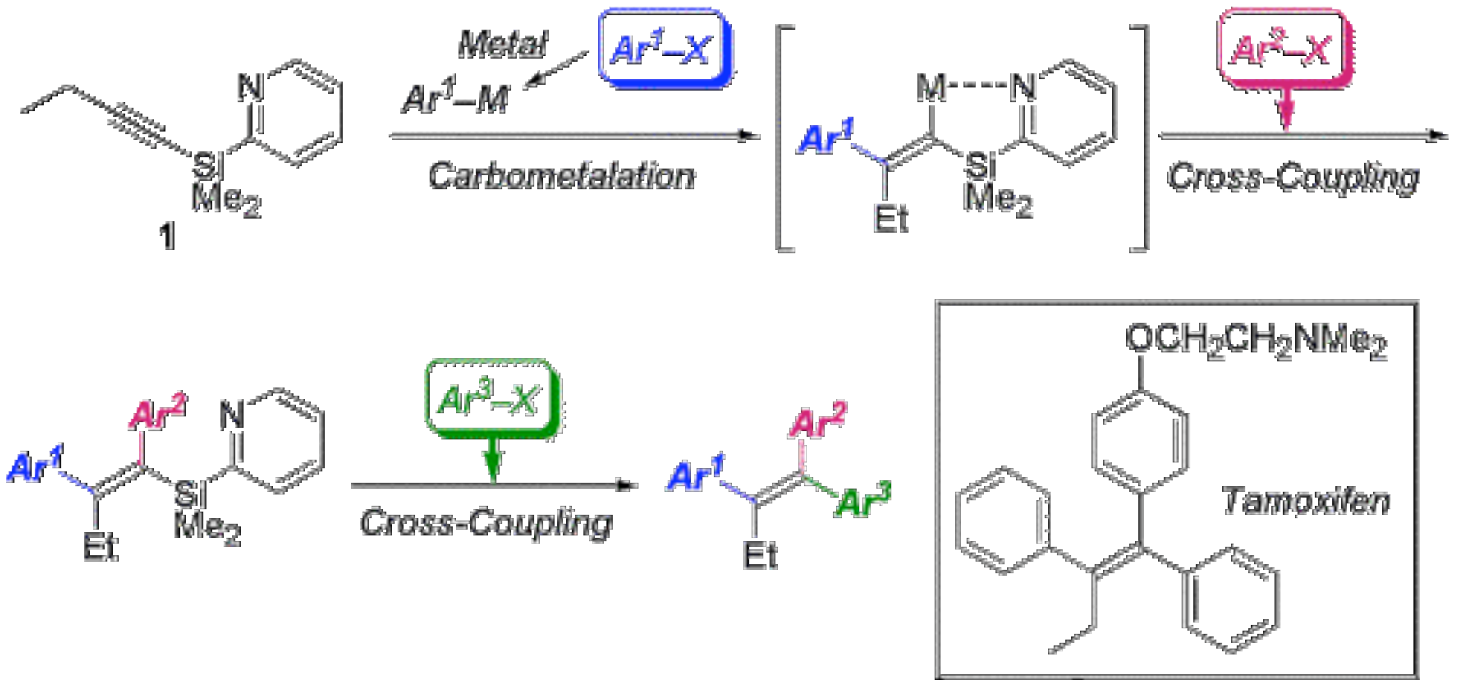
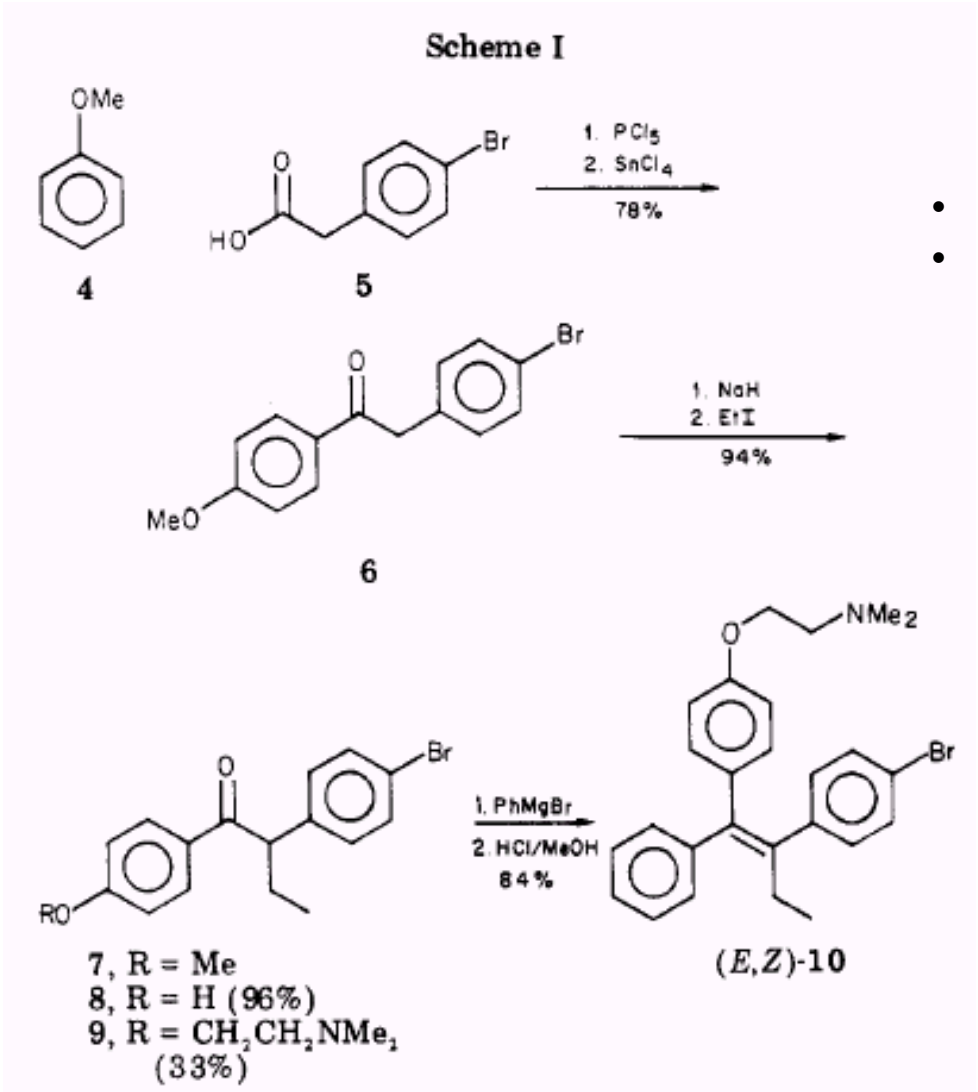
Diversity-Oriented Synthesis of Tamoxifen-type Tetras ubstituted Olefins

