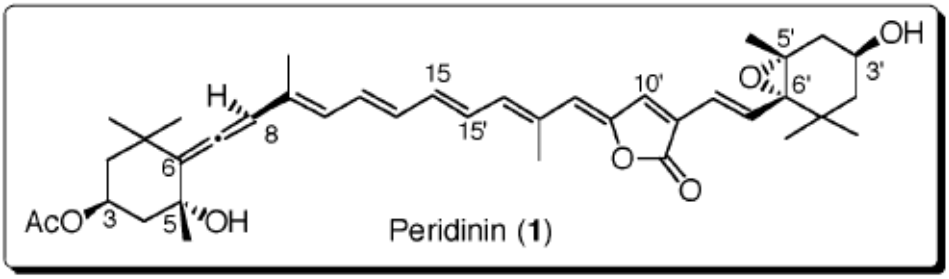
2010/10/13

B5 Tanabe Hirooki

# *Evolution of Boronate Iterative Suzuki Miyaura Coupling*




## *The Ballad of East and West*

Rudyard Kipling (1865–1936)

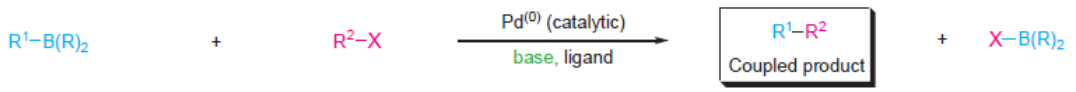
Oh, East is East, and West is West,
and never the twain (two) shall meet,
Till Earth and Sky stand presently
at God's great Judgment Seat;

But there is neither East nor West, Border,
Nor Breed, nor Birth,
When two strong men stand face to face,
though they come
from the ends of the earth!

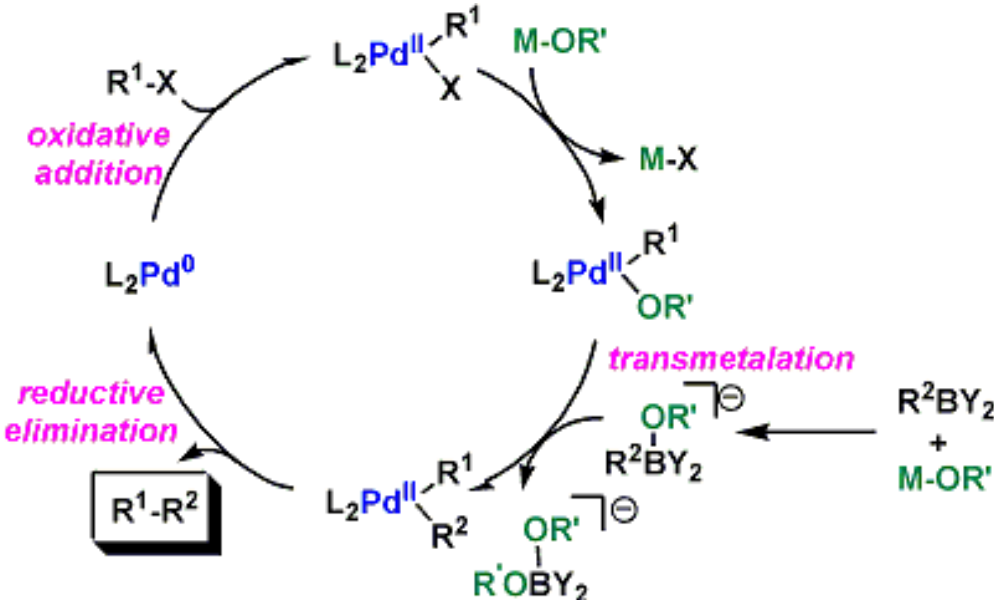
# Contents



## 1 Introduction




$R^1$ = alkyl, allyl, alkenyl, alkynyl, aryl; R = alkyl, OH, O-alkyl; $R^2$ = alkenyl, aryl, alkyl; X = Cl, Br,I, OTf, $OPO(OR)_2$ (enol phosphate); base = $Na_2CO_3$, $Ba(OH)_2$, $K_3PO_4$, $Cs_2CO_3$, $K_2CO_3$, TlOH, KF, CsF, $Bu_4F$, NaOH, $M^+(^-O\text{-alkyl})$



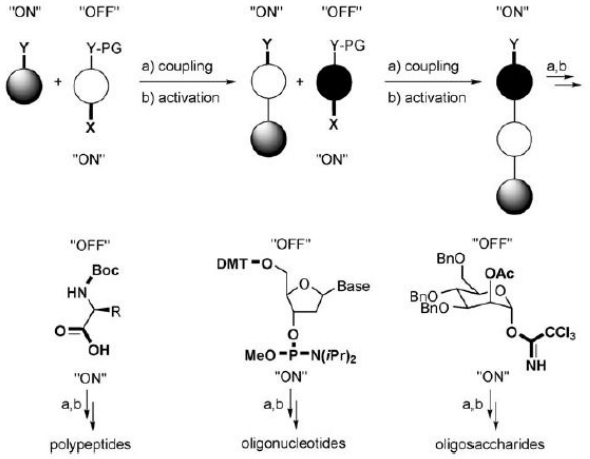
Cross-Coupling

DOI: 10.1002/anie.200901680

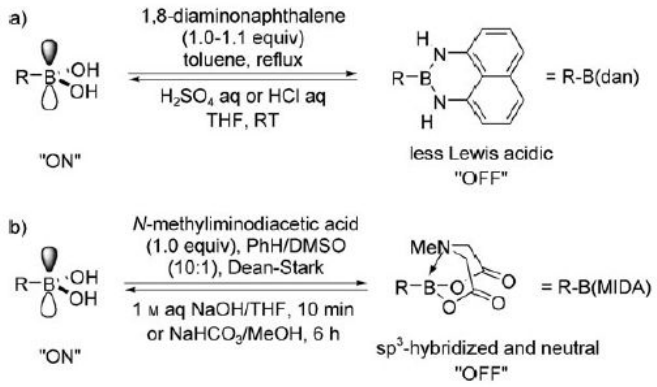
# Controlled Iterative Cross-Coupling: On the Way to the Automation of Organic Synthesis**

*Congyang Wang and Frank Glorius**

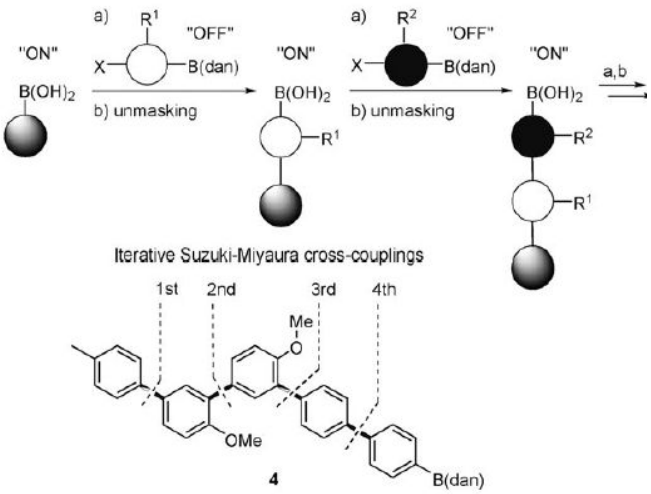
*Angew. Chem. Int. Ed.* **2009**, *48*, 5240 – 5244



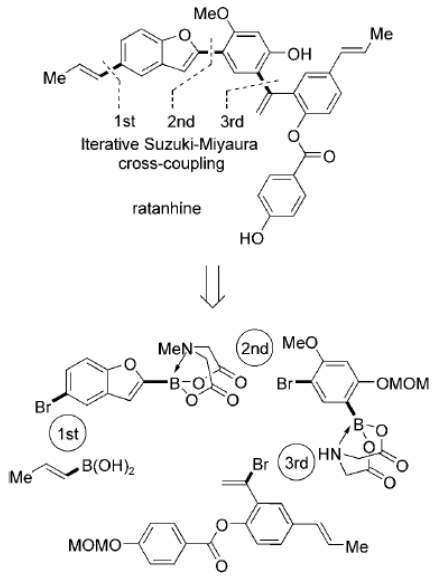

***Scheme 1.*** General iterative coupling sequence and three typical building blocks bearing reactive ("ON") electrophilic and protected ("OFF") nucleophilic functional groups. Bn = benzyl; Boc = *tert*-butoxycarbonyl; DMT = dimethoxytrityl; PG = protecting group.




***Scheme 4.*** Transformation of boronic acids into unreactive boronamides (Suginome, a) and boronates (Burke, b) and reverse activation reaction.




***Scheme 5.*** Iterative Suzuki–Miyaura cross-coupling using a boron-masking strategy by Suginome. Typical reaction conditions: a) [Pd(P*t*Bu$_3$)$_2$] (2 mol%), CsF, dioxane/H$_2$O or THF; b) see Scheme 4a.

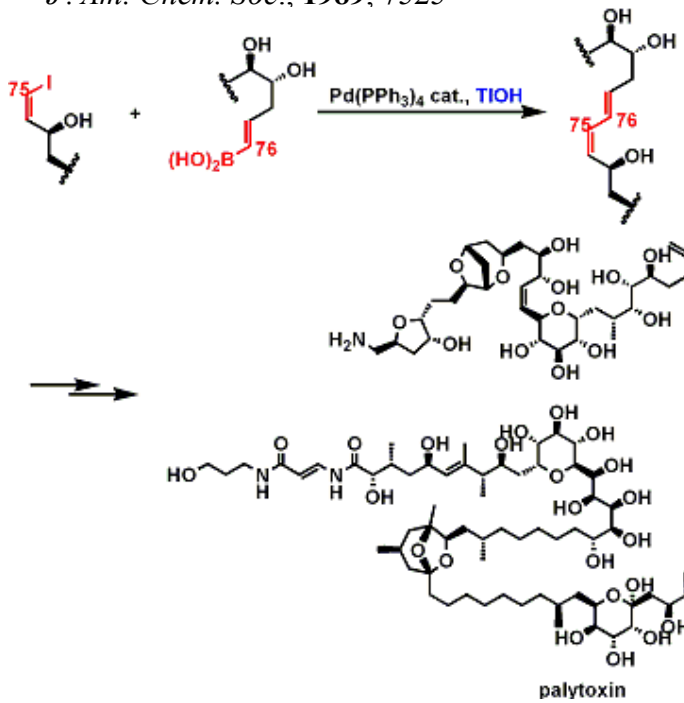



***Scheme 6.*** Iterative Suzuki–Miyaura cross-coupling using MIDA boronates by Burke. Typical coupling conditions: a) $Pd_2dba_3$, 2-(dicyclohexylphosphino)biphenyl, $K_2CO_3$, THF, 65 °C; b) see Scheme 4b. MOM = methoxymethyl.

## 2 Evolution of Base

### Total Synthesis of a Fully Protected Palytoxin Carboxylic Acid

*J. Am. Chem. Soc.*, **1989**, 7525



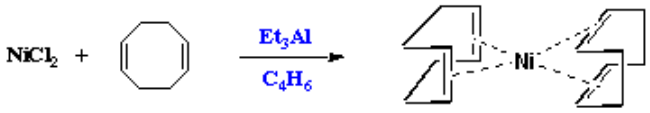

TlOH Accelerated coupling

## 3 Evolution of Ligand

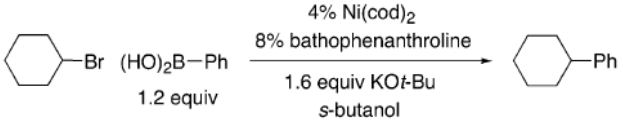
### Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides

Jianrong (Steve) Zhou and Gregory C. Fu*

J. AM. CHEM. SOC. **2004**, *126*, 1340−1341



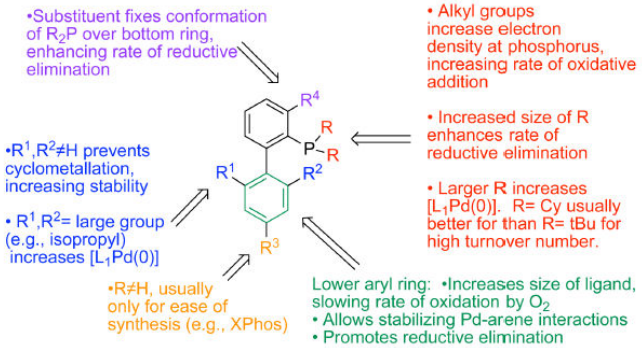

bis(h4-1,5-cyclo-ocotadiene)nickel(0)




### Highly Active Palladium Catalysts for Suzuki Coupling Reactions

*J. Am. Chem. Soc.* **1999,** *121,* 9550−9561

**Buchwald catalyst**



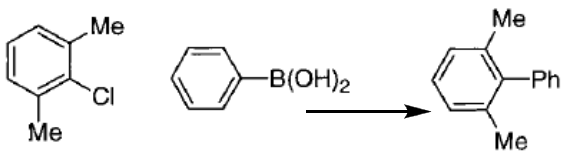




**Figure 3.**
Structural Features of the Dialkylbiarylphosphines and Their Impact on the Efficacy of Catalysts Using These Ligands

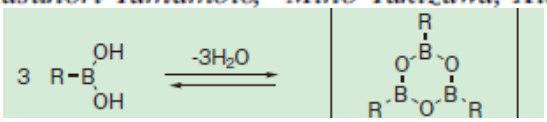
*Acc Chem Res*. 2008 November 18; 41(11): 1461–1473. doi:10.1021/ar800036s.

# 4 Evolution of Boronate

## 4-1 Stable Boronate

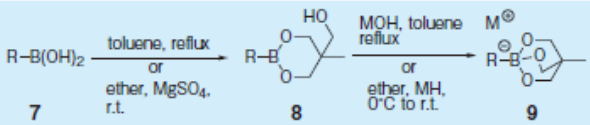
# Cyclic Triolborates: Air- and Water-Stable Ate Complexes of Organoboronic Acids

*Yasunori Yamamoto,* Miho Takizawa, Xiao-Qiang Yu, and Norio Miyaura**



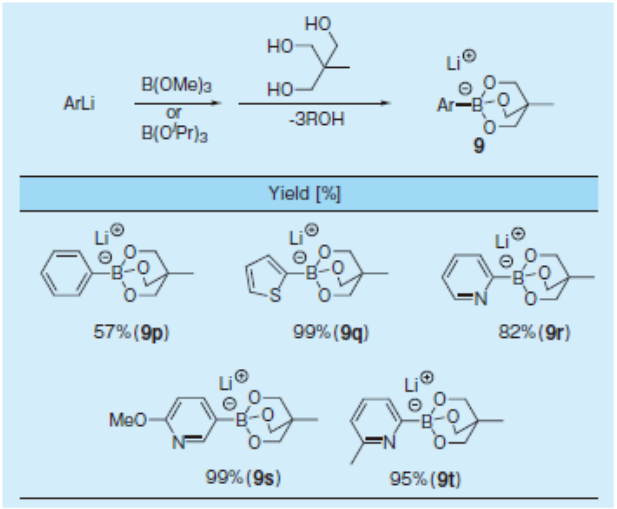
*Angew. Chem. Int. Ed.* 2008, 47, 928–931

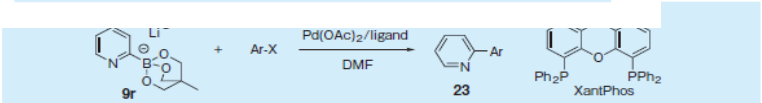
Table 1. 有機環状トリオールボレートナトリウム、カリウム、セシウム塩の調製



| R= | | Yield [%] | MOH or MH | Yield [%] |
|---|---|---|---|---|
| 4-MeO-$C_6H_5$ | (**7a**) | 49 (**8a**) | KOH | 71 (**9a**) |
| 3,4-$CH_2O_2$-$C_6H_3$ | (**7b**) | 99 (**8b**) | KOH | 84 (**9b**) |
| 4-PhO-$C_6H_4$ | (**7c**) | 64 (**8c**) | KOH | 80 (**9c**) |
| 4-*t*-Bu-$C_6H_4$ | (**7d**) | 85 (**8d**) | KOH | 88 (**9d**) |
| 4-Me-$C_6H_4$ | (**7e**) | 96 (**8e**) | KOH | 88 (**9e**) |
| $C_6H_5$ | (**7f**) | 91 (**8f**) | KOH | 91 (**9f**) |
| 4-F-$C_6H_4$ | (**7g**) | 99 (**8g**) | KOH | 84 (**9g**) |
| 4-$CF_3$-$C_6H_4$ | (**7h**) | 99 (**8h**) | KOH | 80 (**9h**) |
| 4-Ac-$C_6H_4$ | (**7i**) | 91 (**8i**) | NaH | 55 (**9i**) |
| 3-pyridyl | (**7j**) | 49 (**8j**) | KOH | 56 (**9j**) |
| *trans*-$C_4H_9CH$=CH | (**7k**) | 75 (**8k**) | KOH | 89 (**9k**) |
| *n*-$C_4H_9$ | (**7l**) | 88 (**8l**) | CsOH | 83 (**9l**) |
| *n*-$C_8H_{15}$ | (**7m**) | 97 (**8m**) | CsOH | 83 (**9m**) |

Table 2. 有機環状トリオールボレートリチウム塩の調製




| Ar-X | Catalyst | CuI [mol%] | t [h] / T [°C] | Yield [%] |
|---|---|---|---|---|
| $O_2N$-Ar-Br | $Pd(OAc)_2$ (3 mol%) $PPh_3$ (6.6 mol%) | 20 | 22 / 80 | 90 |
| Ac-Ar-Br | $Pd(OAc)_2$ (3 mol%) $PPh_3$ (6.6 mol%) | 20 | 22 / 80 | 75 |
| Br-Py | $Pd(OAc)_2$ (3 mol%) $PPh_3$ (6.6 mol%) | 40 | 22 / 80 | 70 |
| MeO-Ar-I | $Pd(OAc)_2$ (6 mol%) XantPhos (6.6 mol%) | 40 | 22 /100 | 74 |
| Me-Ar-I | $Pd(OAc)_2$ (6 mol%) XantPhos (6.6 mol%) | 40 | 22 /100 | 77 |

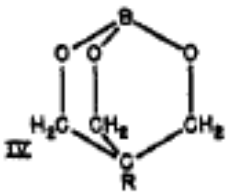
和光純薬時報 Vol.76, No.2 (2008)

**baseb on japanese written review**

## Compounds with Boron at the Bridgehead—A Study of the Steric Consequences of Planar Boron[1]

By Herbert C. Brown and Edward A. Fletcher[2]

2-Ethyl-2-(hydroxymethyl)-1,3-propanediol[3] reacts with boric acid to lose the calculated quantity of water, forming the ester. The product is polymeric. The monomer is not formed from the polymer at 270° and $10^{-3}$ mm. It is concluded that the strain involved in accommodating the planar boron atom at the cage bridgehead (IV) must be exceedingly large. In the product each trimethylolpropane molecule must be combined with two or three different boron atoms—a relatively strain free polymer results. Triethanolamine reacts with boric acid to produce a monomeric ester, a volatile solid (VII or VIII). The product reacts with methyl iodide; the reaction follows second order kinetics, but is much slower than the corresponding reactions of simple tertiary amines. The energy of activation is 18.5 kcal. for triethanolamine borate *versus* 13.0 for triethanolamine itself. The product reacts with strong acids only at a slow, measurable rate. It is concluded from these experiments that the lone pair of the nitrogen atom cannot be free and the product must, therefore, have the "triptych" structure (VIII).




J. Am. Chem. Soc., 1951, 73 (6), pp 2808?2813

# 4-2 Protected Boronate

Michinori SUGINOME

**Interests** Organometallic Chemistry, Organic Synthesis, Polymer Synthesis

**Experience**

1987-1988 **Undergraduate Student with Professors Yoshihiko Ito and Zen-ichi Yoshida**
Department of Synthetic Chemistry, Kyoto University

1988-1993 **Graduate student with Professor Yoshihiko Ito**
Department of Synthetic Chemistry, Kyoto University

1993-2002 **Assistant Professor**
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University

1998-1999 **Visiting Researcher with Professor Gregory C. Fu**
Sabbatical leave to Massachusetts Institute of Technology

2002-2004 **Associate Professor**
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University

2004-present **Professor**
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University

**Education** Kyoto University B.S. in 1988; Ph.D. in 1993

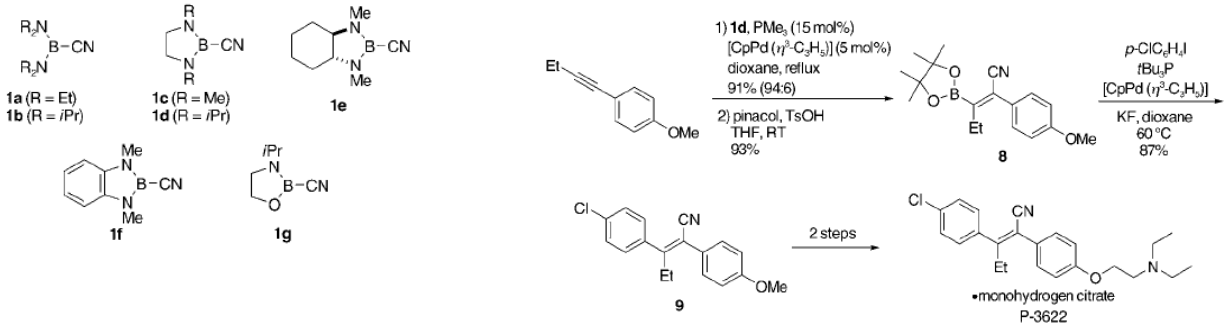
**Awards**

1999 **The Chemical Society of Japan Award for Young Chemist**
2001 **The Society of Silicon Chemistry Japan Award for Young Chemist**
2005 **Nagoya Silver Medal**
2005 **Mukaiyama Award**, Society of Synthetic Organic Chemistry, Japan
2010 **JSPS Prize**, Japan Society for the Promotion of Science

# *A Clue*

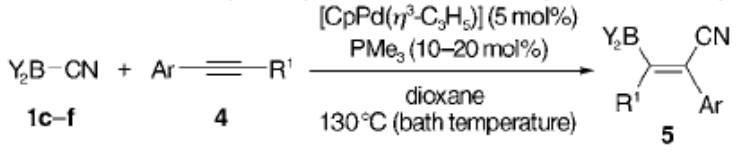
## Palladium-Catalyzed Addition of Cyanoboranes to Alkynes: Regio- and Stereoselective Synthesis of α,β-Unsaturated β-Boryl Nitriles

