Copper-Catalyzed sp^3 α-C−H Activation of Alcohols

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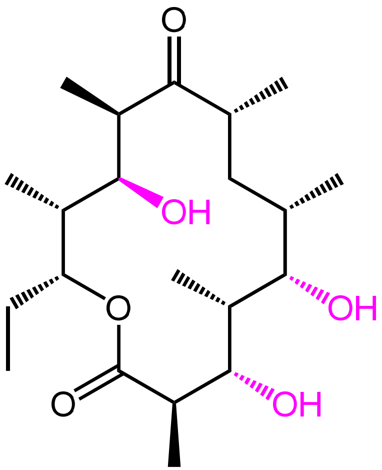
Checker: Mu-Wang Chen

Date: 2015/04/14

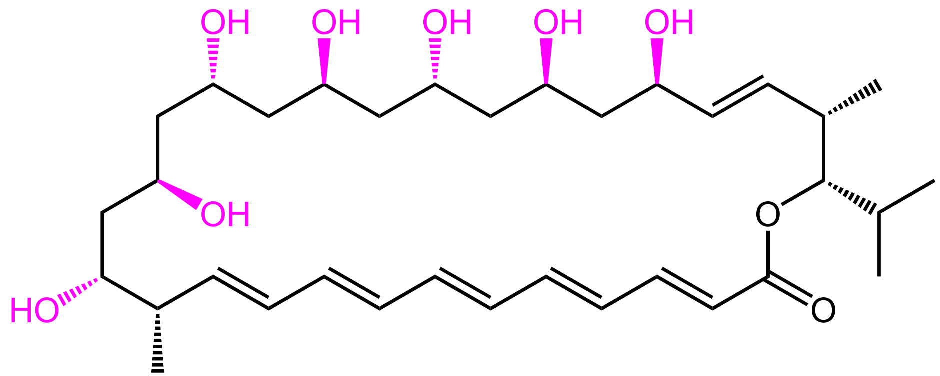
Loh, T.-P. *et al. J. Am. Chem. Soc.* **2015**, *137*, 42.

Content

Introduction



6-Deoxyerythronolide B



(+)-Roxaticin

Introduction

Nucleophilic Addtion

Metal Free

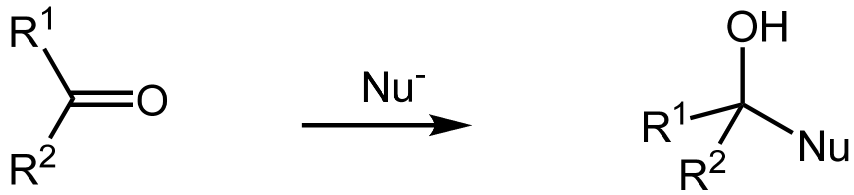
Ru-Catalyzed

Ir-Catalyzed

Cu-Catalyzed

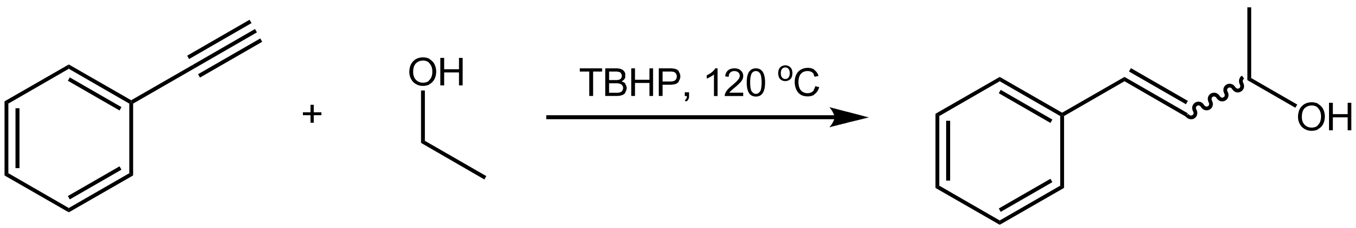
→ Alcohols

Nucleophilic Addition



Kang, J. Y. *et al. J. Am. Chem. Soc*. **2010**, *132*, 7826.
Trost, B. M. *et al*. *Chem. Soc. Rev.* **2010**, *39*, 1600.

