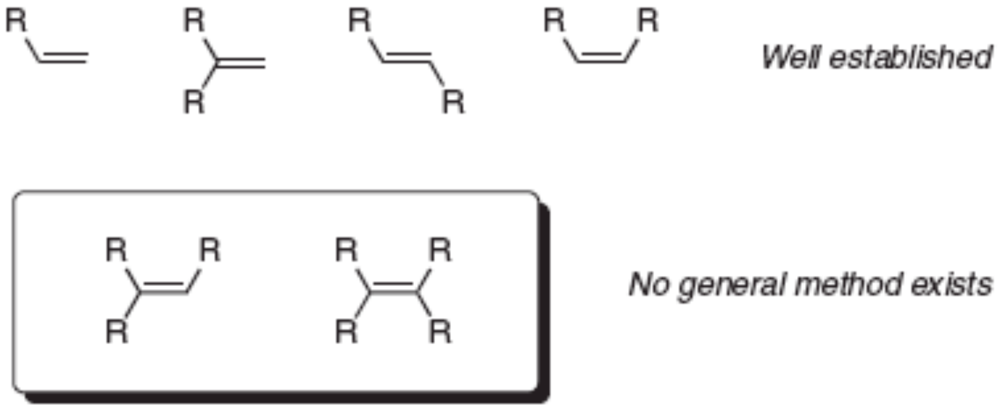
Stereo- and Regioselective Synthesis of Multisubstituted Alkenes

Alexander Predeus

October 12, 2007

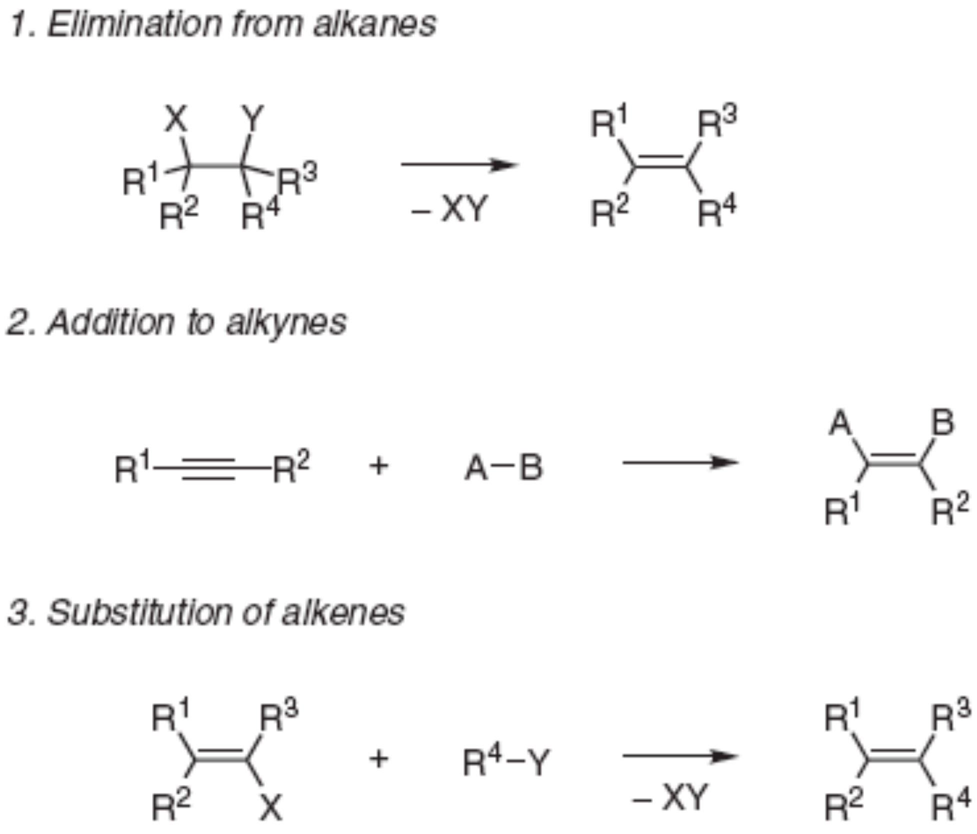
MSU

Accessible Alkenes



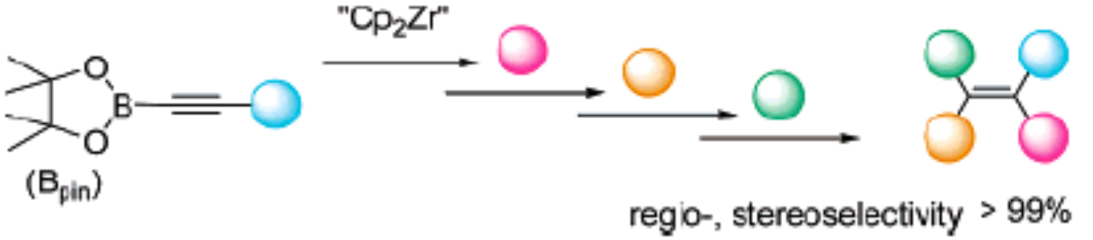
Bull. Chem. Soc. Jpn., 2006, 811, K.Itami, J. Yoshida

Types of Reactions Used in the Synthesis

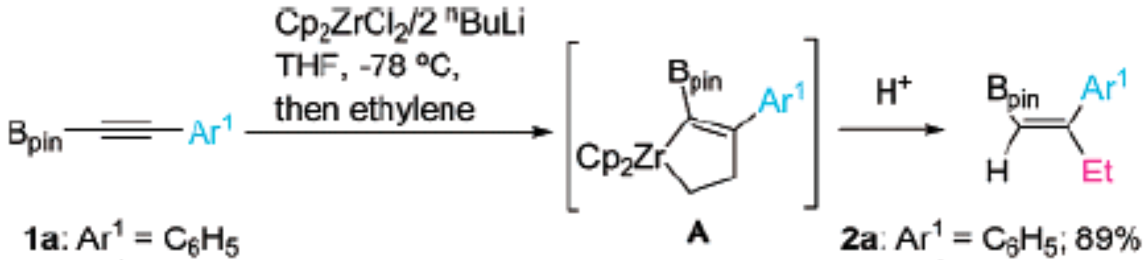


Bull. Chem. Soc. Jpn., 2006, 811, K.Itami, J. Yoshida

Zirconocene-Mediated Synthesis from 1-Alkynylboronates



(1)



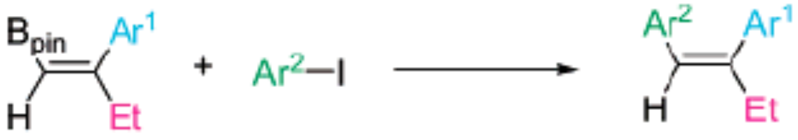
(2)

1a: Ar^1 = C_6H_5
1b: Ar^1 = 4-MeO-C_6H_4
1c: Ar^1 = 4-CF_3-C_6H_4

2a: Ar^1 = C_6H_5; 89%
2b: Ar^1 = 4-MeO-C_6H_4; 72%
2c: Ar^1 = 4-CF_3-C_6H_4; 69%

JACS 2007, ASAP, Y. Nishihara *et. al.*

Table 1. Synthesis of Trisubstituted Ethenes **3** via Stereocontrolled Suzuki–Miyaura Cross-Coupling Reactions of Alkenylboronates **2** with Aryl Iodides[a]



2a-2c **3a-3q**

run	2	Ar^1	Ar^2	3	% yield[b]
1	**2a**	C_6H_5	4-MeO-C_6H_4	**3a**	81
2			4-CF_3-C_6H_4	**3b**	83
3			2-Me-C_6H_4	**3c**	83
4			4-NH_2-C_6H_4	**3d**	80
5			4-F-C_6H_4	**3e**	55
6			4-EtOCO-C_6H_4	**3f**	82
7			2-pyridyl	**3g**	79
8			4-NC-C_6H_4	**3h**	86
9			4-NO_2-C_6H_4	**3i**	92
10			2-HO-C_6H_4	**3j**	58
11			4-MeCO-C_6H_4	**3k**	56
12			1-naphthyl	**3l**	94
13			2-thienyl	**3m**	85
14	**2b**	4-MeO-C_6H_4	C_6H_5	**3n**	85
15			4-CF_3-C_6H_4	**3o**	72
16	**2c**	4-CF_3-C_6H_4	C_6H_5	**3p**	85
17			4-MeO-C_6H_4	**3q**	75

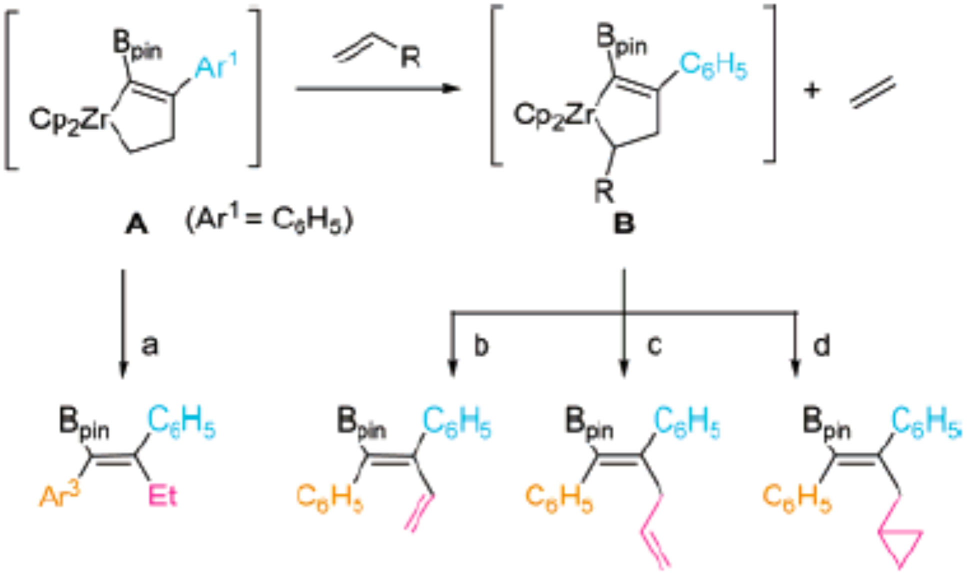
[a] The reactions were carried out at room temperature for 12 h by using **2** (2 mmol), aryl iodides (2.2 mmol), KOH (6.0 mmol), Pd(dba)$_2$ (10 mol %), and P(*t*-Bu)$_3$ (20 mol %) in THF (20 mL). [b] Isolated yield.

JACS 2007

ASAP

Y. Nishihara *et. al.*

Zirconocene-Mediated Synthesis from 1-Alkynylboronates



5a: $Ar^3 = C_6H_5$; 47%
5b: Ar^3 = 4-MeO-C_6H_4; 62%
5c: Ar^3 = 4-CF_3-C_6H_4; 40%

6; 26%

7; 43%

8; 54%

[a] Reagents and conditions: (a) ^{i}PrOH (0.8 equiv), CuCl (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), the corresponding aryl iodide (1.0 equiv), THF, room temp, 1 h; (b) ethyl vinyl ether (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h; (c) allyloxytrimethylsilane (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h; (d) homoallyl bromide (1.5 equiv), 50 °C, 20 h, then CuCl (1.0 equiv), DMPU (1.5 equiv), $Pd(PPh_3)_4$(10 mol %), iodobenzene (1.1 equiv), THF, 50 °C, 3 h.

