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Preparation of Ethyl 2-Aryl 2,3-Alkadienoates via Palladium-Catalyzed Selective Cross-Coupling Reactions

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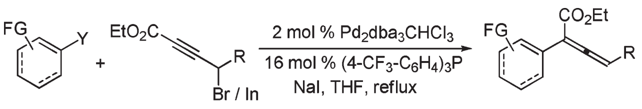

FG = Me, *n*-Bu, MeO, CHO, Ac, EtO$_2$C, BnHNOC, NO$_2$
Y = I, OTf R = H, Me, *n*-Pr

Pd-catalyzed cross-coupling reactions of aryl iodides containing not only an electron-donating group but also an electron-withdrawing group on the aryl ring with organoindium reagents generated in situ from indium and ethyl 4-bromo-2-alkynoates produced selectively ethyl 2-aryl-2,3-alkadienoates in good yield.

Transition-metal-catalyzed cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] Cross-coupling reactions leading to C$-$C bond formation are often key steps in a wide range of organic processes.[2] During the past decades, a variety of organometallic reagents, such as alkyl-, allyl-, allenyl-, benzyl-, vinyl-, and arylmetals, have been used as nucleophiles in cross-coupling reactions.[1] Recently, because allenes have been widely used in organic reactions, development of novel synthetic methods of allenes has been required.[3] In particular, preparation of 2,3-alkadienoates is of synthetic importance and still a very challenging problem since they have been utilized in a variety of molecular transformations such as Michael addition, lactonization, cyclization, and cycloaddition reactions.[3] Although several methods for preparation of 2,3-alkadienoates are known,[4] they seem to lack generality as far as 2-aryl-substituted analogues are concerned. Traditionally, 2,3-alkadienoates were prepared from reaction of stabilized ylide with derivatives of benzyl bromide followed by treatment of acid chloride in the presence of triethylamine (Scheme 1, eq 1).[5] Unfortunately, this method cannot be applied to the preparation of alkyl 2-aryl-2,3-alkadienoates because ylides do not react with aryl halide. Gillmann reported a silver oxide-assisted Pd-catalyzed cross-coupling reaction of methyl 2-halo-2,3-butadienoate with arylboronic acid to produce methyl 2-aryl-2,3-butadienoates (Scheme 1, eq 2).[6] However, not only preparation of ethyl 2-halo-2,3-butadienoate but also introduction of a substituent on the γ-position is difficult.[7] Moreover, the yield of cross-coupling reaction of methyl 2-halo-2,3-butadienoate with phenylboronic acid is variable (Br, 0$-$52%, I, 52$-$98%).[6] Recently, Pd-catalyzed cross-coupling reactions using organoindium reagents have been described.[8] In addition, we reported Pd-catalyzed cross-coupling reactions of allylindiums, allenylindiums, 1,3-butadien-2-ylindiums, tetra(organo)indates, and indium tri(organothiolates) with

SCHEME 1. Synthetic Methods of Alkyl 2,3-Alkadienoates Having a Substituent at the 2-Position

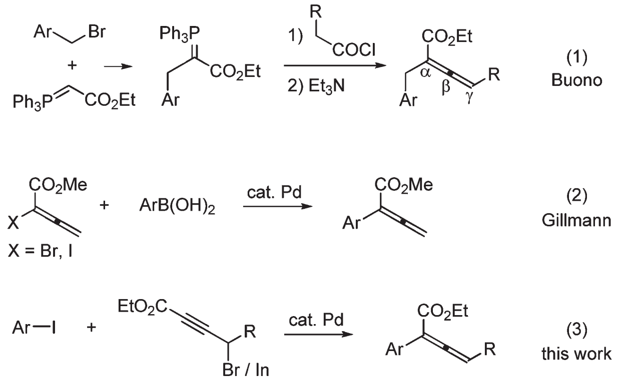

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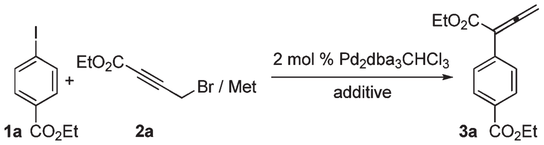
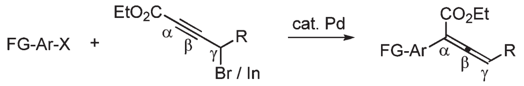
TABLE 1. Optimization of Pd-Catalyzed Cross-Coupling Reactions[a]



