Synthesis of Ethyl Arylpropiolates through Palladium-Catalyzed Cross-Coupling Reactions of Aryl Iodides with In Situ Generated Lithium Tetrakis(ethoxycarbonylethynyl)indates

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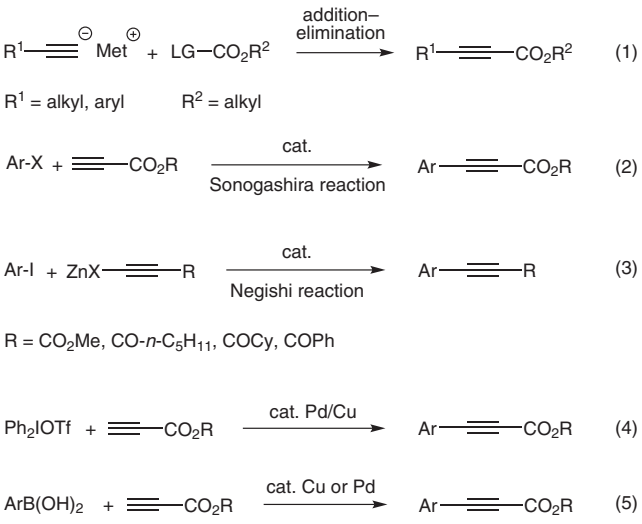
Received: 21.02.2014; Accepted after revision: 13.04.2014

Abstract: An efficient synthetic method to access ethyl arylpropiolates has been developed; it involves a palladium-catalyzed cross-coupling reaction between a wide range of aryl iodides and lithium tetrakis(ethoxycarbonylethynyl)indates (0.35 equiv) generated in situ from indium trichloride and alkynides obtained from ethyl propiolate and *n*-butyllithium.

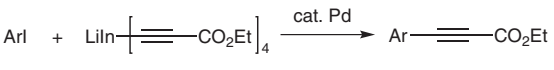
Key words: cross-coupling, palladium, indium, lithium tetrakis(ethoxycarbonylethynyl)indate, propiolates, catalysis

Alkynes are highly useful functional groups found in bioactive compounds, synthetic intermediates, and electroorganic materials.[1] In particular, alkyl 3-arylpropiolates have been receiving attention as important reagents due to their usability in various organic reactions such as Michael and Diels–Alder reactions.[2] In general, synthetic methods available to access alkyl 3-arylpropiolates may be divided into several categories (Scheme 1), such as addition followed by elimination reaction of alkynides with alkoxyformate derivatives (1)[3] and palladium-catalyzed cross-coupling reaction of electrophilic coupling partners with alkoxypropiolates known as the Sonogashira reaction (2).[4] Although the Sonogashira reaction has been recognized as a highly practical method for the synthesis of arylalkynes, the cross-coupling reaction of aryl halides with alkoxypropiolates does not give good results for alkynes bearing electron-withdrawing groups.[5] To overcome the limitation of the cross-coupling reactions, Negishi and co-workers developed an efficient palladium-catalyzed cross-coupling reaction of aryl halides with alkynylzinc derivatives generated in situ from electron-deficient terminal alkynes (3).[6] In addition, palladium/copper-catalyzed arylation of electron-deficient alkynes by using diaryliodonium salts has been reported (4).[7] Recently, copper- or palladium-catalyzed Sonogashira-type coupling of arylboronic acids with terminal alkynes proved to be an efficient synthetic method for ethyl arylpropiolates (5).[8] Nevertheless, efficient synthetic methods to prepare ethyl arylpropiolates are still required to overcome shortcomings such as excessive use of reagents and narrow scope of aryl halides in the previously reported results.



Scheme 1 Synthetic methods providing alkyl arylpropiolates

Recently, we developed a palladium-catalyzed decarboxylative cross-coupling reaction[9] and C–H alkynylation involving propiolic acid[10] and a multitude of palladium-catalyzed cross-coupling reactions using organoindium reagents.[11] Stimulated by these results, we envisioned that in situ generated lithium tetrakis(ethoxycarbonylethynyl)indates could react with electrophiles through palladium-catalyzed cross-coupling reactions to produce ethyl arylpropiolates. Herein we report an atom-economical synthetic method for accessing ethyl arylpropiolates through palladium-catalyzed cross-coupling reactions of aryl iodides with lithium tetrakis(ethoxycarbonylethynyl)indate (0.35 equiv) generated in situ from indium trichloride and the alkynide obtained from ethyl propiolate and *n*-butyllithium (Scheme 2).

