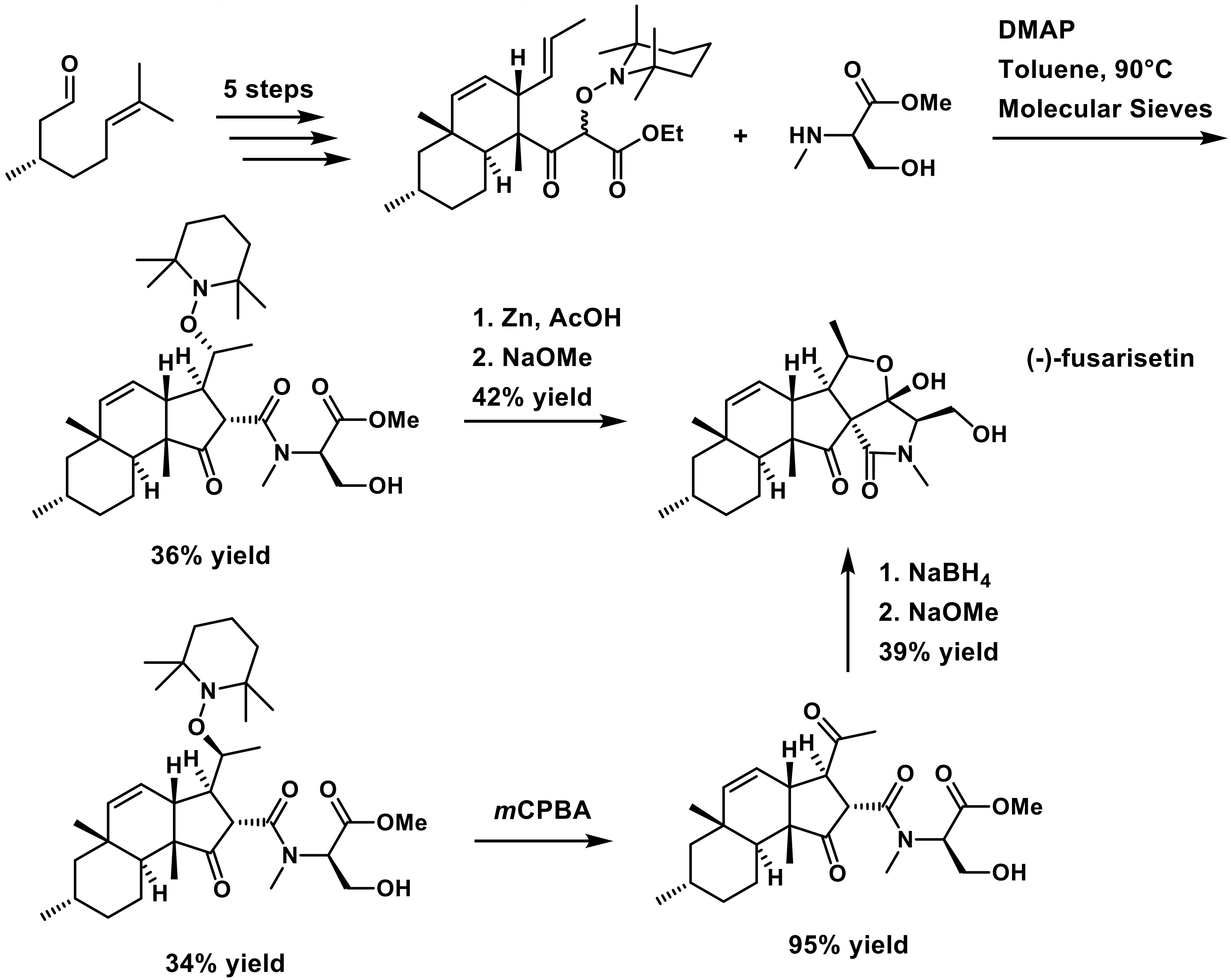
Pattenden's Synthesis of (±)-oestrone





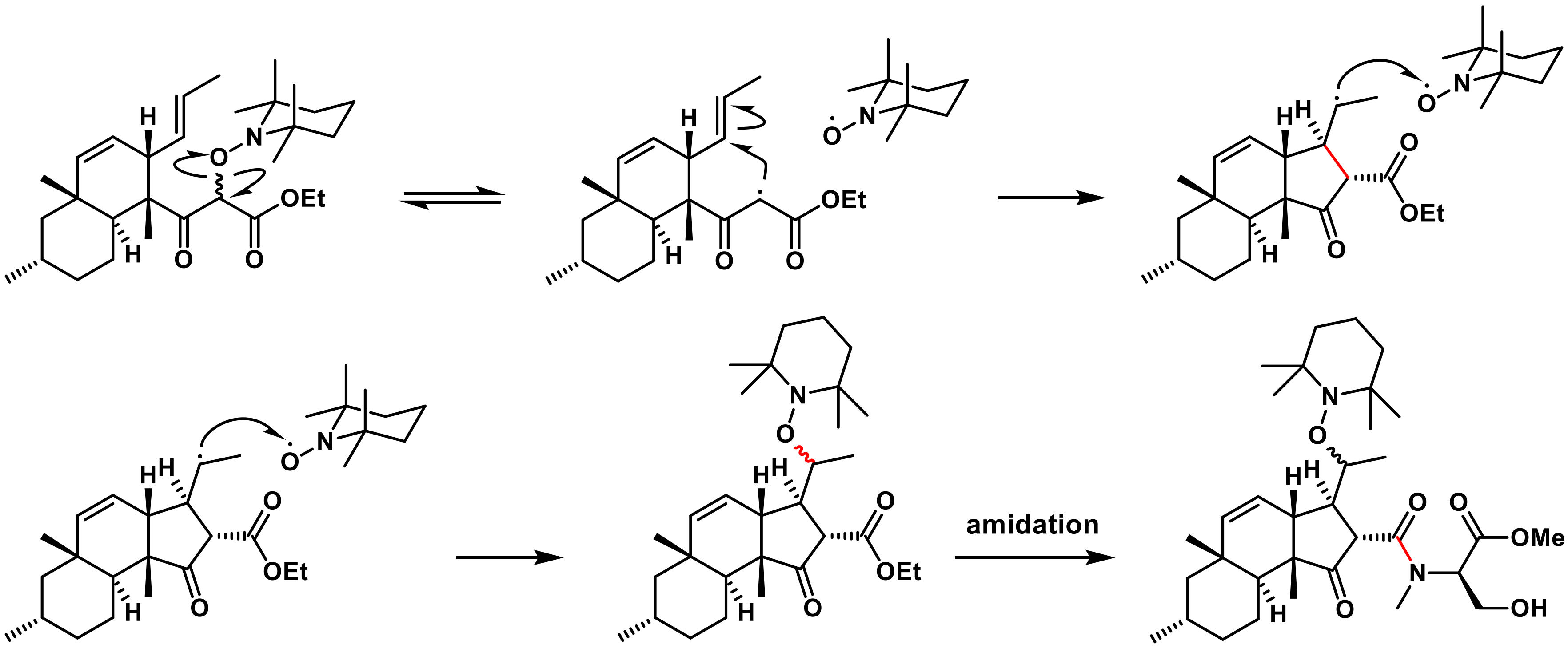
G. Pattenden, L. K. Reddy, A. Walter, *Tetrahedron Lett.* 2004, **45**, 4027 – 4030

