Sulfoxide-Promoted Functionalization of Allylic C-H Bond

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2014-2-24

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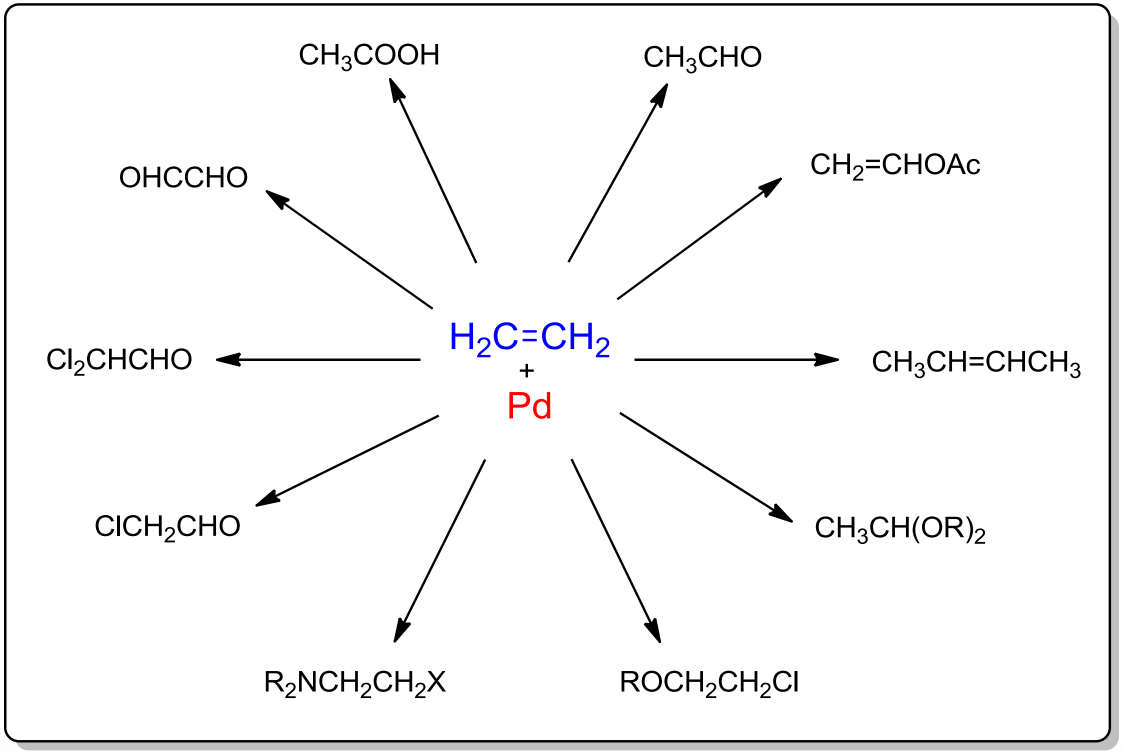
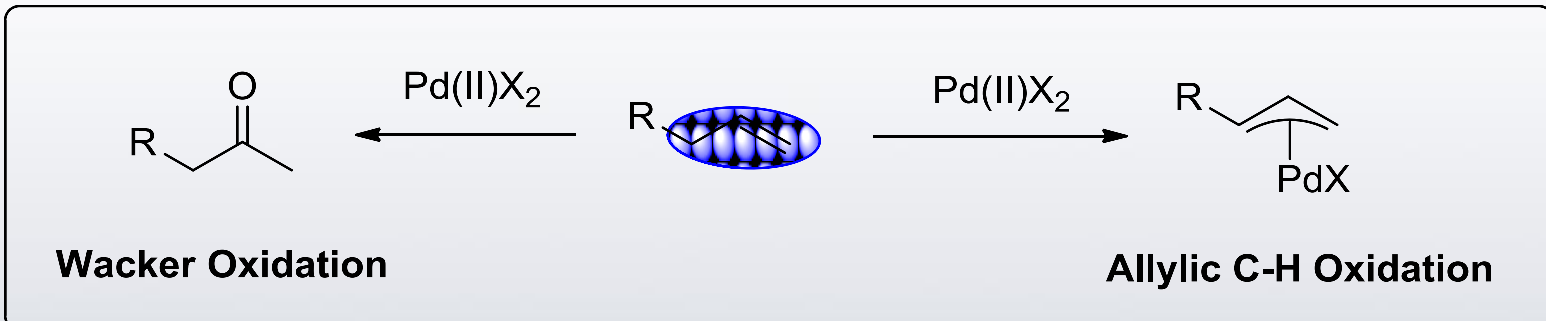
Introduction

Palladium-Mediated Transformation of Olefins

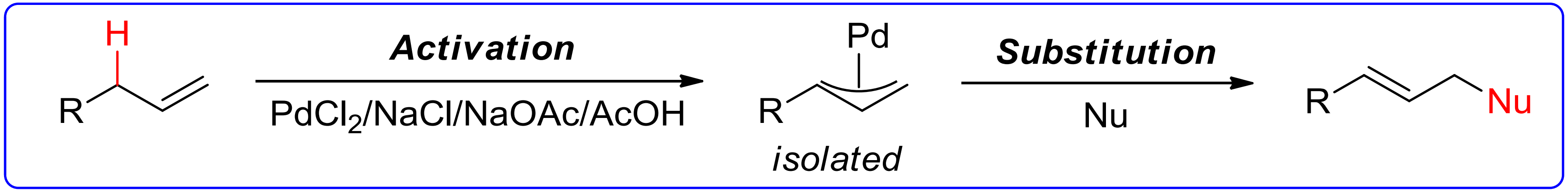


Palladium-Catalyzed Selective Oxidation of Olefins



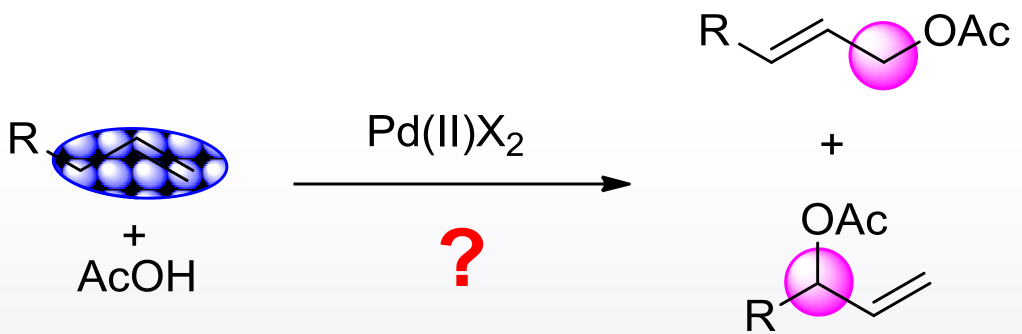
Introduction

Stoichiometric Palladium-Mediated, *Two-Step* Allylic C-H Alkylation



Huttel, R., Christ, H. *Chem. Ber.* **1964**, *97*, 2710.
Huttel, R.; Mcniff, M. *Chem. Ber.* **1973**, *106*, 1789.

Palladium-*Catalyzed, One-Pot* Allylic C-H Functionalization



Allylic C-H Oxidation

How to restrain the Wacker pathway?