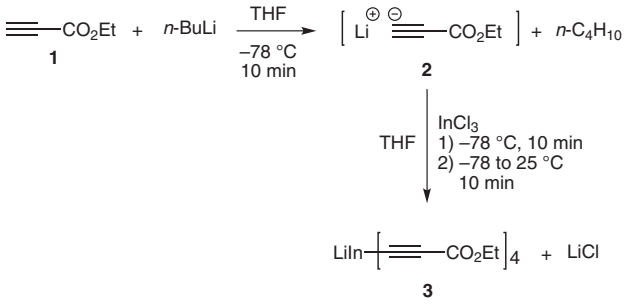


Scheme 2 Cross-coupling reaction using lithium tetrakis(ethoxycarbonylethynyl)indate

First, on the basis of the reported synthetic methods for the in situ generation of tri(organo)indiums[12] and metal tetra(organo)indates,[13] lithium tetrakis(ethoxycarbonylethynyl)indate was efficiently generated in situ from the reaction of indium trichloride with lithium ethoxycarbon-

SYNTHESIS 2014, 46, 2305–2311
Advanced online publication: 28.05.2014
DOI: 10.1055/s-0033-1339110; Art ID: SS-2014-C0123-ST

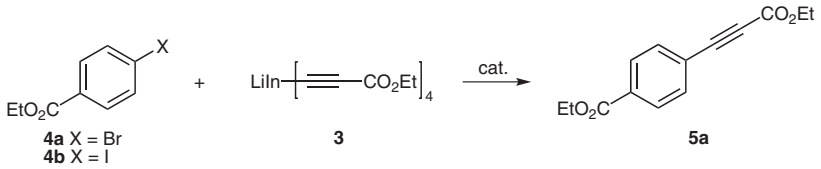
ylethynide, which was obtained from ethyl propiolate and *n*-butyllithium (Scheme 3).



Scheme 3 In situ generation of lithium tetrakis(ethoxycarbonylethynyl)indate

We initiated our studies with the reaction of ethyl 4-bromobenzoate (**4a**) with in situ generated lithium tetrakis(ethoxycarbonylethynyl)indate (**3**) in the presence of a palladium catalyst in tetrahydrofuran at 80 °C (Table 1). First, the catalytic activity of a variety of palladium catalysts was investigated. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) [Pd(dppf)Cl_2; 4 mol%] was not effective (entry 1). Although the tris(dibenzylideneacetone)dipalladium(0)–chloroform complex (2 mol%) as catalyst was used in the presence of a wide range of ligands such as triphenylphosphine (16 mol%), tris(4-trifluoromethylphenyl)phosphine (16 mol%), tris(4-methoxyphenyl)phosphine (16 mol%), and 1,3-bis(diphenylphosphino)propane (DPPP; 8 mol%), the desired coupling product was not produced (entries 2–5). However, when the tris(dibenzylideneacetone)dipalladium(0)–chloroform complex (2 mol%) and (oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEphos; 8 mol%) were used, ethyl 3-(4-ethoxycarbonylphenyl)propiolate (**5a**) was obtained in 26% yield (entry 6). The use of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos; 8 mol%) resulted in a slight increase in yield (30%; entry 7). Treatment of ethyl 4-iodobenzoate (**4b**; 1 equiv) with lithium tetrakis(ethoxycarbonylethynyl)indate (**3**; 0.35 equiv) gave the best result in the presence of the tris(dibenzylideneacetone)dipalladium(0)–chloroform complex (2 mol%) and Xantphos (8 mol%); **5a** is produced in 88% yield in tetrahydrofuran at 80 °C after three hours (entry 9). These results indicate that lithium tetrakis(ethoxycarbonylethynyl)indate (**3**) is more reactive than (ethoxycarbonylethynyl)zinc chloride and (ethoxycarbonylethynyl)tributyltin chloride, because these reagents gave the corresponding alkynes in 30% and 6% yields, respectively (see the Supporting Information).[4d,5b,6] When lithium tetrakis(ethoxycarbonylethynyl)indate (**3**; 0.30 equiv) was used, the cross-coupling reaction was not completed, and **5a** was produced in 75% yield together with **4b** (17%) (entry 10).

