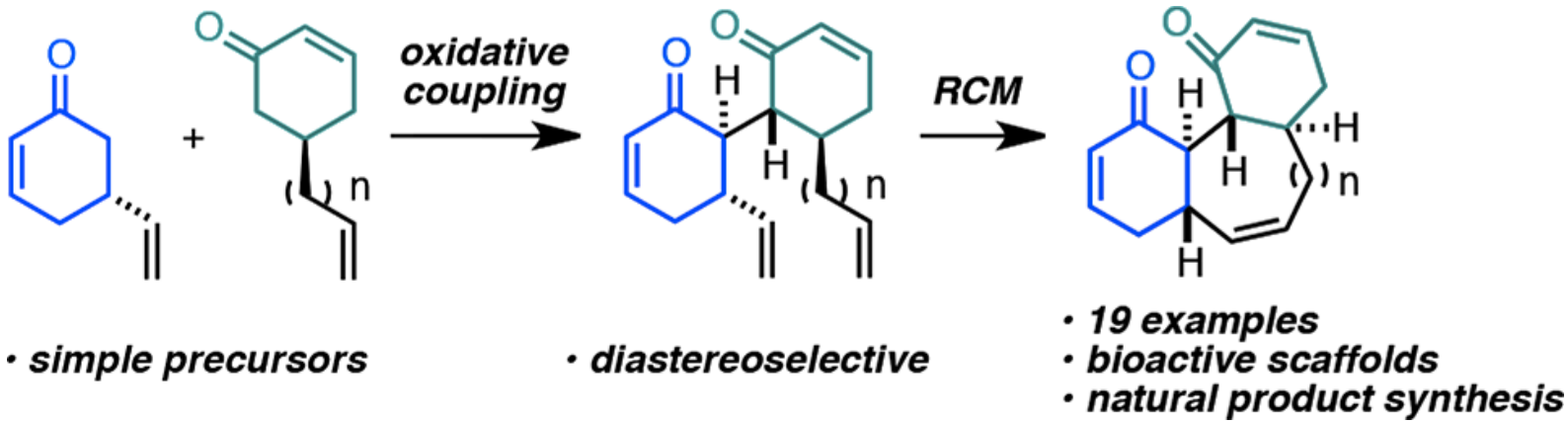
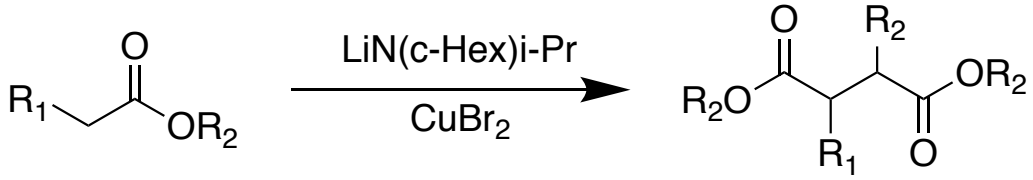
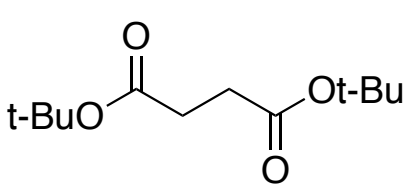
A Strategy for the Convergent and Stereoselective Assembly of Polycyclic Molecules



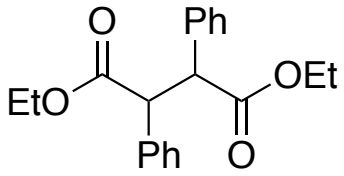
Emily E. Robinson and Regan J. Thompson
J. Am. Chem. Soc., **2018**, *140*, 1956-1965

Oxidative Coupling of Enolates

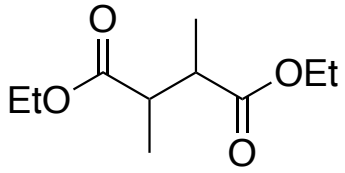




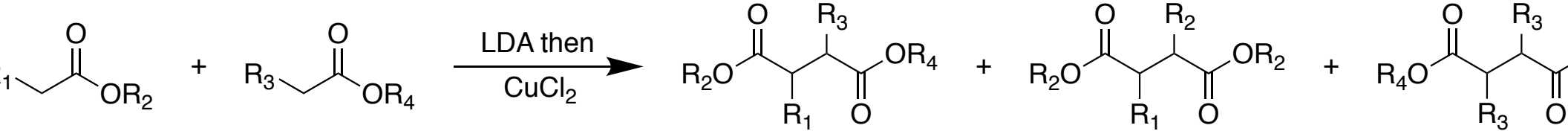
85%



75%

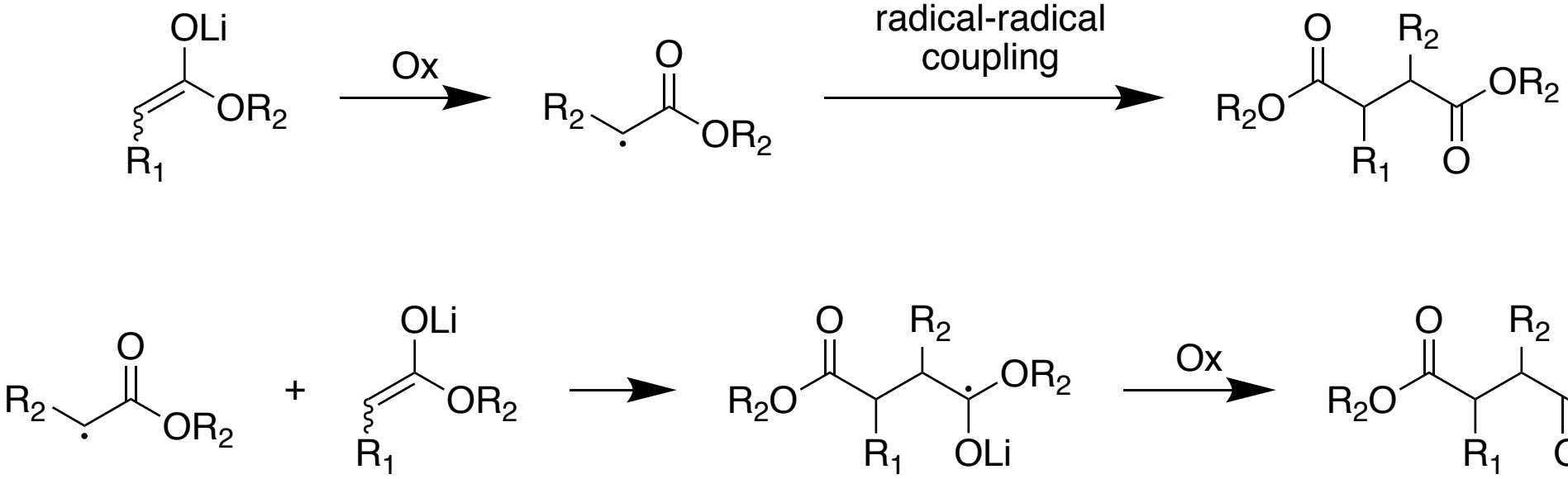


81%



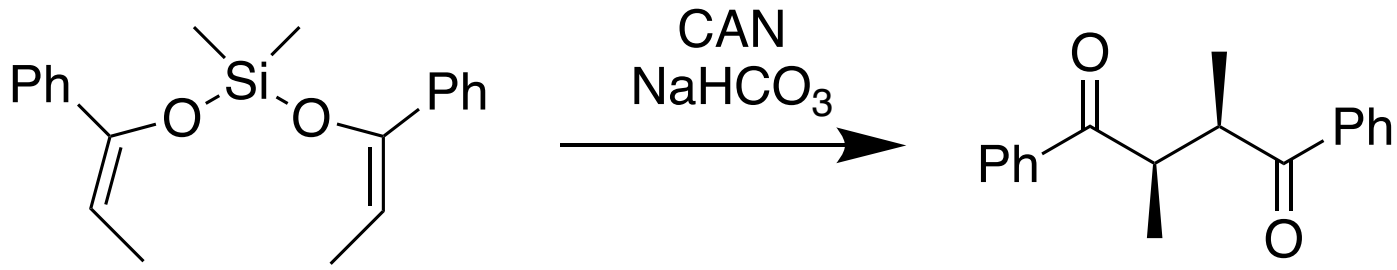
M. Rathke and A. Lindert *J. Am. Chem Soc*., **1971**, *93*, 4605.