Kenichiro Itami,* Toshiyuki Kamei, and Jun-ichi Yoshida*

J. AM. CHEM. SOC. **2003**, *125*, 14670-14671

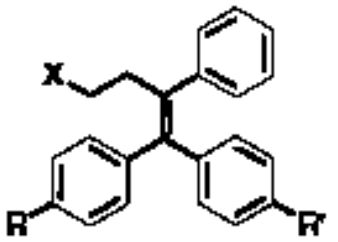


Tamoxifen is the most important anti-breast cancer drug in clinical use and has the potenti al to be used as a chemopreventive breast cancer agent.



- Friedel-Crafts acylation, dehydration
- (trans/cis ratio of 1.3:l) seperable

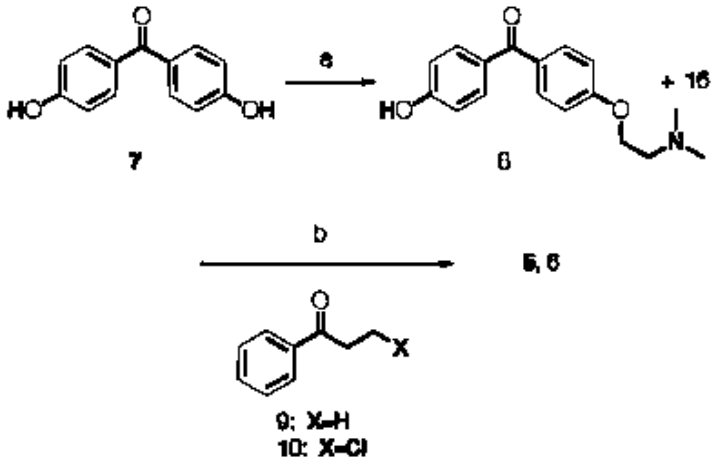
Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1982,** *47,* 2387



	R	R'	X
1	H	$O(CH_2)_2N(CH_3)_2$	H
2	H	$O(CH_2)_2N(CH_3)_2$	Cl
3	OH	$O(CH_2)_2N(CH_3)_2$	H
4	OH	$O(CH_2)_2N(CH_3)_2$	Cl
5	$O(CH_2)_2N(CH_3)_2$	OH	H
6	$O(CH_2)_2N(CH_3)_2$	OH	Cl

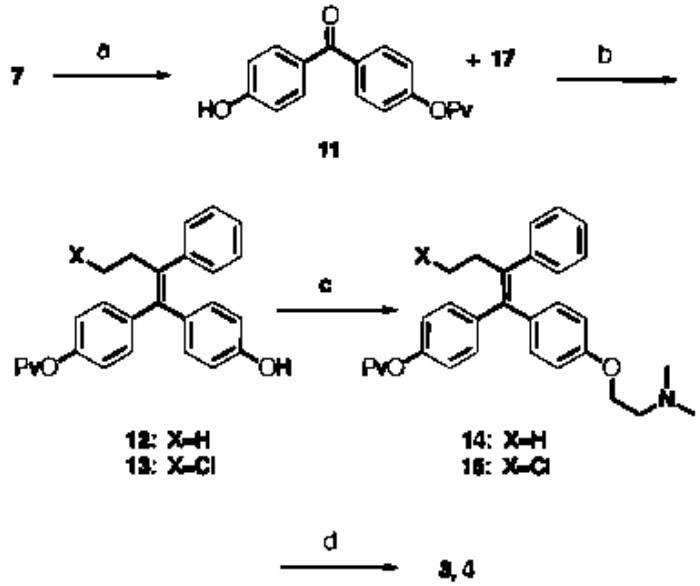
- Gauthier, S; Mailhot, J.; Labrie, F.*J. Or g. Chem.* **1996,** *61,* 3890-3893
- Hydroxyl derivatives.
- McMurry coupling.
- $TiCl_4$/Zn/**9** = 4:8:3
- 87% yield, **3:5** (*Z:E* = 1:5.7)**.**
- **9** or **10** gave *E* isomer as the major pr oduct.
- **12** (*E/Z* = 14:1), and **13** (*E/Z* = 22:1)
- In vivo,tamoxifen is transformed to hyd roxytamoxifen, which has a much high er binding affinity for the estrogen rece ptor and appears to be the compound responsible, in part, for the biological a ctions of tamoxifen.

