A Catalytic, Bronsted Base Strategy for the Intermolecular Allylic C-H Amination

Sean A. Reed, Anthony R. Mazzotti, and M. Christina White. *J. Am. Chem. Soc*. **2009**,

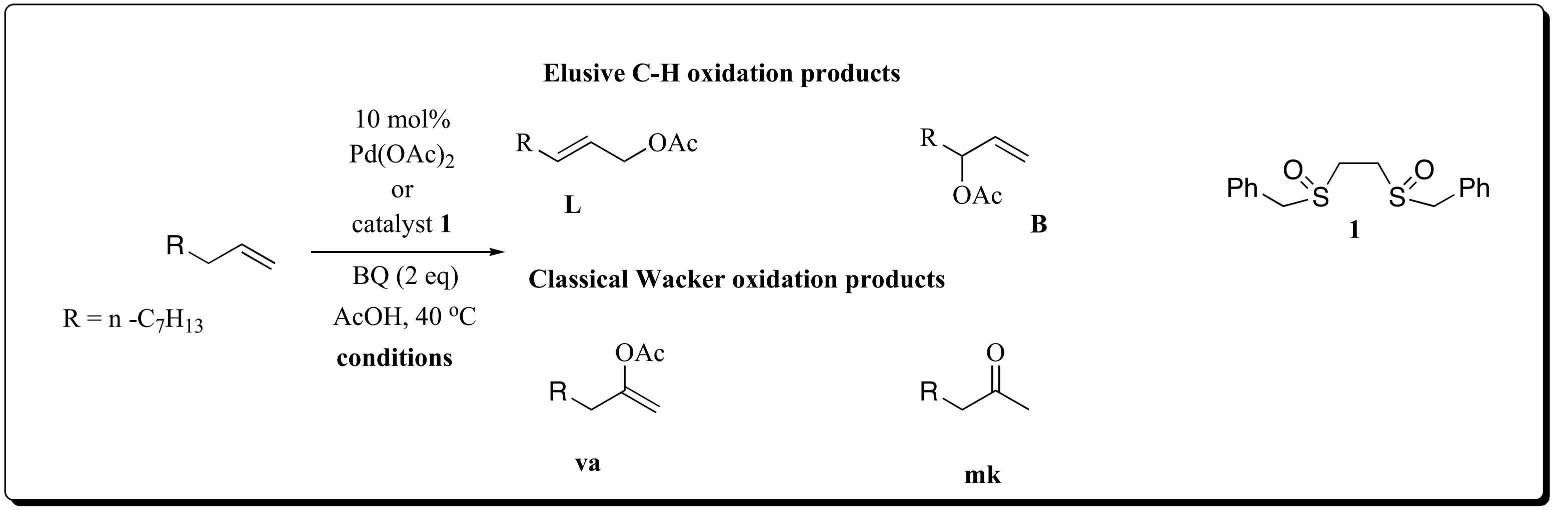
Early View

Allylic C-H Amination for the Preparation of syn-1,3-Amino Alcohol Motifs

Grant T. Rice and M. Christina White. *J. Am. Chem. Soc*. **2009**, Early View

Eric E. Buck
Current Literature
August 15, 2009

Sulfoxide-Promoted C-H activation



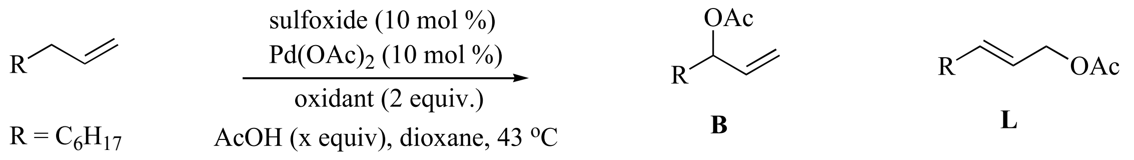
		% yield (GC), 48 h				
entry	conditions	L	B	va	mk	[L:B]
1	AcOH	3	5	17	14	1:2
2	DMSO: AcOH (1:1)	40	2	3	6	20:1
3	**1** (10 mol %) DCM: AcOH (1:1)	8	66	<1	<1	1:8

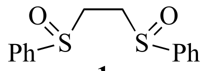
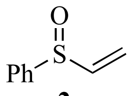
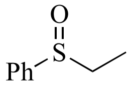
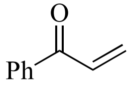
Change of product distribution when DMSO is present