*Angew. Chem. Int. Ed.* **2005**, *44*, 2380–2382




***Scheme 1.*** Formal synthesis of the potential squalene synthetase inhibitor P-3622. Ts = *p*-toluenesulfonyl.

***Table 2:*** Palladium-catalyzed cyanoboration of unsymmetrical alkynes.[a]

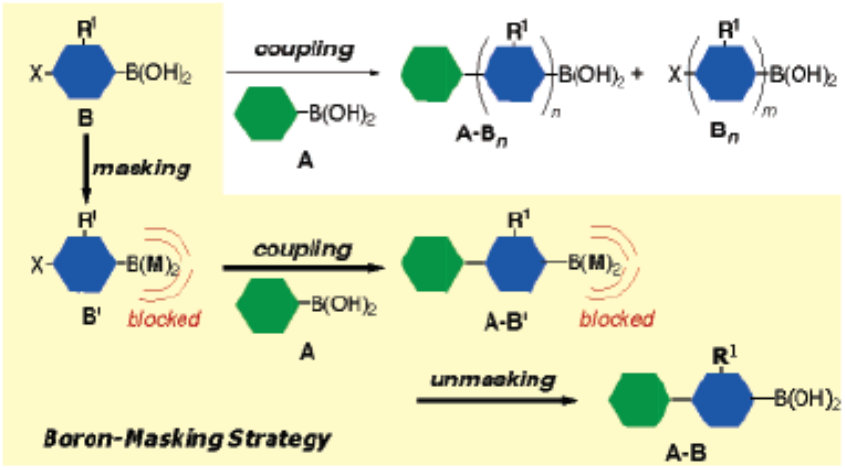


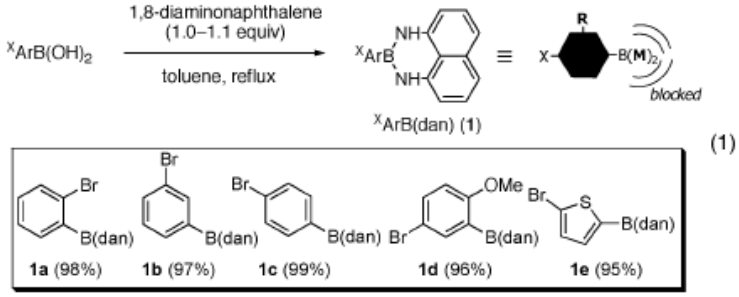

**1c–f** **4** **5**

# Boron-Masking Strategy for the Selective Synthesis of Oligoarenes Iterative Suzuki−Miyaura Coupling

*J. Am. Chem. Soc.*, **2007**, 758

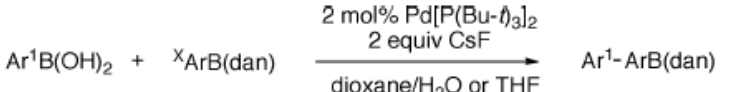
***Scheme 1.*** Boron-Masking Strategy in the Synthesis of Biarylboronic Acid via Suzuki−Miyaura Coupling

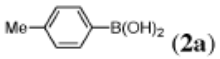
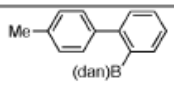
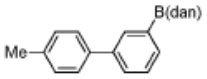
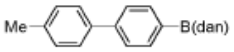
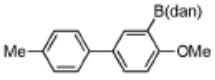
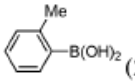
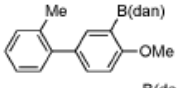
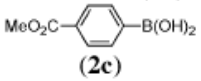
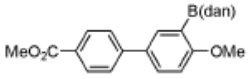
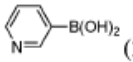
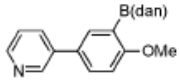
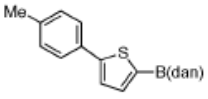



(1)

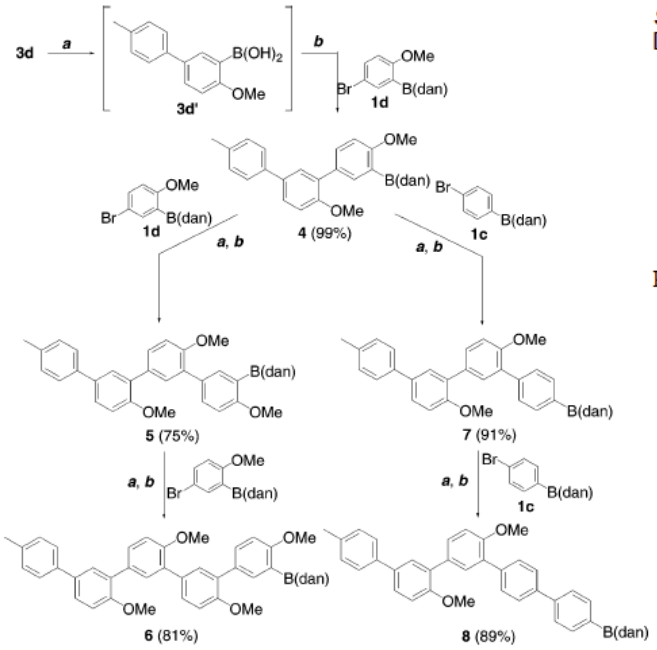
***Table 1.*** Pd-Catalyzed Coupling of Arylboronic Acids with Bromoarylboronic Acid 1,8-Diaminonaphthalene Amides[a]




| entry | 2 | 1 | product | yield /%[b] |
|---|---|---|---|---|
| 1 |  (2a) | 1a |  | 95 (3a) |
| 2 | 2a | 1b |  | 99 (3b) |
| 3 | 2a | 1c |  | 97 (3c) |
| 4 | 2a | 1d |  | 99 (3d) |
| 5 |  (2b) | 1d |  | 99 (3e) |
| 6 |  (2c) | 1d |  | 89 (3f) |
| 7 |  (2d) | 1d |  | 99 (3g) |
| 8 | 2a | 1e |  | 95 (3h) |

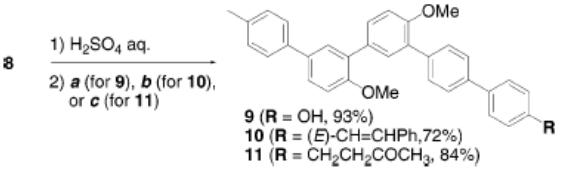
[a] 2 (0.43 mmol), 1 (0.43 mmol), Pd[P(*t*Bu$_3$)]$_2$ (8.5 $\mu$mol), and CsF (0.85 mmol). [b] Isolated yield.

***Scheme 3.*** Synthesis of Teraryl, Quarteraryls, and Quinquearyls via Iterative Cross-Coupling[a]




[a] Reaction conditions: (a) $H_2SO_4$ aq. or HCl aq., THF, rt; (b) $Pd[P(^tBu_3)]_2$ (2 mol %), CsF (2 equiv), THF, 60 °C.

***Scheme 4.*** Functionalization of the Terminus of Quinquearyl Derivative **8**



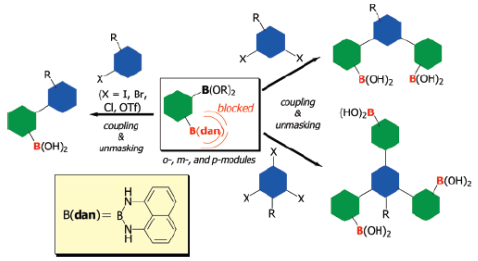

Reaction conditions: (a) $H_2O_2$, NaOH aq.; (b) (*E*)-BrCH=CHPh, $Pd[P(^tBu)_3]_2$, NaOH aq.; (c) $CH_2$=CHCOCH$_3$, Rh(acac)($C_2H_4$), BINAP.

# Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes


ORGANIC LETTERS

2008
Vol. 10, No. 3
377−380

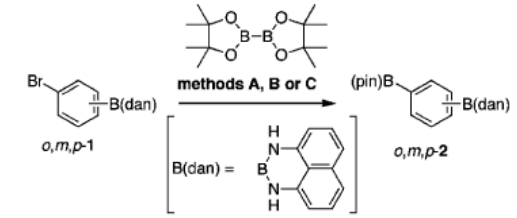

## ABSTRACT





On the basis of the boron-masking strategy, new divalent cross-coupling modules have been designed for the efficient synthesis of boron-substituted oligoarenes. The modules, i.e., monoprotected *o*-, *m*-, and *p*-benzenediboronic acid derivatives, undergo highly selective Suzuki–Miyaura coupling with $sp^2$ iodides, bromides, chlorides, and triflates, affording coupling products in which the protected boronyl groups are left intact.


**Scheme 2.** Synthesis of Monoprotected Benzenediboronic Acid Derivatives




**method A** (for *p*-**1**): 3 mol % $PdCl_2$(dppf), KOAc, DMSO, 80 °C
**method B** (for *m*-**1**): 3 mol % $Pd(dba)_2$/ $PCy_3$, KOAc, dioxane, 100 °C
**method C** (for *o*-**1**): 3 mol % $PdCl_2$(dppf), KOAc, DMSO, 100 °C

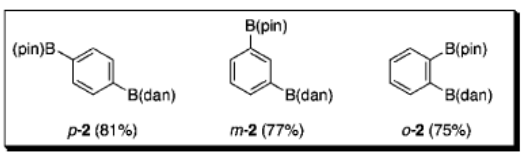
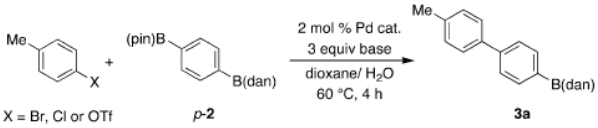



**Table 1.** Optimization of Suzuki−Miyaura Coupling Reaction Conditions[a]




X = Br, Cl or OTf  *p*-**2**  **3a**

| entry | X | catalyst | base | % yield[b] |
|---|---|---|---|---|
| 1 | Br | $Pd[P(t\text{-}Bu)_3]_2$ | KF | 37 |
| 2 | Br | $Pd[P(t\text{-}Bu)_3]_2$ | CsF | 51 |
| 3 | Br | $Pd[P(t\text{-}Bu)_3]_2$ | $Na_2CO_3$ | 58 |
| 4 | Br | $Pd[P(t\text{-}Bu)_3]_2$ | $K_3PO_4$ | 97 |
| 5 | Br | $Pd[P(t\text{-}Bu)_3]_2$ | NaOH | 99 (99) |
| 6 | Br | $Pd(OAc)_2/PPh_3$ (1/2) | NaOH | 99 |
| 7 | Br | $Pd(OAc)_2$/dppf (1/1) | NaOH | 99 |
| 8[c] | Cl | $Pd[P(t\text{-}Bu)_3]_2$ | NaOH | 92 (90) |
| 9[c] | Cl | $Pd(OAc)_2/PPh_3$ (1/2) | NaOH | N.R. |
| 10 | OTf | $Pd(OAc)_2$/(2-biphenyl)$PCy_2$ (1/2) | NaOH | (94) |

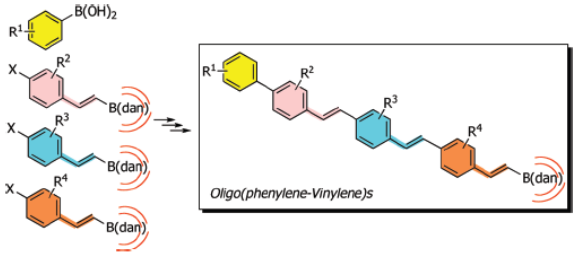
[a] A mixture of aryl halide (0.14 mmol), *p*-**2** (0.14 mmol), a catalyst (2.7 μmol), and base (0.41 mmol) was stirred at 60 °C for 4 h. [b] NMR yield. Isolated yield in the parentheses. [c] 3 mol % of catalyst at 80 °C for 24 h.

# Synthesis of B-Protected β-Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminatoborane Leading to Iterative Synthesis of Oligo(phenylenevinylene)s

ORGANIC LETTERS

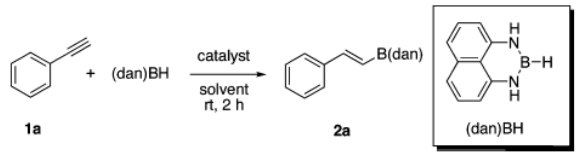
2009
Vol. 11, No. 9
1899−1902

## ABSTRACT



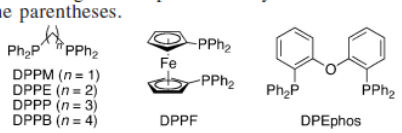

Hydroboration of aromatic and aliphatic alkynes with 1,8-naphthalenediaminatoborane ((dan)BH) proceeded in the presence of $[IrCl(cod)]_2$ complex with a DPPM or DPEphos ligand, affording alkenylboronic acids whose boronyl groups are masked by the diaminonaphthalene group. The masked alkenylboronic acids thus obtained from alkynes bearing halo-substituted aryl groups served as new coupling modules in an iterative Suzuki−Miyaura cross-coupling reaction for the synthesis of oligo(phenylenevinylene)s.

**Table 1.** Optimization of Hydroboration of Phenylacetylene with (dan)BH[a]



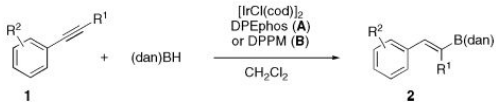

| ent | catalyst | solvent | ligand | % yield of 4[b] |
|---|---|---|---|---|
| 1 | $RhCl(PPh_3)_3$ | $CH_2Cl_2$ | | 5 |
| 2 | $[RhCl(cod)]_2$ | $CH_2Cl_2$ | $PPh_3$ | 3 |
| 3 | $[Rh(cod)_2]BF_4$ | $CH_2Cl_2$ | $PPh_3$ | 20 |
| 4 | $[Ir(cod)_2]BF_4$ | $CH_2Cl_2$ | $PPh_3$ | 34 |
| 5 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | $PPh_3$ | 50 |
| 6 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPPM | 81 |
| 7 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPPE | 76 |
| 8 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPPP | 60 |
| 9 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPPB | 26 |
| 10 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPPF | 61 |
| 11 | $[IrCl(cod)]_2$ | $CH_2Cl_2$ | DPEphos | 83 |
| 12 | $[IrCl(cod)]_2$ | toluene | DPEphos | 76 (84) |
| 13 | $[IrCl(cod)]_2$ | THF | DPEphos | 68 (85) |
| 14 | $[IrCl(cod)]_2$ | dioxane | DPEphos | 59 (77) |
| 15 | $[IrCl(cod)]_2$ | $CH_3CN$ | DPEphos | 52 (73) |

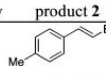
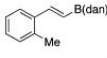
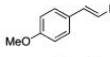
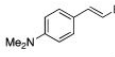
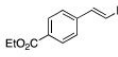
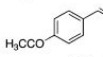
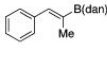
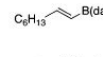
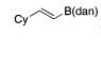
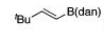
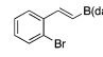
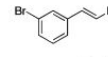
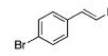
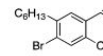
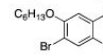
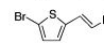
[a] A mixture of **1**, alkyne (1.5 equiv), transition metal complex (5 mol % Rh or Ir), and ligand (6.0 mol %) in $CH_2Cl_2$ was stirred at room temperature for 2 h under a nitrogen atmosphere. [b] GC yield. Yields after 24 h are shown in the parentheses.




(13) Typical procedure for the hydroboration of alkynes with (dan)BH. Synthesis of **2o**. A mixture of $[IrCl(cod)]_2$ (15.8 mg, 24 μmol) and DPPM (21.7 mg, 56 μmol) in $CH_2Cl_2$ (4 mL) was stirred at rt for 10 min under a nitrogen atmosphere. (dan)BH (149 mg, 0.89 mmol) and 4-bromo-2,5-dihexylphenylacetylene (494 mg, 1.41 mmol) in $CH_2Cl_2$ (10 mL) was added to the solution. The mixture was stirred at 50 °C for 8 h. The resultant solution was evaporated under vacuum and purified by silica gel column chromatography ($SiO_2$ pretreated with 1% $Et_3N$ in hexane, AcOEt/hexane 1:30), affording **2o** (368 mg, 80%).

**Table 2.** Iridium-Catalyzed Hydroboration of Alkynes with (dan)BH[a]

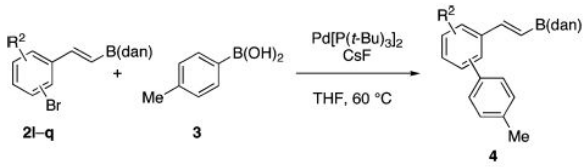


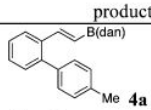
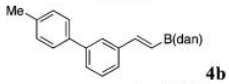
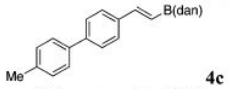
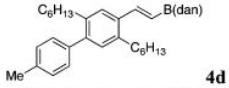
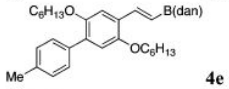
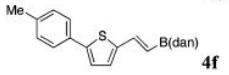

| entry | product **2** | ligand | temp, time | % yield[b] |
|---|---|---|---|---|
| 1 |  **2b** | A | 25 °C, 2 h | 84 |
| 2 |  **2c** | A | 25 °C, 2 h | 84 |
| 3 |  **2d** | A | 25 °C, 2 h | 83 |
| 4 |  **2e** | A | 25 °C, 2 h | 72 |
| 5 |  **2f** | A | 50 °C, 8 h | 69 |
| 6 |  **2g** | A | 50 °C, 8 h | 75 |
| 7 |  **2h** | B | 25 °C, 24 h | 81 |
| 8 |  **2i** | A | 25 °C, 2 h | 82 (10:1)[c] |
| 9 |  **2j** | A | 25 °C, 2 h | 80 |
| 10 |  **2k** | A | 25 °C, 2 h | 65 (>20:1)[c] |
| 11 |  **2l** | B | 50 °C, 12 h | 63 |
| 12 |  **2m** | A | 25 °C, 12 h | 63 |
| 13 |  **2n** | A | 50 °C, 8 h | 81 |
| 14 |  **2o** | B | 50 °C, 8 h | 80 |
| 15 |  **2p** | B | 50 °C, 8 h | 70 |
| 16 |  **2q** | B | 50 °C, 8 h | 41 |

[a] A mixture of **1**, alkyne (1.5 equiv), $[IrCl(cod)]_2$ (5.0 mol % Ir), and ligand (6.0 mol %) in $CH_2Cl_2$ was stirred at 25 or 50 °C under a nitrogen atmosphere. [b] Isolated yield for isomerically pure material unless otherwise noted. [c] *Trans*:*cis*.

Please see Kenta Saitou Literature Seminar

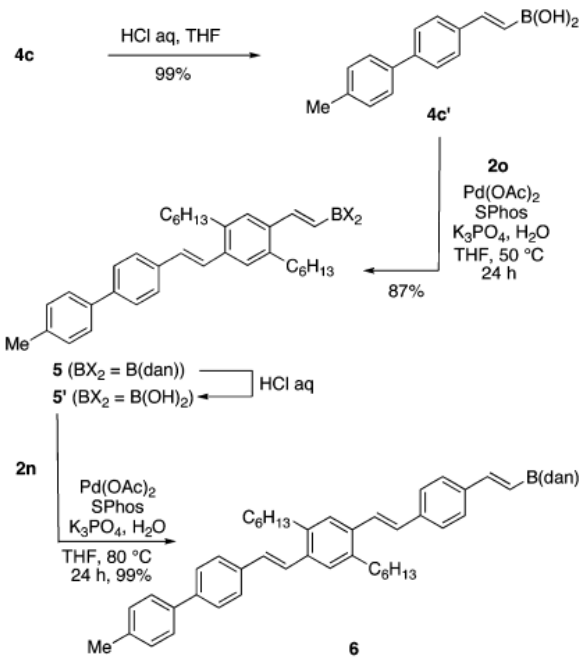
**Table 3.** Suzuki−Miyaura Coupling of Masked $\beta$-Styrylboronic Acids[a]




| entry | masked module | product | % yield[b] |
|---|---|---|---|
| 1 | **2l** |  **4a** | 83 |
| 2 | **2m** |  **4b** | 99 |
| 3 | **2n** |  **4c** | 87 |
| 4 | **2o** |  **4d** | 85 |
| 5 | **2p** |  **4e** | 86 |
| 6 | **2q** |  **4f** | 82 |

[a] See ref 13 for experimental details. [b] Isolated yield.

**Scheme 1.** Iterative Synthesis of Oligo(phenylenevinylene) **6**



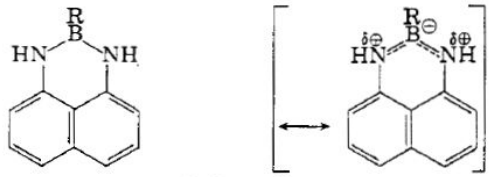

(14) Typical procedure for the cross-coupling reaction of **2**. Synthesis of **4c**. To a mixture of **2n** (49.2 mg, 0.141 mmol), *p*-tolylboronic acid (**3**) (19.2 mg, 0.141 mmol), and CsF (42.8 mg, 0.282 mmol) in THF (0.7 mL) was added $Pd(P^tBu_3)_2$ (1.44 mg, 0.00282 mmol) under a nitrogen atmosphere. The mixture was stirred at 60 °C for 4 h. After extraction with $CH_2Cl_2$, the organic phase was washed with brine and dried over $Na_2SO_4$. Filtration, evaporation, and purification by silica gel column chromatography ($CH_2Cl_2$/hexane 1:1 (5% $NEt_3$)) gave **4c** (42.0 mg, 87%).

(15) Typical procedure for the unmasking step. Synthesis of **4c′**. To a solution of **4c** (43 mg, 0.068 mmol) in THF (0.54 mL) was added hydrochloric acid (5 N, 54 $\mu$L, 0.27 mmol). The solution was stirred at room temperature for 4 h, resulting in precipitation of protonated 1,8-diaminonaphthalene. The suspension was filtered through a pad of Celite, and the solution was dried over $K_2CO_3$. Filtration and evaporation of the solvent in vacuo gave the corresponding boronic acid (35.3 mg, 99% yield) as a colorless solid. The boronic acid was used in the subsequent cross-coupling reaction without further purification.

(17) Typical procedure for the cross-coupling using SPhos as a ligand. Synthesis of **5**. To a mixture of $Pd(OAc)_2$ (0.40 mg, 1.78 $\mu$mol), SPhos (1.46 mg, 3.56 $\mu$mol), **2o** (46.0 mg, 0.0899 mmol), **4c′** (21.2 mg, 0.0890 mmol), and $K_3PO_4$ (dried, 56.7 mg, 0.267 mmol) in THF (0.750 mL) was added $H_2O$ (4.80 mg, 0.267 mmol) under a nitrogen atmosphere. The mixture was stirred at 50 °C for 24 h. After extraction with $CH_2Cl_2$, the organic phase was washed with brine and dried over $Na_2SO_4$. Filtration, evaporation, and purification by silica gel column chromatography (pretreated with 1% $NEt_3$ in hexane, $CH_2Cl_2$/hexane 1:5) gave coupling product **5** (48.8 mg, 87%).

*J. Org. Chem.* **1961** 2157

In view of the recent interest in pseudo-aromatic heterocyclic compounds containing boron and nitrogen,[1,4] we wish to report the preparation of 8-bora-7,9-diazaro-*peri*-naphthene (I).




