Synthesis of 1,1-Disubstituted Olefins via Catalytic Alkyne Hydrothiolation/ Kumada Cross Coupling

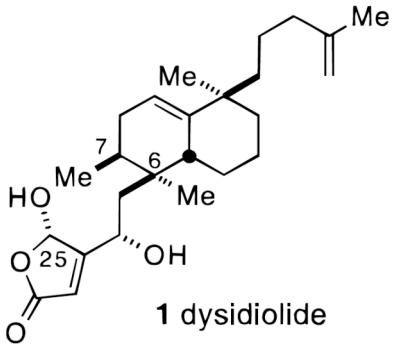
*Anthony Sabarre and Jennifer Love**

University of British Columbia

Org. Lett., ASAP

1,1-Disubstituted Alkenes

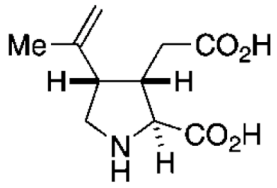
Antitumor agent



1 dysidiolide

J. Am. Chem. Soc. **1997**, *119*, 12425-12431.

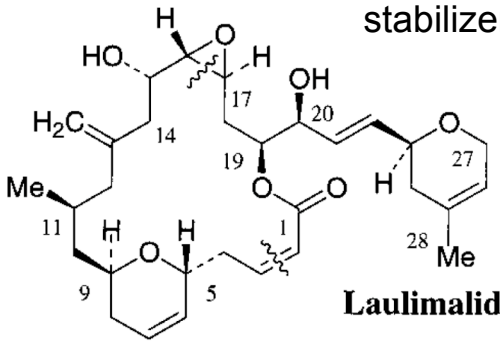
CNS stimulant



(–)-Kainic acid (**1**)

Org. Lett. **2008**, *10*, 1711-1714.

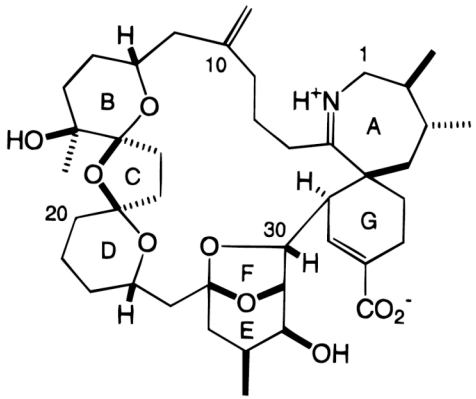
Microtubule stabilizer



Laulimalide (1)

J. Am. Chem. Soc. **2000**, *122*, 11027-11028.

Neurotoxin

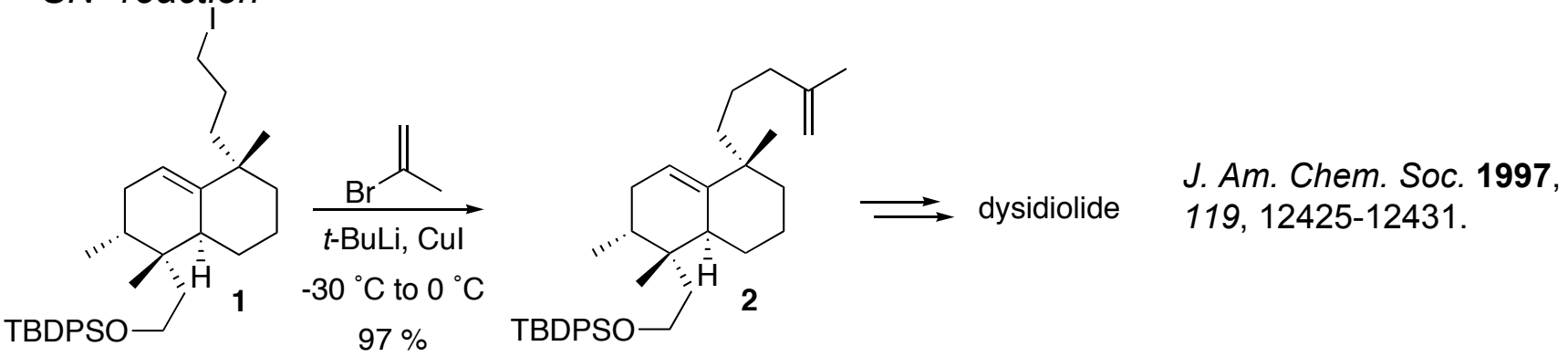


Pinnatoxin A (**1**)