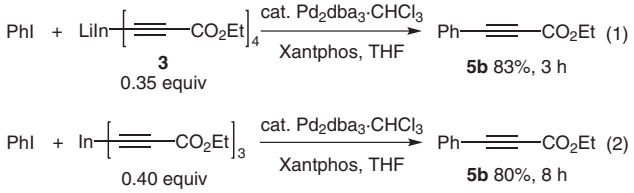
Table 1 Optimization of Palladium-Catalyzed Cross-Coupling Reactions Using Lithium Tetrakis(ethoxycarbonylethynyl)indate[a]



Entry	X	Cat. (mol%)	Ligand (mol%)	Time (h)	Yield (%)[b]
1	Br	Pd(dppf)Cl_2 (4)	none	24	0
2	Br	Pd_2dba_3·$CHCl_3$ (2)	Ph_3P (16)	24	0
3	Br	Pd_2dba_3·$CHCl_3$ (2)	$(4\text{-}F_3CC_6H_4)_3P$ (16)	24	0
4	Br	Pd_2dba_3·$CHCl_3$ (2)	$(4\text{-}MeOC_6H_4)_3P$ (16)	24	0
5	Br	Pd_2dba_3·$CHCl_3$(2)	DPPP (8)[c]	24	0
6	Br	Pd_2dba_3·$CHCl_3$ (2)	DPEphos (8)[d]	24	26
7	Br	Pd_2dba_3·$CHCl_3$(2)	Xantphos (8)[e]	24	30
8	I	Pd(dppf)Cl_2 (4)	none	12	60
9	I	Pd_2dba_3·$CHCl_3$ (2)	Xantphos (8)[e]	3	88
10	I	Pd_2dba_3·$CHCl_3$ (4)	Xantphos (8)[e]	4	75(17)[f]

[a] Reaction conditions: **4** (0.3 mmol), **3** (0.105 mmol, 0.35 equiv), THF, 80 °C (unless otherwise noted).
[b] Isolated yield.
[c] DPPP = 1,3-bis(diphenylphosphino)propane.
[d] DPEphos = (oxydi-2,1-phenylene)bis(diphenylphosphine).
[e] Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.
[f] Reaction conditions: **4b** (0.3 mmol), **3** (0.09 mmol, 0.30 equiv), THF, 80 °C. Number in parentheses indicates recovered yield of **4b**.

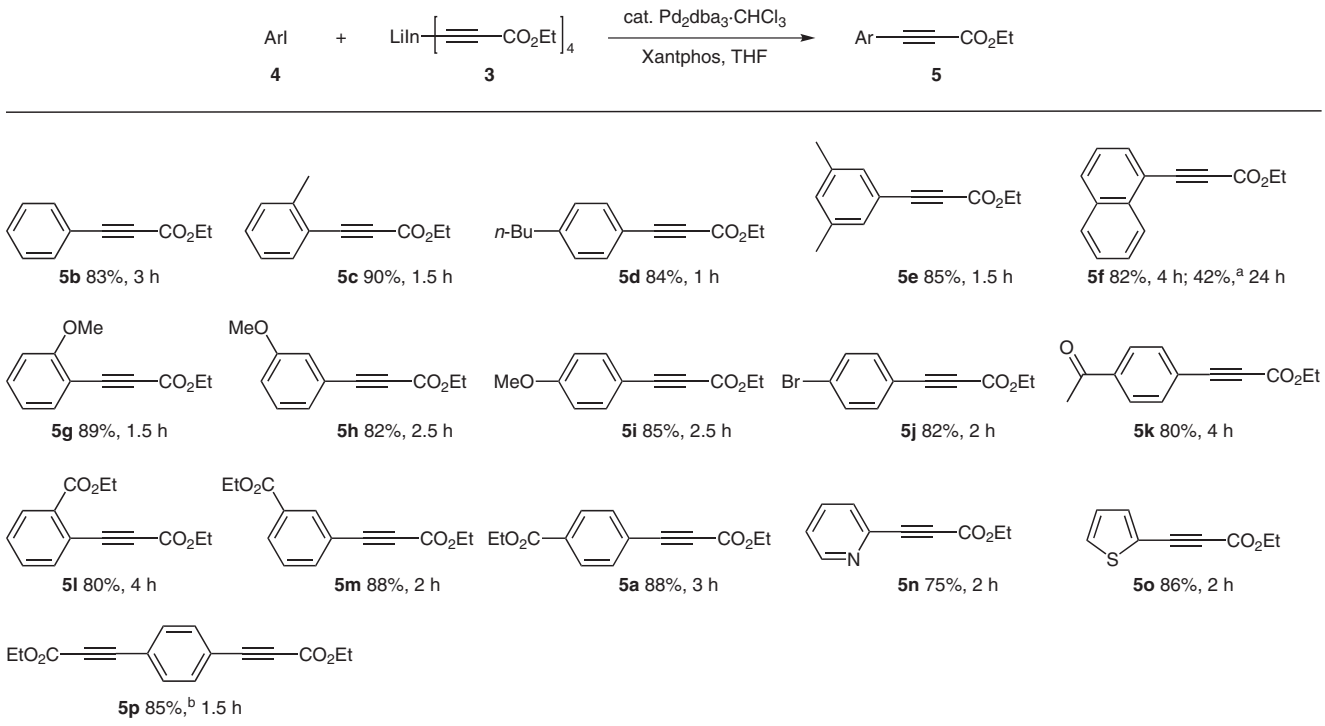
When lithium tetrakis(ethoxycarbonylethynyl)indate (**3**; 0.35 equiv) reacted with phenyl iodide (Scheme 4), the cross-coupling reaction was complete, producing ethyl phenylpropiolate (**5b**) in 83% yield, after three hours (1). However, use of tris(ethoxycarbonylethynyl)indium (0.40 equiv) gave **5b** in 80% yield after eight hours (2). These results indicate that the type of indium reagent is different in these two reactions. Accordingly, in situ generation of lithium tetrakis(ethoxycarbonylethynyl)indate was assumed in the present reaction. In general, ate complexes are more reactive than the corresponding neutral organometallic reagents.[13]