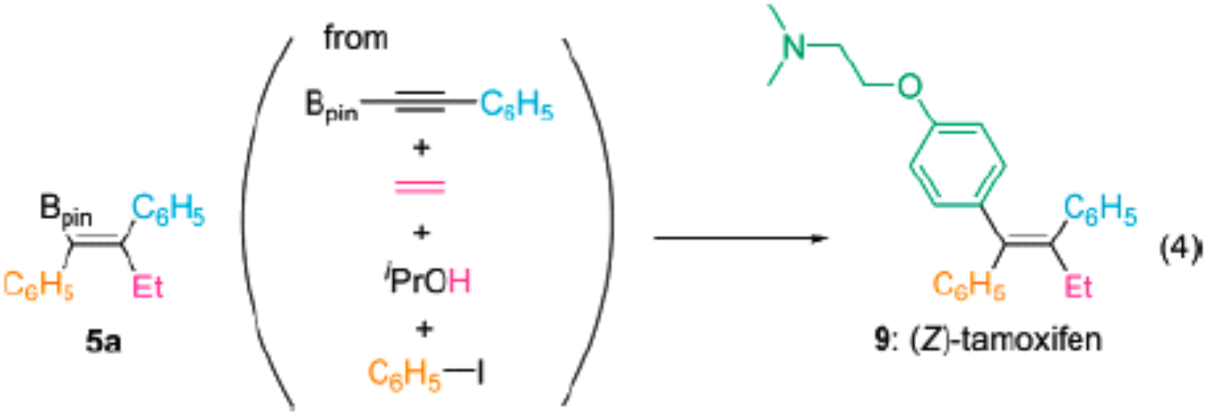
JACS 2007

ASAP

Y. Nishihara *et. al.*

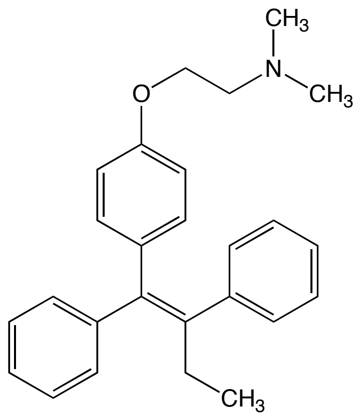
Why these olefins?

- Attractive chemistry, allowing for unusual ideas and creativity
- Generally useful multisubstituted alkenes
- A ~$1.000.000.000 drug (tamoxifen) might have something to do with it



JACS 2007, ASAP, Y. Nishihara *et. al.*

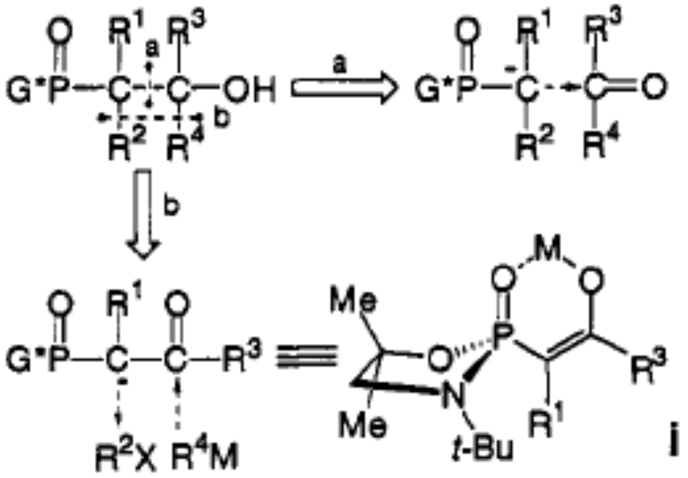
Tamoxifen Facts



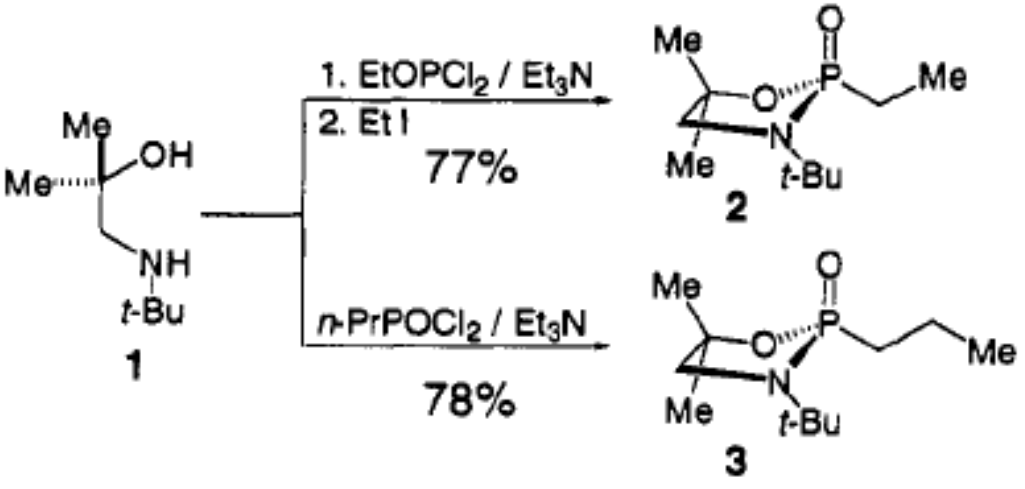
- Tamoxifen is currently used for the treatment of both early and advanced ER+ breast cancer in pre- and post-menopausal women
- Tamoxifen is used to treat infertility in women with anovulatory disorders.
- In men, tamoxifen is sometimes used to treat gynecomastia which arises for example as a side effect of antiandrogen prostate cancer treatment. Tamoxifen is also used by bodybuilders to prevent or reduce drug-induced gynecomastia caused by the estrogenic metabolites of anabolic steroids
- There are some serious side effects (including increased risk of endometrial cancer) and other endometrial changes, “fatty liver”, reduction of libido; There also are some safer (less general) alternatives. The drug is still very popular.
- Patent protection in most of the world ran from around 1965. In 1985, around the time this protection was being lost, the unclear position in the US was resolved, awarding Zeneca, as ICI Pharmaceuticals had now become, 17 years of protection there.

Phosphorus Heterocycles-Mediated Way to Trisubstituted Alkenes

Scheme I



Scheme II



JACS 1993,

10386

S.E.Denmark *et. al.*

Phosphorus Heterocycles-Mediated Way to Trisubstituted Alkenes

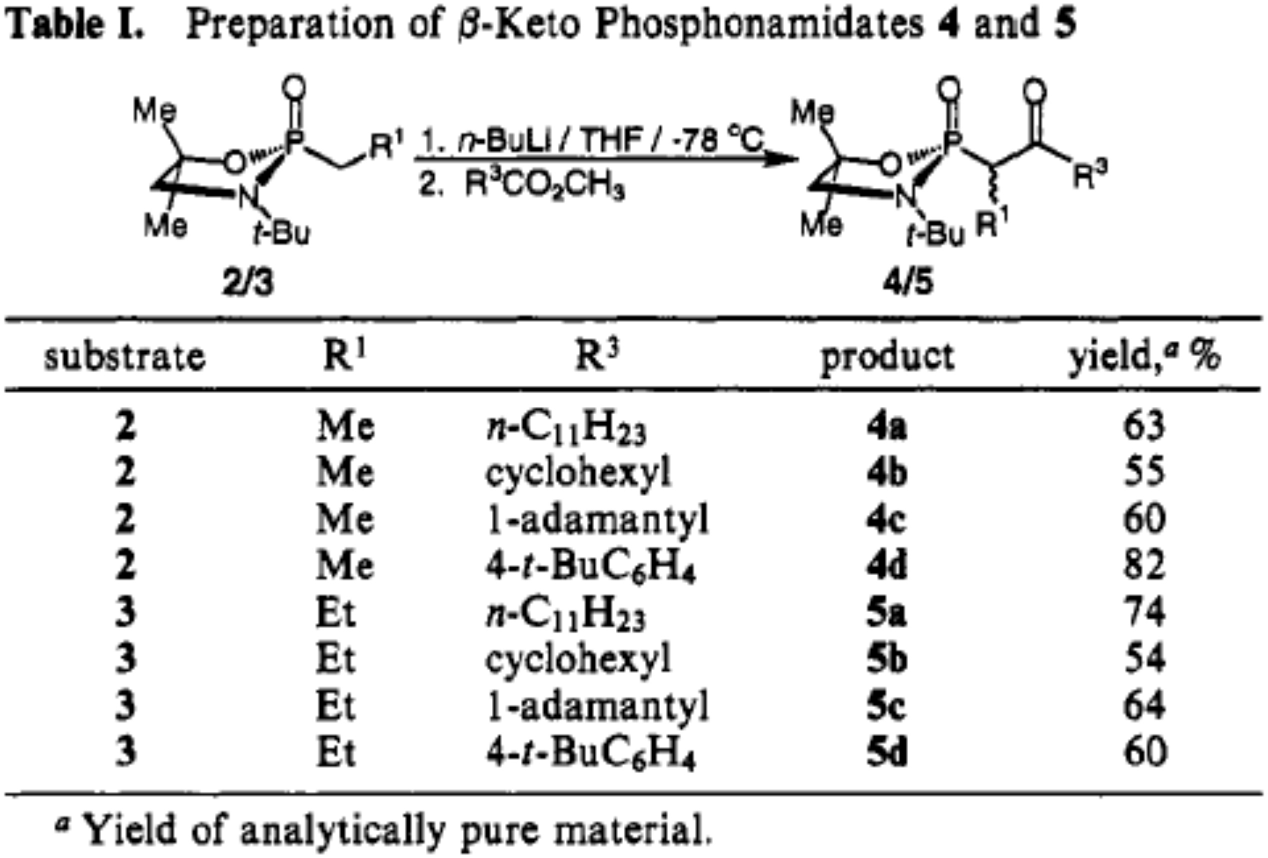


Table I. Preparation of β-Keto Phosphonamidates **4** and **5**

2/3 **4/5**

substrate	R^1	R^3	product	yield,[a] %
2	Me	n-$C_{11}H_{23}$	**4a**	63
2	Me	cyclohexyl	**4b**	55
2	Me	1-adamantyl	**4c**	60
2	Me	4-t-BuC_6H_4	**4d**	82
3	Et	n-$C_{11}H_{23}$	**5a**	74
3	Et	cyclohexyl	**5b**	54
3	Et	1-adamantyl	**5c**	64
3	Et	4-t-BuC_6H_4	**5d**	60

[a] Yield of analytically pure material.