J. Am. Chem. Soc. **1998**, *120*, 7647-7648.

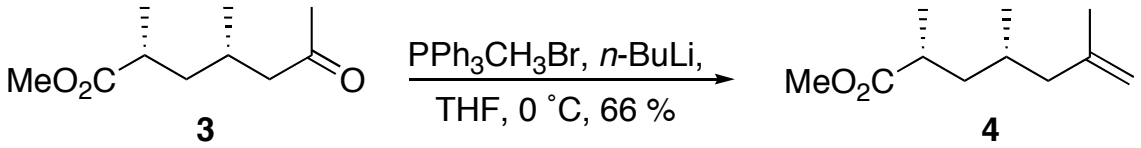
Synthesis of 1,1-Disubstituted Alkenes

■ *SN2 reaction*



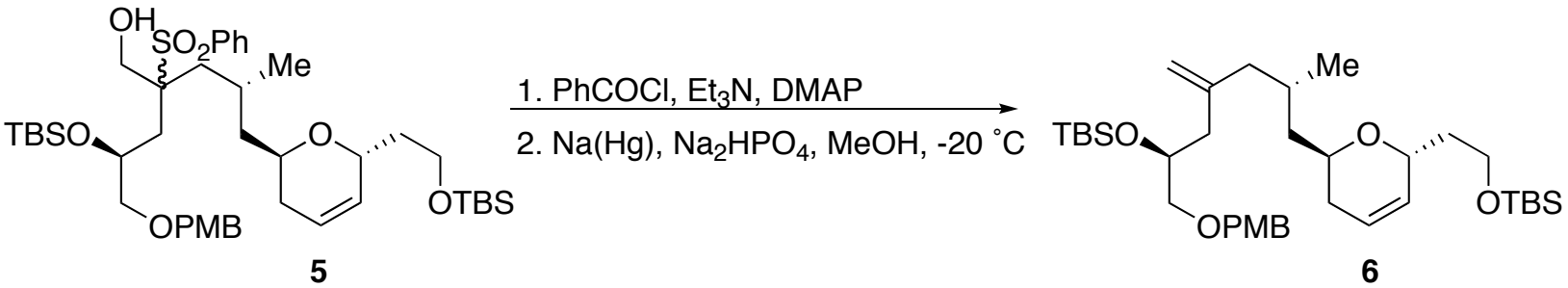
J. Am. Chem. Soc. **1997**, *119*, 12425-12431.