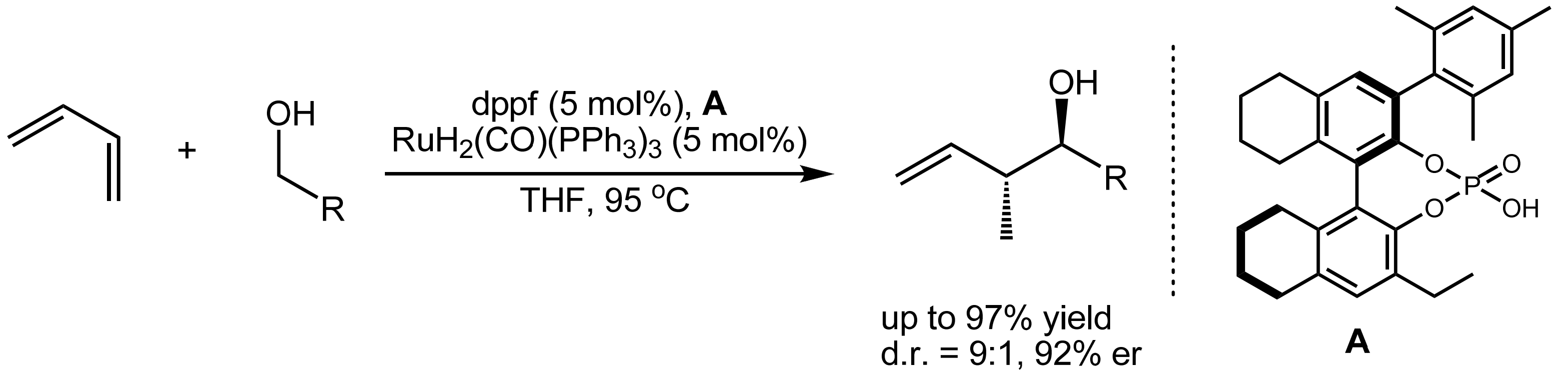
Metal Free



E/*Z* = 1:1
up to 95% yield

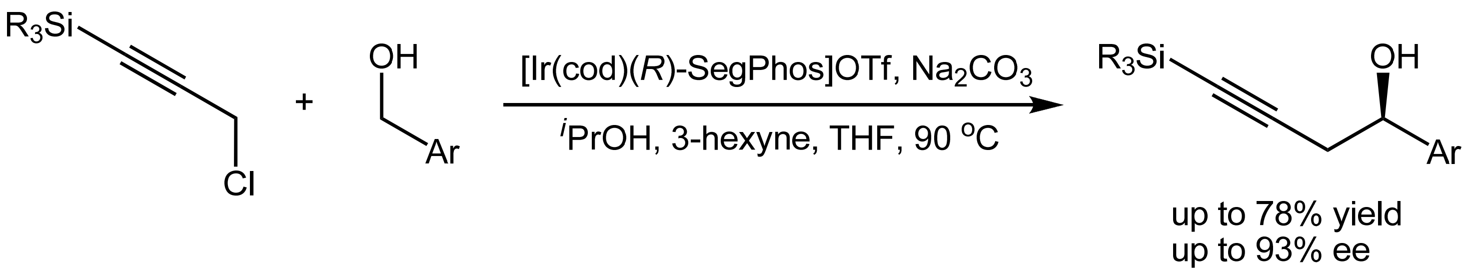
Liu, Z.-Q. *et al*. *Org. Lett.* **2009**, *11*, 1437.

Ru-Catalyzed



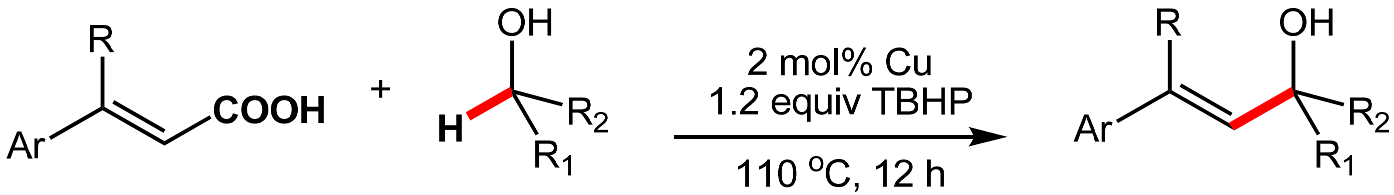
Krische, M. J. *et al*. *Science* **2012**, *336*, 324.

Ir-Catalyzed



Krische, M. J. *et al*. *Angew. Chem. Int. Ed*. **2012**, *51*, 7830.

Copper-Catalyzed Decarboxylative Alkenylation

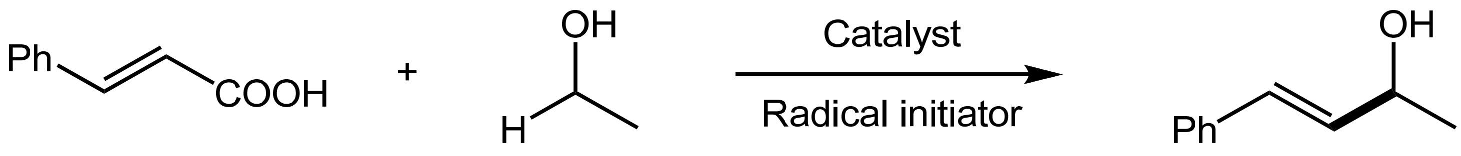


Ar = phenyl, pyridyl,
furyl, thienyl

38 examples
up to 99% yield
E-alkene only

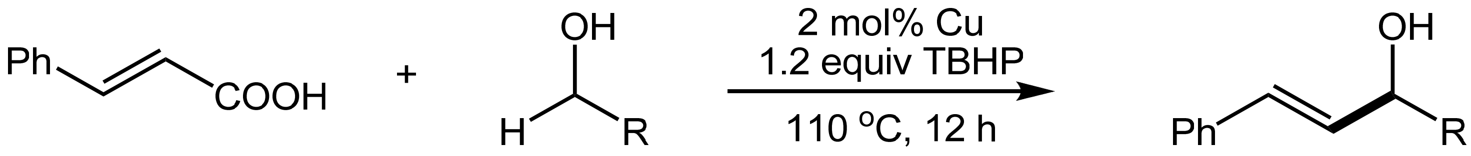
Liu, Z.-Q. *et al*. *Chem. Sci*. **2012**, *3*, 2853.