JACS 1993,10386, S.E.Denmark *et. al.*

Phosphorus Heterocycles-Mediated Way to Trisubstituted Alkenes

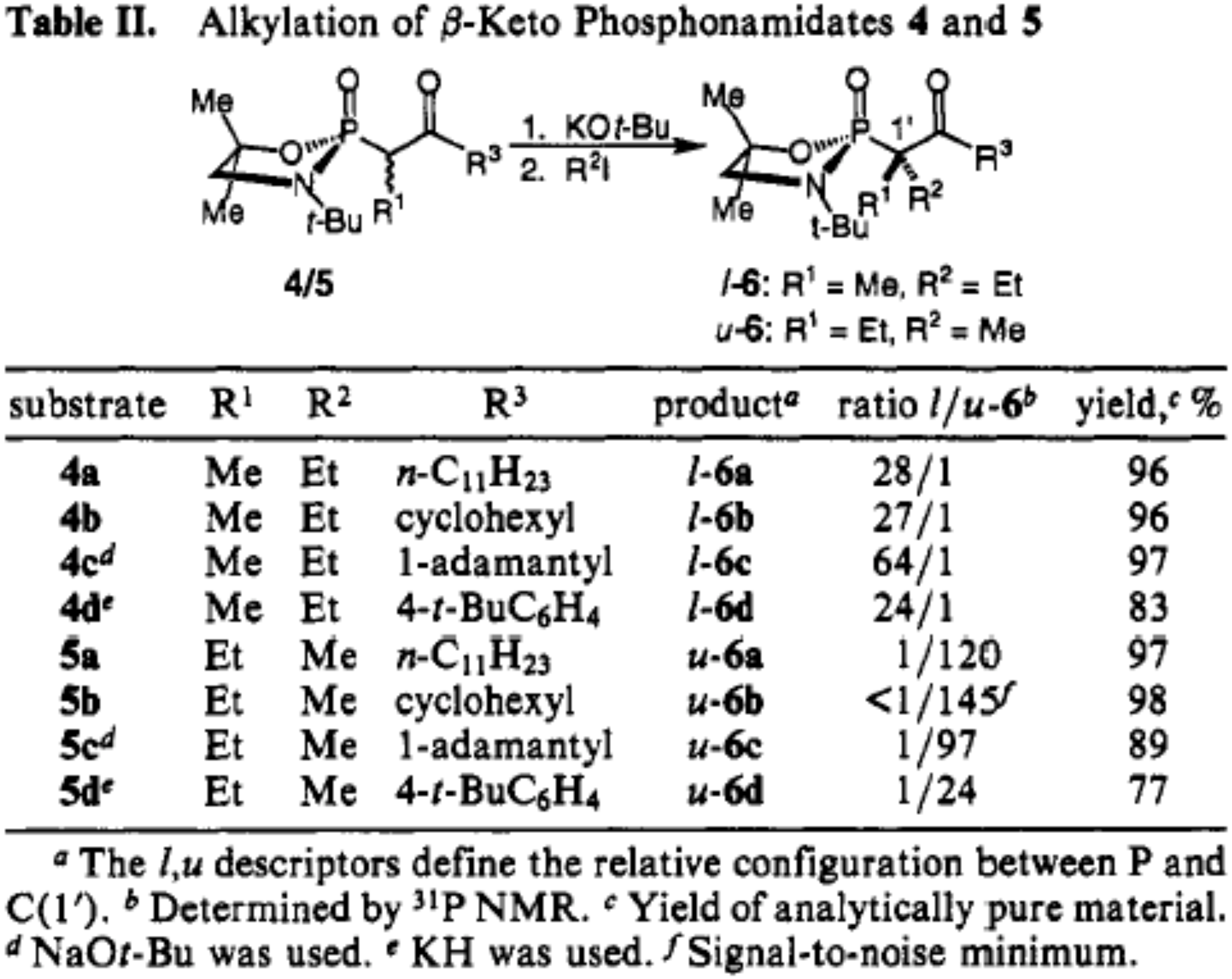


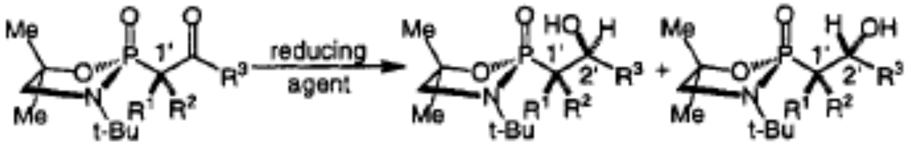
Table II. Alkylation of β-Keto Phosphonamidates **4** and **5**

substrate	R^1	R^2	R^3	product[a]	ratio *l*/*u*-**6**[b]	yield,[c] %
4a	Me	Et	*n*-$C_{11}H_{23}$	*l*-**6a**	28/1	96
4b	Me	Et	cyclohexyl	*l*-**6b**	27/1	96
4c[d]	Me	Et	1-adamantyl	*l*-**6c**	64/1	97
4d[e]	Me	Et	4-*t*-BuC_6H_4	*l*-**6d**	24/1	83
5a	Et	Me	*n*-$C_{11}H_{23}$	*u*-**6a**	1/120	97
5b	Et	Me	cyclohexyl	*u*-**6b**	<1/145[f]	98
5c[d]	Et	Me	1-adamantyl	*u*-**6c**	1/97	89
5d[e]	Et	Me	4-*t*-BuC_6H_4	*u*-**6d**	1/24	77

[a] The *l*,*u* descriptors define the relative configuration between P and C(1′). [b] Determined by ^{31}P NMR. [c] Yield of analytically pure material. [d] NaO*t*-Bu was used. [e] KH was used. [f] Signal-to-noise minimum.

JACS 1993,10386, S.E.Denmark *et. al.*

Table III. Reduction of β-Keto Phosphonamidates **6**

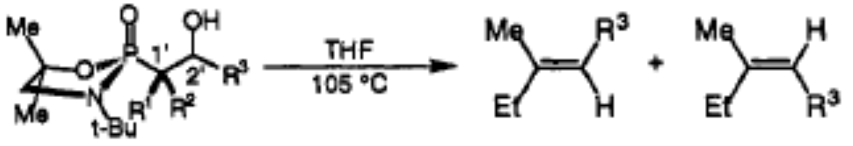


6 (*x*,*l*)-**7** (*x*,*u*)-**7**

substrate	R^1	R^2	R^3	reducing agent	product[a]	ratio (*x*/*l*)-**7**/(*x*/*u*)-**7**[b]	yield,[c] %
l-**6a**	Me	Et	*n*-$C_{11}H_{23}$	$CeCl_3/NaBH_4$	(*l*,*u*)-**7a**	1/150	93
u-**6a**	Et	Me	*n*-$C_{11}H_{23}$	$LiBHEt_3$	(*u*,*u*)-**7a**	1/24	99
l-**6b**	Me	Et	cyclohexyl	*i*-Bu_2AlH	(*l*,*l*)-**7b**	14/1	78
u-**6b**	Et	Me	cyclohexyl	*i*-Bu_2AlH	(*u*,*l*)-**7b**	65/1	97
l-**6c**	Me	Et	1-adamantyl	*i*-Bu_2AlH	(*l*,*l*)-**7c**	73/1	99
u-**6c**	Et	Me	1-adamantyl	*i*-Bu_2AlH	(*u*,*l*)-**7c**	>97/1	89
l-**6d**	Me	Et	4-*t*-BuC_6H_4	$CeCl_3/NaBH_4$	(*l*,*u*)-**7d**	1/44	83
u-**6d**	Et	Me	4-*t*-BuC_6H_4	$LiBH(s\text{-}Bu)_3$	(*u*,*u*)-**7d**	1/19	84

[a] The *l*,*u* descriptors define the relative configuration between P and (C(1′), C(2′)). [b] Determined by ^{31}P NMR. [c] Yield of analytically pure material.

Table IV. Formation of Trisubstituted Olefins (*E*)- and (*Z*)-**8**



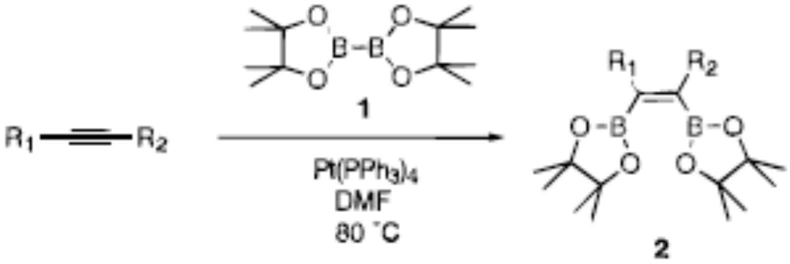
7 (*E*)-**8** (*Z*)-**8**

substrate[a]	R^1	R^2	R^3	time, h	product	ratio[b] (*E*)/(*Z*)-**8**	yield,[c] %
(*u*,*u*)-**7a**	Et	Me	*n*-$C_{11}H_{23}$	20	(*E*)-**8a**	102/1	92
(*l*,*u*)-**7a**	Me	Et	*n*-$C_{11}H_{23}$	22	(*Z*)-**8a**	1/160	86
(*l*,*l*)-**7b**[d]	Me	Et	cyclohexyl	12	(*E*)-**8b**	21/1	85
(*u*,*l*)-**7b**	Et	Me	cyclohexyl	18	(*Z*)-**8b**	1/184	96
(*l*,*l*)-**7c**	Me	Et	1-adamantyl	9	(*E*)-**8c**	104/1[e]	98
(*u*,*l*)-**7c**	Et	Me	1-adamantyl	10	(*Z*)-**8c**	<1/99[e]	94
(*u*,*u*)-**7d**	Et	Me	4-*t*-BuC_6H_4	6	(*E*)-**8d**	130/1	94
(*l*,*u*)-**7d**	Me	Et	4-*t*-BuC_6H_4	10	(*Z*)-**8d**	1/121	98

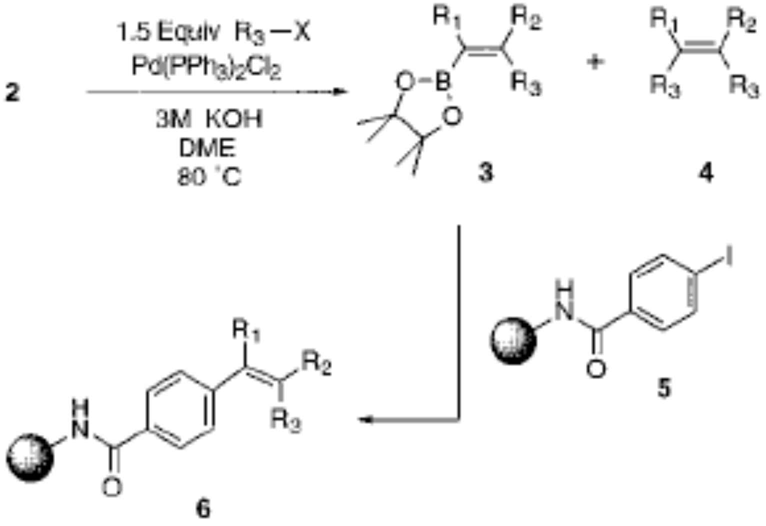
[a] >100/1 diastereomeric purity by ^{31}P NMR. [b] Determined by capillary GC (50-m HP U-2). [c] Yield of analytically pure material. [d] 21/1 by ^{31}P NMR. [e] Determined by ^1H NMR integration (400 MHz).