I. R = H
II. R = $OCH_3$
III. R = $C_6H_5$

The unsubstituted compound (I) was prepared in 54% yield by reaction of 1,8-diaminonaphthalene with boron trichloride followed by reduction with lithium aluminum hydride without isolation of the B-chloro intermediate. The product was a colorless to slightly pink crystalline solid which discolored to purple during prolonged storage under nitrogen or exposure to air for several hours. Methanolysis of (I) produced 8-methoxy-8-bora-7,9-diazaro-*peri*-naphthene (II) and hydrogen. 8-Phenyl-8-bora-7,9-diazaro-*peri*-naphthene (III) was prepared in 64% crude yield by reaction of 1,8-diaminonaphthalene with phenyldichloroborane in benzene solution. Compounds I and III were very difficult to purify, apparently because they are easily oxidized when in solution, but can be handled in air as the pure solids for short periods without oxidizing significantly. The structures of these compounds were assigned on the basis of their method of preparation, carbon and hydrogen analyses, infrared, and ultraviolet spectra. A previously published attempt[5] to prepare (III) from 1,8-diaminonaphthalene and benzeneboronic acid gave an unidentified crude product melting about 18° lower than III.

Journal of Organometallic Chemistry 694 (2009) 1713–1717

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# Synthesis of masked haloareneboronic acids via iridium-catalyzed aromatic C–H borylation with 1,8-naphthalenediaminatoborane (danBH)

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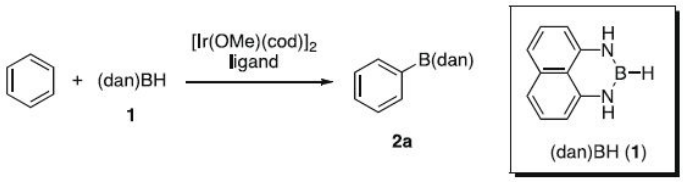
"Masked" areneboronic acids have been prepared by Ir-catalyzed C–H borylation of arenes. A $[Ir(OMe)(cod)]_2$ complex with a DPPE ligand showed the highest catalytic activity in the C–H borylation of benzene at 80 °C. The reaction system can be applied to substituted arenes, including halogen-substituted arenes. 1,3-Dihalobenzenes undergo the C–H borylation at their 5-positions in a regioselective fashion, affording 3,5-dihaloareneboronic acid derivatives, which serve as useful coupling modules for the convergent dendrimer synthesis.

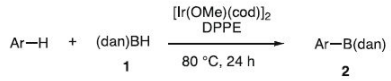
**Table 1**
Optimization of Ir-catalyzed C–H borylation of benzene with (dan)BH.[a]

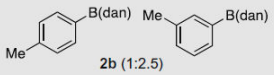
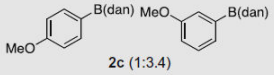
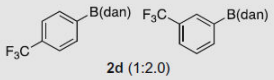
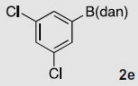
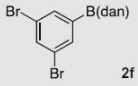
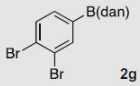
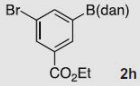
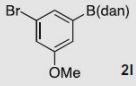
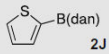



| Entry | Ligand[b] | Ir complex | Benzene (equiv.) | Temperature (°C) | % Yield[c] |
|---|---|---|---|---|---|
| 1 | DTBPY | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 12 |
| 2 | None | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 4 |
| 3 | $PPh_3$ | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 2 |
| 4 | BINAP | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 3 |
| 5 | DPPF | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 3 |
| 6 | DPPM | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 3 |
| 7 | DPPE | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 62 |
| 8 | DMPE | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 2 |
| 9 | DPPP | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 10 |
| 10 | DPPB | $[Ir(OMe)(cod)]_2$ | 60 | 80 | 4 |
| 11 | DPPE | $[Ir(OMe)(cod)]_2$ | 60 | 60 | 14 |
| 12 | DPPE | $[Ir(OMe)(cod)]_2$ | 30 | 80 | 32 |
| 13 | DPPE | $[Ir(OMe)(cod)]_2$ | 90 | 80 | 83 |
| 14 | DPPE | $[Ir(OMe)(cod)]_2$ | 120 | 80 | 93 (87) |
| 15 | DPPE | $[IrCl(cod)]_2$ | 120 | 80 | 30 |
| 16 | DPPE | $[Ir(cod)_2]BF_4$ | 120 | 80 | 5 |

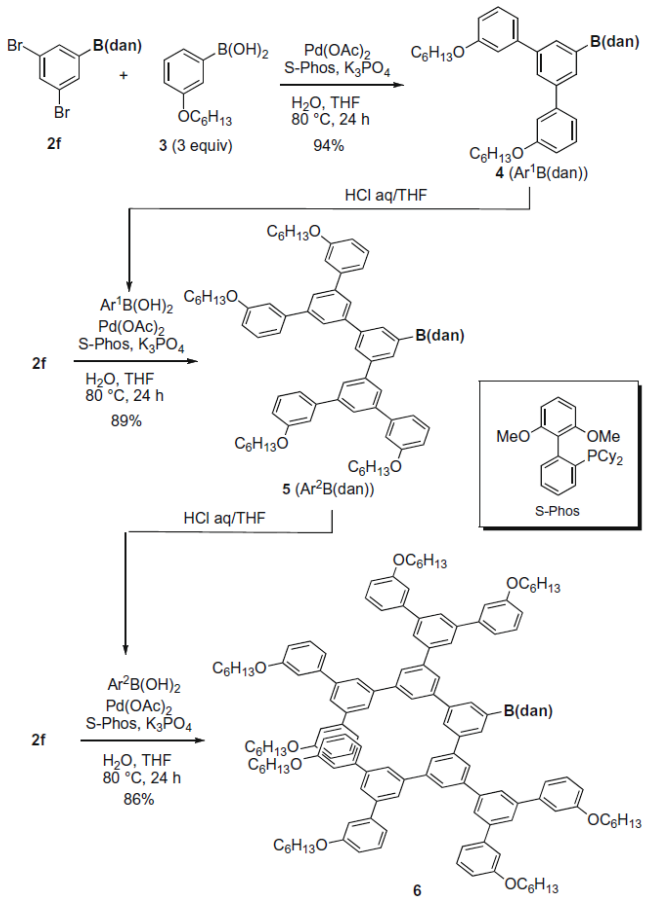
[a] A mixture of (dan)BH, benzene, an iridium complex (5 mol% Ir), and ligand (5 mol% for the bidentate ligands and 10 mol% for $PPh_3$) was stirred.
[b] DTBPY: 4,4′-di-*t*-butyl-2,2′-bipyridyl; BINAP: 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl; DPPF: 1,1′-bis(diphenylphosphino)ferrocene; DPPM: bis(diphenylphosphino)methane; DPPE: 1,2-bis(diphenylphosphino)ethane; DMPE: 1,2-bis(dimethylphosphino)ethane; DPPP: 1,3-bis(diphenylphosphino)propane; DPPB: 1,4-bis(diphenylphosphino)butane.
[c] GC yield. Isolated yield in the parenthesis.

Optimization of Ir-catalyzed C–H borylation of benzene with (dan)BH.[a]




| Entry | Ar–H (equiv.) | Product(s) | %Yield[b] |
|---|---|---|---|
| 1 | Toluene (120) |  **2b** (1:2.5) | 81 |
| 2 | Anisol (120) |  **2c** (1:3.4) | 61 |
| 3 | Trifluoromethylbenzene (120) |  **2d** (1:2.0) | 50 |
| 4 | *m*-Dichlorobenzene (30) |  **2e** | 80 |
| 5 | *m*-Dibromobenzene (30) |  **2f** | 83 |
| 6 | *o*-Dibromobenzene (30) |  **2g** | 73 |
| 7 | Ethyl m-bromobenzoic acid (30) |  **2h** | 58 |
| 8 | *m*-Bromoanisol (30) |  **2l** | 71 |
| 9 | Thiophene (30) |  **2J** | 77 |

[a] A mixture of (dan)BH, aromatic compound, an iridium complex (5 mol% Ir), and DPPE (5 mol%) was stirred at 80 °C for 24 h.
[b] Isolated yields.

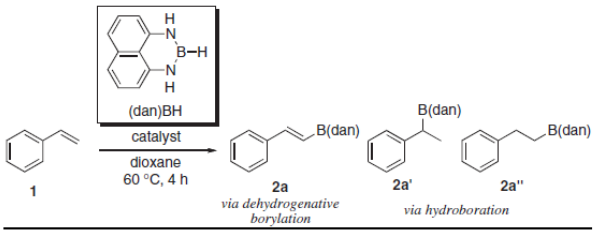



**Scheme 1.** Iterative synthesis of building blocks for the convergent dendrimer synthesis using **2f** as the cross-coupling module.

# Rhodium-catalyzed Dehydroborylation of Styrenes with Naphthalene-1,8-diaminatoborane [(dan)BH]: New Synthesis of Masked β-Borylstyrenes as New Phenylene–Vinylene Cross-coupling Modules

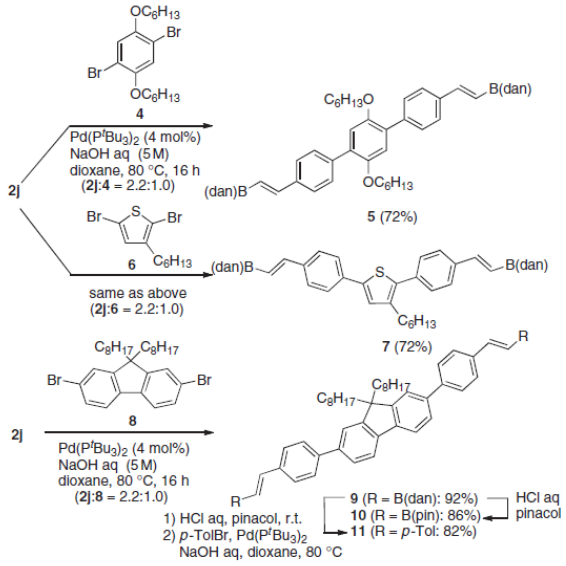
*Chem. Lett.* **2010**, *39*, 558–560

**Table 1.** Optimization of dehydroborylation of styrene with (dan)BH[a]



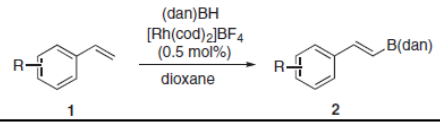

| Entry | Catalyst | Ligand | Yield **2a**[b]/% | **2a**:**2a′**:**2a″** |
|---|---|---|---|---|
| 1 | $[IrCl(cod)]_2$ | — | 27 | 30:51:19 |
| 2 | $[Ir(cod)_2]BF_4$ | — | 26 | 28:48:24 |
| 3 | $[RuCl_2(p\text{-cymene})]_2$ | — | 6 | 6:8:86 |
| 4 | $Ru_3(CO)_{12}$ | — | 44 | 82:0:18 |
| 5 | $[RhCl(cod)]_2$ | — | 0 | — |
| 6 | $[Rh(cod)_2]BF_4$ | — | 99 (91) | 99[c]:0.6:0.7 |
| 7 | $[Rh(cod)_2]BF_4$ | $PPh_3$ | 5 | 5:86:9 |

[a]A mixture of **1a** (0.3 mmol), styrene (0.75 mmol), transition-metal complex (1.5 μmol, Ir, Ru, or Rh), and ligand (3.3 μmol) in dioxane was stirred at 60 °C for 4 h under a nitrogen atmosphere. [b]GC yield. Isolated yield is shown in the parentheses. [c]>99% *E*.



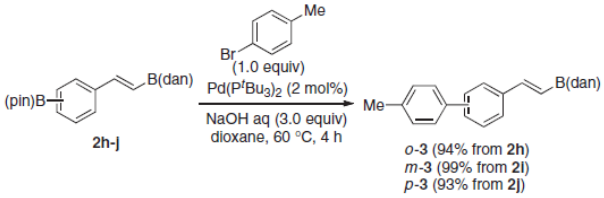

**Scheme 2.**

**Table 2.** Rhodium–catalyzed dehydrogenative borylation of styrene derivatives with (dan)BH[a]




| Entry | R | Temp/°C | Time/h | Yield[b]/% |
|---|---|---|---|---|
| 1 | *p*-Me (**2b**) | 60 | 4 | 93 |
| 2 | *p*-MeO (**2c**) | 60 | 4 | 94 |
| 3 | *p*-F (**2d**) | 60 | 4 | 93 |
| 4 | *p*-Cl (**2e**) | 60 | 4 | 83 |
| 5 | *p*-$CO_2$Et (**2f**) | 60 | 4 | 85 |
| 6 | *o*-Me (**2g**) | 60 | 4 | 82 |
| 7 | *o*-B(pin) (**2h**) | 80 | 24 | 59 |
| 8 | *m*-B(pin) (**2i**) | 60 | 4 | 67 |
| 9 | *p*-B(pin) (**2j**) | 60 | 24 | 84 |

[a]A mixture of **1** (0.3 mmol), styrene (0.75 mmol), [Rh(cod)$_2$]BF$_4$ (1.5 μmol) in dioxane was stirred under a nitrogen atmosphere. [b]Isolated yield for isomerically pure material.




**Scheme 1.**

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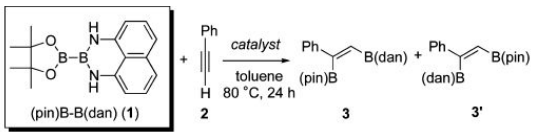
Published on Web 02/08/2010

# Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives

*J. Am. Chem. Soc.*, **2010**, 2548

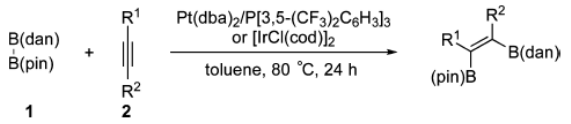
***Table 1.*** Optimization of the Diboration of Phenylacetylene Using Unsymmetrical Diboron **1**[a]




| entry | complex (mol %) | ligand (mol %) | % yield[b] | 3/3'[c] |
|---|---|---|---|---|
| 1 | $Pt(dba)_2$ (2) | – | 79 | 81:19 |
| 2 | $Pt(dba)_2$ (2) | $Ph_3P$ (2.2) | 59 | 73:27 |
| 3 | $Pt(dba)_2$ (2) | $(4\text{-}MeOC_6H_4)_3P$ (2.2) | 73 | 62:38 |
| 4 | $Pt(dba)_2$ (2) | $(2\text{-}MeC_6H_4)_3P$ (2.2) | 62 | 69:31 |
| 5 | $Pt(dba)_2$ (2) | $(4\text{-}CF_3C_6H_4)_3P$ (2.2) | 83 | 84:16 |
| 6 | $Pt(dba)_2$ (2) | $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (2.2) | 74[d] | 96:4 |
| 7 | $Pd(dba)_2$ (3) | – | 0 | – |
| 8 | $Pd(dba)_2$ (3) | $Ph_3P$ (3.3) | 21 | 53:47 |
| 9 | $Ni(cod)_2$ (3) | – | 0 | – |
| 10 | $Ni(cod)_2$ (3) | $Ph_3P$ (3.3) | 6 | 88:12 |
| 11 | $[RhCl(cod)]_2$ (1.5) | – | 5 | 58:42 |
| 12 | $[RhCl(cod)]_2$ (1.5) | $Ph_3P$ (3.3) | 3 | 87:13 |
| 13 | $[IrCl(cod)]_2$ (1) | – | 51 | 98:2 |
| 14 | $[IrCl(cod)]_2$ (1.5) | $Ph_3P$ (3.3) | 0 | – |

[a] **1** (0.1 mmol), **2** (0.15 mmol), metal complex (2–3 $\mu$mol of metal), and ligand were stirred in toluene (0.75 mL) at 80 °C for 24 h, unless otherwise noted. [b] GC yields. [c] Determined by GC analysis of the crude reaction mixture. [d] Reaction time 48 h.

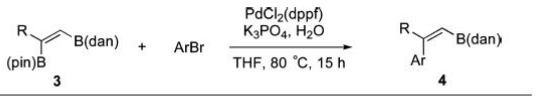
***Table 2.*** Pt- or Ir-Catalyzed Diboration of Alkynes Using Unsymmetrical Diboron **1**




| | | | | Pt catalysis[a] | | Ir catalysis[b] | |
|---|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | product | % yield[c] | 3/3'[d] | % yield[c] | 3/3'[d] |
| 1 | Ph | H | **3a** | 69[e] | 96:4 | 85[f] | 99:1 |
| 2 | $4\text{-}MeC_6H_4$ | H | **3b** | 67 | 93:7 | 67 | 93:7 |
| 3 | $2\text{-}MeC_6H_4$ | H | **3c** | 96 | 95:5 | 79 | 95:5 |
| 4 | $4\text{-}MeOC_6H_4$ | H | **3d** | 90[e] | 93:7 | 57[f] | 85:15 |
| 5 | $4\text{-}EtO_2CC_6H_4$ | H | **3e** | 92[e] | 97:3 | 74[f] | 98:2 |
| 6 | $4\text{-}AcC_6H_4$ | H | **3f** | 77 | 95:5 | 84[f] | 98:2 |
| 7 | $4\text{-}BrC_6H_4$ | H | **3g** | 81 | 96:4 | 83 | 98:2 |
| 8 | $3\text{-}BrC_6H_4$ | H | **3h** | 65 | 94:6 | 81 | 99:1 |
| 9 | 2-thiophenyl | H | **3i** | 61 | 89:11 | 64[e,g] | 99:1 |
| 10 | *n*-Hex | H | **3j** | 73 | 93:7 | 74 | 93:7 |
| 11 | Ph | Me | **3k** | 92 | 97:3 | 49 | 83:17 |

[a] **1** (0.1 mmol), **2** (0.15 mmol), $Pt(dba)_2$ (2 $\mu$mol), and the ligand (2.2 $\mu$mol) were stirred in toluene (0.75 mL) at 80 °C for 24 h, unless otherwise noted. [b] **1** (0.1 mmol), **2** (0.15 mmol), and $[IrCl(cod)_2]_2$ (1.5 $\mu$mol) were stirred in toluene (0.75 mL) at 80 °C for 24 h, unless otherwise noted. [c] Isolated yield. [d] Determined by GC or $^1H$ NMR analysis of the crude reaction mixture. [e] Reaction time 48 h. [f] At 110 °C. [g] Using 3.0 mol % $[IrCl(cod)]_2$.

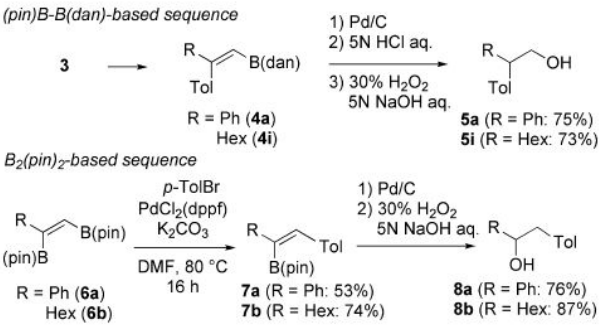
***Table 3.*** Internal-Selective Suzuki–Miyaura Coupling of **3**[a]




| entry | 3 (R) | Ar | product (% yield)[b] | ratio (stereo)[c] |
|---|---|---|---|---|
| 1 | **3a** (Ph) | *p*-Tol | **4a** (91) | 99:1 |
| 2 | **3a** (Ph) | $4\text{-}MeOC_6H_4$ | **4b** (96) | 95:5 |
| 3 | **3a** (Ph) | $4\text{-}EtO_2CC_6H_4$ | **4c** (79) | 99:1 |
| 4 | **3a** (Ph) | *o*-Tol | **4d** (99) | 95:5 |
| 5 | **3a** (Ph) | 2-thiophenyl | **4e** (75) | 83:17 |
| 6 | **3d** ($4\text{-}MeOC_6H_4$) | *p*-Tol | **4f** (88) | 98:2 |
| 7 | **3f** ($4\text{-}AcC_6H_4$) | *p*-Tol | **4g** (99) | 98:2 |
| 8 | **3i** (2-thiophenyl) | *p*-Tol | **4h** (93) | 98:2 |
| 9 | **3j** (*n*-Hex) | *p*-Tol | **4i** (88) | 98:2 |

[a] **3** (0.070 mmol), aryl bromide (0.077 mmol), $PdCl_2(dppf)$ (1.4 $\mu$mol), base (0.21 mmol), and $H_2O$ (0.7 mmol) were stirred in THF (0.75 mL) at 80 °C for 15 h. [b] Isolated yield. [c] Ratio of **4** and its stereoisomer **4'** (GC analysis and/or $^1H$ NMR).