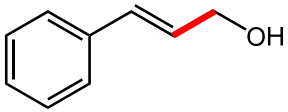
Optimization of Reaction Condition



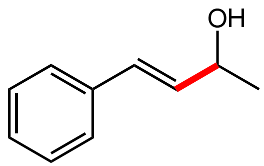
Entry	Catalyst (mol%)	Radical initiator (equiv)	T (^oC)	Yield (%)
1	—	TBHP (1.2)	110	—
2	CuBr (5)	TBHP (1.2)	110	17
3	$Cu(OAc)_2 \cdot H_2O$ (5)	TBHP (1.2)	110	45
4	Cu (5)	TBHP (1.2)	110	72
5	**Cu (2)**	**TBHP (1.2)**	**110**	**73**
6	Cu (1)	TBHP (1.2)	110	62
7	**Cu (2)**	**TBHP (2.0)**	**110**	**99**
8	Cu (2)	TBHP (2.0) 70% aqueous	110	49
9	Cu (2)	DTBP	110	14
10	Cu (2)	BPO	110	24
11	Cu (2)	TBHP	90	53

The Substrate Scope

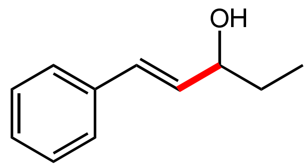




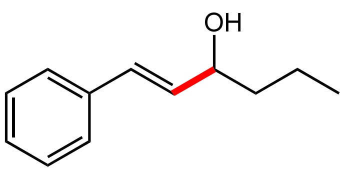
72%



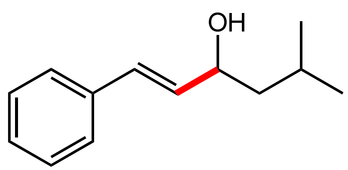
73% (99%)



57%



52% (75%)



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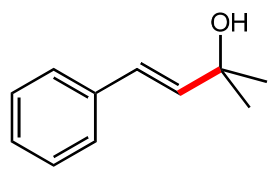
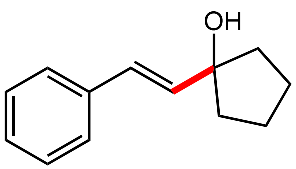


86%



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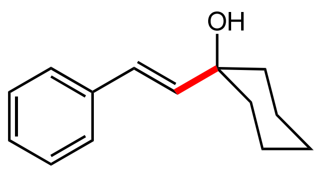
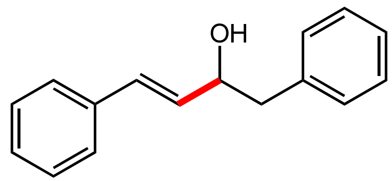
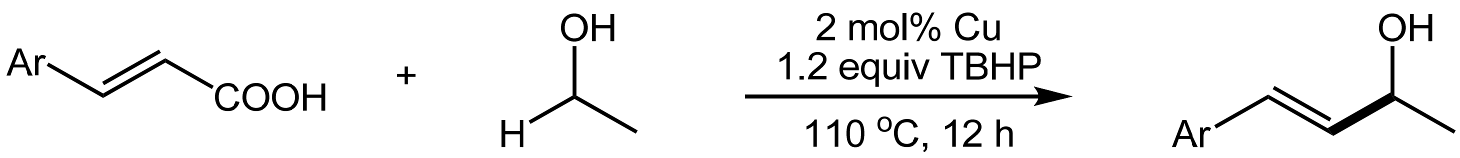


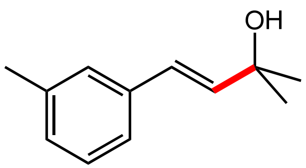
59%



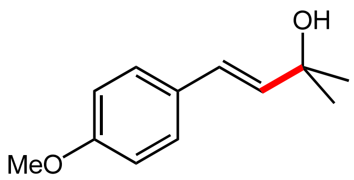
68%

The Substrate Scope





96%



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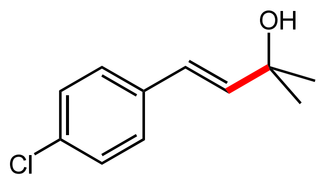

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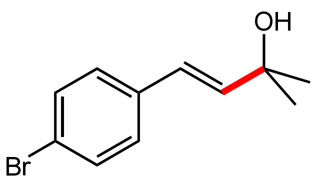

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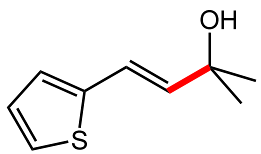

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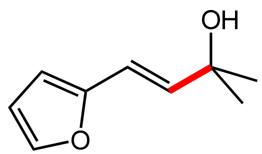
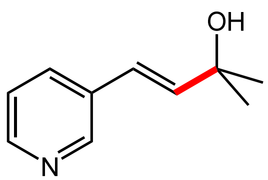
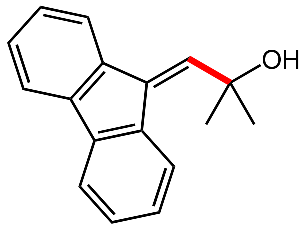