Scheme 4

To establish the efficiency and scope of the present method, we applied this catalytic system to the reactions of a number of aryl iodides with lithium tetrakis(ethoxycarbonylethynyl)indate (**3**) (Scheme 5). 2-Iodotoluene underwent the palladium-catalyzed cross-coupling reaction to give ethyl 3-(2-methylphenyl)propiolate (**5c**) in 90% yield. The sterically hindered 2-iodo-*m*-xylene was not totally ineffective. Subjecting 1-*n*-butyl-4-iodobenzene to palladium catalysis provided the coupling product **5d** in 84% yield. The present method worked equally well with 3,5-dimethyl-1-iodobenzene, resulting in the production of **5e** in 85% yield. 1-Iodonaphthalene was treated with **3** to afford ethyl 3-(1-naphthyl)propiolate **5f** in 82% yield.

However, 1-naphthyl triflate was less reactive, producing **5f** in 42% yield after 24 hours (Scheme 5). Aryl iodides bearing a strongly electron-donating methoxy group on the phenyl ring turned out to be compatible with the reaction conditions. In particular, 2-iodoanisole was smoothly converted into the desired propiolate **5g** in 89% yield despite steric repulsion. Also, 4-iodoanisole worked equally well. The cross-coupling reaction between electron-deficient aryl iodides and **3** proceeded efficiently, affording the desired ethyl arylpropiolates. 1-Bromo-4-iodobenzene was selectively subjected to the coupling reaction to provide ethyl 3-(4-bromophenyl)propiolate (**5j**) in 82% yield. The tolerance of the bromo group on the phenyl ring is especially important, as it potentially allows subsequent catalytic cross-couplings. In addition, functional groups commonly used in organic synthesis were tolerated. Substrates possessing ketone and ester groups all smoothly reacted with **3** to afford ethyl arylpropiolates **5k**, **5l**, and **5m** in good yields. These results indicate that the present cross-coupling reactions were not largely affected by either electronic or steric effects on the aryl ring. We were pleased to obtain the desired coupling products from substrates containing heterocyclic moieties. For example, 2-iodopyridine and 2-iodothiophene were treated with **3** to produce ethyl 3-(2-pyridyl)propiolate (**5n**) and ethyl 3-(2-thienyl)propiolate (**5o**) in 75% and 86% yields, respectively. Encouraged by this result, we applied the present



Scheme 5 Palladium-catalyzed cross-coupling reactions of indate **3** with electrophiles. *Reagents and conditions*: **3** (0.35 equiv), $Pd_2dba_3 \cdot CHCl_3$ (2 mol%), Xantphos (8 mol%), THF, 80 °C. [a] 1-Naphthyl triflate was used. [b] Indate **3** (0.7 equiv) was used.

method to dihalogenated aromatic compounds to obtain disubstituted benzene. Gratifyingly, the reaction of 1,4-diiodobenzene with 0.70 equiv of lithium tetrakis(ethoxycarbonylethynyl)indate **3** produced 1,4-bis(ethoxycarbonylethynyl)benzene (**5p**) in 85% yield, indicating that ethoxycarbonylethynyl group attached to indium was effectively transformed to electrophiles (Scheme 5).

In conclusion, we have developed an efficient palladium-catalyzed cross-coupling reactions of aryl iodides with lithium tetrakis(ethoxycarbonylethynyl)indate (**3**; 0.35 equiv), generated in situ from indium trichloride and the alkynide obtained from ethyl propiolate and *n*-butyllithium, producing ethyl arylpropiolates in good to excellent yields. These results indicate that the ethoxycarbonylethynyl group attached to indium was effectively transformed to an electrophile. Because alkynes with electron-withdrawing groups are generally poor nucleophiles in the Sonogashira reaction, these results afford good options and tools for C–C bond-forming reactions.