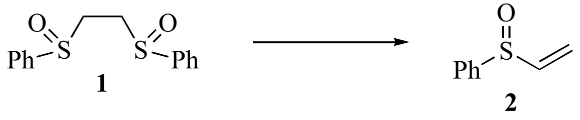
No link observed between solvent polarity and C-H oxidation

Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* ***2004****, 126 (5), 1346 - 1347*

Serial Ligand Catalysis

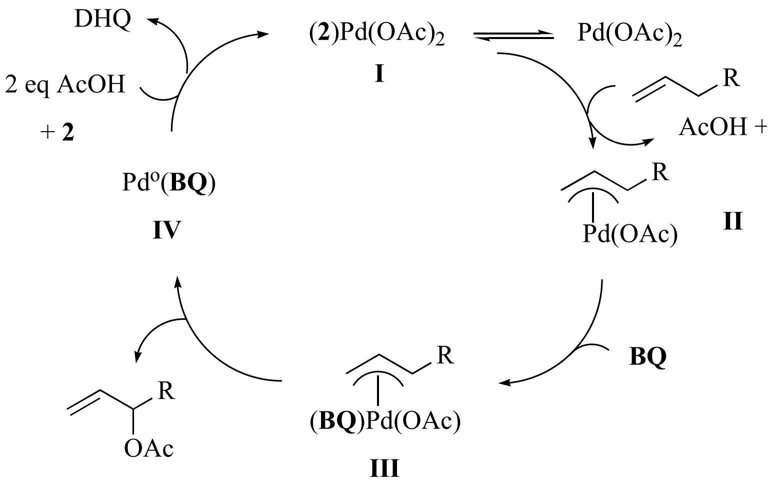


entry	sulfoxide		AcOH (equiv.)	oxidant	% yield GC, 48h, **B**	[**B**:**L**]
1	none		52	BQ	3%	3:1
2	 **1**		52	BQ	73%	11:1
3	 **2**	a.	52	BQ	66%	12:1
		b.	4	BQ	64%	31:1
		f.	4	$BQ(Me)_2$	15%	21:1
4	 **3**		52	BQ	3%	2:1
5	 **4**		52	BQ	4%	3:1



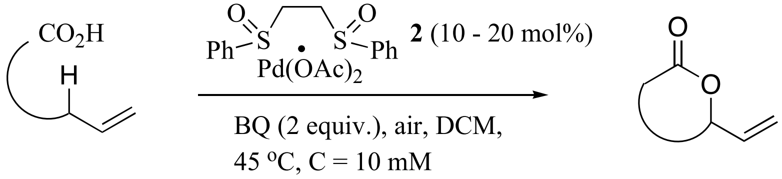
BQ acts as a functionalization-promoting ligand.

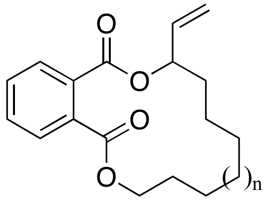
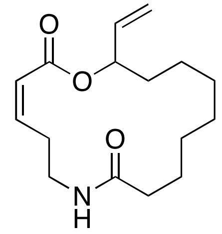
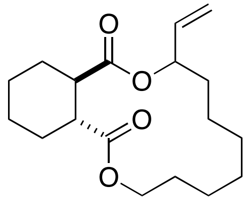
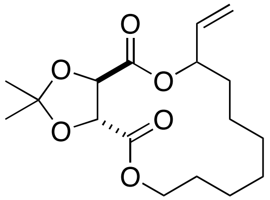
The observed regioselectivity is the result an electronically dissymmetric π-allyl intermediate.



Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* ***2005**, 127 (19), 6970 - 6971*

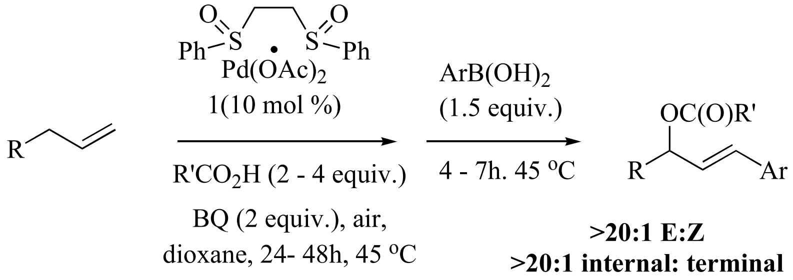
Macrolactonization and allylic C-H oxidation/Vinylic C-H arylation