Theodorakis' Synthesis of (-)-Fusarisetin



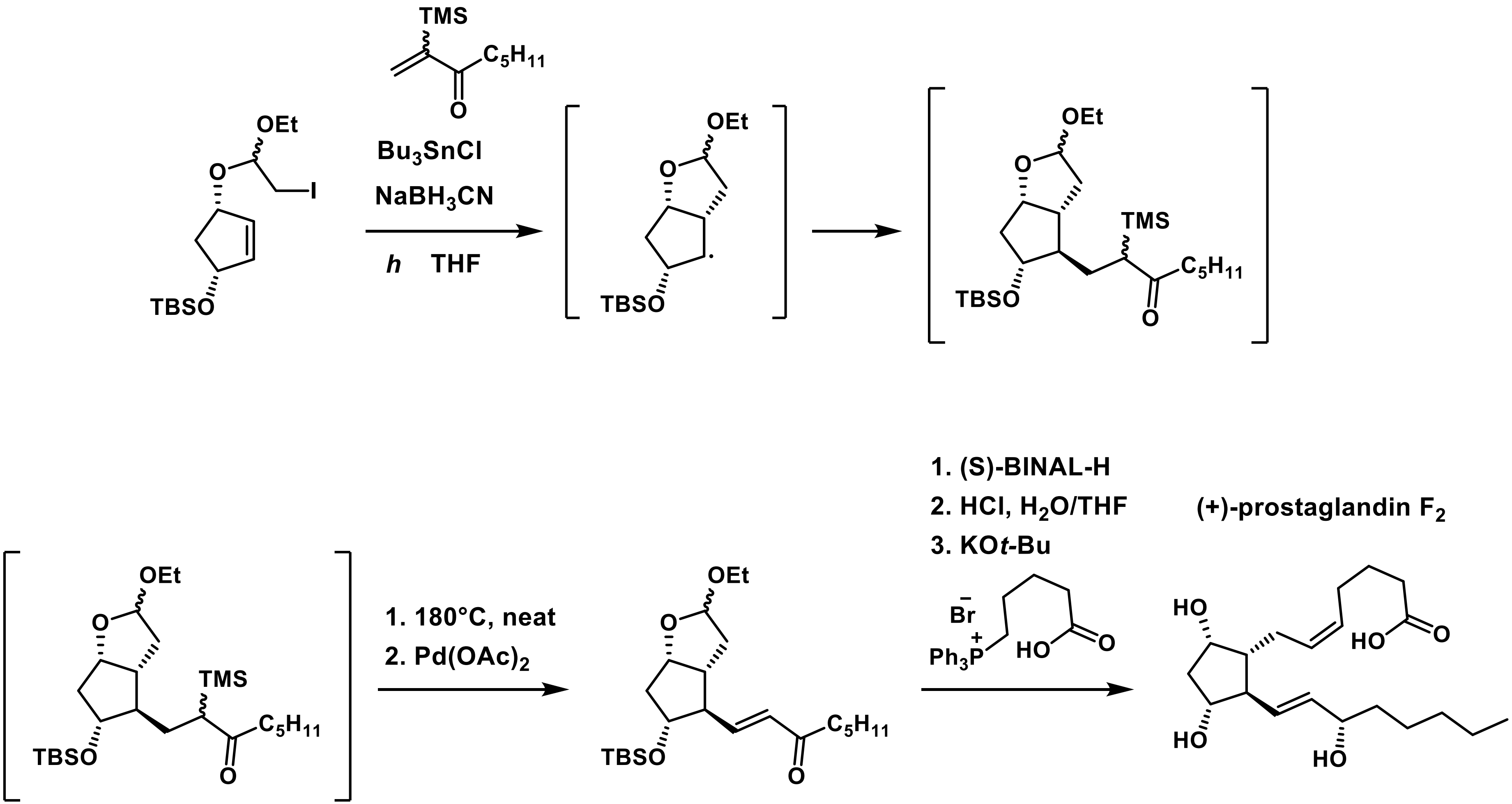
E. A. Theodorakis, et. al., *J. Am. Chem. Soc.* , 2012, **134**, 5072–5075

Theodorakis' Synthesis of (-)-Fusarisetin (mechanism)