Scheme 1[a]



[a]Reagents and conditions: (a) $Cl(CH_2)_2N(CH_3)_2 \cdot HCl$ Cs_2CO_3, DMF, 80 °C, 18 h; (b) 9 or 10, $TiCl_4$, Zn, THF, reflux, 5 h.

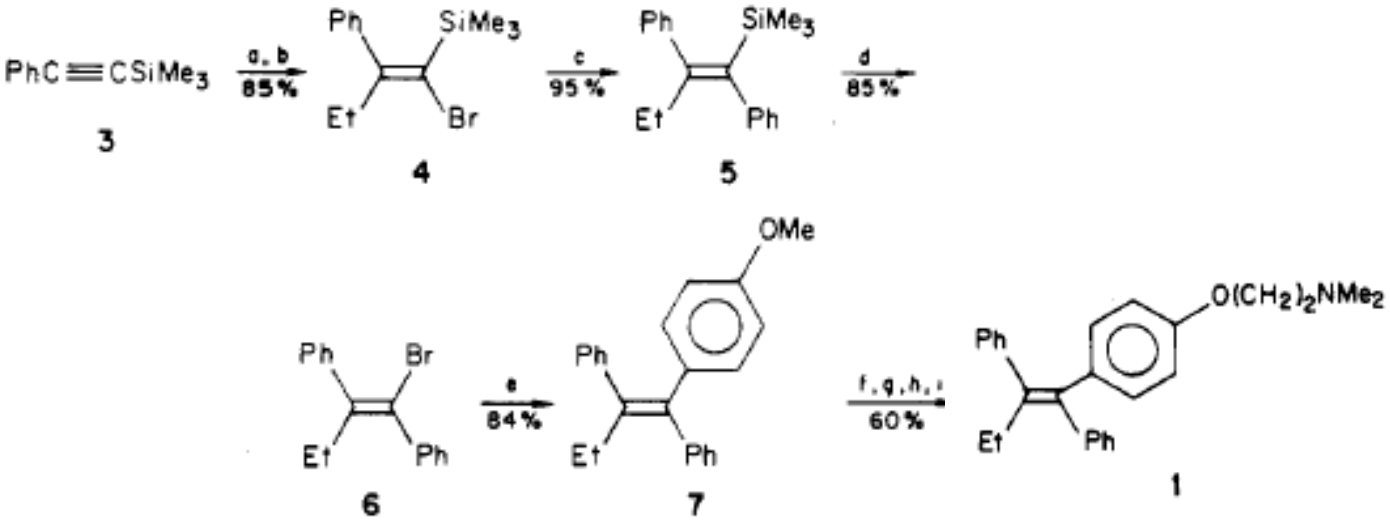
Scheme 2[a]



[a]Reagents and conditions: (a) PvCl, NaH, THF, 0 °C to rt, 2 h; (b) 9 or 10, $TiCl_4$, Zn, THF, reflux, 5 h; (c) $Cl(CH_2)_2N(CH_3)_2$, K_2CO_3, acetone, H_2O, reflux, 5 h; (d) MeLi, THF, -78 °C, 2 h.

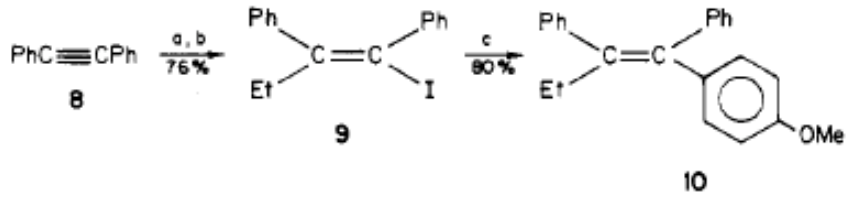
metal-mediated synthetic methods for tamoxifen.

Scheme I[a]



[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) NBS, −78 °C; (c) PhZnCl, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (d) Br_2, CH_2Cl_2, NaOMe/MeOH, −78 °C → room temperature; (e) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (f) NaSEt, DMF, reflux; (g) $ClCH_2CH_2NMe_2 \cdot HCl$, NaOEt, EtOH, reflux; (h) HCl(g), Et_2O; (i) 0.5 N NaOH.