entry	Met	ligand	solvent	additive (equiv)	time (h)	yield^{b} (%)
1	In	16 mol % Ph_3P	DMF	LiI (3)	18	0
2	In	16 mol % Ph_3P	DMF	LiCl (3)	18	0
3	In	8 mol % Xantphos	DMF	LiI (3)	24	0
4	In	8 mol % Xantphos	THF	LiI (3)	15	0
5	In	8 mol % DPEphos	DMF	LiI (3)	15	0
6	In	16 mol % $(4\text{-}CH_3OC_6H_4)_3P$	DMF	LiI (3)	12	0
7	In	16 mol % $(4\text{-}CH_3OC_6H_4)_3P$	THF	NaI (1)	12	0
8	In	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	DMF	LiI (3)	3	0
9	In	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	THF	NaI (1)	3	56
10	In	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	THF	NaI (1.5)	3	58
11	In	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	DMF	NaI (1.5)	5	0
12	In	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	THF	NaI (1.5)	3	79^{c}
13	In		DMF	LiI (3)	10	0^{d}
14	Mg	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	THF	NaI (1.5)		0
15	Zn	16 mol % $(4\text{-}CF_3C_6H_4)_3P$	THF	NaI (1.5)		0

[a] Reactions performed with In (1 equiv) and **2a** (1.5 equiv). [b] Isolated yield. [c] In (1.5 equiv) and **2a** (2.3 equiv) were used. [d] $Pd(dppf)Cl_2$ was used as a catalyst.

SCHEME 2. Preparation of Ethyl 2-Aryl-2,3-alkadienoates



a variety of electrophiles.[9] During the course of our research program aimed at finding new indium-mediated organic reactions,[10] we envisioned the possibility of ethyl 2,3-alkadien-2-yl cross-coupling reactions by using indium and ethyl 4-bromo-2-alkynoates. Herein, we report that cross-coupling reaction of a variety of aryl iodides with organoindium reagents generated in situ from indium and ethyl 4-bromo-2-alkynoate produced ethyl 2-aryl-2,3-alkadienoates with complete regioselectivity and chemoselectivity (Scheme 2).

Our initial study focused on Pd-catalyzed cross-coupling reactions of ethyl 4-iodobenzoate (**1a**) with organoindium reagent[11] generated in situ from indium and ethyl 4-bromo-2-butynoate (**2a**)[12] (Table 1). Reaction of **1a** with organoindium did not proceed with 2 mol % of $Pd_2dba_3CHCl_3$ and a variety of ligands such as Ph_3P, Xantphos,[13] DPEphos,[14] $(4\text{-}CH_3OC_6H_4)_3P$, and $(4\text{-}CF_3C_6H_4)_3P$ in the presence of MX (M = Li and Na, X = Cl and I) as an additive in DMF or THF (entries 1−8). However, 2 mol % of $Pd_2dba_3CHCl_3$ and 16 mol % of $(4\text{-}CF_3C_6H_4)_3P$ in the presence of NaI (1 equiv) afforded selectively ethyl 2-(4-ethoxycarbonylphenyl)-2,3-butadienoate **3a** in 56% yield in THF, indicating that an electron-poor ligand is better than an electron-rich ligand (entry 7 vs 9). In addition, comparison of solvents suggests that THF is critically important for a successful reaction (entry 11 vs 12). Of the catalytic systems examined, the best results were obtained with 2 mol % of $Pd_2dba_3CHCl_3$ and 16 mol % of $(4\text{-}CF_3C_6H_4)_3P$ in the presence of NaI (1.5 equiv) in THF at 70 °C for 3 h, producing selectively **3a** in 79% yield (entry 12). There is no propargylic cross-coupling product formed. Organoindium generated in situ from indium (1.5 equiv) and **2a** (2.3 equiv) gave the best result as a coupling partner. The high selectivity of the present reaction was compared to Grignard and organozinc reagents. Under the optimum

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(11) ^{1}H NMR (400 MHz, DMF-d_7, 25 °C) spectrum of organoindium reagents showed two signals (δ 4.01 and 3.88) for the methylene group, indicating that two types of propargylindium reagents (ratio = 2.62:1 for 30 min, 2.40:1 for 45 min and 1.86:1 for 60 min) were produced and the corresponding allenylindium reagent was not formed.