Proposed Mechanism

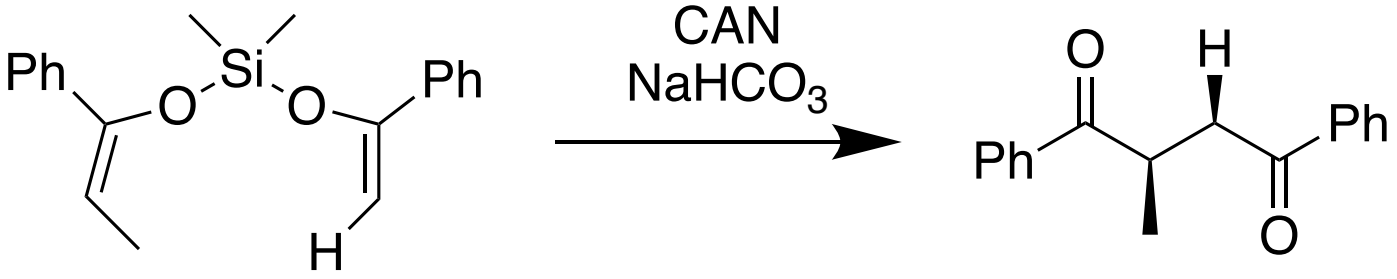


Oxidizing agents: Cu(II), Fe(III), I_2, Ti(IV) and Ag(I).

Oxidative Coupling of Enol Silanes



59%
9:1 dr



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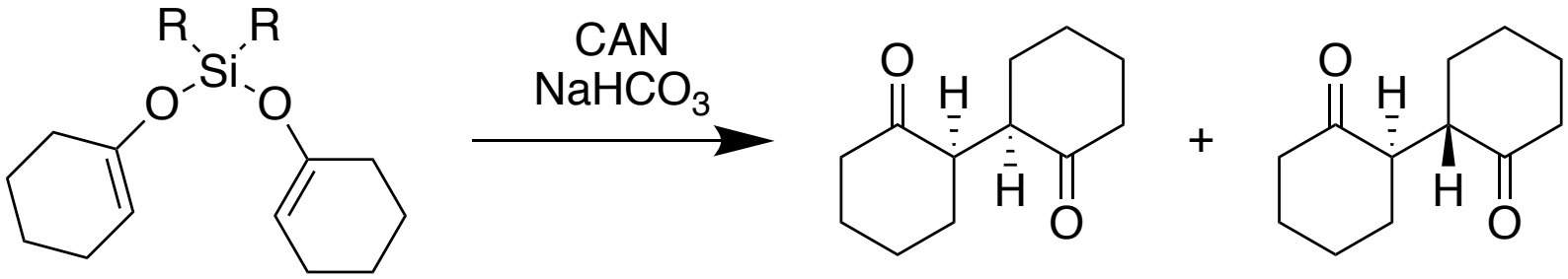
9:1 dr

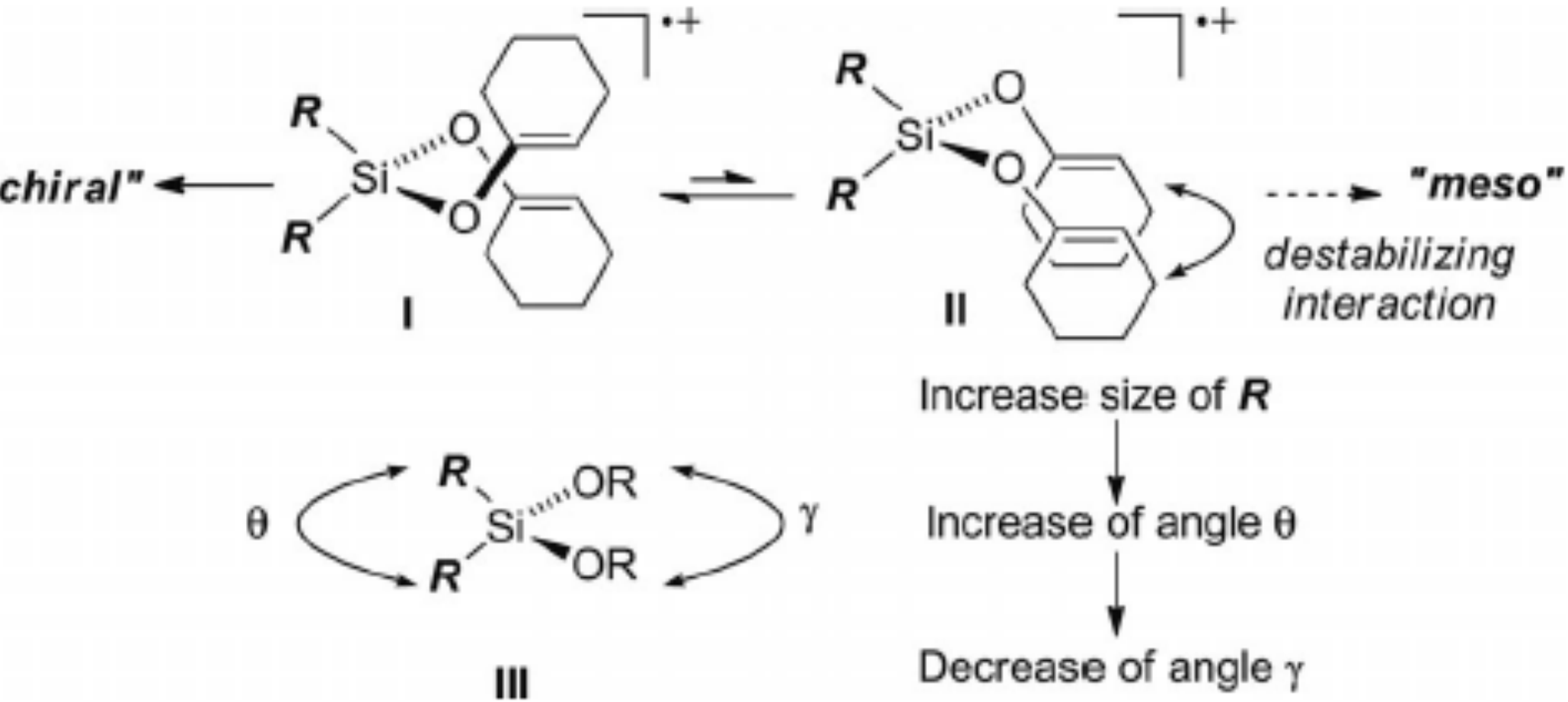
M. Schmittel et al., *J. Org. Chem.*, **1998**, *63*, 396.



chiral D/L **1** meso **2**

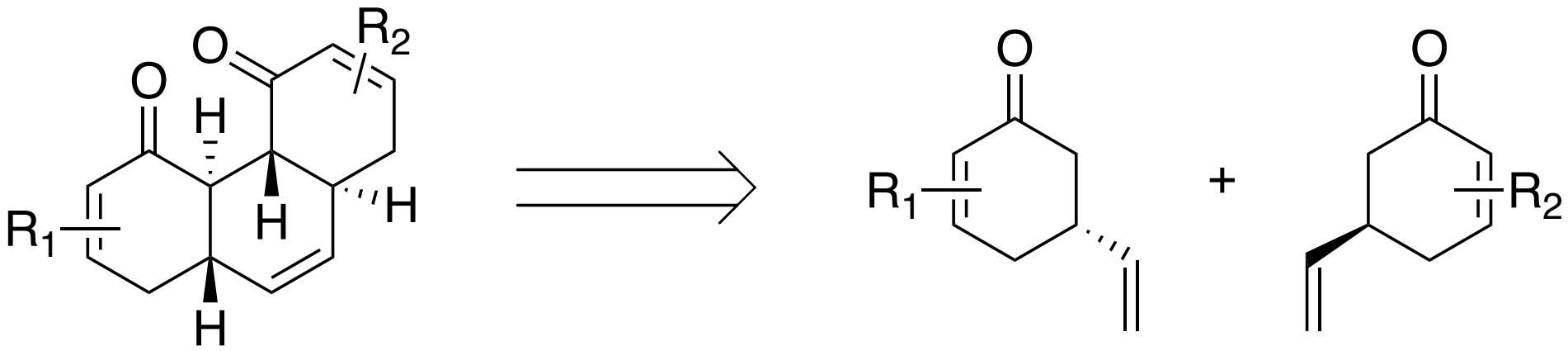
Entry	R	dr (1:2)	% Yield 1
1	Me	2.4:1	29
2	Et	5:1	47
3	Ph	5:1	29
4	i-Pr	10:1	57
5	$-C_4H_8-$	3:1	31
6	$-C_5H_{10}-$	6:1	56

