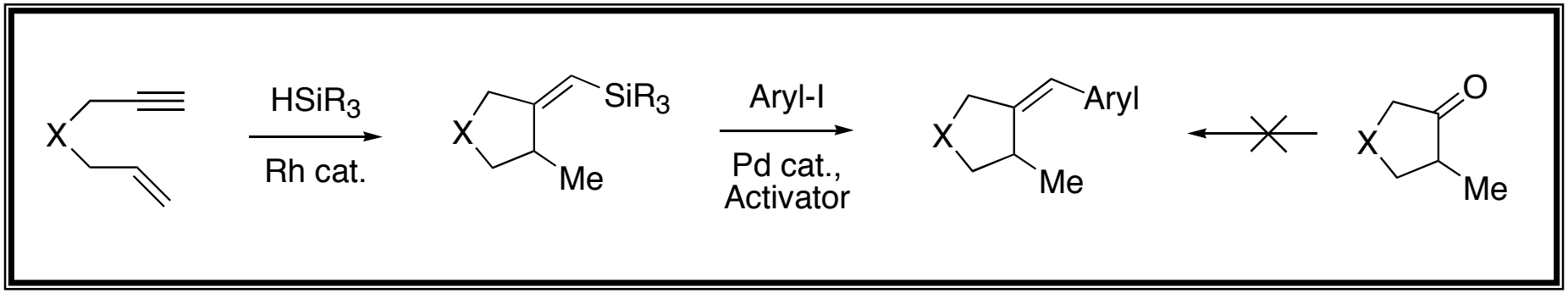
Sequential Silylcarbocyclization/Silicon-Based Cross-Coupling Reactions