55%



61%



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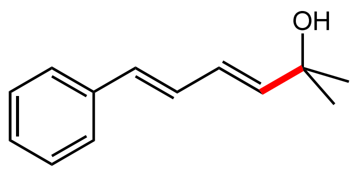
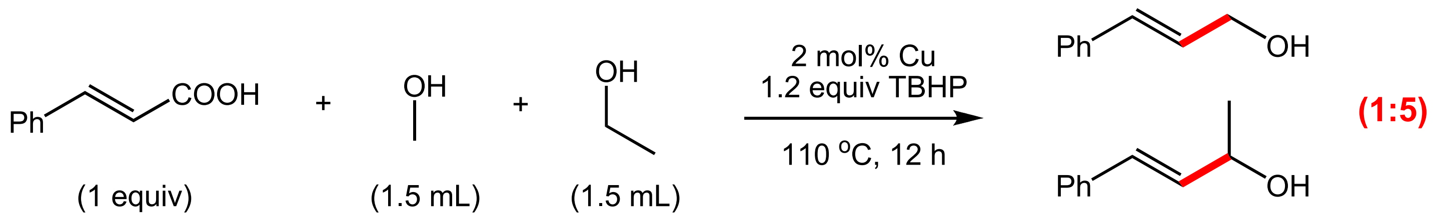
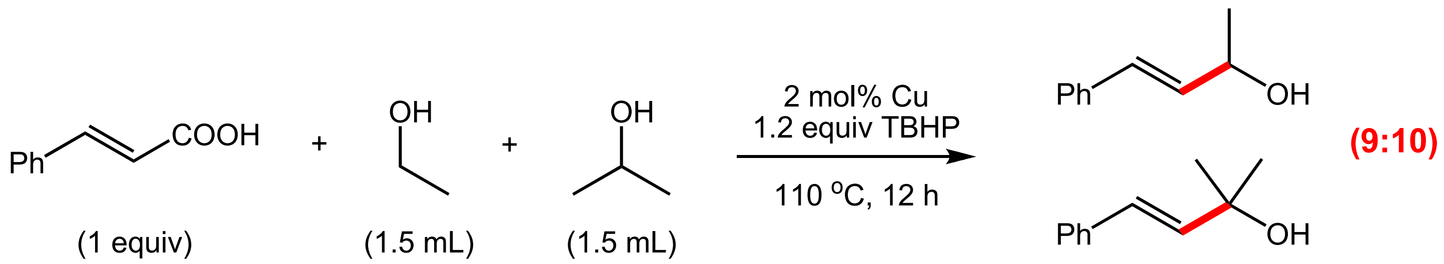


