Selective Co/Ti Cooperatively Catalyzed Biaryl Couplings of Aryl Halides with Aryl Metal Reagents


---

**Co/Ti Cooperative C(sp²)–C(sp²) Cross-Coupling Reactions**

\[
\text{(Het)Ar}^1 \text{–X} + \text{(Het)Ar}^2 \text{–M} \xrightarrow{\text{THF, r.t., 4 h}} \text{(Het)Ar}^1 \text{–(Het)Ar}^2 \\
\] up to 98% yield

\[
\begin{align*}
\text{CoCl}_2 & (7.5 \text{ mol%}) \\
\text{Bu}_3\text{P} & (15 \text{ mol%}) \\
\text{Ti(OEt)}_4 & (0.56-0.96 \text{ equiv}) \\
\end{align*}
\]

Selected examples:

\[
\begin{align*}
\text{Ph} & \text{O} \text{CF}_3 & \text{82% yield} \\
\text{Ph} & \text{O} \text{CN} & \text{72% yield} \\
\text{SMe}_2\text{N} & \text{O} \text{O} & \text{81% yield} \\
\text{HO}_2\text{C} & \text{OMe} & \text{72% yield} \\
\text{N} & \text{HO}_2\text{C} \text{CF}_3 & \text{87% yield} \\
\text{N} & \text{CO}_2\text{H} & \text{81% yield} \\
\text{N} & \text{EtO}_2\text{C} & \text{73% yield} \\
\end{align*}
\]

**Significance:** A novel method for cobalt-catalyzed cross-coupling reactions between aryl chlorides or bromides and aromatic magnesium or lithium reagents is reported by Duan and co-workers. The presence of 40 mol% of Ti(OEt)$_4$ suppresses undesired homocoupling side-products resulting from the organometallic reagent.

**Comment:** Interestingly, the reaction can also take place in the presence of a free carboxylic acid, a hydroxyl, or an amide residue. Therefore, this protocol allows an efficient arylation of highly functionalized aryl halides without protection–deprotection sequences.
**Palladium-Catalyzed Anti-Markovnikov Hydroalkylation of Homoallylic Alcohols**

**Significance:** Lin and Qing report a mild and convenient protocol for the anti-Markovnikov hydroalkylation of β,β-difluorinated homoallylic alcohols. The palladium-catalyzed reaction with alkylzinc reagents furnishes the products in good to excellent yields.

**Comment:** The reported protocol affords a wide range of synthetically useful gem-difluorinated compounds with good functional-group compatibility. Moreover, the results show that the transposition of CH₂ into CF₂ at the allylic position of homoallylic alcohols can modify the electronic and steric environment of the alkene.

**Selected examples:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Product 1" /></td>
<td>78%</td>
</tr>
<tr>
<td><img src="image2" alt="Product 2" /></td>
<td>64%</td>
</tr>
<tr>
<td><img src="image3" alt="Product 3" /></td>
<td>59%</td>
</tr>
<tr>
<td><img src="image4" alt="Product 4" /></td>
<td>71%</td>
</tr>
<tr>
<td><img src="image5" alt="Product 5" /></td>
<td>60%</td>
</tr>
<tr>
<td><img src="image6" alt="Product 6" /></td>
<td>62%</td>
</tr>
<tr>
<td><img src="image7" alt="Product 7" /></td>
<td>81%</td>
</tr>
<tr>
<td><img src="image8" alt="Product 8" /></td>
<td>73%</td>
</tr>
<tr>
<td><img src="image9" alt="Product 9" /></td>
<td>67%</td>
</tr>
</tbody>
</table>

**Equation:**

\[ \text{R}^1 = \text{Ar, Alk} \]
\[ \text{R}^2 = \text{Alk} \]
\[ \text{X} = \text{OH, OBn, NBn}_2 \]

**Conditions:**

- **(1 equiv)**
- **(6 equiv)**
- **Pd(OAc)₂ (5 mol%)**
- **Zn(OTf)₂ (1 equiv)**
- **Benzoquinone (4 equiv)**
- **Dioxane–DMA (2:1)**
- **Air, 25 °C, 5 h**

**Yields:**

- 78% yield
- 64% yield
- 59% yield
- 71% yield
- 60% yield
- 62% yield
- 81% yield
- 73% yield
- 67% yield
A. SIMONNEAU, M. OESTREICH* (TECHNISCHE UNIVERSITÄT BERLIN, GERMANY)

3-Silylated Cyclohexa-1,4-dienes as Precursors for Gaseous Hydrosilanes: The B(C₆F₅)₃-Catalyzed Transfer Hydrosilylation of Alkenes


B(C₆F₅)₃-Catalyzed Transfer Hydrosilylation of Alkenes

**Significance:** Herein, the easy-to-handle B(C₆F₅)₃-catalyzed ionic transfer hydrosilylation of various alkenes using 3-silylated cyclohexa-1,4-dienes is described. The corresponding hydrosilylated alkenes are obtained in high yields.