***Scheme 1.*** Regiocomplementary Synthesis of $\beta$-Arylethanols



Professor Martin D. Burke

**Education**

| | |
|---|---|
| 1998-2005 | National Institutes of Health Fellow in the Medical Scientist Training Program<br>Harvard Medical School/Massachusetts Institute of Technology<br>Division of Health Sciences and Technology: Boston, Massachusetts<br>Degree awarded: M.D. |
| 1999-2003 | Howard Hughes Medical Institutes Predoctoral Fellow<br>Harvard University, Department of Chemistry and Chemical Biology<br>Cambridge, Massachusetts, Degree Awarded: Ph.D.<br>Thesis advisor: Professor Stuart L. Schreiber |
| 1994-1998 | Johns Hopkins University, Baltimore, Maryland<br>Degree Awarded: B.A. Chemistry<br>Research advisors: Professors Henry Brem and Gary H. Posner |

# A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki–Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks

Eric P. Gillis and Martin D. Burke*

*J. Am. Chem. Soc.* **2007**, 6716

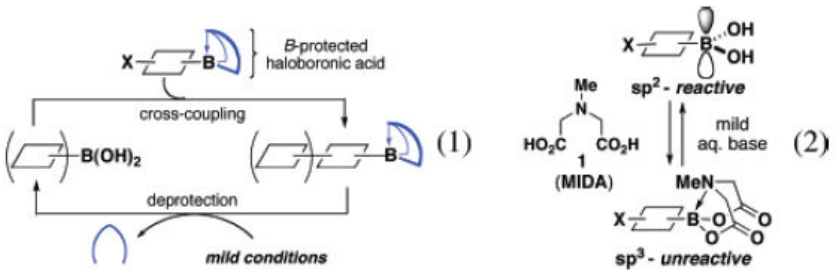
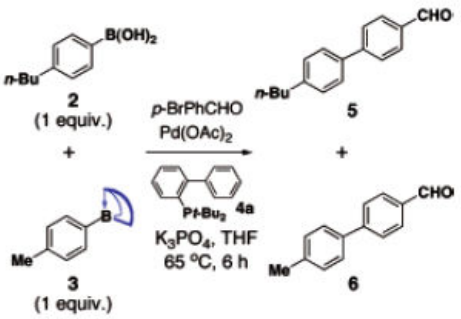
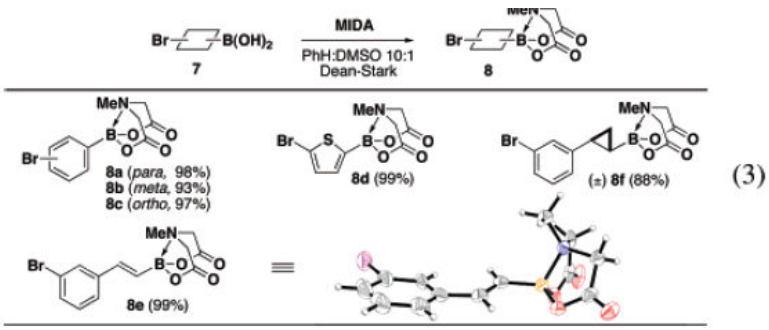
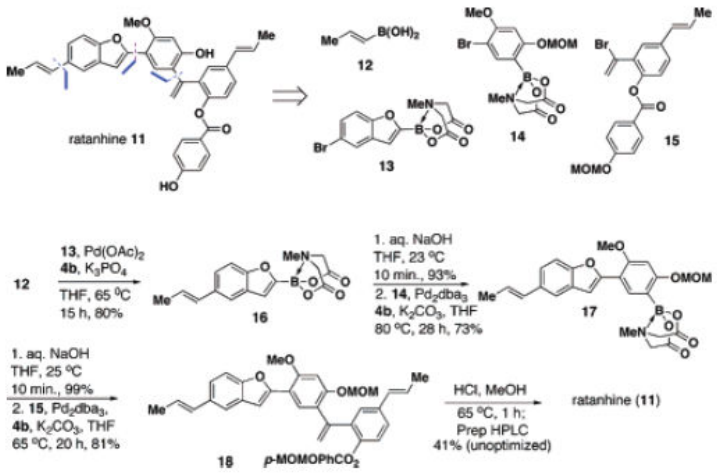



***Table 1***

| Entry | p-Tol– | 5 : 6 |
|---|---|---|
| 1 | 3a | 24 : 1.0 |
| 2 | 3b | 1.0 : 1.0 |
| 3 | 3c | 26 : 1.0 |
| 4 | 3d | 1.0 : 1.0 |





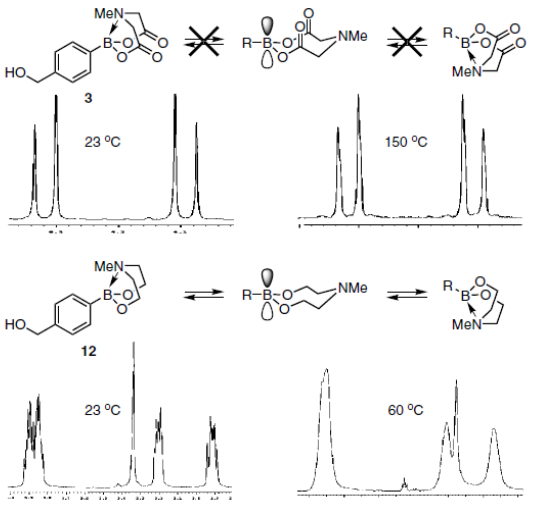
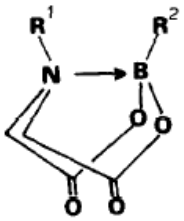
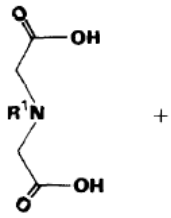




**Figure 2.** Variable-Temperature NMR Studies in DMSO-$d_6$ with MIDA Boronate and *N*-Methyldiethanolamine Adducts That Demonstrate the Unique and Remarkable Conformational Rigidity of the MIDA Boronate Framework. *(Ref. 6)*

*Journal of Organometallic Chemistry*, 307 (1986) 1–6



| $R^1$ | $R^2$ | Nr. |
|---|---|---|
| H | $C_6H_5$ | **1** |
| $CH_3$ | $C_6H_5$ | **2** |
| H | $C(CH_3)_2CH(CH_3)_2$ | **3** |
| $CH_3$ | $C(CH_3)_2CH(CH_3)_2$ | **4** |



$$+ R^2B(OR^3)_2 \xrightarrow[55°C]{(CH_3)_2SO/C_6H_6} \mathbf{1–4}$$

(**5**, $R^1 = H$; (**7**, $R^2 = C_6H_5$, $R^3 = H$;
**6**, $R^1 = CH_3$) **8**, $R^2 = C(CH_3)_2CH(CH_3)_2$, $R^3 = CH_3$)

**Summary**

The reactions of phenylboronic acid or dimethylthexylboronic ester with iminodiacetic- or *N*-methyliminodiacetic acids lead in high yield to the air-stable bicyclic esters (N–B)phenyl[iminodiacetate-*O*,*N*]borane (**1**), (N–B)phenyl[*N*-methyliminodiacetate-*O*,*N*]borane (**2**), (N–B)thexyl[iminodiacetate-*O*,*N*]borane (**3**) and (N–B)thexyl[*N*-methyliminodiacetate-*O*,*N*]borane (**4**). These are shown by $^1H$, $^{11}B$ and $^{13}C$ NMR spectroscopy to have rigid bicyclic structures of strong intramolecular N–B coordination.

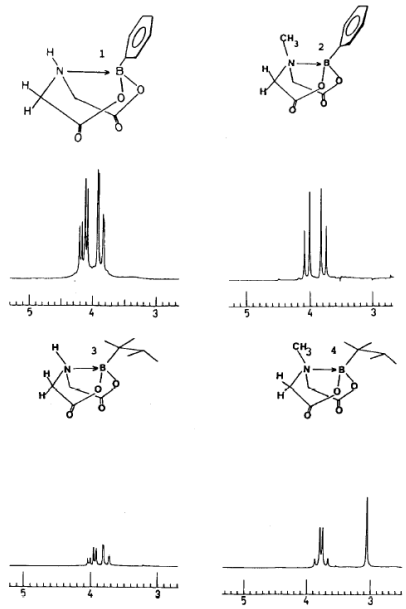


Fig. 1. Methylene $^1H$ resonances of compounds **1–4** at 25°C; these remain unchanged up to 125°C (**1**, **2** and **4**) or 140°C (**3**). The additional coupling $^3J$(HNCH) in **1** and **4** disappears upon addition of $D_2O$.

# Simple, Efficient, and Modular Syntheses of Polyene Natural Products via Iterative Cross-Coupling

*J. Am. Chem. Soc.* **2008**, 466.

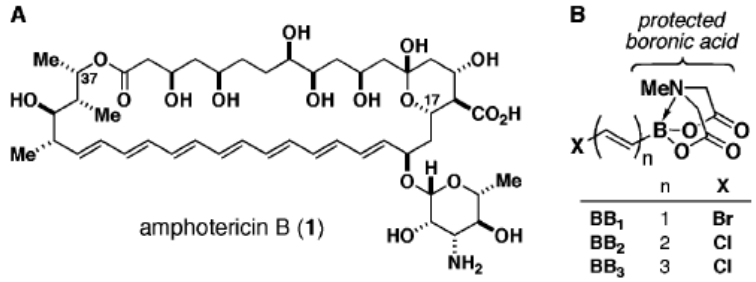
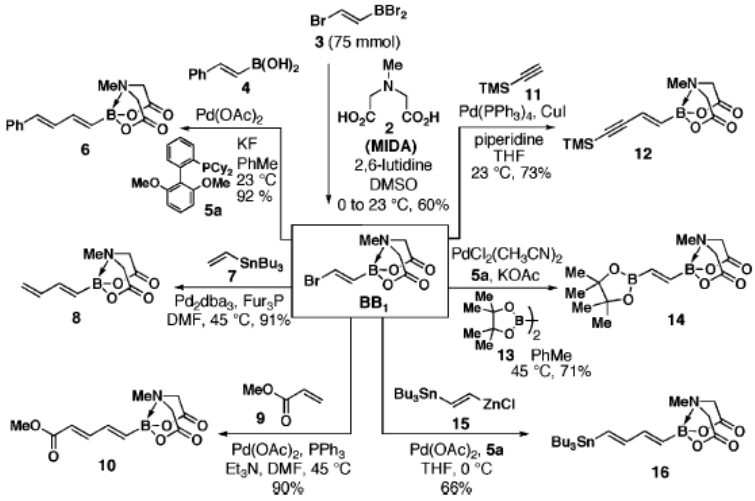
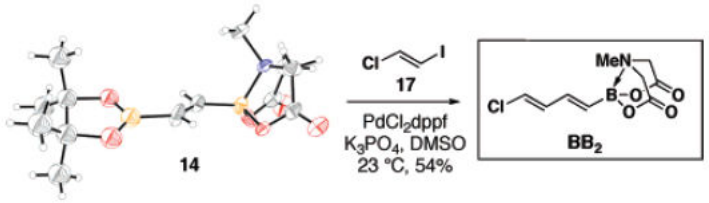



***Figure 1.*** (A) Channel-forming natural product amphotericin B. (B) Series of B-protected haloalkenylboronic acid building blocks for polyene synthesis.

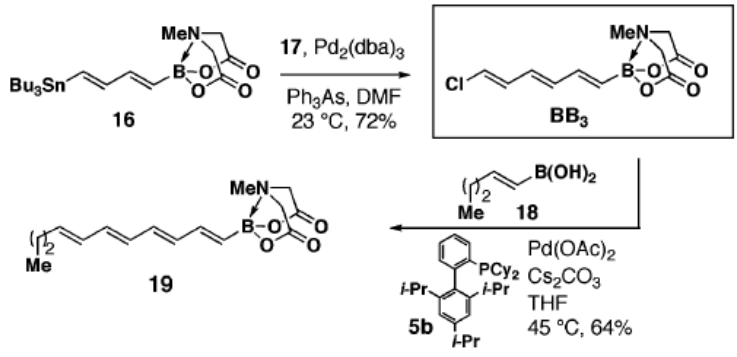
***Scheme 1***



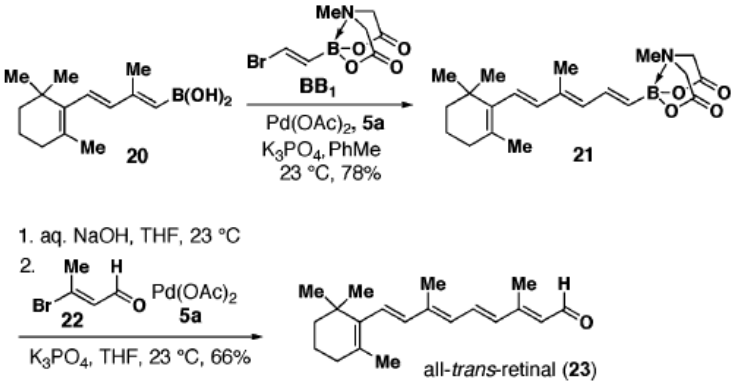

***Scheme 2***



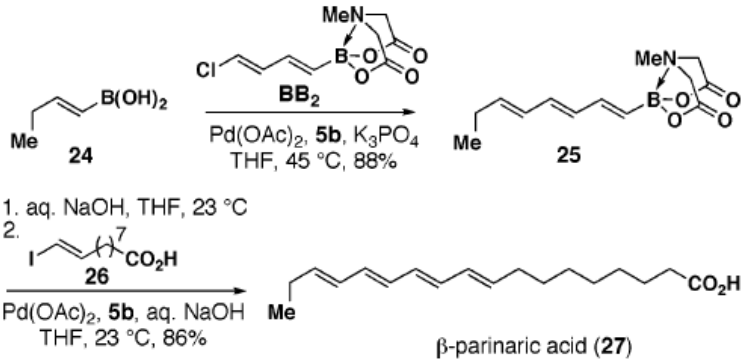

***Scheme 3***



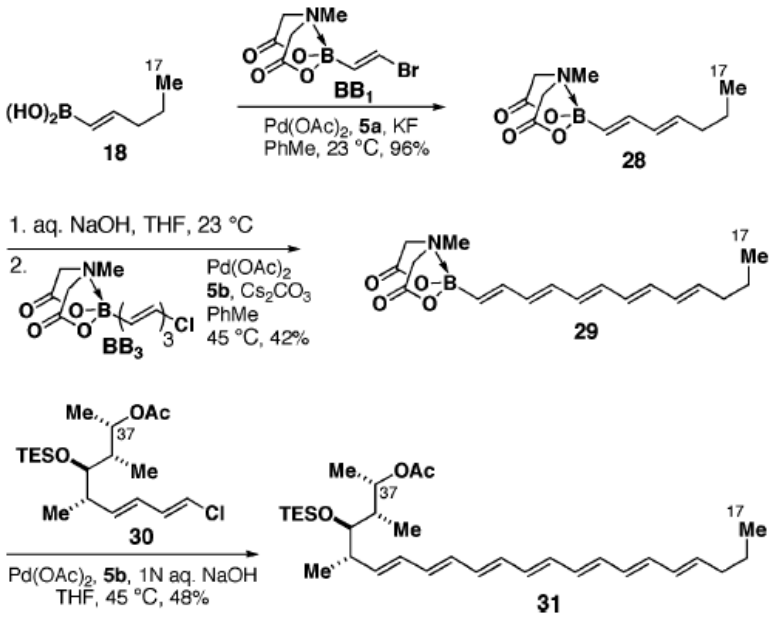
***Scheme 4***




***Scheme 5***



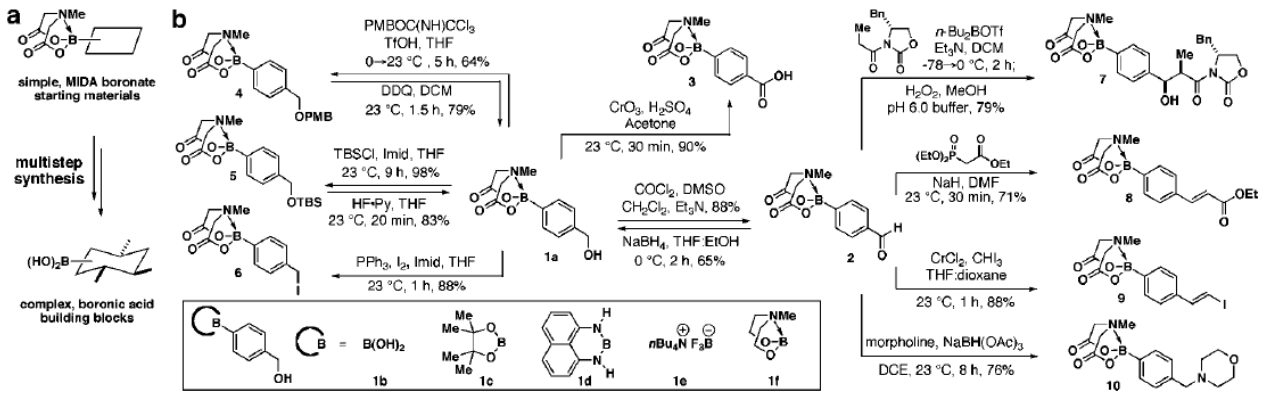

***Scheme 6***



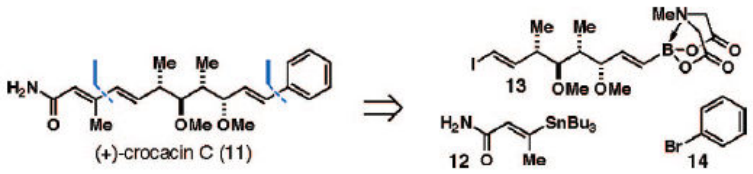
# Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates

*J. Am. Chem. Soc.* **2008**, 14084

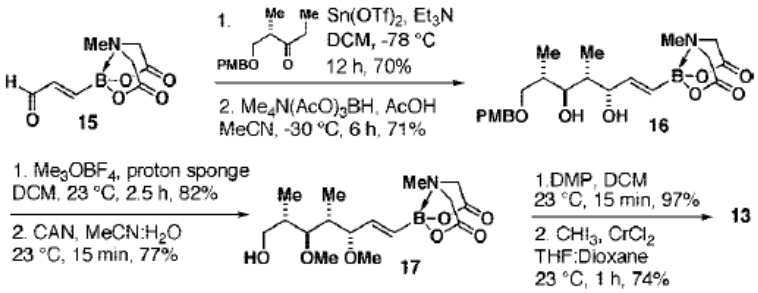
***Scheme 1***



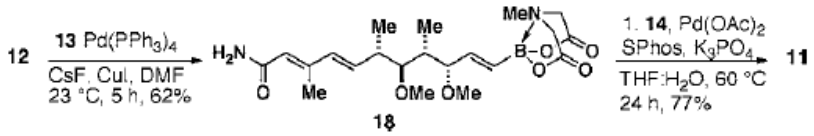

***Scheme 2***




***Scheme 3***



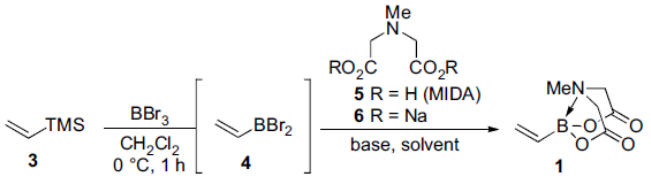

***Scheme 4***



# Vinyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis

Tetrahedron 65 (2009) 3130–3138

**Table 1**
Synthesis of **1** from vinyltrimethylsilane (**3**)




| Entry | Ligand | Base | Solvent | % Yield |
|---|---|---|---|---|
| 1 | **5** | 2,6-Lutidine | DMSO | 51 |
| 2 | **6** | None | DMSO | 18 |
| 3 | **6** | None | $CH_3CN$ | 86 |

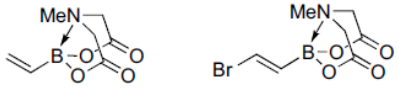
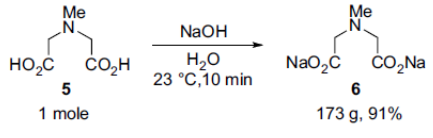
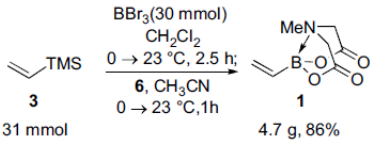
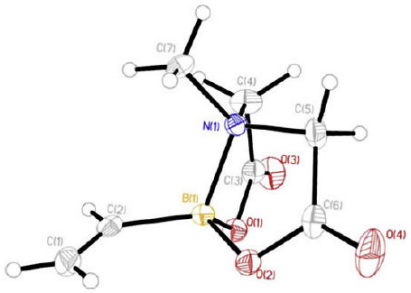


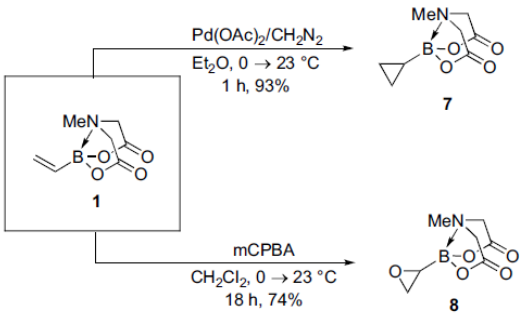

**Figure 1.** Air-stable alkenyl MIDA boronate building blocks for small molecule synthesis.

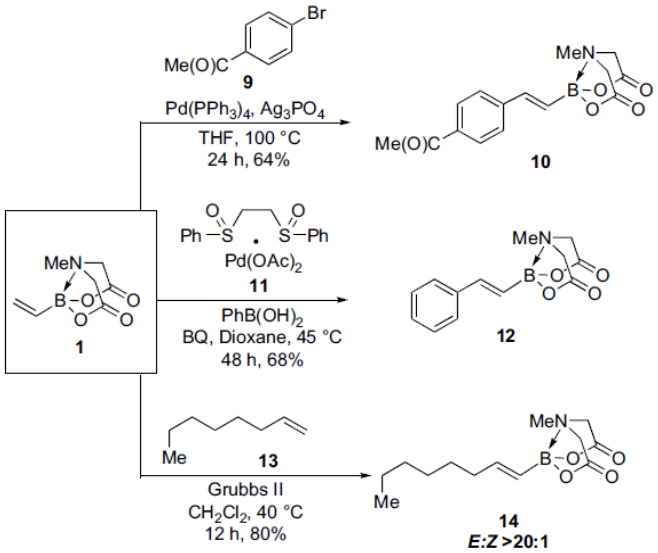



**Scheme 1.**



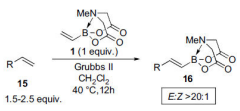



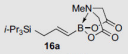
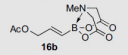
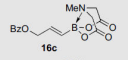
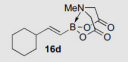
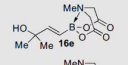
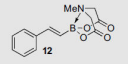



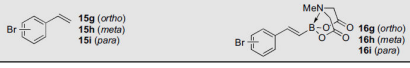



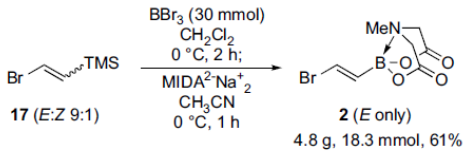

**Scheme 4.**

**Table 2**




| Entry | Cross partner | Cross Product | Isolated yield (%) |
|---|---|---|---|
| 1 |  **15a** |  **16a** | 85 |
| 2 |  **15b** |  **16b** | 84 |
| 3 |  **15c** (*E*:*Z* 1:1) |  **16c** | 98 |
| 4 |  **15d** |  **16d** | 96 |
| 5 |  **15e** |  **16e** | 94 |
| 6 |  **15f** |  **12** | 93 |
| 7 | **15g** (*ortho*) | **16g** (*ortho*) | 81 |
| 8 | **15h** (*meta*) | **16h** (*meta*) | 91 |
| 9 | **15i** (*para*) | **16i** (*para*) | 89 |




**Scheme 5.**

# A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates

*J. Am. Chem. Soc.* **2009**, 6961

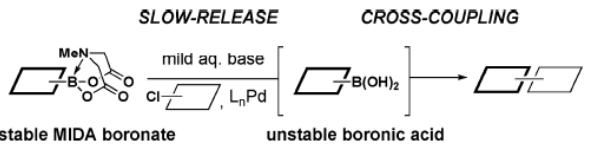
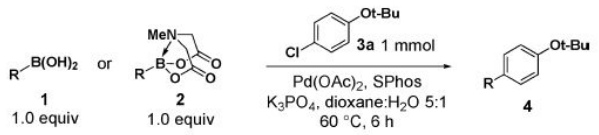



*Figure 1*

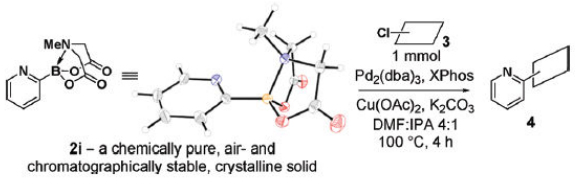
*Table 1.* Benchtop Stability and Cross-Coupling Efficiency of Boronic Acids and the Corresponding MIDA Boronates




| entry | R | % remaining after benchtop storage under air[a] 1 (15 days) | 2 (60 days) | 4 | % isolated yield from cross-coupling[c] 1 | 2 |
|---|---|---|---|---|---|---|
| 1 | a | 7 | >95[b] | 4a | 68 | **94** |
| 2 | b | 88 | >95 | 4b | 50 | **92** |
| 3 | c | 80 | >95 | 4c | 37 | **94** |
| 4 | d | 80 | >95[b] | 4d | 45 | **96** |
| 5 | e | <5 | >95 | 4e | 61 | **90** |
| 6 | f | <5 | >95 | 4f | 14 | **93** |
| 7[d] | g | 5 | >95[b] | 4g | 79 | **98** |
| 8[d] | h | 31 | >95 | 4h | 95 | **96** |

[a] Freshly prepared boronic acids **1** and MIDA boronates **2** were stored as solids on the benchtop under air for 15 and 60 days, respectively.[18] [b] Stored for 107 days. [c] Reaction conditions: 1.0 equiv of **3a** (1 mmol), 1.0 equiv of **1** (freshly prepared, >95% pure) or **2**, 5 mol % $Pd(OAc)_2$, 10 mol % SPhos, 7.5 equiv of $K_3PO_4$, 0.07 M in 5:1 dioxane/$H_2O$, 60 °C, 6 h. [d] Cross-couplings were run at 100 °C.