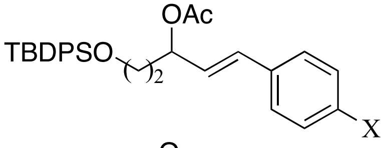
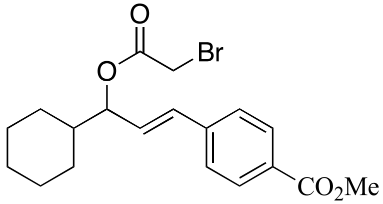
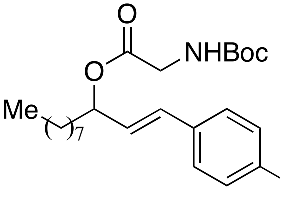


entry	macrolactone product	ring size	isolated yield (%)
1		14	61
2		15	52
3		16	60
4		17	53
5		16	52
7		14	60
8		14	54

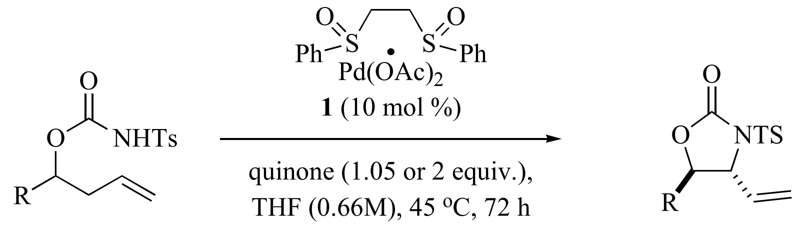
Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* ***2006****, 128 (28), 9032 - 9033*

Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* ***2006****, 128 (28), 9032 - 9033*



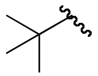
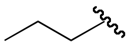
entry	product	isolated yield (%)
1		X = H, 74%
2		OMe, 52%
4		F, 74%
11		62%
13		75%

Allylic C-H Amination and Linear Allylic C-H Amination



1 (10 mol %)

quinone (1.05 or 2 equiv.), THF (0.66M), 45 °C, 72 h

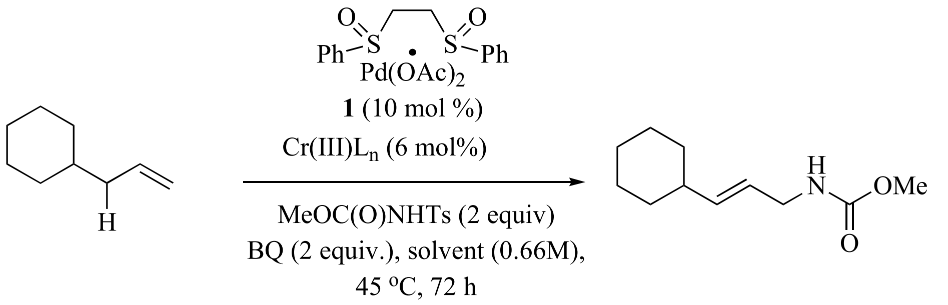
entry	R	quinone (equiv.)	isolated yield (%)	dr (anti:syn)
1	i-Pr	BQ (2)[a]	37	7:1
2	i-Pr	BQ (2)[a,b]	3	--
3	i-Pr	BQ (2)	50	7:1
4	i-Pr	PhBQ (2)	66	6:1
5	i-Pr	PhBQ (1.05)	72	6:1
7		PhBQ (1.05)	8	18:1
8		PhBQ (1.05)	86	1.6:1

[a] Reaction run at 0.33 M. [b] Reaction run using 10 mol % $Pd(OAc)_2$

Weak lewis basicity of nucleophile prevents interference during C-H activation step

Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* ***2007****, 129 (23), 7274 - 7276*

Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* ***2008****, 130 (11), 3316 - 3318*



1 (10 mol %)

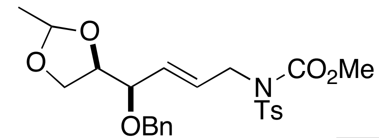
$Cr(III)L_n$ (6 mol%)

MeOC(O)NHTs (2 equiv)