Synthesis of Tetrasubstituted Ethylenes on Solid Support

Scheme 1

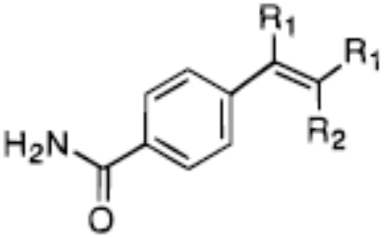


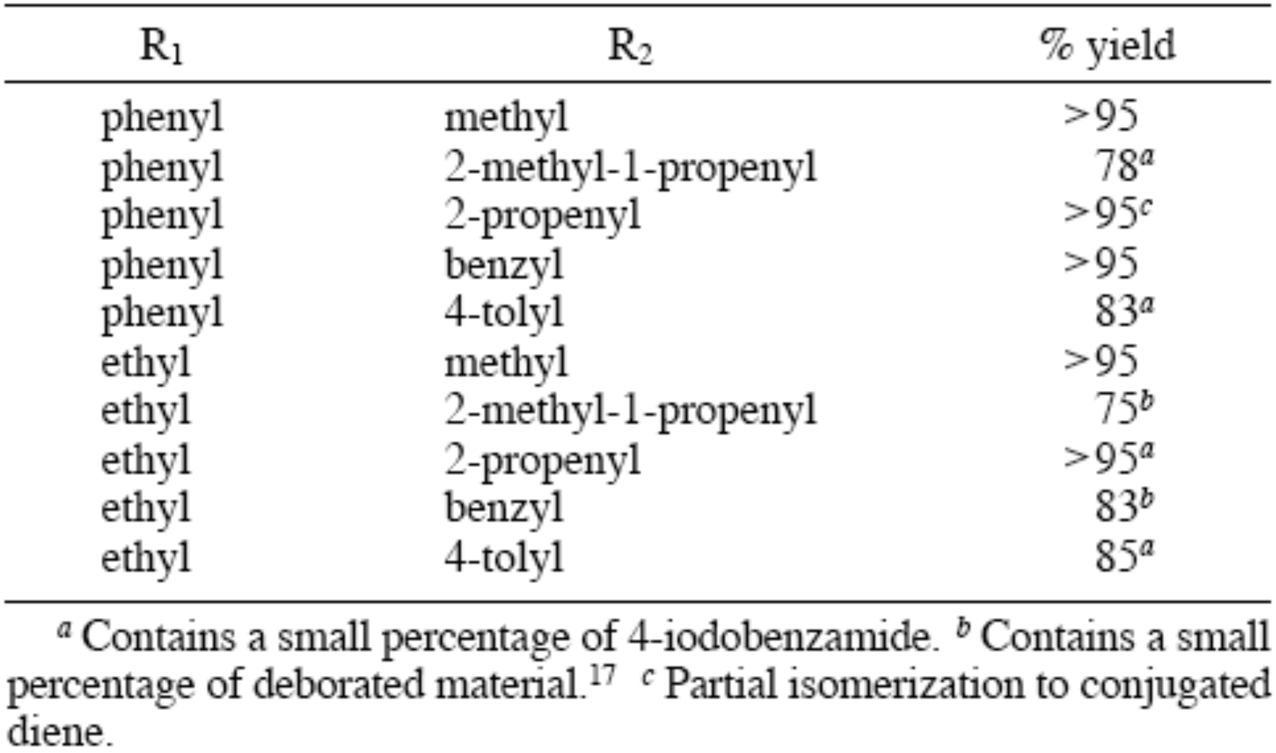
Scheme 2



JACS 1996, 6331, R.W.Armstrong *et. al.*

Synthesis of Tetrasubstituted Ethylenes on Solid Support



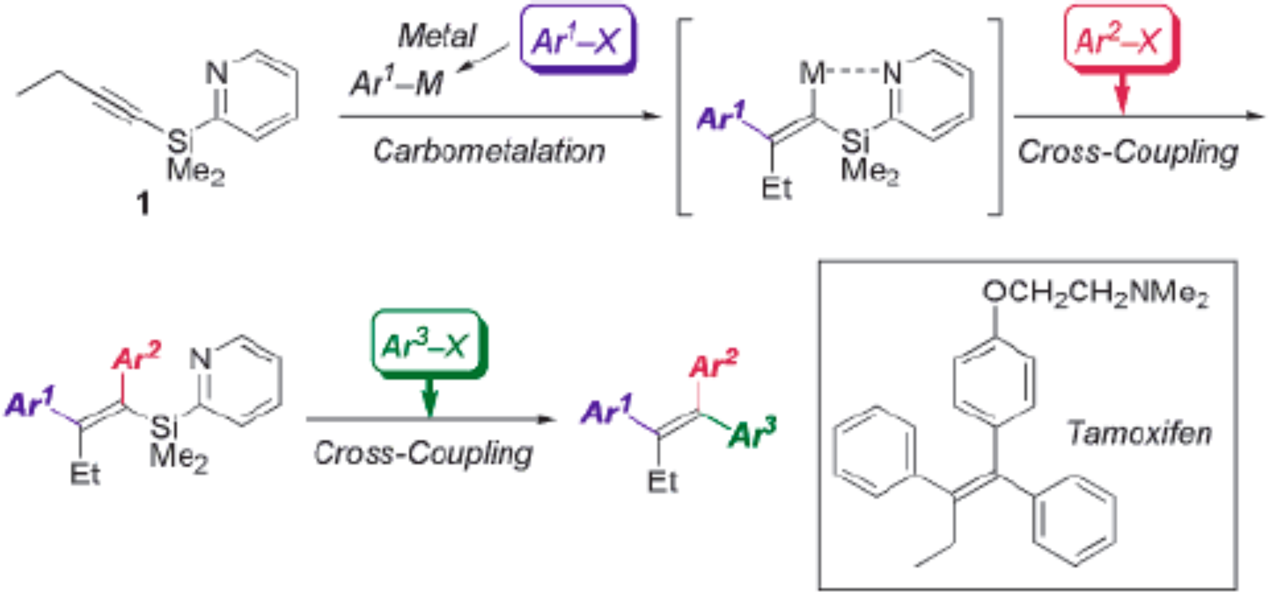


R_1	R_2	% yield
phenyl	methyl	>95
phenyl	2-methyl-1-propenyl	78[a]
phenyl	2-propenyl	>95[c]
phenyl	benzyl	>95
phenyl	4-tolyl	83[a]
ethyl	methyl	>95
ethyl	2-methyl-1-propenyl	75[b]
ethyl	2-propenyl	>95[a]
ethyl	benzyl	83[b]
ethyl	4-tolyl	85[a]

[a] Contains a small percentage of 4-iodobenzamide. [b] Contains a small percentage of deborated material.[17] [c] Partial isomerization to conjugated diene.

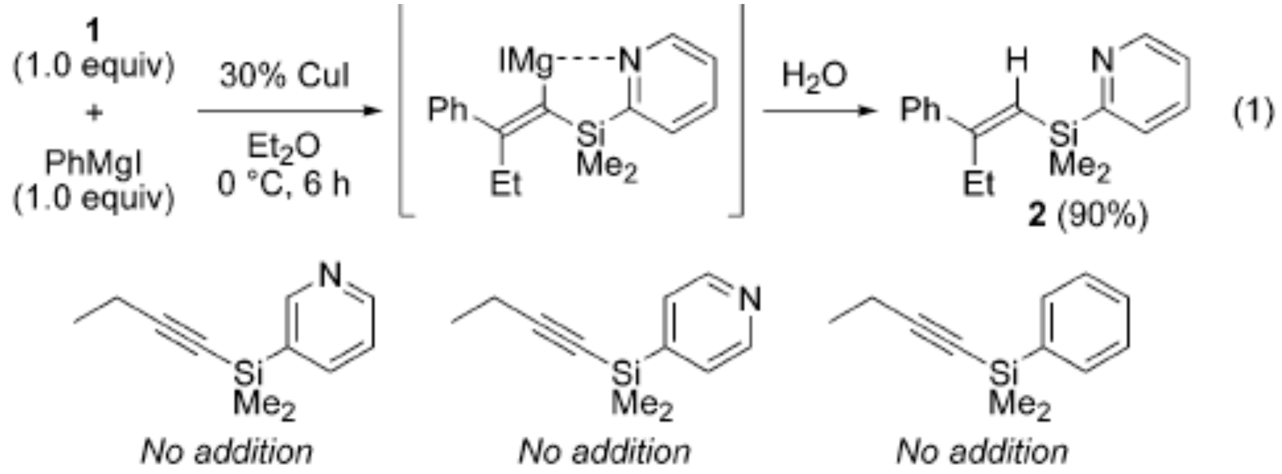
JACS 1996, 6331, R.W.Armstrong *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation



JACS 2003, 14670, J.Yoshida *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation



JACS 2003, 14670, J.Yoshida *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation

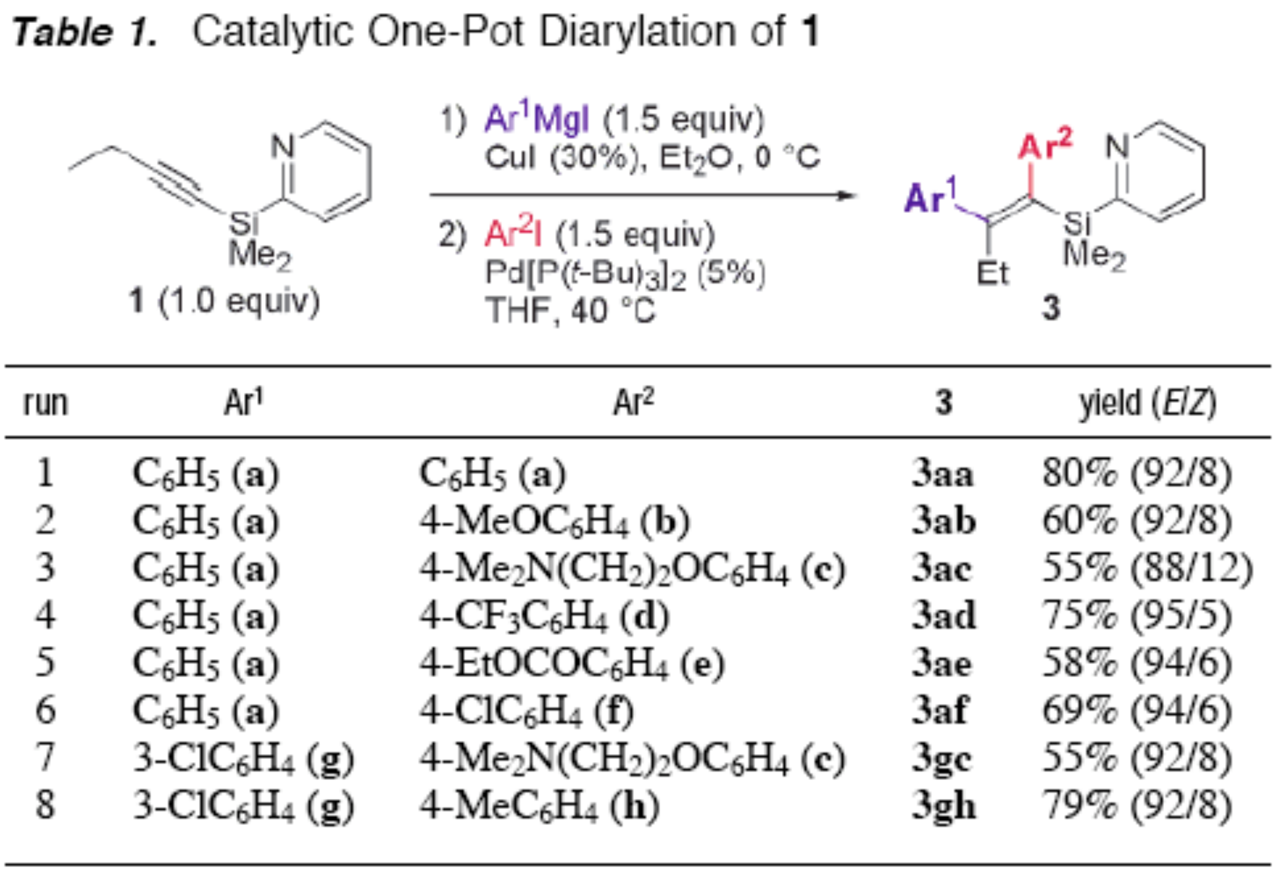
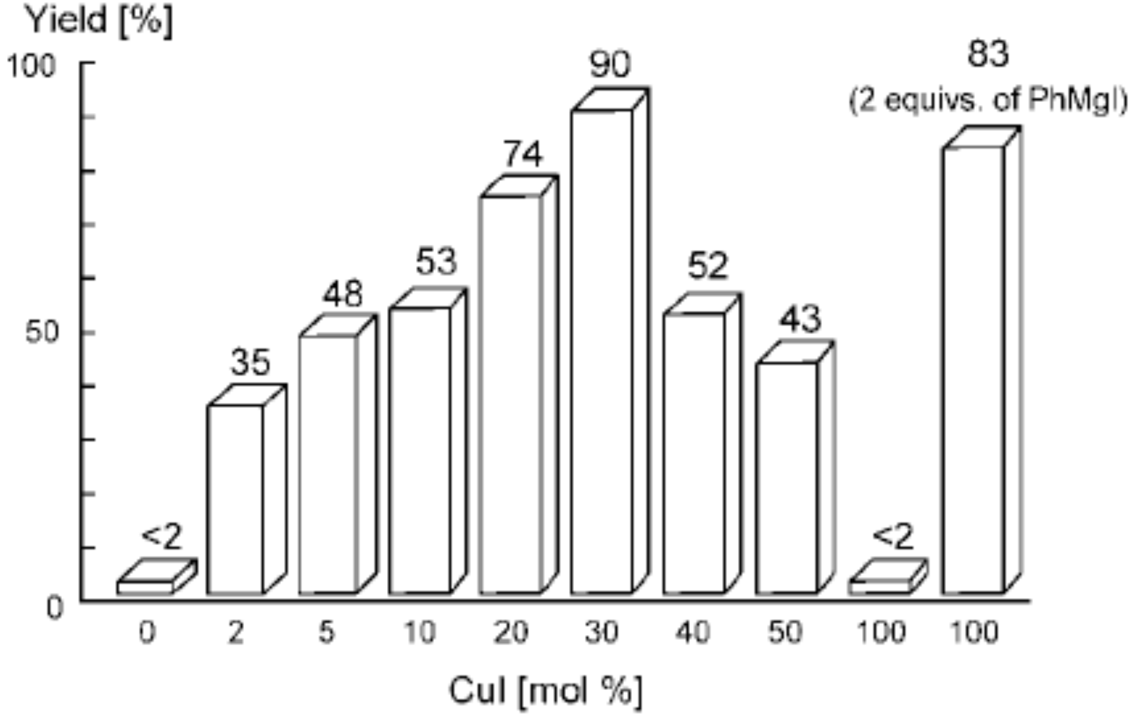