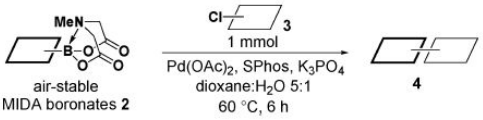
*Table 3.* Slow-Release Cross-Coupling of Air-Stable 2-Pyridyl MIDA Boronate **2i** with Aryl and Heteroaryl Chlorides[a]




| entry | 3 | 4 | % isolated yield |
|---|---|---|---|
| 1 | 3j | 4dd | 72 |
| 2 | 3k | 4ee | 60 |
| 3 | 3i | 4ff | 79 |
| 4 | 3e | 4gg | 52 |
| 5 | 3l | 4hh | 74 |

[a] Reaction conditions: 1.0 equiv of aryl halide **3** (1 mmol), 1.5 equiv of MIDA boronate **2i**, 1.5 mol % $Pd_2(dba)_3$, 6 mol % XPhos, 50 mol % $Cu(OAc)_2$, 5 equiv of $K_2CO_3$, 0.1 M in 4:1 DMF/IPA, 100 °C, 4 h.

*Table 2.* Slow-Release Cross-Coupling of Air-Stable 2-Heterocyclic, Vinyl, and Cyclopropyl MIDA Boronates with Aryl and Heteroaryl Chlorides[a]

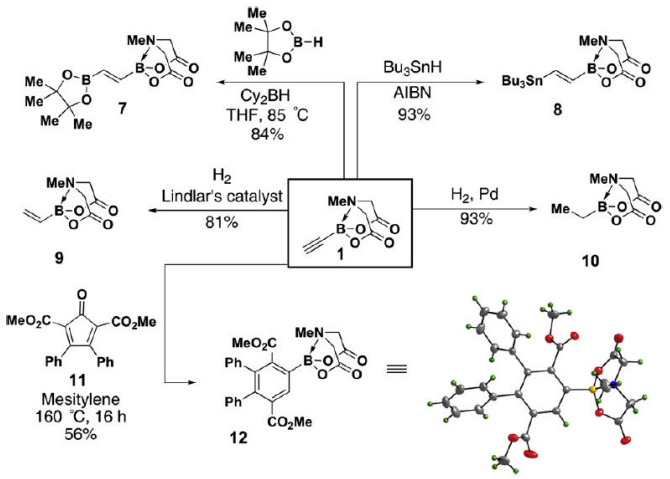



| entry | 2 | 3 | 4 | % isolated yield |
|---|---|---|---|---|
| 1 | 2a | 3b | 4i | 99 |
| 2 | 2a | 3c | 4j | 97 |
| 3 | 2a | 3d | 4k | 99 |
| 4 | 2a | 3e | 4l | 91 |
| 5 | 2b | 3b | 4m | 94 |
| 6 | 2b | 3f | 4n | 94 |
| 7[b] | 2b | 3g | 4o | 85 |
| 8[b] | 2b | 3h | 4p | 85 |
| 9 | 2c | 3b | 4q | 98 |
| 10 | 2c | 3d | 4r | 99 |
| 11 | 2c | 3i | 4s | 97 |
| 12[c] | 2e | 3b | 4t | 81 |
| 13[c] | 2e | 3d | 4u | 98 |
| 14 | 2f | 3b | 4v | 97 |
| 15 | 2f | 3d | 4w | 93 |
| 16[d,e] | 2g | 3c | 4x | 91 |
| 17[d,e] | 2g | 3i | 4y | 87 |
| 18[d,e] | 2g | 3g | 4z | 76 |
| 19[d,e] | 2g | 3d | 4aa | 96 |
| 20[b,d,f] | 2h | 3c | 4bb | 79 |
| 21[d] | 2h | 3b | 4cc | 97 |

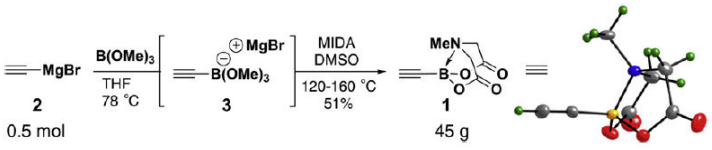
[a] General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.2 equiv of MIDA boronate, 5 mol % $Pd(OAc)_2$, 10 mol % SPhos, 7.5 equiv of $K_3PO_4$, 0.07 M in 5:1 dioxane/$H_2O$, 60 °C, 6 h. [b] Using 1.5 equiv of MIDA boronate. [c] Using 0.5 mmol of aryl halide, 0.6 mmol of MIDA boronate (1.2 equiv) [d] At 100 °C. [e] Reaction time 2 h. [f] Reaction time 24 h.

# Ethynyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis

Tetrahedron 66 (2010) 4710–4718

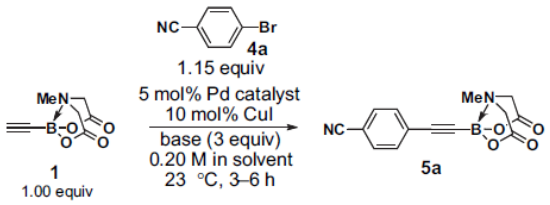



Scheme 3.

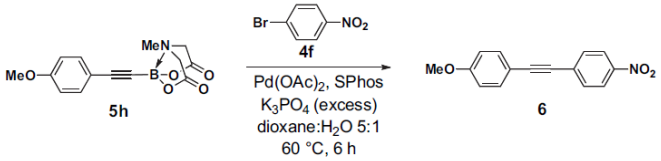



Scheme 1. (Ref. 10).

**Table 1**

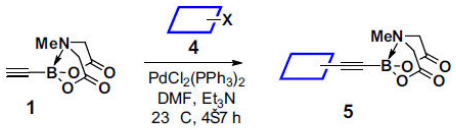



| Entry | Pd catalyst | Base | Solvent | % Yield |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | Piperidine | THF | 30 |
| 2 | $PdCl_2(PPh_3)_2$ | $ET_3N$ | THF | 78 |
| 3 | $PdCl_2(PPh_3)_2$ | $ET_3N$ | DMSO | 47 |
| 4 | $PdCl_2(PPh_3)_2$ | $ET_3N$ | $CH_3CN$ | 59 |
| 5 | $PdCl_2(PPh_3)_2$ | $ET_3N$ | DMF | 93 |




Scheme 2.

**Table 2**



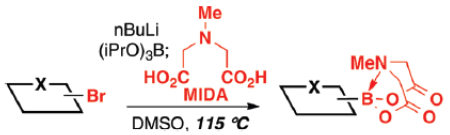

| Entry | 4 | 5 | Isolated yield (%) |
|---|---|---|---|
| 1 | 4a | 5a | 93 |
| 2 | 4b | 5b | 95 |
| 3 | 4c | 5c | 92 |
| 4 | 4d | 5d | 69 |
| 5 | 4e | 5e | 80 |
| 6 | 4f | 5f | 65 |
| 7 | 4g | 5g | 72 |
| 8 | 4h | 5h | 33 |
| 9 | 4i | 5h | 80 |
| 10 | 4j | 5i | 75 |
| 11 | 4k | 5j | 88 |
| 12 | 4l | 5k | 88 |
| 13 | 4m | 5l | 67 |
| 14 | 4n | 5m | 55 |

# General Method for Synthesis of 2-Heterocyclic *N*-Methyliminodiacetic Acid Boronates

ORGANIC LETTERS

2010
Vol. 12, No. 10
2314−2317

## ABSTRACT




A wide range of 2-pyridyl and other difficult-to-access heterocyclic *N*-methyliminodiacetic acid boronates can be readily prepared from the corresponding bromides via a new method involving direct transligation of 2-heterocyclic trialkoxyborate salts with *N*-methyliminodiacetic acid (MIDA) at elevated temperatures.

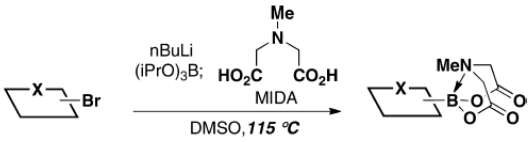



**Figure 1.** New method that provides access to a wide range of 2-pyridyl and other difficult-to-access MIDA boronates from the corresponding readily available bromides.

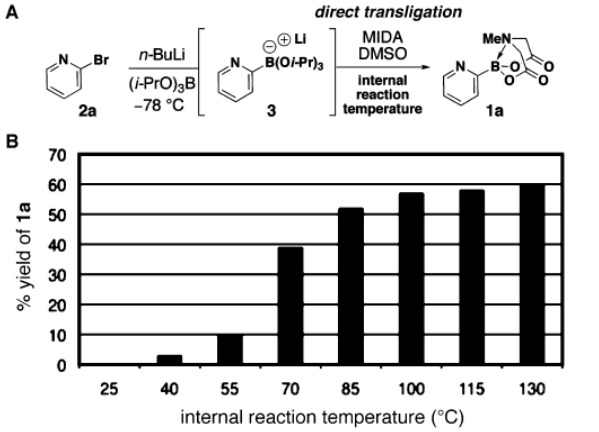
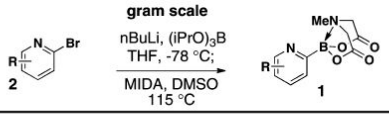


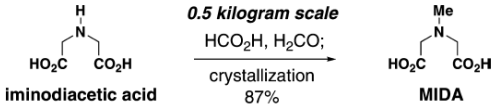

**Figure 2.** (A) Method for the preparation of 2-pyridyl MIDA boronate **1a** from **2a** via the intermediacy of triisopropoxyborate salt **3**. (B) Yield of **1a** (via $^1$H NMR, average of two runs) as a function of the internal reaction temperature.

**Table 1.** Synthesis of 2-Pyridyl MIDA Boronates

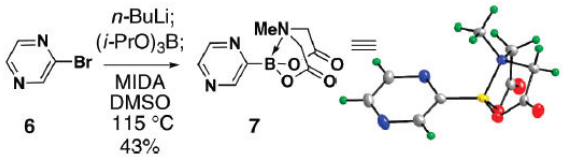



| entry | 2 | 1 | isolated yield (%) |
|---|---|---|---|
| 1 | 2a | 1a | 59 |
| 2 | 2b | 1b | 58 |
| 3 | 2c | 1c | 51 |
| 4 | 2d | 1d | 42 |
| 5 | 2e | 1e | 81 |
| 6 | 2f | 1f | 89 |
| 7 | 2g | 1g | 56 |
| 8 | 2h | 1h | 53 |
| 9 | 2i | 1i | 47 |
| 10 | 2j | 1j | 69 |

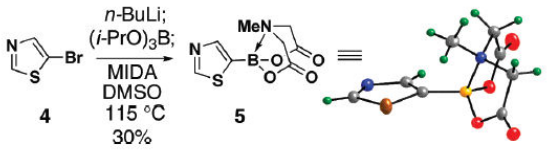
**Scheme 1**




**Scheme 3**

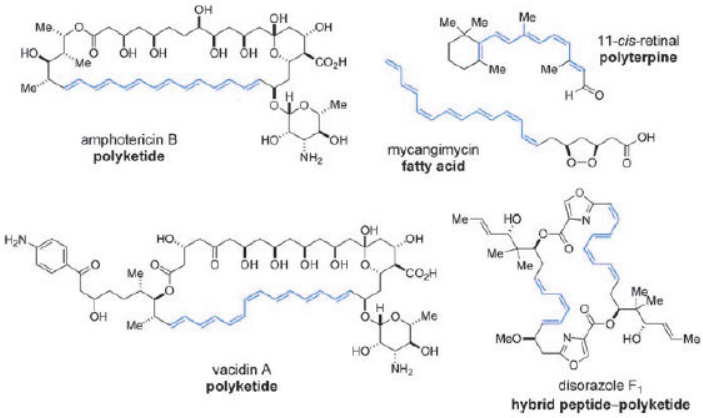



**Scheme 2**

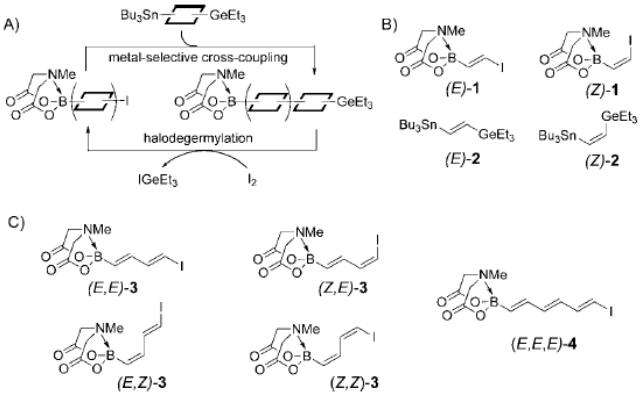


# A Simple and General Platform for Generating Stereochemically Complex Polyene Frameworks by Iterative Cross-Coupling**

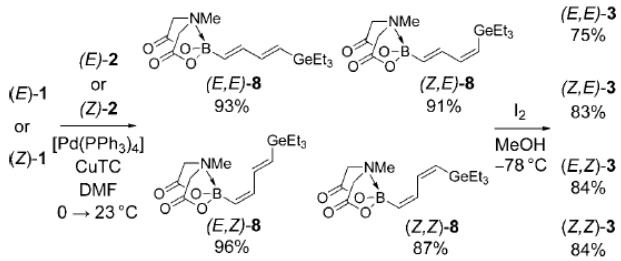
*ACIE* **asap**



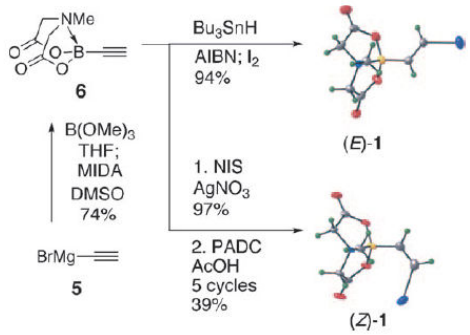

***Scheme 1.*** Polyene natural products derived from a wide range of biosynthetic pathways.



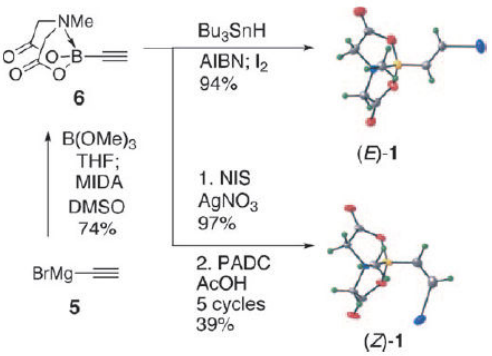

***Scheme 2.*** A) A strategy for ICC of halogen-masked bifunctional building blocks. B) Core building blocks to enable general access to stereoisomeric iodopolyenyl MIDA boronates. C) New iodopolyenyl MIDA boronates for the synthesis of polyene natural products.



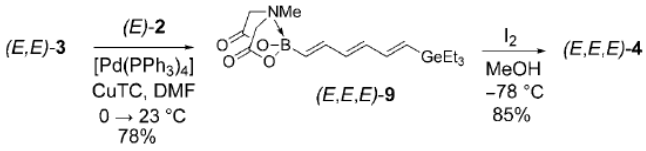

***Scheme 5.*** Efficient and stereospecific syntheses of all possible stereoisomers of **3** by metal-selective ICC. TC = thiophene-2-carboxylate.



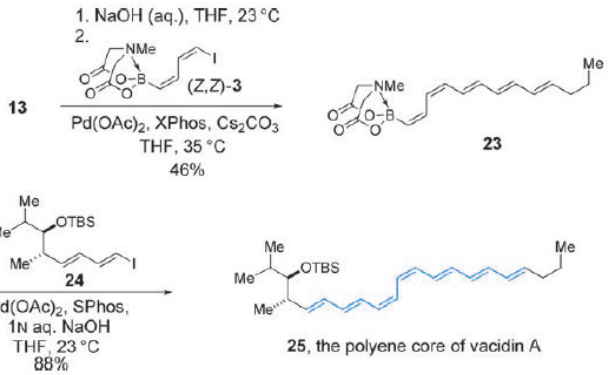

***Scheme 3.*** Synthesis of bifunctional MIDA boronate building blocks (*E*)-**1** and (*Z*)-**1** from the common intermediate ethynyl MIDA boronate **6**. Color code: red, O; gray, C; green, H; yellow, B; light blue, N; dark blue, I. DMSO = dimethyl sulfoxide, AIBN = azobisisobutyronitrile, NIS = *N*-iodosuccinimide, PADC = potassium azodicarboxylate.




***Scheme 3.*** Synthesis of bifunctional MIDA boronate building blocks (*E*)-**1** and (*Z*)-**1** from the common intermediate ethynyl MIDA boronate **6**. Color code: red, O; gray, C; green, H; yellow, B; light blue, N; dark blue, I. DMSO = dimethyl sulfoxide, AIBN = azobisisobutyronitrile, NIS = *N*-iodosuccinimide, PADC = potassium azodicarboxylate.

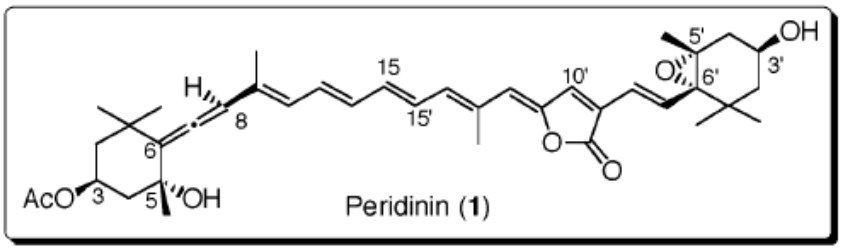



***Scheme 6.*** Preparation of iodotrienyl MIDA boronate (*E*,*E*,*E*)-**4** by metal-selective ICC.




***Scheme 7.*** Synthesis of the stereochemically complex heptaene core of vacidin A.

# 5 Total Synthetis of Peridinin




**accomplished by**
**Ito group**
**Katsumura group**
**Brukner group**
**de Lera group**
**Burke group**

## 5-1 Katsumura group

### Highly Efficient Stereocontrolled Total Synthesis of the Polyfunctional Carotenoid Peridinin**

*Angew. Chem. Int. Ed.* **2002**, *41*, **1023**

### Stereocontrolled Total Synthesis of a Polyfunctional Carotenoid, Peridinin

*J. Org. Chem.* **2004**, *69*, 7949−7959

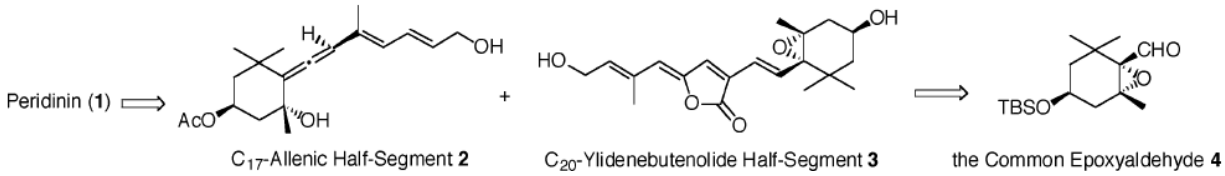
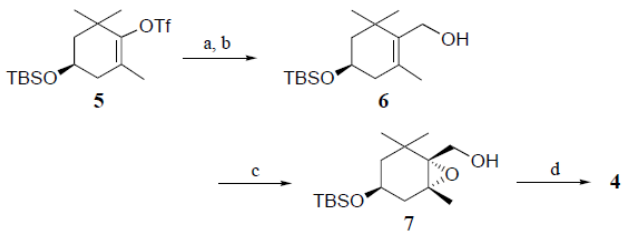
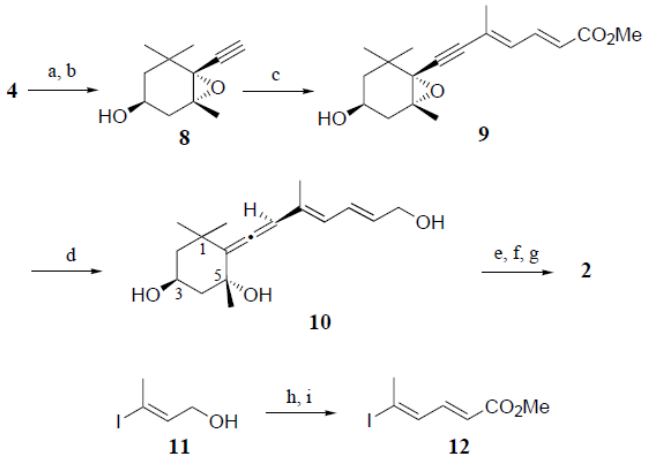



**FIGURE 2.** Retrosynthetic analysis.

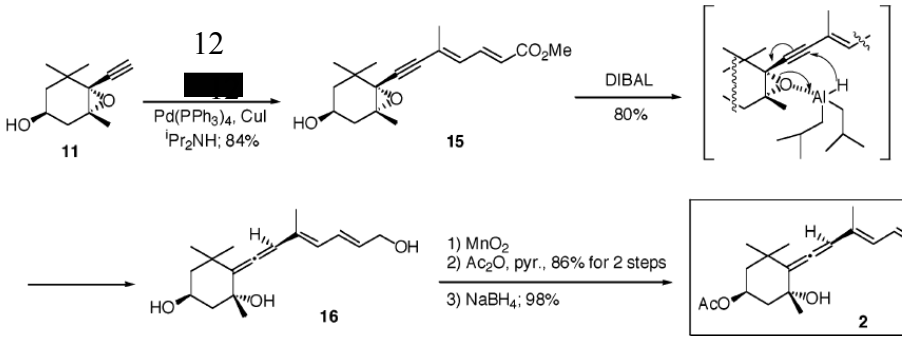


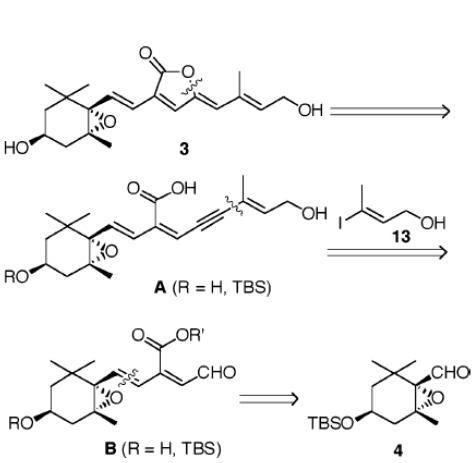

Scheme 2. Synthesis of **4**: a) CO, $[Pd(PPh_3)_4]$, $Et_3N$, MeOH, DMF, 70 °C, 15 h (97 %); b) $LiAlH_4$, THF, 45 °C, 20 h (87 %); c) (−)-diethyl-D-tartrate, $Ti(OiPr)_4$, 1.5 M TBHP in toluene, molecular sieves (4 Å), $CH_2Cl_2$, −20 °C, 30 min (99 %, 92 % *de*); d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 40 min; $Et_3N$, 10 min (100 %). DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TBHP = *tert*-butylhydroperoxide.