Scheme II[a]

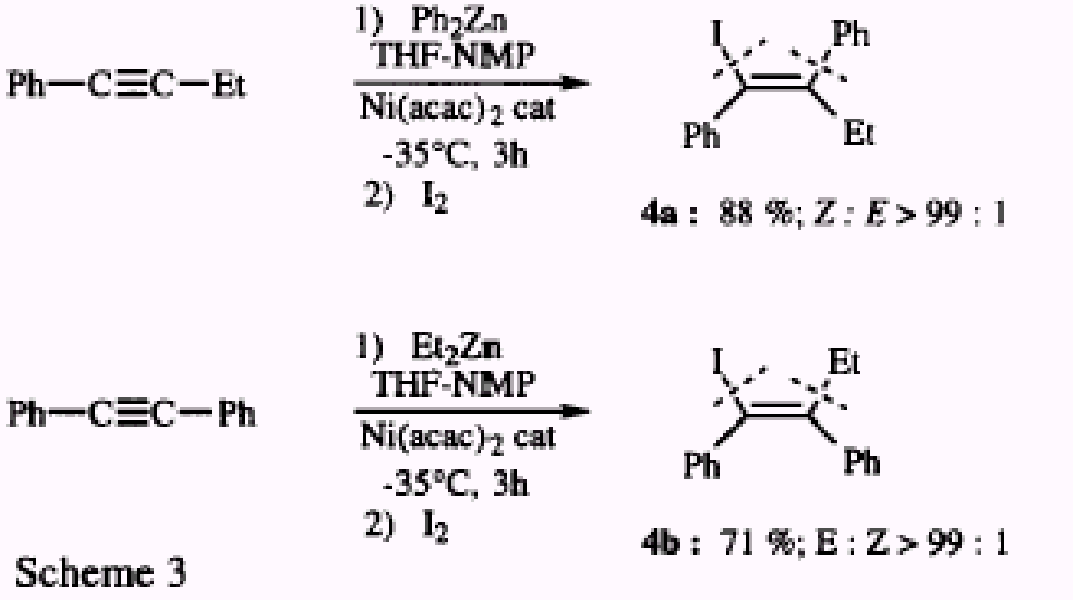


[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) I_2, −78 °C; (c) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux.

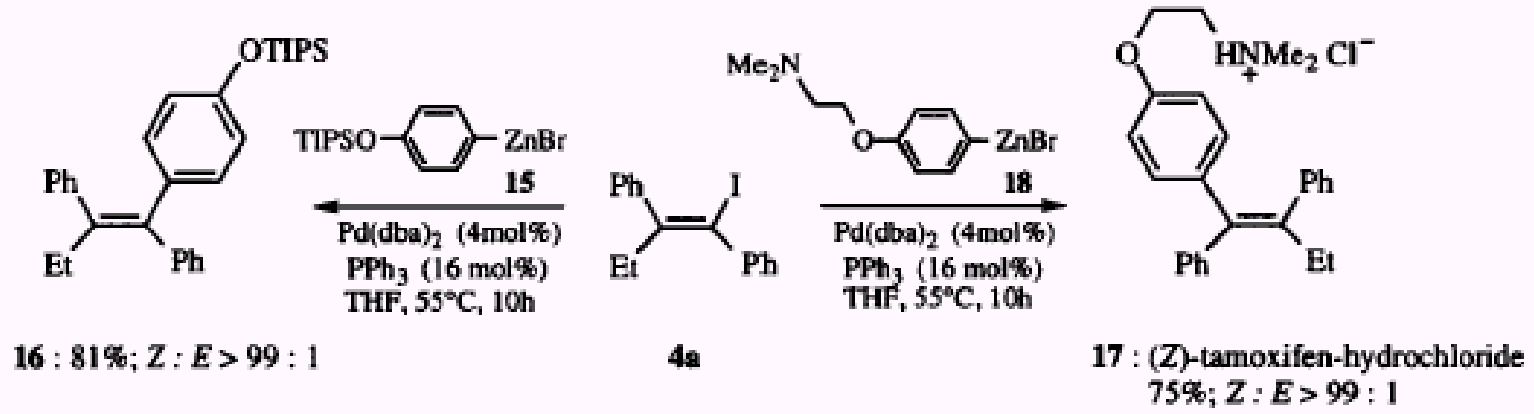
- carbometalated with diethylaluminum chloride-titanocene dichloride to give an organometallic intermediate

Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121-2123

A Nickel-Catalyzed Carbozincation of Aryl-Substituted Alkynes



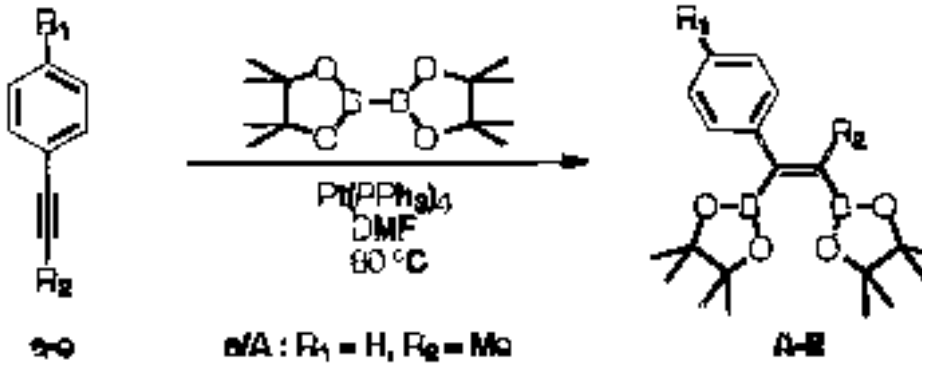
Scheme 3



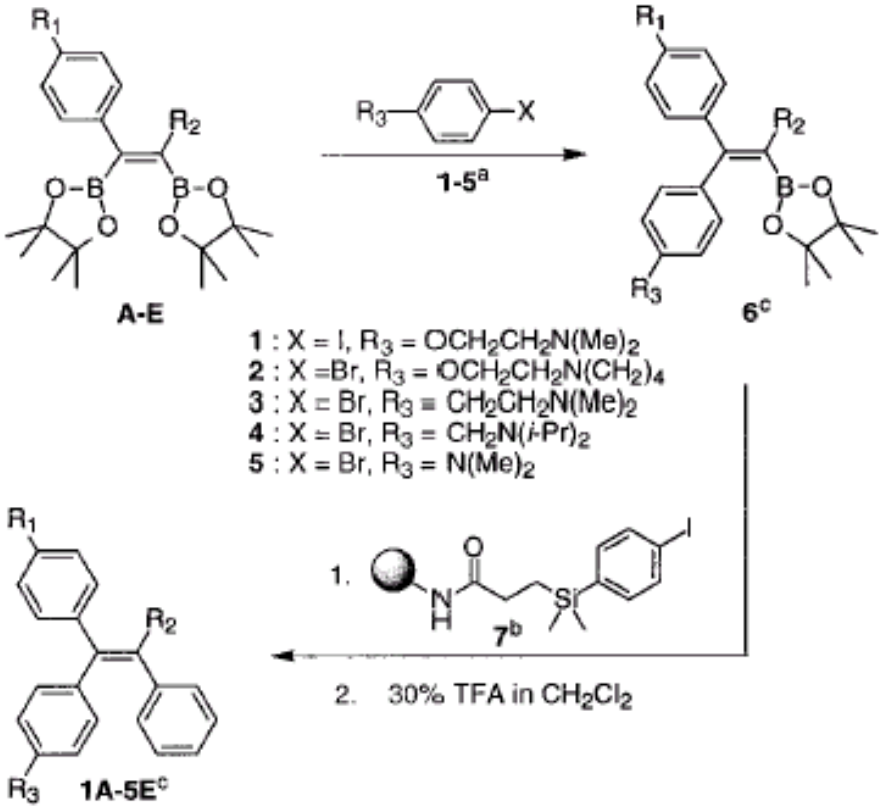
Scheme 9

Stiidemann, T.; Ibrahim-Ouali. M; Knochel, P. *Tetrahedron*,**1998**, *54*, 1299-1316

Scheme 1



Scheme 2

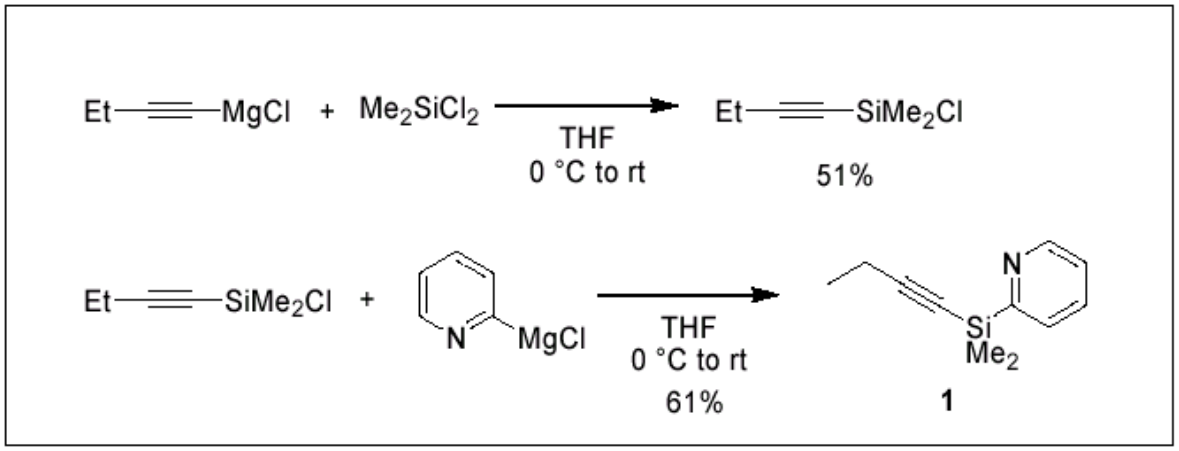


[a] Bis(boryl)alkene (10 equiv), aryl halide (15 equiv), $Pd(dppf)Cl_2$ (0.5 equiv), 3,5-dimethoxyphenol (50 equiv), 6 M KOH (50 equiv), DME, 25 °C, 18 h. [b] **7** (1 equiv), 6 M KOH (100 equiv), 25 °C, 18 h. [c] For simplicity, only one of two possible regioisomers is shown.