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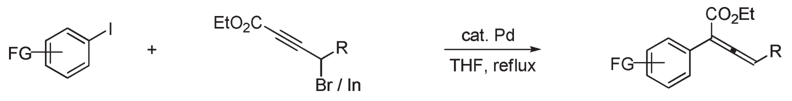
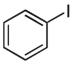
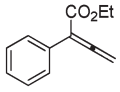
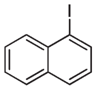
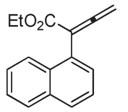
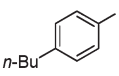
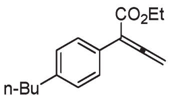
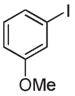
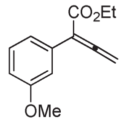
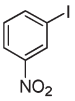
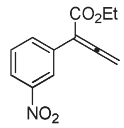
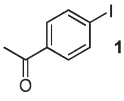
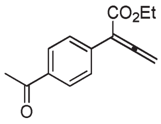
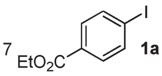
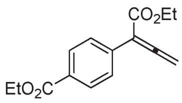
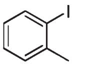
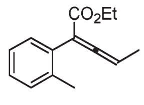
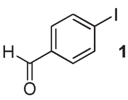
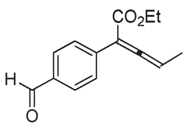
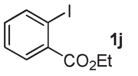
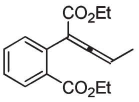
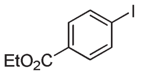
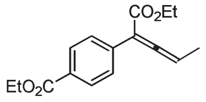
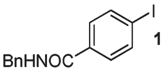
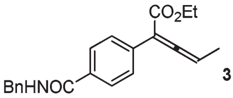
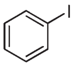
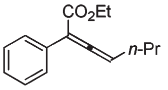
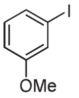
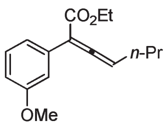
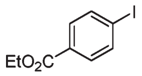
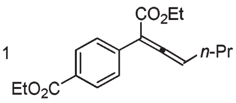
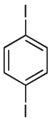
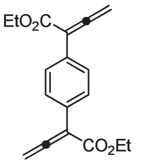
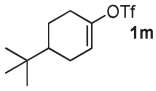
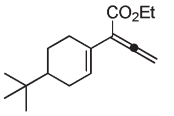
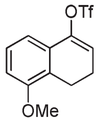
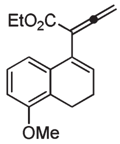
(13) Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

(14) DPEphos: bis(2-diphenylphosphinophenyl)ether.

TABLE 2. Preparation of Ethyl 2-Aryl-2,3-alkadienoates via Pd-Catalyzed Cross-Coupling Reactions with Organoindium[a]



1 R = H (**2a**), Me (**2b**), *n*-Pr (**2c**) **3**

entry	aryl halide	R	time (h)	product	yield[b] (%)
1	 **1b**	H	2	 **3b**	85
2	 **1c**	H	7	 **3c**	53
3	 **1d**	H	3	 **3d**	79
4	 **1e**	H	2	 **3e**	65
5	 **1f**	H	2	 **3f**	82
6	 **1g**	H	1	 **3g**	81
7	 **1a**	H	1	 **3a**	79
8	 **1h**	Me	2	 **3h**	85
9	 **1i**	Me	2	 **3i**	72
10	 **1j**	Me	3	 **3j**	85[c]
11	 **1a**	Me	1	 **3k**	79
12	 **1k**	Me	1	 **3l**	76
13	 **1b**	*n*-Pr	2	 **3m**	85
14	 **1e**	*n*-Pr	2	 **3n**	64
15	 **1a**	*n*-Pr	1	 **3o**	77
16	 **1l**	H	4	 **3p**	65[d]
17	 **1m**	H	2	 **3q**	63[e]
18	 **1n**	H	5	 **3r**	54[e]

[a] Reactions performed with 2 mol % of $Pd_2dba_3CHCl_3$ and 16 mol % of $(4\text{-}CF_3C_6H_4)_3P$ in the presence of NaI (3 equiv) in refluxing THF. Organoindium was obtained from In (1.5 equiv) and **2** (2.3 equiv). [b] Isolated yields. [c] Organoindium (2 equiv) was used. [d] **2a** (4.5 equiv), In (3 equiv), and NaI (3 equiv) were used. [e] KBr (1.5 equiv) was used instead of NaI.