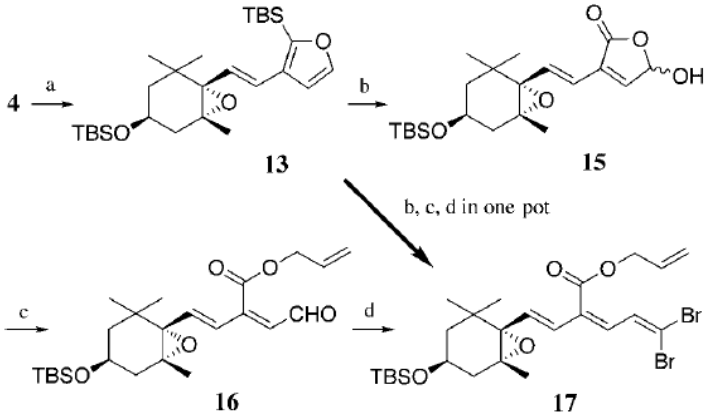



Scheme 3. Synthesis of **2**: a) $ClCH_2P^+Ph_3Cl^-$, *n*BuLi, THF, −30 °C, 3 h; b) *t*BuOK, DMSO, room temperature, 20 min (53 % over two steps); c) **12**, $[Pd(PPh_3)_4]$, CuI, $iPr_2NH$, room temperature, 1 h (84 %); d) DIBAL, $CH_2Cl_2$, 0 °C, 10 min (80 %); e) $MnO_2$, diethyl ether, room temperature, 3 h; f) $Ac_2O$, pyridine, room temperature, 15 h (86 % over two steps); g) $NaBH_4$, MeOH, room temperature 15 min (98 %); h) $MnO_2$, diethyl ether, room temperature, 2 h; i) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, room temperature, 5 min (74 % over two steps). DMSO = dimethyl sulfoxide, DIBAL = diisobutylaluminum hydride.

**SCHEME 3**



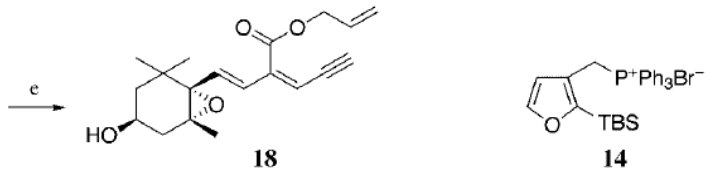
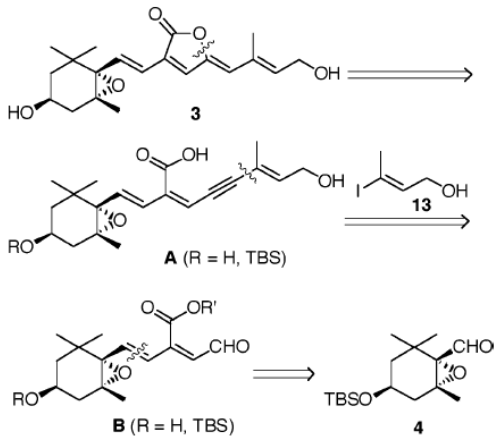
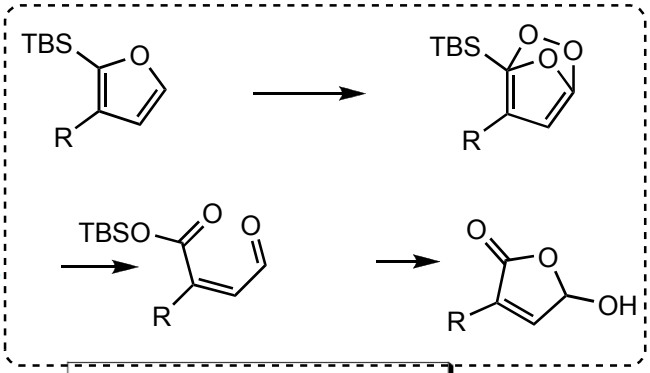




**FIGURE 3.** First-generation synthetic strategy for th ylidenebutenolide segment **3**.

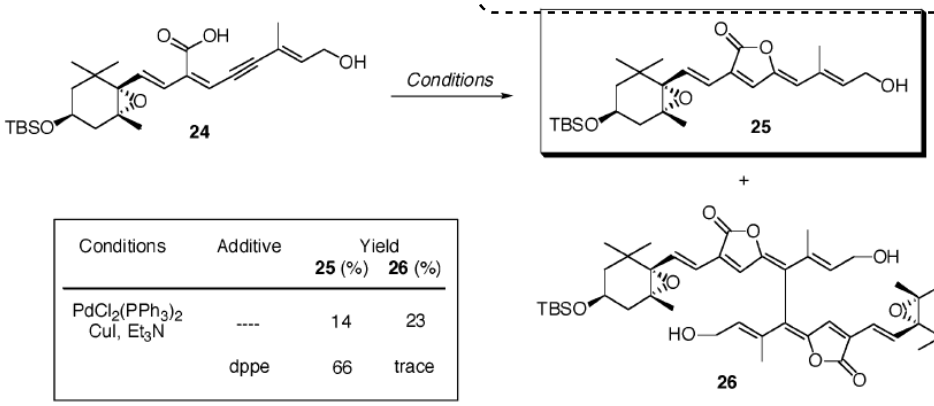



Scheme 4. Synthesis of **18**: a) **14**, *n*BuLi, diethyl ether, 0 °C, 3 h; b) $O_2$, TPP, $CH_2Cl_2$, *hv*, − 78 °C, 30 min (77 % over two steps); c) *i*$Pr_2$EtN, DMSO, room temperature, 3 h, then allyl bromide, room temperature, 1 h (70 %); d) $CBr_4$, $PPh_3$, $Et_3N$, $CH_2Cl_2$, − 60 °C, 1 h (89 %); e) TBAF, THF, 45 °C, 20 h (81 %). TPP = 5,10,15,20-tetraphenyl-21 *H*,23 *H*-porphine, TBAF = tetra-*n*-butylammonium fluoride.

**FIGURE 3.** First-generation synthetic strategy for the ylidenebutenolide segment **3**.




**SCHEME 6**




| Conditions | Additive | Yield **25** (%) | **26** (%) |
|---|---|---|---|
| $PdCl_2(PPh_3)_2$ CuI, $Et_3N$ | ---- | 14 | 23 |
| | dppe | 66 | trace |

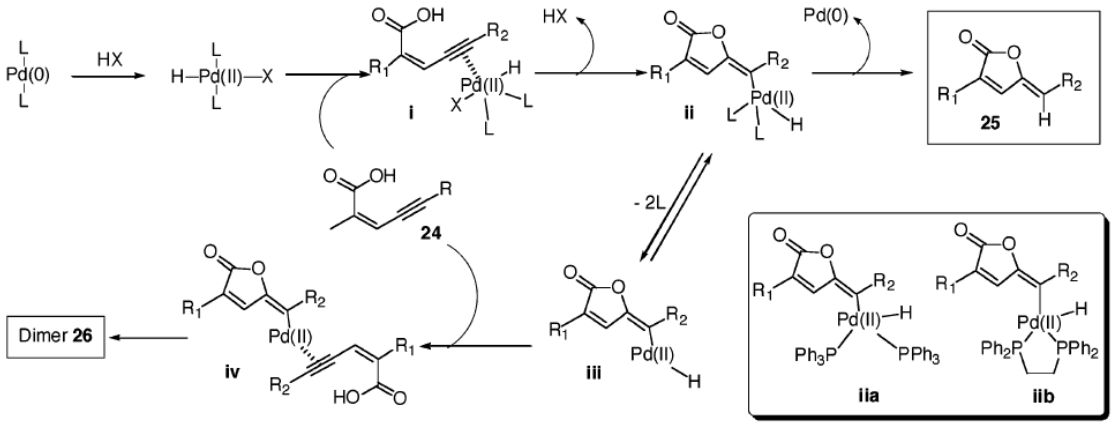
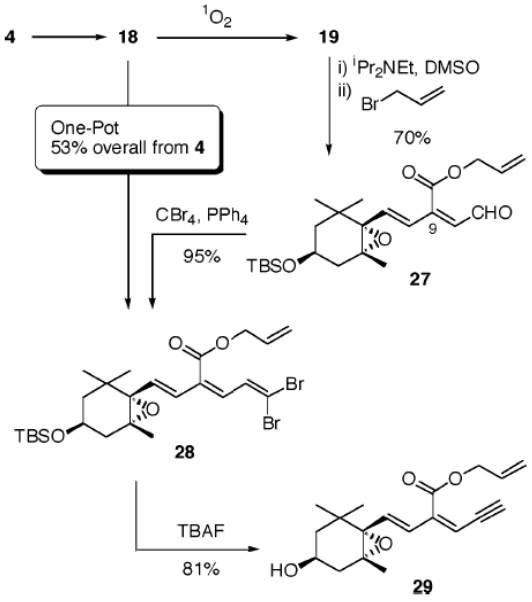
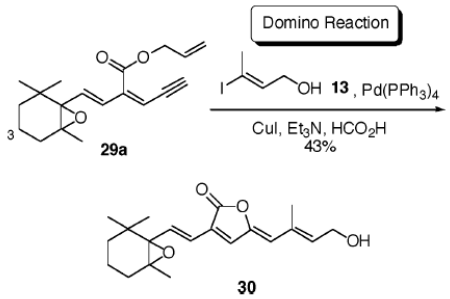



**FIGURE 4.** Possible mechanism for the Pd-catalyzed intramolecular lactonization.

**SCHEME 7**




**SCHEME 8**



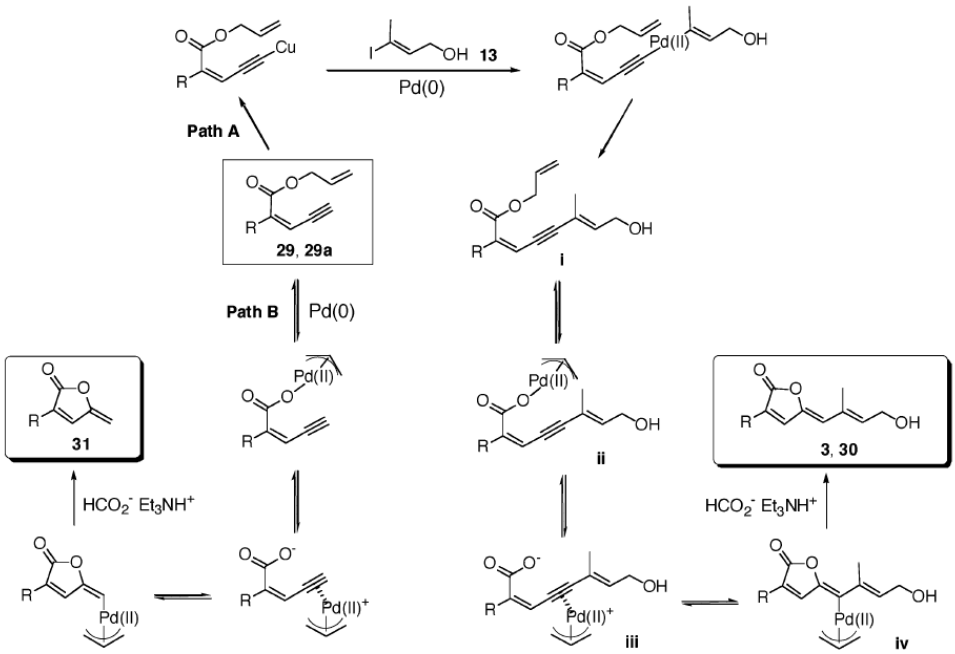
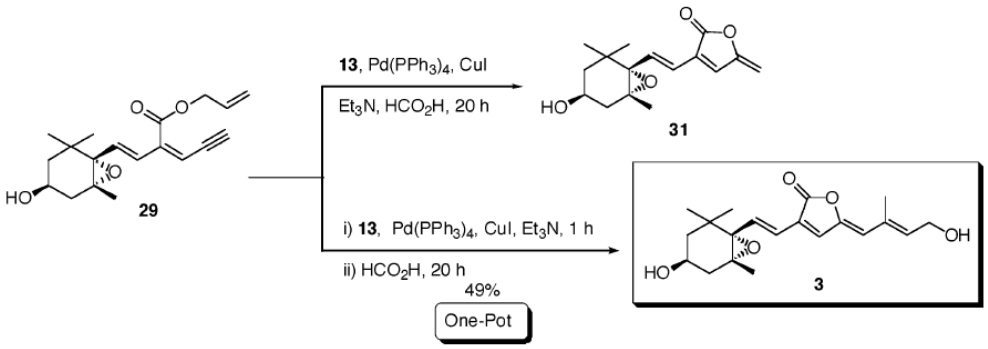
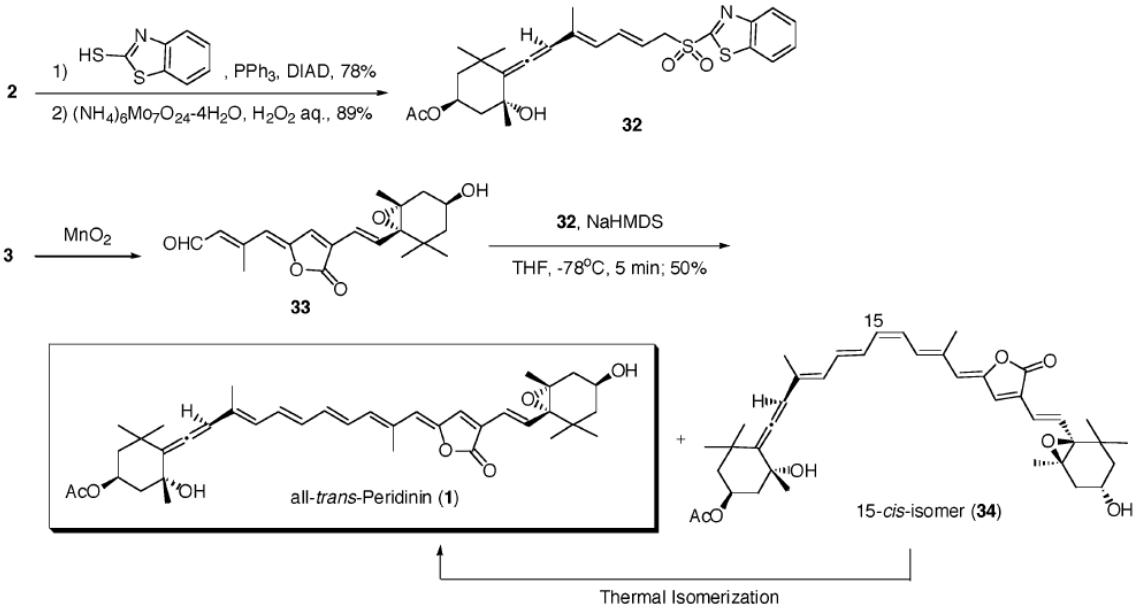




**FIGURE 5.** Possible mechanism for the Pd-catalyzed domino ylidenebutenolide formation reaction.

**SCHEME 9**




**SCHEME 10**




## Summary

In summary, we achieved an efficient and convergent total synthesis of the polyfunctional carotenoid peridinin by controlling the stereochemistry of all six asymmetric carbons and the geometry of the seven double bonds in this molecule. Our synthesis focuses on the stereocontrolled preparation of the common intermediate **4** by utilizing Sharpless asymmetric epoxidation under restrictedly optimized conditions, the stereocontrolled construction of the conjugated polyene moiety including (*Z*)-$\gamma$-ylidenebutenolide by Pd-catalyzed reactions, and a modified Julia−Kocienski olefination. In particular, the construction of the characteristic conjugated (*Z*)-$\gamma$-ylidenebutenolide moiety was achieved in a one-pot procedure utilizing Pd(0)- and Pd(II)-catalyzed reactions.

We believe that this is the first example of controlling the stereochemistry of polyfunctional allenic carotenoids and that the methodology developed here will be applicable to other carotenoid synthesis.

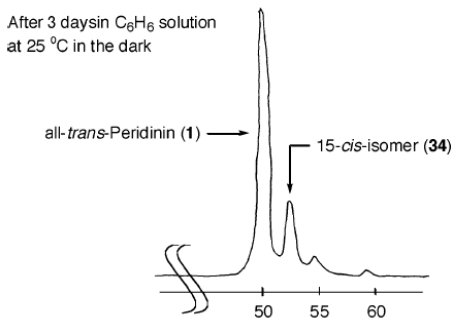


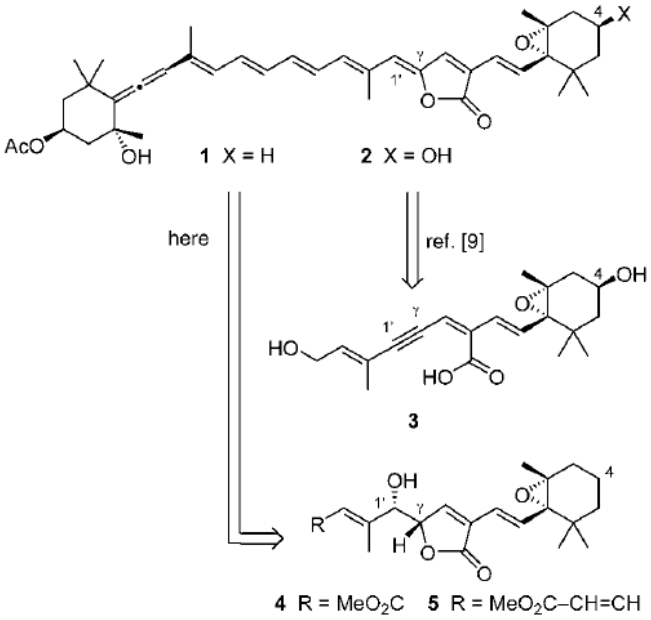

**FIGURE 6.** HPLC analysis after the thermal isomerization. Conditions: column, Develosil CN−UG (0.6 × 25 cm); UV detection, 450 nm; mobile phase, acetone/*n*-hexane = 1/10; flow rate, 1.54 mL/min.

# 5-2 Brukner group

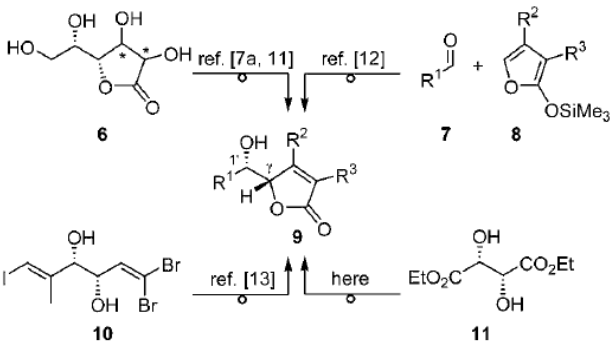
## model study

# Novel Strategy for the Synthesis of the Butenolide Moiety of Peridinin**

*Angew. Chem. Int. Ed.* **2005**, *44*, 1553–1557




***Scheme 1.*** Strategies for the syntheses of the butenolide moieties of peridinin (**2**) and deoxyperidinin (**1**).

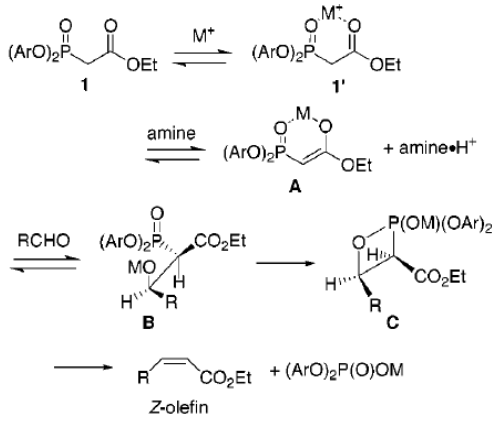


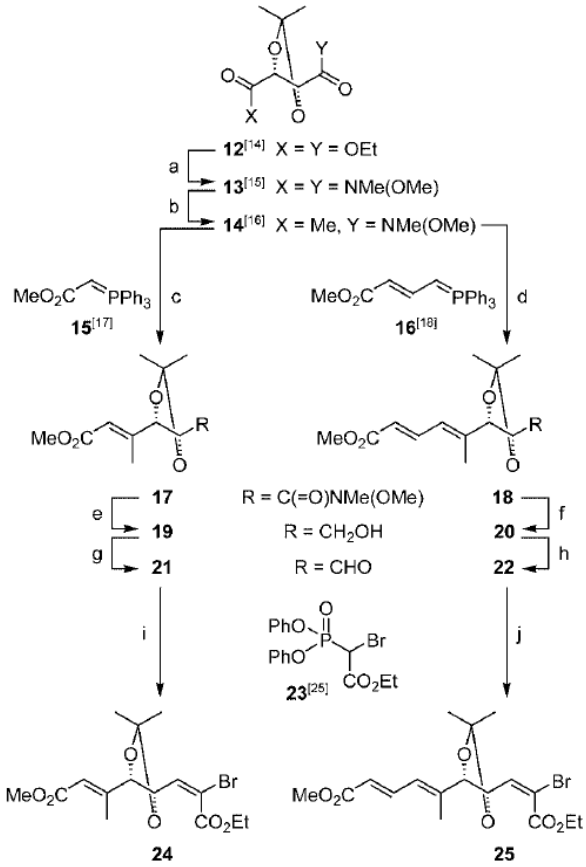

***Scheme 2.*** Routes to γ-(α-hydroxyalkyl)butenolides **9**, which correspond to structures of type **4**/**5** in Scheme 1 and are precursors of γ-alkylidenebutenolides of type **1**/**2** structures in Scheme 1.