Table 1. Catalytic One-Pot Diarylation of **1**

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)

JACS 2003, 14670, J.Yoshida *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation



JACS 2003, 14670, J.Yoshida *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation

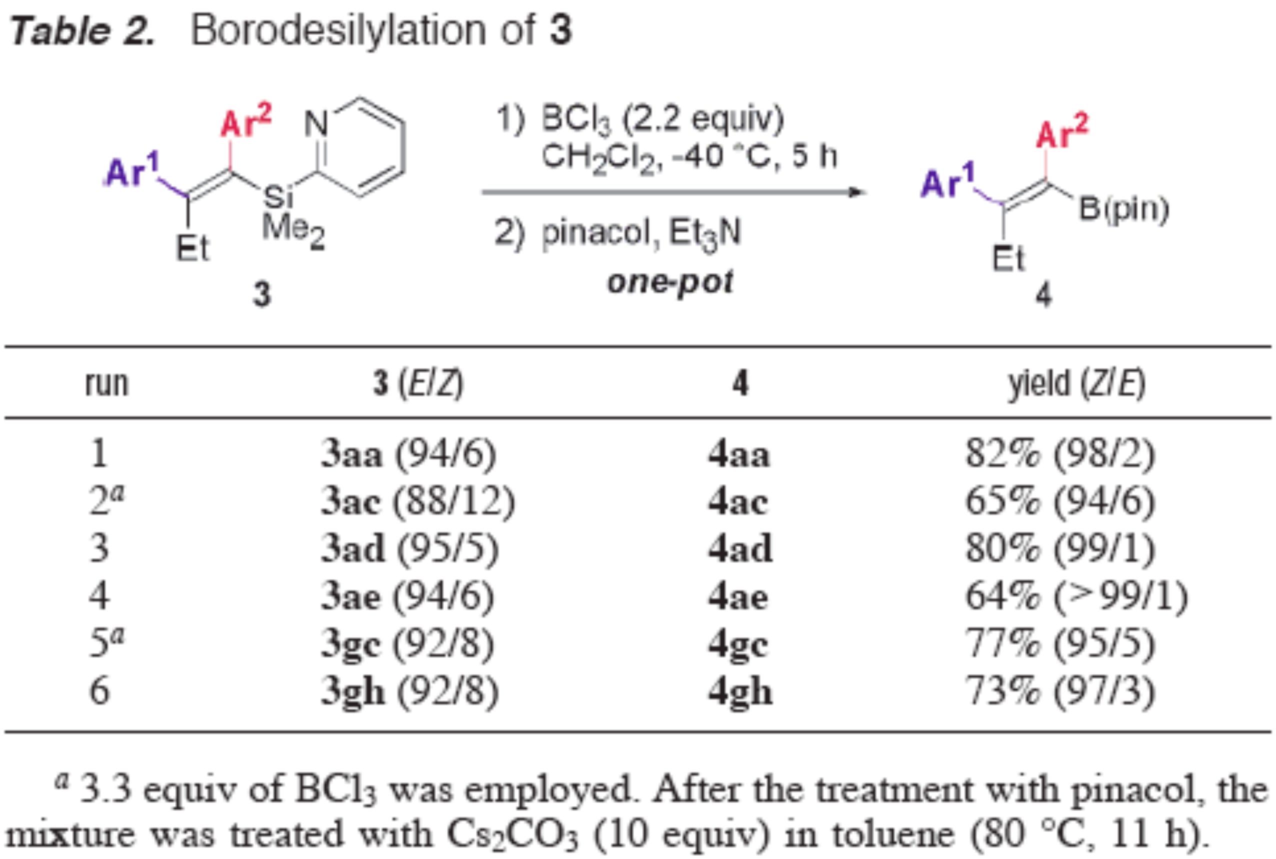


Table 2. Borodesilylation of **3**

1) BCl_3 (2.2 equiv)
CH_2Cl_2, -40 °C, 5 h

2) pinacol, Et_3N

one-pot

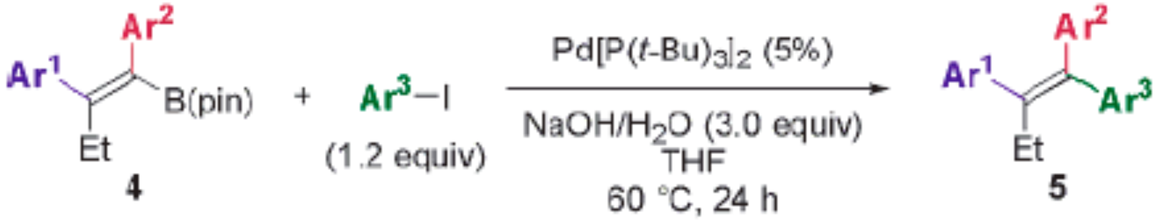
run	**3** (*E*/*Z*)	**4**	yield (*Z*/*E*)
1	**3aa** (94/6)	**4aa**	82% (98/2)
2[a]	**3ac** (88/12)	**4ac**	65% (94/6)
3	**3ad** (95/5)	**4ad**	80% (99/1)
4	**3ae** (94/6)	**4ae**	64% (>99/1)
5[a]	**3gc** (92/8)	**4gc**	77% (95/5)
6	**3gh** (92/8)	**4gh**	73% (97/3)

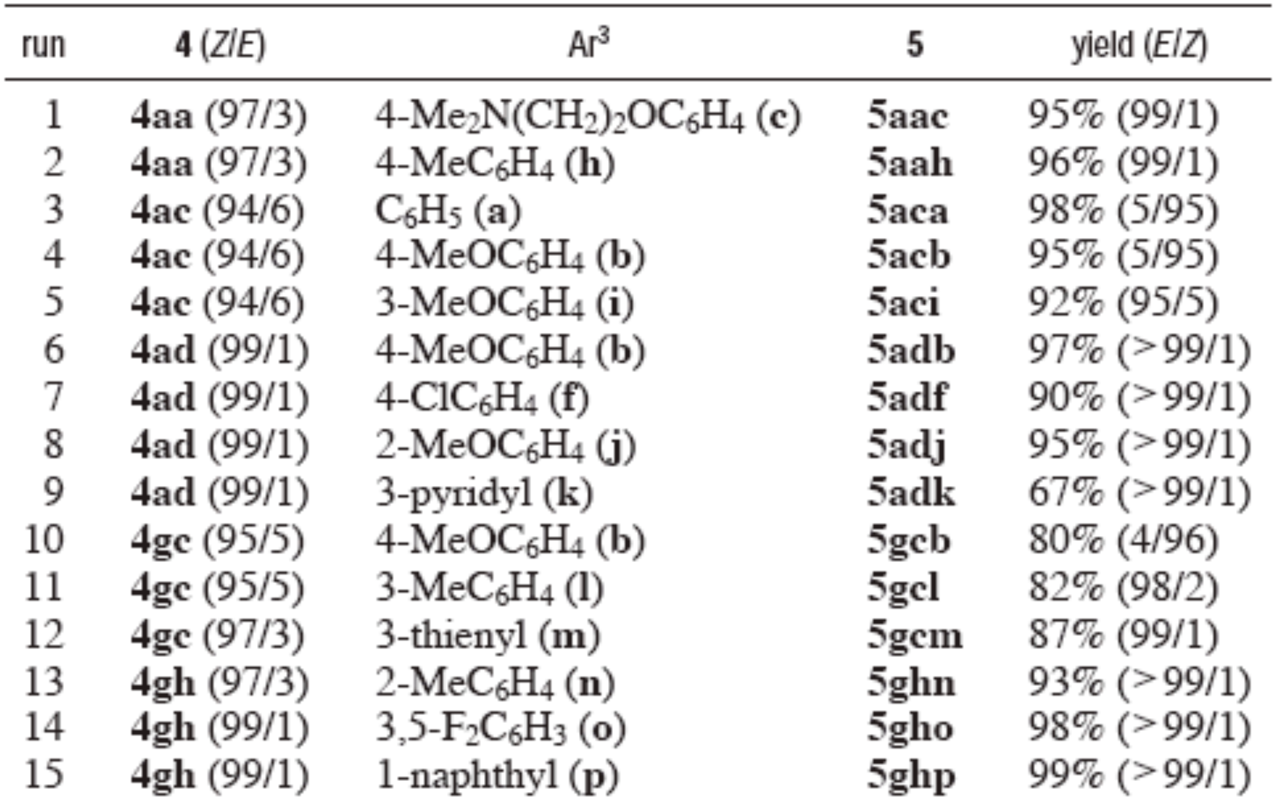
[a] 3.3 equiv of BCl_3 was employed. After the treatment with pinacol, the mixture was treated with Cs_2CO_3 (10 equiv) in toluene (80 °C, 11 h).