Scott E. Denmark and Jack Hung-Chang Liu

J. Am. Chem. Soc. **2007**, *129, 3737*



Adam Hoye

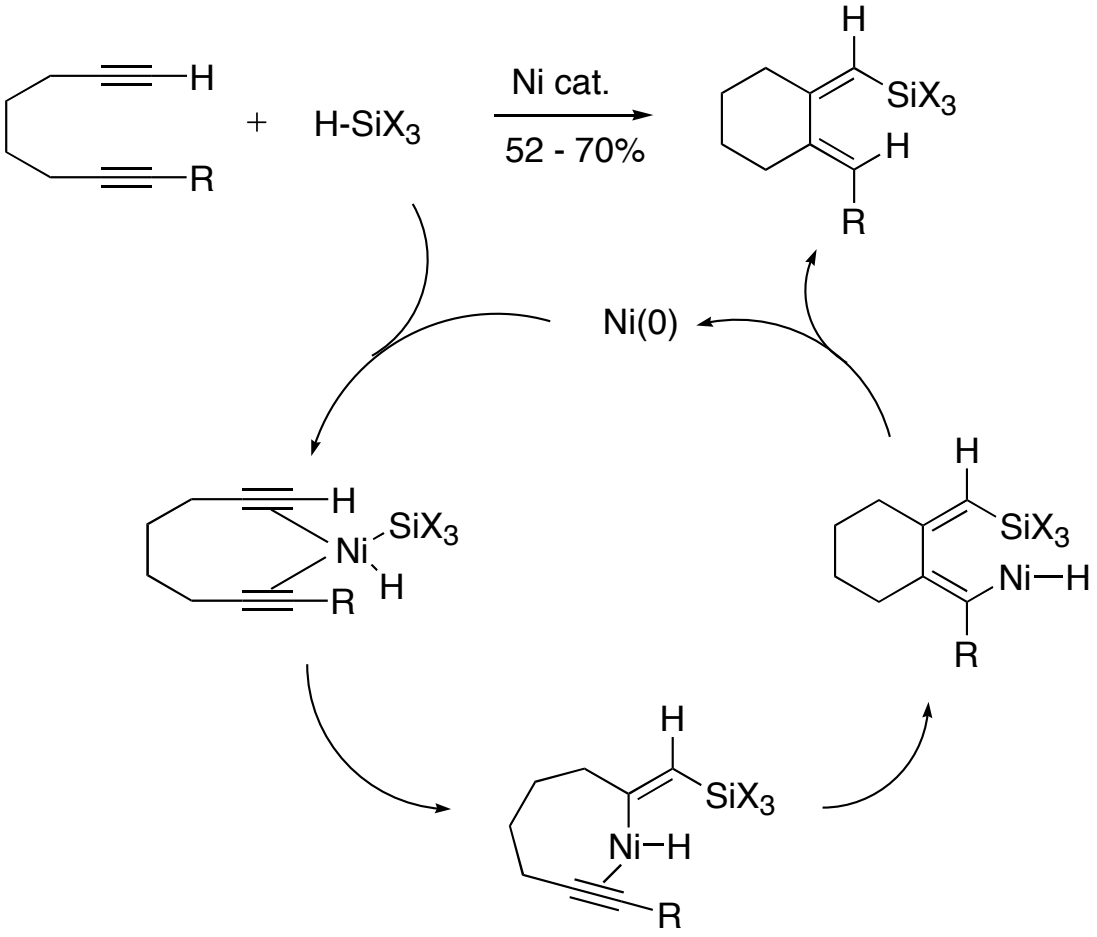
Current Literature

April 7, 2007

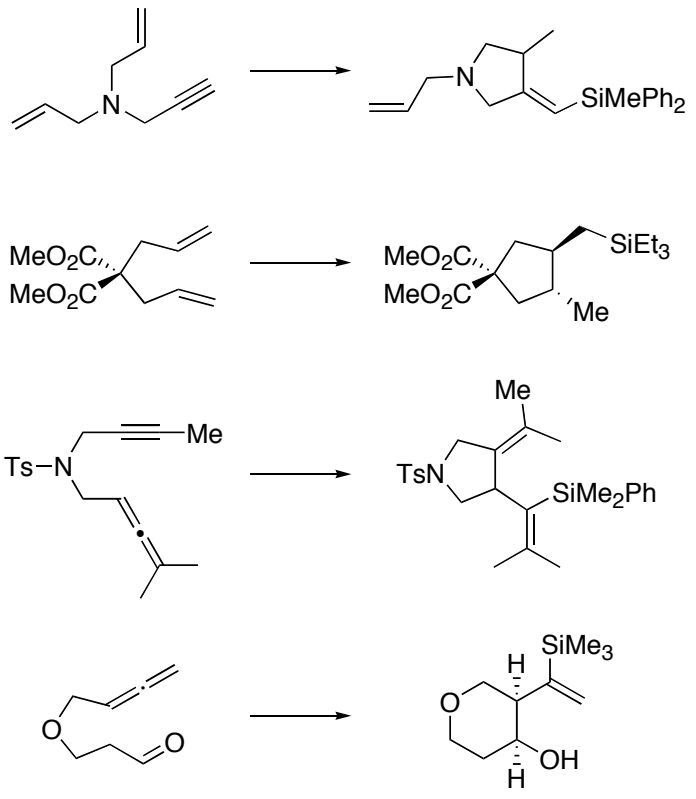
Wipf Group

Silylcarbocyclizations

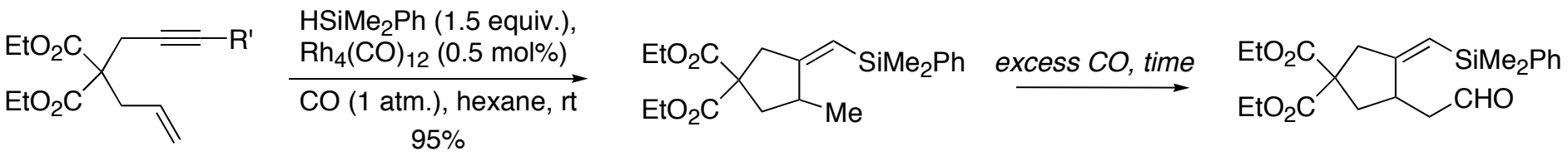
Tamao and Ito (*J. Am. Chem. Soc.* **1989**, *111*, 6478):