52%

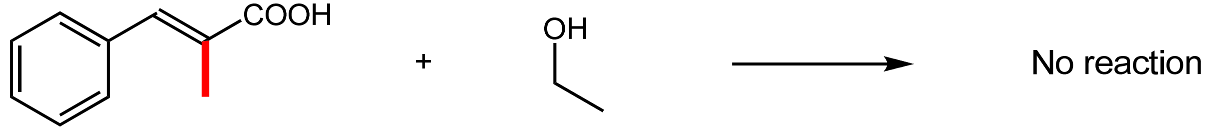
Reaction Selectivity

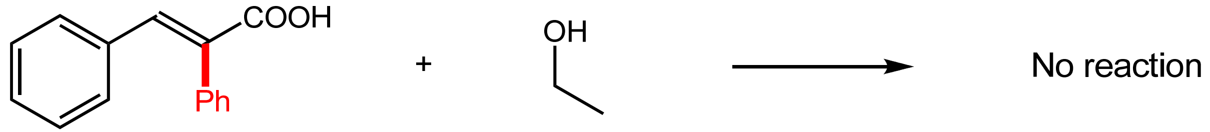


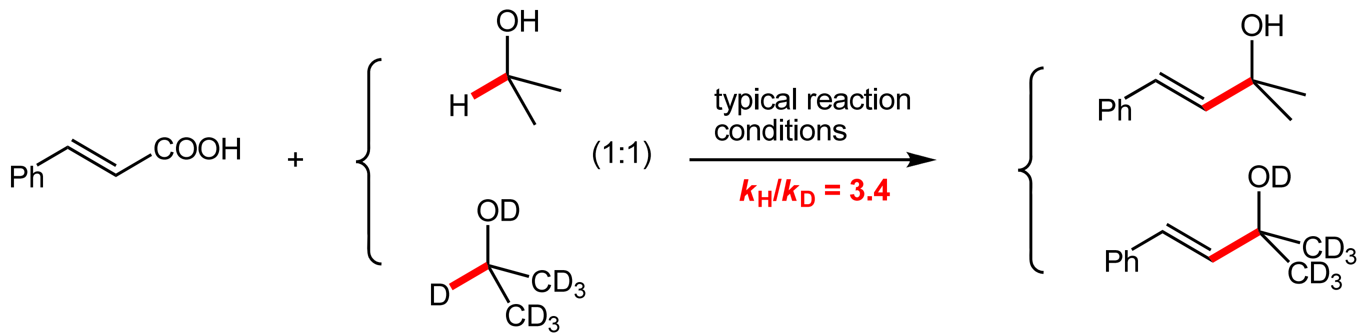


Tertiary ≥ Secondary > Primary

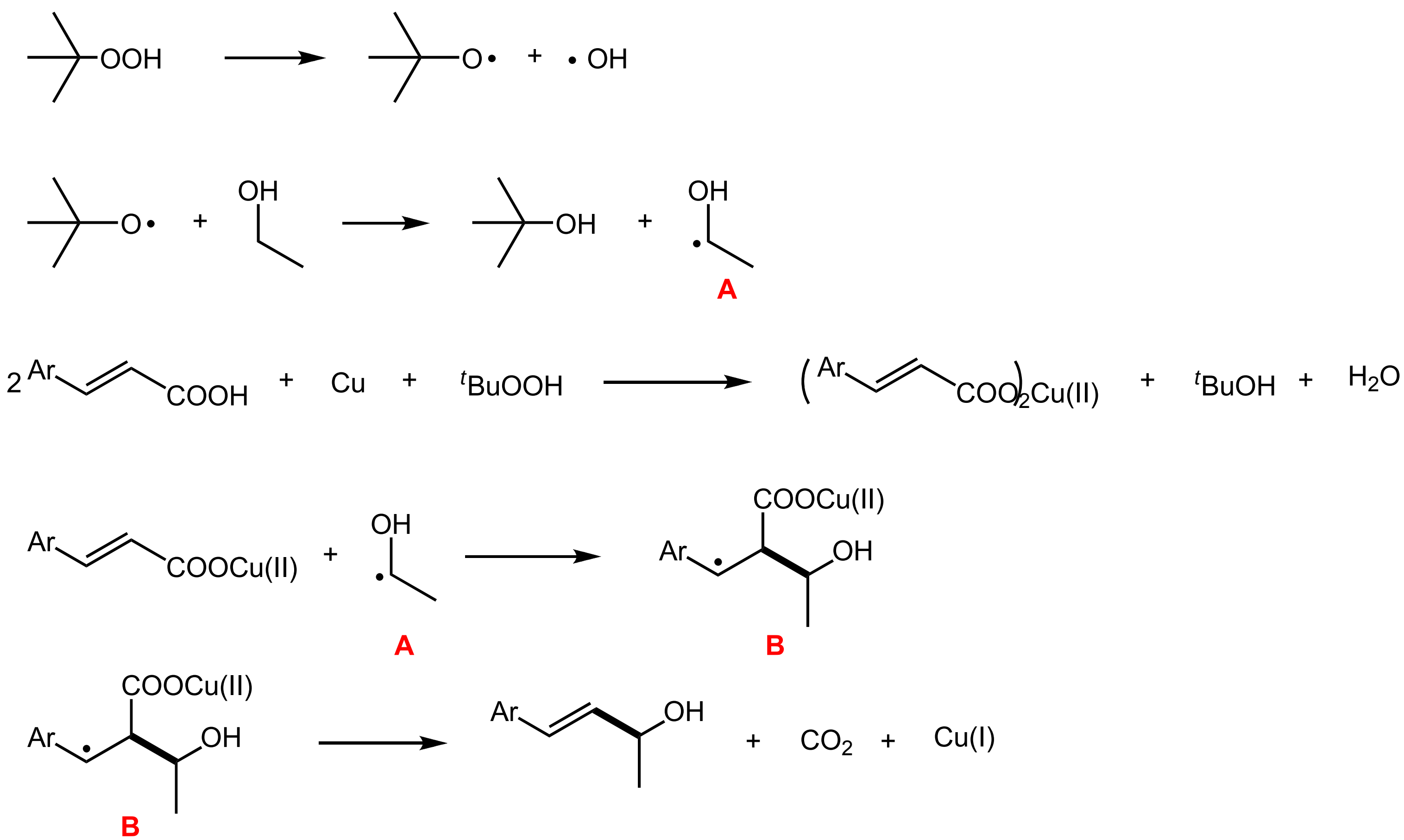
Mechanistic Study



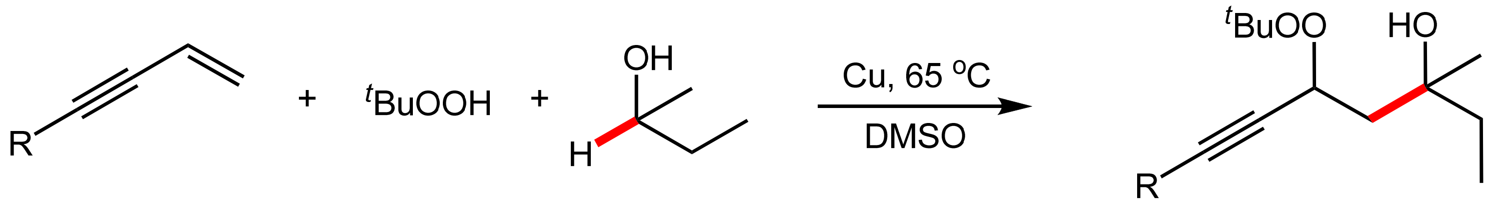




Possible Mechanism



Copper-Catalyzed Direct Coupling



up to 73% yield
d.r. = 1:1

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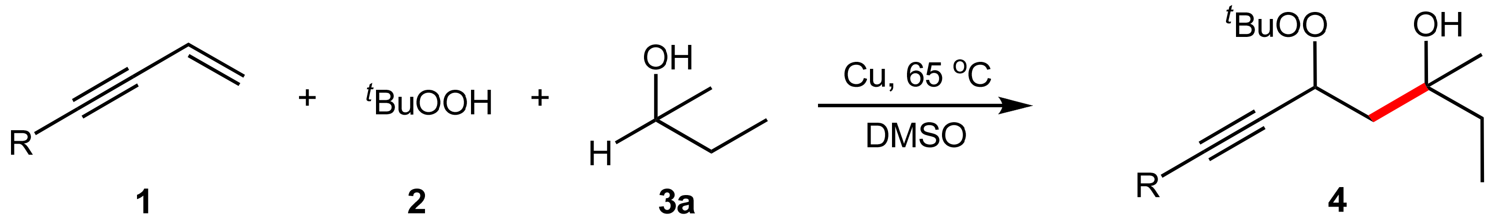
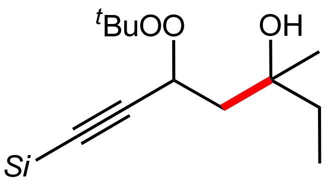
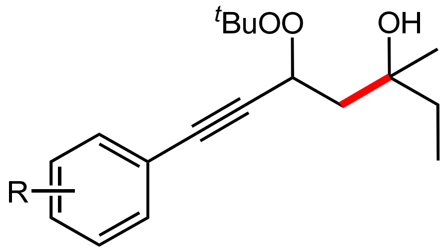
The Substrate Scope

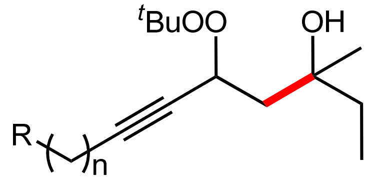