E. A. Theodorakis, et. al., *J. Am. Chem. Soc.* , 2012, **134**, 5072–5075

Stork's Synthesis of (+)-prostaglandin $F_{2\alpha}$

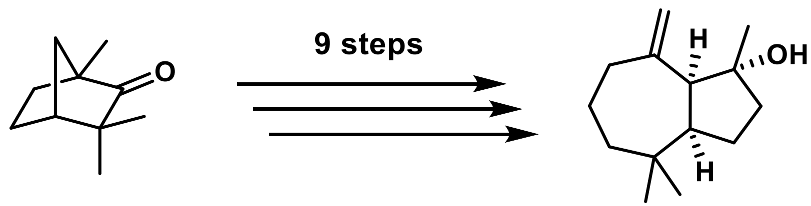


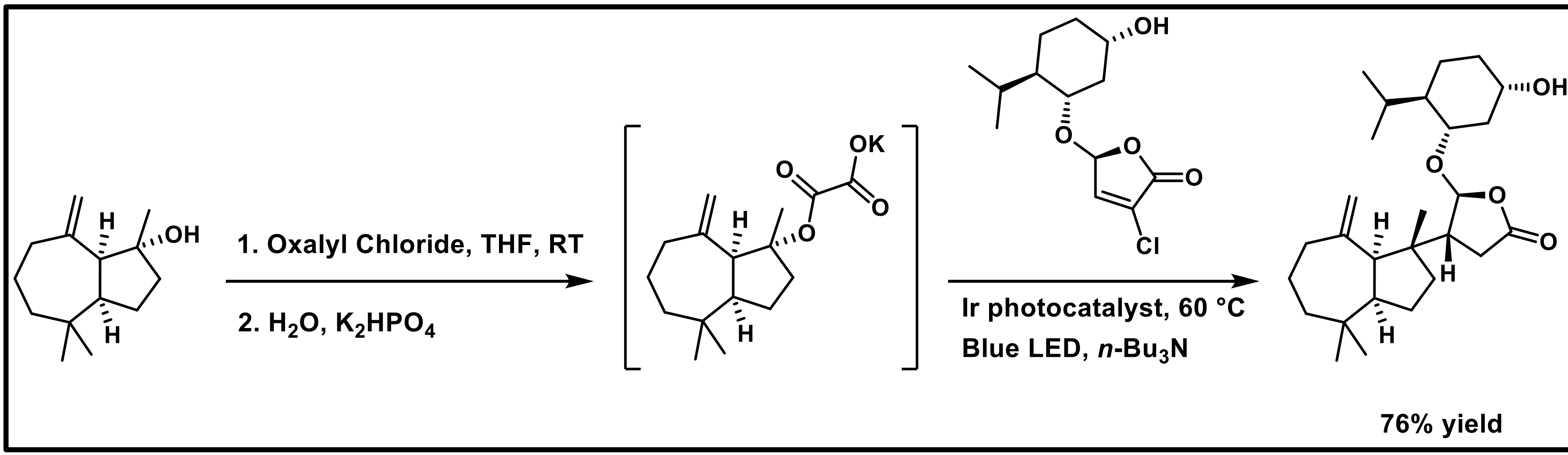
58% yield over 3 steps

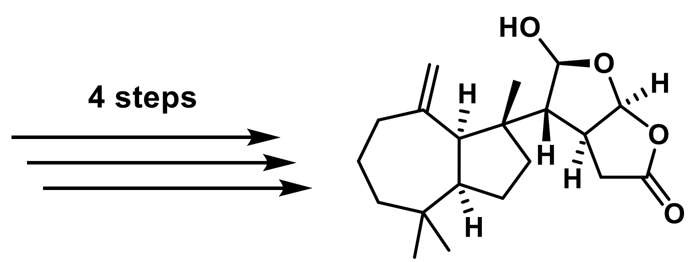
54% yield over 3 steps

G. Stork, et. al. *J. Am. Chem.* 1986, **108**, 6385 – 6387

Overman's Synthesis of Cheloviolene A