Reactions were carried out in flame-dried test tubes under a nitrogen atmosphere. $Pd_2dba_3{\cdot}CHCl_3$ and Xantphos were purchased and were used as received. Commercially available reagents were used without purification. THF was dried over Na and benzophenone. All reaction mixtures were stirred magnetically and were monitored by TLC (silica gel pre-coated glass plates, visualized with UV light and then developed by using either I_2 or a solution of anisaldehyde). Flash column chromatography was carried out on silica gel (230–400 mesh). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX FR (400 MHz) NMR spectrometer. $CDCl_3$ was used as the solvent, and chemical shift values (δ) are reported relative to the residual signals of this solvent (δ = 7.26 for ^{1}H and δ = 77.2 for ^{13}C). IR spectra were recorded on a Jasco FT/IR 460 Plus FT-IR spectrophotometer; samples were prepared as either a thin film pressed between two NaCl plates or as a solid suspended in a KBr disk. Mass spectra were obtained from the KBSI using a VG Autospec Ultima high-resolution mass spectrometer. Melting points were determined in open capillary tubes by using an Electrothermal 9100 apparatus.

Lithium Tetrakis(ethoxycarbonylethynyl)indate (3)
A solution of 1.6 M *n*-BuLi in hexane (0.42 mmol) was slowly added to a solution of ethyl propiolate (**1**; 0.42 mmol, 43 μL) in THF (0.5 mL) at –78 °C under a N_2 atmosphere. After being stirred for 10 min, this mixture was added to a solution of $InCl_3$ (23.3 mg, 0.105 mmol) in THF (0.5 mL) at –78 °C. The mixture was stirred for 10 min, and then the cooling bath was removed, and the reaction mixture was warmed to r.t. over 10 min.

Ethyl 3-(4-Ethoxycarbonylphenyl)propiolate (5a); Typical Procedure
A mixture of $Pd_2dba_3{\cdot}CHCl_3$ (6.2 mg, 2 mol%), Xantphos (14.0 mg, 8 mol%), and ethyl 4-iodobenzoate (50.5 μL, 0.3 mmol) in THF (0.5 mL) was stirred for 10 min at r.t. This mixture was added to a 0.105 M solution of lithium tetrakis(ethoxycarbonylethynyl)indate in anhydrous THF (**3**; 0.105 mmol) under a N_2 atmosphere. The reaction mixture was heated at reflux for 3 h. After cooling to r.t., the reaction mixture was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were sequentially washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane, 1:20) to give **5a**.

Yield: 88% (65.0 mg); white solid; mp 38–40 °C; R_f = 0.3 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 1711, 1422, 1271, 1195, 896, 716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 8.3 Hz, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 1.42–1.35 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 154.1, 133.1, 132.4, 130.0, 124.4, 85.0, 83.0, 62.7, 61.8, 14.7, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0894.

Ethyl 3-Phenylpropiolate (5b)[14]
Yield: 83% (43.4 mg); colorless oil; R_f = 0.3 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 2305, 2212, 1705, 1421, 1266, 896, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.57 (m, 2 H), 7.47–7.42 (m, 1 H), 7.39–7.35 (m, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 133.4, 131.0, 129.0, 120.0, 86.4, 81.1, 62.5, 14.5.

Ethyl 3-*o*-Tolylpropiolate (5c)
Yield: 90% (51.0 mg); colorless oil; R_f = 0.4 (EtOAc–hexane, 1:20).

IR (film) 3054, 2987, 2305, 1704, 1422, 1260, 896, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.61 Hz, 1 H), 7.33 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.23 (d, *J* = 7.7 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 2.49 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 142.6, 133.8, 131.0, 130.1, 126.2, 120.0, 85.5, 84.8, 62.4, 21.0, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}O_2$: 188.0837; found: 188.0837

Ethyl 3-(4-Butylphenyl)propiolate (5d)
Yield: 84% (58.0 mg); colorless oil; R_f = 0.4 (EtOAc–hexane, 1:15).

IR (film): 3054, 2987, 1703, 1422, 1259, 1176, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.2 Hz, 2 H), 7.18 (d, *J* = 8.2 Hz, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 1.63–1.55 (m, 2 H), 1.37–1.31 (m, 5 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 146.6, 133.4, 129.1, 117.1, 87.1, 80.8, 62.4, 36.1, 33.6, 22.7, 14.5, 14.3.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}O_2$: 230.1307; found: 230.1308.

Ethyl 3-(3,5-Dimethylphenyl)propiolate (5e)
Yield: 85% (52.0 mg); colorless oil; R_f = 0.5 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 1704, 1265, 1157, 855, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 2 H), 7.07 (s, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 2.30 (s, 6 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 138.6, 133.0, 131.1, 119.6, 87.1, 80.5, 62.4, 21.4, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}O_2$: 202.0994; found: 202.0995.