⇓

DMSO

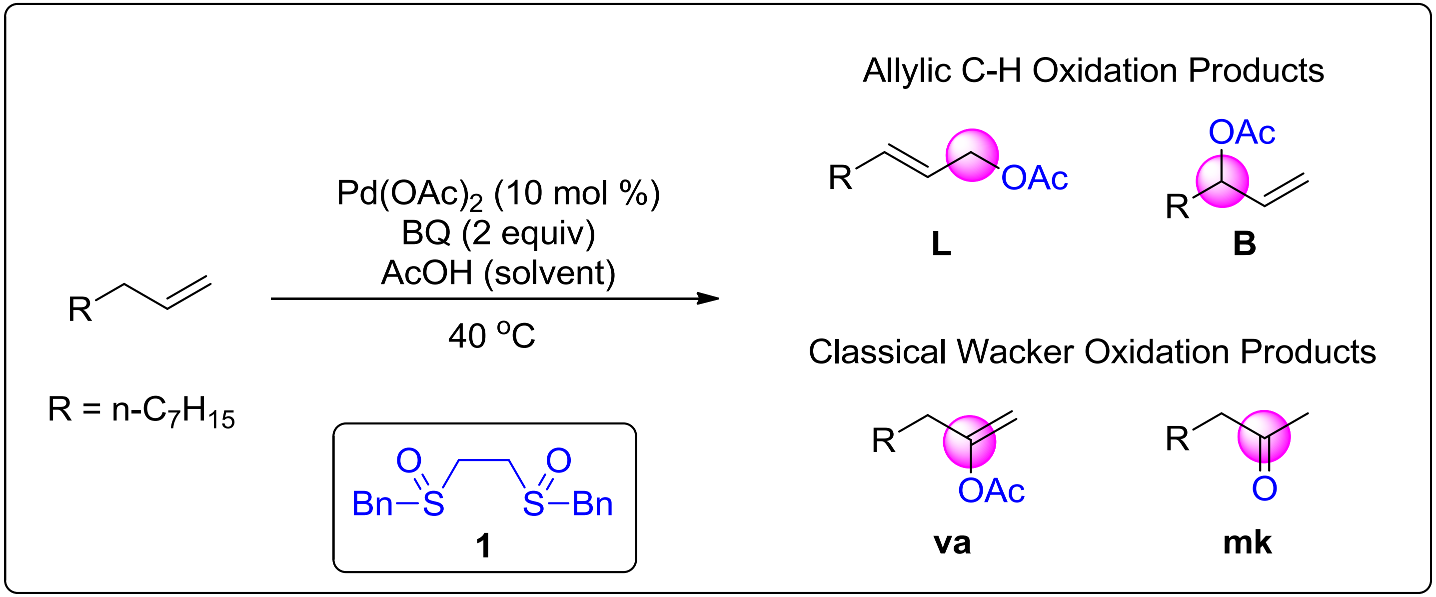
⇓

bis-sulfoxide

Chen, M. S., White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

Contents

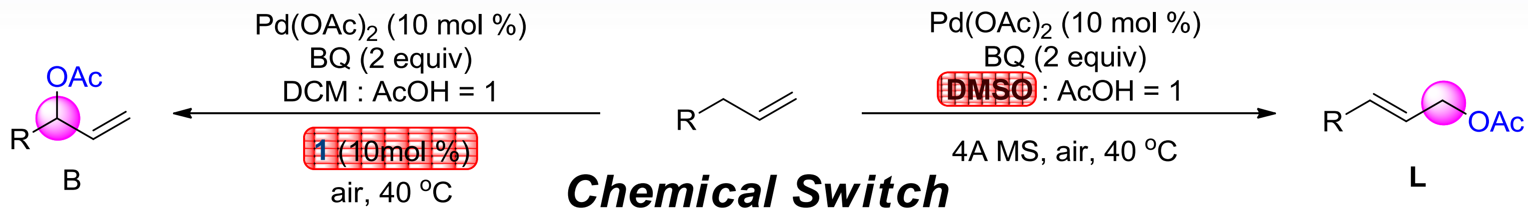
Original Reaction

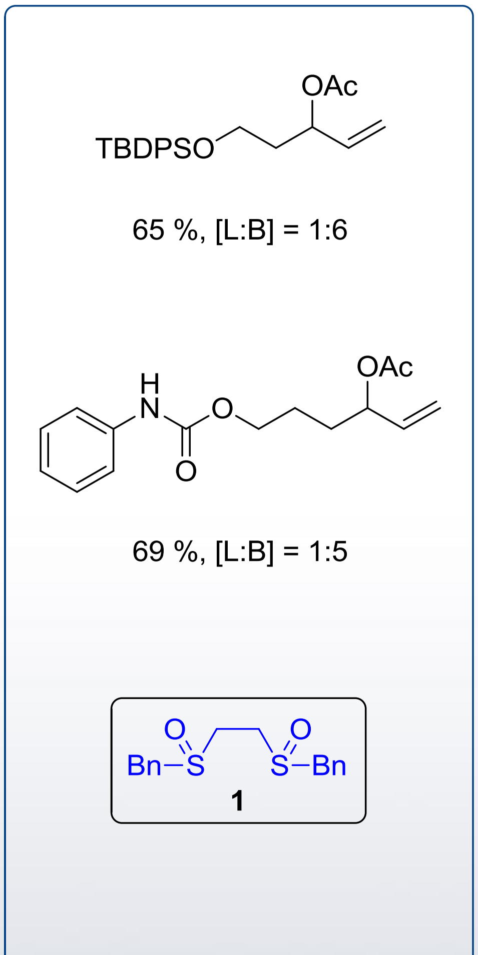


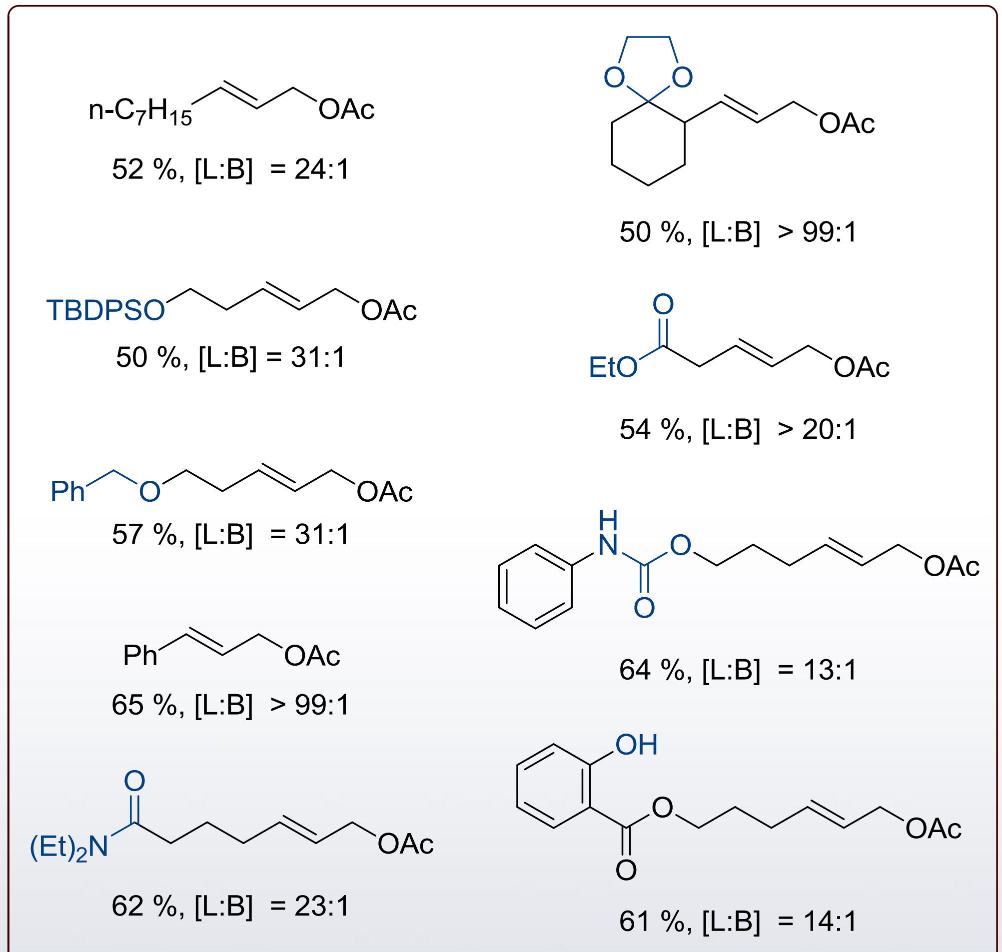
entry	additive	% yield (GC), 48 h				[**L**:**B**]
		L	**B**	**va**	**mk**	
1	none	3	5	17	14	1:2
2	DMSO (50 % V)	40	2	3	6	**20:1**
3	**1** (10 mol %) DCM:AcOH (1:1)	8	66	<1	<1	**1:8**

Chen, M. S., White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

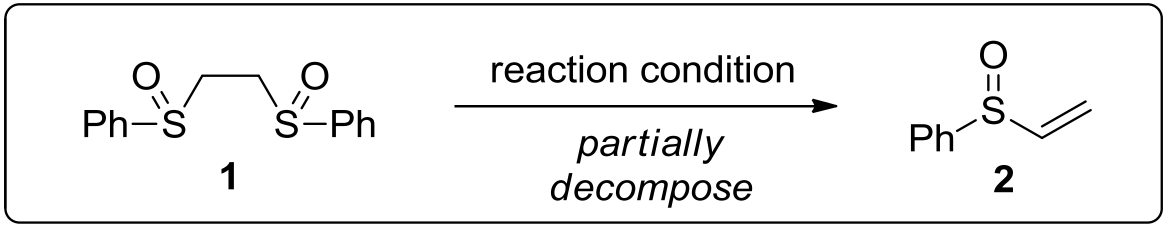
Original Reaction



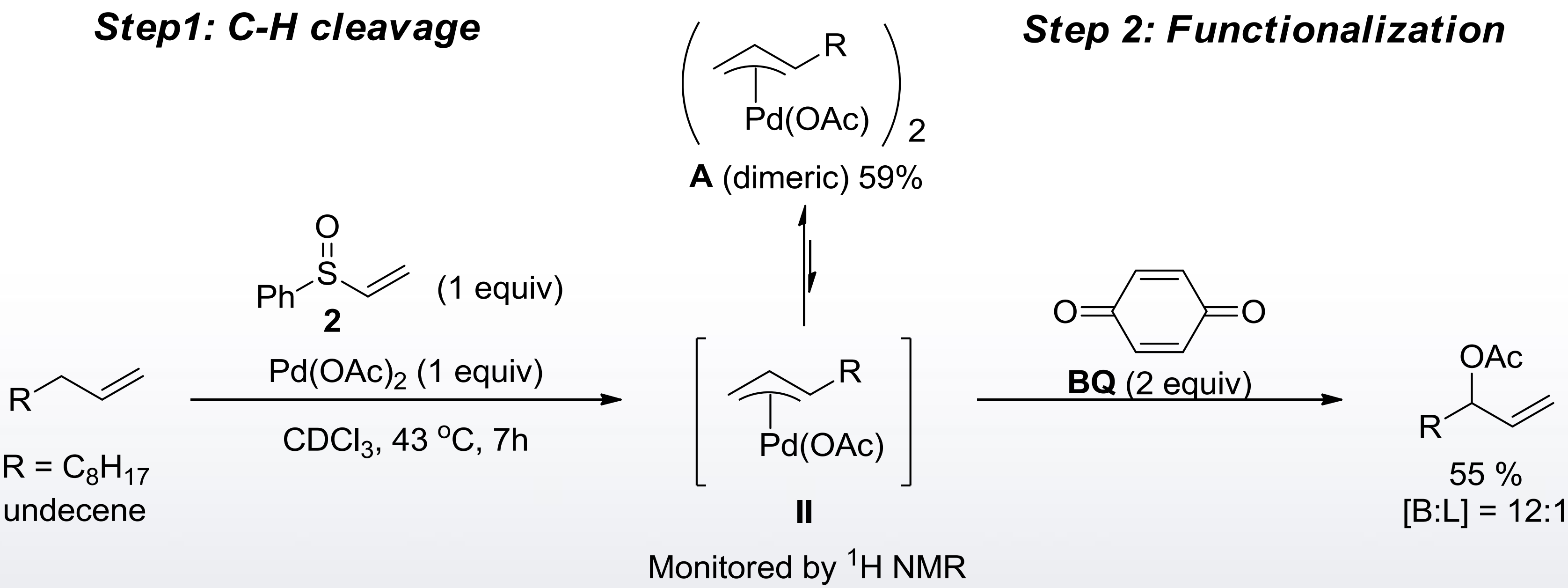




Mechanism Details

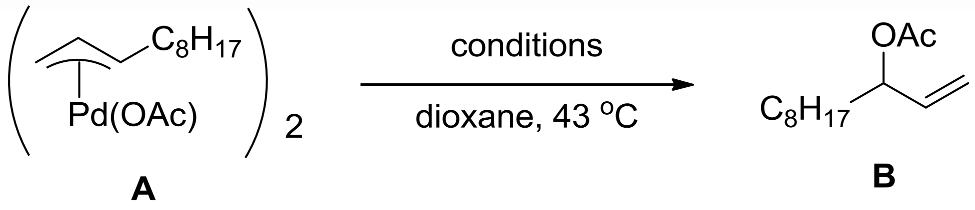


Khiar, N.; Araujo, C.; Alcudia, F.; Fernandez, I. *J. Org. Chem.* **2002**, *67*, 345.