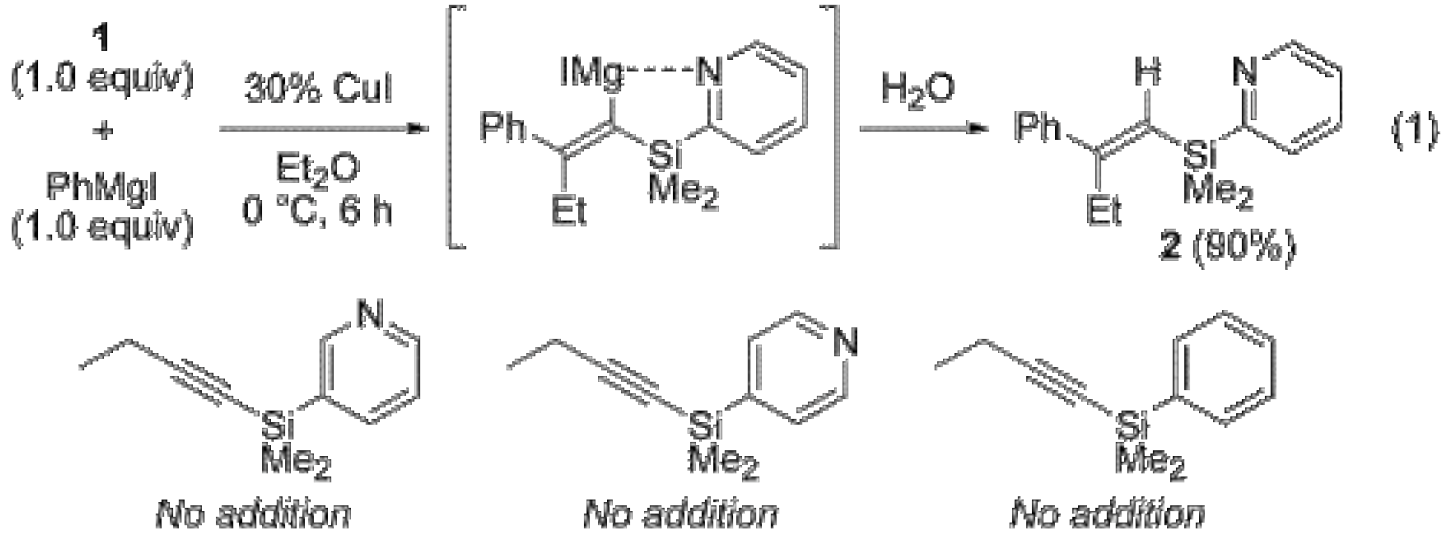
1. Parallel Synthesis of Tamoxifen and Derivatives on S olid Support via Resin Capture
2. 5*5 library. 13-68 %. 1:0 to 1: 1 ratio.
3. 90 % piurity.

Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997,** *62,* 7076-7077

1-Butynyldimethyl(2-pyridyl)silane (1).

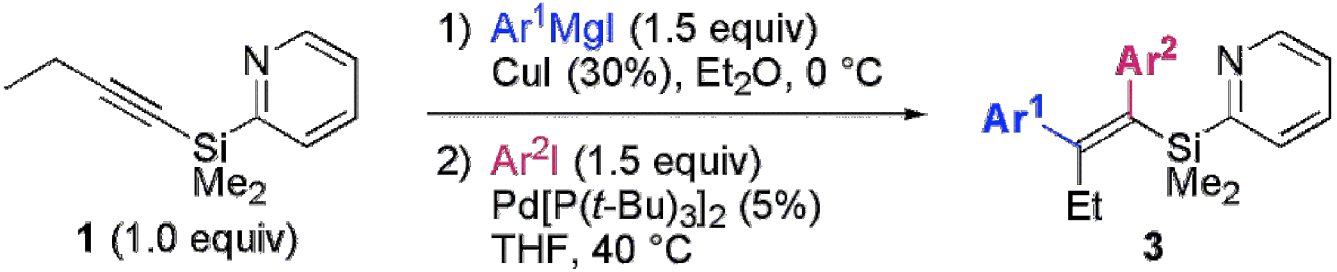


- directing effect of 2-pyridyl group



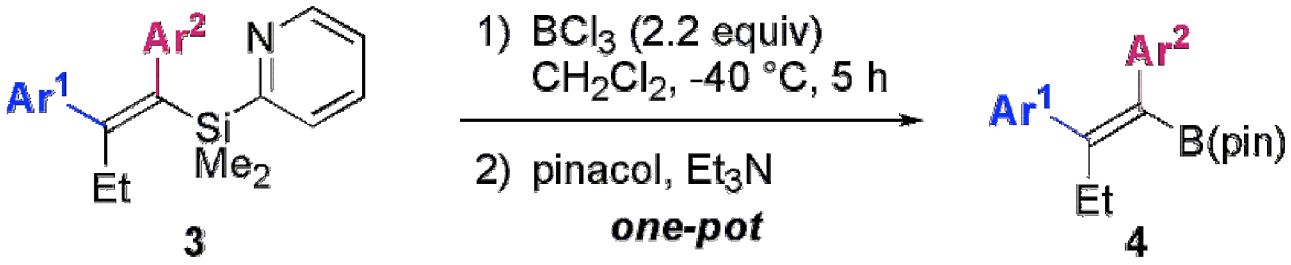
J. AM. CHEM. SOC. **2003**, *125*, 14670-14671

table1. catalytic one-pot diarylation through the catalytic carbomagnesation/cross-coupling sequence. .