Ethyl 3-(1-Naphthyl)propiolate (5f)[1]
Yield: 82% (55.2 mg); colorless oil; R_f = 0.4 (EtOAc–hexane, 1:15).

IR (film): 3054, 2987, 1704, 1265, 1207, 804, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.86 (t, *J* = 8.6 Hz, 2 H), 7.65–7.61 (m, 1 H), 7.56 (td, *J* = 8.1, 1.1 Hz, 1 H), 7.46 (dd, *J* = 8.1, 7.4 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 134.1, 133.4, 131.7, 128.9, 128.0, 127.3, 126.2, 125.5, 117.6, 85.8, 84.8, 62.6, 14.6.

Ethyl 3-(2-Methoxyphenyl)propiolate (5g)[14]
Yield: 89% (54.5 mg); colorless oil; R_f = 0.2 (EtOAc–hexane, 1:15).

IR (film): 3054, 2986, 1703, 1492, 1421, 1259, 895, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 7.6, 1.71 Hz, 1 H), 7.43–7.38 (m, 1 H), 6.96–6.89 (m, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.90 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 154.6, 135.3, 132.7, 120.9, 111.2, 109.2, 85.0, 83.5, 62.4, 56.2, 14.5.

Ethyl 3-(3-Methoxyphenyl)propiolate (5h)[15]
Yield: 82% (50.2 mg); colorless oil; R_f = 0.2 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 2305, 2221, 1705, 1422, 1265, 1234, 896, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.9 Hz, 1 H), 7.18 (d, *J* = 7.5 Hz, 1 H), 7.09 (dd, *J* = 2.5, 1.3 Hz, 1 H), 7.01–6.98 (m, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.80 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 154.4, 130.1, 125.9, 121.0, 117.9, 117.8, 86.4, 80.8, 62.5, 55.7, 14.5.

Ethyl 3-(4-Methoxyphenyl)propiolate (5i)[16]
Yield: 85% (52.0 mg); colorless oil; R_f = 0.2 (EtOAc–hexane, 1:15).

IR (film): 3054, 2986, 1701, 1421, 1266, 1168, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (dt, *J* = 9.5, 2.3 Hz, 2 H), 6.88 (dt, *J* = 9.3, 2.3 Hz, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 3.83 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 154.7, 135.3, 114.7, 111.8, 87.3, 80.5, 62.3, 55.8, 14.5.

Ethyl 3-(4-Bromophenyl)propiolate (5j)
Yield: 82% (62.3 mg); yellow oil; R_f = 0.4 (EtOAc–hexane, 1:20).

IR (film): 3054, 2986, 1707, 1422, 1272, 1072, 1012, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.5 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 134.7, 132.4, 125.8, 119.0, 85.1, 82.0, 62.6, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9BrO_2$: 251.9786; found: 251.9785.

Ethyl 3-(4-Acetylphenyl)propiolate (5k)[17]
Yield: 80% (52.0 mg); pale yellow solid; mp 82–83.5 °C; R_f = 0.3 (EtOAc–hexane, 1:10).

IR (film): 3054, 2986, 2305, 1707, 1688, 1422, 1265, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, 2 H), 7.68 (d, *J* = 8.3 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 2.62 (s, 3 H), 1.37 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4, 154.1, 138.4, 133.4, 128.7, 124.7, 84.8, 83.3, 62.8, 27.1, 14.5.

Ethyl 3-(2-Ethoxycarbonylphenyl)propiolate (5l)
Yield: 80% (59.0 mg); colorless oil; R_f = 0.2 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 2305, 1706, 1422, 1264, 1195, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.02 (m, 1 H), 7.70–7.67 (m, 1 H), 7.56–7.49 (m, 2 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 154.4, 135.5, 133.7, 132,2 131.2, 130.5, 120.5, 85.1, 84.9, 62.5, 62.1, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0894.

Ethyl 3-(3-Ethoxycarbonylphenyl)propiolate (5m)
Yield : 88% (65.0 mg); colorless oil; R_f = 0.3 (EtOAc–hexane, 1:20).

IR (film): 3054, 2987, 1708, 1639, 1304, 1191, 896, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 8.12 (dt, *J* = 7.9, 1.3 Hz, 1 H), 7.75 (dt, *J* = 7.7, 1.2 Hz, 1 H), 7.47 (t, *J* = 7.8 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 1.43–1.35 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 154.2, 137.1, 134.4, 131.9, 131.5, 129.2, 120.4, 85.1, 81.6, 62.6, 61.8, 14.7, 14.5.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}O_4$: 246.0892; found: 246.0894.