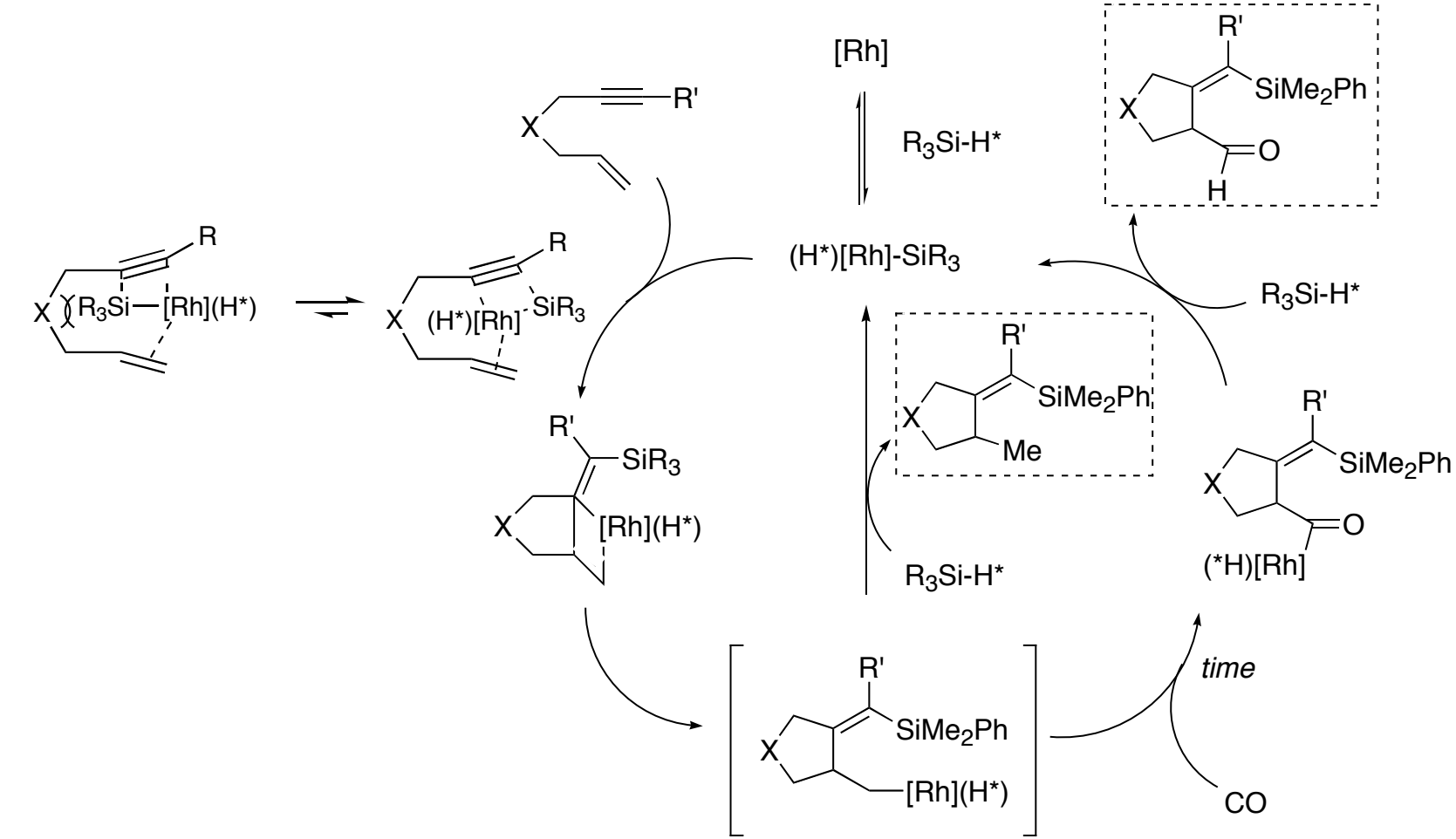


Substrate Elaborations (others)



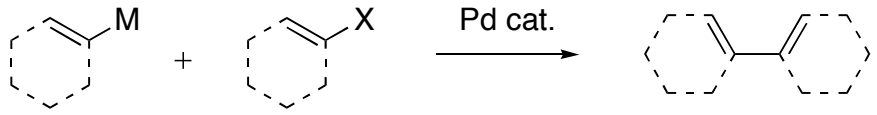
Ojima Rh-catalyzed Enyne Cyclization





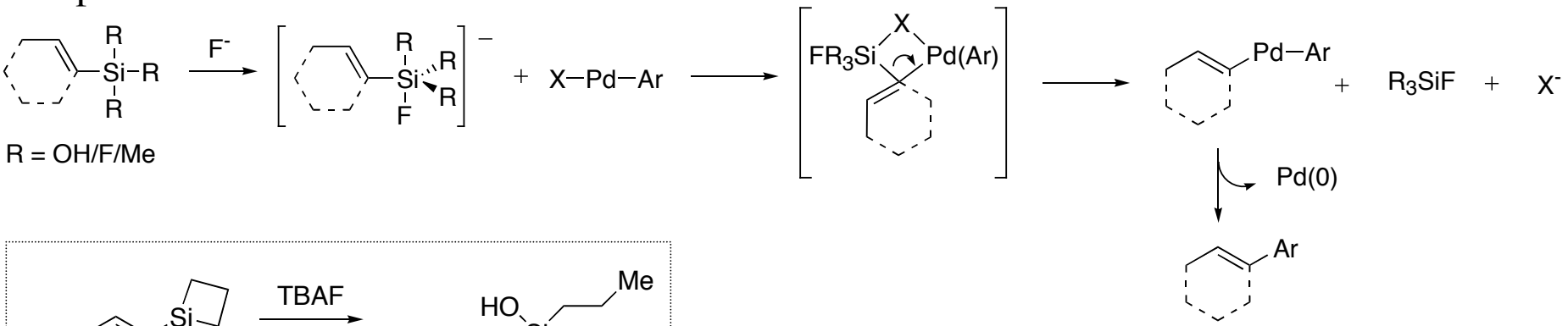
Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Maralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc*. **2002**, *124*, 9164