R. Thompson et. al., *Org. Lett.*, **2008**, *10*, 5621

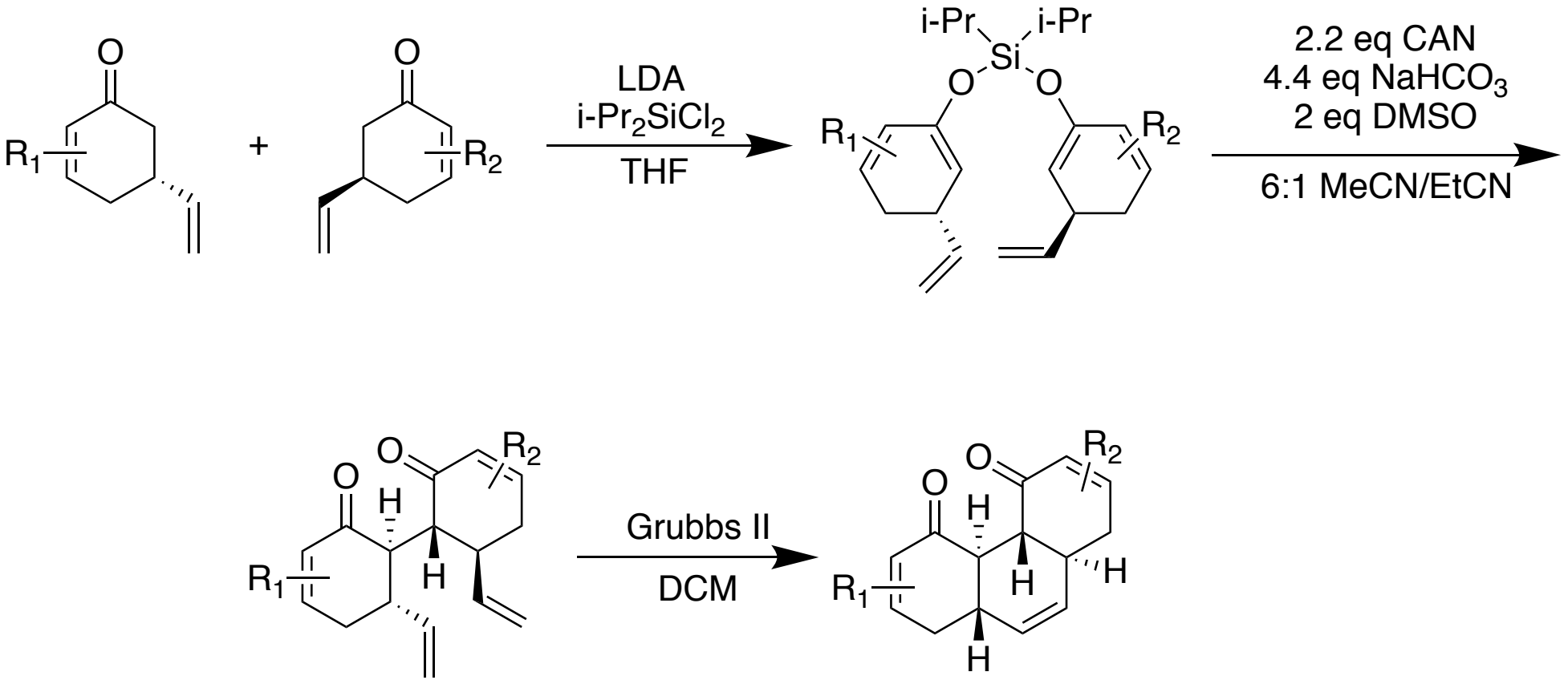


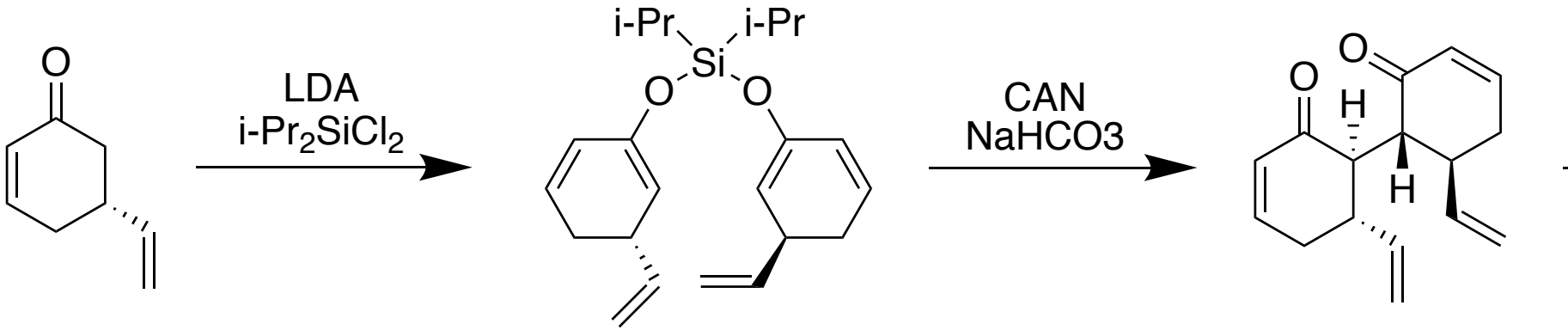
R. Thompson et. al., *Org. Lett.*, **2008**, *10*, 5621

Title Paper

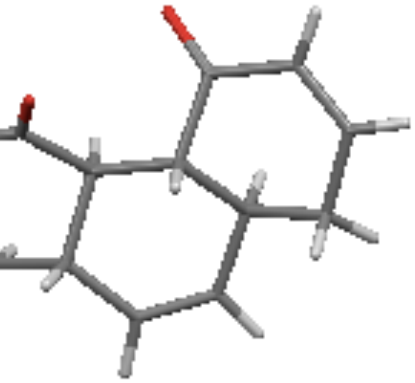


General route





50%



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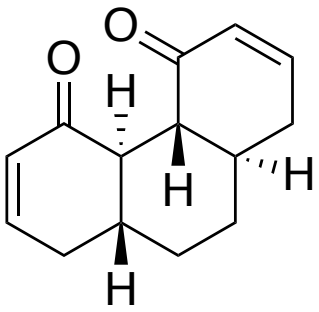

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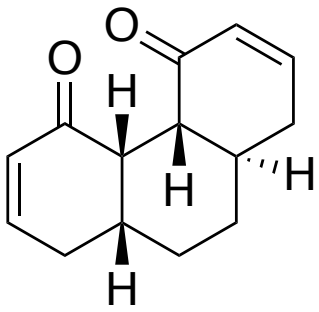