**Comment:** Often, work in the laboratory with Me₃SiH and Me₂SiH₂ is prohibited because of safety considerations. Since the silylated cyclohexadienes are precursors for the analogous gaseous hydrosilanes, which are generated in situ by a B(C₆F₅)₃-catalyzed release of these hydrosilanes, this protocol is a safe alternative for the hydrosilylation of alkenes.

**Significance:** Herein, the easy-to-handle B(C₆F₅)₃-catalyzed ionic transfer hydrosilylation of various alkenes using 3-silylated cyclohexa-1,4-dienes is described. The corresponding hydrosilylated alkenes are obtained in high yields.

**Comment:** Often, work in the laboratory with Me₃SiH and Me₂SiH₂ is prohibited because of safety considerations. Since the silylated cyclohexadienes are precursors for the analogous gaseous hydrosilanes, which are generated in situ by a B(C₆F₅)₃-catalyzed release of these hydrosilanes, this protocol is a safe alternative for the hydrosilylation of alkenes.
Significance: An efficient method for the introduction of a prenyl group onto the β-position of chalcones by zinc-mediated conjugate addition in the presence of tin(IV) chloride (SnCl₄) is reported. The corresponding products are obtained in high yields and excellent α/γ-selectivities.

Comment: The reaction has proven to be highly α-regioselective in a 1,4-manner. Moreover, the α-regioselectivity of these additions is higher than that of the corresponding addition of allylic barium, lithium, and copper reagents.
Synthesis of 2,5-Diarylated Thiophene 1,1-Dioxides

Significance: The authors disclose the palladium-catalyzed diarylation of distannylated thiophene 1,1-dioxide (electron-poor aryl coupling partners) and diiodo thiophene 1,1-dioxide (electron-rich aryl coupling partners) by Stille cross-coupling reactions to synthesize various 2,5-bis(aryl)thiophene dioxides in moderate yields. Furthermore, the electrochemical and photophysical properties of these diarylated thiophene dioxides were investigated using cyclic voltammetry and fluorescence spectroscopy.

Comment: The corresponding distannylated thiophene 1,1-dioxides are obtained by treatment of 2,5-bis(trimethylsilyl)thiophene 1,1-dioxide with tetrabutylammonium fluoride (TBAF) and bis(tributyltin) oxide. A wide range of these diarylated thiophene dioxides show significant quantum yields, and their appropriate reduction and oxidation potentials may easily be tuned by the use of electron-donating and -withdrawing aryl groups.

**Selected examples:**

- ![MeO](image1)
  - 27% yield (method A)
- ![F3C](image2)
  - 28% yield (method B)
- ![NC](image3)
  - 44% yield (method B)
- ![O2N](image4)
  - 52% yield (method A)
- ![O2N](image5)
  - 58% yield (method A)
- ![N](image6)
  - 20% yield (method B)

**Synthesis of 2,5-Diarylated Thiophene 1,1-Dioxides**

**Method A:**

- ArSnMe3 (2.5 equiv)
- Pd2(dba)3 (5 mol%), Ph3As (40 mol%)
- or Pd(PPh3)4 (10 mol%)
- dioxane or PhMe, 100 °C

**Method B:**

- ArBr (2.5 equiv)
- Pd2(dba)3 (2.5 mol%), Ph3As (20 mol%)
- dioxane, 100 °C

Ar = Ph, 4-MeOC6H4, 4-F3CC6H4, 4-NCC6H4, 4-O2NC6H4, 2-thienyl, 2-furyl, 5-thiazolyl
Asymmetric Lithiation Trapping of \(N\)-Boc Heterocycles

**Significance:** The asymmetric lithiation trapping of various \(N\)-Boc heterocycles is disclosed, using \(s\)-BuLi and chiral diamines such as \((-\)sparteine and \((+\)sparteine surrogate at temperatures above –78 °C. The corresponding chiral heterocycles are obtained in high yields and with good enantiomeric ratios.