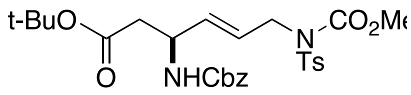
BQ (2 equiv.), solvent (0.66M), 45 °C, 72 h

entry	$Pd(II)L_n$	$Cr(III)L_n$	isolated yield (%)	L:B	E:Z
1[a]	1	----	----	----	----
2[a]	----	(salen)Cr(III)Cl **2**	----	----	----
3[a]	1	**2**	43	>100:1	65:1
4[a]	$Pd(OAc)_2$	**2**	17	----	----
6[a]	1	(TPP)Cr(III)Cl	25	>100:1	71:1
7[b]	1	**2**	53	>100:1	57:1
10[b]	1	(salen)Mn(III)Cl	44	>100:1	78:1

[a] THF. [b] TBME.

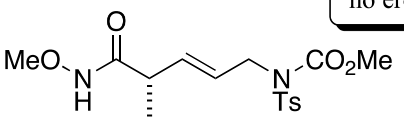


63%

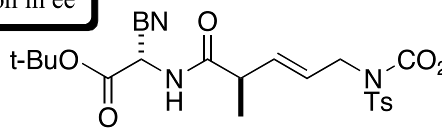


55%

>20:1 E:Z
>20:1 L:B
no erosion in ee

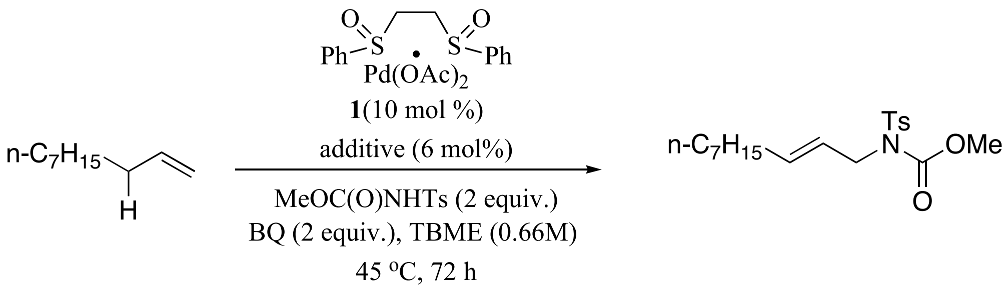


54%

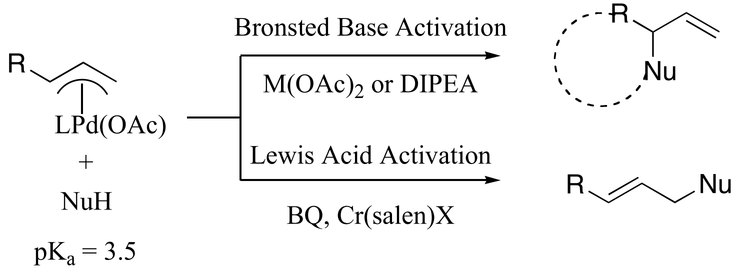


50%

Bronsted Base Strategy for intermolecular Allylic C-H Amination



entry	additive	yield(%)	L:B	E:Z
1	none	1	----	----
2	(S,S)-Cr(salen)Cl **2**	50	11:1	19:1
3	pyridine	9	12:1	14:1
4	2,6-di-*tert*-butylpyridine	----	----	----
5	N-isopropylamine	----	----	----
6	N,N-diisopropylamine	66	12:1	15:1
7	TEA	60	14:1	15:1
8	DIPEA	66	11:1	17:1
9	MeOC(O)NTs-DIPEAH	9	6:1	10:1



Lewis acid activation incompatible with lewis basic functionality

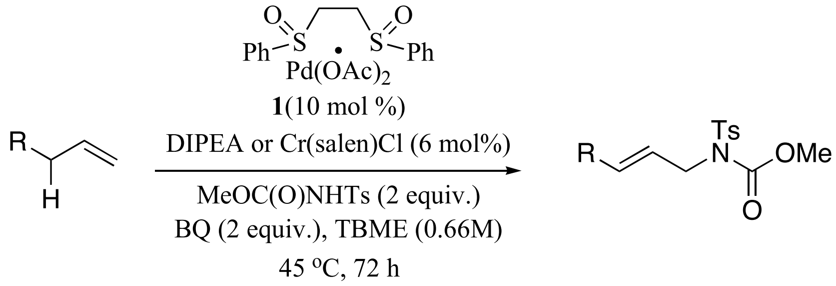
Potential Isomerization of activated terminal olefins