Chen, M. S., Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

Exploration of Functionalization Step



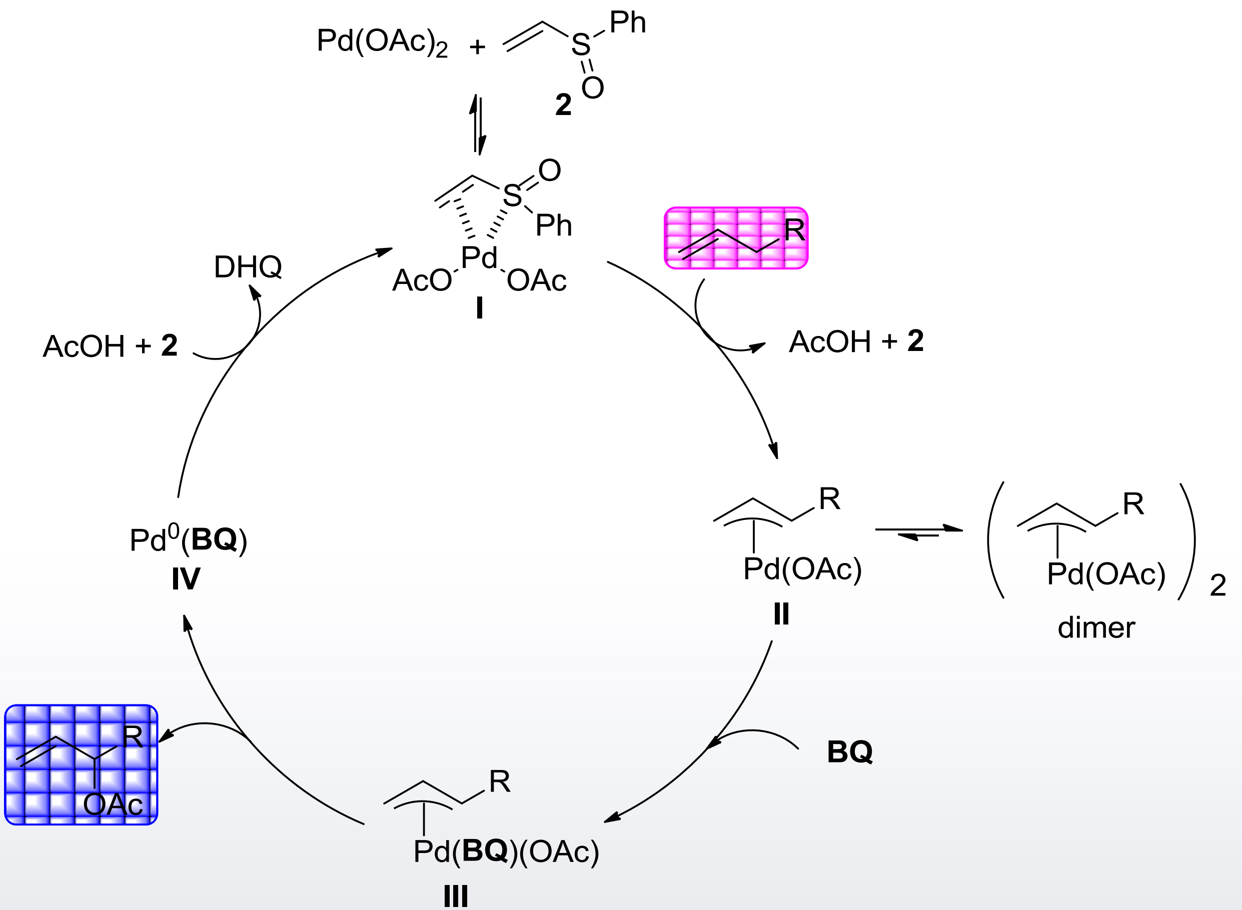
entry	conditions	yield (GC)	[B:L]
1	AcOH (40 equiv)	<1%	-
2	**2** (1 equiv)	<1%	-
3	BQ (20 equiv)	58%	32:1
4	2 (1 equiv) BQ (20 equiv)	68%	34:1
5	PPh_3 (20 equiv)	42%	1:1
6	dppe (10 equiv)	44%	1:1

The role of benzoquinone (BQ):

- An oxidant of Pd(0) to give Pd(II)
- A π-acidic ligand to activate π-allyl-Pd toward reductive elimination
- Regenerates $^{-}$OAc to activate allylic C-H bond *in situ*.

Proposed Mechanism

Serial Ligand Catalysis



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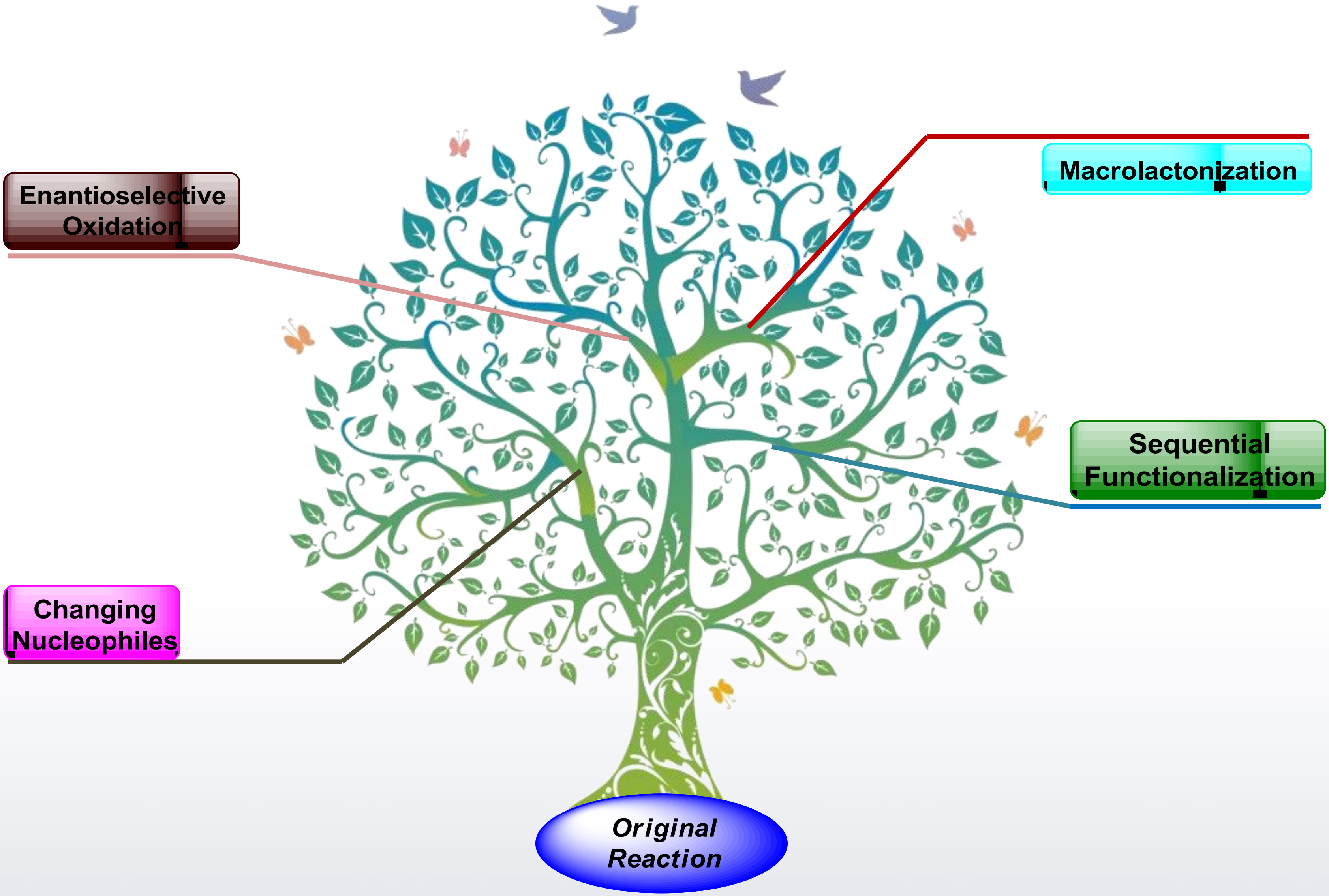
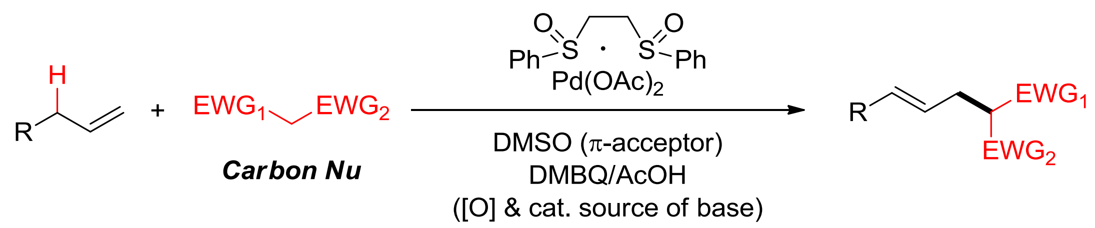
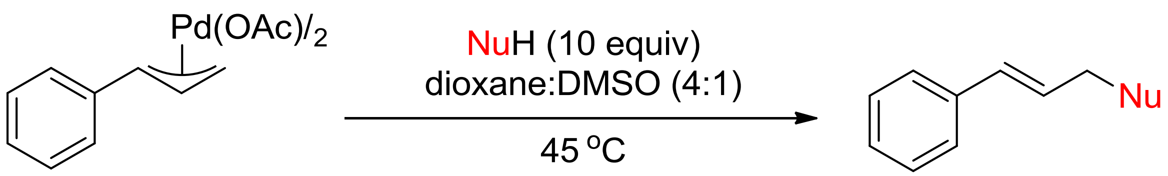
Reaction Evolution and Derivation



Changing Nucleophiles





entry	NuH	yield (L+B)	L:B
1	$PhO_2SCH_2CO_2Me$, **3**	9%	--
2	NO_2CH_2COPh, **4**	82%	8:1
3	$NO_2CH_2CO_2Me$, **5**	86%	4:1
4	$NO_2CH_2SO_2Ph$, **6**	89%	16:1
5	**5** (no DMSO)	--	--

Acidity of nucleophiles is crucial for allylic C-H alkylation!

