Supporting Information

Toward a Protecting-Group-Free Halogen–Metal Exchange Reaction: Practical, Chemoselective Metalation of Functionalized Aromatic Halides Using Dianion-Type Zincate, ^{t}Bu$_4$ZnLi$_2$

Masanobu Uchiyama,[*,†,‡,§] Taniyuki Furuyama,[†,§] Minoru Kobayashi,[†,§] Yotaro Matsumoto,[†,§] Kentaro Tanaka,[¶]

Graduate School of Pharmaceutical Sciences and School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan; Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198 Japan

General Comments. Melting points were determined with a Yazawa micro melting point apparatus and uncorrected. NMR spectra were obtained on a Bruker AV-400 NMR spectrometer and a JEOL ECA-500 spectrometer. Unless otherwise noted, samples were recorded in $CDCl_3$. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). ^{1}H-NMR spectra were referenced to a tetramethylsilane as an internal standard. ^{13}C-NMR spectra were referenced to a $CDCl_3$ signal (77.0 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and brs = broad singlet. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded on a Bruker microTOF sprecrtometer. All experiments were done under Ar atmosphere with dry solvent.

Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification (distillation or recrystalization). MeLi in Et_2O, ^{n}BuLi in ^{n}hexane, and ^{t}BuLi in n-pentane were obtained from

---

[†] Graduate School of Pharmaceutical Sciences, The University of Tokyo
[‡] RIKEN
[§] PRESTO (JST)
[¶] School of Science, The University of Tokyo

Kanto Chemical Co. Ltd. The concentrations of MeLi, ⁿBuLi, and ᵗBuLi were determined by titration prior to use. [1]

NMR Spectroscopic Analyses of Organometallic Species.

^1H, ^{13}C and ^7Li NMR spectra were obtained on a JEOL ECA-500 spectrometer, operating at 500.160, 125.765 and 194.381 MHz, respectively. All samples were run in THF solution at -100°C. The capillary tube contained THF-d_8 used as the ^{13}C chemical shift reference and lock solvent. ^1H NMR spectra were referenced to a solvent signal (3.58 ppm). ^{13}C NMR spectra were referenced to a THF-d_8 signal (67.4 ppm). ^7Li NMR spectra were referenced to external 0.5 M LiBr in THF-d_8 at the temperature at which each sample was run (0.0 ppm). Complete ^1H and ^{13}C chemical shift assignments were made on the basis of decoupled 1D NMR and DEPT experiments.

$^tBu_2Zn$ were prepared by using a modification of the literature method: [2] A solution of ^tBuLi in pentane (1.32 M, 22.5 ml, 30 mmol) and $ZnCl_2$ in THF (0.5 M, 30 ml, 15 mmol) was stirred at 0°C for 30 min. The solution was distilled (34- 35°C/ 9 mmHg) to give $^tBu_2Zn$ (no lithium ion was detected by ^7Li NMR).

Table S-1. NMR Data of 1M THF Solution of ^tBuLi, $^tBu_2Zn$, and $^tBu_4ZnLi_2$[a]

	^1H	^{13}C	^7Li
^tBuLi	0.74	17.0 (a), 40.6 (b)	-1.26
$^tBu_2Zn$	0.85	22.7 (a), 34.4 (b)	–
$^tBu_4ZnLi_2$	0.69	24.2 (a), 36.7 (b)	-2.13

[a] Spectra were recorded at -100 °C. The capillary tube contained THF-d_8 used as the ^{13}C chemical shift reference and lock solvent. ^1H and ^{13}C NMR spectra (ppm) were referenced to a solvent signal. ^7Li NMR spectra (ppm) were referenced to external 1 M LiBr in THF-d_8 at -100 °C.

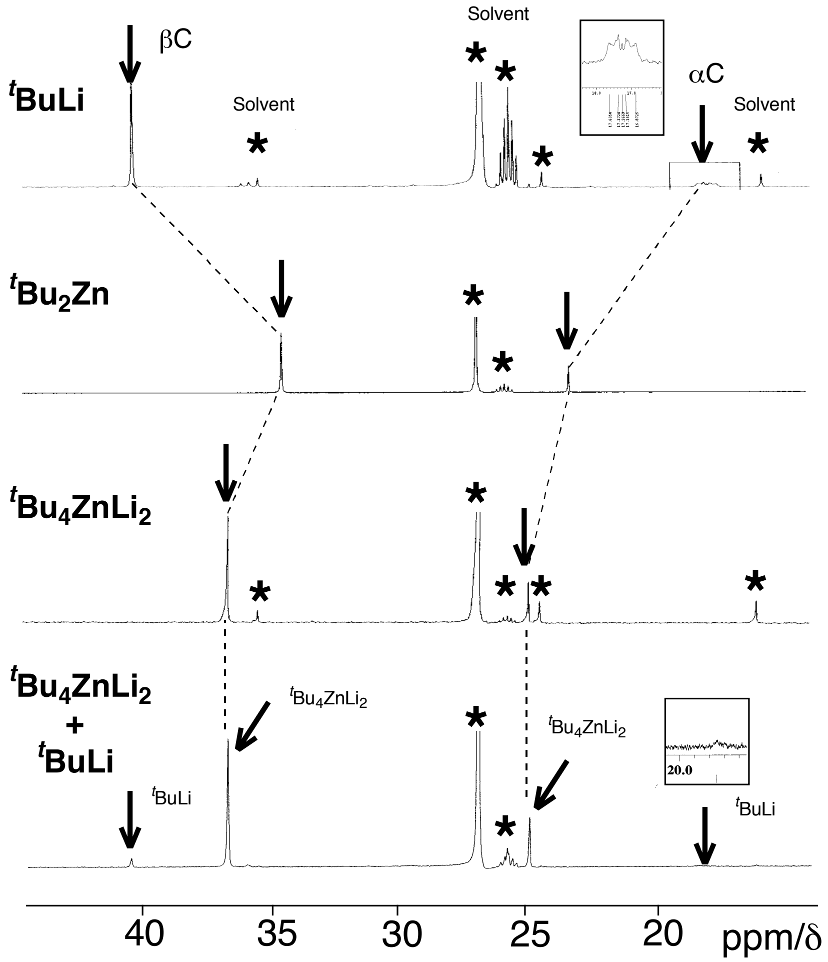
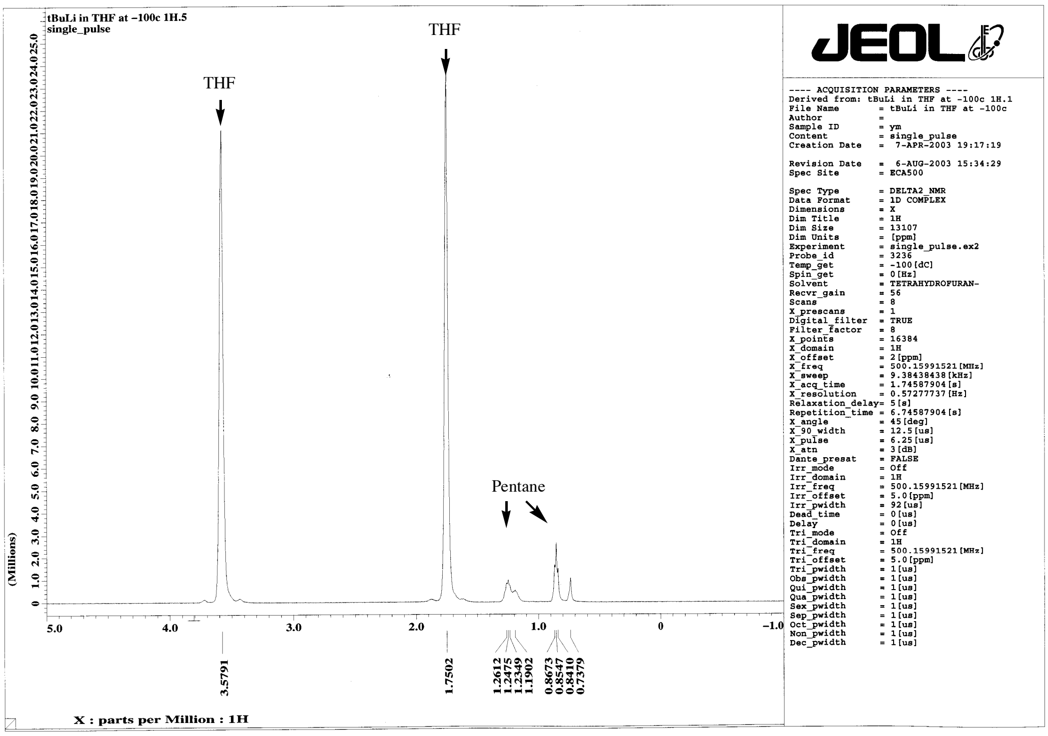
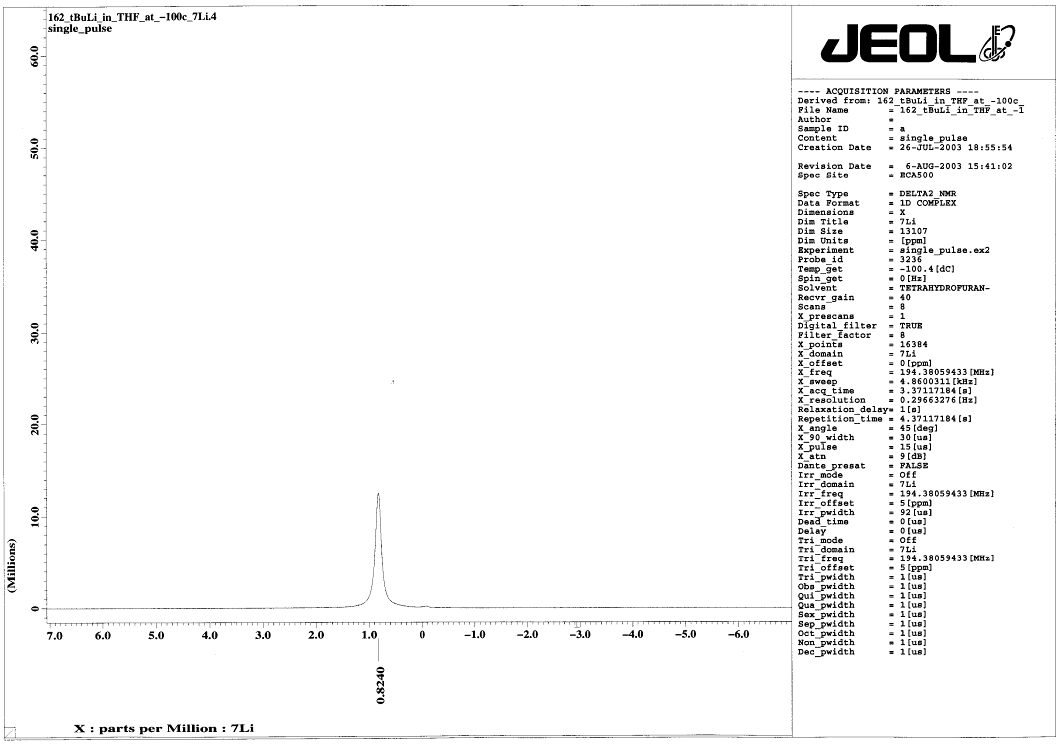