**Comment:** The experiments can be conveniently performed, since asymmetric lithiation trappings of, for example, \(N\)-Boc pyrrolidine may be conducted at –30 °C, still furnishing the chiral heterocycles with a high enantiomeric ration of about 9:1.

\[
\text{Asymmetric Lithiation Trapping of } N\text{-Boc Heterocycles}
\]

1. \(s\text{-BuLi}/(+\text{-sparteine surrogate (1.3 equiv)} \text{ Et}_2\text{O, up to } –20 \, \text{°C}

2. \(E^+\text{ up to 91% yield \text{ er up to 95:5}

\(E^+ = \text{PhCHO, MeO}_2\text{CCI, Ph}_2\text{CO, Me}_2\text{SO}_4, \text{PhNCO, allyl bromide, PhBr}

Selected examples:

- \(N\text{Boc}\text{H}\text{OH Ph} \text{Ph} \text{56% yield \text{ er = 86:14 –30 °C}

- \(N\text{Boc}\text{H}\text{CH}_3 \text{55% yield \text{ er = 92:8 –30 °C

- \(N\text{Boc}\text{H}\text{NPh} \text{58% yield \text{ er = 89:11 –30 °C

- \(N\text{Boc}\text{H}\text{Ph} \text{58% yield \text{ er = 92:8 –30 °C

- \(N\text{Boc}\text{H}\text{CO}_2\text{Me} \text{64% yield \text{ er = 80:20 –40 °C

- \(N\text{Boc}\text{H} \text{Bu} \text{OH Ph} \text{58% yield \text{ er = 82:18 –50 °C

- \(N\text{Boc}\text{H} \text{CO}_2\text{Me} \text{71% yield \text{ er = 82:18 –50 °C

SYNFACTS Contributors: Paul Knochel, Nadja M. Barl

Synfacts 2014, 10(1), 0076   Published online: 13.12.2013

DOI: 10.1055/s-0033-1340374; Reg-No.: P16413SF
Iridium-Catalyzed Preparation of SF₅-Substituted Aryl Trifluoroborates

**Significance:** A novel method for the preparation of pentafluorosulfanyl-substituted potassium aryl trifluoroborates via iridium-catalyzed C–H borylation is reported. The corresponding products were obtained in high yields and have been submitted to Suzuki–Miyaura cross-couplings furnishing 3,5-disubstituted pentafluorosulfanylbenzenes.

**Comment:** The described protocol is very versatile since the prepared compounds are potential important building blocks for drug discovery and agrochemicals. Moreover, the reaction proceeds under relatively mild conditions and tolerates various functional groups.
A Broadly Applicable $^{18}$F Trifluoromethylation of Aryl Iodides and Heteroaryl Iodides for PET Imaging

**Nature Chem. 2013, 5, 941–944.**

**[18F]Trifluoromethylation of Aryl and Heteroaryl Iodides**

**Significance:** The authors disclose the easy and broadly applicable late-stage $^{18}$F trifluoromethylation of various aryl and heteroaryl iodides using methyl chlorodifluoroacetate, CuI, TMEDA, and $^{[18F]}$fluoride. The $^{[18F]}$trifluoromethylated (hetero)aryls, which serve as $^{[18F]}$-PET (positron emission tomography) tracers, are obtained in good yields.

**Comment:** Usually, access to $^{[18F]}$-labelled probes is limited by the short half-life of $^{18}$F and the small availability of parent $^{18}$F sources that show a suitable reactivity, such as $^{[18F]}$F$^-$ and $^{[18F]}$F$_2$. Furthermore, this operational simple $^{[18F]}$CuCF$_3$-based strategy excludes the tedious preparation of complex organometallic precursors and may be performed on air. The active $^{[18F]}$CF$_3$Cu is generated in situ.