1 **2** **3a** **4**

d.r. = 1:1





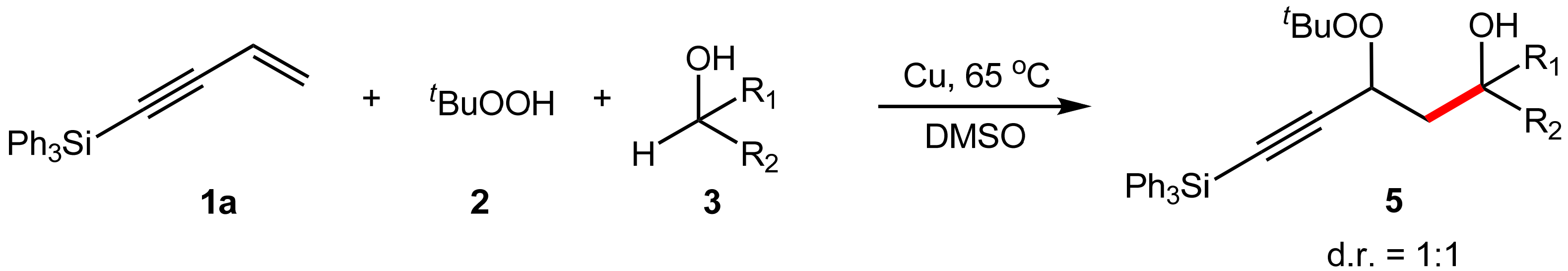


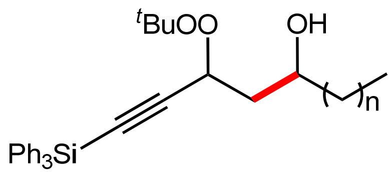
4a: *Si* = Ph_3Si		68%
4b:	= $^iPr_3Si$	36%
4c:	= $Me_2{}^tBuSi$	50%
4d:	= Et_3Si	33%

4e: R = 4-H		58%
4f:	= 4-Cl	51%
4g:	= 4-Br	58%
4h:	= 4-F	51%
4i:	= 2-F	43%

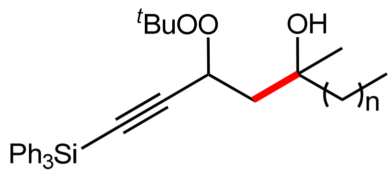
4j:	n = 0,	R = cyclopentyl	35%
4k:	n = 0,	= cyclohexyl	38%
4l:	n = 1,	= cyclohexyl	42%
4m:	n= 2 ,	= phenyl	63%

The Substrate Scope

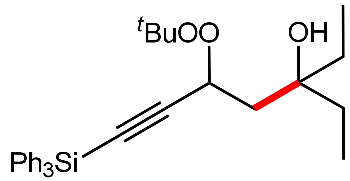




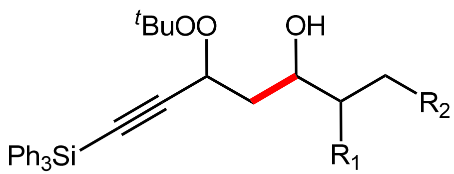
5a, n = 0, 26%
5b, n = 1, 55%
5c, n = 2, 40%