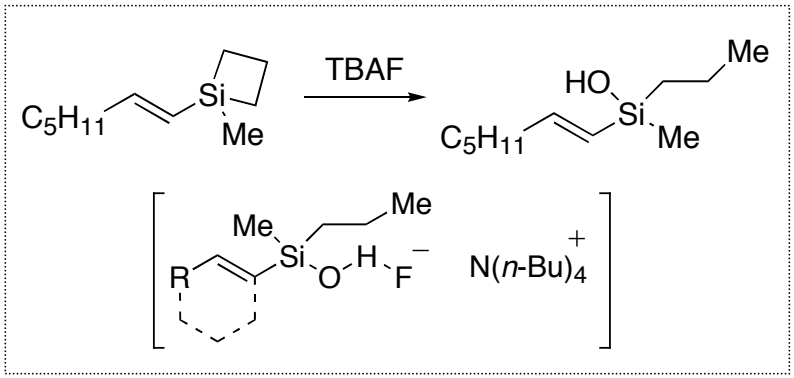
Silicon-Based Cross-Coupling Reactions

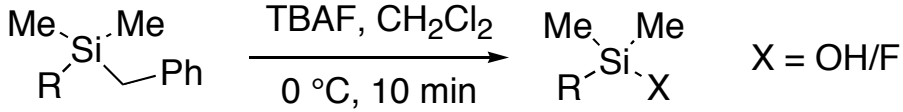


M = SnR_3 (Stille)
ZnR (Negishi)
$B(OR)_2$ (Suzuki)
MgX (Kumada)
$SiR_{(3-n)}F_n$ (Hiyama)

Proposed Mechanism:





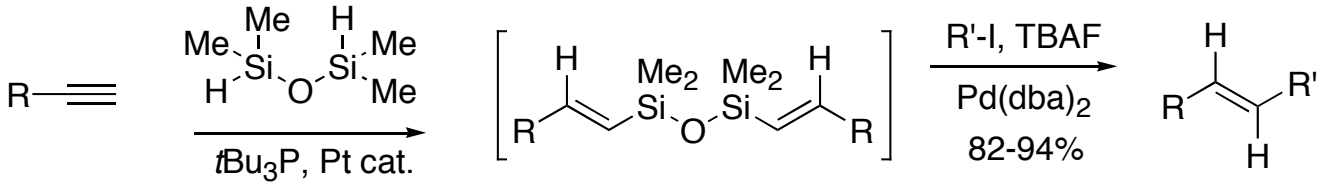


Trost, B.M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895

Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835
Denmark, S. E.; Ober, M. H. *Adrichimica Acta*, **2003**, *36*, 75
Hatanaka, Y.; Hiyama, T. *Synlett*, **1991**, 845

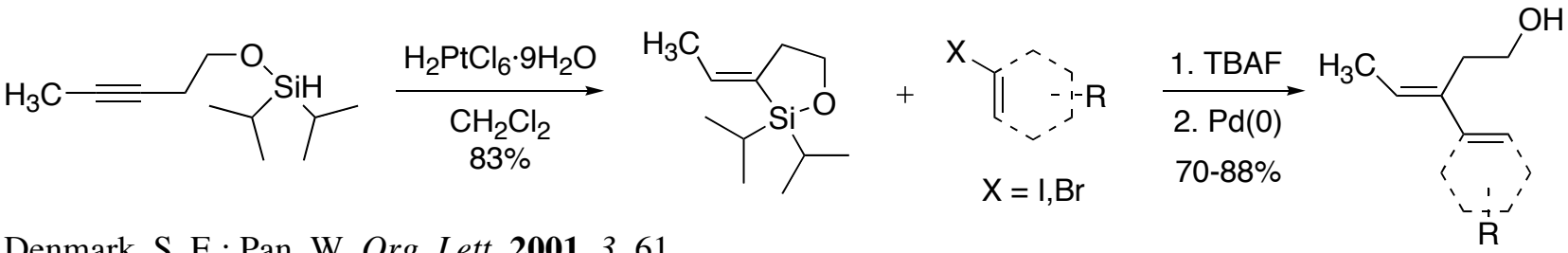
Previous Work in the Denmark Group

Hydrosilylation/ Si-Based Cross-Coupling



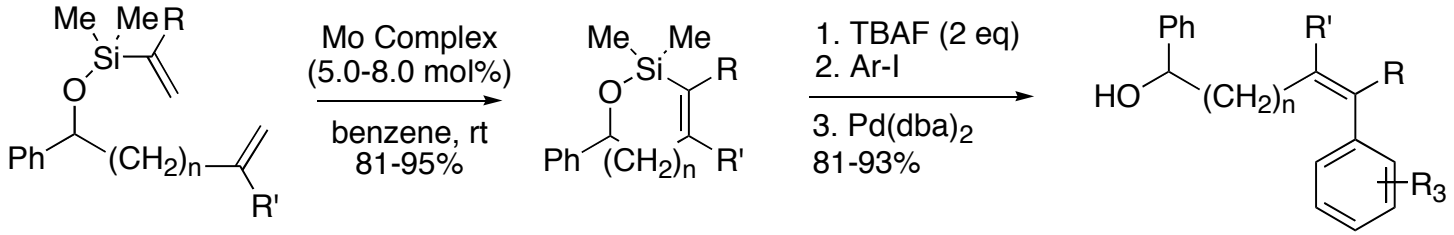
Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073