■ *Wittig reaction*



Tetrahedron Lett. **2008**, *49*, 2013

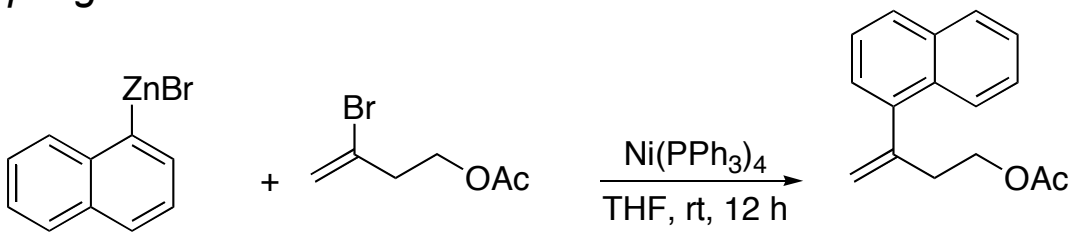
■ *Julia Olefination*



J. Am. Chem. Soc. **2000**,*122*, 11027-11028.

Synthesis of 1,1-Disubstituted Alkenes

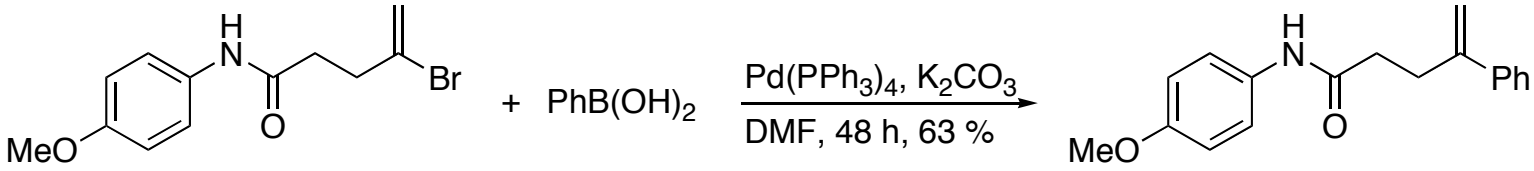
■ *Negishi Coupling*



1 **2** **3**

Tetrahedron **2006**, *62*, 7521-7533.

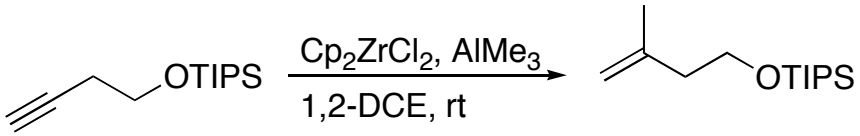
■ *Suzuki Coupling*



4 **5**

Eur. J. Org. Chem. **2007**, *3*, 437-444.

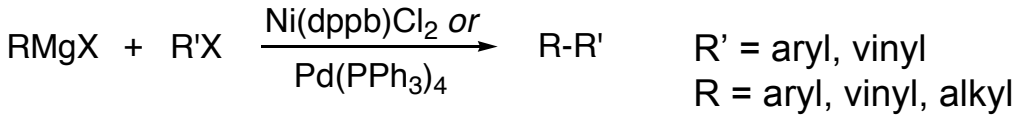
■ *Alkyne Carbometallation/H⁺*



6 **7**

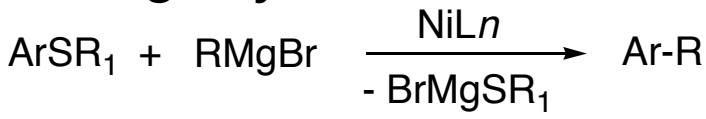
J. Am. Chem.Soc. **2006**, *128*, 15396-15398