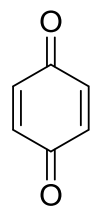
$pK_a < 6$

Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090.

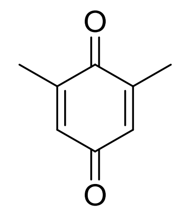
Changing Nucleophiles

Select a suitable oxidant:

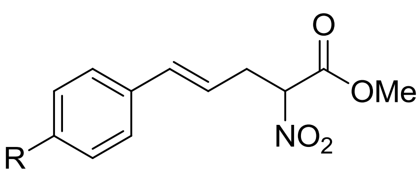
Pd(OAc)$_2$/bis-sulfoxide/**BQ**



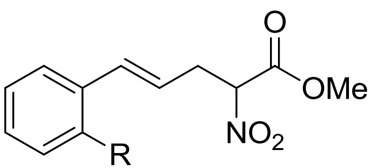
Pd(OAc)$_2$/bis-sulfoxide/**DMBQ**



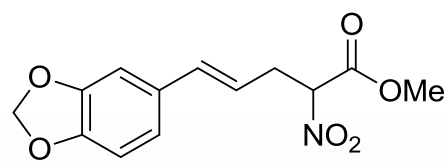
sterically hindered oxidant



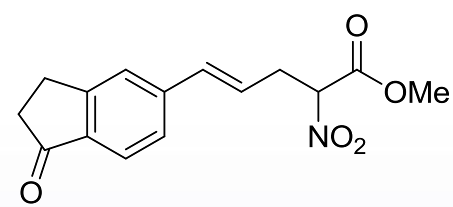
R =		
OMe,	50%,	[L:B] = 1.7:1
Me,	61%,	[L:B] = 3:1
CH_2=CH_2,	63%,	[L:B] = 3:1
H,	62%,	[L:B] = 4:1
Br,	60%,	[L:B] = 4:1
NTsMe,	63%,	[L:B] = 4:1
F,	65%,	[L:B] = 4:1
CO_2Me,	61%,	[L:B] = 10:1
C(O)Me,	66%,	[L:B] = 10:1
CF_3,	56%,	[L:B] = 10:1
CN,	65%,	[L:B] = 12:1



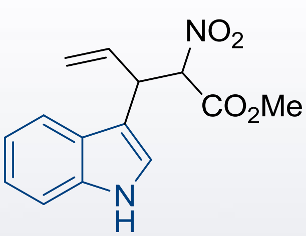
R =		
Me,	62%,	[L:B] = 5:1
CF_3,	59%,	[L:B] > 20:1
OTf,	57%,	[L:B] = 15:1
OTBS,	58%,	[L:B] = 3:1



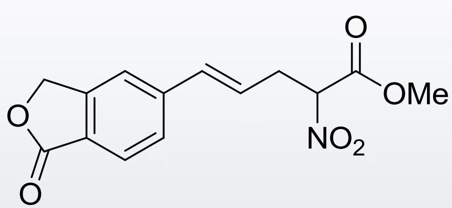
56%, [L:B] = 3:1



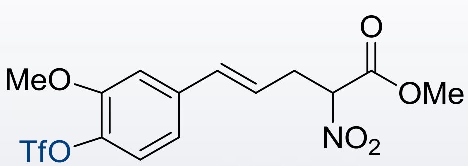
62%, [L:B] = 12:1



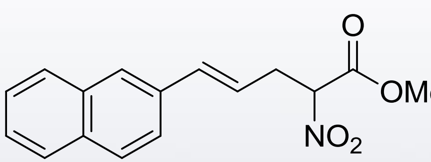
42%, [L:B] = 1:5



70%, [L:B] = 15:1



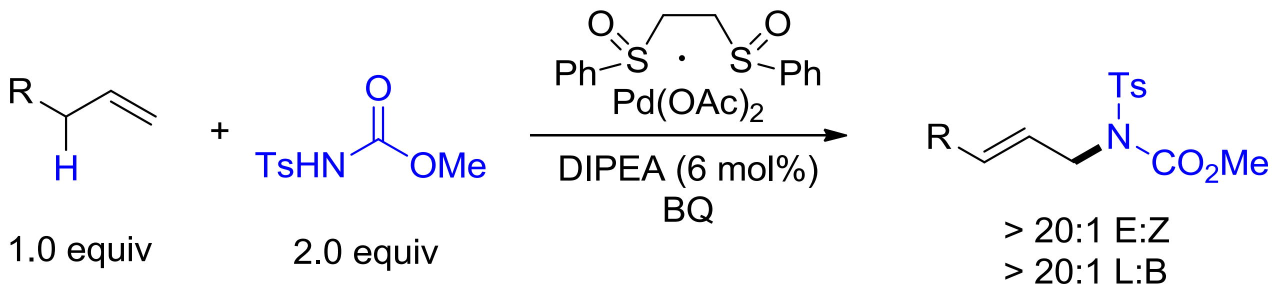
64%, [L:B] = 5:1



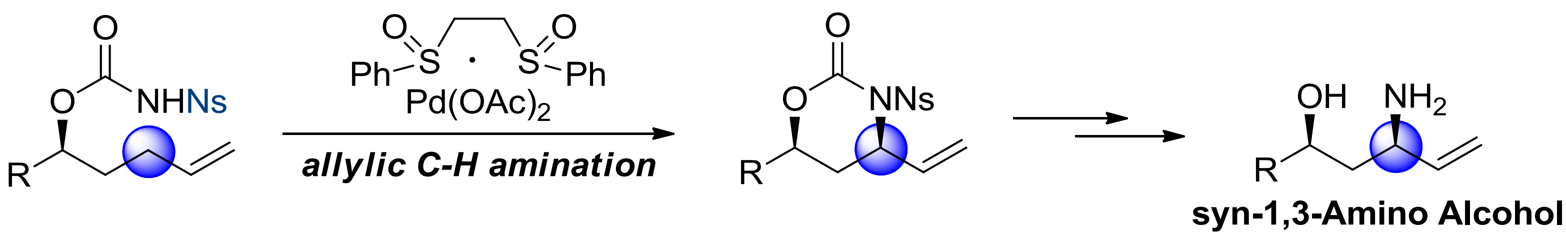
65%, [L:B] = 4:1

Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090.

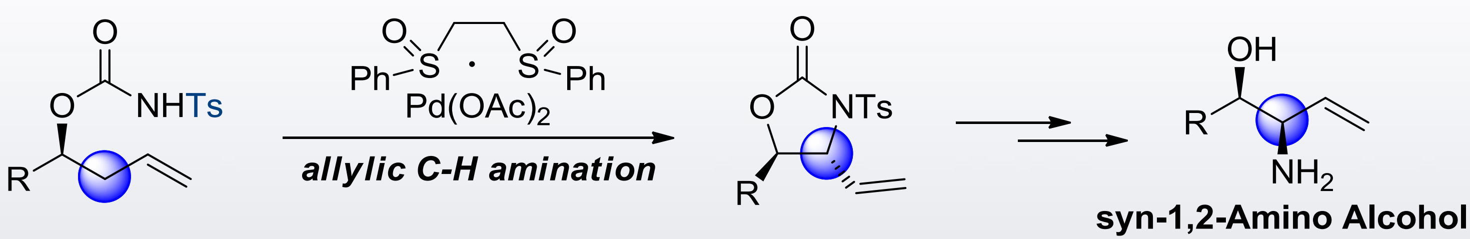
Changing Nucleophiles



Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc*. **2009**, *131*, 11701.



Rice, G. T.; White, M. C. *J. Am. Chem. Soc*. **2009**, *131*, 11707.