Strongly basic but stericly encumbered amines gave highest observed yield

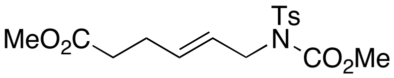
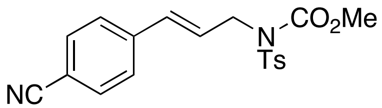
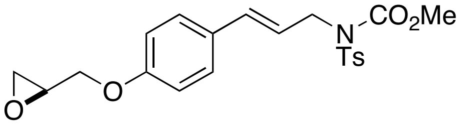
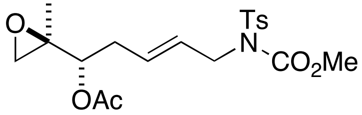
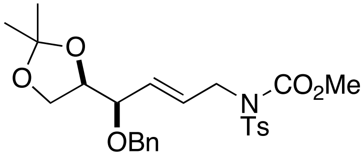
One or more steps in the catalytic cycle are incompatible with high concentrations of a coordinating anionic nucleophile

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

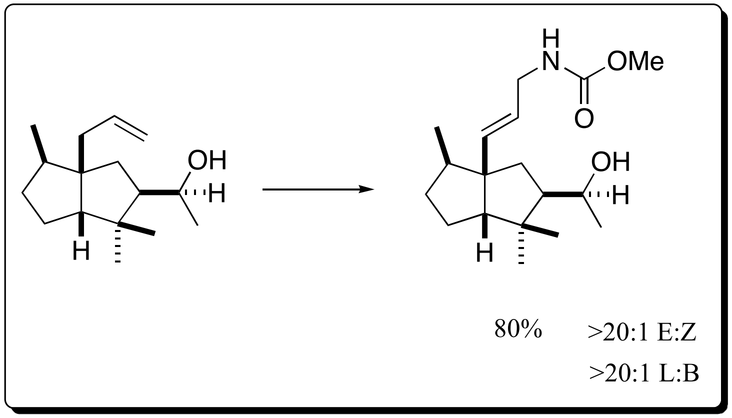
Effect of DIPEA and Comparison Between additives



1(10 mol %)
DIPEA or Cr(salen)Cl (6 mol%)
MeOC(O)NHTs (2 equiv.)
BQ (2 equiv.), TBME (0.66M)
45 °C, 72 h

entry	**product**	**isolated yield(%)**	
		DIPEA	Cr(salen)Cl
1		61	37
3		79	59
6		54	<1
8		64	<1
10		76	63

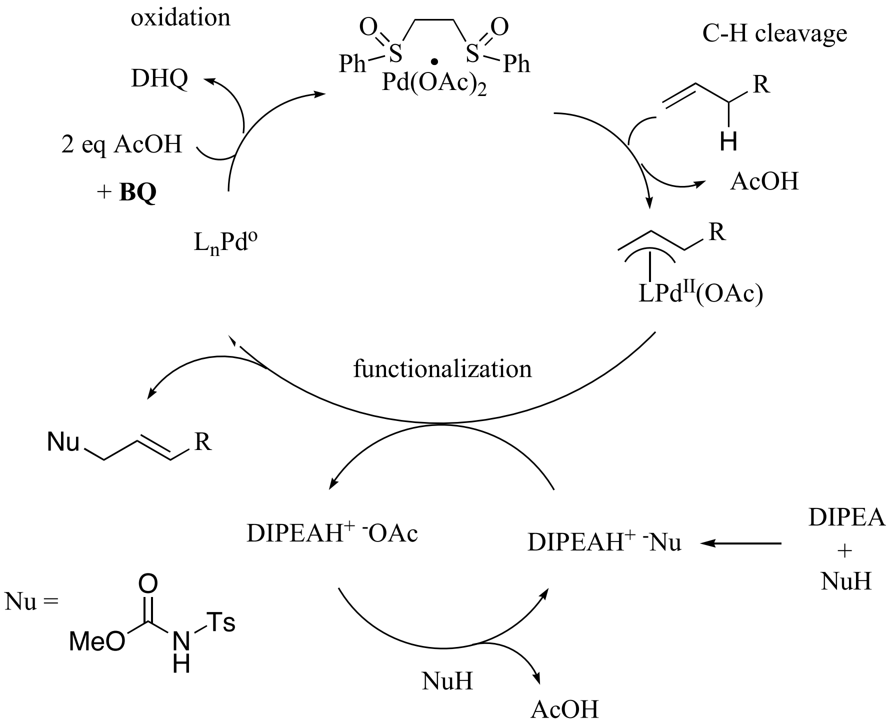
Optimal mol% of DIPEA between 6 - 10 mol%