Figure S-1. ^{13}C NMR Spectrums of ^{t}BuLi, ^{t}Bu$_2$Zn, ^{t}Bu$_4$ZnLi$_2$, and a mixture of ^{t}BuLi and ^{t}Bu$_4$ZnLi$_2$ in THF at -100°C.



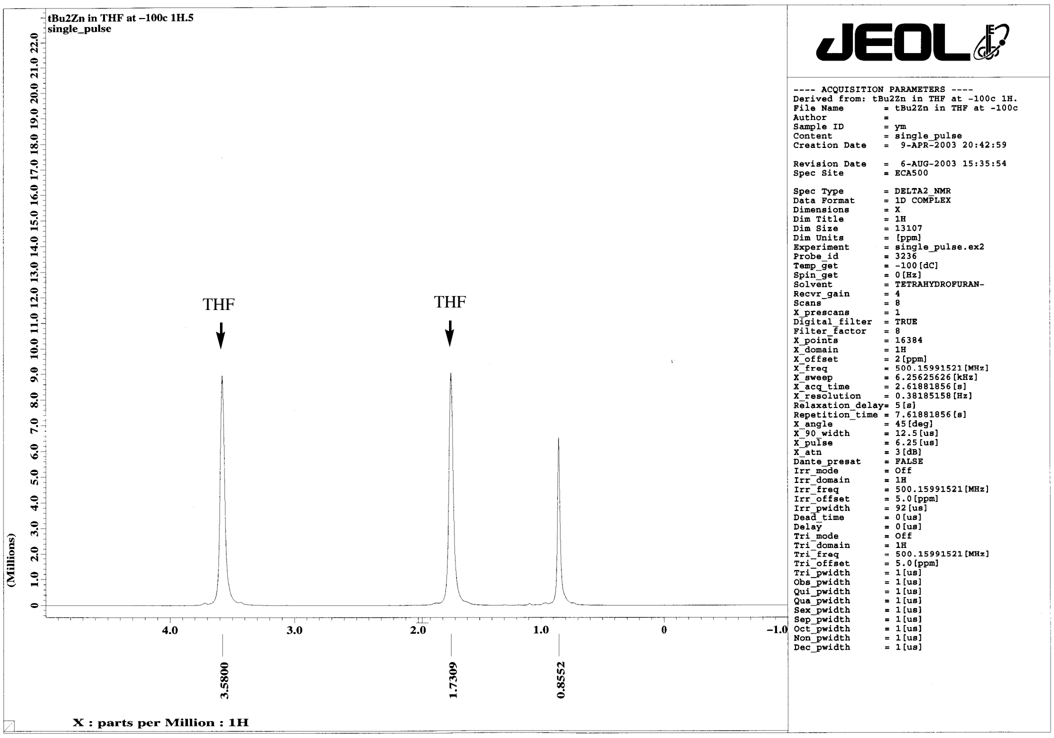
```
---- ACQUISITION PARAMETERS ----
Derived from: tBuLi in THF at -100c 1H.1
File Name        = tBuLi in THF at -100c
Author           =
Sample ID        = ym
Content          = single_pulse
Creation Date    =  7-APR-2003 19:17:19

Revision Date    =  6-AUG-2003 15:34:29
Spec Site        = ECA500

Spec Type        = DELTA2_NMR
Data Format      = 1D COMPLEX
Dimensions       = X
Dim Title        = 1H
Dim Size         = 13107
Dim Units        = [ppm]
Experiment       = single_pulse.ex2
Probe_id         = 3236
Temp_get         = -100[dC]
Spin_get         = 0[Hz]
Solvent          = TETRAHYDROFURAN-
Recvr_gain       = 56
Scans            = 8
X_prescans       = 1
Digital_filter   = TRUE
Filter_factor    = 8
X_points         = 16384
X_domain         = 1H
X_offset         = 2[ppm]
X_freq           = 500.15991521[MHz]
X_sweep          = 9.38438438[kHz]
X_acq_time       = 1.74587904[s]
X_resolution     = 0.57277737[Hz]
Relaxation_delay= 5[s]
Repetition_time = 6.74587904[s]
X_angle          = 45[deg]
X_90_width       = 12.5[us]
X_pulse          = 6.25[us]
X_atn            = 3[dB]
Dante_presat     = FALSE
Irr_mode         = Off
Irr_domain       = 1H
Irr_freq         = 500.15991521[MHz]
Irr_offset       = 5.0[ppm]
Irr_pwidth       = 92[us]
Dead_time        = 0[us]
Delay            = 0[us]
Tri_mode         = Off
Tri_domain       = 1H
Tri_freq         = 500.15991521[MHz]
Tri_offset       = 5.0[ppm]
Tri_pwidth       = 1[us]
Obs_pwidth       = 1[us]
Qui_pwidth       = 1[us]
Qua_pwidth       = 1[us]
Sex_pwidth       = 1[us]
Sep_pwidth       = 1[us]
Oct_pwidth       = 1[us]
Non_pwidth       = 1[us]
Dec_pwidth       = 1[us]
```