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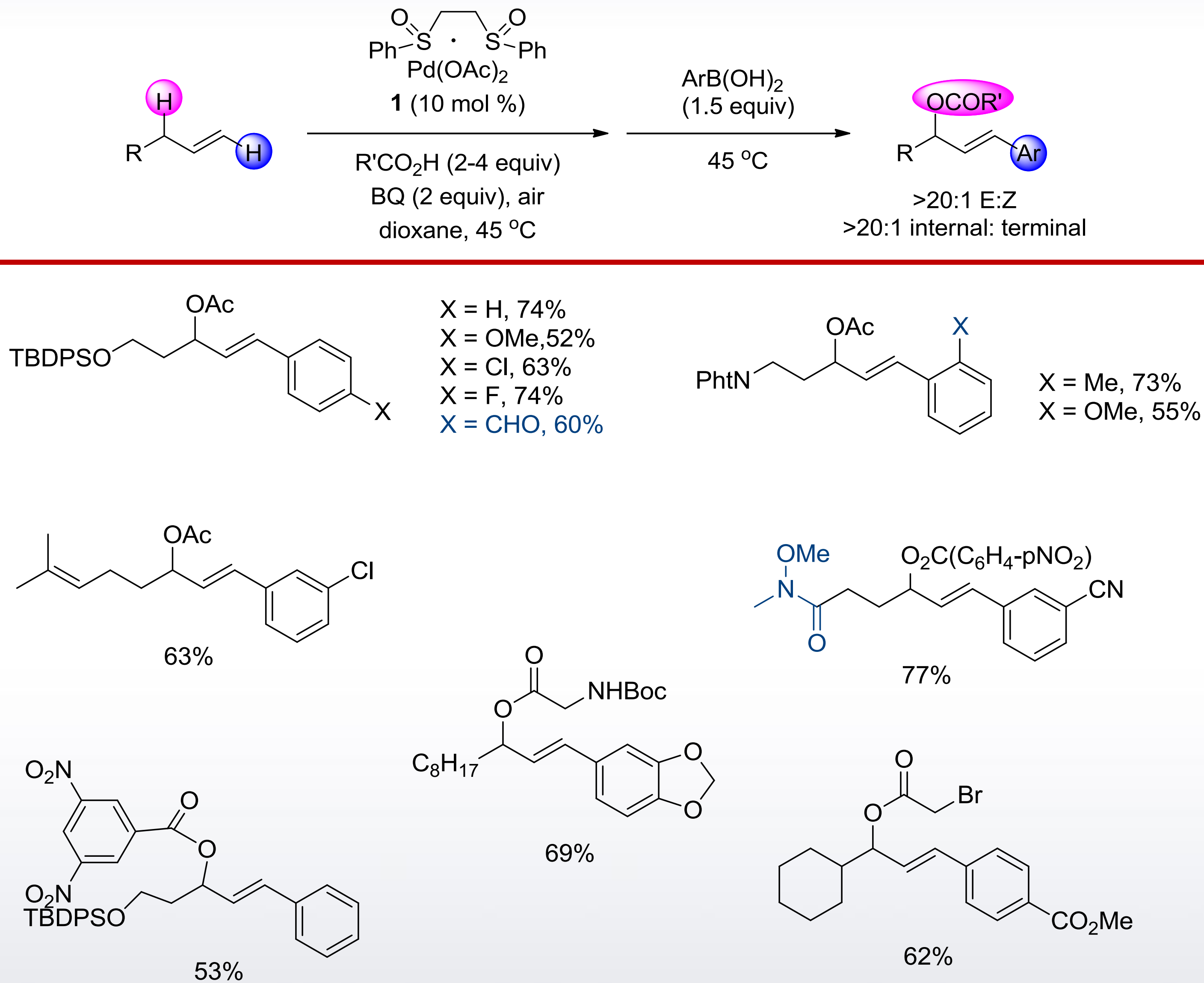
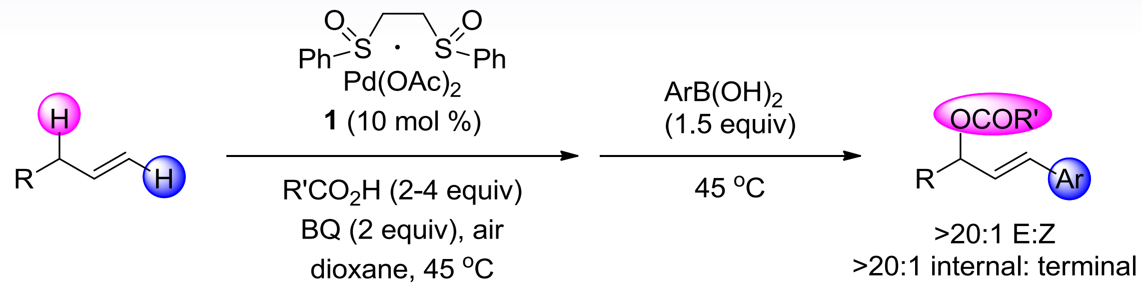
Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc*. **2007**, *129*, 7274.

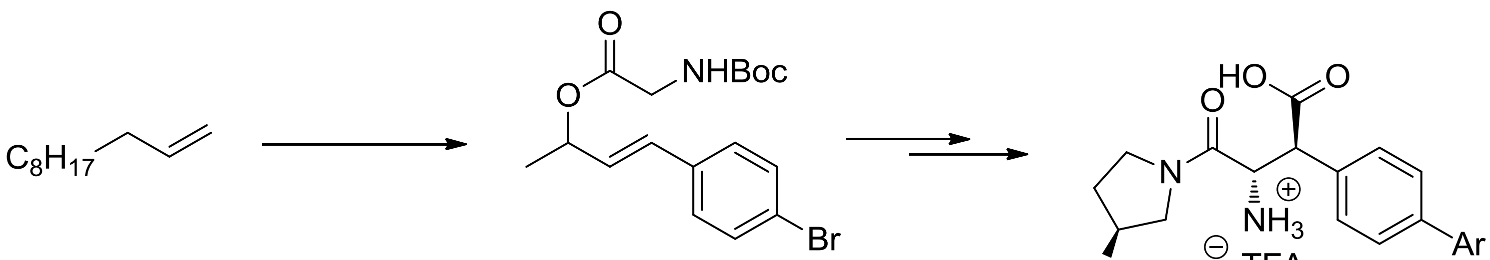
Sequential Functionalization



Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076.

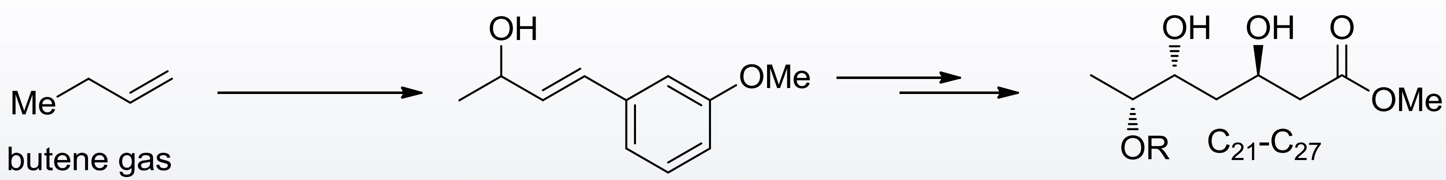
Sequential Functionalization





75%

dipeptidyl peptidase inhibitor

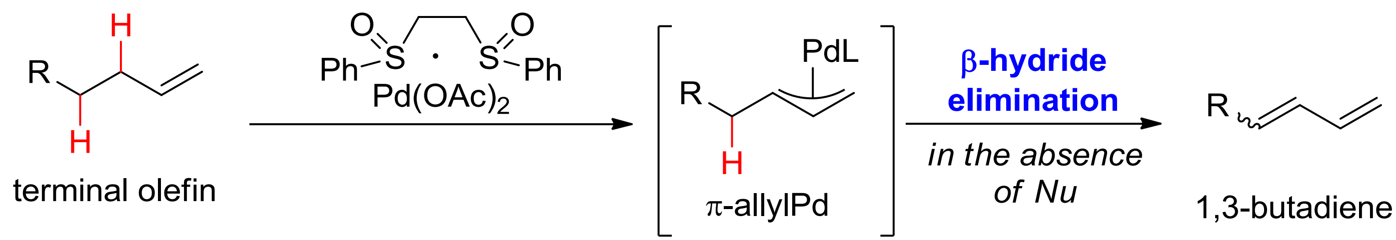


77%

bryostain 1

Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc*. **2006**, *128*, 15076.

Dehydrogenation of Terminal Olefins ?



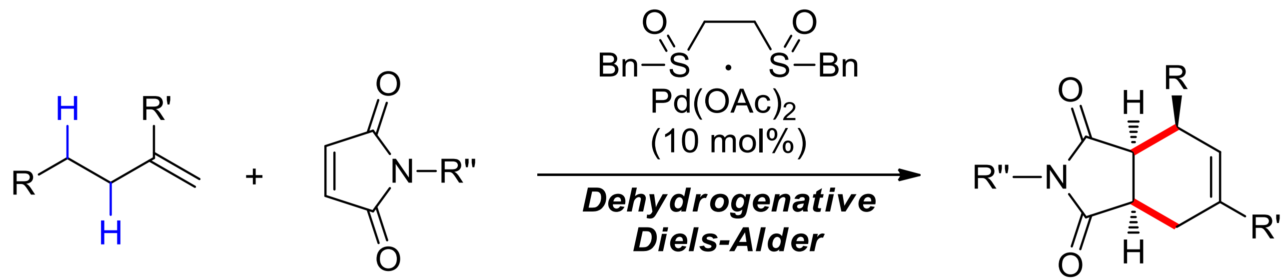
Chanllenge

- Dienes are prone to isomerization and oxidantions.
- The electrophilic catalysts often catalyze diene oligomer- and polymeraization processes.

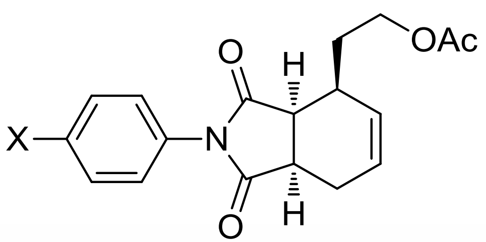
Strategy

Add a reactive component capable of furnishing a stable product

Sequential Functionalization

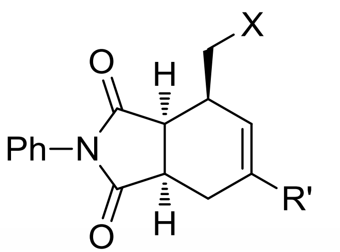


1 equiv.   1 equiv.   > 20:1 *d.r.*



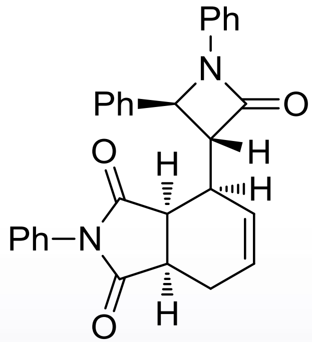
X = OMe	73%
X = Ac	75%
X = F	76%
X = Br	61%