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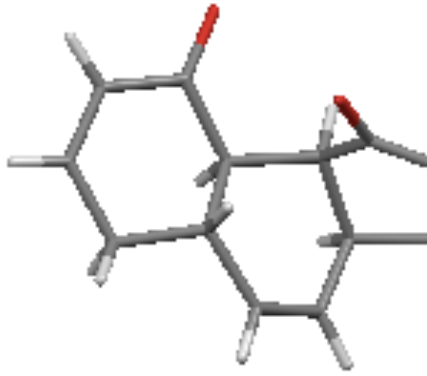
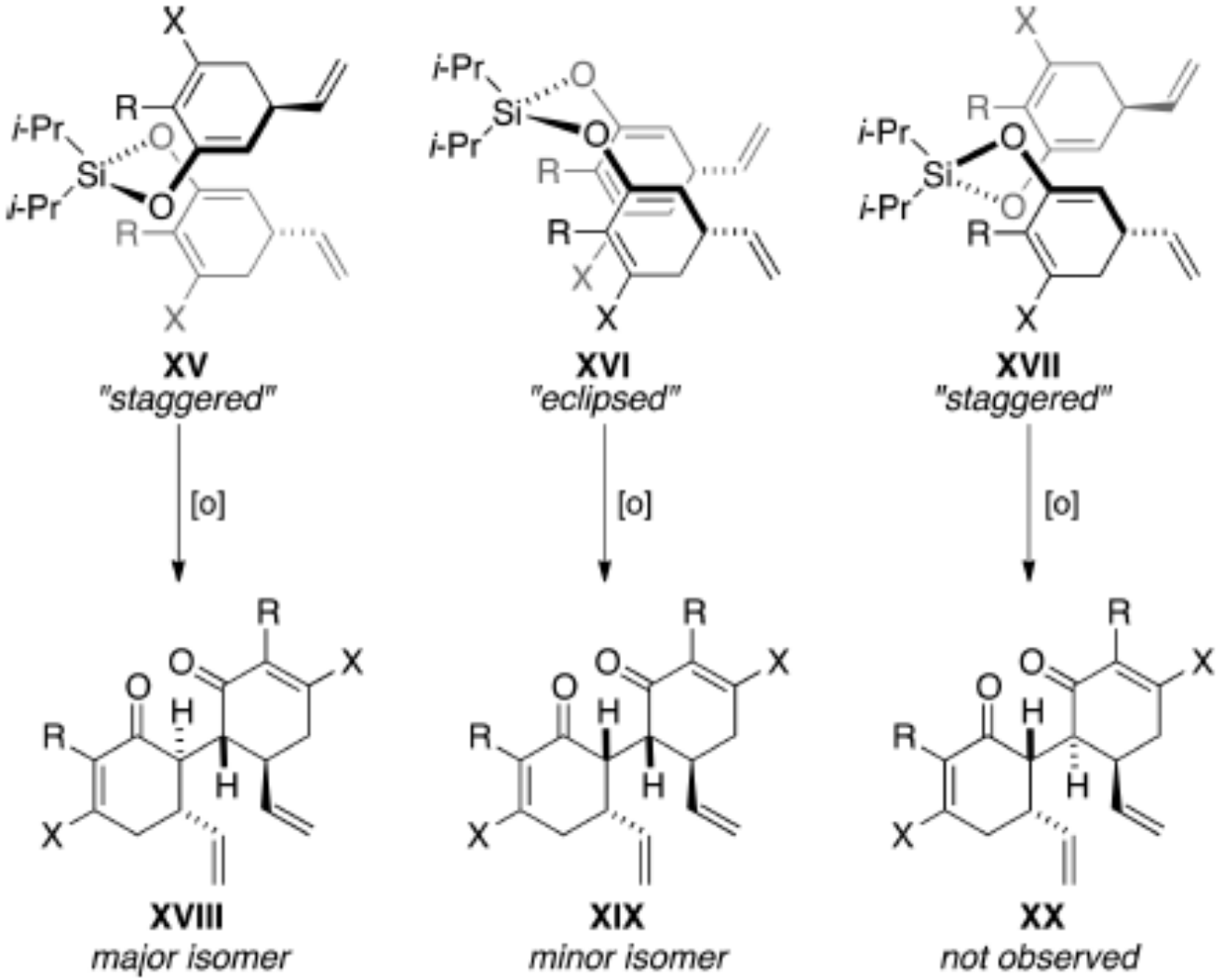
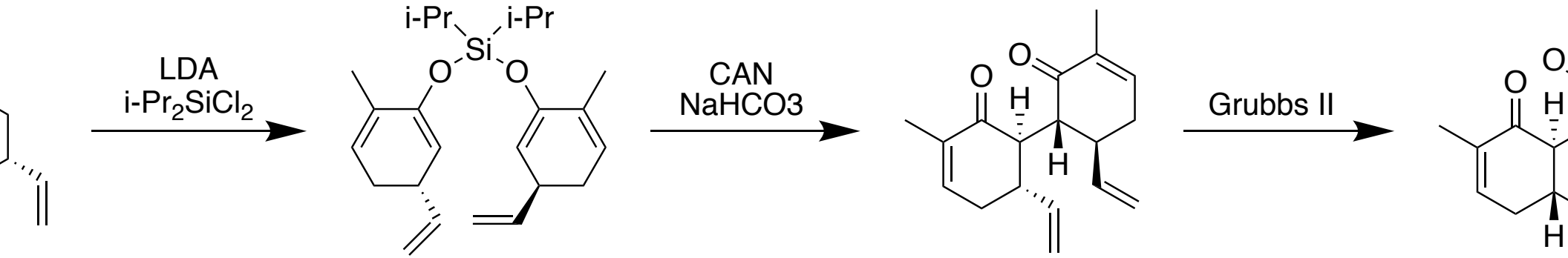


86% 3:1 dr
43% over 2 steps

epi isomer

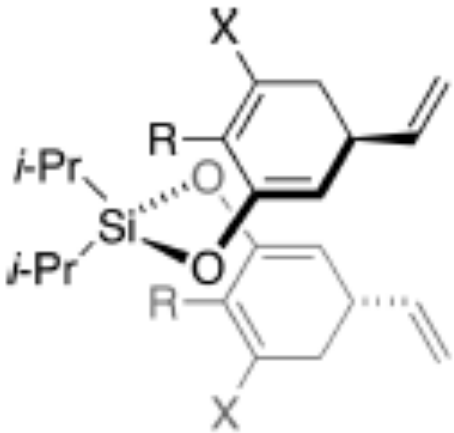
Stereochemical model



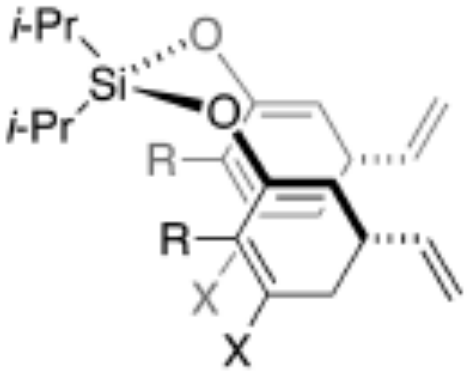


68%

84% 2(
57% over

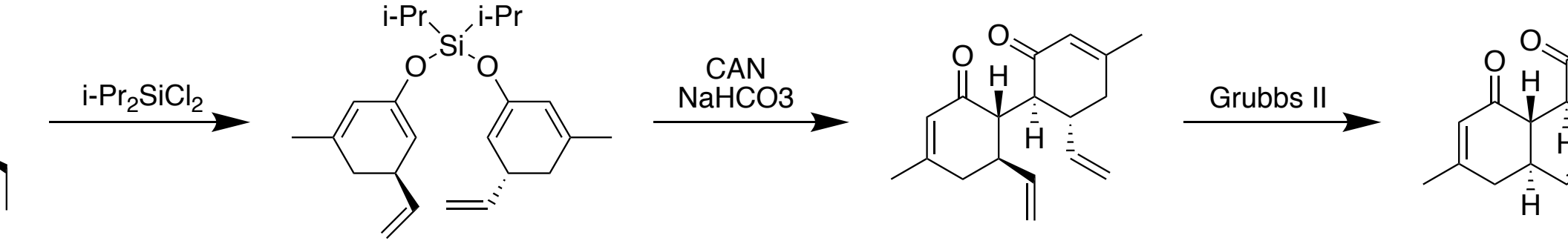


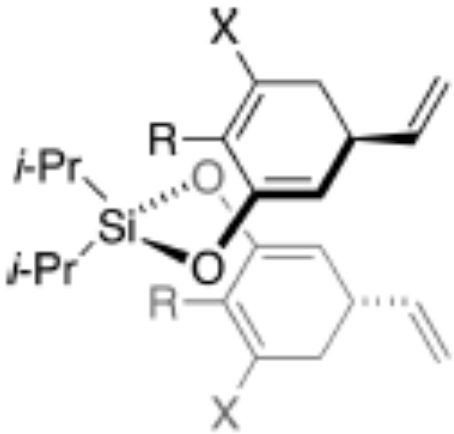
XV
"staggered"