Kumada Coupling

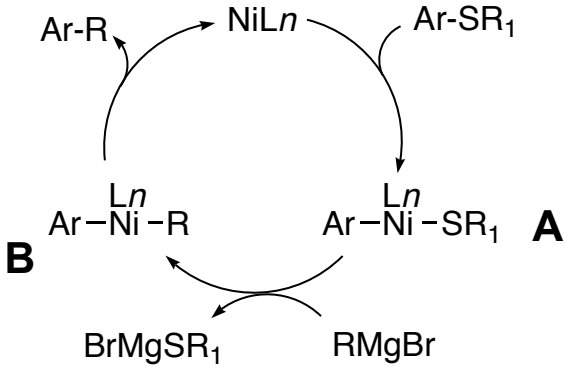


- low functional group tolerance

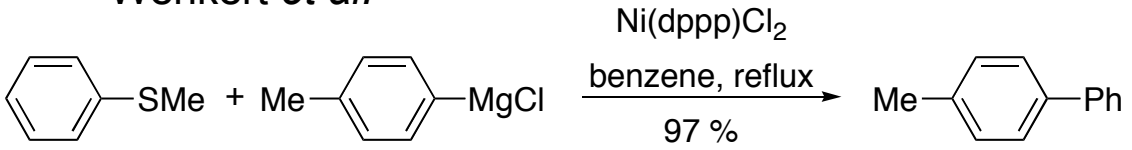
■ *Kumada Coupling using aryl sulfides*



The catalytic cycle

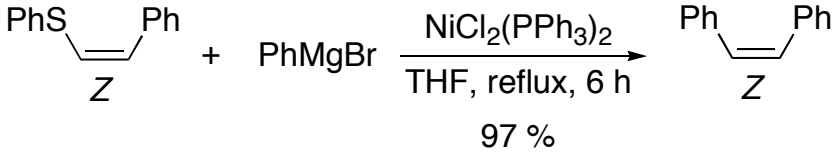


Wenkert *et al.*



Chem. Commun. **1979**, *637-638.*

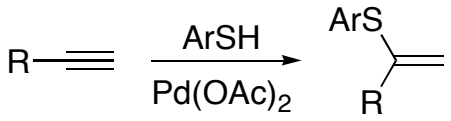
Takei *et al.*



Tetrahedron Lett. **1979**, *20*, 43-46.