80% >20:1 E:Z
>20:1 L:B

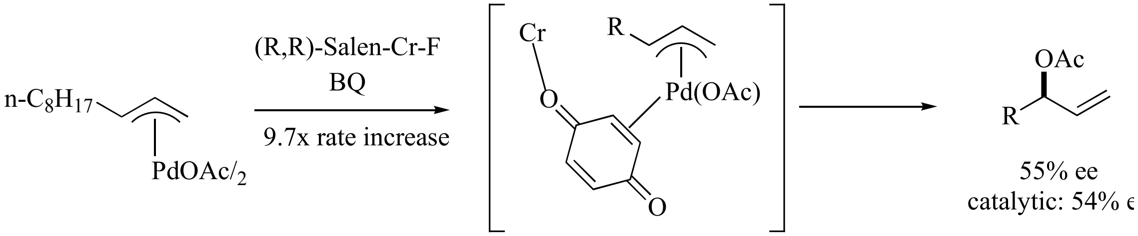
Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* ***2009****, ASAP*

Proposed mechanism and Quinone sterics



Increased sterics of quinone resulted in no substantial yield difference when DIPEA system was used. Substantial decrease in yields were observed for the Cr(salen)Cl system.

Using stoiciometric $(n\text{-Bu})_4NOAc$ and DIPEAH$^+$ $^-$OAc resulted in similar yields



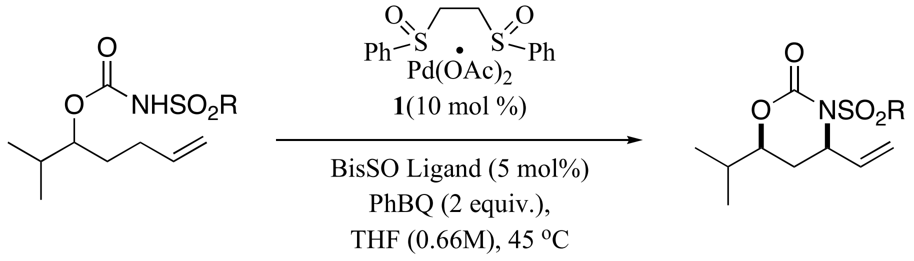
Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009***, ASAP*

Covell, D. J.; White, M. C. *Angew. Chwm., Int. Ed.* **2008**, 4, 6448

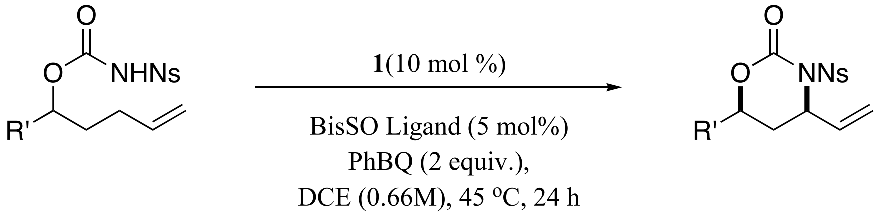
Decreasing Nitrogen Electron Density and Branching Effects

Unlike the allylic C-H amination system, the branching substrate has little effect on diastereoselectivity.

Addivtives include *p*-nitrobenzoic acid and O_2 to promote palladium (0) oxidation.



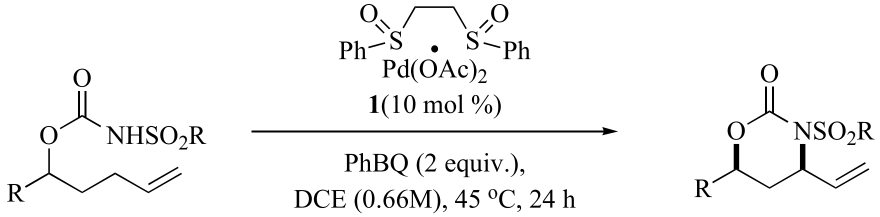
entry	R	time	isolated yield(%)	dr
1	*p*-Tol	72 h	15	5.1:1
2	*p*-ClPh	24 h	38	3.7:1
3	*p*-NO_2Ph	24 h	67	4.4:1
4	*o*-NO_2Ph	24 h	63	2.6:1



entry	R'	isolated yield(%)	dr	isolated Syn
5	*i*Propyl	80	6.0:1	65
6	Ethyl	87	4.3:1	67
7	*t*Butyl	84	6.3:1	68