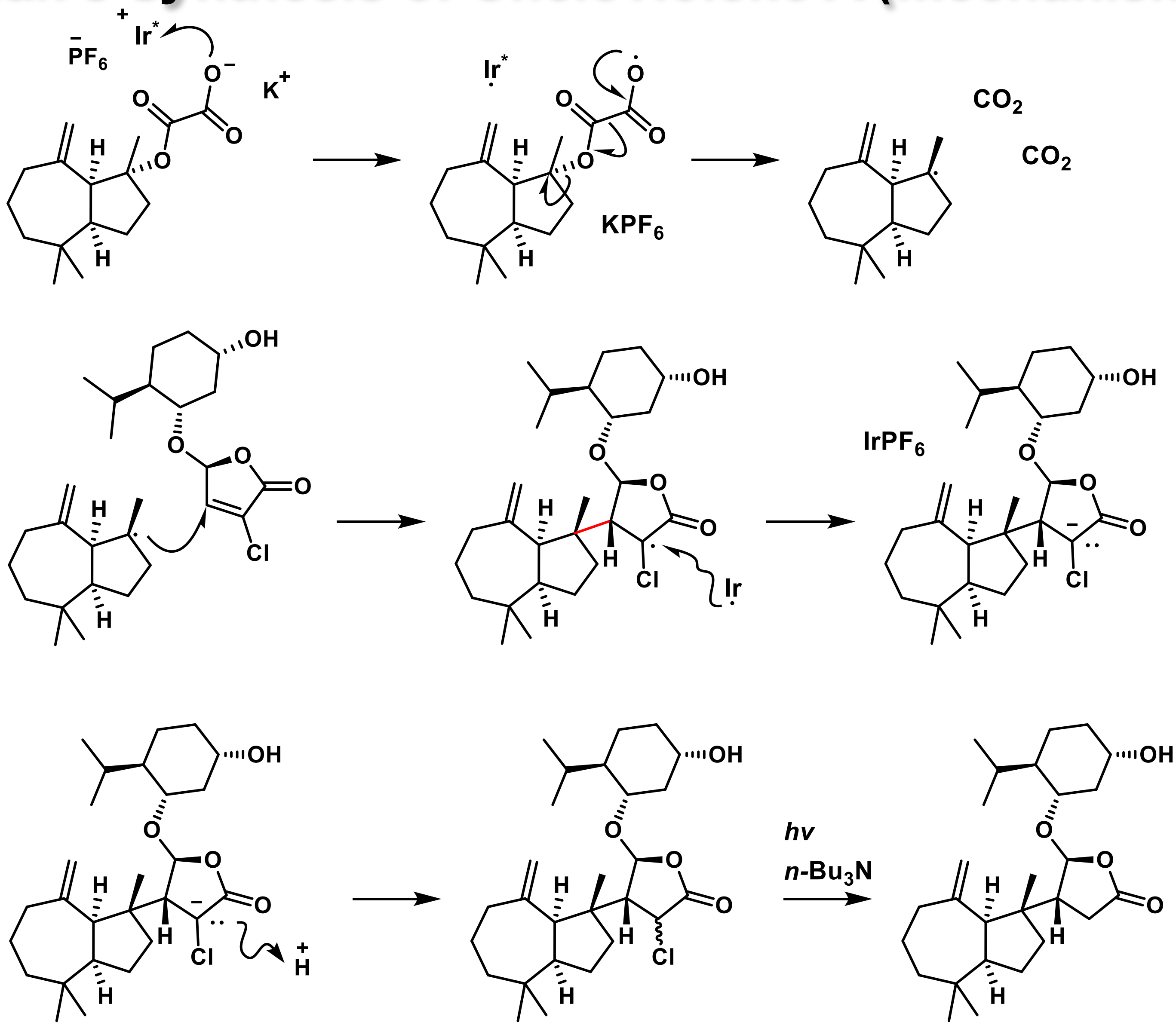






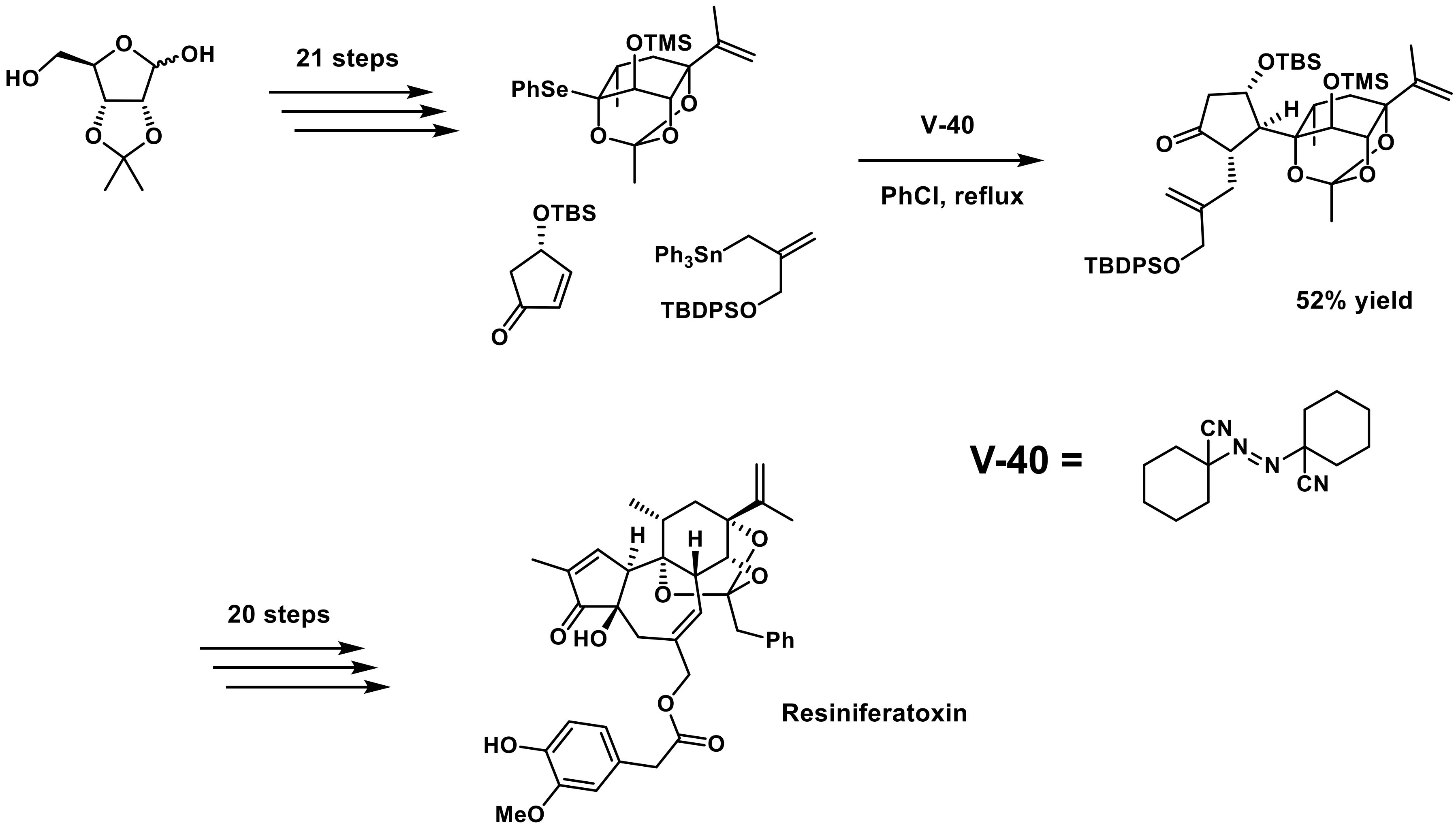
(+)-Cheloviolene A

Overman's Synthesis of Cheloviolene A (mechanism)

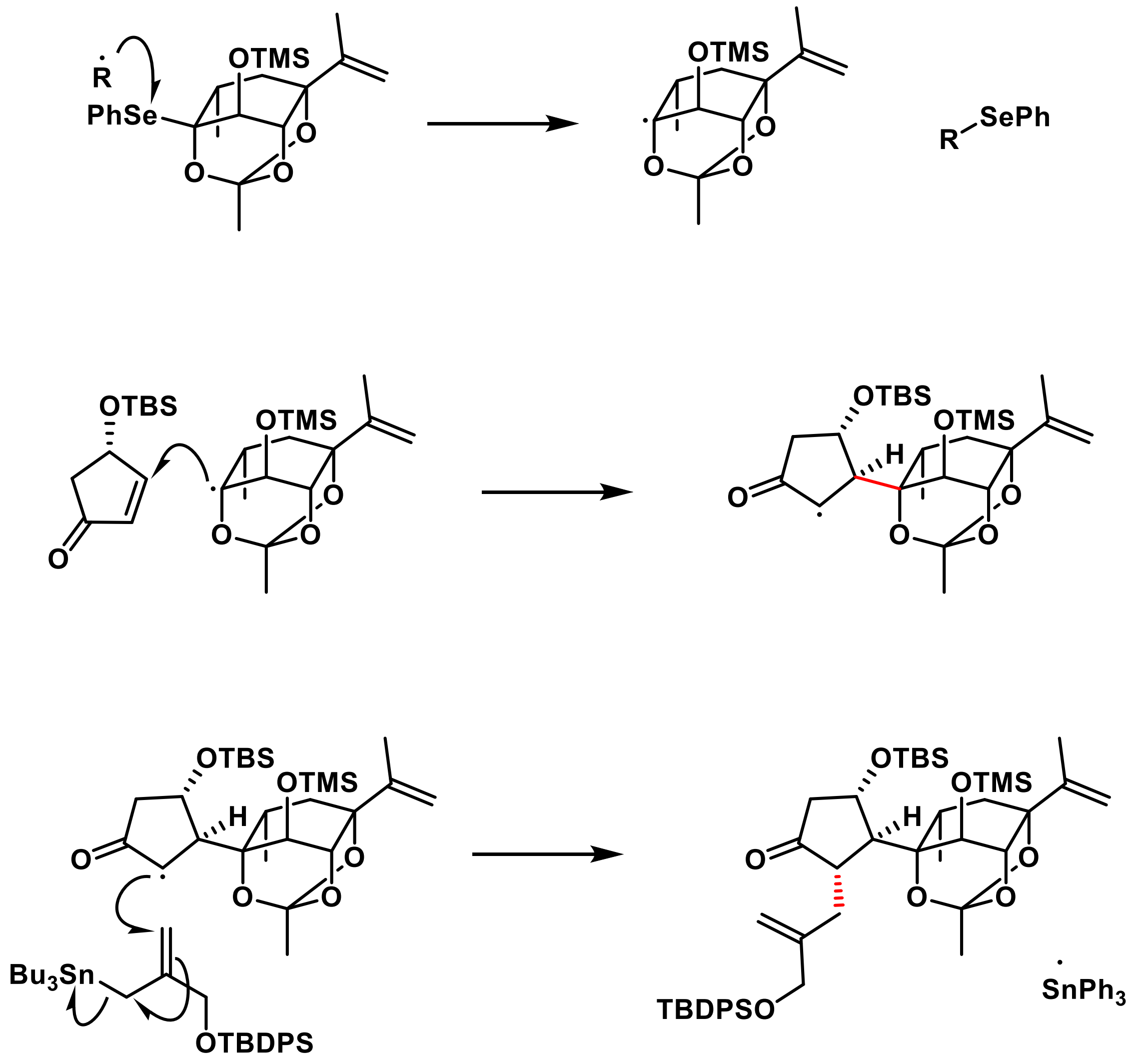


L. Overman, et. al., *J.Am.Chem.Soc*. 2017, **139**, 7192−7195

Inoue's Synthesis of Resiniferatoxin

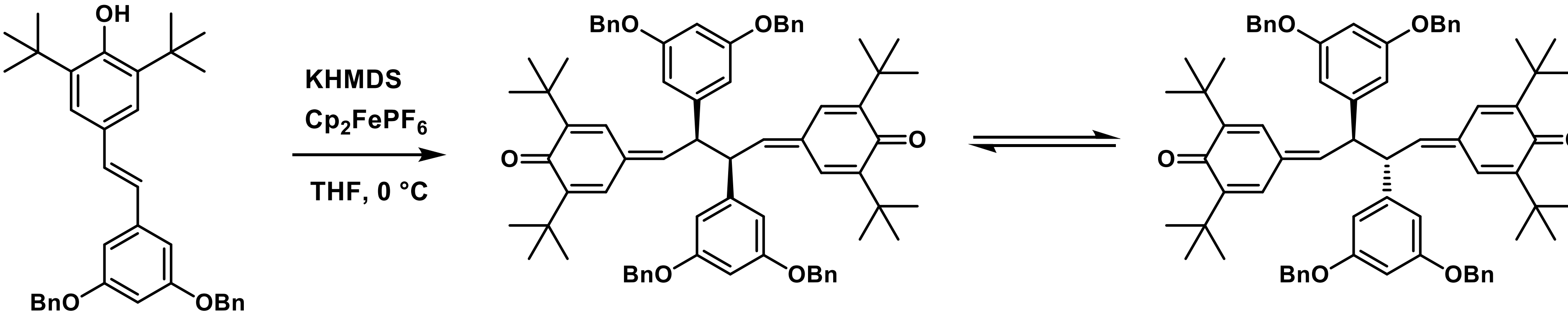


Inoue's Synthesis of Resiniferatoxin (mechanism)