Alkyne Hydrothiolation

Addition of aromatic thiols to terminal alkynes

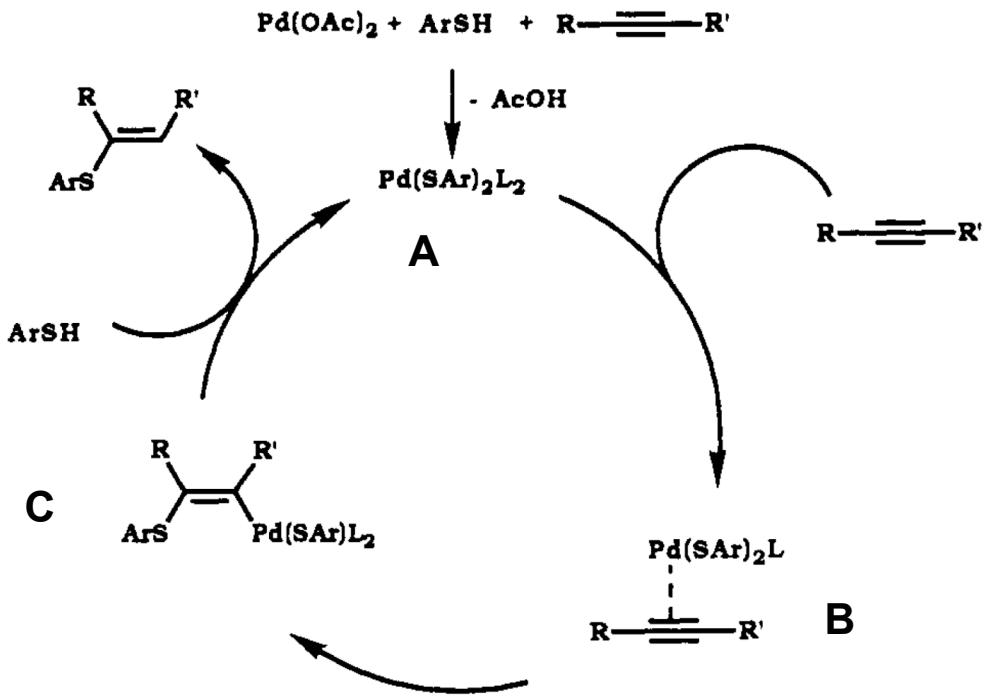


55-86 %

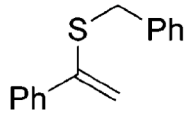
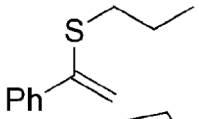
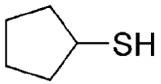
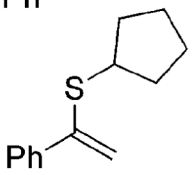
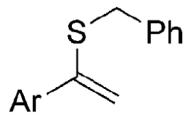
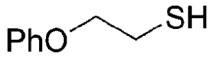
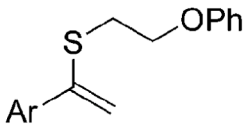
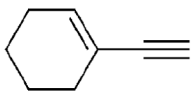
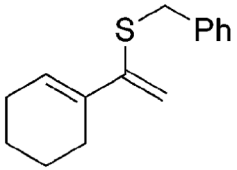
J. Am. Chem. Soc. **1992**, *114*, 5902-5903.

- wide range of functional groups tolerated

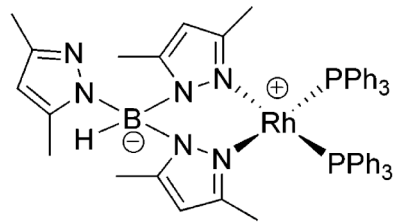
Proposed catalytic cycle



Addition of Aliphatic Thiols to Alkynes

Entry[a]	Thiol	Alkyne	Product	Cond, Time, Yield[b,c]
1	$PhCH_2SH$	Ph—		A, 20 min, 90%
2	*n*-PrSH	Ph—		B, 80 min, 87%
3		Ph—		A, 2 h, 78%
4	$PhCH_2SH$	*p*-$CH_3OC_6H_4$—		B, 80 min, 93%[d,e]
5		*p*-$CH_3OC_6H_4$—		A, 2 h, 83%[d]
6	$PhCH_2SH$			A, 10 h, 81%

A = rt; B = 0 ˚C to rt



Complex **I**, $Tp^*Rh(PPh_3)_2$.

Rh-pyrazolylborate

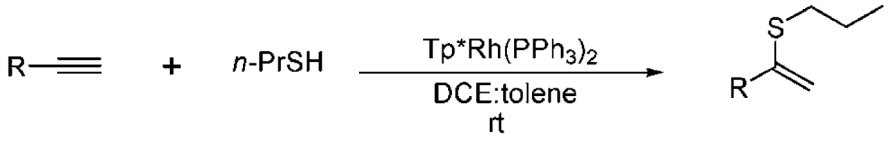
J. Am. Chem. Soc. **2005**,*127*, 17614-17615.

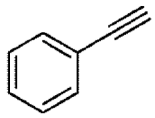
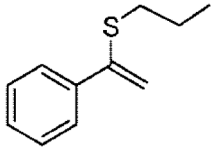
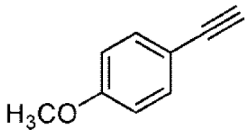
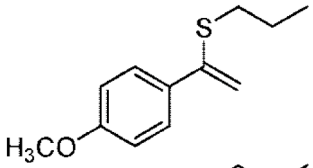
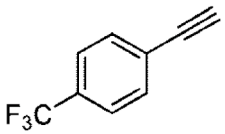
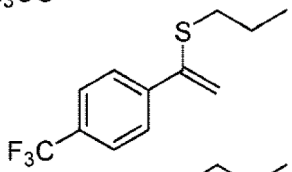
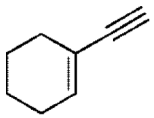
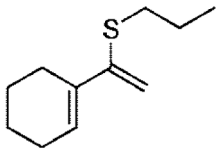
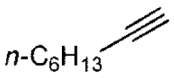
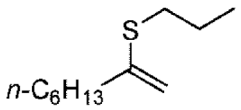
1,1-Disubstituted Vinyl Sulfides

Sulfide partner:
- efficient cross coupling
- low mol. wt. to minimize waste

Use of *n*-PrSH:
- excellent reactivity
- mass comparable to Br^-, typical leaving group