Figure S-2. ^{1}H NMR Spectra of ^{t}BuLi in THF at -100°C



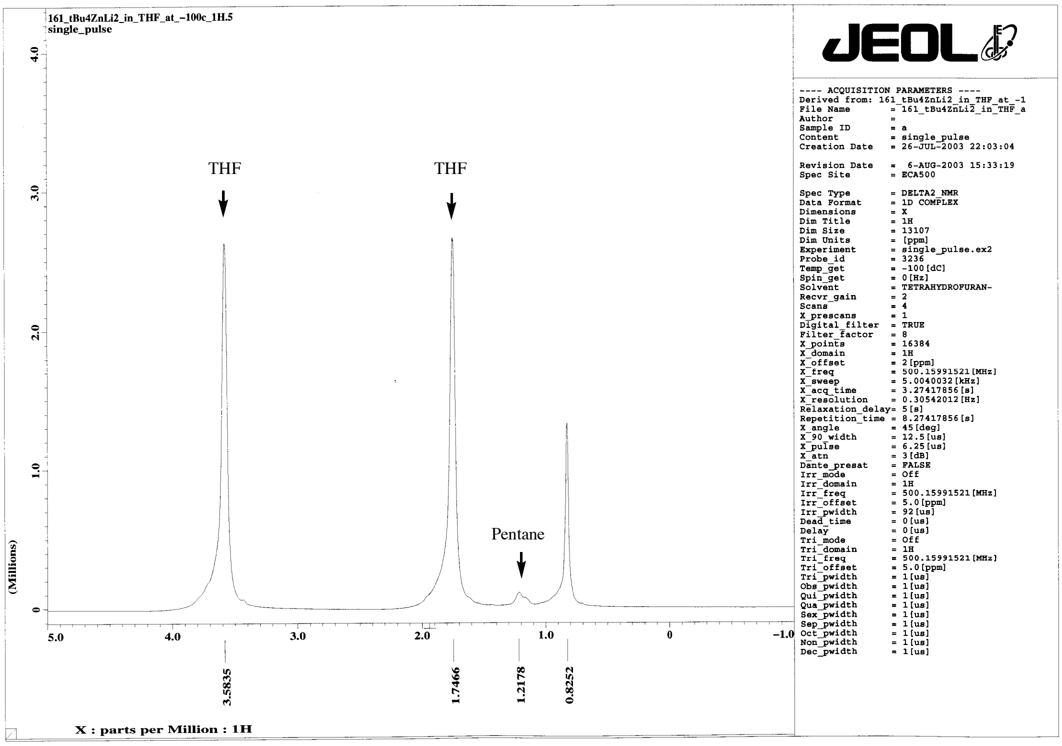
```
---- ACQUISITION PARAMETERS ----
Derived from: 162_tBuLi_in_THF_at_-100c_
File Name        = 162_tBuLi_in_THF_at_-1
Author           =
Sample ID        = a
Content          = single_pulse
Creation Date    = 26-JUL-2003 18:55:54

Revision Date    =  6-AUG-2003 15:41:02
Spec Site        = ECA500

Spec Type        = DELTA2_NMR
Data Format      = 1D COMPLEX
Dimensions       = X
Dim Title        = 7Li
Dim Size         = 13107
Dim Units        = [ppm]
Experiment       = single_pulse.ex2
Probe_id         = 3236
Temp_get         = -100.4[dC]
Spin_get         = 0[Hz]
Solvent          = TETRAHYDROFURAN-
Recvr_gain       = 40
Scans            = 8
X_prescans       = 1
Digital_filter   = TRUE
Filter_factor    = 8
X_points         = 16384
X_domain         = 7Li
X_offset         = 0[ppm]
X_freq           = 194.38059433[MHz]
X_sweep          = 4.8600311[kHz]
X_acq_time       = 3.37117184[s]
X_resolution     = 0.29663276[Hz]
Relaxation_delay= 1[s]
Repetition_time = 4.37117184[s]
X_angle          = 45[deg]
X_90_width       = 30[us]
X_pulse          = 15[us]
X_atn            = 9[dB]
Dante_presat     = FALSE
Irr_mode         = Off
Irr_domain       = 7Li
Irr_freq         = 194.38059433[MHz]
Irr_offset       = 5[ppm]
Irr_pwidth       = 92[us]
Dead_time        = 0[us]
Delay            = 0[us]
Tri_mode         = Off
Tri_domain       = 7Li
Tri_freq         = 194.38059433[MHz]
Tri_offset       = 5[ppm]
Tri_pwidth       = 1[us]
Obs_pwidth       = 1[us]
Qui_pwidth       = 1[us]
Qua_pwidth       = 1[us]
Sex_pwidth       = 1[us]
Sep_pwidth       = 1[us]
Oct_pwidth       = 1[us]
Non_pwidth       = 1[us]
Dec_pwidth       = 1[us]
```

Figure S-3. ^{7}Li NMR Spectra of ^{t}BuLi in THF at -100°C



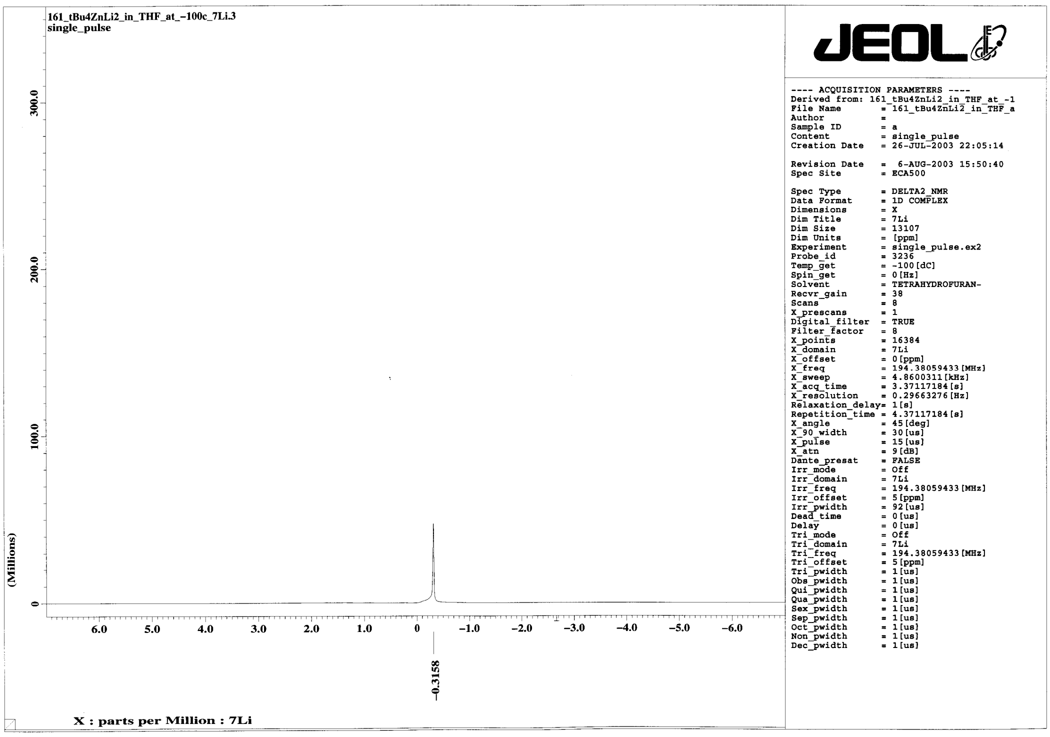
```
---- ACQUISITION PARAMETERS ----
Derived from: tBu2Zn in THF at -100c 1H.
File Name          = tBu2Zn in THF at -100c
Author             =
Sample ID          = ym
Content            = single_pulse
Creation Date      =  9-APR-2003 20:42:59

Revision Date      =  6-AUG-2003 15:35:54
Spec Site          = ECA500

Spec Type          = DELTA2_NMR
Data Format        = 1D COMPLEX
Dimensions         = X
Dim Title          = 1H
Dim Size           = 13107
Dim Units          = [ppm]
Experiment         = single_pulse.ex2
Probe_id           = 3236
Temp_get           = -100[dC]
Spin_get           = 0[Hz]
Solvent            = TETRAHYDROFURAN-
Recvr_gain         = 4
Scans              = 8
X_prescans         = 1
Digital_filter     = TRUE
Filter_factor      = 8
X_points           = 16384
X_domain           = 1H
X_offset           = 2[ppm]
X_freq             = 500.15991521[MHz]
X_sweep            = 6.25625626[kHz]
X_acq_time         = 2.61881856[s]
X_resolution       = 0.38185158[Hz]
Relaxation_delay= 5[s]
Repetition_time = 7.61881856[s]
X_angle            = 45[deg]
X_90_width         = 12.5[us]
X_pulse            = 6.25[us]
X_atn              = 3[dB]
Dante_presat       = FALSE
Irr_mode           = Off
Irr_domain         = 1H
Irr_freq           = 500.15991521[MHz]
Irr_offset         = 5.0[ppm]
Irr_pwidth         = 92[us]
Dead_time          = 0[us]
Delay              = 0[us]
Tri_mode           = Off
Tri_domain         = 1H
Tri_freq           = 500.15991521[MHz]
Tri_offset         = 5.0[ppm]
Tri_pwidth         = 1[us]
Obs_pwidth         = 1[us]
Qui_pwidth         = 1[us]
Qua_pwidth         = 1[us]
Sex_pwidth         = 1[us]
Sep_pwidth         = 1[us]
Oct_pwidth         = 1[us]
Non_pwidth         = 1[us]
Dec_pwidth         = 1[us]
```