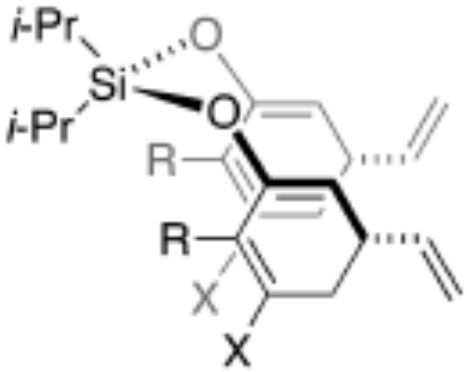
XVI
"eclipsed"

R=Me X=H
Greater destabilization of eclipsed conformer leads to a better dr





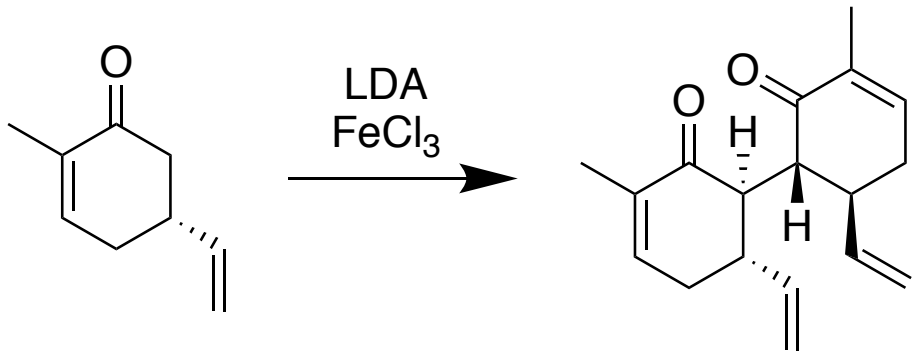
XV
"staggered"



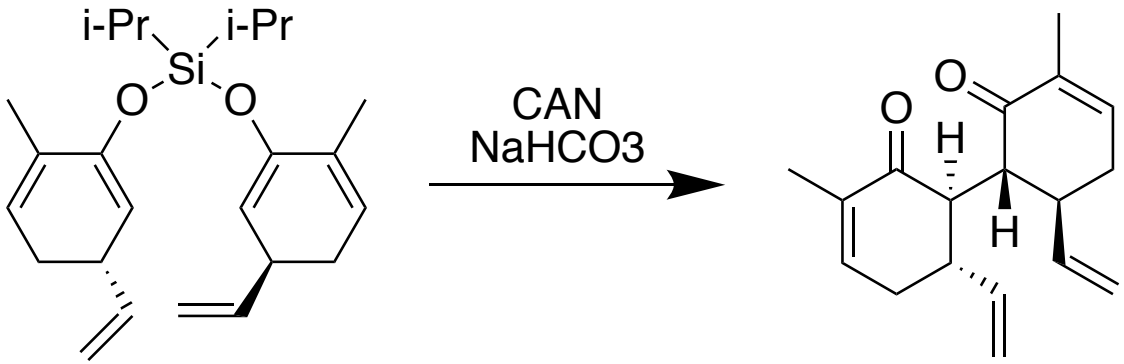
XVI
"eclipsed"

R=H X=Me
Further away from bond forming site
Less effect of isopropyl substituents on silicon