Intramolecular Hydrosilylation/ Si-Based Cross-Coupling



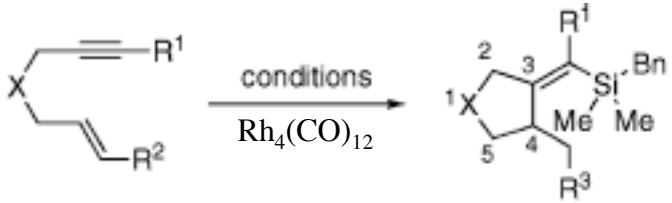
Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61

Metathesis/ Si-Based Cross-Coupling

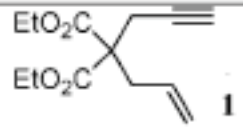
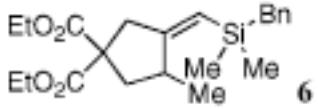
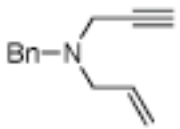
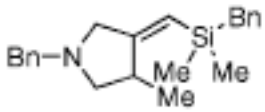
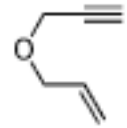
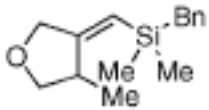
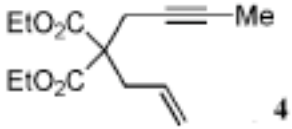
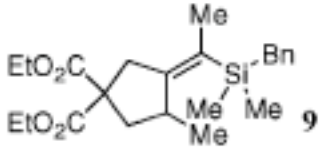
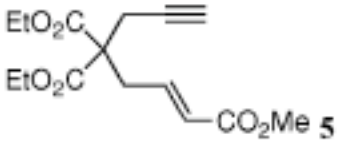
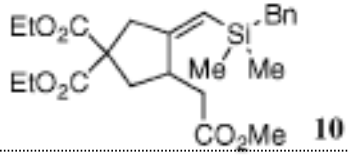
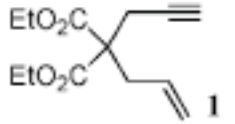
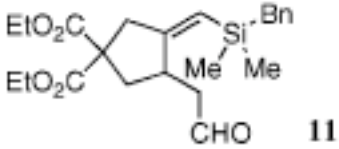


Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749

Denmark Enyne Cyclization Scope



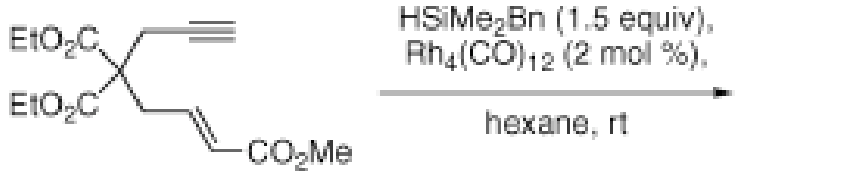
1-5 6-11

entry	substrate	silane loading, equiv	catalyst loading,[b] mol %	temperature, °C	atmosphere	time	product	yield,[c] %
1	 1	1.5	0.5	rt	CO (1 atm)	10 min	 6	84
2	 2	1.5	0.5	rt	CO (1 atm)	15 min	 7	95
3[d]	 3	1.5	5	70	CO (1 atm)	20 min	 8	53
4	 4	2.0	2	50	CO (1 atm)	15 min	 9	81
5	 5	1.5	2	rt	CO (8 mol %)/Ar	3.5 h	 10	87
6[e]	 1	1.05	1	105	CO (20 atm)	48 h	 11	83

Acid Sensitive (HCl in $CDCl_3$)