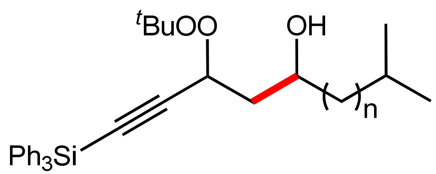
5d, n = 0, 62%
5e, n = 3, 40%



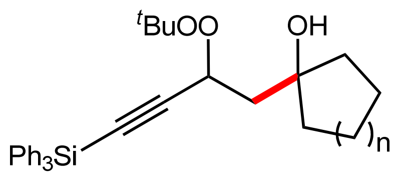
5f 35%



5g, R_1 = Me, R_2 = Me, 46%
5h, R_1 = H, R_2 = Ph, 57%

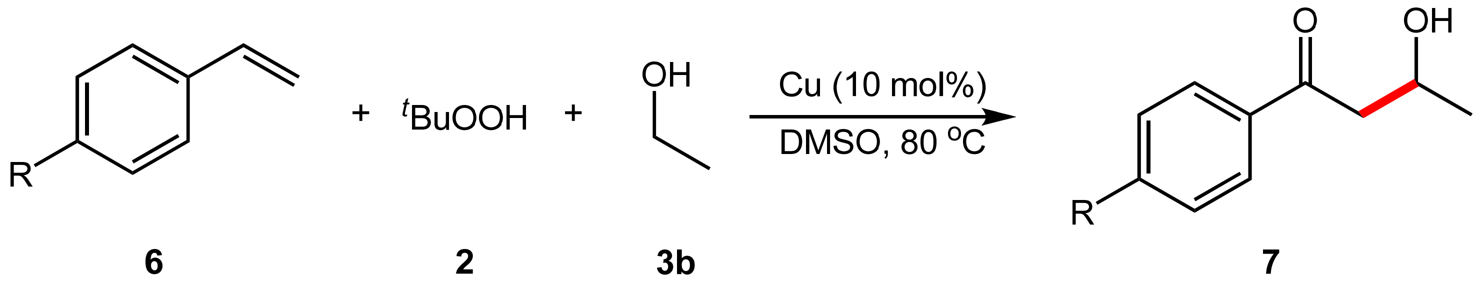


5i, n = 0, 55%
5j, n = 1, 39%



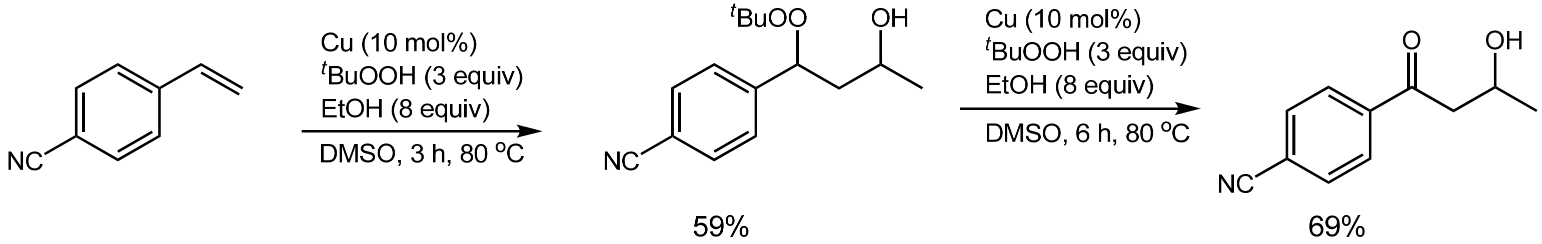
5k, n = 1, 48%
5l, n = 2, 33%
5m, n = 4, 30%