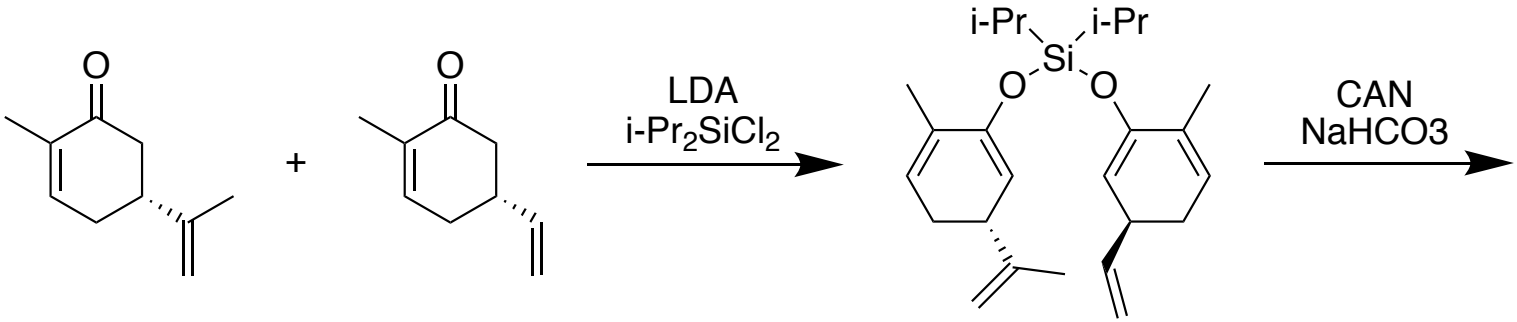
Effect of Silicon tether

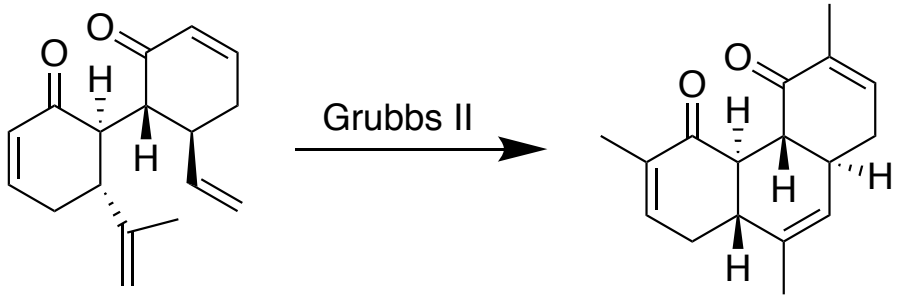


3:1 dr



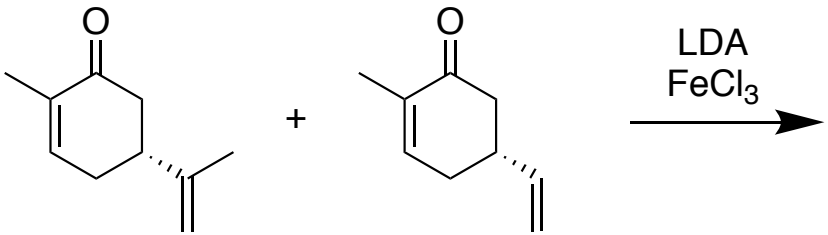
20:1 dr



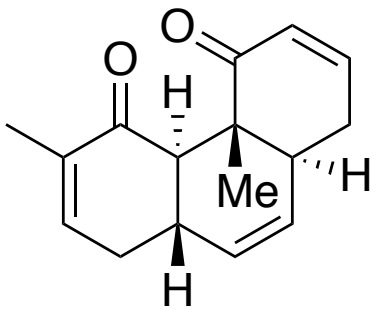


50%

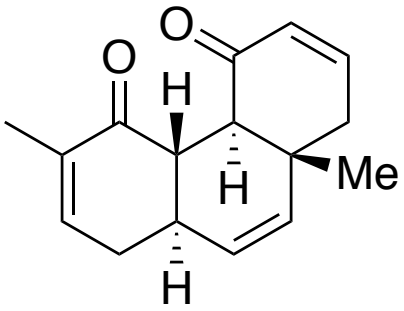
87% 20:1 dr
44% over 2 steps



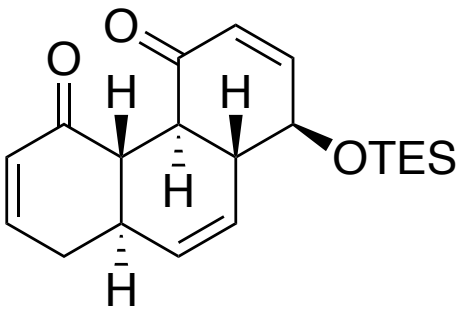
Mixture of diastereomeric products



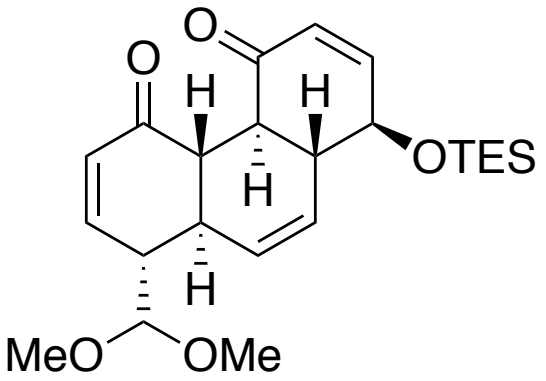
44% over 2 steps
20:1 dr



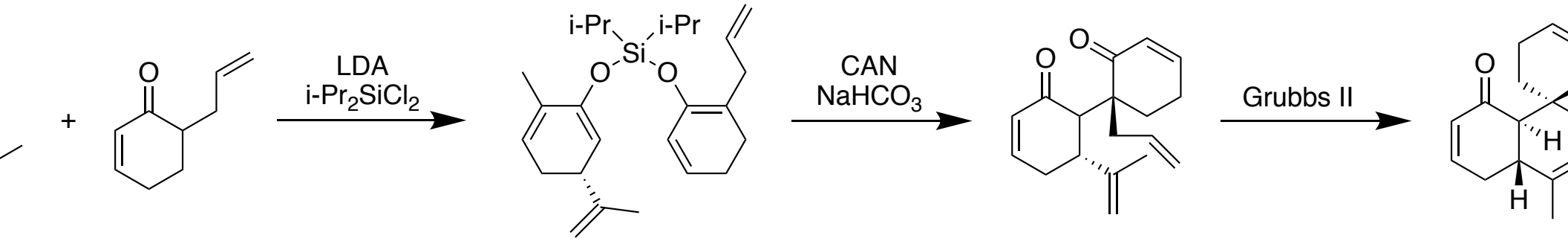
34% over 2 steps
10:1 dr

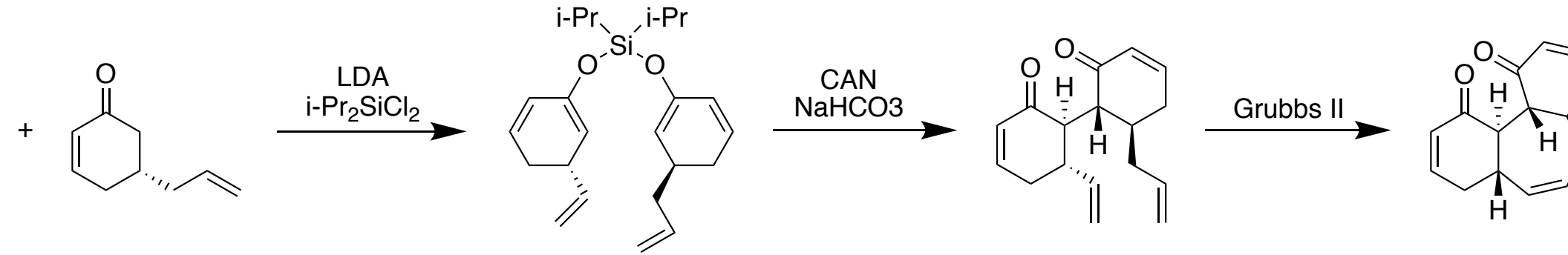


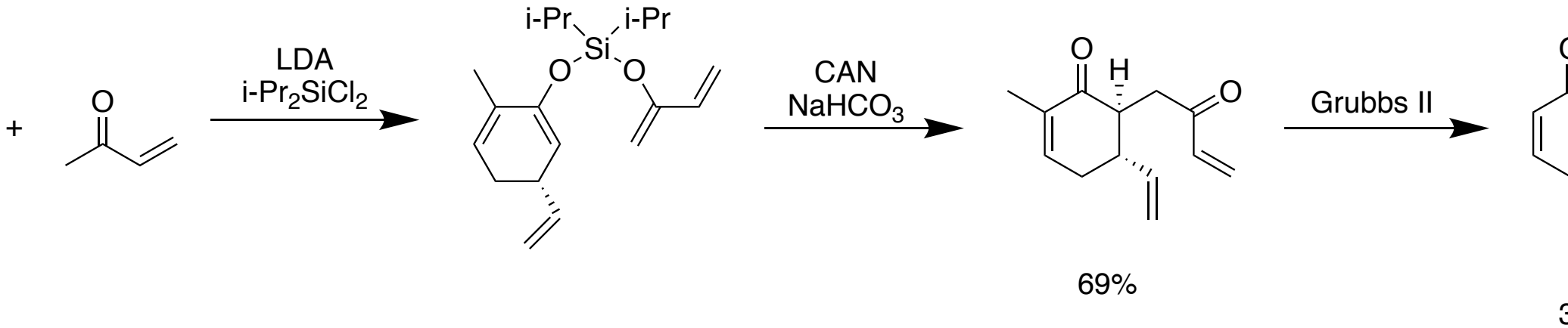
35% over 2 steps
20:1 dr



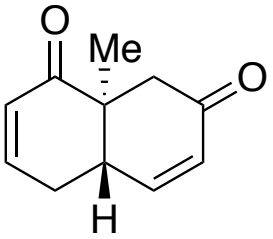
37% over 2 steps
20:1 dr


+
O
LDA
i-Pr2SiCl2
i-Pr
i-Pr
Si
O
O
CAN
NaHCO3
O
O
57%
Grubbs II
O
H
H
91%
52% over
20:1

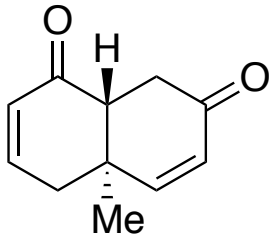

+
O
LDA
i-Pr2SiCl2
i-Pr
i-Pr
Si
O
O
CAN
NaHCO3
O
O
H
H
42%
Grubbs II
O
O
H
H
72%
30% over 2
5:1 dr