N-Boc led to decomposition

Optimization of Silylcarbocyclization



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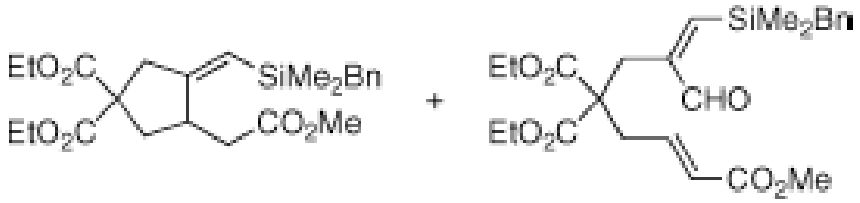
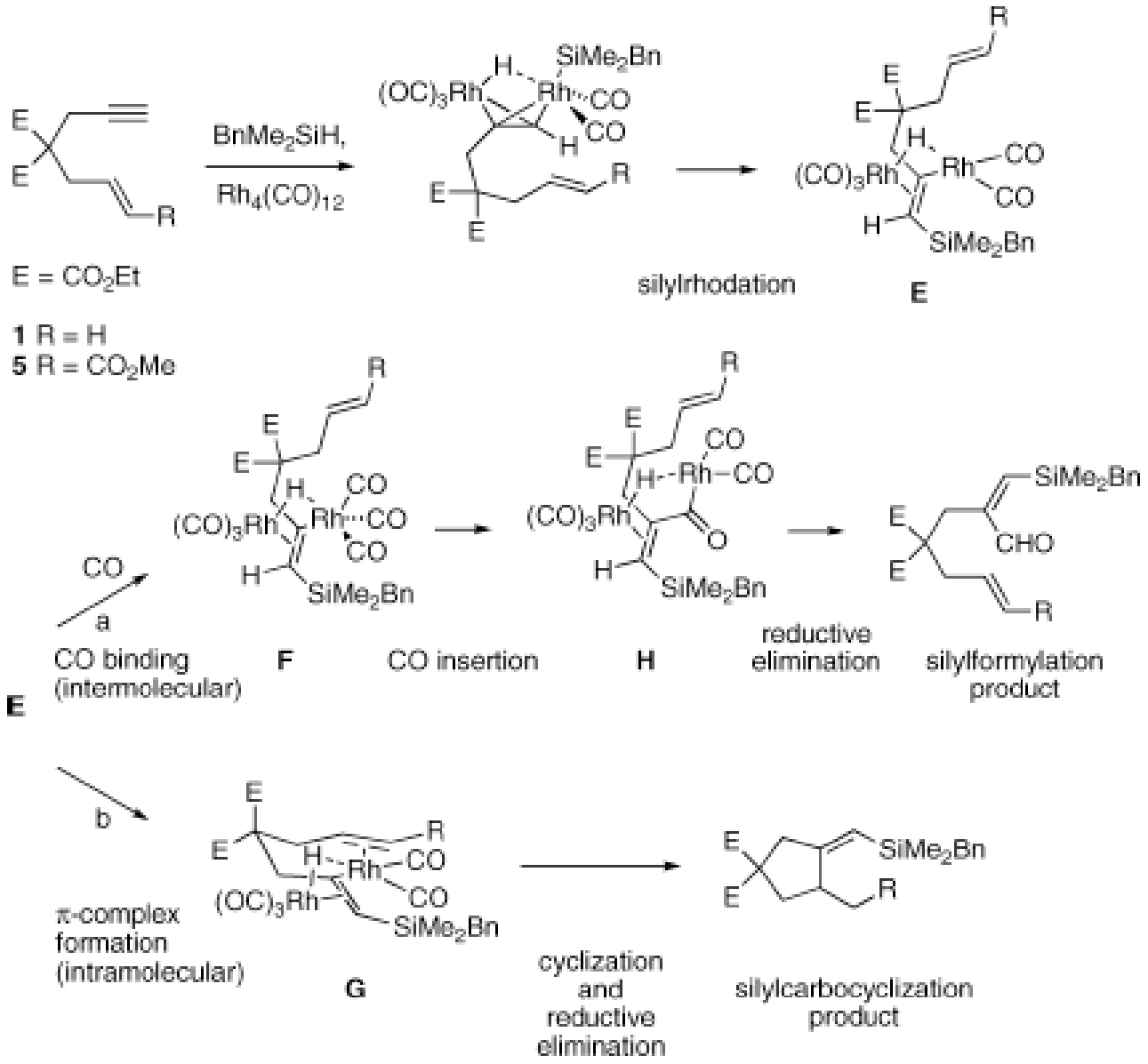


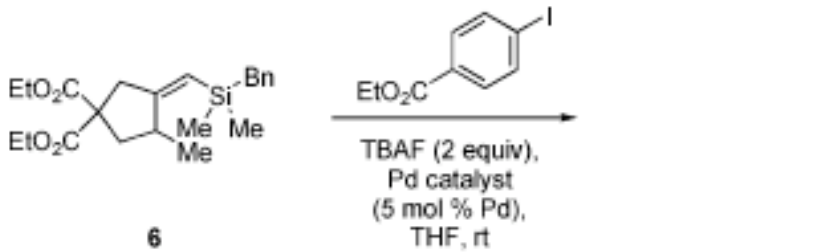
10 **15**

entry	scale, mmol	atmosphere	time, h	yield,[b] %	remark[c]
1	0.50	dynamic CO	2	nd	**10/15** ≈ 3/1
2	1.75	static Ar	12	76	
3	2.00	24 mol % CO/Ar	2.5	72	**10/15** ≈ 17/1
4	2.00	8 mol % CO/Ar	3.5	90	**10/15** ≈ 33/1
5	5.00	8 mol % CO/Ar	3.0	91	**10/15** ≈ 14/1