Figure S-4. ^{1}H NMR Spectra of ^{t}Bu$_2$Zn in THF at -100°C



```
---- ACQUISITION PARAMETERS ----
Derived from: 161_tBu4ZnLi2_in_THF_at_-1
File Name          = 161_tBu4ZnLi2_in_THF_a
Author             =
Sample ID          = a
Content            = single_pulse
Creation Date      = 26-JUL-2003 22:03:04

Revision Date      =  6-AUG-2003 15:33:19
Spec Site          = ECA500

Spec Type          = DELTA2_NMR
Data Format        = 1D COMPLEX
Dimensions         = X
Dim Title          = 1H
Dim Size           = 13107
Dim Units          = [ppm]
Experiment         = single_pulse.ex2
Probe_id           = 3236
Temp_get           = -100[dC]
Spin_get           = 0[Hz]
Solvent            = TETRAHYDROFURAN-
Recvr_gain         = 2
Scans              = 4
X_prescans         = 1
Digital_filter     = TRUE
Filter_factor      = 8
X_points           = 16384
X_domain           = 1H
X_offset           = 2[ppm]
X_freq             = 500.15991521[MHz]
X_sweep            = 5.0040032[kHz]
X_acq_time         = 3.27417856[s]
X_resolution       = 0.30542012[Hz]
Relaxation_delay= 5[s]
Repetition_time = 8.27417856[s]
X_angle            = 45[deg]
X_90_width         = 12.5[us]
X_pulse            = 6.25[us]
X_atn              = 3[dB]
Dante_presat       = FALSE
Irr_mode           = Off
Irr_domain         = 1H
Irr_freq           = 500.15991521[MHz]
Irr_offset         = 5.0[ppm]
Irr_pwidth         = 92[us]
Dead_time          = 0[us]
Delay              = 0[us]
Tri_mode           = Off
Tri_domain         = 1H
Tri_freq           = 500.15991521[MHz]
Tri_offset         = 5.0[ppm]
Tri_pwidth         = 1[us]
Obs_pwidth         = 1[us]
Qui_pwidth         = 1[us]
Qua_pwidth         = 1[us]
Sex_pwidth         = 1[us]
Sep_pwidth         = 1[us]
Oct_pwidth         = 1[us]
Non_pwidth         = 1[us]
Dec_pwidth         = 1[us]
```

Figure S-5. ^{1}H NMR Spectra of ^{t}Bu$_4$ZnLi$_2$ in THF at -100°C

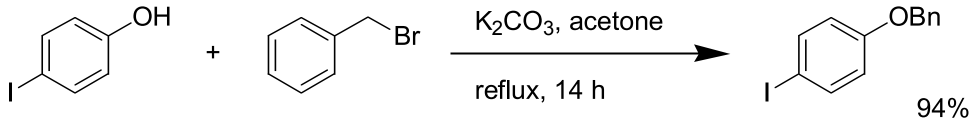


```
---- ACQUISITION PARAMETERS ----
Derived from: 161_tBu4ZnLi2_in_THF_at_-1
File Name          = 161_tBu4ZnLi2_in_THF_a
Author             =
Sample ID          = a
Content            = single_pulse
Creation Date      = 26-JUL-2003 22:05:14

Revision Date      =  6-AUG-2003 15:50:40
Spec Site          = ECA500

Spec Type          = DELTA2_NMR
Data Format        = 1D COMPLEX
Dimensions         = X
Dim Title          = 7Li
Dim Size           = 13107
Dim Units          = [ppm]
Experiment         = single_pulse.ex2
Probe_id           = 3236
Temp_get           = -100[dC]
Spin_get           = 0[Hz]
Solvent            = TETRAHYDROFURAN-
Recvr_gain         = 38
Scans              = 8
X_prescans         = 1
Digital_filter     = TRUE
Filter_factor      = 8
X_points           = 16384
X_domain           = 7Li
X_offset           = 0[ppm]
X_freq             = 194.38059433[MHz]
X_sweep            = 4.8600311[kHz]
X_acq_time         = 3.37117184[s]
X_resolution       = 0.29663276[Hz]
Relaxation_delay=  1[s]
Repetition_time  = 4.37117184[s]
X_angle            = 45[deg]
X_90_width         = 30[us]
X_pulse            = 15[us]
X_atn              = 9[dB]
Dante_presat       = FALSE
Irr_mode           = Off
Irr_domain         = 7Li
Irr_freq           = 194.38059433[MHz]
Irr_offset         = 5[ppm]
Irr_pwidth         = 92[us]
Dead_time          = 0[us]
Delay              = 0[us]
Tri_mode           = Off
Tri_domain         = 7Li
Tri_freq           = 194.38059433[MHz]
Tri_offset         = 5[ppm]
Tri_pwidth         = 1[us]
Obs_pwidth         = 1[us]
Qui_pwidth         = 1[us]
Qua_pwidth         = 1[us]
Sex_pwidth         = 1[us]
Sep_pwidth         = 1[us]
Oct_pwidth         = 1[us]
Non_pwidth         = 1[us]
Dec_pwidth         = 1[us]
```

Figure S-6. ^{7}Li NMR Spectra of ^{t}Bu$_4$ZnLi$_2$ in THF at -100°C

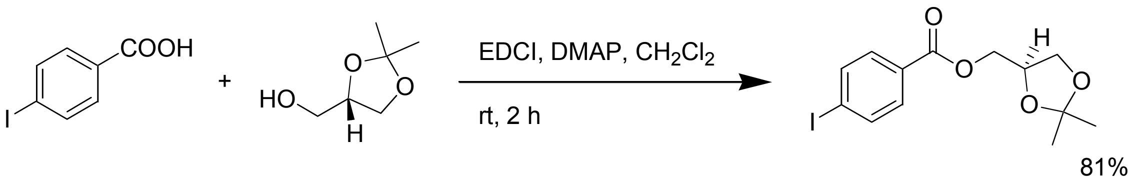
Preparation of Substrates

Table 2, Entry 1 [3]



To a flask, 4-Iodophenol (2.11 g, 9.6 mmol), K_2CO_3 (6.66 g, 48.2 mmol), and Benzyl bromide (0.95 mL, 8.0 mmol) were dissolved in 60 mL of acetone and the mixture was stirred under reflux for 14 h. After filtered to remove the solid and concentrated *in vacuo*, the residue was dissolved in 30 mL of Et_2O, washed with H_2O (10 mL X 2), and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane) yielded title compound as a colorless solid (2.05 g, 94%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.55 (d, 2H, J = 8.8 Hz), 7.44-7.29 (m, 5H), 6.74 (d, 2H, J = 8.8 Hz), 5.03 (s, 2H). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 158.6, 138.2, 136.5, 128.6, 128.1, 127.4, 117.3, 83.0, 70.1.