Table 1. Catalytic Alkyne Hydrothiolation



entry[a]	alkyne	product	time, yield
1			2 h, 74%
2			2 h, 72%
3			16 h, 15%
4			2 h, 83%
5			16 h, 86%

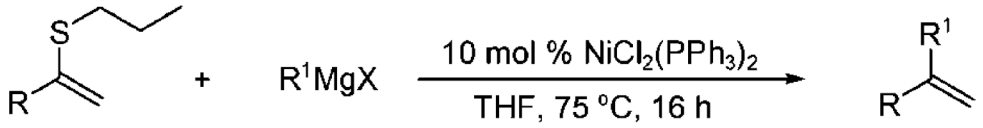
[a] Reactions conducted with 0.03 equiv of $Tp^*Rh(PPh_3)_2$, 1 equiv of alkyne, and 1.1 equiv of thiol.

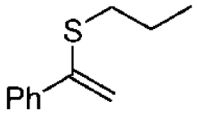
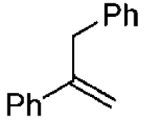
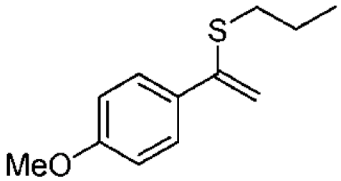
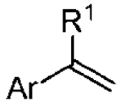
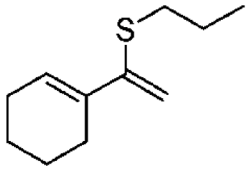
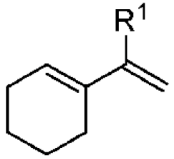
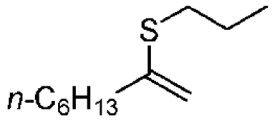
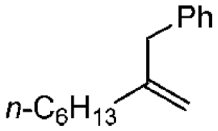
- Electron-rich aryl alkynes well-tolerated
- Electron-poor aryl alkynes: significantly reduced yields
- Aliphatic aldehydes well-tolerated

Sabarre and Love, *Org. Lett., ASAP*

Kumada Cross Coupling

Table 2. Nickel-Catalyzed Cross-Coupling of Vinyl Sulfide with Grignard Reagent



entry[a]	vinyl sulfide	Grignard	product	yield[b]
1		$PhCH_2MgCl$		51%[c]
2		$PhCH_2MgCl$		61%
3		PhMgBr		43%
4		*p*-FC_6H_4MgBr		38%
5		$TMS\text{-}CH_2MgCl$		60%[d]
6		$PhCH_2MgCl$		55%
7		PhMgBr		41%
8		*p*-FC_6H_4MgBr		37%
9		$TMS\text{-}CH_2MgCl$		81%
10		$PhCH_2MgCl$		51%

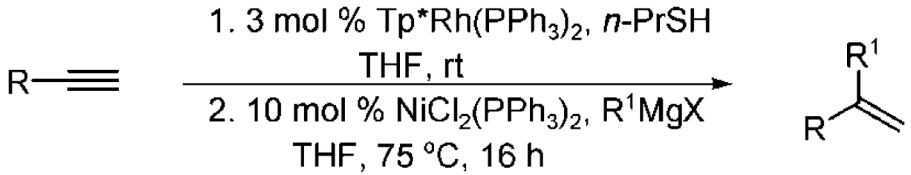
[a] Reaction conducted with 0.1 equiv of $NiCl_2(PPh_3)_2$, 1 equiv of vinyl sulfide, and 4 equiv of Grignard reagent (1.0 M in THF or Et_2O). [b] Isolated yields. [c] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] $R^1 = CH_3$.