**Selected examples:**

$\text{Ar} = \text{NO}_2, \text{CO}_2\text{Et}, \text{CHO}, \text{Ac}, \text{CO}_2\text{H}, \text{CN}, \text{Br}, \text{Ph}, \text{OAc}, \text{OPiv}, \text{OH}, \text{OBn}, \text{OMe}, \text{CONH}_2, \text{NH}_2, \text{NHC(O)}\text{Me}, \text{NHBoc}$, chiral dipeptide, chiral carbohydrate

$\text{HetAr} = \text{pyridyl, pyrazyl, quinolyl, benzothiazolyl, thiienyl, uracilyl and indolyl derivatives}$

**ClCF$_2$CO$_2$Me (1.5 equiv)**

**CuI (1.5 equiv)**

**TMEDA (1.5 equiv)**

$^{[18F]}$KF, kryptofix

**DMF, 150 °C**

$\text{ArHetCF}_3^{18}\text{F}$

up to 87% yield

R = NO$_2$, CO$_2$Et, CHO, Ac, CO$_2$H, CN, Br, Ph, OAc, OPiv, OH, OBn, OMe, CONH$_2$, NH$_2$, NHC(O)Me, NHBoc, chiral dipeptide, chiral carbohydrate

HetAr = pyridyl, pyrazyl, quinolyl, benzothiazolyl, thiienyl, uracilyl and indolyl derivatives

19% yield (obtained by C–H functionalization)
Stereoselective Synthesis of syn-β-Hydroxy-α-vinyl Carboxylate Esters

Significance: The authors report a novel enantio- and diastereoselective synthesis of syn-β-hydroxy-α-vinyl carboxylate esters. The reaction proceeds via a reductive aldol reaction of an ethyl allene carboxylate with 10-TMS-9-borabicyclo[3.3.2]decane.

Comment: The exclusive formation of syn-β-hydroxy-α-vinyl carboxylate esters can be explained by an aldol reaction via a chair-like transition state. DFT calculations suggest that the allene hydroboration involves a 1,4-reduction of the ethyl allene carboxylate with 10-TMS-9-borabicyclo[3.3.2]decane.

Selected examples:

- R = Ph, Cy, (CH2)2Ph, CH2OTBDPS, CHCHPh, 3-pyridyl, 2-furyl

86% yield, 82% ee dr > 40:1
80% yield, 83% ee dr > 40:1
91% yield, 82% ee dr > 40:1
68% yield, 73% ee dr > 40:1
79% yield, 78% ee dr > 40:1
83% yield, 89% ee dr > 40:1
Bismuth-Mediated Switchable Regioselective Carbometalation

Significance: Baba and co-workers report a novel carbobismuthination reaction of alkenes using bismuth trihalides and ketene silyl acetals. Furthermore, in this protocol, the first switch in regioselectivity of the carbometalation using BiCl$_3$ instead of BiBr$_3$ is reported.

Comment: The resultant alkylbismuth compounds react with a range of reagents in order to give functionalized aliphatics. Therefore, reaction with N-bromosuccinimide furnishes the bromide, reaction with AIBN and PhSSPh introduces a thiophenyl group, and Ph(OAc)$_2$ in combination with TMSOAc gives the acetate.
Lithiation–Borylation of Secondary Alkyl Benzoates

Against common wisdom, Aggarwal and co-workers have now shown that secondary 2,4,6-triisopropyl benzoates (TIP esters) can be deprotonated at –60 °C using a combination of s-BuLi and TMEDA in cyclopentyl methyl ether (CPME). The resulting lithium reagents were allowed to react with various neopentyl boronic esters which after 1,2-metalate rearrangement and oxidation furnished a range of tertiary alcohols in good enantioselectivity.

**Significance:** This lithiation reaction cannot be performed in THF. Simply switching from THF to diethyl ether increased the yield of the lithiated benzoate. The extent of lithiation was increased further by using CPME. Interestingly, the subsequent borylation reaction occurs with complete retention of configuration.

**Comment:**

**Selected examples:**

- R1 = CH2Bn, (CH2)2CHCH2, (CH2)3OTHP
  - R2 = Me, Et
  - R3 = Et, i-Pr, Ph, allyl, 3-(2-fluoropyridyl), (CH2)2CO2t-Bu, CHCHCH3
  - (R4)2 = pin, neo, Et2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Er</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1H R2OH</td>
<td>80%</td>
<td>99:1</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>78%</td>
<td>99:1</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>77%</td>
<td>98:2</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>78%</td>
<td>99:1</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>73%</td>
<td>99:1</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>72%</td>
<td>99:1</td>
</tr>
<tr>
<td>R1Bn R2OH</td>
<td>74%</td>
<td>99:1</td>
</tr>
</tbody>
</table>

(TMSCl was added after aminolysis)

(MeOH was added after aminolysis)
Zn/Cu-Mediated Aminocyclopropanation

Significance: The authors report a novel method for the preparation of carbamate-protected aminocyclopropanes. The reaction proceeds via aminocyclopropanation of alkenes using carbamates in the presence of metallic zinc and copper. The conditions are very mild (room temperature) using only 3.2 equivalents of carbamate.