Table 2, Entry 3



To a flask, 4-Iodobenzoic acid (1.74 g, 7.0 mmol), (*S*)-2,2-Dimethyl-1,3-dioxolane-4-methanol (0.99 g, 7.5 mmol), DMAP (0.87 g, 7.2 mmol), and EDCI (1.50 g, 7.8 mmol) were dissolved in 10 mL of CH_2Cl_2 and the mixture was stirred for 2 h at room temperature. After it was diluted 30 mL of CH_2Cl_2, washed with H_2O (20 mL), sat. $NaHCO_3$ aq (20 mL X 2), 2N HCl (20 mL X 2) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane-ethyl acetate 8:1) yielded title compound (2.06 g, 81%). Recrystallized from ^{n}hexane. Colorless needles (>99% ee). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.81 (d, 2H, J = 8.8 Hz), 7.76 (d, 2H, J = 8.8 Hz), 4.49-4.30 (m, 3H), 4.14 (dt, 1H, J = 2.3, 7.3 Hz), 3.86 (dt, 1H, J = 2.3, 7.3 Hz), 1.45 (s, 3H), 1.39 (s, 3H). 125 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 165.9, 137.8, 131.2, 129.2, 110.0, 101.1, 73.6, 66.3, 65.3, 26.7, 25.4.

HRMS-ESI Calcd for $C_{13}H_{15}INaO_4$ (M^++Na): 384.9907. Found: 384.9943.

HPLC conditions: DAICEL CHIRALPAK IB, eluent: ^{n}hexane-isopropanol 95:5, flow: 1.0 mL/min, detection: 254 nm, t_R (*RS*)- (left): 7.0 min, 10.9 min; (*R*)- (right): 10.7 min (see below).

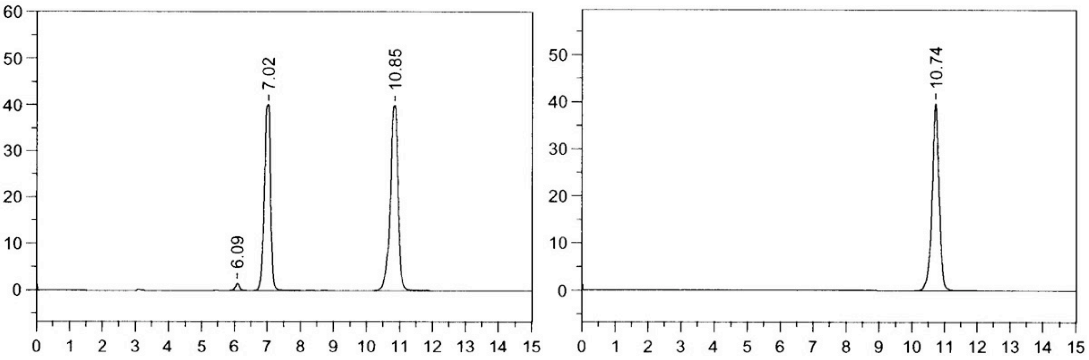
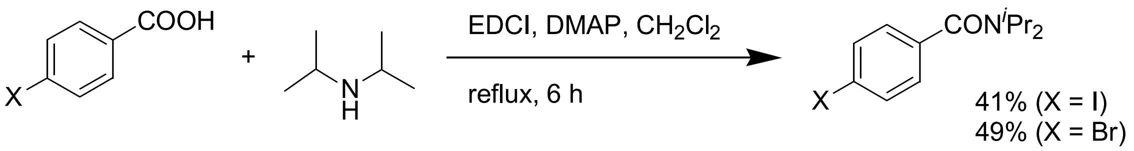


Table 2, Entry 4, 12 [4]

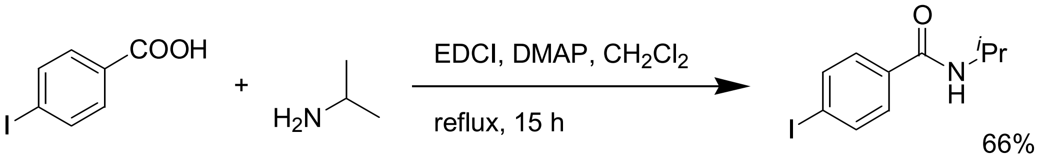


The procedure described for (*R*)-4-Iodo-benzoic acid 2, 2-dimethyl-[1, 3]dioxolan-4-ylmethyl ester was used with 4-Iodobenzoic acid (2.48 g, 10.0 mmol), Diisopropylamine (1.55 mL, 11 mmol), DMAP (2.49 g, 20.4 mmol), and EDCI (3.22 g, 16.8 mmol) to give 4-Iodo-*N*, *N*-diisopropylbenzamide as a yellow oil (1.35 g, 41%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.73 (d, 2H, *J* = 8.6 Hz), 7.06 (d, 2H, *J* = 8.6 Hz), 3.65 (brs, 2H), 1.44 (brs, 6H), 1.22 (brs, 6H).

HRMS-ESI Calcd for $C_{13}H_{19}INO$ (M^++H): 332.0506. Found: 332.0506.

The procedure described for (*R*)-4-Iodo-benzoic acid 2, 2-dimethyl-[1, 3]dioxolan-4-ylmethyl ester was used with 4-Bromobenzoic acid (2.03 g, 10.1 mmol), Diisopropylamine (1.55 mL, 11 mmol), DMAP (2.44 g, 20.0 mmol), and EDCI (2.84 g, 14.8 mmol) to give 4-Bromo-*N*, *N*-diisopropylbenzamide as a colorless solid (1.41 g, 49%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.52 (d, 2H, *J* = 8.3 Hz), 7.18 (d, 2H, *J* = 8.3 Hz), 3.65 (brs, 2H), 1.39 (brs, 6H), 1.25 (brs, 6H).

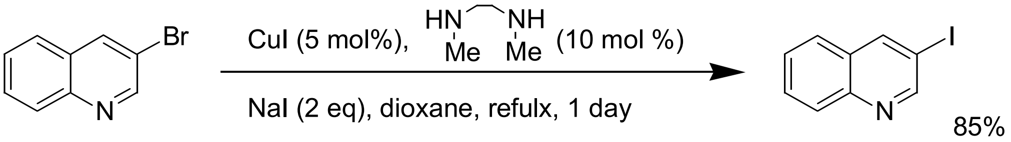
Table 2, Entry 5



The procedure described for (*R*)-4-Iodo-benzoic acid 2, 2-dimethyl-[1, 3]dioxolan-4-ylmethyl ester was used with 4-Iodobenzoic acid (2.00 g, 8.1 mmol), Isopropylamine (0.47 g, 7.9 mmol), DMAP (1.00 g, 8.2 mmol), and EDCI (1.77 g, 9.2 mmol) to give title compound as a colorless cotton (1.51 g, 66%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.78 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz), 5.84 (brs, 1H), 4.27 (septet, 1H, *J* = 6.6 Hz), 1.26 (d, 6H, *J* = 6.6 Hz).

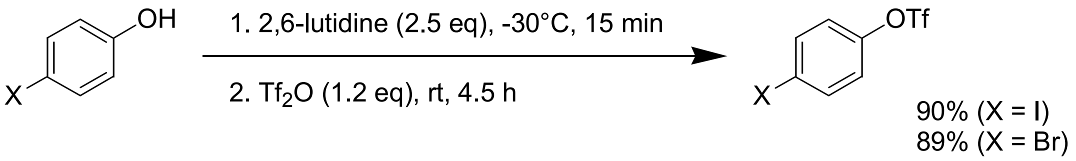
HRMS-ESI Calcd for $C_{10}H_{13}INO$ (M^++H): 290.0036. Found: 290.0034.

Table 2, Entry 8 [5]



To a flask, Copper (I) Iodide (48.9 mg, 0.25 mmol) and Sodium Iodide (1.5 g, 10.0 mmol) were dissolved in 5 mL of 1, 4-dioxane. Then, 3-Bromoquinoline (0.68 mL, 5 mmol) and *N*, *N'*-dimethylethylenediamine (46.4 mg, 0.50 mmol) were added to the mixture, and it was heated and refluxed for 1 day. The reaction mixture was cooled to room temperature, diluted 25% NH_3aq (30 mL) and extracted with $CHCl_3$ (15 mL X 3). The organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane-ethyl acetate 10:1) yielded title compound (1.1 g, 85%). Recrystallized from ^{n}hexane. Yellow needles. 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 9.04 (d, 1H, *J* = 2.0 Hz), 8.55 (d, 1H, *J* = 1.8 Hz), 8.07 (dd, 1H, *J* = 0.52, 8.3 Hz), 7.77-7.70 (m, 2H), 7.60-7.55 (m, 1H).