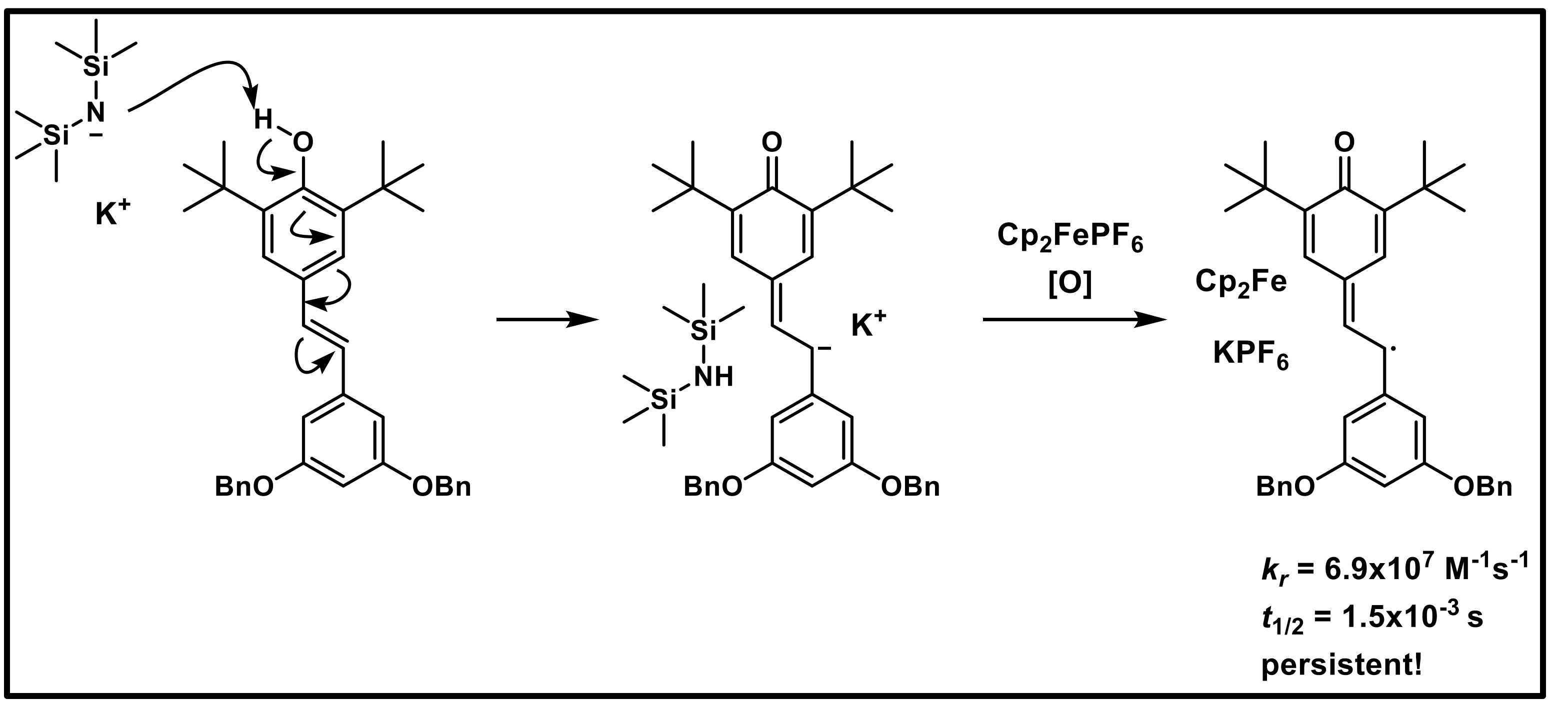


M. Inoue, et. al., *J. Am. Chem. Soc.* , 2017, **139**, 16420–16429

Stephenson's Synthesis of Resveratrol Dimers

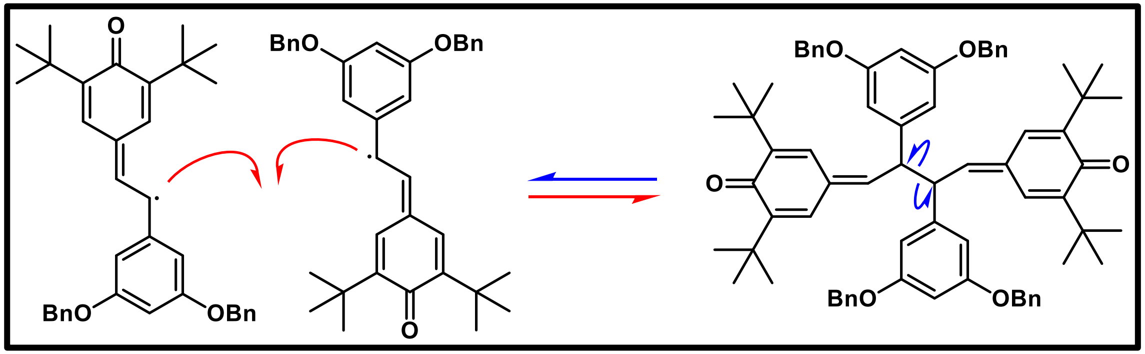


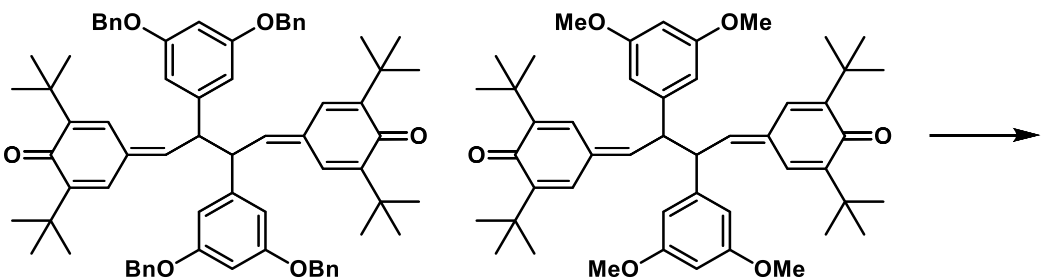
95% yield, 3:4, *dl*:*meso*

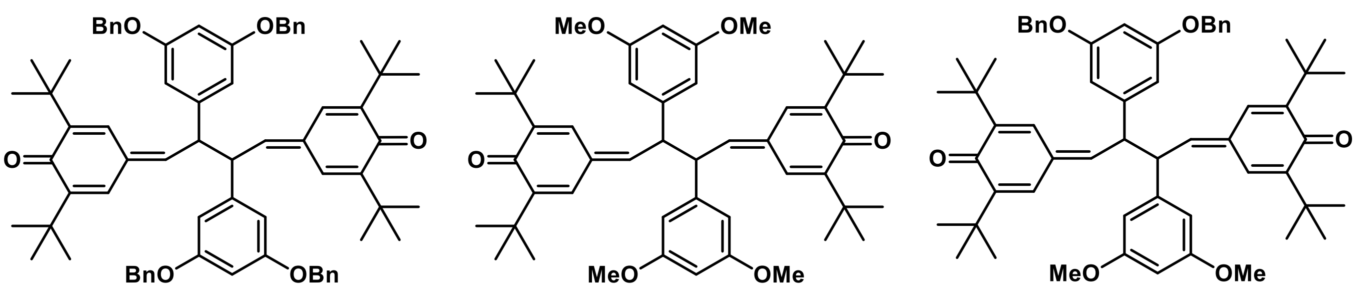


C. R. J. Stephenson, D. A. Pratt, et. al., *Angew. Chem. Int. Ed.* 2015, **54**, 3754 –3757

Stephenson's Synthesis of Resveratrol Dimers



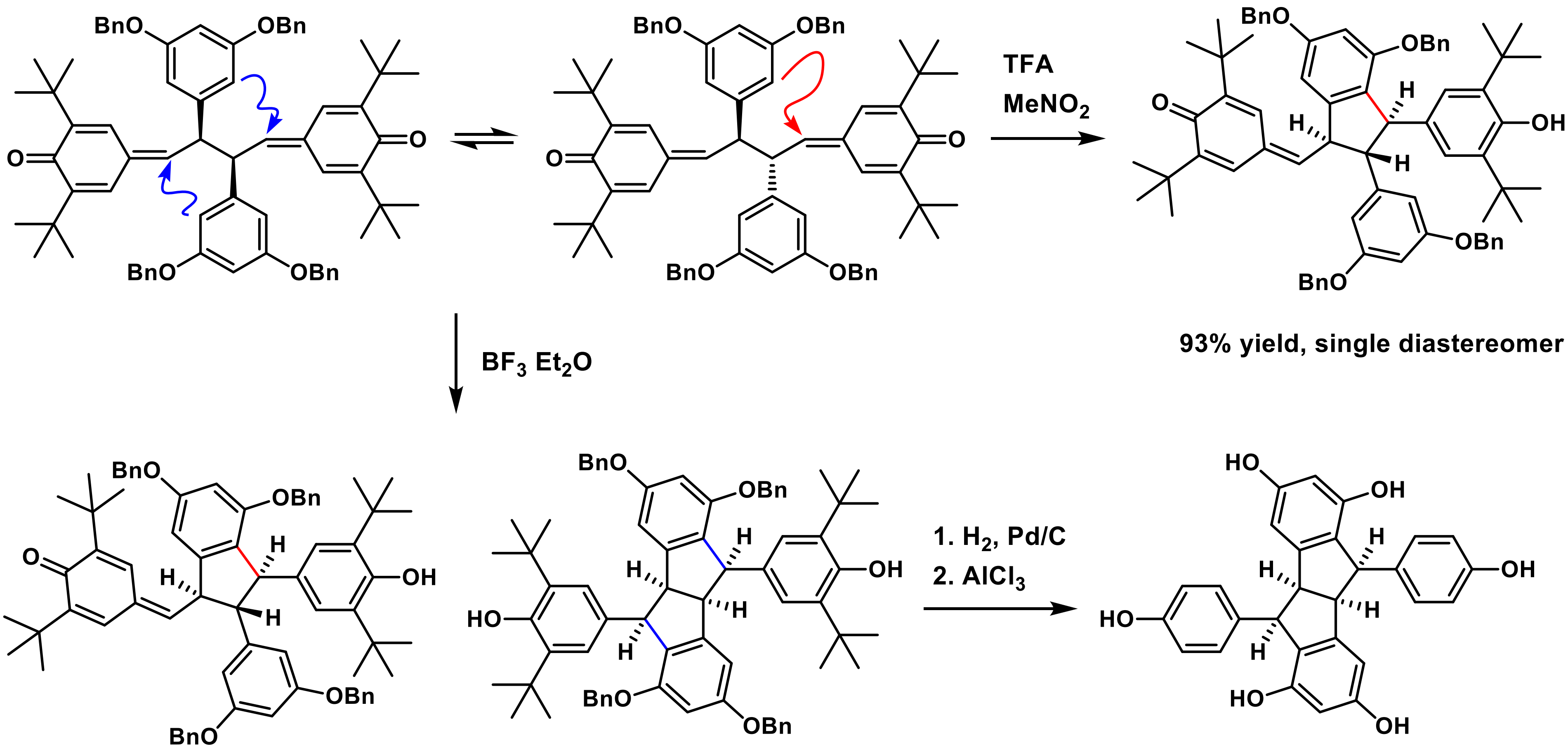