Ethyl 3-(2-Pyridyl)propiolate (5n)[18]
Yield: 75% (40.0 mg); pale yellow oil; R_f = 0.3 (EtOAc–hexane, 1:5).

IR (film): 3054, 2987, 1710, 1422, 1257, 1206, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 5.1 Hz, 1 H), 7.73 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.60 (dd, *J* = 6.7, 0.9 Hz, 1 H), 7.38–7.34 (m, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 150.9, 141.0, 136.7, 128.9, 125.0, 84.1, 79.6, 62.7, 14.4.

Ethyl 3-(2-Thienyl)propiolate (5o)[19]
Yield: 86% (46.5 mg); pale yellow oil; R_f = 0.4 (EtOAc–hexane, 1:10).

IR (film): 3054, 2986, 2212, 1701, 1421, 1174, 896, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 3.6, 0.9 Hz, 1 H), 7.46 (dd, *J* = 5.0, 0.9 Hz, 1 H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 136.9, 131.5, 127.9, 119.8, 85.3, 80.4, 62.5, 14.5.

1,4-Bis(ethoxycarbonylethynyl)benzene (5p)[17]
A solution of 1.6 M *n*-BuLi in hexane (0.84 mmol) was slowly added to a solution of ethyl propiolate (**1**; 0.84 mmol, 85 μL) in THF (0.5 mL) at –78 °C under a N_2 atmosphere. After being stirred for 10 min, this mixture was added to a solution of $InCl_3$ (46.5 mg, 0.21 mmol) in THF (0.5 mL) at –78 °C. The mixture was stirred for 10 min, and then the cooling bath was removed, and the reaction mixture was warmed to r.t. over 10 min. A mixture of $Pd_2dba_3{\cdot}CHCl_3$ (6.2 mg, 2 mol%), Xantphos (14.0 mg, 8 mol%) and 1,4-diiodobenzene (99.0 mg, 0.3 mmol) in THF (0.5 mL) was stirred for 10 min at r.t. This mixture was added to a 0.21 M solution of lithium tetrakis(ethoxycarbonylethynyl)indate in anhydrous THF (**3**; 0.21 mmol) under a N_2 atmosphere. The reaction mixture was heated at reflux for 1.5 h. After cooling to r.t., the reaction mixture was quenched with sat. aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were sequentially washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane, 1:20) to give **5p**.

Yield: 85% (69.0 mg); pale yellow solid; mp 90–92 °C; R_f = 0.2 (EtOAc–hexane, 1:30).

IR (film): 3054, 2987, 1706, 1257, 1196, 895, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 4 H), 4.31 (q, *J* = 7.1 Hz, 4 H), 1.36 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 133.3, 122.2, 84.8, 83.3, 62.7, 14.5.

Acknowledgment

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014001403). This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2013R1A6A3A01058945).

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

References

(1) (a) Bohlmann, F.; Burkhart, F. T.; Zero, C. *Naturally Occurring Acetylenes*; Academic Press: London, **1973**. (b) Hunstman, V. D. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley-Interscience: London, **1978**, 553. (c) Martin, R. E.; Diederich, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 1350. (d) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632. (e) Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605. (f) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791. (g) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

(2) (a) Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 1772. (b) Obrecht, D. *Helv. Chim. Acta* **1991**, *74*, 27. (c) Obrecht, D.; Zumbrunn, C.; Müller, K. *J. Org. Chem.* **1999**, *64*, 6182. (d) Thiemann, T.; Fujii, H.; Ohira, D.; Arima, K.; Li, Y.; Mataka, S. *New J. Chem.* **2003**, *27*, 1377. (e) Khalaf, A.; Grée, D.; Abdallah, H.; Jaber, N.; Hachem, A.; Grée, R. *Tetrahedron* **2011**, *67*, 3881. (f) Punner, F.; Schieven, J.; Hilt, G. *Org. Lett.* **2013**, *15*, 4888.

(3) (a) Hendrickson, J. B.; Hussoin, M. S. *Synthesis* **1989**, 217. (b) Bottcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J.; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3555. (c) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715. (d) Sarhan, A. E. A. O.; Murakami, M.; Izumi, T. *J. Heterocycl. Chem.* **2002**, *39*, 691. (e) Furst, M.; Ruck-Braun, K. *Synlett* **2002**, 1991. (f) Stefani, H. A.; Cella, R.; Doerr, F. A.; de Pereira, C. M. P.; Gomes, F. P.; Zeni, G. *Tetrahedron Lett.* **2005**, *46*, 2001. (g) Gao, H.; Zhang, J. *Chem. Eur. J.* **2012**, *18*, 2777.