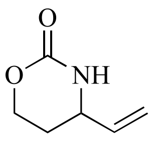
Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009***, ASAP*

Reaction scope and Origin of Diastereoselectivity

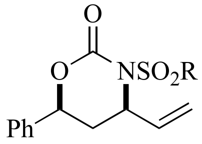


1(10 mol %)

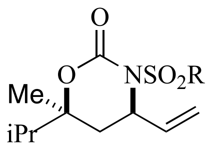
PhBQ (2 equiv.),
DCE (0.66M), 45 ºC, 24 h



70% yield

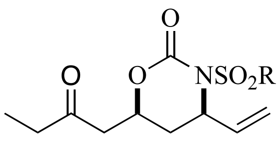


83% Yield, 6.8:1 dr

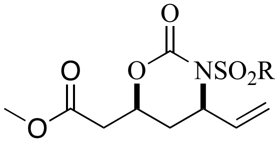


82% Yield, 2.5:1 dr

Carbonyls

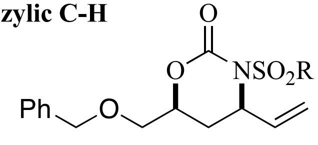


76% Yield, 3.4:1 dr

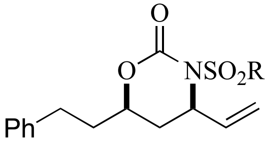


73% Yield, 4.3:1 dr

Benzylic C-H

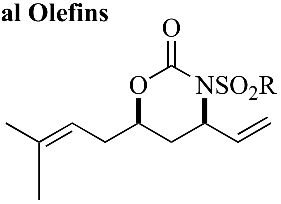


80% yield, 4.4:1 dr

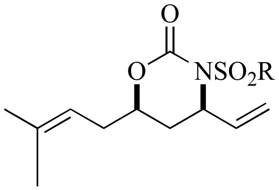


83% Yield, 5.3:1

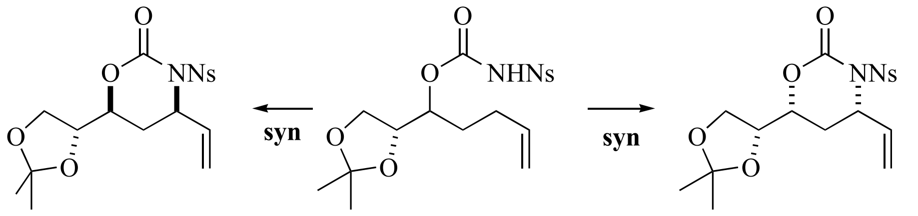
internal Olefins



67% Yield, 4.5:1 dr



67% Yield, 4.2:1 dr

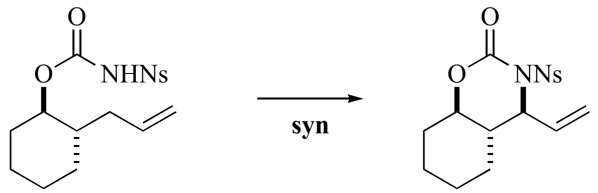


87% Yield, 3.6:1 dr

(+)-13-*syn*-diol

(-)-14-*anti*-diol

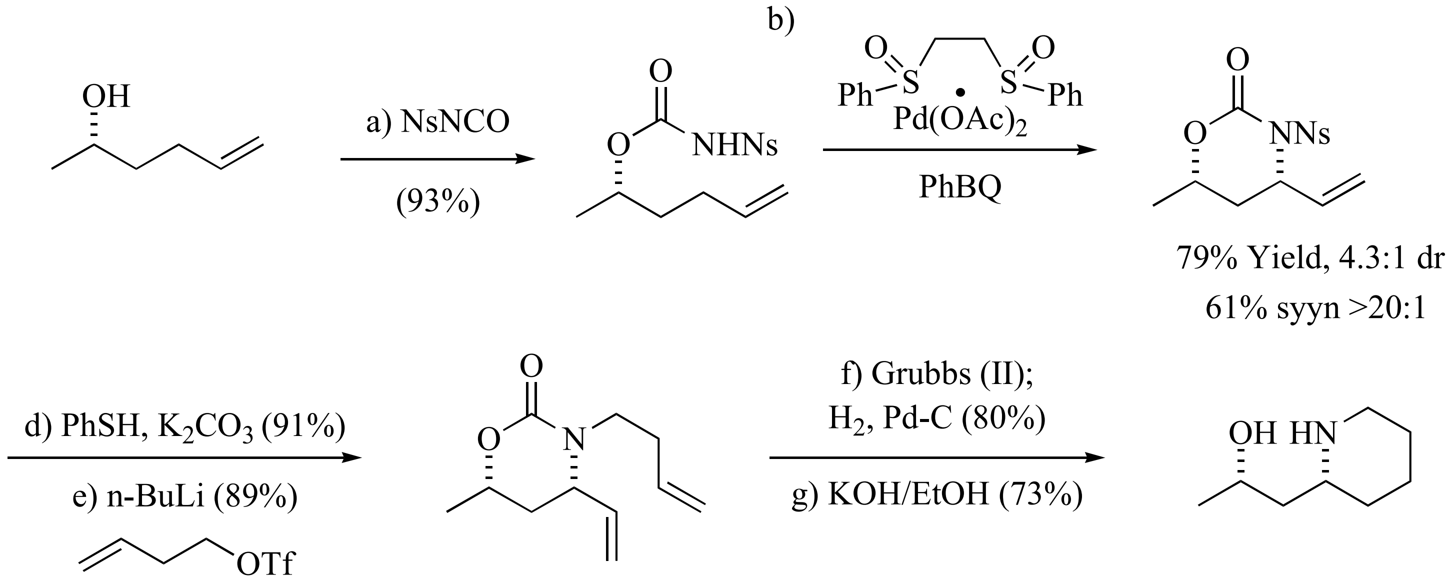
73% Yield, 4.7:1 dr



58% Yield
>20:1

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

Total synthesis of (+)-Allosedridine



(+)-allosedridine

6 steps, 27% yield
>99% ee

Previous Syntheses: 10 steps (15.8%, >98% ee