1:1:2 mixture

C. R. J. Stephenson, D. A. Pratt, et. al., *Angew. Chem. Int. Ed.* 2015, **54**, 3754 –3757
C. R. J. Stephenson, D. A. Pratt, et. al., *Science*, 2016, **354**, 1260–1265

Stephenson's Synthesis of Resveratrol Dimers



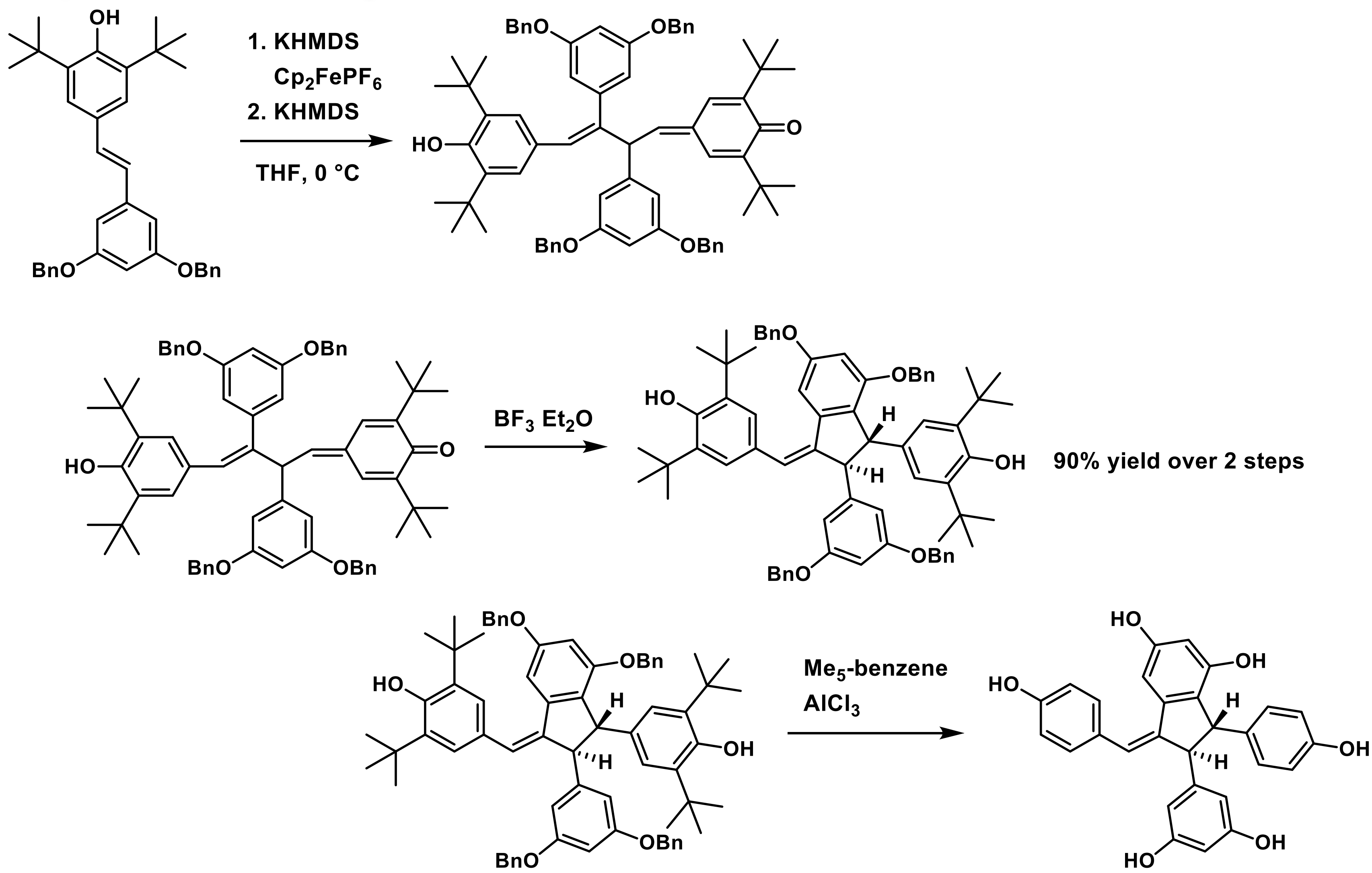
88% yield,1:1 ratio of products

Pallidol

76% over 2 steps

C. R. J. Stephenson, D. A. Pratt, et. al., *Angew. Chem. Int. Ed.* 2015, **54**, 3754 –3757
C. R. J. Stephenson, D. A. Pratt, et. al., *Science*, 2016, **354**, 1260–1265