Dienephile Scope

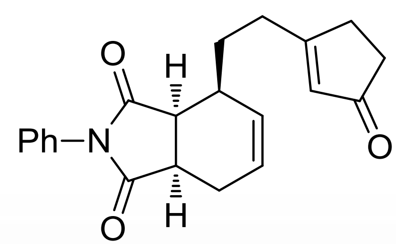


R' = H,	X = OTBS	76%
R' = Me,	X = OTBS	76%
R' = H,	X = NPhth	76%
R' = H,	X = $(CH_2)_3NO_3$	76%

Olefin Scope



65%
β-lactam

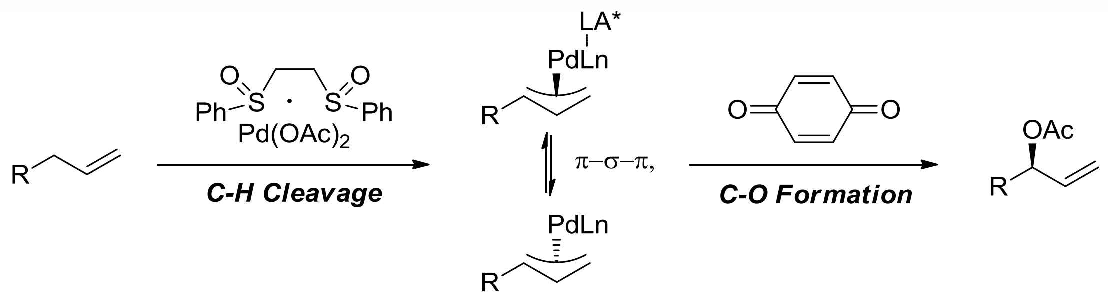


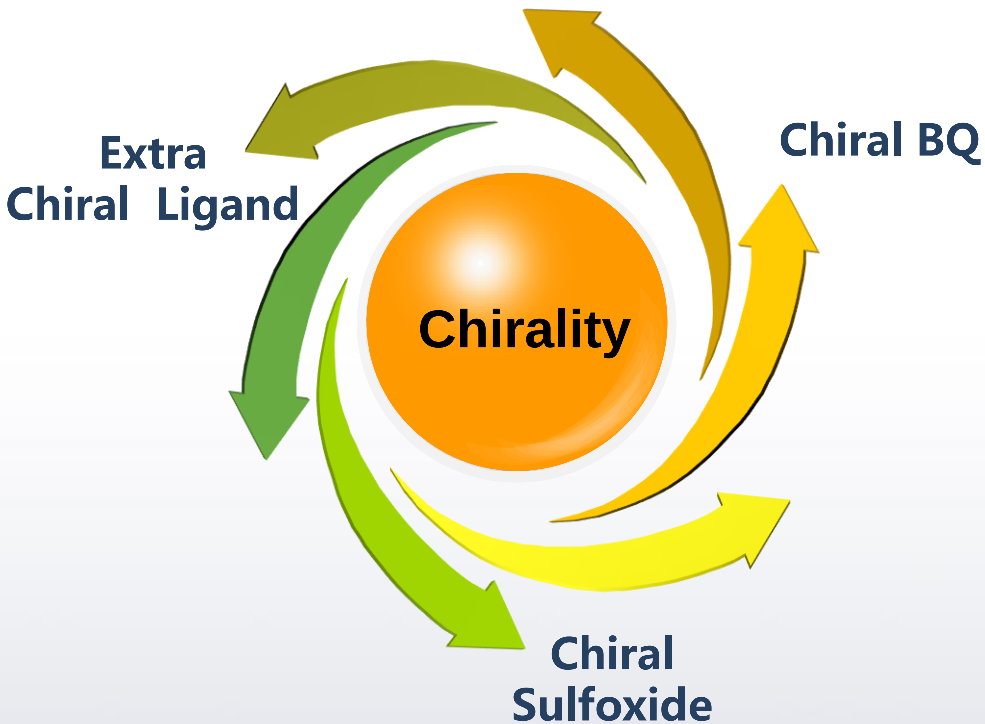
68%
Guanacastepene A
core precursor

Medicinally Important Motifs

Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892.

Enantioselective C-H Oxidation

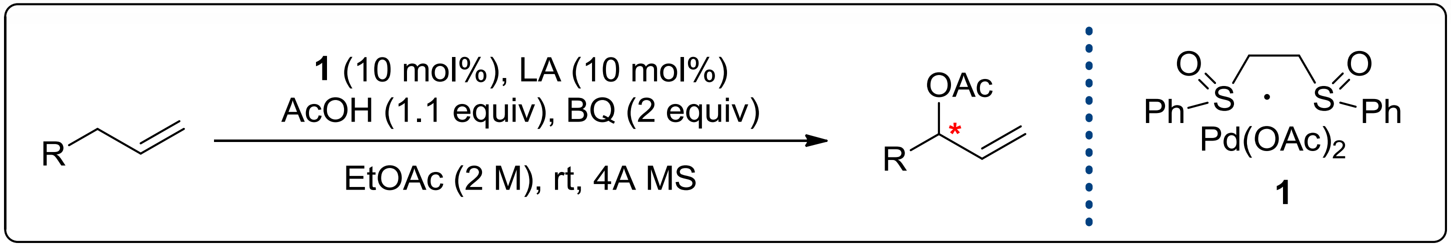


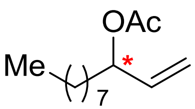


Chanllenge

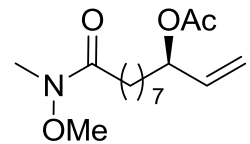
- Reaction system can not tolerate strongly cordination ligands.
- Chiral sulfoxides were ineffective due to the rapid isomerization.
- Functionalization of BQ is impractical for covalent chiral modification,
- An oxophilic, chiral LA would increase the acid of BQ, and transmitt chiral information to the metal center.

Enantioselective C-H Oxidation

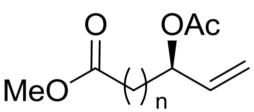




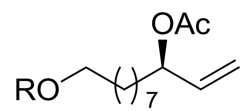
(R,R)-(salen)Cr^{III}F, 92%, ee 59%, [B:L] = 5.3:1
(S,S)-(salen)Cr^{III}F, 92%, ee 59%, [B:L] = 5.3:1



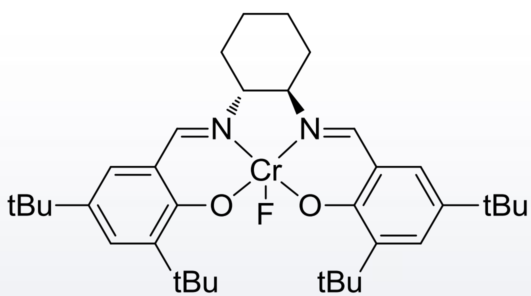
81%, ee 54%, [B:L] = 4.4:1



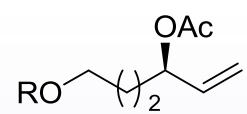
n = 7, 89%, ee 57%, [B:L] = 4.8:1
n = 2, 69%, ee 50%, [B:L] = 4.6:1



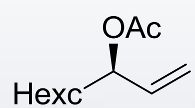
R = TBDPS, 84%, ee 63%, [B:L] = 4.4:1
R = H, 83%, ee 50%, [B:L] = 4.4:1



(salen)Cr^{III}F



R = THP, 94%, ee 49%, [B:L] = 3.6:1
R = Bn, 90%, ee 45%, [B:L] = 4.3:1

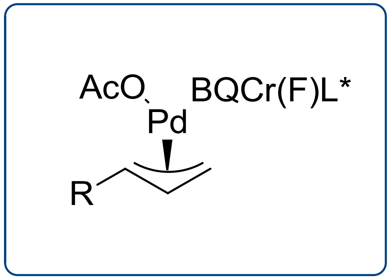


78%, ee 62%, [B:L] = 1.5:1

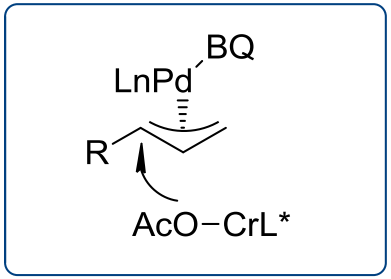
Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448.

Enantioselective C-H Oxidation

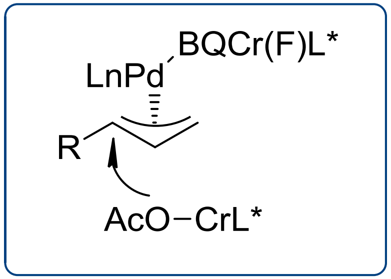
Three Mechanistic Scenarios



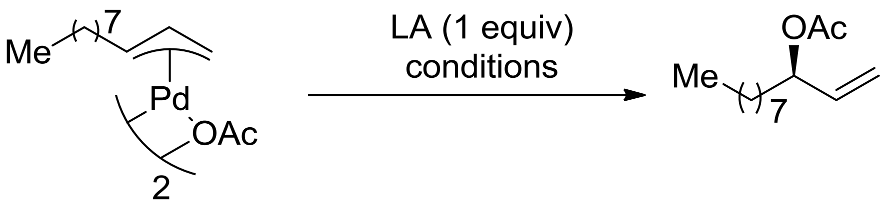
I



II



III

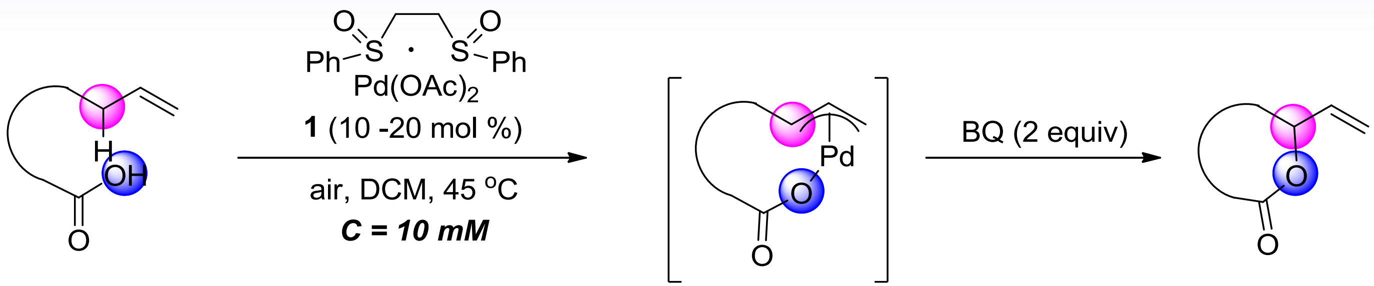


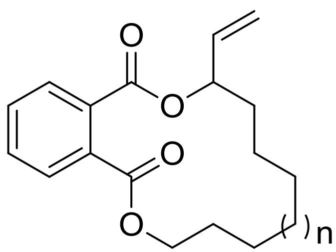
Entry	LA	K_{rel}	Yield	B:L	ee
1	--	1.0	20%	>20:1	--
2	(R,R)-**3**	9.7	85%	5.2:1	55%
3[a]	(R,R)-**3**	--	0	--	--
4	(R,R)-**4**[b]	3.8	41%	2.2:1	29%

[a] No BQ added. [b] (R,R)-salen-Cr(OAc).

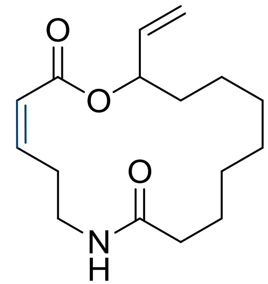
Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448.