## *Z*-Selective Horner–Wadsworth–Emmons Reaction of Ethyl (Diarylphosphono)acetates Using Sodium Iodide and DBU

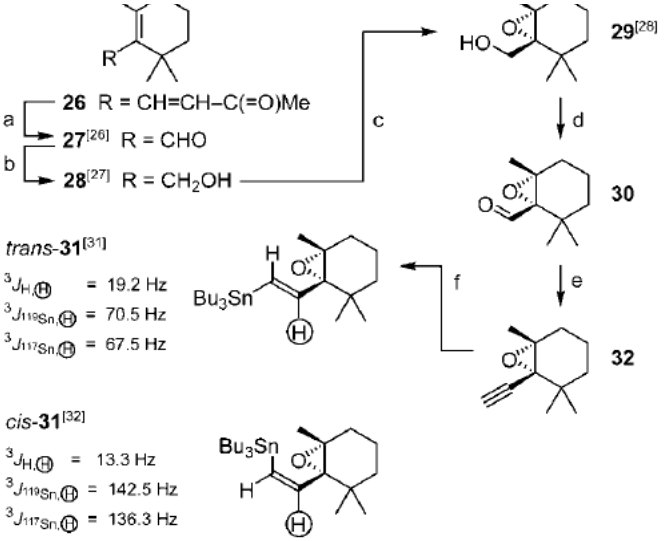
*J. Org. Chem.* **2000**, *65*, 4745–4749

**Scheme 4**

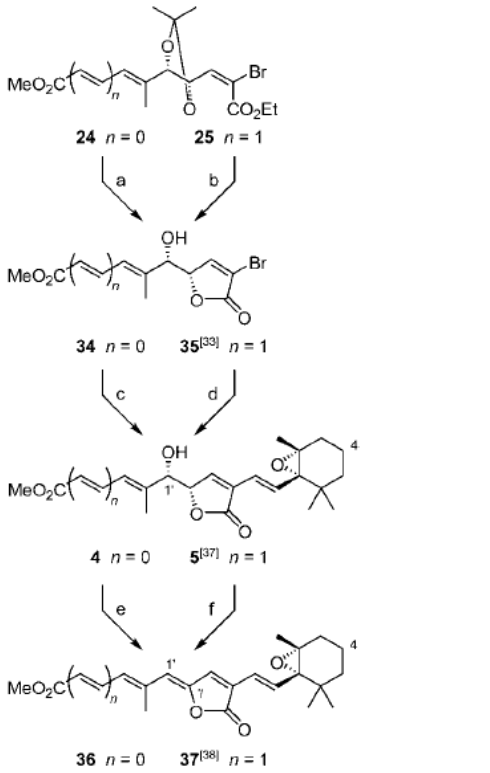



***Scheme 3.*** Syntheses of bromoacrylate intermediates **24** and **25**. a) HNMe(OMe)·HCl (4 equiv), $Me_3Al$ (4 equiv), $CH_2Cl_2$, −15 °C, 1 h, 99%; b) MeMgBr (1.0 equiv), THF, 0 °C, 1 h, 66%; c) **15** (2.0 equiv), toluene, reflux, 27 h, 77%, *E*:*Z* = 86:14; d) **16** (2.0 equiv), toluene, reflux, 30 h, 90%, *E*:*Z* > 99:1; e) $NaBH_4$ (8.0 equiv), MeOH, 25 °C, 18 h, 98%; f) same as (e) but 20 h, 92%; g) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), $NEt_3$ (6.0 equiv), −78 °C → 0 °C, 30 min, 90%; h) same as (g) but −78 °C, 90 min, 79%; i) **23** (1.2 equiv), NaH (1.0 equiv), THF, 0 °C, 30 min, 75%, *E*:*Z* = 95:5; j) same as (i) but 90 min, 82%, *E*:*Z* = 98:2. DMSO = dimethyl sulfoxide.



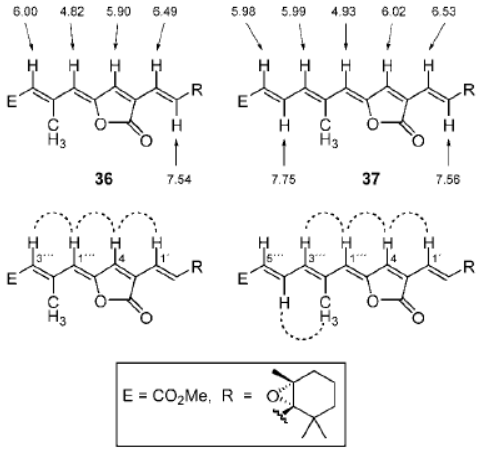

***Scheme 4.*** a) $O_3$, MeOH, −78 °C, 2.5 h; Zn (1.5 equiv), HOAc/$H_2O$ (1:1), 93 %; b) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 1 h, 25 °C, 12 h, 76 %; c) *t*BuOOH (2.0 equiv), $Ti(OiPr)_4$ (0.1 equiv), (−)-DIPT (0.1 equiv), 4 Å MS, $CH_2Cl_2$, −25 °C, 12 h, 67 %, 99.8 % *ee*; d) DMSO (3.0 equiv), $(COCl)_2$ (1.5 equiv), $NEt_3$ (4.5 equiv), −78 °C, 1 h, 99 %; e) $Bu_3SnH$ (1.1 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), THF, 25 °C, 2 h, 83 %; f) $Me_3SiCH{=}N_2$ (1.2 equiv), LDA (1.2 equiv), −78 °C, 30 min, 57 %. DIPT = diisopropyl tartrate, LDA = lithium diisopropylamide.




***Scheme 5.*** Butenolide syntheses. a) MeOH, Amberlyst 15, reflux, 28 h, 95 %; b) MeOH, TsOH (0.05 equiv), reflux, 1 h, 94 %; c) *trans*-**31** (1.2 equiv), CuI (1.65 equiv), $[Pd_2dba_3]{\cdot}CHCl_3$ (0.05 equiv), P(2-furyl)$_3$ (0.3 equiv), NMP, 25 °C, 19 h, 84 %; d) same as (c), 82 %; e) DEAD (2.0 equiv), $PPh_3$ (2.0 equiv), THF, −30 °C, 90 min, 62 %; f) same as (e) except for THF (degassed, 250 ppm di-*tert*-butylcresol) and exclusion of light, 90 %. DEAD = diethyl azodicarboxylate, NMP = *N*-methylpyrrolidone, Ts = *para*-toluenesulfonyl.

**37** was just one constituent of a mixture of the four 1,3-diene isomers. Compound **37**[38] could be prepared free from isomers only when:

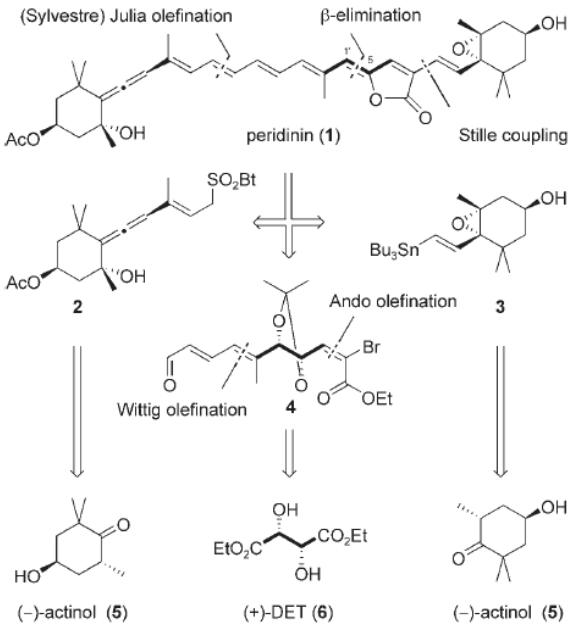
- daylight was excluded throughout the reaction and chromatography,
- the solvent (THF) was degassed and contained di-*tert*-butylcresol as a radical scavenger,
- no aqueous workup was performed but rather the solvent was removed by vacuum distillation at −30 °C,
- and the cyclohexane/ethyl acetate mixture used as the eluent in flash chromatography was degassed. Remarkably, the yield of **37** was then 90 %.[39]



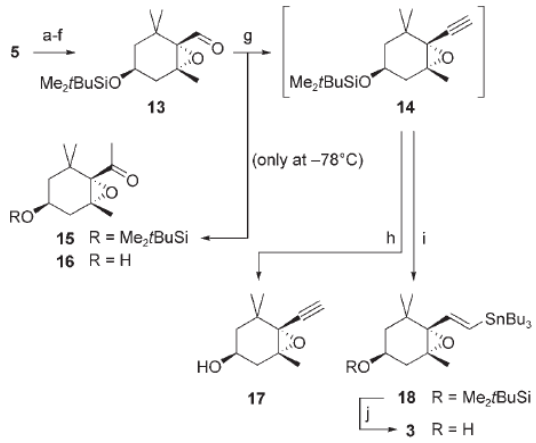

***Scheme 6.*** $^1H$ NMR experiments (500 MHz): NOEs (−−−; **36** in $CDCl_3$ and **37** in $C_6D_6$); characteristic chemical shifts for alkylidenebutenolides **36** and **37** (both in $C_6D_6$).

# Total Synthesis of the Light-Harvesting Carotenoid Peridinin**

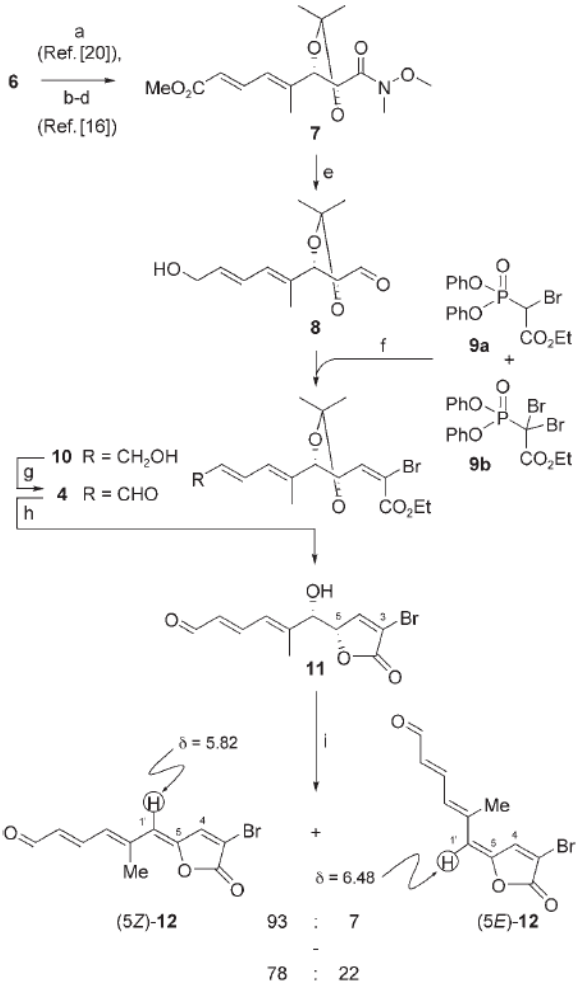
*Angew. Chem. Int. Ed.* **2006**, *45*, 4023–4027



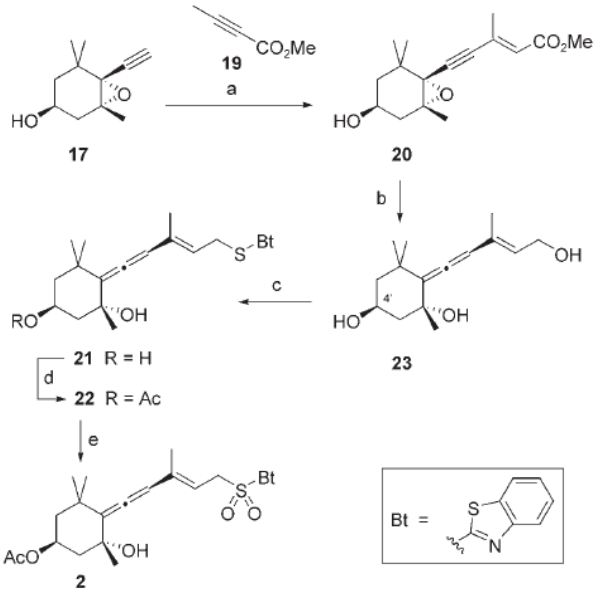

***Scheme 1.*** Retrosynthetic analysis of peridinin (**1**). Bt = benzothiazolyl (formula in bottom line of Scheme 4).



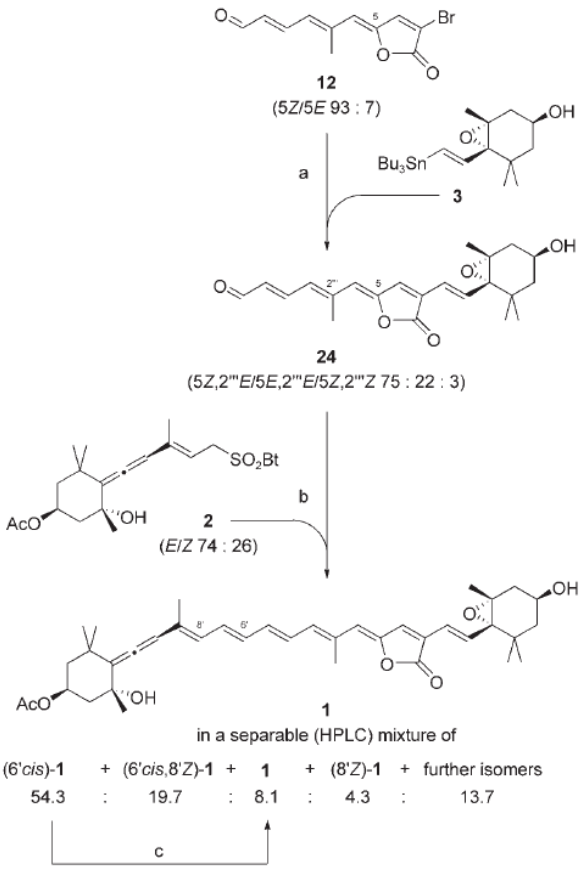

***Scheme 3.*** Synthesis of alkenylstannane **3**. a) $Me_2tBuSiCl$ (1.07 equiv), $NEt_3$ (1.1 equiv), DMAP (1.05 equiv), $CH_2Cl_2$, 0 °C, 6 h, 97% (Ref. [10b] 93%); b) LDA (1.12 equiv), addition of product from (a), −78 °C, 1 h, addition of $PhN(SO_2CF_3)_2$ (1.5 equiv), 25 °C, 2 d, 81% (Ref. [10b] 89%); c) stream of CO, MeOH (30 equiv), $[Pd(PPh_3)_4]$ (3 mol%), $NEt_3$ (3 equiv), DMF, 80 °C, 24 h, 99% (Ref. [11]: 97%); d) DIBAL (2.5 equiv), $CH_2Cl_2$, −78 °C, 1 h, 81% (Ref. [11] with $LiAlH_4$: 87%); e) *t*BuOOH (2.0 equiv), $Ti(OiPr)_4$ (1.5 equiv), (−)-diisopropyl tartrate (2.3 equiv), 4 Å molecular sieves, $CH_2Cl_2$, −30 °C, 30 min, 95%, *de* > 98% (Ref.[11] 99%, 92% *de*; Ref. [12] 98%, > 98% *de*); f) Dess–Martin periodinane,[25] $CH_2Cl_2$, 25 °C, 45 min, 92% (Swern oxidations: Ref. [11] 100%, Ref. [12] 91%); g) $Me_3SiCH{=}N{=}N$ (1.2 equiv), LDA (1.1 equiv), THF, −30 °C, 10 min (Ref. [12]: 92%); h) $Bu_4NF$ (3 equiv), THF, 25 °C, 100 min, 75% over two steps (Ref. [12]: 78%); i) $Bu_3SnH$ (1.1 equiv), $[Pd(PPh_3)_4]$ (2 mol%), THF, 0 °C, 90 min, 53% over two steps; j) $Bu_4NF$ (3 equiv), THF, 25 °C, 19 h, 63%. DMAP = 4-dimethylaminopyridine, DMF = dimethyl formamide, LDA = lithium diisopropylamide.




***Scheme 2.*** Synthesis of the butenolide moiety **12** [$^1$H NMR shifts (500 MHz, $CDCl_3$) supporting the configuration assignment are circled] of peridinin (**1**) via oxobromoacrylate **4**. a) 2,2-Dimethoxypropane (1.2 equiv), *p*-TsOH (cat.), toluene, reflux, 2 h, 87% diethyl (*R*,*R*)-2,3-*O*,*O*-isopropylidenetartrate and 11% ethyl methyl (*R*,*R*)-2,3-*O*,*O*-isopropylidenetartrate (in a mixture; Σ = 98%; Ref. [20]: Σ = 96%); b) Ref. [16]: HNMe(OMe)·HCl (4 equiv), $Me_3Al$ (4 equiv), $CH_2Cl_2$, −15 °C, 1 h, 99%; c) Ref. [16]: MeMgBr (1.0 equiv), THF, 0 °C, 1 h, 56%; d) Ref. [16]: $MeO_2C{-}CH{=}CH{-}CH{=}PPh_3$ (2.0 equiv), toluene, reflux, 30 h, 90%, *E*/*Z* > 99:1; e) $NaAlH_4$ (3.0 equiv), THF, −40 °C, 15 min; f) **9a**/**9b** mixture[22] (0.83 and 0.46 equiv, respectively, Σ = 1.29 equiv), NaH (1.0 equiv), THF, 0 °C, 10 min, addition of **8**, 3 h, 47% (over two steps), 95:5 *E*/*Z* mixture; g) $MnO_2$ (40 equiv), $CH_2Cl_2$, 25 °C, 2 h, 84% crude product; h) $F_3CCO_2H/H_2O$ (9:1), 25 °C, 5 min, 92%; i) 1,1′-thiocarbonyldiimidazole (5 equiv), $CH_2Cl_2$ (degassed), di-*tert*-butylcresol (250 ppm), exclusion of light, −78 °C, 10 min, 51%.




***Scheme 4.*** Synthesis of the allenylsulfone **2**. a) **19** (1.2 equiv), [Pd-(OAc)$_2$] (5 mol%), tris(2,6-dimethoxyphenyl)phosphane (5 mol%), THF, 25 °C, 44 h, 61%; b) DIBAL (8 equiv), $CH_2Cl_2$, 0 °C, 10 min, 91%; c) $PPh_3$ (1.0 equiv), 2-mercaptobenzothiazole (1.0 equiv), diethyl azodicarboxylate (1.0 equiv), THF, 25 °C, 10 min, 86%; d) $Ac_2O$ (3 equiv), DMAP (10 mol%), pyridine, 25 °C, 10 min, 97%, 98:2 *E*/*Z* mixture; e) $H_2O_2$ (50 equiv), $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.3 equiv), EtOH, 25 °C, 2.5 h, 99%, 74:26 *E*/*Z* mixture.



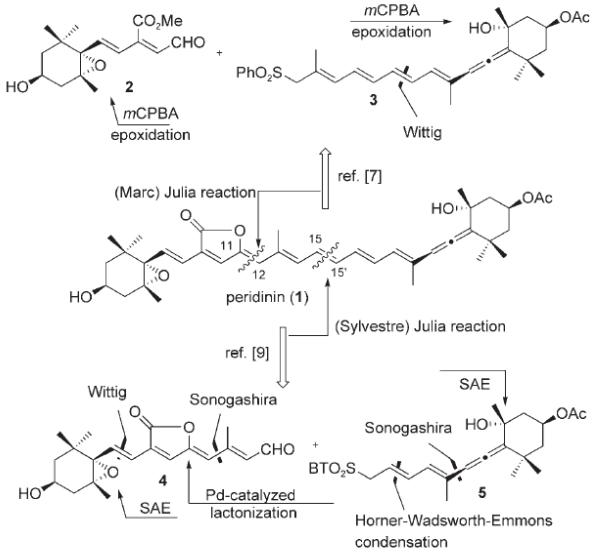

***Scheme 5.*** Total synthesis of peridinin (**1**[18]). a) **3** (1.2 equiv), [Pd-($PPh_3$)$_4$] (10 mol%), CuI (1.65 equiv), di-*tert*-butylcresol (250 ppm), *N*-methylpyrrolidone (degassed), exclusion of light, 25 °C, 18 h, 83% yield of the isomeric mixture; b) addition of KHMDS (5.0 equiv) to solution of **24** (1.0 equiv of indicated mixture) and **2** (1.2 equiv of indicated mixture) in THF (degassed), di-*tert*-butylcresol (250 ppm), exclusion of light, −78 °C, 5 min, 61%; c) $CH_3CN/H_2O$ (70:30), 25 °C, exclusion of light, 37 d, HPLC, 57% pure **1** [or 89% **1** taking into account 37% yield of recovered (6′*cis*)-**1**]. KHMDS = potassium hexamethyldisilazanide.

In summary, we have accomplished a highly convergent total synthesis of peridinin (**1**). Starting from actinol (**5**) and diethyl tartrate (**6**), **1** was synthesized in 15 steps plus two HPLC separations in the longest linear sequence. A single HPLC separaration may have sufficed if the isomerization (6′*cis*)-**1**→**1** had been effected with the originally obtained (6′*cis*)-**1**/**1**/(6′*cis*,8′*Z*)-**1**/(8′*Z*)-**1** mixture rather than with pure (6′*cis*)-**1**. The overall yield was 7.7% and the total number of steps[41] 29.[42] Key transformations were the differential reduction **7**→**8** of an ester-containing Weinreb amide, the *E*-selective olefination **8**→**10** by the Ando-type bromophosphonates **9a**/**9b**, the *anti*-selective β-elimination **11**→**12** upon treatment with 1,1′-thiocarbonyldiimidazole, which established the $C^{1'}{=}C^{5}$ bond *Z*-selectively in an unprecedented manner, and the *cis*→*trans* isomerization (6′*cis*)-**1**→**1** as the ultimate step.

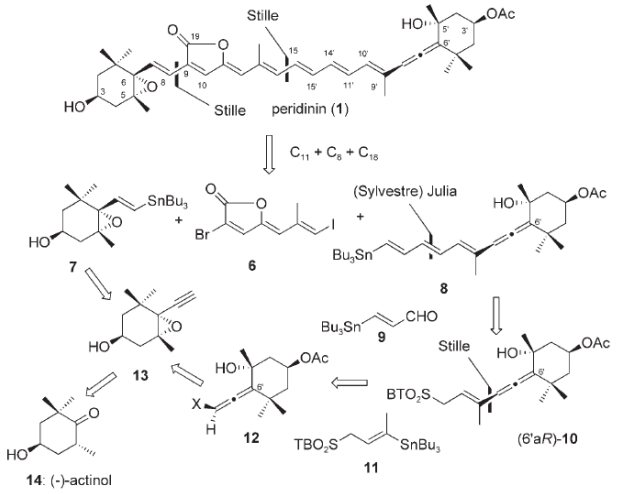
# 5-3 de Lera group **introduce briefly**

## Total Synthesis of Peridinin and Related $C_{37}$-Norcarotenoid Butenolides

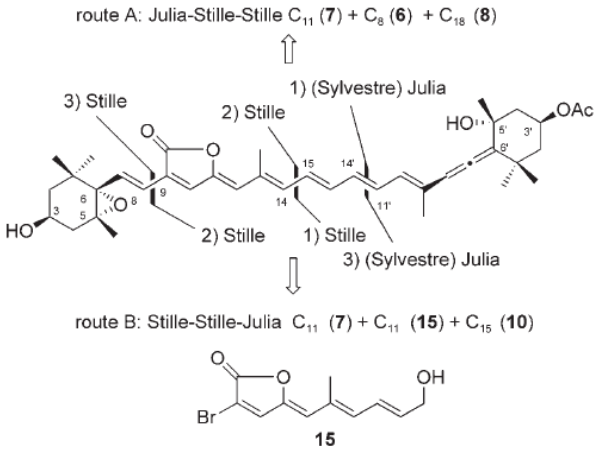
*Chem. Eur. J.* **2007**, *13*, 1273 – 1290



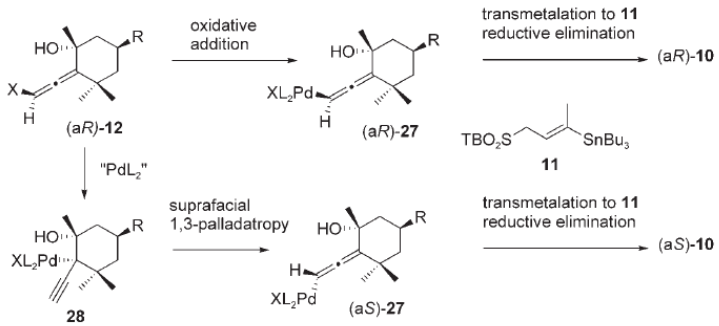

Scheme 1. Previous approaches to peridinin (**1**), highlighting the key disconnections.