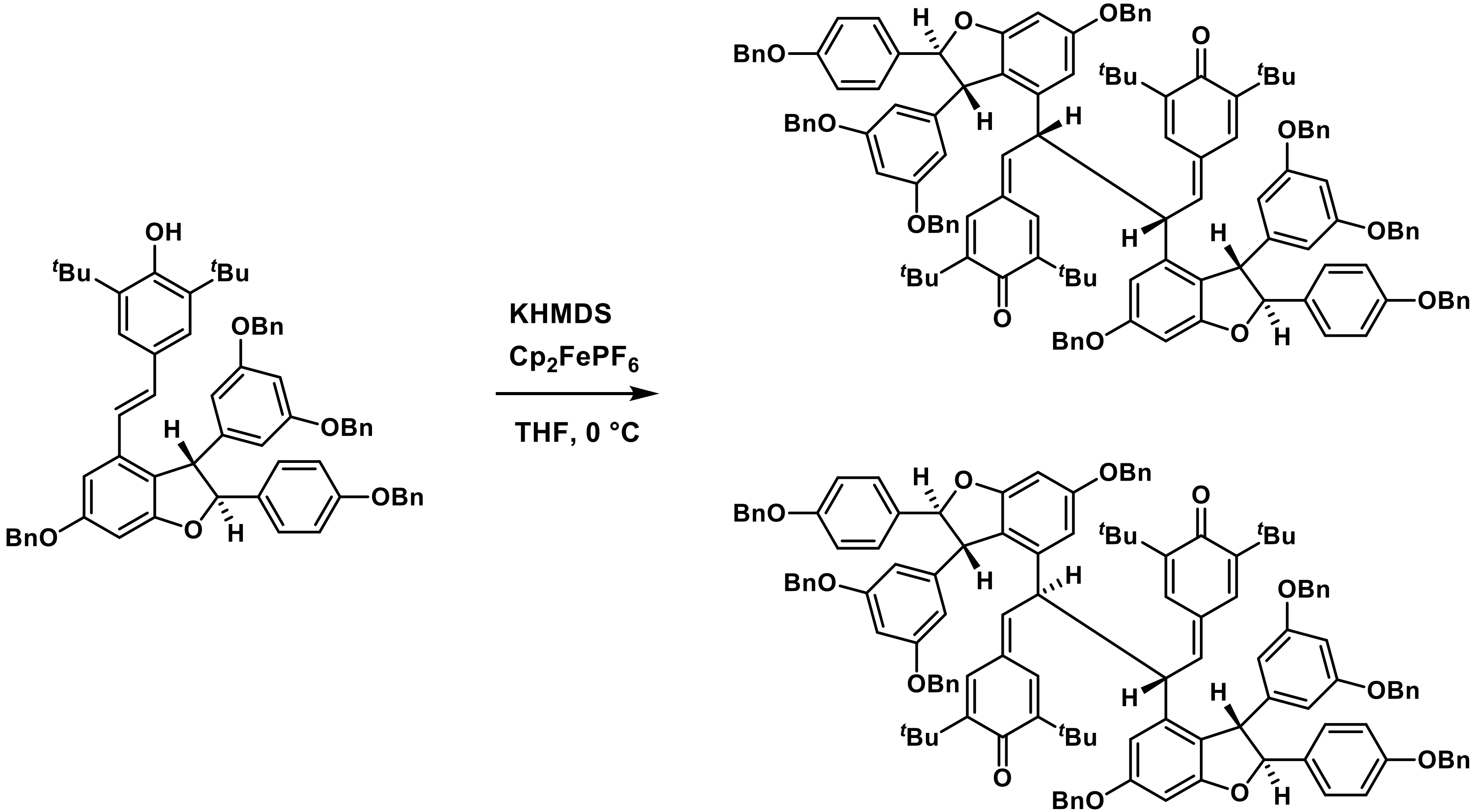
Stephenson’s Synthesis of Resveratrol Dimers



quadrangularin A
73% yield

C. R. J. Stephenson, D. A. Pratt, et. al., *Angew. Chem. Int. Ed.* 2015, **54**, 3754 –3757

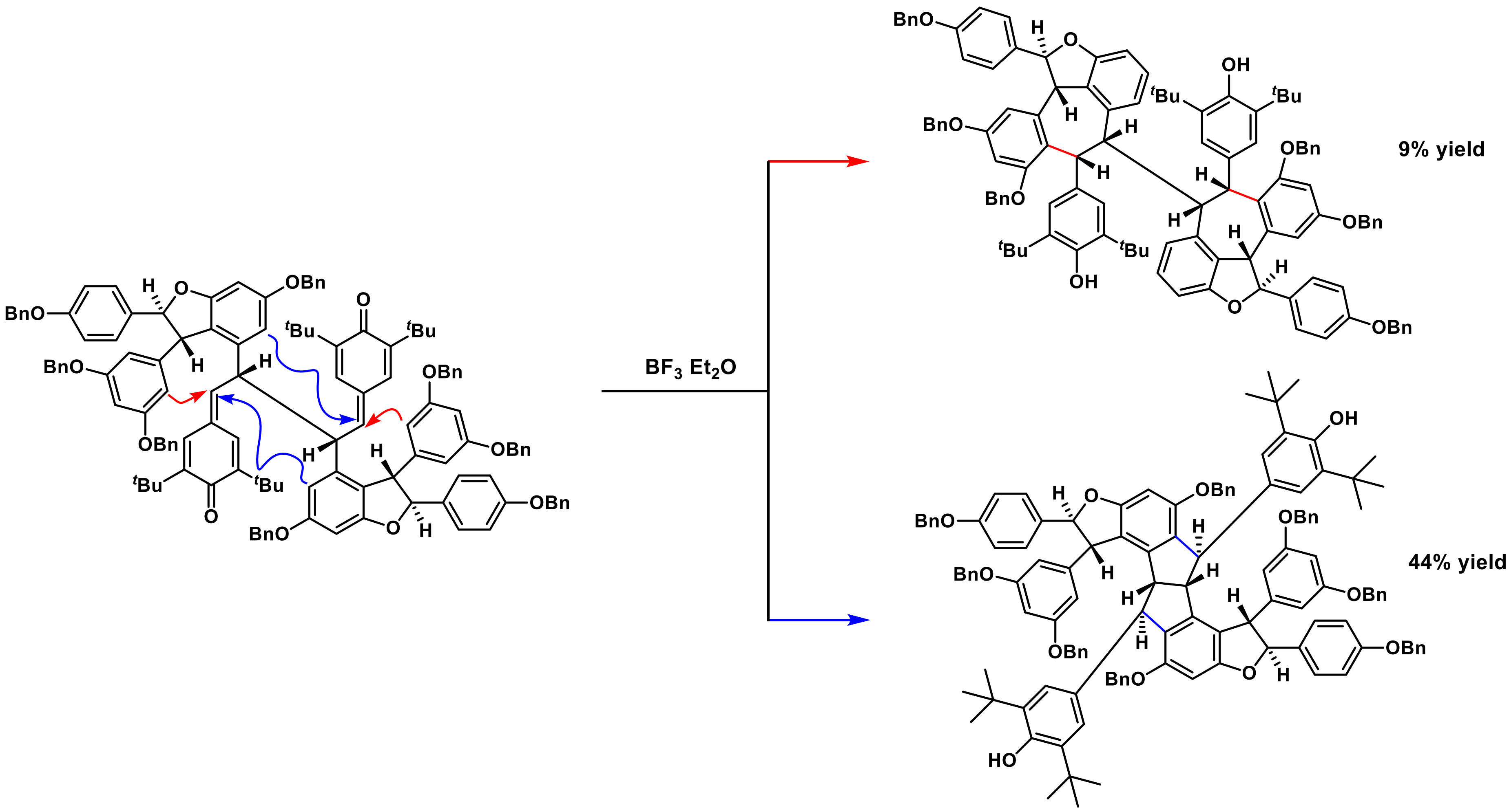
Stephenson's Synthesis of Viniferin Dimers (Resveratrol Tetramers)