Macrolactonization

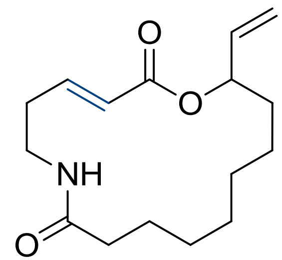




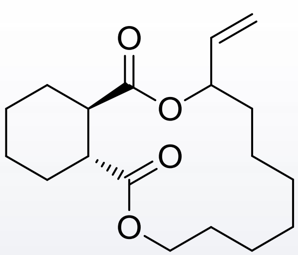
n = 1, 61%
1 g scale, 62%
n = 2, 52%
n = 3, 60%
n = 4, 53%



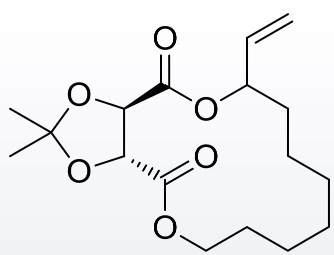
16-membered ring
52%, 98:2 (Z:E)



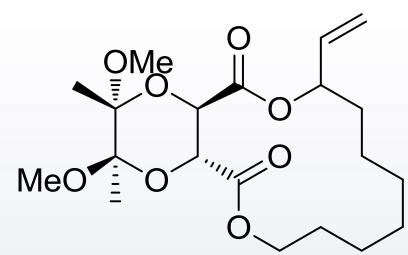
16-membered ring
63%, 99:1 (Z:E)



14-membered ring
60%, 1.4:1 (d.r.)



14-membered ring
54%, 1:1 (d.r.)

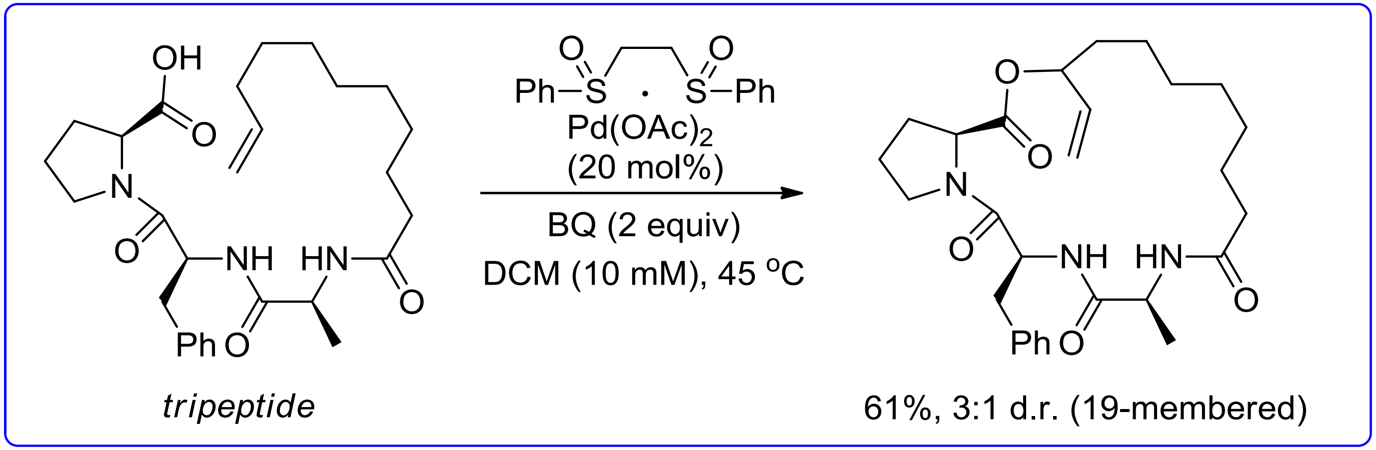


14-membered ring
60%, 1.4:1 (d.r.)

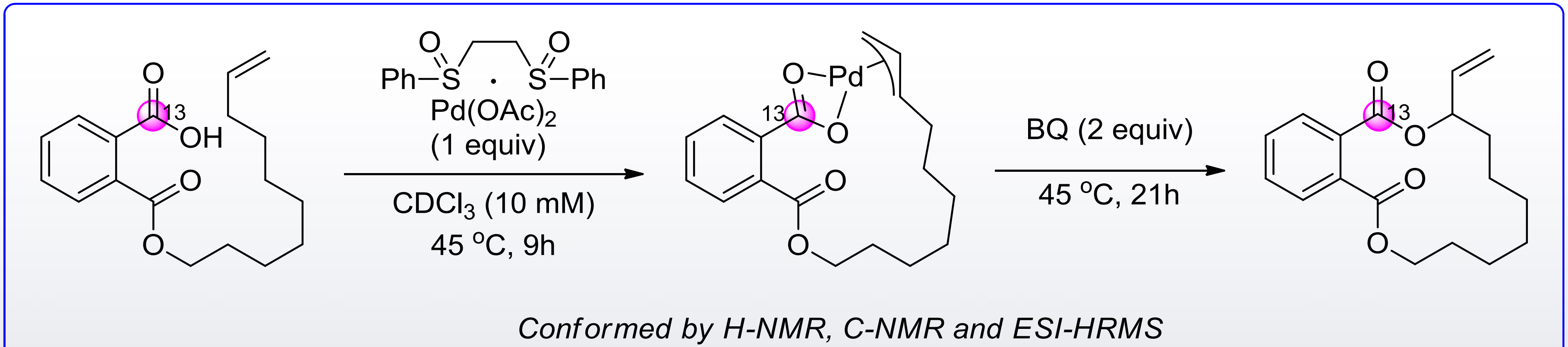
Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

Macrolactonization

Macrocyclic Depsipeptide Synthesis



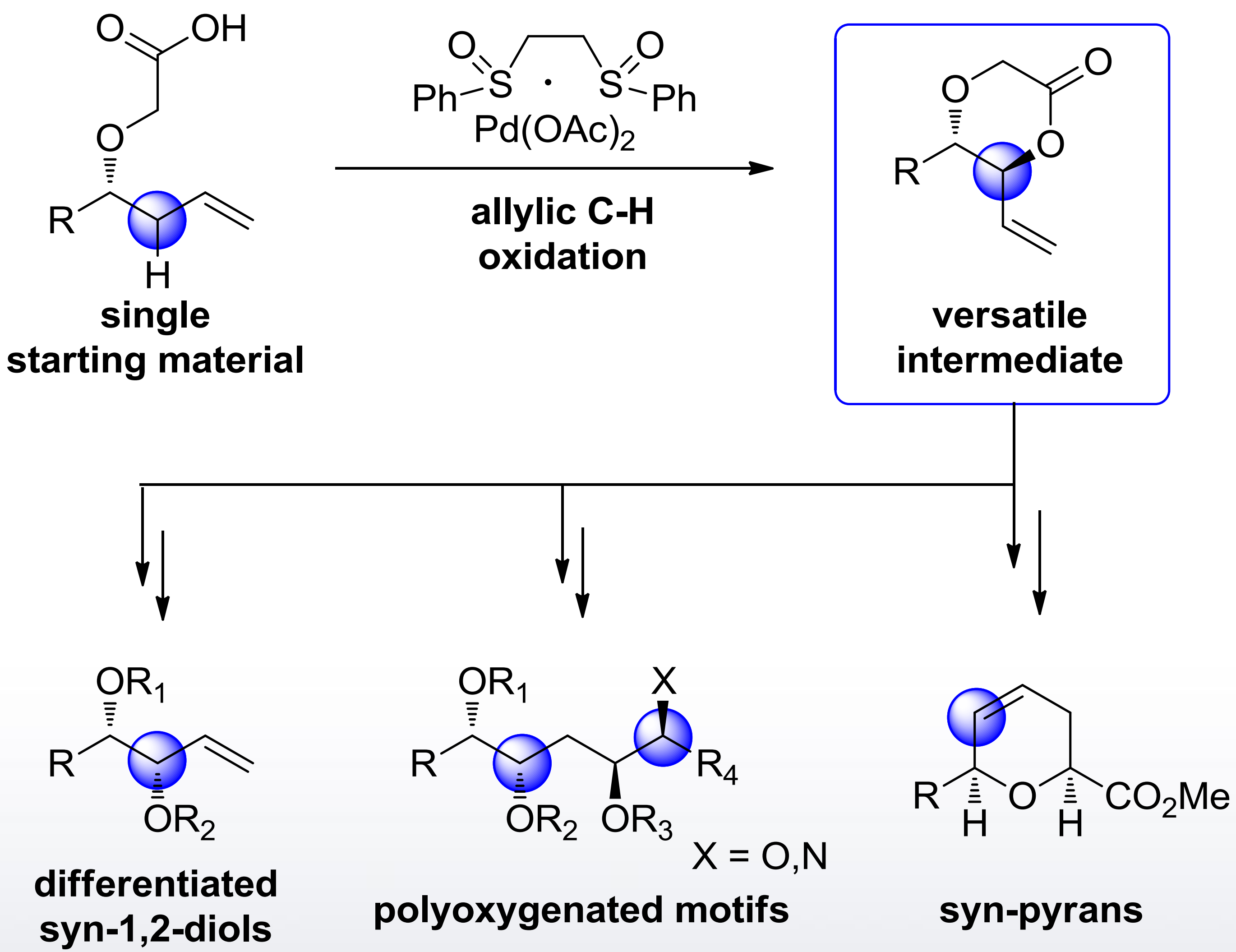
^{13}C-Labeled Experiment



Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

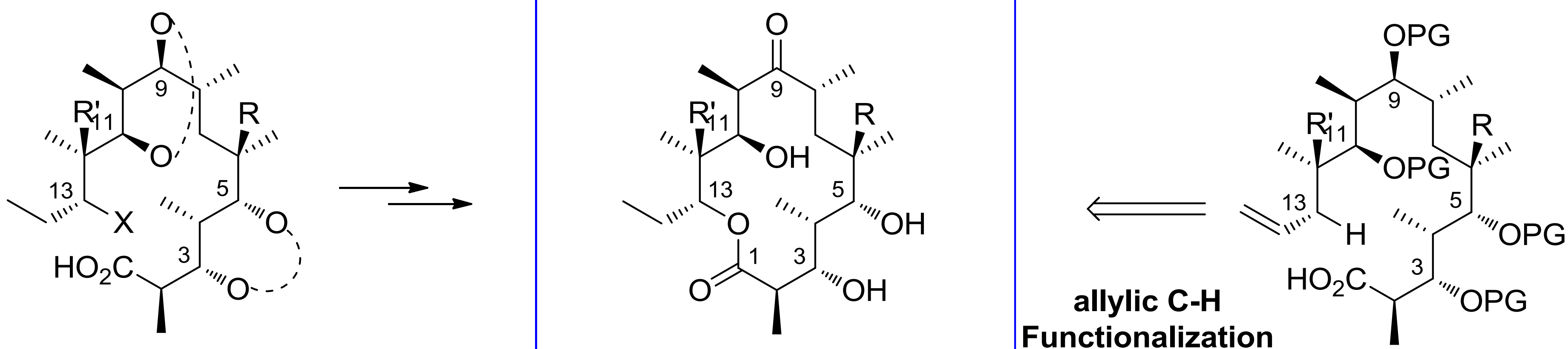
Contents

Rapid access to Complex Structures



Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584.