JACS 2003, 14670, J.Yoshida *et. al.*

Synthesis of Tetrasubstituted Olefins via Heteroatom Directed Metallation

Table 3. Suzuki–Miyaura Coupling of **4** with Aryl Iodides





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)

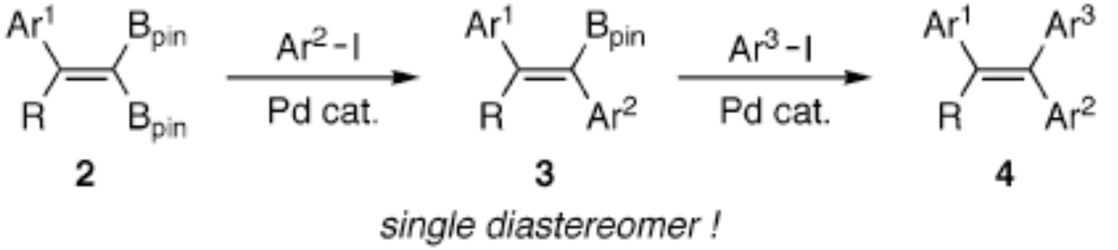
JACS 2003

14670

J.Yoshida *et. al.*

Triarylalkenes via Selective Suzuki-Miyaura Coupling

Scheme 1. Stereocontrolled Approach to 1,1,2-Triaryl-1-alkenes **4** Based on Sequential Cross-Coupling Reaction of 1,1-Diborylated Alkenes **2** (B_{pin} is pinacolatoboryl)



JACS 2005, 12506, M.Shimizu *et. al.*

Triarylalkenes via Selective Suzuki-Miyaura Coupling

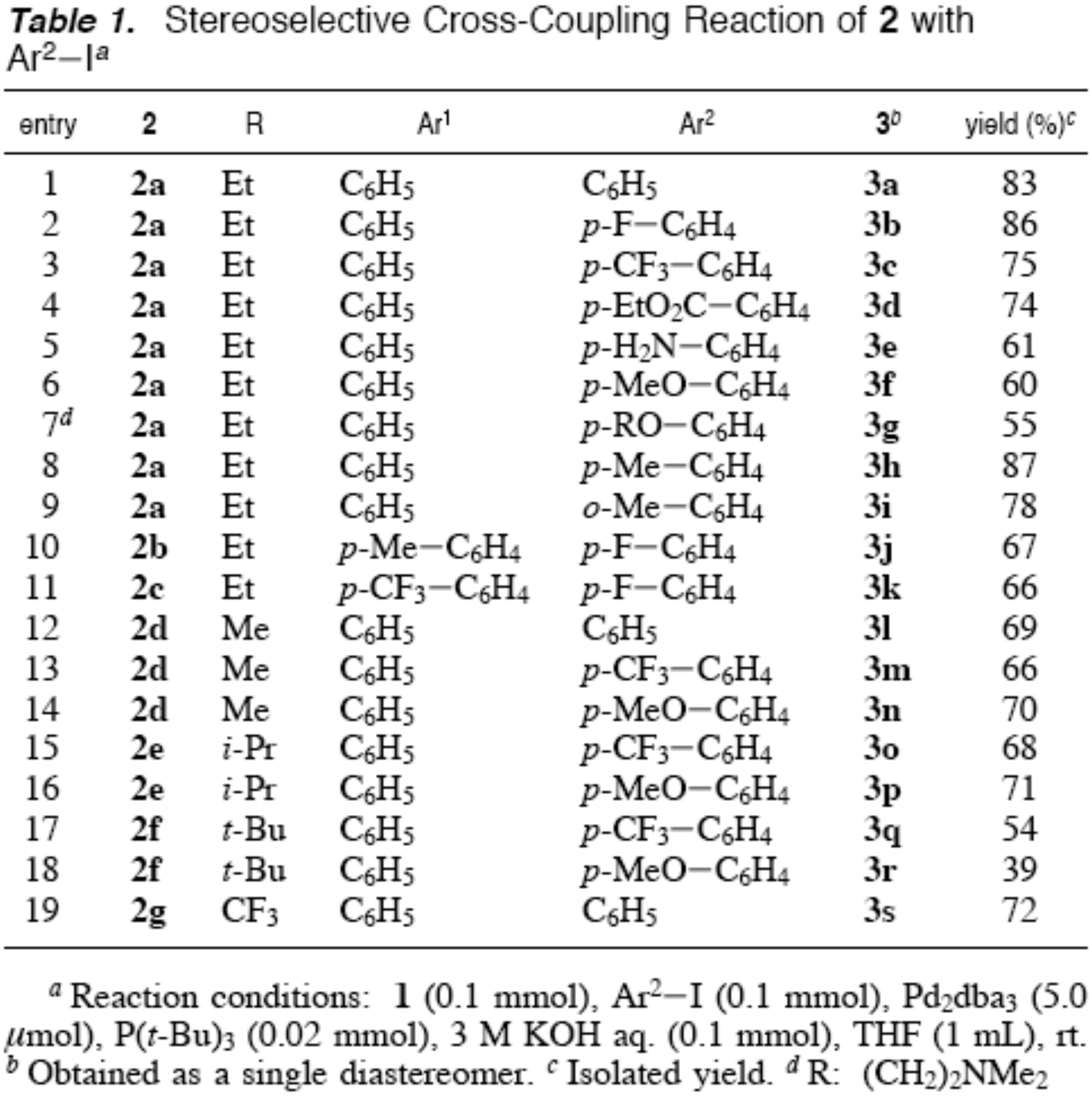


Table 1. Stereoselective Cross-Coupling Reaction of **2** with $Ar^2{-}I$[a]

entry	**2**	R	Ar^1	Ar^2	**3**[b]	yield (%)[c]
1	**2a**	Et	C_6H_5	C_6H_5	**3a**	83
2	**2a**	Et	C_6H_5	*p*-F$-C_6H_4$	**3b**	86
3	**2a**	Et	C_6H_5	*p*-$CF_3-C_6H_4$	**3c**	75
4	**2a**	Et	C_6H_5	*p*-$EtO_2C-C_6H_4$	**3d**	74
5	**2a**	Et	C_6H_5	*p*-$H_2N-C_6H_4$	**3e**	61
6	**2a**	Et	C_6H_5	*p*-MeO$-C_6H_4$	**3f**	60
7[d]	**2a**	Et	C_6H_5	*p*-RO$-C_6H_4$	**3g**	55
8	**2a**	Et	C_6H_5	*p*-Me$-C_6H_4$	**3h**	87
9	**2a**	Et	C_6H_5	*o*-Me$-C_6H_4$	**3i**	78
10	**2b**	Et	*p*-Me$-C_6H_4$	*p*-F$-C_6H_4$	**3j**	67
11	**2c**	Et	*p*-$CF_3-C_6H_4$	*p*-F$-C_6H_4$	**3k**	66
12	**2d**	Me	C_6H_5	C_6H_5	**3l**	69
13	**2d**	Me	C_6H_5	*p*-$CF_3-C_6H_4$	**3m**	66
14	**2d**	Me	C_6H_5	*p*-MeO$-C_6H_4$	**3n**	70
15	**2e**	*i*-Pr	C_6H_5	*p*-$CF_3-C_6H_4$	**3o**	68
16	**2e**	*i*-Pr	C_6H_5	*p*-MeO$-C_6H_4$	**3p**	71
17	**2f**	*t*-Bu	C_6H_5	*p*-$CF_3-C_6H_4$	**3q**	54
18	**2f**	*t*-Bu	C_6H_5	*p*-MeO$-C_6H_4$	**3r**	39
19	**2g**	CF_3	C_6H_5	C_6H_5	**3s**	72

[a] Reaction conditions: **1** (0.1 mmol), $Ar^2{-}I$ (0.1 mmol), Pd_2dba_3 (5.0 μmol), P(*t*-Bu)$_3$ (0.02 mmol), 3 M KOH aq. (0.1 mmol), THF (1 mL), rt. [b] Obtained as a single diastereomer. [c] Isolated yield. [d] R: $(CH_2)_2NMe_2$

JACS 2005

12506

M.Shimizu *et. al.*

Triarylalkenes via Selective Suzuki-Miyaura Coupling

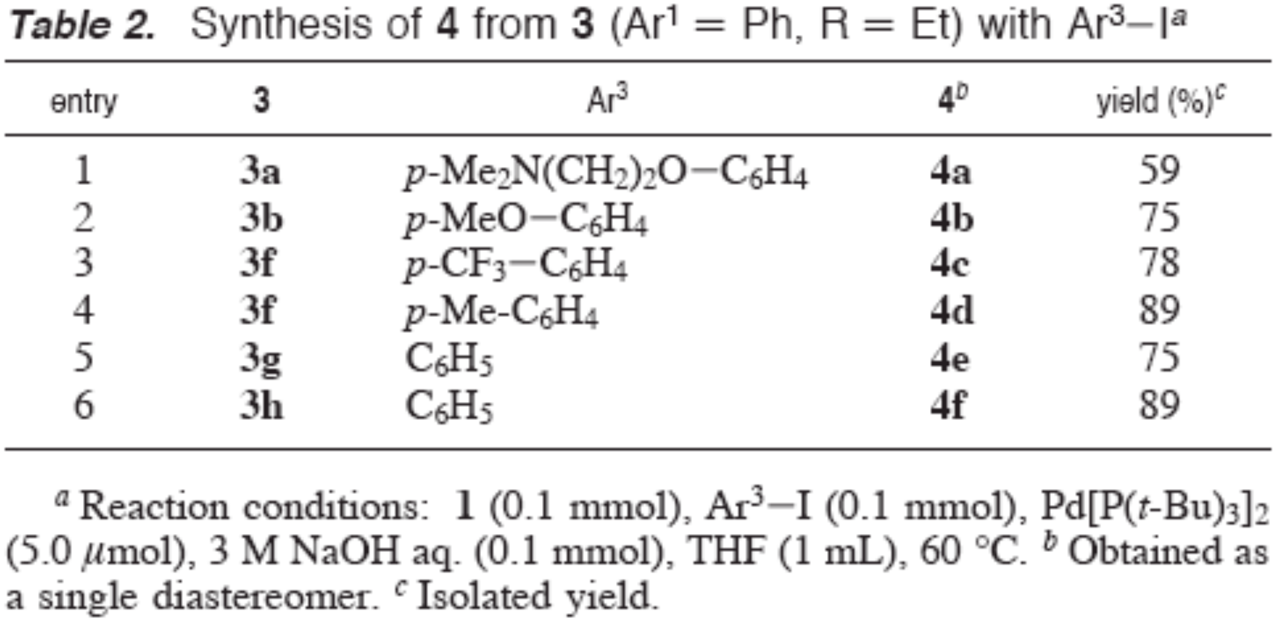


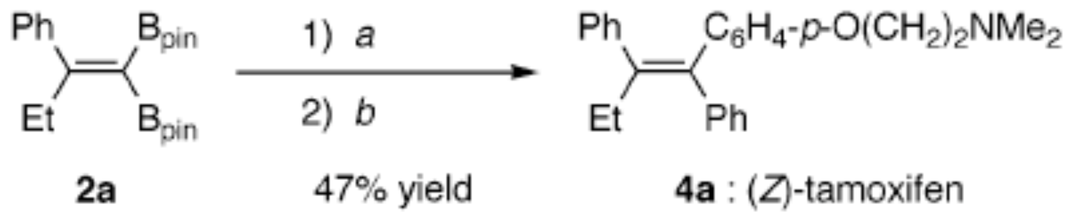
Table 2. Synthesis of **4** from **3** (Ar^1 = Ph, R = Et) with Ar^3–I[a]

entry	3	Ar^3	4[b]	yield (%)[c]
1	**3a**	p-$Me_2N(CH_2)_2O-C_6H_4$	**4a**	59
2	**3b**	p-$MeO-C_6H_4$	**4b**	75
3	**3f**	p-$CF_3-C_6H_4$	**4c**	78
4	**3f**	p-Me-C_6H_4	**4d**	89
5	**3g**	C_6H_5	**4e**	75
6	**3h**	C_6H_5	**4f**	89

[a] Reaction conditions: **1** (0.1 mmol), Ar^3–I (0.1 mmol), Pd[P(t-Bu)$_3$]$_2$ (5.0 μmol), 3 M NaOH aq. (0.1 mmol), THF (1 mL), 60 °C. [b] Obtained as a single diastereomer. [c] Isolated yield.