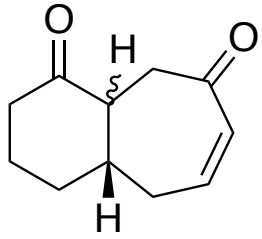
69%



26% overall
1.3:1 dr

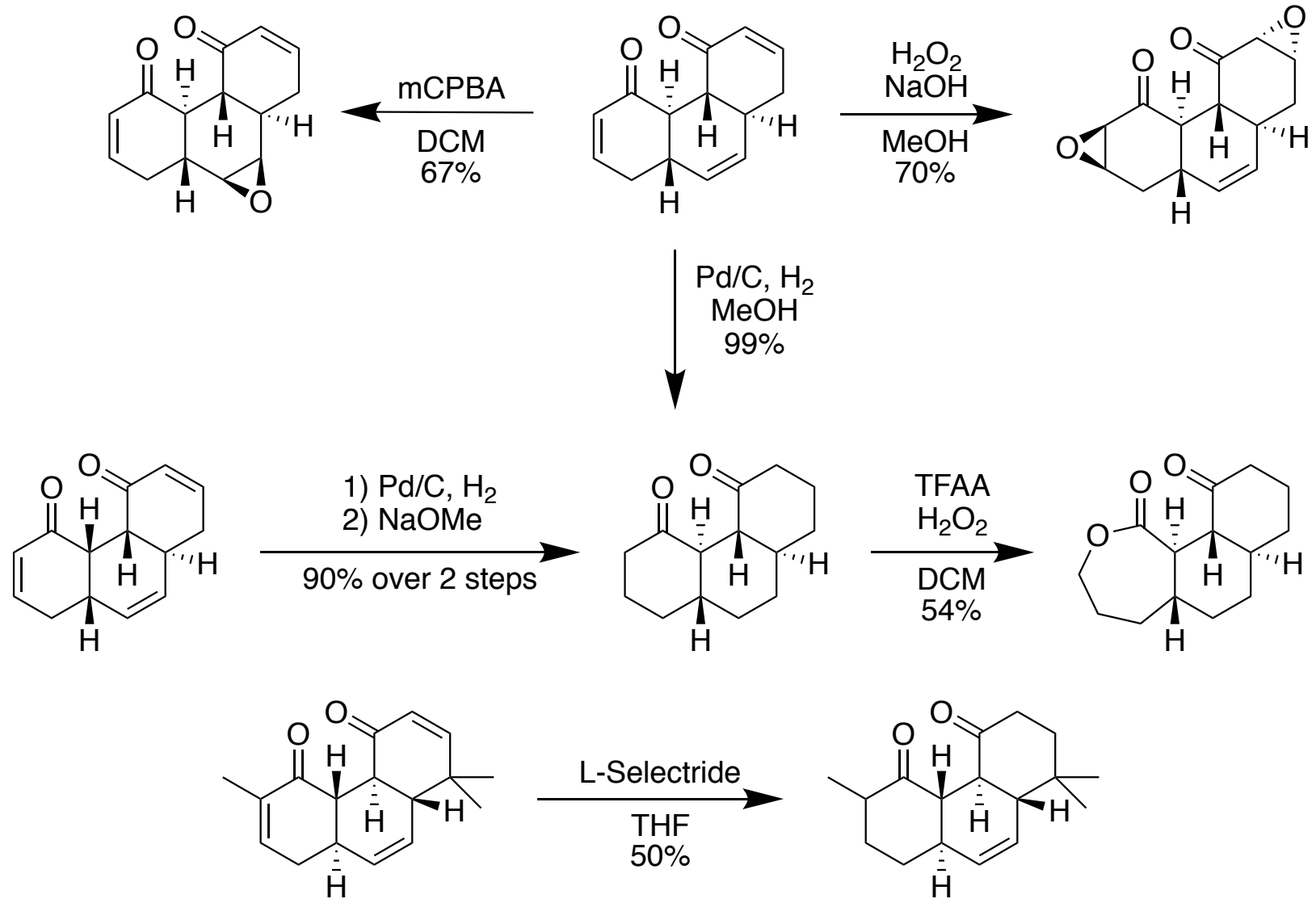


32% overall
1.6:1 dr



45% overall
1.3:1 dr

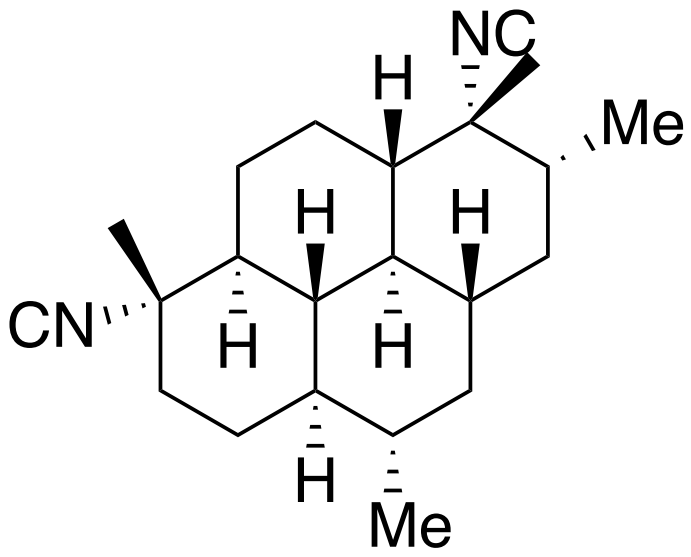
Chemoselective Transformations



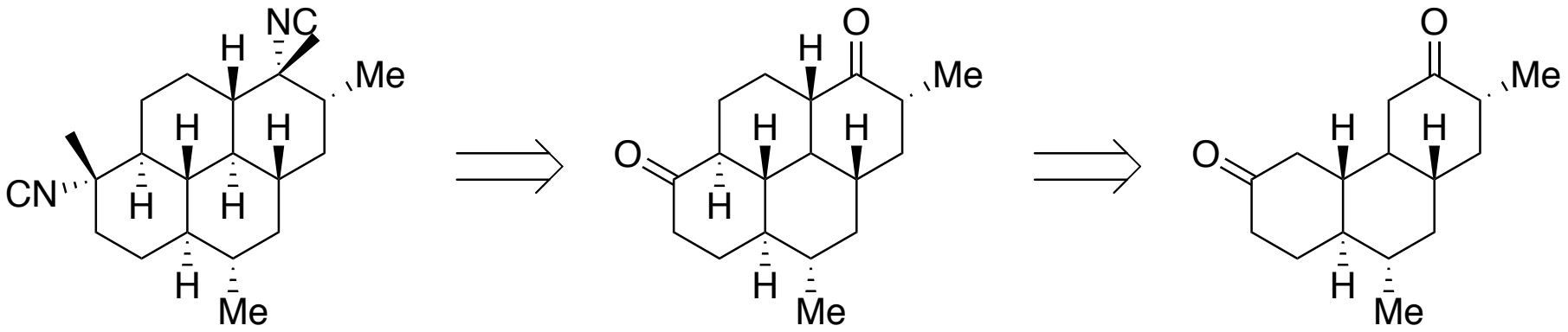
Formal Synthesis of 7,20-Diisocyanoadociane

elongs to the *Amphimedon* family (isolated first in 1977).
C_{50} = 4.7 nM against malaria parasite *Plasmodium alciparum*

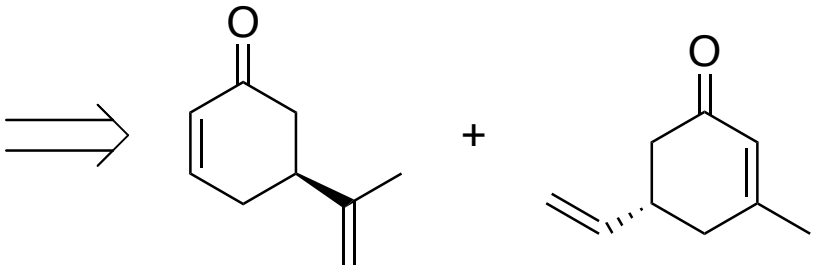
revious total (and formal) synthesis:
) Corey and Magriotis (1987) 26 steps
) Mander and Fairweather (2006) 42 steps
) Miyaoka and coworkers (2011) 32 steps
) Vanderwal and Roosen (2016) 24 steps
) Shenvi and co-workers (2016) 17 steps

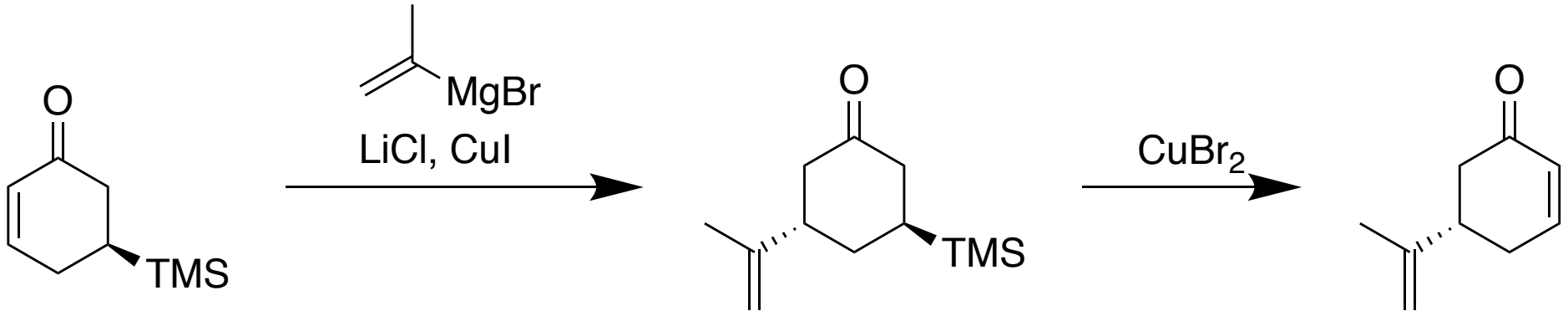


Disconnection using newly developed strategy

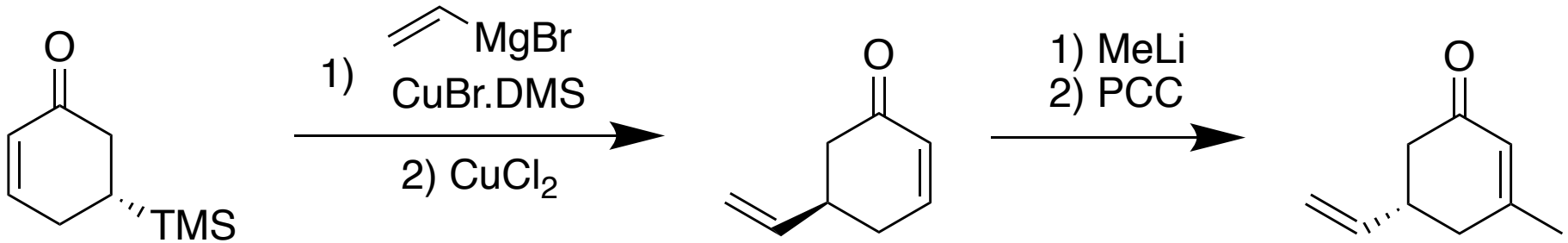


"Corey dione"