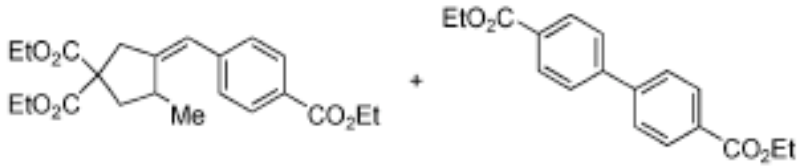
Proposed Mechanism



Cross-Coupling Catalyst Screening



6

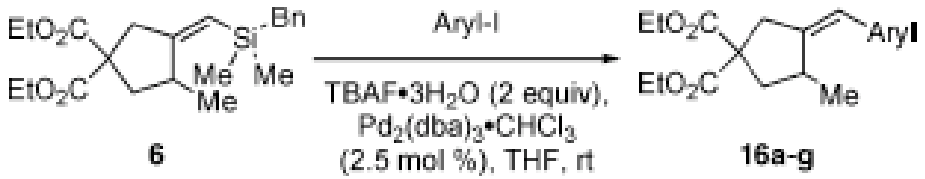


16a **17**

entry	Pd catalyst	time, h	HPLC yield,[b] % 16a	17[c]
1	$Pd(dba)_2$	2	92	1
		4	104	2
2	$Pd_2(dba)_3$	2	83	1
		4	90	2
3	$Pd_2(dba)_3 \cdot CHCl_3$	2	99	2
		4	100	2
4	$[allylPdCl]_2$	2	80	1
		4	78	3

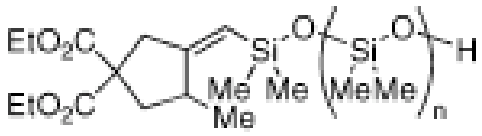
as the coupling partner.[24] Thus, 1.1 equiv of **6** was treated with 2.0 equiv of TBAF (1.0 M in tetrahydrofuran (THF)), and the resulting light-yellow solution was stirred at room temperature for 3 min before the palladium catalyst (5 mol % of Pd) and 1.0 equiv of aryl iodide were added sequentially. This reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by HPLC analysis.

Cross-Coupling Reactions (Coupling Partners)

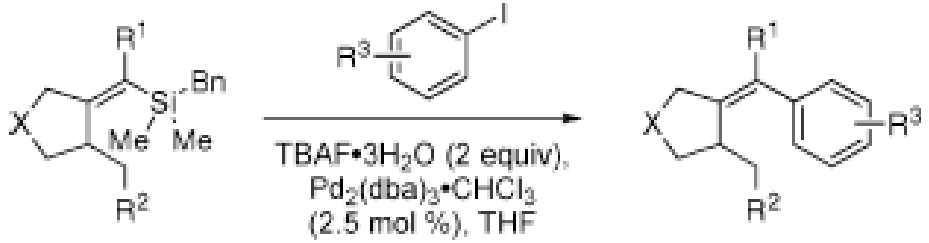


entry	Aryl-I	product	yield,[b] %
1	4-(EtO_2C)C_6H_4I	**16a**	90
2	4-(MeCO)C_6H_4I	**16b**	86
3	4-NCC_6H_4I	**16c**	76
4	4-$MeOC_6H_4I$	**16d**	82
5	2-MeC_6H_4I	**16e**	81
6	3-($MOMOCH_2$)C_6H_4I (**18**)	**16f**	85
7	1-iodonaphthalene	**16g**	93

-Silanol byproducts
(can be difficult to remove)



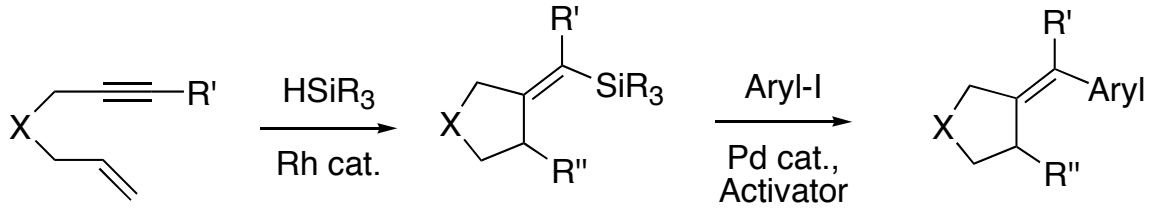
Cross-Coupling Reactions (Substrate Scope)