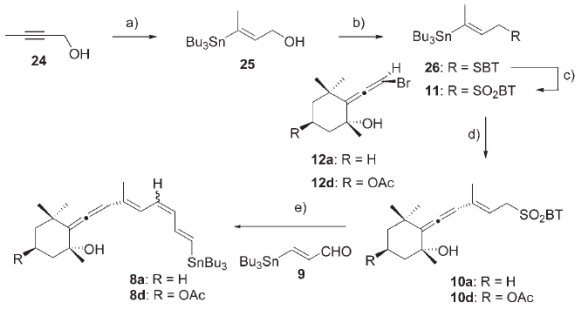

Scheme 2. Retrosynthetic analysis of peridinin (**1**) based on sequential Stille cross-coupling reactions.




Scheme 3. Two routes to peridinin (**1**) explored in this work, with the order and nature of the last three synthetic steps.




Scheme 7. Alternative pathways for the reaction of haloallenes **12** and stannane **11** catalyzed by palladium complexes.




Scheme 6. a) $(Bu_3Sn)_2$, *n*-BuLi, CuCN, MeOH, THF, −10 °C (89 %); b) BTSH, $PPh_3$, DIAD, THF, 25 °C (98 %); c) 35 % $H_2O_2$, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 25 °C (56 %); d) (a*R*)-**12**, $[Pd(PhCN)_2Cl_2]$, $(iPr)_2NEt$, DMF/THF, 40 °C (69 % for **10a**, 64 % for **10d**); e) **10**, NaHMDS, THF, −78 °C, then **9** (79 % for **8a**, 70 % for **8d**). BTSH = 2-mercaptobenzothiazole; HMDS = hexamethyldisilazane.

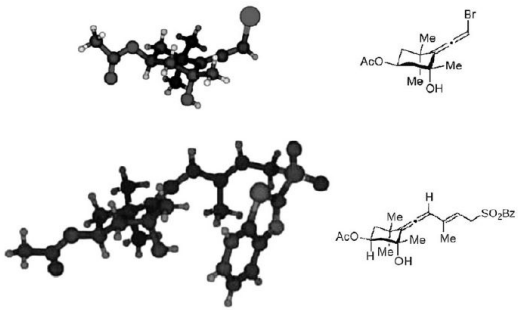
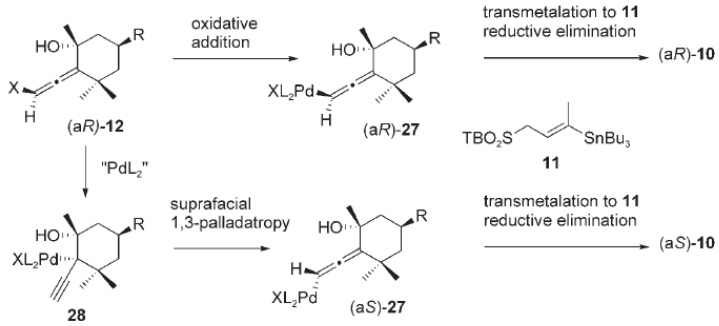
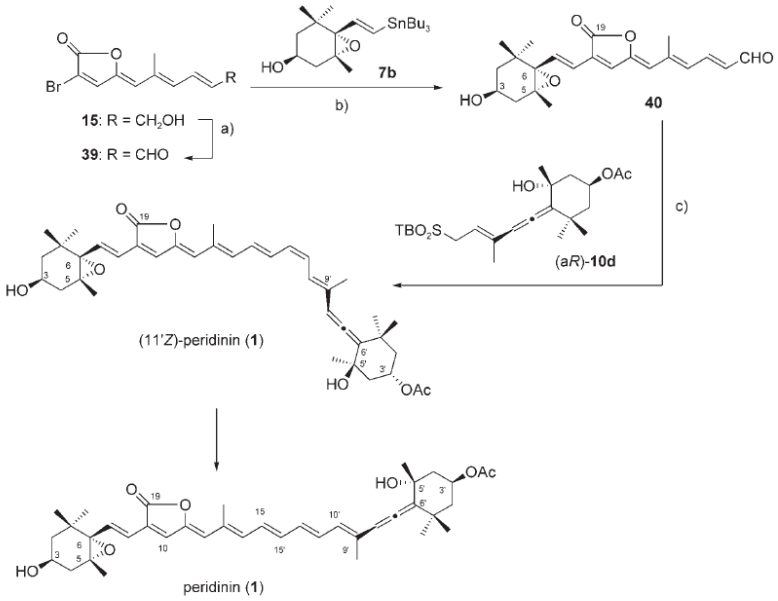


Figure 2. Stereostructure of (a*R*)-**12d** (CCDC-267168) and (*aS*)-**10d** (CCDC-267166).




Scheme 7. Alternative pathways for the reaction of haloallenes **12** and stannane **11** catalyzed by palladium complexes.




Scheme 12. a) $MnO_2$, $Na_2CO_3$, $CH_2Cl_2$, 0 °C, 2 h (72 %); b) $[Pd_2(dba)_3]{\cdot}CHCl_3$, $[AsPh_3]$, $Bu_4N^+Ph_2PO_2^-$, DMF, 70 °C, 26 h (64 %); c) NaHMDS, THF, −78 °C to 0 °C (53 %); d) $[Pd_2(dba)_3]{\cdot}CHCl_3$ (0.13 equiv), $[AsPh_3]$ (1.04 equiv), DMF, 25 °C, 7 h (83 %).

# 5-4 Burke group

## Stereoretentive Suzuki–Miyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (−)-Peridinin

J. AM. CHEM. SOC. 2010, *132*, 6941–6943

### Scheme 1

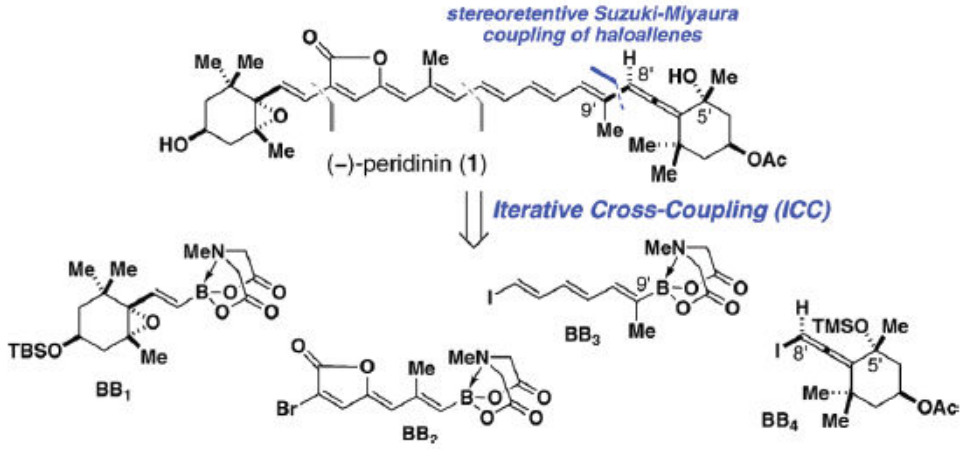
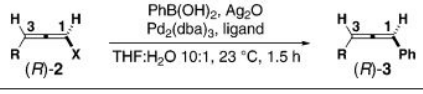


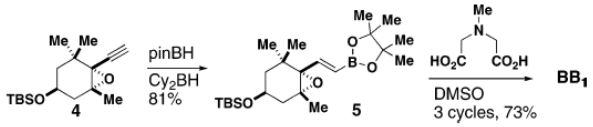

***Table 1.*** Development of the First Stereocontrolled SM Coupling of Chiral Haloallenes



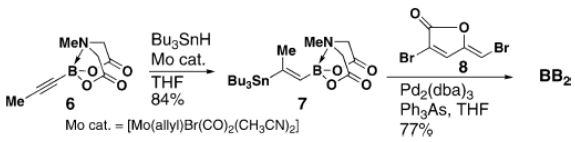

| entry | 2 | R | X | ligand | 3 | % stereoretention[a,b] |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**2a** | *t*-Bu | Cl | $PPh_3$ | (*S*)-**3a** | −78 |
| 2 | (*R*)-**2b** | *t*-Bu | Br | $PPh_3$ | (*S*)-**3a** | −78 |
| 3 | (*R*)-**2c** | *t*-Bu | I | $PPh_3$ | (*R*)-**3a** | 72 |
| 4 | (*R*)-**2d** | 3-pentyl | I | $PPh_3$ | (*R*)-**3b** | 58 |
| 5 | (*R*)-**2e** | *n*-pentyl | I | $PPh_3$ | (*R*)-**3c** | 25 |
| 6 | (*R*)-**2c** | *t*-Bu | I | $PFur_3$ | (*R*)-**3a** | 80 |
| 7 | (*R*)-**2c** | *t*-Bu | I | $PCy_3$ | (*R*)-**3a** | 50 |
| 8 | (*R*)-**2c** | *t*-Bu | I | P*t*-$Bu_2Me$ | (*R*)-**3a** | 71 |
| 9 | (*R*)-**2c** | *t*-Bu | I | P*o*-$Tol_3$ | (*R*)-**3a** | 91 |
| 10 | (*R*)-**2c** | *t*-Bu | I | P*t*-$Bu_3$ | (*R*)-**3a** | 93 |
| 11 | (*R*)-**2c** | *t*-Bu | I | XPhos | (*R*)-**3a** | 91 |
| 12[c] | (*R*)-**2c** | *t*-Bu | I | XPhos | (*R*)-**3a** | >99[d] |
| 13[c] | (*R*)-**2d** | 3-pentyl | I | XPhos | (*R*)-**3b** | >99 |
| 14[c] | (*R*)-**2e** | *n*-pentyl | I | XPhos | (*R*)-**3c** | 85 |

[a] % stereoretention = ee product/ee starting material (chiral GC, average of 2 runs); negative values reflect net stereoinversion. [b] Unoptimized GC yields ranged from 10 to 83%. [c] Hexane:THF:$H_2O$ 9:1:1 was used as solvent. [d] Isolated yield = 61%.

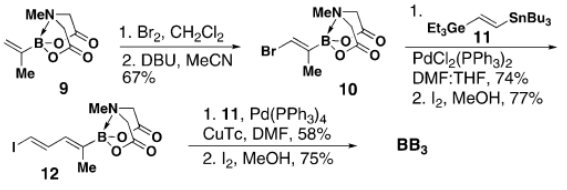
### Scheme 2

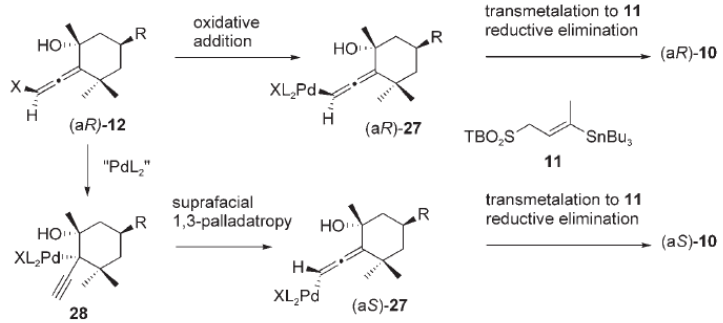



### Scheme 3




### Scheme 4

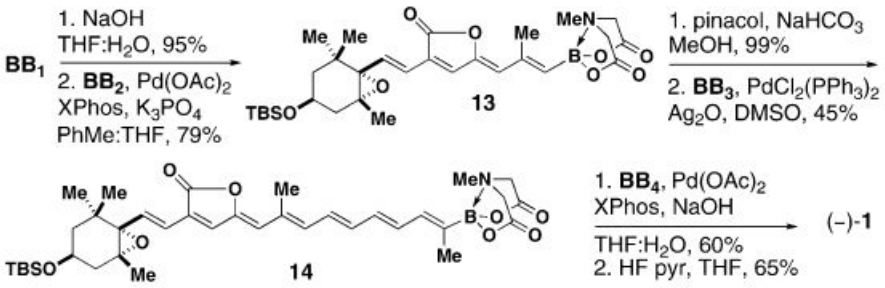



Scheme 7. Alternative pathways for the reaction of haloallenes **12** and stannane **11** catalyzed by palladium complexes.

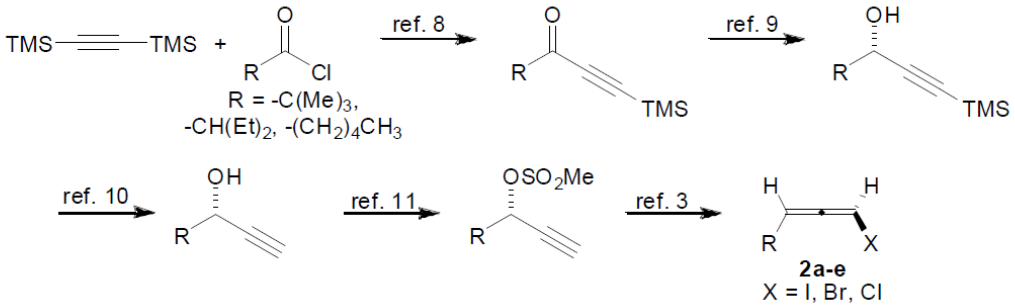
**Stille coupling**

## *Scheme 5*




**Haloallenes 2a-e.**

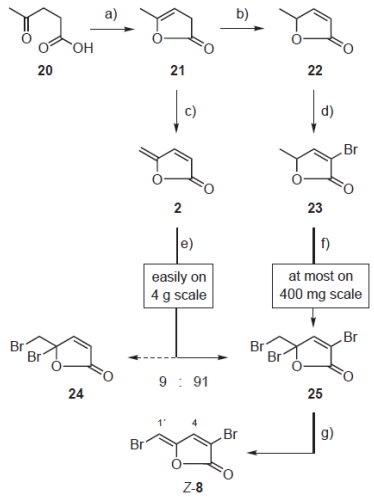
The general reaction scheme for the synthesis of haloallenes **2a-e** is shown below and reaction references are provided (Figure 1).[8, 9, 10, 11]




[8] Representative procedure: Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.
[9] Representative procedure: Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
[10] Representative procedure: Fouad, F.S.; Wright, J.M.; Plourde, G.; Purohit, A.D.; Wyatt, J.K.; El-Shafey, A.; Hynd, G.; Crasto, C.F.; Lin, Y.; Jones, G.B. *J. Org. Chem.* **2005**, *70*, 9789.
[11] Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390.
[12] Fang, L. Y.; Kauffman, G.B. *Inorganic Syntheses* **1983**, *22*, 101.

## Stepwise Cross-Couplings of a Dibromo-γ-methylenebutenolide as an Access to *Z*-Configured α-Alkenyl-γ-alkylidenebutenolides. Straightforward Synthesis of the Antibiotic Lissoclinolide

*SYNLETT* 2005, No. 8, pp 1286–1290




**Scheme 4** *Reagents and conditions:* a) $H_3PO_4$ (cat.), distillation (60%; Ref.[10] 90%); b) $Et_3N$ (0.5 equiv), benzene, Δ, 15 h (43%; Ref.[17] 58%); c) $Br_2$ (0.98 equiv), $CCl_4$, 0 °C, 1 h; quinoline (2.1 equiv), benzene, 0 °C → r.t., 5 h [50% (when mixed with residual quinoline) or 37% (pure); Ref.[11] 90%]; d) $Br_2$ (1.52 equiv), $CCl_4$, reflux, 3 h; $Et_3N$ (1.52 equiv), 4 h (46%; Ref.[12] 71%); e) $Br_2$ (2.2 equiv), $CCl_4$, 0 °C→reflux, 2.5 h; $Et_3N$ (1.0 equiv), 0 °C → r.t. (**25**: 73%, **24**: 7%); f) NBS (2.7 equiv, added in 12 h intervals), AIBN (0.22 equiv), $CCl_4$, reflux, 39 h (34%; Ref.[12] 63%); g) Hydroquinone (cat.), $Et_3N$ (1.10 equiv), $CH_2Cl_2$, –78 °C→0 °C, 1 h (78%).

# 6 Other application of developed boronates

## Chiral Boronate Derivatives via Catalytic Enantioselective Conjugate Addition of Grignard Reagents on 3-Boronyl Unsaturated Esters and Thioesters

J. AM. CHEM. SOC. 2010, *132*, 5544–5545

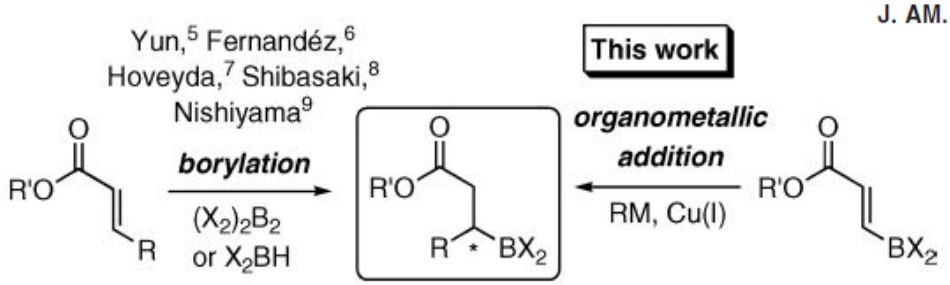
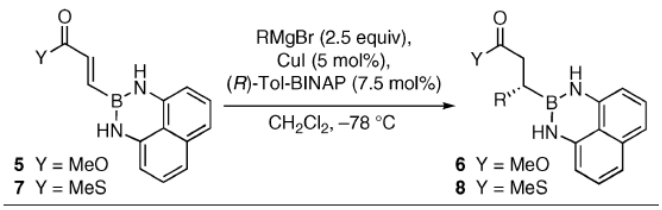
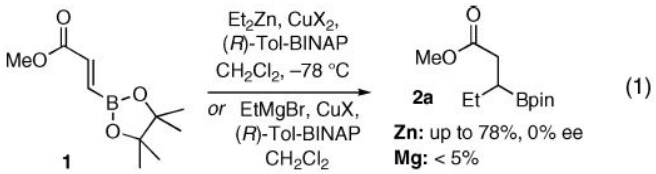


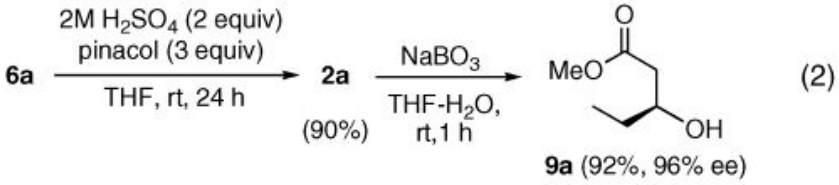

***Figure 1.*** Possible conjugate addition approaches to chiral boronates.

***Table 2.*** Study of Scope for the Grignard Reagent[a]

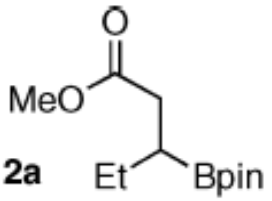


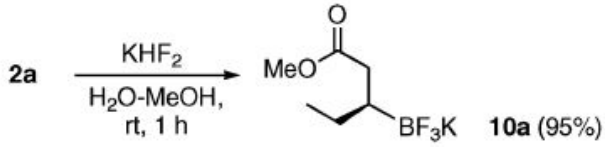




(1)



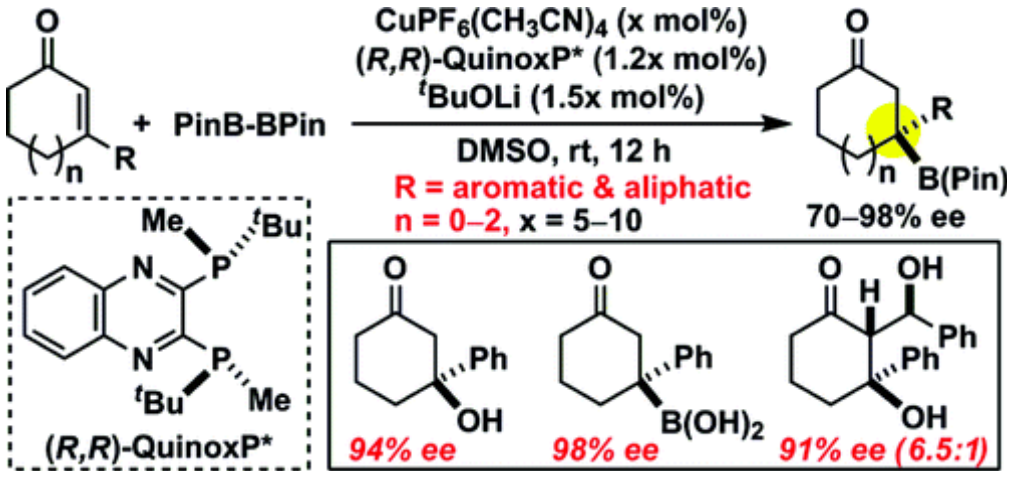

(2)




(3)

*J. Am. Chem. Soc.*, **2009**, 11664 **Our group**



# 7 Conclusion

Cross-Coupling

DOI: 10.1002/anie.200901680

## Controlled Iterative Cross-Coupling: On the Way to the Automation of Organic Synthesis**

*Congyang Wang and Frank Glorius**

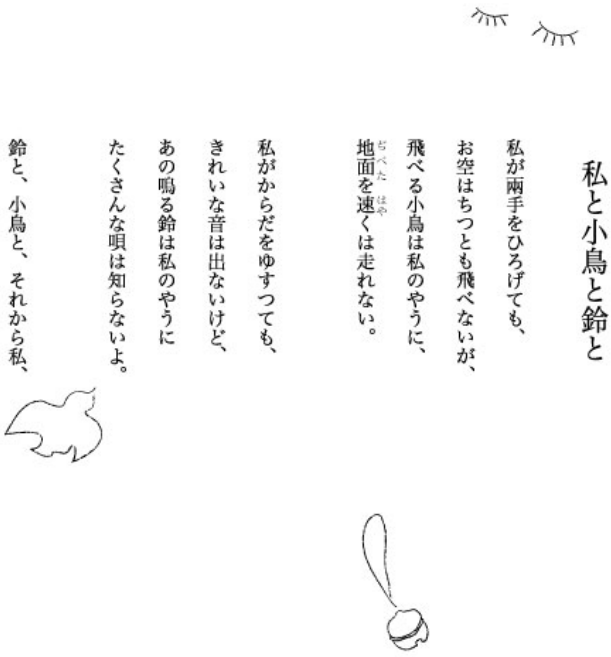
*Angew. Chem. Int. Ed.* **2009**, *48*, 5240 – 5244

Ideal Iterative Suzuki Miyaura Coupling
criterion by Prof. Glorius

- many differently substituted building blocks are readily available and inexpensive; → **good**
- coupling and activation/deprotection step are high yielding, are tolerant of many different functional groups, and do not require nor produce toxic compounds; → **not enough**
- handling, separation, and purification are facile; → **good**
- the iterative coupling sequence is reliable and predictable, which are important aspects for applications in natural product synthesis and in industry; → **good**
- the sequence is suitable for solid phase synthesis and automation. → **not developed yet**

**Iterative Suzuki Miyaura Coupling and relevant work will be developed further more.**

**New protecting group**
**general condition .....**



私と小鳥と鈴と

私が両手をひろげても、
お空はちつとも飛べないが、
飛べる小鳥は私のやうに、
地面を速くは走れない。

私がからだをゆすつても、
きれいな音は出ないけど、
あの鳴る鈴は私のやうに
たくさんな唄は知らないよ。

鈴と、小鳥と、それから私、
みんなちがつて、みんないい。