reaction conditions, reaction of **1a** with **2a** (1.8 equiv) and Mg (1.5 equiv) or Zn (1.5 equiv) in refluxing THF did not proceed (entries 14 and 15). Aromatic bromides and chlorides did not react with organoindium reagent.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to reactions of a variety of aryl iodides with organoindium reagent generated in situ from indium and ethyl 4-bromo-2-alkynoates (Table 2). Reaction of iodobenzene (**1b**) with **2a** and indium gave selectively ethyl 2-phenyl-2,3-butadienoate (**3b**) in 85% yield (entry 1) However, bromobenzene and chlorobenzene did not react with **2a**. Under the optimum conditions, 1-iodonaphthalene (**1c**) was converted to ethyl 2-(1-naphthyl)-2,3-butadienoate (**3c**) in 53% yield (entry 2). Electronic variation on the aromatic substituents, such as methyl, *n*-butyl, methoxy, nitro, formyl, acetyl, ethoxycarbonyl, and *N*-benzylamido group, did not diminish the efficiency and selectivity in Pd-catalyzed cross-coupling reactions (entries 3−15). Treatment of **1d** and **1e** having an electron-donating group (*n*-Bu and MeO) with organoindium produced the desired products **3d** and **3e** in 79% and 65% yields, respectively (entries 3 and 4). 4-Iodoacetophenone was subjected to cross-coupling reaction with **2a** and indium, affording **3g** in 81% yield (entry 6). Organoindium generated in situ from ethyl 4-bromo-2-pentynoate (**2b**) and indium reacted with 2-iodotoluene (**1h**) to give selectively **3h** in 85% yield (entry 8). The reaction conditions were mild enough to tolerate a formyl group, which would be incompatible with other organometallic reagents (entry 9). Ethyl iodobenzoate (**1j** and **1a**) and *N*-benzyl 4-iodobenzamide (**1k**) worked equally well with organoindium generated in situ from **2b** and indium, producing 2-aryl-2,3-pentadienoates (**3j**, **3k**, and **3l**) in good yields (entries 10−12). Subjecting **1b** to ethyl 4-bromo-2-heptynoate (**2c**) and indium provided **3m** in 85% yield (entry 13). 3-Iodoanisole (**1e**) turned out to be compatible with the employed reaction conditions, producing **3n** in 64% yield (entry 14). We were pleased to obtain ethyl 2-(4-ethoxycarbonylphenyl)-2,3-heptadienoate **3o** in 77% yield from the reaction of **1a** with organoindium under the optimum reaction conditions (entry 15). Reaction of 1,4-diiodobenzene with **2a** (4.5 equiv), indium (3.0 equiv), and NaI (3.0 equiv) proceeded smoothly to produce bis(allenyl)benzene **3p** in 65% yield (entry 16). Treatment of vinyl triflate **1m** and **1n** with **1a** and indium in the presence of KBr (1.5 equiv) instead of NaI provided selectively the corresponding products **3q** and **3r** in 63% and 54% yields, respectively (entries 17 and 18).

In conclusion, we demonstrated an efficient synthetic method for the preparation of ethyl 2-aryl-2,3-alkadienoates through Pd-catalyzed selective allenyl cross-coupling reactions of aryl iodides with organoindiums generated in situ from indium and ethyl 4-bromo-2-alkynoate. Because introduction of aryl group to C2-position of 2,3-alkadienoate is difficult, this method would pave a new way to synthetically valuable processes of a wide range of functionalized 2-aryl-2,3-alkadienoates.

Experimental Section

Ethyl 2-(4-Ethoxycarbonylphenyl)-2,3-butadienoate (3a). To a suspension of $Pd_2dba_3CHCl_3$ (6.2 mg, 0.6×10^{-2} mmol) and $(p\text{-}CF_3C_6H_4)_3P$ (22.0 mg, 4.8×10^{-2} mmol) in THF (0.5 mL) was added ethyl 4-iodobenzoate (**1a**) (50.5 μL, 0.3 mmol) at room temperature under nitrogen atmosphere. After being stirred for 30 min, organoindium reagent generated in situ from indium (52.0 mg, 0.45 mmol), sodium iodide (67.5 mg, 0.45 mmol), and **2a** (129.0 mg, 0.68 mmol) in THF (1.0 mL) was added, and the mixture was stirred at 70 °C for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane =1:30) to give **3a** (62.0 mg, 0.24 mmol, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.44 Hz, 2H), 7.60 (d, J = 8.44 Hz, 2H), 5.48 (s, 2H), 4.38 (q, J = 7.09 Hz, 2H), 4.30 (q, J = 7.12 Hz, 2H), 1.39 (t, J = 7.09 Hz, 3H), 1.33 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 166.7, 165.9, 137.1, 129.90, 129.86, 128.7, 103.0, 81.1, 61.9, 61.4, 14.7, 14.6; IR (film) 2982, 1953, 1716, 1607, 1447, 1366, 1275, 1104, 1021, 704 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}O_4$ M^+ 260.1049, found 260.1046.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.