run	Ar^1	Ar^2	3	yield (*E*/*Z*)
1	C_6H_5 (**a**)	C_6H_5 (**a**)	**3aa**	80% (92/8)
2	C_6H_5 (**a**)	4-$MeOC_6H_4$ (**b**)	**3ab**	60% (92/8)
3	C_6H_5 (**a**)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**3ac**	55% (88/12)
4	C_6H_5 (**a**)	4-$CF_3C_6H_4$ (**d**)	**3ad**	75% (95/5)
5	C_6H_5 (**a**)	4-$EtOCOC_6H_4$ (**e**)	**3ae**	58% (94/6)
6	C_6H_5 (**a**)	4-ClC_6H_4 (**f**)	**3af**	69% (94/6)
7	3-ClC_6H_4 (**g**)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**3gc**	55% (92/8)
8	3-ClC_6H_4 (**g**)	4-MeC_6H_4 (**h**)	**3gh**	79% (92/8)

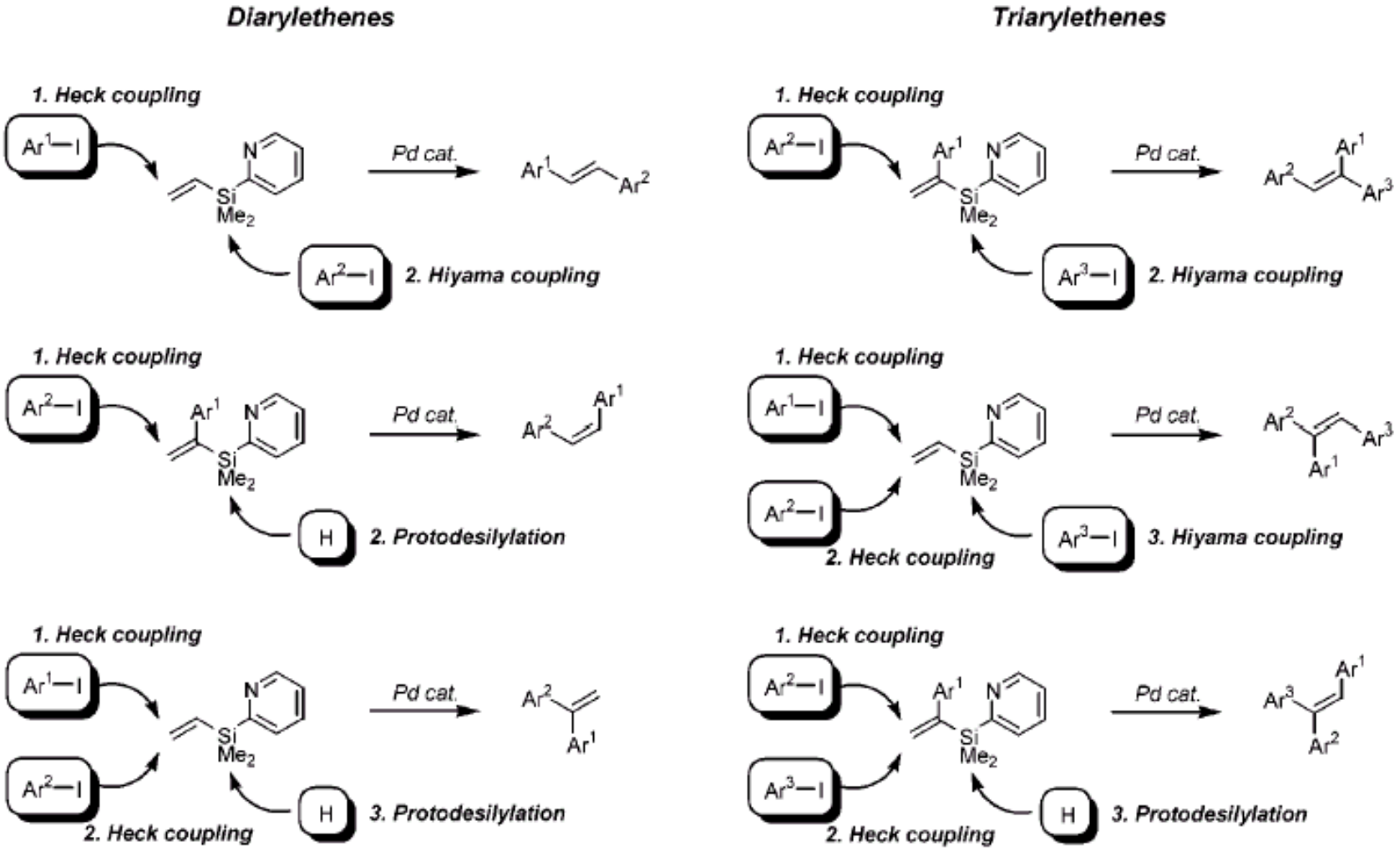
- The two aryl groups (Ar 1 and Ar 2) are introduced in a cis fashion, which is in accordan ce with syn carbometalation and retention of stereochemistry during the sub-sequent cro ss-coupling.