Comment: The prepared cyclopropane carbamates can be deprotected using iodo(trimethyl)silane in chloroform and methanol. Subsequent isolation furnishes the corresponding aminocyclopropanes as their crystalline HI salts in high yields.

Selected examples:

- **78% yield**
  - **dr = 1.2:1**

- **80% yield**
  - **dr > 20:1**

- **83% yield**
  - **dr = 7:1**

- **77% yield**
  - **dr = 7:1**

- **95% yield**
  - **dr = 1:20**

**Chemical reaction formula:**

\[
\text{MeO}^+\text{NH}_2 (3.2 \text{ equiv}) + R^1\text{R}^2\text{R}^3 (1 \text{ equiv}) + (\text{EtO})_3\text{CH} (1 \text{ equiv}) \xrightarrow{\text{Zn} (20 \text{ equiv}), \text{Cu} (1.4 \text{ equiv}), \text{ZnCl}_2 (3 \text{ equiv}), \text{TMSCl} (11 \text{ equiv}), \text{Et}_2\text{O}, \text{r.t.}, 3-16 \text{ h}} \text{ZnCl}_2 (3 \text{ equiv}) \xrightarrow{\text{up to 95% yield, dr up to >20:1}}
\]
Terminal Olefin Synthesis via Reaction of Aldehydes with Allylsamarium Bromide

**Significance:** A simple and efficient one-pot protocol for the synthesis of terminal alkenes has been reported. The reaction of carbonyl compounds with allylsamarium bromide in the presence of diethyl phosphate furnishes the corresponding olefins in good to excellent yields.

**Comment:** Allylsamarium bromide acts in the reported reaction as both, a nucleophilic reagent and a single electron transfer reagent. Moreover, the described methodology is very versatile since several functional groups are tolerated.

\[
\text{RCHO} + \overset{(1 \text{ equiv})}{\text{SmBr}} \overset{(3 \text{ equiv})}{(\text{EtO})_2\text{P(O)}\text{H} \ (2 \text{ equiv})} \overset{\text{THF, 65 °C, 12 h}}{\rightarrow} \text{R} \overset{\text{up to 91% yield}}{\rightarrow} \]

**Selected examples:**

- MeS
  - 83% yield
- O
  - 76% yield
- 88% yield
- 62% yield
- 71% yield
- 51% yield
- 42% yield
- 91% yield
- 89% yield
Synthesis of Trisubstituted Alkenylstannanes Starting from Alkynoates

**Significance:** The authors report a highly regioselective copper-catalyzed synthesis of trisubstituted alkenylstannanes. Through a three-component coupling of alkylboranes, alkynoates and tributyltin methoxide, these trisubstituted alkenylstannanes are obtained in good yields with high syn selectivity. The appropriate alkylboranes are easily accessible by hydroboration of the corresponding alkenes with the 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer.

**Comment:** Standard methods for the synthesis of alkenylstannanes described by Shirakawa and Hiyama include the palladium- or nickel-catalyzed carbostannylation of internal alkynes with organostannanes which are somewhat difficult to prepare.

**Key words:**
- tin
- boron
- copper
- alkynoates
- tributyltin methoxide
- trisubstituted alkenylstannanes

**Synthesis route:**

\[
\begin{align*}
\text{R}^1 & = \text{Ph, n-Bu, n-Pent, (CH}_2\text{)}_3\text{phthalimide, (CH}_2\text{)}_3\text{OTHP, C(Me)}_2\text{CH}_2\text{CO}_2\text{Me, 4-BrC}_6\text{H}_4, (\text{CH}_2\text{)}_3\text{OTIPS} \\
\text{R}^2 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{MeO}_2\text{CC}_6\text{H}_4, 2-\text{MeC}_6\text{H}_4, \text{Me, CH}_2\text{OTHP, CH}_2\text{OBn, 4-FC}_6\text{H}_4, 2\text{-thienyl derivative}
\end{align*}
\]

- **Selected examples:**
  - 61% yield
  - 49% yield
  - 74% yield
  - 49% yield
  - 77% yield
  - 63% yield
  - 80% yield
  - 77% yield