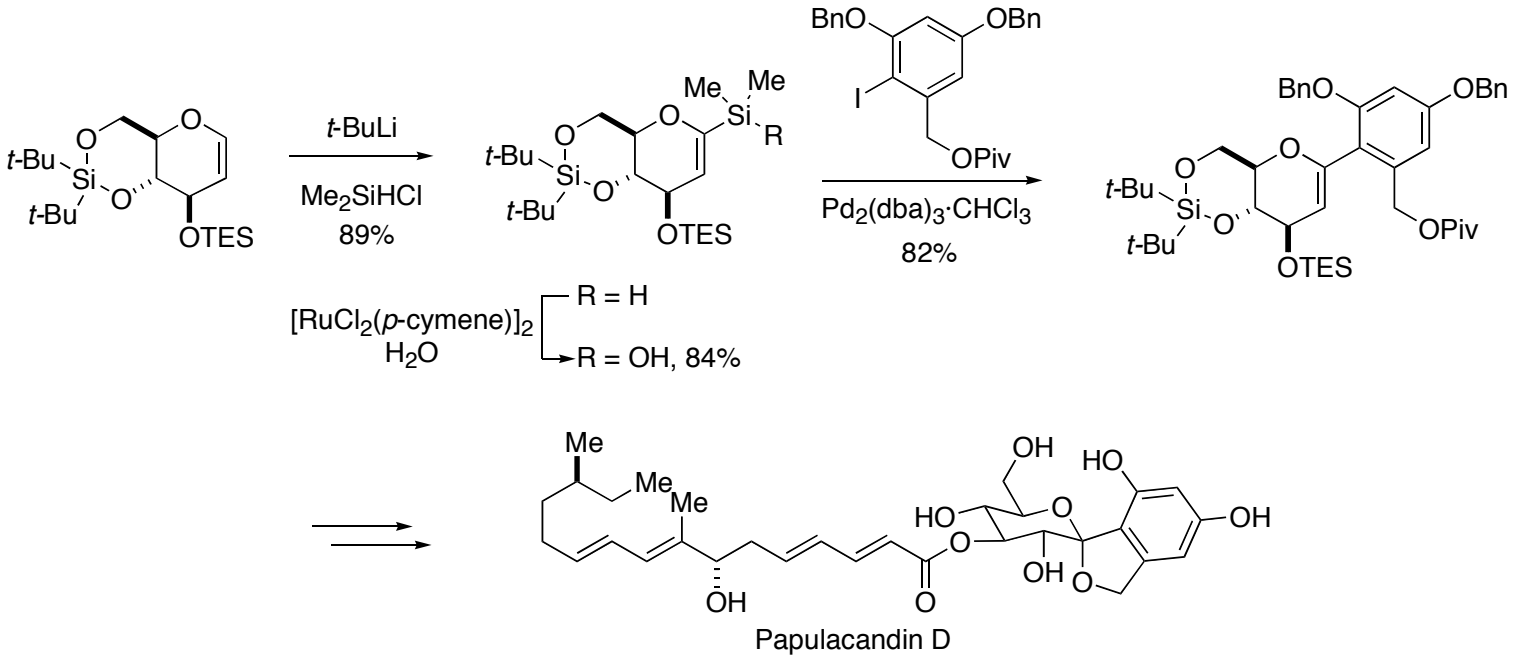
7-10 **19-22**

entry	substrate	X	R^1	R^2	R^3	temp, °C	product	yield,[b] %
1	**7**	N-Bn	H	H	4-CO_2Et	rt	**19a**	72[c]
2	**7**	N-Bn	H	H	4-OMe	rt	**19b**	90[c]
3	**7**	N-Bn	H	H	2-Me	rt	**19c**	85[c]
4	**8**	O	H	H	4-CO_2Et	rt	**20a**	88[c]
5	**8**	O	H	H	4-OMe	rt	**20b**	89[c]
6	**8**	O	H	H	2-Me	rt	**20c**	77
7	**9**	$C(CO_2Et)_2$	Me	H	4-CO_2Et	35	**21a**	72
8	**9**	$C(CO_2Et)_2$	Me	H	4-OMe	35	**21b**	74
9	**9**	$C(CO_2Et)_2$	Me	H	2-Me	35	**21c**	64
10	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-CO_2Et	rt	**22a**	74
11	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-OMe	rt	**22b**	77
12	**10**	$C(CO_2Et)_2$	H	CO_2Me	2-Me	rt	**22c**	73

Summary/ Future Work



- Sequential silylcarbocyclization and silicon-based cross-coupling has been developed
  - -Exclusive (*Z*)-olefin selectivity
  - -Substitution (X) well tolerated
  - -R' tolerated (slower coupling)
  - -Ar-I with different electronic properties/substitution patterns tolerated



Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc*. **2007**, *129*, 2774