Natural Product Synthesis



Erythronolide A, R=R'=OH
Erythronolide B, R=OH, R'=H

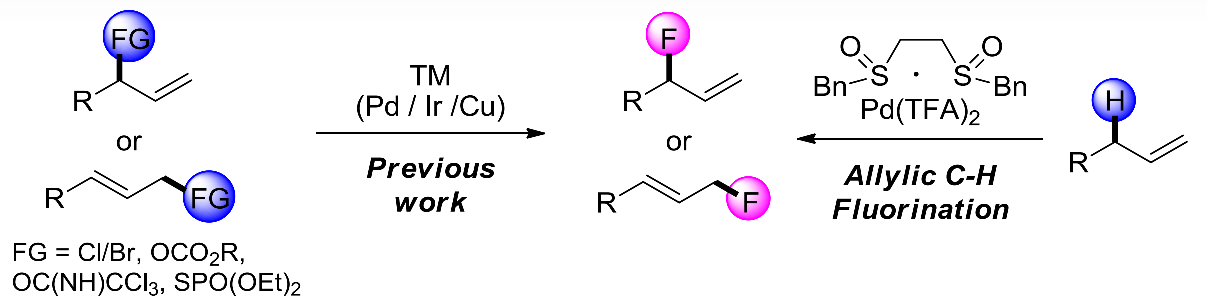
Woodward (1981)
Stork (1987)
Nakata (1989)
Danishefsky (1990)
Hoffmann (1993)
Evans (1998)
White (2009)
Nelson (2010)

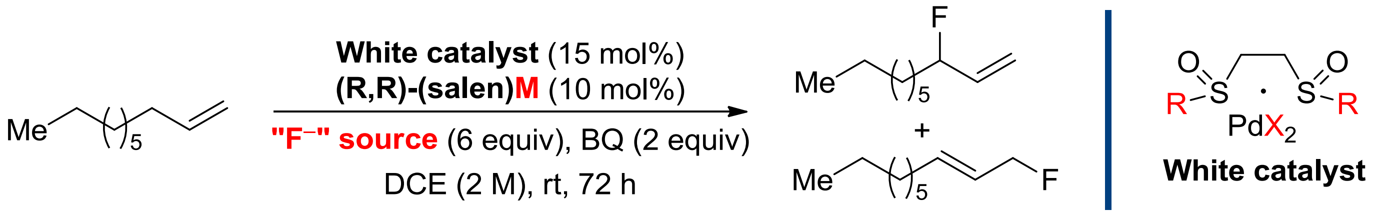
"certain structural features such as ..cyclic protecting groups at C-3/C-5 and C-9/C-11 are required for efficient lactonization"

Preorganization is not required, although such elements can significantly improve the diastereomeric outcome of the cyclization.

Stang, E. M.; White, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 2094.

Allylic C-H Fluorination

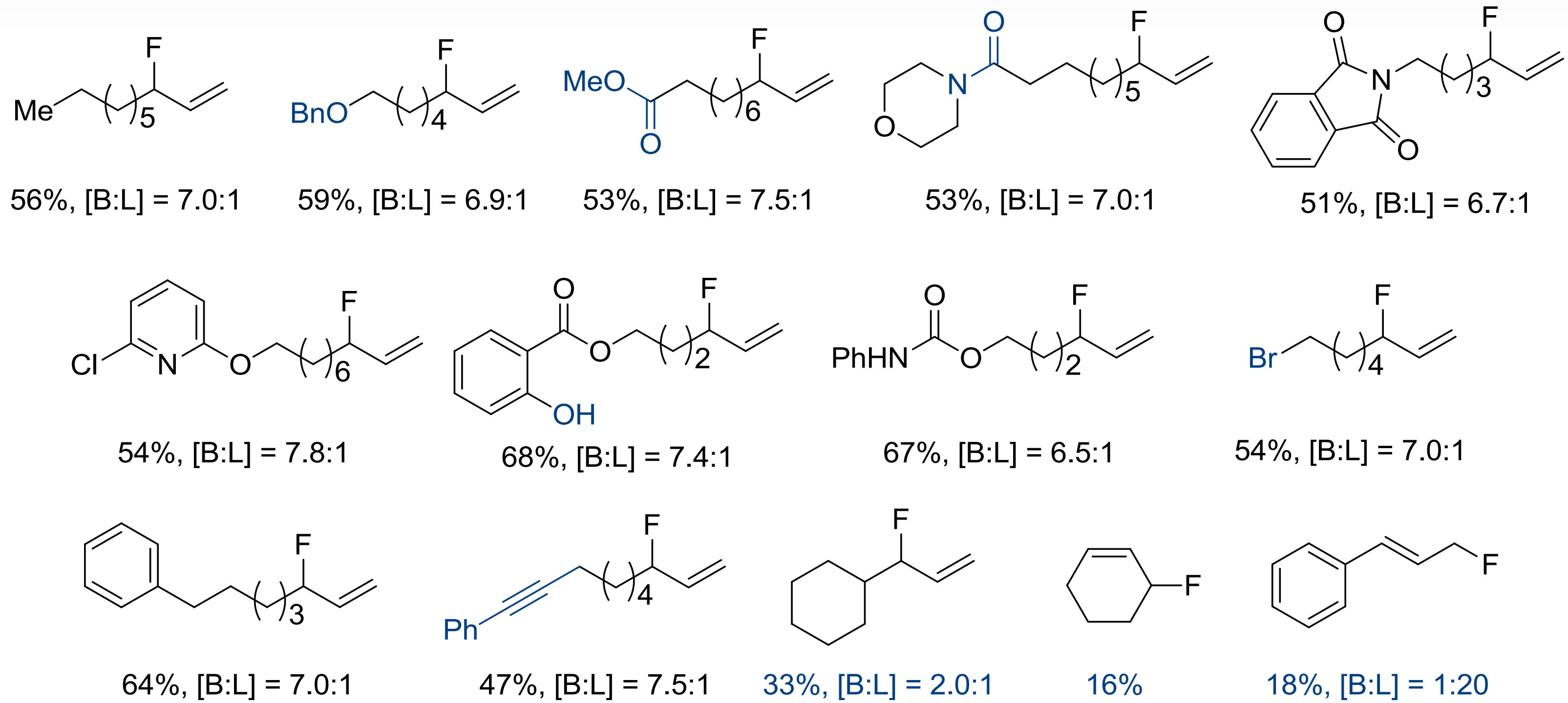


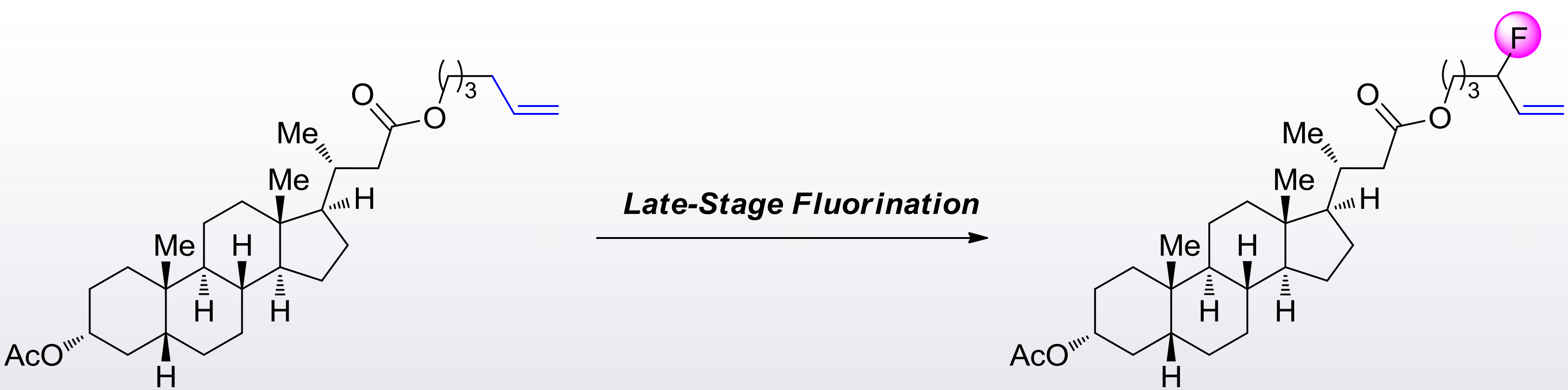


Entry	"F-" source	M	R	X	yield (%)	[B:L]
1	AgF	–	Ph	OAc	0	–
2	KF	–	Ph	OAc	0	–
3	KHF2	–	Ph	OAc	0	–
4	Py*9HF	–	Ph	OAc	0	–
5	TEA*3HF	–	Ph	OAc	33	6.6:1
6	TEA*3HF	CrCl	Ph	OAc	51	7.0:1
7	TEA*3HF	CoCl	Ph	OAc	6	7.9:1
8	TEA*3HF	MnCl	Ph	OAc	14	7.2:1
9	TEA*3HF	CrF	Ph	OAc	28	5.3:1
10	TEA*3HF	CrCl	Bn	OAc	65	6.0:1
11	TEA*3HF	CrCl	Bn	TFA	70	7.3:1

Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.

Allylic C-H Fluorination





Braun, M. G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.


Thank you for
your attentions!