97% yield, 19:1 dr

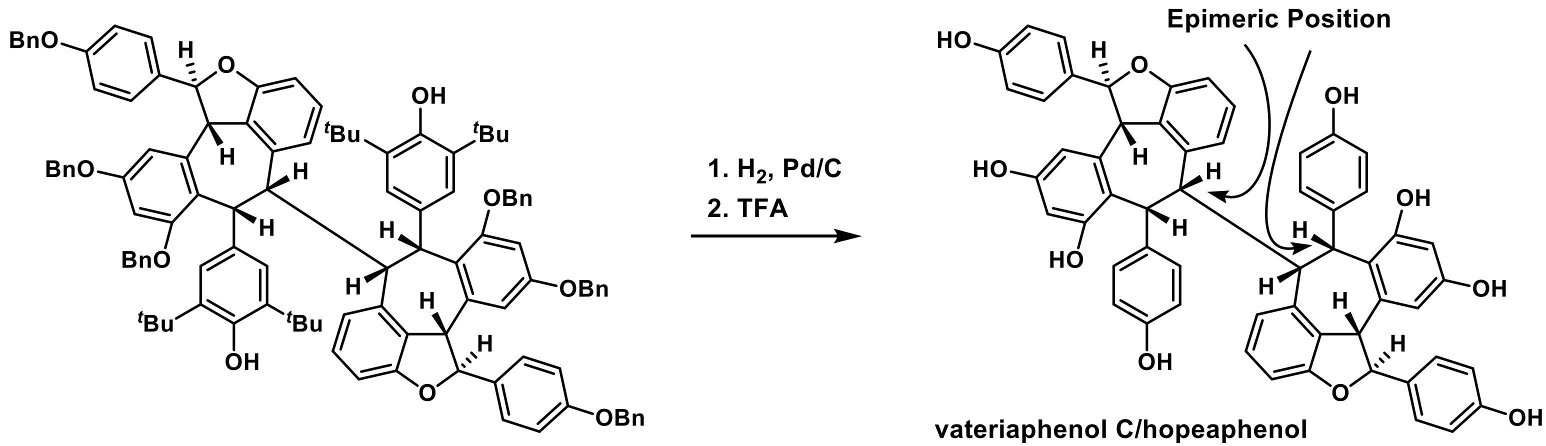
C. R. J. Stephenson, D. A. Pratt, et. al., *Science*, 2016, **354**, 1260–1265

Stephenson's Synthesis of Viniferin Dimers (Resveratrol Tetramers)

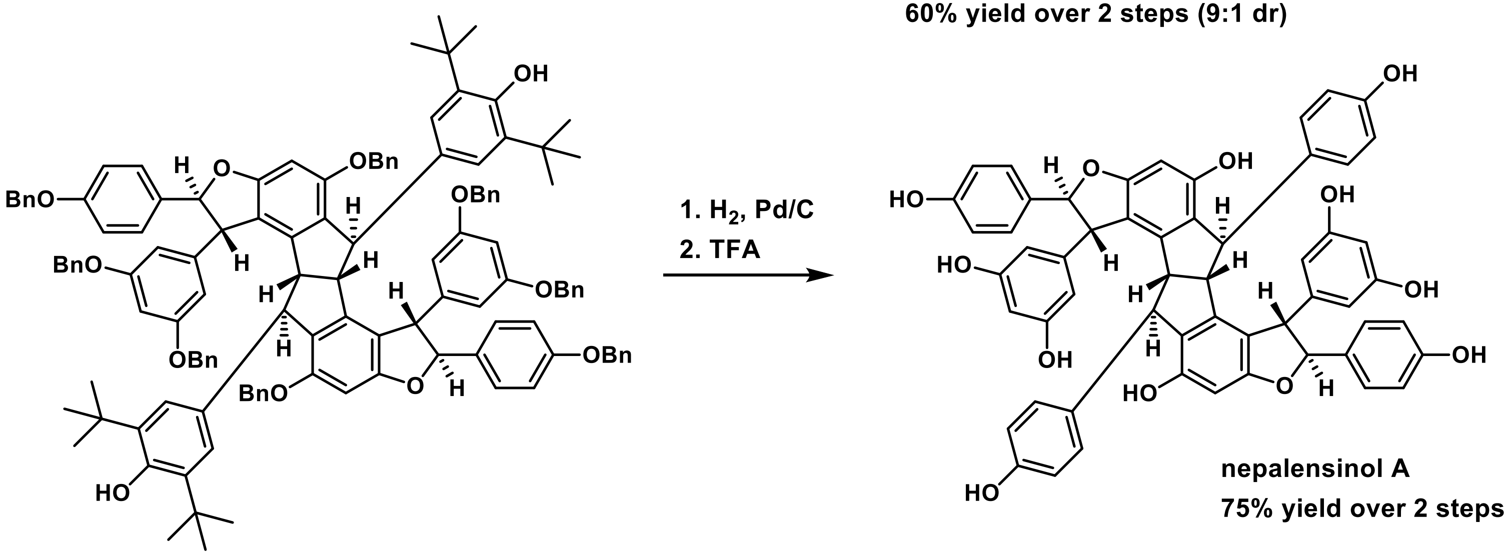


C. R. J. Stephenson, D. A. Pratt, et. al., *Science*, 2016, **354**, 1260–1265

Stephenson's Synthesis of Viniferin Dimers (Resveratrol Tetramers)



vateriaphenol C/hopeaphenol
60% yield over 2 steps (9:1 dr)



nepalensinol A
75% yield over 2 steps

C. R. J. Stephenson, D. A. Pratt, et. al., *Science*, 2016, **354**, 1260–1265

Summary

- Basic tutorial on kinetic and thermodynamic parameters relating to reactivity of carbon-centered radicals

- Introduce persistent radicals and how they lead to selectivity in total synthesis

- Shared some examples of total syntheses where a persistent and/or stabilized radical was an important feature