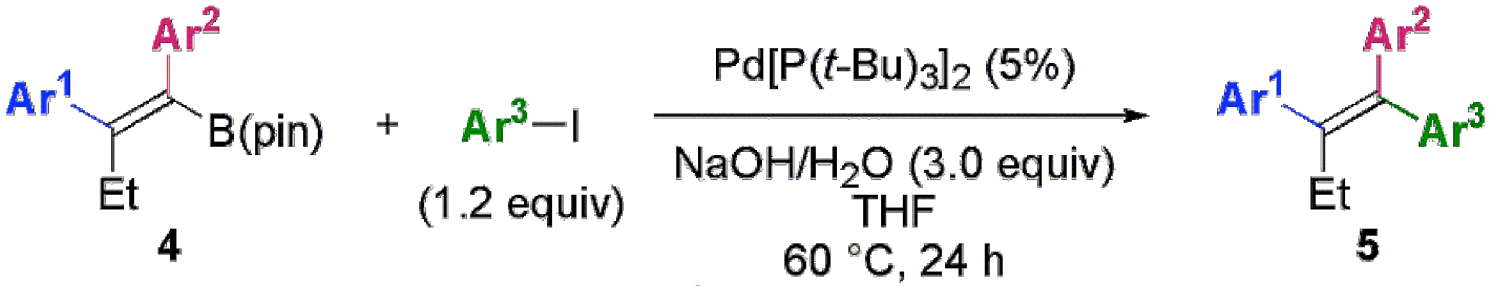


run	3 (*E*/*Z*)	4	yield (*Z*/*E*)
1	**3aa** (94/6)	**4aa**	82% (98/2)
2[a]	**3ac** (88/12)	**4ac**	65% (94/6)
3	**3ad** (95/5)	**4ad**	80% (99/1)
4	**3ae** (94/6)	**4ae**	64% (>99/1)
5[a]	**3gc** (92/8)	**4gc**	77% (95/5)
6	**3gh** (92/8)	**4gh**	73% (97/3)

- the cross-coupling of **3** at the C-Si bond (Hiyama cross-coupling) was no s uccess. (steric)
- Borodesilylation.

Scheme 5


Diarylethenes
Triarylethenes
1. Heck coupling
Pd cat.
2. Hiyama coupling
2. Protodesilylation
3. Protodesilylation
3. Hiyama coupling
2. Heck coupling



run	4 (*Z*/*E*)	Ar^3	5	yield (*E*/*Z*)
1	**4aa** (97/3)	4-$Me_2N(CH_2)_2OC_6H_4$ (**c**)	**5aac**	95% (99/1)
2	**4aa** (97/3)	4-MeC_6H_4 (**h**)	**5aah**	96% (99/1)
3	**4ac** (94/6)	C_6H_5 (**a**)	**5aca**	98% (5/95)
4	**4ac** (94/6)	4-$MeOC_6H_4$ (**b**)	**5acb**	95% (5/95)
5	**4ac** (94/6)	3-$MeOC_6H_4$ (**i**)	**5aci**	92% (95/5)
6	**4ad** (99/1)	4-$MeOC_6H_4$ (**b**)	**5adb**	97% (> 99/1)
7	**4ad** (99/1)	4-ClC_6H_4 (**f**)	**5adf**	90% (> 99/1)
8	**4ad** (99/1)	2-$MeOC_6H_4$ (**j**)	**5adj**	95% (> 99/1)
9	**4ad** (99/1)	3-pyridyl (**k**)	**5adk**	67% (> 99/1)
10	**4gc** (95/5)	4-$MeOC_6H_4$ (**b**)	**5gcb**	80% (4/96)
11	**4gc** (95/5)	3-MeC_6H_4 (**l**)	**5gcl**	82% (98/2)
12	**4gc** (97/3)	3-thienyl (**m**)	**5gcm**	87% (99/1)
13	**4gh** (97/3)	2-MeC_6H_4 (**n**)	**5ghn**	93% (> 99/1)
14	**4gh** (99/1)	3,5-$F_2C_6H_3$ (**o**)	**5gho**	98% (> 99/1)
15	**4gh** (99/1)	1-naphthyl (**p**)	**5ghp**	99% (> 99/1)

a wide array of electronically and structurally diverse tetrasubstituted olefins in a regiocontrolled, stereocontrolled, and diversity-oriented manner.

scheme should be easily expanded to the construction of a more general tetrasubstituted olefin structure.

- Suzuki-Miyaura Coupling