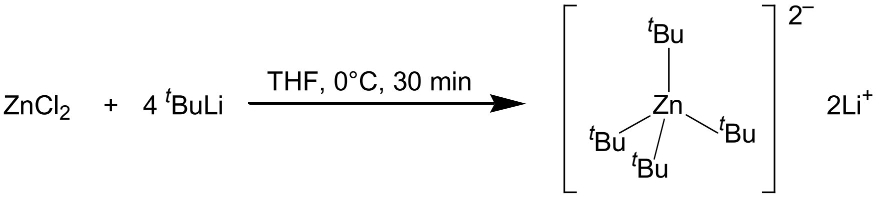
Table 2, Entry 14 [6]**, 15** [7]



To a flask, 4-Iodophenol (1.11 g, 5.0 mmol) was dissolved in 30 mL of CH_2Cl_2. The solution was cooled to –30°C, 2, 6-lutidine (1.43 mL, 12.5 mmol) was added, and stirred for 15 min at same temperature. Then, Tf_2O (1.0 mL, 6.0 mmol) was added to the solution, warmed up to room temperture, and stirred for 4.5 h. The reaction mixture was quenched 10 mL of H_2O at 0°C, and extracted with CH_2Cl_2 (20 mL X 2). The organic layer was washed with 2N HCl (20 mL X 2), 2N NaOHaq (30 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane-ethyl acetate 12:1) yielded title compound as a colorless oil (1.59 g, 90%). ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.78 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz).

The procedure described for Trifluoro-methanesulfonic acid 4-iodo-phenyl ester was used with 4-Bromophenol acid (0.86 g, 5.0 mmol), 2, 6-lutidine (1.43 mL, 12.5 mmol), and Tf_2O (1.0 mL, 6.0 mmol) to give Trifluoro-methanesulfonic acid 4-bromo-phenyl ester as a colorless oil (1.36 g, 89%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.58 (d, 2H, *J* = 9.0 Hz), 7.17 (d, 2H, *J* = 9.0 Hz).

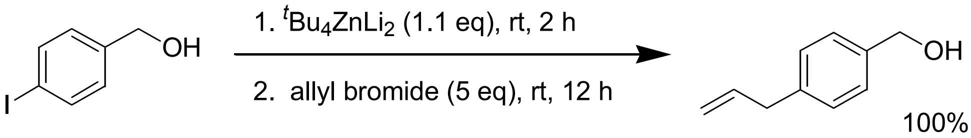
Preparation of ^{t}Bu$_4$ZnLi$_2$ THF Solution (1.1 mmol)



2.2 mL of $ZnCl_2$ (0.5 M THF solution, 1.1 mmol) was added to 5 mL of dry THF. Then, 3.17 mL of ^{t}BuLi (1.39 M ^{n}pentane solution, 4.4 mmol) was added dropwise to the solution at –78°C and it was stirred for 30min at 0°C to give a pale yellow ^{t}Bu$_4$ZnLi$_2$ THF solution (1.1 mmol).

A Halogen-Zinc Exchange Reaction by ^{t}Bu$_4$ZnLi$_2$

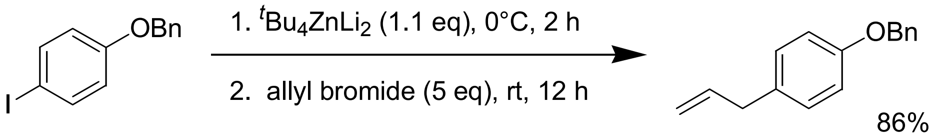
Typical Procedure: Compound 2, Table 1, Entry 10



A solution of the 4-Iodobenzylalcohol (242.5 mg, 1.01 mmol) in 5 mL of dry THF was added dropwise to a solution of ^{t}Bu$_4$ZnLi$_2$ (1.1 mmol) in THF at –78°C, warmed to rt and stirred for 2 h. Then, 0.43mL of allyl bromide (5 mmol) added to the solution and it was warmed to rt and stirred for 12 h. The reaction mixture was quenched with 2 mL of sat. NH_4Cl aq, diluted 2N HCl (10 mL) and extracted with Et_2O (10 mL X 3). The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane-ethyl acetate 2:1) yielded title compound as a colorless oil (149.5 mg, 100%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.29 (d, 2H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 6.01-5.91 (m, 1H), 5.11-5.05 (m, 2H), 4.65 (s, 2H), 3.39 (d, 2H, *J* = 6.7 Hz). 125 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 139.5, 138.6, 137.2, 128.7, 127.1, 115.8, 65.1, 39.8.
LRMS-ESI (*m/z*): 149 (M^++H).

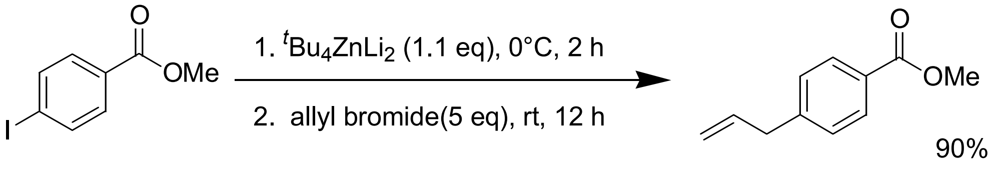
Metalation of Various Functionalized Organic Halides (Table 2)

Entry 1



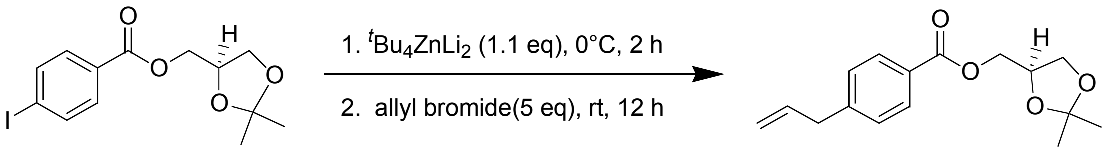
Colorless oil. 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ□(ppm): 7.46-7.40 (m, 2H), 7.40-7.35 (m, 2H), 7.34-7.28 (m, 1H), 7.10 (d, 2H, *J* = 8.6 Hz), 6.91 (d, 2H, *J* = 8.6 Hz), 6.01-5.89 (m, 1H), 5.10-5.01 (m, 2H), 5.04 (s, 2H), 3.33 (d, 2H, *J* = 6.8 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ□(ppm): 157.2, 137.8, 137.2, 132.4, 129.5, 128.5, 127.9, 127.4, 115.4, 114.8, 70.1, 39.3.
HRMS-ESI Calcd for $C_{16}H_{16}O$ (M^+): 224.1196. Found: 224.1189.

Entry 2 [8]



Colorless oil. 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.98 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 8.4 Hz), 6.01-5.90 (m, 1H), 5.13-5.05 (m, 2H), 3.90 (s, 3H), 3.44 (d, 2H, *J* = 6.6 Hz).