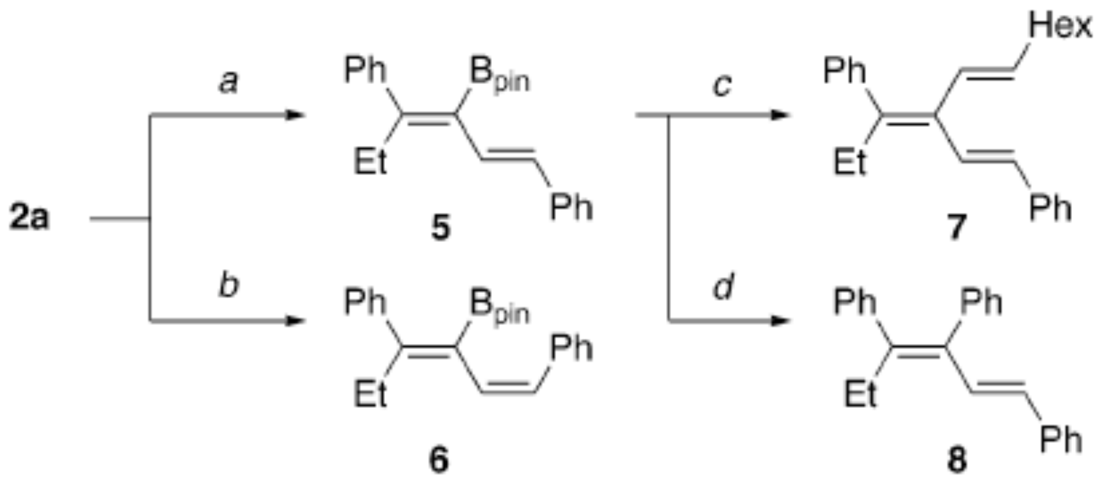
JACS 2005, 12506, M.Shimizu *et. al.*

Scheme 2. One-Pot Synthesis of (*Z*)-Tamoxifen[a]



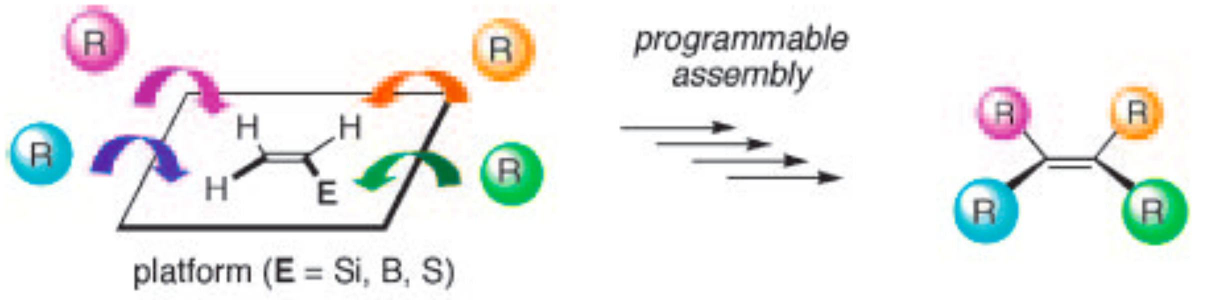
[a] Reagents and conditions: (a) **2a** (1.0 equiv), Ph-I (1.0 equiv), Pd_2dba_3 (5 mol %), P(*t*-Bu)$_3$ (20 mol %), 3 M KOH aqueous solution, dioxane, rt, 2 h; (b) $Me_2N(CH_2)_2O{-}C_6H_4{-}I$ (1.0 equiv), 100 °C, 22 h.

Scheme 3. Cross-Coupling Reaction of **2a** with Alkenyl Halides Leading to Polysubstituted 1,3-Dienes and [3]Dendralene[a]



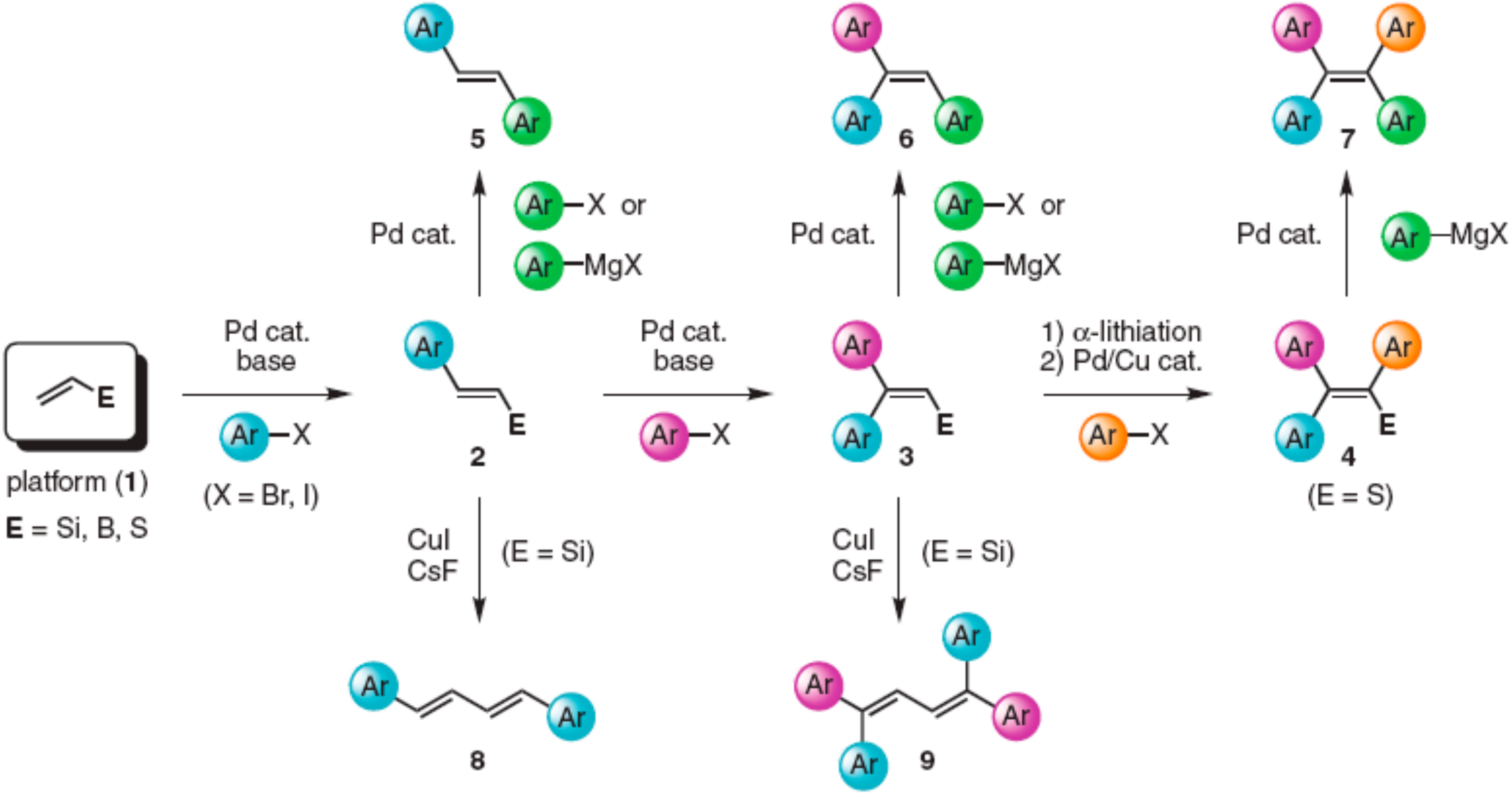
[a] Reagents and conditions: (a) (*E*)-PhHC=C(H)I, $Pd(PPh_3)_4$ (5 mol %), 3 M KOH aq., THF, rt, 73% yield (2*E*4*E*:2*E*4*Z* = 98:2); (b) (*Z*)-PhHC=C(H)Br, $Pd(PPh_3)_4$ (5 mol %), 3 M KOH aq., THF, 40 °C, 72% yield (2*Z*4*E*:2*Z*4*Z* = 96:4); (c) (*E*)-HexHC=C(H)I, $PdCl_2(dppf)$ (5 mol %), 3 M KOH aq., DME, 40 °C, 81% yield; (d) Ph-I, $PdCl_2(dppf)$ (5 mol %), 3 M KOH aq., THF, 60 °C, 81% yield.