The Substrate Scope

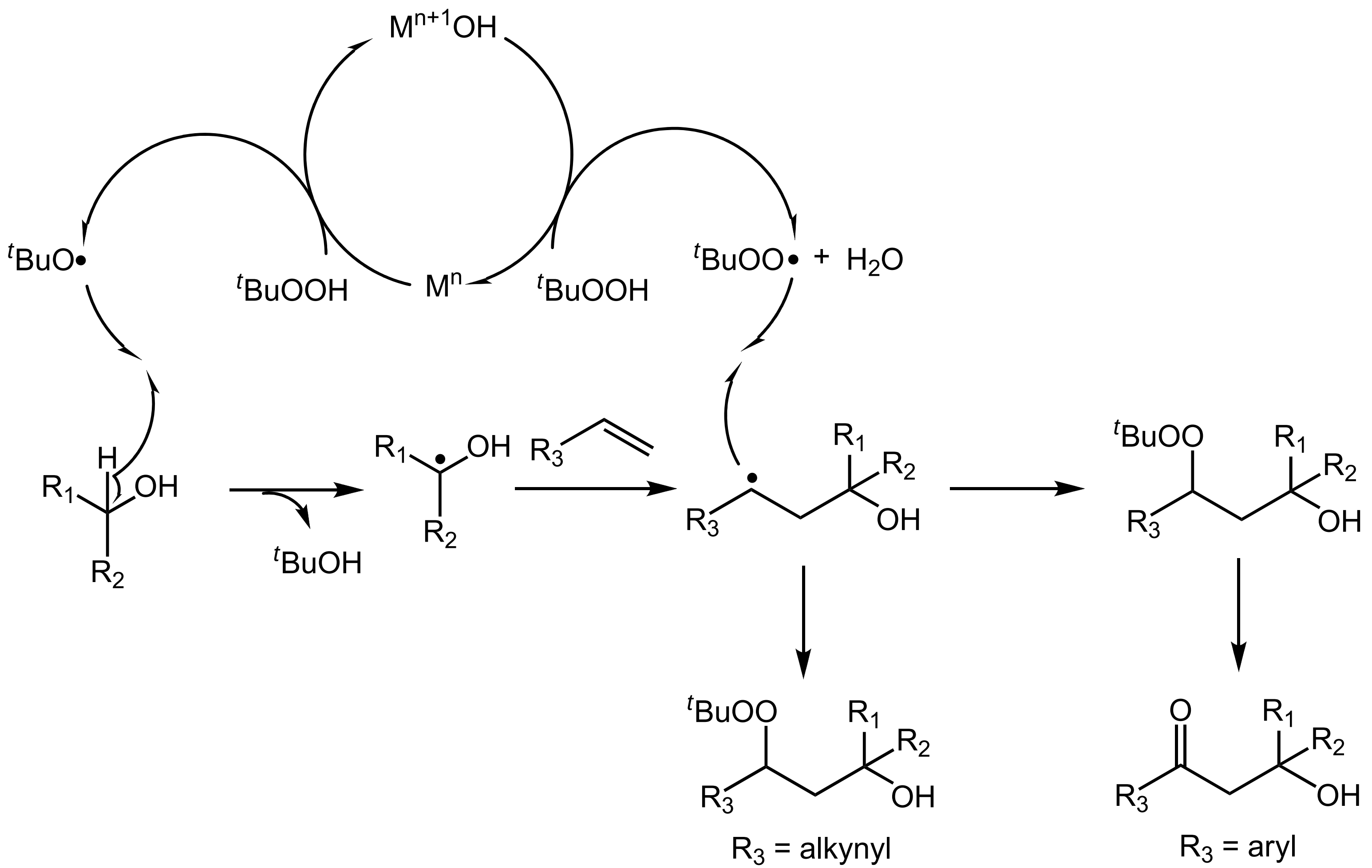


Product	R	Yield (%)	Product	R	Yield (%)
7a	H	48	**7e**	COOMe	39
7b	Br	32	**7f**	CN	40
7c	Cl	50	**7g**	OCOMe	31
7d	F	45	**7h**	CF_3	53

Mechanistic Study

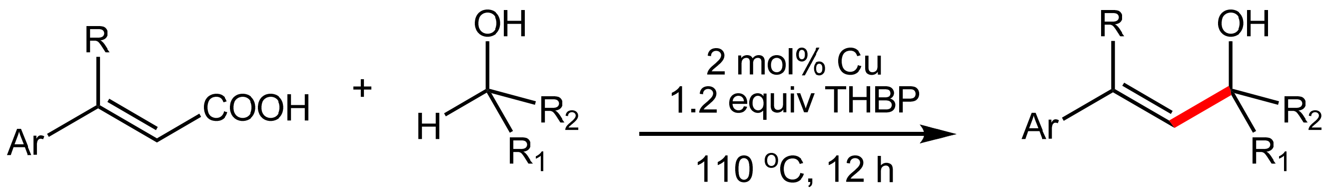


Possible Mechanism



Summary

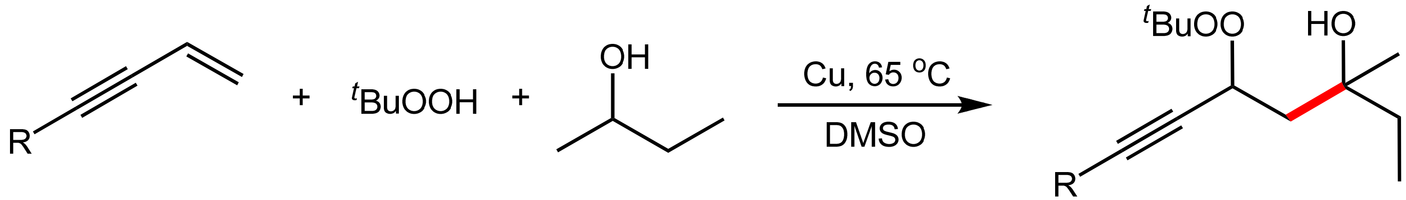
Copper-Catalyzed Decarboxylative Alkenylation



Ar = phenyl, pyridyl,
furyl, thienyl

38 examples
up to 99% yield
***E*-alkene only**

Copper-Catalyzed Direct Coupling



up to 73% yield
d.r. = 1:1

Liu, Z.-Q. *et al*. *Chem. Sci*. **2012**, *3*, 2853.
Loh, T.-P. *et al. J. Am. Chem. Soc.* **2015**, *137*, 42.

The direct sp^3 α-C−H bond activation and functionalization of alcohols and ethers will provide one of the most efficient entries to more functionalized alcohols and ethers. Particularly, the ability to construct new a C−C bond with the β-carbon of alcohols with concomitant retention of the active hydroxyl group in the final products renders this synthetic approach more attractive than the classical methods which utilized the corresponding carbonyl compounds. Furthermore, alcohols are expedient coupling partners as they are readily available, more stable, less toxic, and easier to handle than the corresponding aldehydes. Accordingly, there has been much interest in the generation of α-hydroxy carbon radicals and the subsequent addition to radical acceptors.

In conclusion, we have developed a novel copper- and cobalt-catalyzed three-component oxidative coupling of olefins with hydroperoxides and alcohols which involved the α-C−H activation of alcohols. Various aliphatic, silylated, and aryl 1,3-enynes underwent alkylation peroxidation to assemble β-peroxy alcohols, which further allowed access to propargylic 1,3-diols and β-hydroxyynones. Further studies directed toward the synthetic utilization of enynes are currently underway in our laboratory.