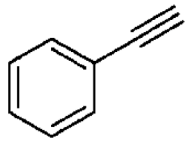
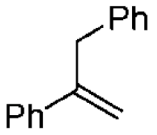
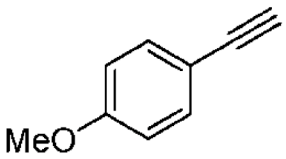
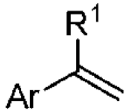
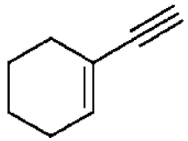
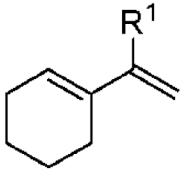
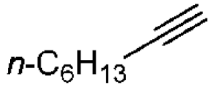
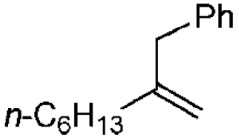
Salient Features:

- moderate to good yield of the product
- competing grignard reagent homocoupling
- *n*-BuMgCl and vinylmagnesium bromide did not give the desired product
- cross-coupling products from ethynyl cyclohexene: potential Diels-Alder precursors

Sabarre and Love, *Org. Lett., ASAP*

One-Pot Hydrothiolation/Kumada Coupling



entry[a]	alkyne	Grignard	product	yield[b]
1		$PhCH_2MgCl$		30%[c] (51)
2		$PhCH_2MgCl$		65% (61)
3		$PhMgBr$		37% (43)
4		$p\text{-}FC_6H_4MgBr$		37% (38)
5		$TMS\text{-}CH_2MgCl$		63%[d] (60)
6		$PhCH_2MgCl$		66% (55)
7		$PhMgBr$		30% (41)
8		$p\text{-}FC_6H_4MgBr$		40% (37)
9		$TMS\text{-}CH_2MgCl$		60% (81)
10		$PhCH_2MgCl$		78% (51)

[a] Reactions conducted with 0.027 mmol of $Tp^*Rh(PPh_3)_2$, 0.9 mmol of alkyne, 0.99 mmol of thiol, 0.09 mmol of $NiCl_2(PPh_3)_2$, and 3.6 mmol of Grignard reagent (1.0 M in THF or Et_2O). [b] Isolated yields. [c] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] $R^1 = CH_3$.

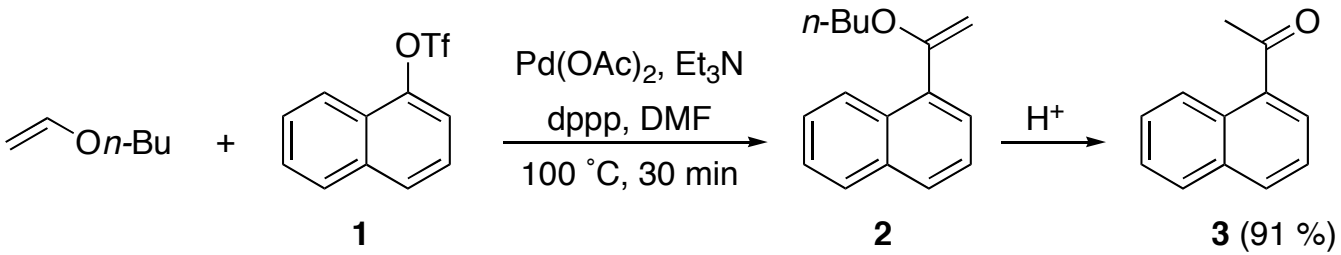
- *Yields comparable or superior compared to the two-step protocol*
- *Greatly improved efficiency in the cross-coupling reactions*

Sabarre and Love, *Org. Lett., ASAP*

Conclusions

- Authors demonstrated Tp*Rh(PPh_3)$_2$ catalyzed hydrothiolation using *n*-PrSH with aliphatic and aryl alkynes.
- The resulting vinyl sulfides underwent Ni-catalyzed Kumada cross coupling with Grignard reagents; synthesis of 1,1-disubstituted alkenes.
- One-pot hydrothiolation/Kumada coupling protocol has been developed.

■ *Heck Reaction*



1 **2** **3** (91 %)

J. Org. Chem. **1992**, *57*, 1481-1486.

Catalytic Cycle