(4) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (c) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (d) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (e) Tykwinski, R. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 1566. (f) Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**, 317–394. (g) Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834. (h) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

(5) (a) Yoneda, N.; Matsuoka, S.; Miyaura, N.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2124. (b) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746. (c) Kundu, N. G.; Dasgupta, S. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657. (d) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327.

(6) (a) Negishi, E.-i.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597. (b) Anastasia, L.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 3111.

(7) Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859.

(8) (a) Zou, G.; Zhu, J.; Tang, J. *Tetrahedron Lett.* **2003**, *44*, 8709. (b) Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J. *Tetrahedron Lett.* **2009**, *50*, 5044. (c) Zhou, M.-B.; Wei, W.-T.; Xie, Y.-X.; Lei, Y.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5635.

(9) Kim, H.; Lee, P. H. *Adv. Synth. Catal.* **2009**, *351*, 2827.

(10) Kim, J.; Kang, D.; Yoo, E. J.; Lee, P. H. *Eur. J. Org. Chem.* **2013**, 7902.

(11) (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (b) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (c) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (d) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3901. (e) Lee, P. H.; Seomoon, D.; Lee, K.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Sridhar, M. *Adv. Synth. Catal.* **2004**, *346*, 1641. (f) Lee, P. H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* **2004**, *6*, 4825. (g) Lee, P. H.; Shim, E.; Lee, K.; Seomoon, D.; Kim, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 157. (h) Lee, P. H.; Lee, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3253. (i) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343. (j) Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139. (k) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 5197. (l) Lee, J.-Y.; Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 1929. (m) Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 1165. (n) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (o) Lee, W.; Kang, Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 4326. (p) Lee, K.; Lee, P. H. *Tetrahedron Lett.* **2008**, *49*, 4302. (q) Kim, S.; Seomoon, D.; Lee, P. H. *Chem. Commun.* **2009**, *45*, 1873. (r) Kim, H.; Lee, K.; Kim, S.; Lee, P. H. *Chem. Commun.* **2010**, *46*, 6341. (s) Mo, J.; Kim, S. H.; Lee, P. H. *Org. Lett.* **2010**, *12*, 424. (t) Lee, P. H.; Mo, J.; Kang, D.; Eom, D.; Park, C.; Lee, C.-H.; Jung, Y. M.; Hwang, H. *J. Org. Chem.* **2011**, *76*, 312. (u) Mo, J.; Hwang, H.; Lee, P. H. *Bull. Korean Chem. Soc.* **2011**, *32*, 2911. (v) Lee, K.; Kim, H.; Mo, J.; Lee, P. H. *Chem. Asian J.* **2011**, *6*, 2147. (w) Lee, D.; Ryu, T.; Park, Y.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1144.

(12) (a) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (b) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555. (c) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (d) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387. (e) Takami, K.; Yorimitsu, H.; Shnokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (f) Pena, M. A.; Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246. (g) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405. (h) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780. (i) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (j) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2005**, 485. (k) Barbero, M.; Cadamuro, S.; Dughera, S.; Giaveno, C. *Eur. J. Org. Chem.* **2006**, 4884. (l) Croix, C.; Balland-Longeau, A.; Duchene, A.; Thibonnet, J. *Synth. Commun.* **2006**, *36*, 3261. (m) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271. (n) Caeiro, J.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Eur. J.* **2008**, *14*, 741. (o) Riveiros, R.; Saya, L.; Sestelo, J. P.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2008**, 1959. (p) Lee, P. H.; Park, Y.; Park, S.; Lee, E.; Kim, S. *J. Org. Chem.* **2011**, *76*, 760. (q) Mo, J.; Eom, D.; Kim, S. H.; Lee, P. H. *Chem. Lett.* **2011**, *40*, 980.

(13) (a) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (b) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H. *J. Org. Chem.* **2004**, *69*, 4852. (c) Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2004**, *69*,

8136. (d) Kang, D.; Eom, D.; Kim, D. H.; Lee, P. H. *Eur. J. Org. Chem.* **2010**, 2330.
(14) Hapke, M.; Kral, K.; Spannenberg, A. *Synthesis* **2011**, 642.
(15) Nie X.: Liu, S.; Zong, Y.; Sun, P.; Bao, J. *J. Organomet. Chem.* **2011**, *696*, 1570.
(16) Li, Y.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 310.
(17) Walspurger, S.; Vasil'ev, A. V.; Sommer, J.; Pale, P.; Savechenkov, Y. P.; Rudenko, A. P. *Russ. J. Org. Chem.* **2005**, *41*, 1485.
(18) Beveridge, R. E.; Arndtsen, B. A. *Synthesis* **2010**, 1000.
(19) Kang, S.-K.; Yoon, S.-K.; Kim, Y.-M. *Org. Lett.* **2011**, *3*, 2697.