Entry 3

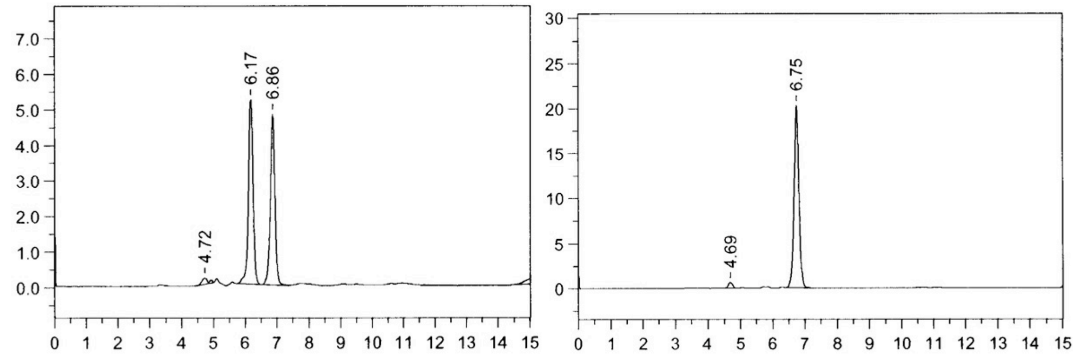


74%

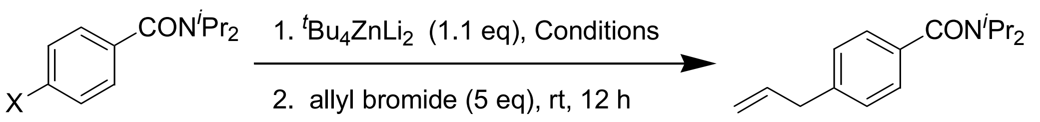
Colorless oil (>99% ee). 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 7.99 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 2H, *J* = 8.4 Hz), 6.02-5.89 (m, 1H), 5.15-5.04 (m, 2H), 4.49-4.31(m, 3H), 4.14 (dt, 1H, *J* = 2.6, 6.8 Hz), 3.88 (dt, 1H, J = 2. 6, 6.8 Hz), 3.44 (d, 2H, *J* = 6.6 Hz), 1.46 (s, 3H), 1.39 (s, 3H).

HRMS-ESI Calcd for $C_{16}H_{20}NaO_4$ (M^++Na): 299.1254. Found: 299.1259.

HPLC conditions: DAICEL CHIRALPAK IB, eluent: ^{n}hexane-isopropanol 98:2, flow: 1.0 mL/min, detection: 254 nm, t_R (*RS*)- (left): 6.2 min, 6.9 min; (*R*)- (right): 6.8 min (see below).



Entry 4, 12

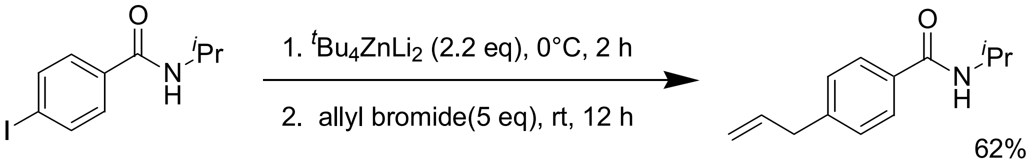


79% (X = I, 0°C, 2 h)
87% (X = Br, 60°C, 2 h)

Colorless oil. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ□(ppm): 7.25 (d, 2H, *J* = 8.1 Hz), 7.19 (d, 2H, *J* = 8.1 Hz), 6.02-5.90 (m, 1H), 5.14-5.05 (m, 2H), 3.68 (brs, 2H), 3.40 (d, 2H, J = 6.6 Hz), 1.46 (brs, 6H), 1.21 (brs, 6H). 100 MHz ^{13}C-NMR (CDCl$_3$) δ□(ppm): 171.1, 140.6, 137.0, 136.8, 128.6, 125.8, 116.1, 40.0, 20.7.

HRMS-ESI Calcd for $C_{16}H_{24}NO$ (M^++H): 246.1852. Found: 246.1855.

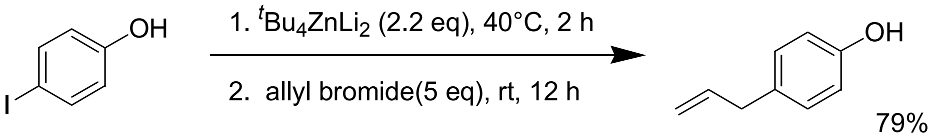
Entry 5



Recrystallized from ^{n}hexane / Et$_2$O. Colorless needles. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 7.68 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 6.01-5.89 (m, 1H), 5.86 (brs, 1H), 5.12-5.04 (m, 2H), 4.29 (septet, 1H, *J* = 6.6 Hz), 3.43 (d, 2H, *J* = 6.6 Hz), 1.26 (d, 6H, *J* = 6.6 Hz) ; mp 125-126°C.

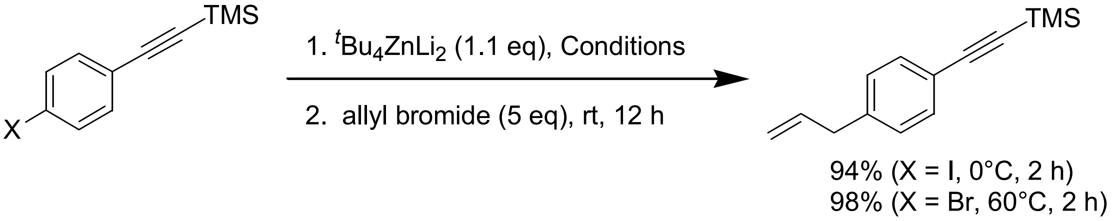
HRMS-ESI Calcd for $C_{13}H_{17}NNaO$ (M^++Na): 226.1202. Found: 226.1192.

Entry 6 [9]



Colorless oil. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 7.05 (d, 2H, *J* = 8.1 Hz), 6.76 (d, 2H, *J* = 8.1 Hz), 5.99-5.89 (m, 1H), 5.08-5.02 (m, 2H), 3.31 (d, 2H, *J* = 8.1 Hz). 100 MHz ^{13}C-NMR (CDCl$_3$) δ (ppm) 153.8, 137.8, 132.2, 129.7, 120.3, 115.4, 39.3.

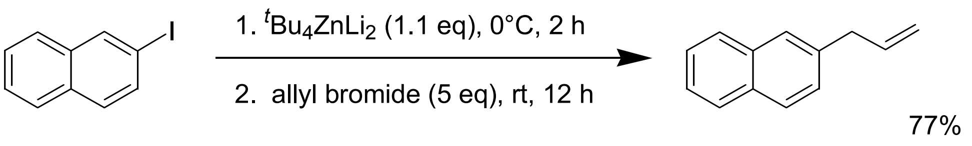
Entry 7, 11



Colorless oil. 500 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 7.40 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 5.94-5.91 (m, 1H), 5.08-5.04 (m, 2H), 3.37 (d, 2H, *J* = 6.9 Hz), 0.24 (s, 9H). 125 MHz ^{13}C-NMR (CDCl$_3$) δ (ppm): 140.6, 136.8, 132.0, 128.5, 120.7, 116.2, 105.1, 93.5, 40.0, -0.04.

HRMS-ESI Calcd for $C_{14}H_{19}Si$ (M^++H): 215.1251. Found: 215.1243.

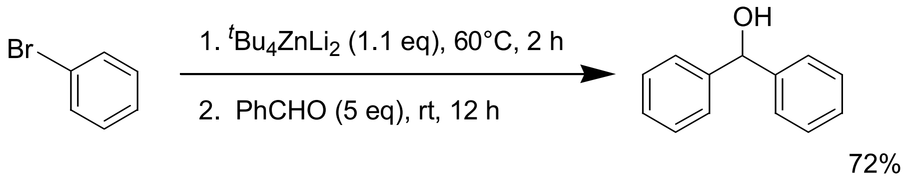
Entry 8



Orange oil. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 8.78 (d, 1H, *J* = 2.0 Hz), 8.09 (d, 1H, *J* = 8.3 Hz), 7.92 (d, 1H, *J* = 1.3 Hz), 7.77 (dd, 1H, *J* = 1.0, 8.3 Hz), 7.69-7.64 (m, 1H), 7.56-7.50 (m, 1H), 6.10-5.96 (m, 1H), 5.22-5.09 (m, 2H), 3.57 (d, 2H, *J* = 7.1 Hz). 100 MHz ^{13}C-NMR (CDCl$_3$) δ (ppm): 152.0, 146.9, 136.0, 134.6, 132.6, 129.2, 128.7, 128.1, 127.4, 126.6, 117.0, 37.3.