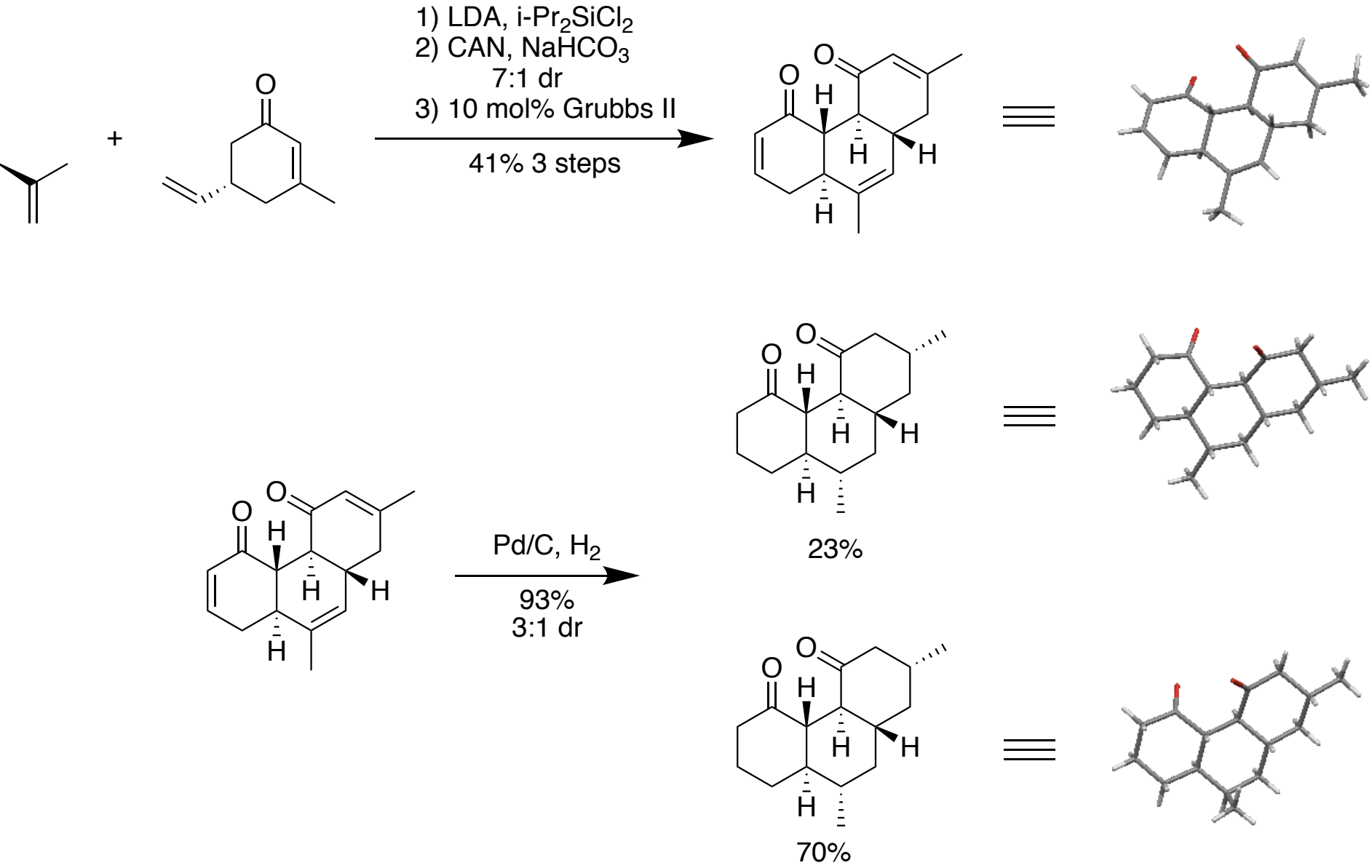


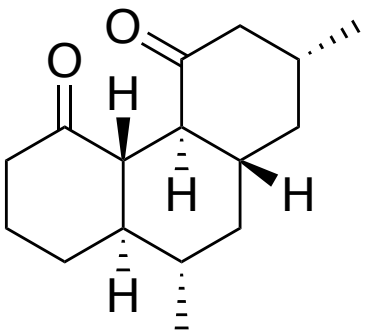


47% (2 steps



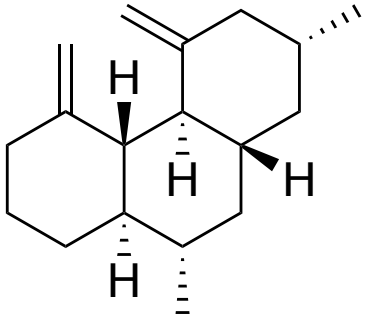
39% (4 steps)


1) LDA, i-Pr2SiCl2
2) CAN, NaHCO3
7:1 dr
3) 10 mol% Grubbs II
41% 3 steps
Pd/C, H2
93%
3:1 dr
23%
70%



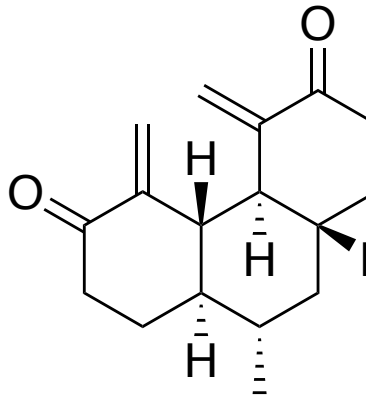
KOt-Bu
Ph_3PMeBr

82%



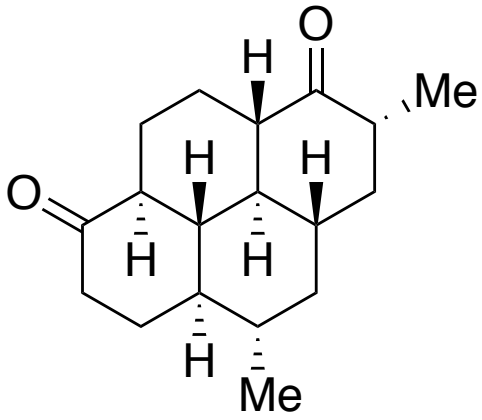
1) SeO_2
2) DMP

50% (2 steps)



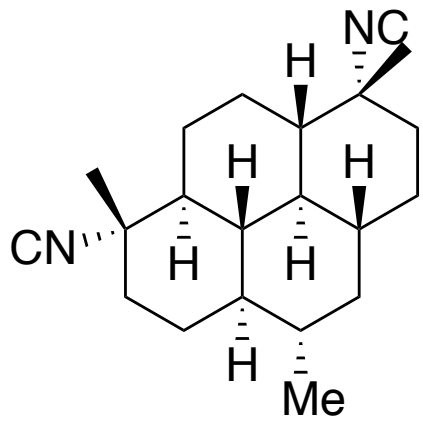
3.5 mol% $Ru(bpy)_3Cl_2$
HCOOH, i-Pr_2NEt
$h\upsilon$

92%
single stereoisomer



"Corey dione"

1) MeLi
2) TFAA, py
3) $TiCl_4$, TMSCN



Conclusion

1) Developed a general synthetic route to access fused carbocyclic structures from relatively simple ketone building blocks using an oxidative coupling/RCM sequence.
2) Strategy tolerates a wide variety of substitution patterns, as well as structural modifications of the formed carbocyclic scaffolds.
3) Demonstrated the application of the methodology in the total synthesis of the natural product (+)-7,20-diisocyanoadociane (2.4% yield in 17 steps from commercial material).