8 steps (2.7%, 85% ee)

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

Takahata,H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999***, 64, 8594*

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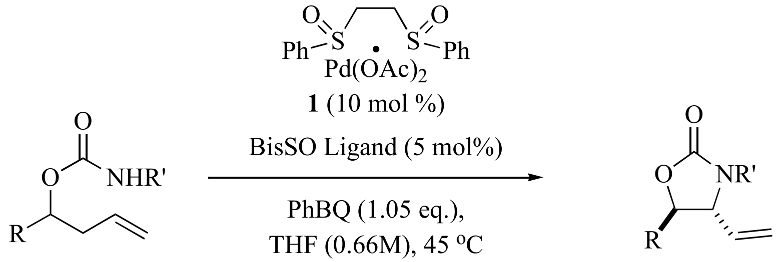
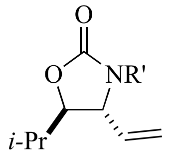
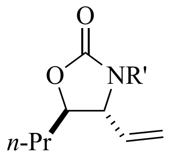
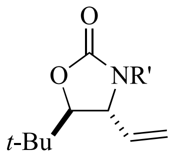
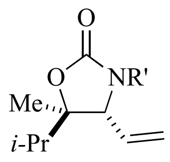
1,2-Amination rate increase and conclusion



entry	Product	R'	isolated yield (%)	dr
1		Tosyl Nosyl	76 78	6.0:1 5.0:1
2		Tosyl Nosyl	86 79	1.6:1 1.7:1
3		Tosyl Nosyl	8 20	18:1 >20:1
4		Nosyl	<1	----

Conclusion

Over the last 5 years the White group has developed mild C-H oxidation and amination reactions using the electrophilic Pd(II) catalyst, **1**.

They have developed methods for the construction of syn-1,2- and syn-1,3-amino alcohols.

Used DIPEA to improve functional group tolerance and a more electrophilic pro-nucleophile to increase reaction rates

This methodology should be employed in a more complex setting.

Other ways to trap the intermediate alkyl-palladium species

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