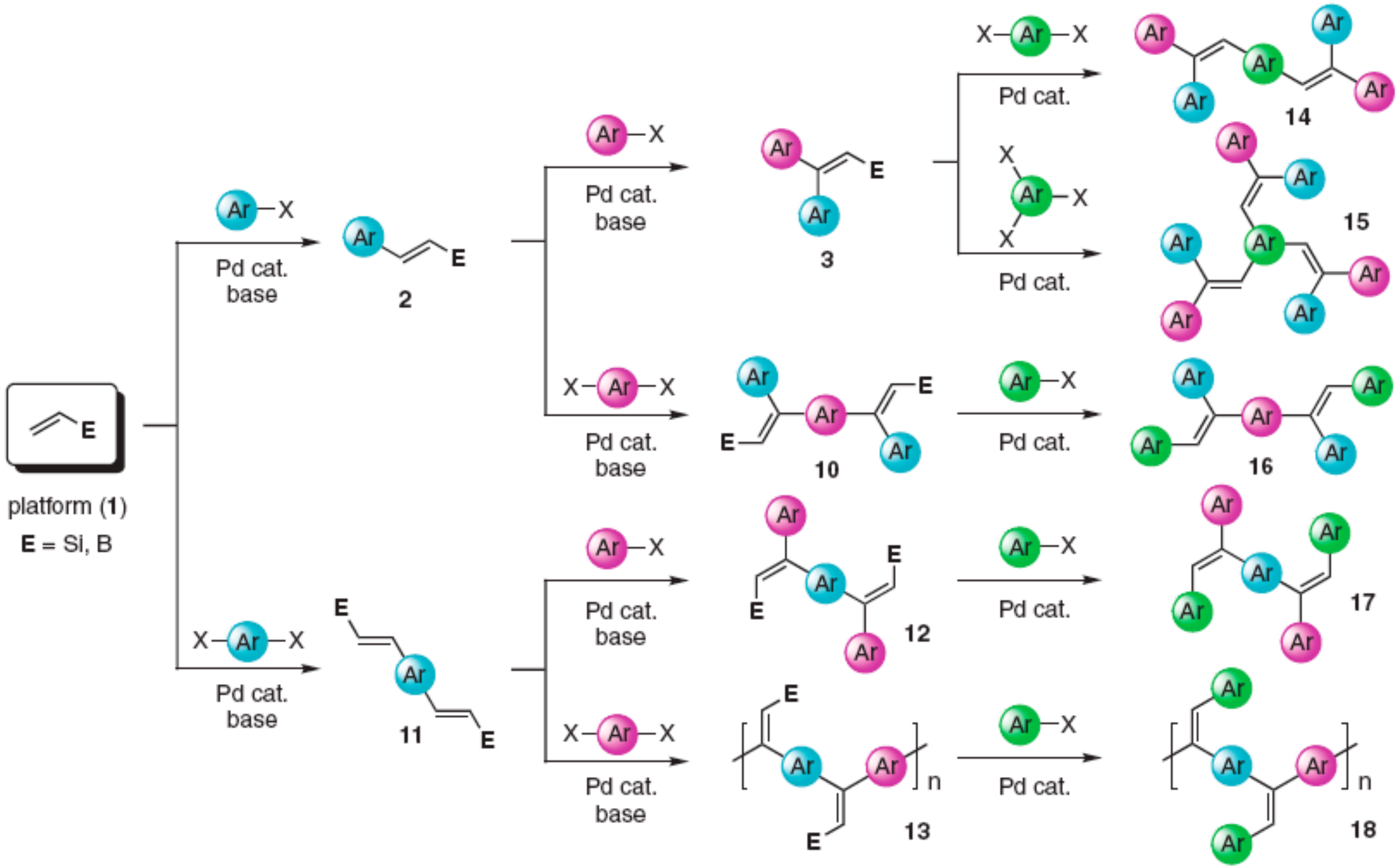
The “New” Concept: Platform Synthesis of Multisubstituted Olefins

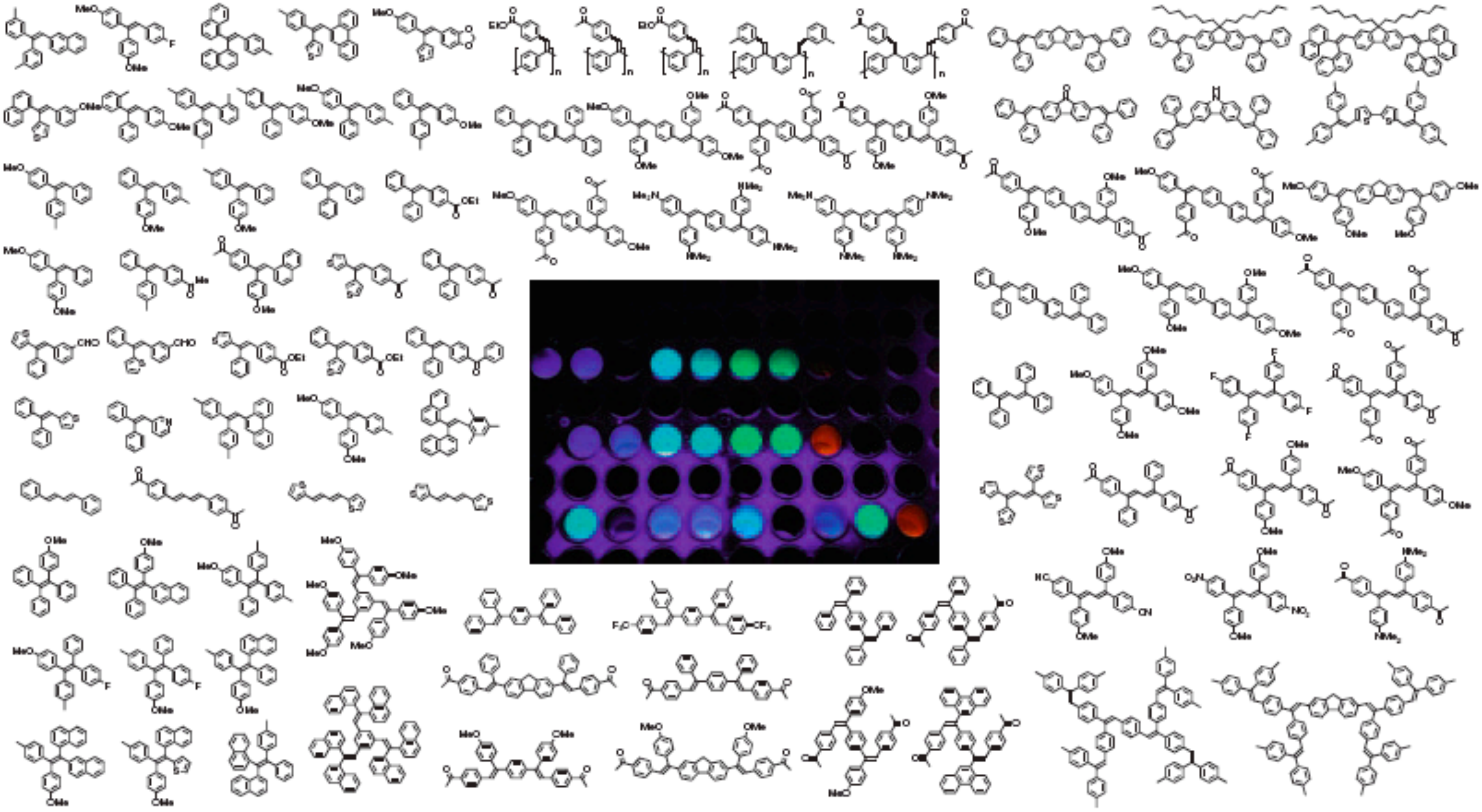


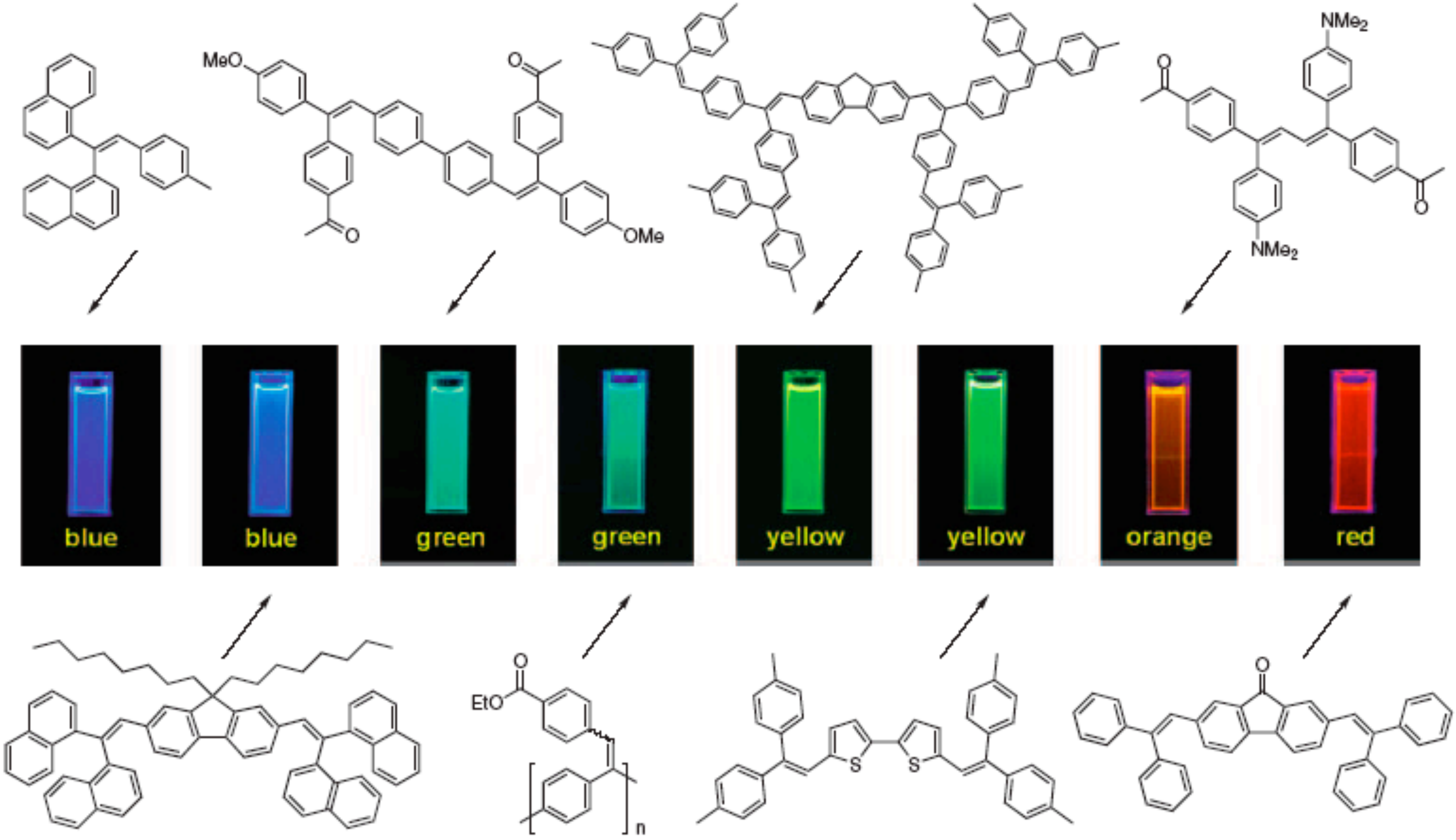
Sequential site-selective assembly of components onto a vinyl-element platform

Bull. Chem. Soc. Jpn., 2006, 811, K.Itami, J. Yoshida


E
platform (1)
E = Si, B, S
Pd cat.
base
Ar—X
(X = Br, I)
Ar
E
2
Pd cat.
base
Ar—X
Ar
Ar
E
3
1) α-lithiation
2) Pd/Cu cat.
Ar—X
Ar
Ar
Ar
E
4
(E = S)
Pd cat.
Ar—X or
Ar—MgX
Ar
Ar
5
Pd cat.
Ar—X or
Ar—MgX
Ar
Ar
Ar
6
Pd cat.
Ar—MgX
Ar
Ar
Ar
Ar
7
CuI
CsF
(E = Si)
Ar
Ar
8
CuI
CsF
(E = Si)
Ar
Ar
Ar
Ar
9


E
platform (1)
E = Si, B
Ar—X
Pd cat.
base
2
X—Ar—X
Pd cat.
base
11
Ar—X
Pd cat.
base
3
X—Ar—X
Pd cat.
base
10
Ar—X
Pd cat.
base
12
X—Ar—X
Pd cat.
base
13
n
X—Ar—X
Pd cat.
14
X
Ar—X
X
Pd cat.
15
Ar—X
Pd cat.
16
Ar—X
Pd cat.
17
Ar—X
Pd cat.
18
n




MeO
O
O
OMe
NMe2
O
O
NMe2
blue
blue
green
green
yellow
yellow
orange
red
O
EtO
n
S
S
O