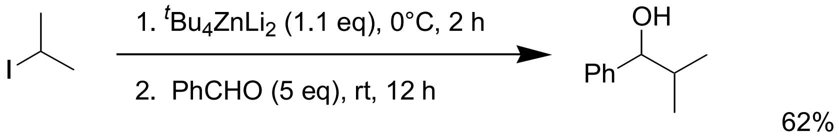
HRMS-ESI Calcd for $C_{12}H_{12}N$ (M$^+$+H): 170.0964. Found: 170.0956.

Entry 9 [10]



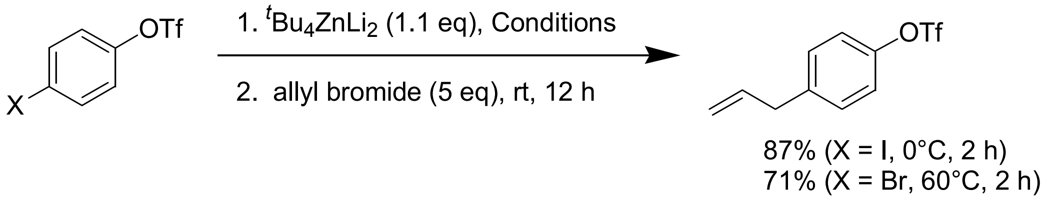
Recrystallized from ^{n}hexane. Colorless needles. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ□(ppm): 7.42-7.24 (m, 10H), 5.86 (s, 1H).

Entry 10 [11]



Colorless oil. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ□(ppm): 7.38-7.24 (m, 5H), 4.37 (d, 1H, *J* = 6.8 Hz), 1.96 (octet, 1H, *J* = 6.8 Hz), 1.82 (brs, 1H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.80 (d, 3H, *J* = 6.8 Hz).

Entry 14, 15

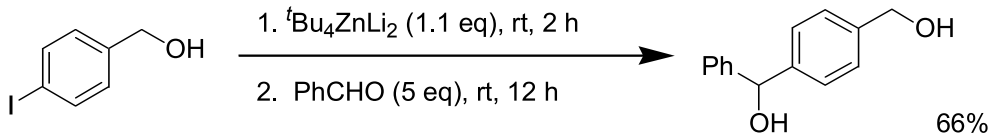


Colorless oil. 400 MHz ^{1}H-NMR (CDCl$_3$/TMS) δ (ppm): 7.26 (d, 2H, *J* = 8.4 Hz), 7.19 (d, 2H, *J* = 8.4 Hz), 6.00-5.86 (m, 1H), 5.17-5.04 (m, 2H), 3.41 (d, 2H, *J* = 6.8 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ□(ppm): 148.0, 140.6, 136.3, 130.3, 121.2, 120.3, 116.8, 39.4.

LRMS-ESI (*m/z)*: 267 (M^++H).

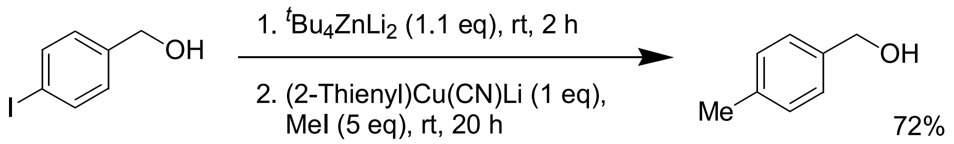
Electrophilic Trapping of the Functionalized Phenyl Intermediate (Chart 1)

Compound 6 [12]



A solution of the 4-Iodobenzylalcohol (240.8 mg, 1.00 mmol) in 5 mL of dry THF was added dropwise to a solution of $^tBu_4ZnLi_2$ (1.1 mmol) in THF at -78°C. After the mixture was stirred for 2 h at rt, 0.53 mL of benzaldehyde (5 mmol) was added to the mixture at -78°C. It was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with 2 mL of sat. NH_4Cl aq, diluted 2N HCl (10 mL) and extracted with Et_2O (10mL X 3). The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography ($CHCl_3$-Methanol 20:1) yielded title compound (141.4 mg, 66%) as a colorless solid. 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.41-7.28 (m, 9H), 5.86 (d, 1H, *J* = 2.8 Hz), 4.68 (d, 2H, *J* = 4.8 Hz).

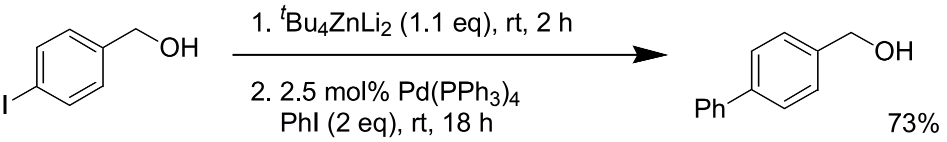
Compound 7 [10]



A solution of the 4-Iodobenzylalcohol (241.5 mg, 1.00 mmol) in 5 mL of THF was added dropwise to a solution of $^tBu_4ZnLi_2$ (1.1 mmol) in THF at -78°C. After the mixture was stirred for 2 h at rt, 0.31 mL of MeI (5 mmol) and 4 mL of (2-Thienyl)Cu(CN)Li (0.25 M THF solution, 1.0 mmol) were added sequentially to the mixture at -78°C. It was warmed to room temperature and stirred for 20 h. The reaction mixture was quenched with 2 mL of sat. NH_4Cl aq, diluted 2N HCl (10 mL) and extracted with $CHCl_3$ (10mL X 3). The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by

SiO_2 open column chromatography (^{n}hexane-ethyl acetate 4:1) yielded title compound as a pale yellow solid (87.3 mg, 72%). 400 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.26 (d, 2H, J = 8.0 Hz), 7.17 (d, 2H, J = 8.0 Hz), 4.65 (s, 2H), 2.35 (s, 3H).

Compound 8 [10]



A solution of the 4-Iodobenzylalcohol (241.1 mg, 1.00 mmol) in 5 mL of dry THF was added dropwise to a solution of $^tBu_4ZnLi_2$ (1.1 mmol) in THF at -78°C. After the mixture was stirred for 2 h at rt, a solution of the $Pd(PPh_3)_4$ (28.0 mg, 0.025 mmol) in 5 mL of THF, and 0.19 mL of iodobenzene (2 mmol), were added sequentially to the mixture at -78°C. It was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with 2 mL of sat. NH_4Cl aq, diluted 2N HCl (10 mL) and extracted with $CHCl_3$ (10mL X 3). The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by SiO_2 open column chromatography (^{n}hexane-ethyl acetate 4:1) yielded title compound (133.9 mg, 73%). Recrystallized from ^{n}hexane / Et_2O. Colorless plates. 500 MHz ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm): 7.63-7.57 (m, 4H), 7.48-7.41 (m, 4H), 7.38-7.32 (m, 1H), 4.75 (s, 2H). 125 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 140.8, 140.7, 139.9, 128.8, 127.5, 127.3, 127.1, 65.1; mp 98-99°C.

References for *Supporting Information*

[1] (a) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *46*, 1879-1880. (b) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-168.

[2] (a) Abraham, M. H. *J. Chem. Soc.* **1960**, 4130. (b) Coates, P. D.; Roberts, P. D.; Downs, A. J. *J. Chem. Soc. (A), Inorg. Phys. Theor.* **1967**, 1085.

[3] Oldfield, M. F.; Chen, L.; Botting, N. P. *Tetrahedron* **2004**, *60*, 1887-1893.

[4] Picard, F.; Schulz, T.; Hartmann, R. W. *Bioorg. Med. Chem.* **2002**, *10*, 437-448.

[5] Klapars, S.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.

[6] Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*,

1654-1657.

[7] Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717-4718.

[8] Gomes, P.; Gosmini, C.; Perichon, J. *Org. Lett.* **2003**, *5*, 1043-1045.

[9] Gu, W.; She, X.; Pan, X.; Yang, T.-K. *Tetrahedron Assym.* **1998**, *9*, 1377-1380.

[10] Book: Pouchert, C. J.; Behnke, J. In *The Aldrich Library of* ^{13}*C and* ^{1}*H FT NMR Spectra*; Aldrich, Inc.: United States, 1993.

[11] Chen, D.-W.; Ochiai, M.; *J. Org. Chem.*, **1999**, *64*, 6804-6814.

[12] Gomez, C.; Huerta, F. F.; Yus, M. *Tetrahedron* **1998**, *54*, 1853-1866.