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Synthesis of Indenes via Palladium-Catalyzed Carboannulation of Diethyl 2-(2-(1-alkynyl)phenyl)malonate and Organic Halides

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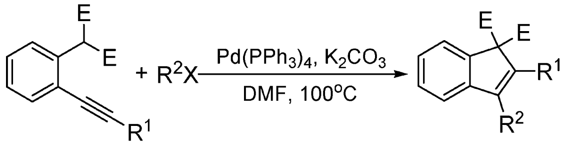
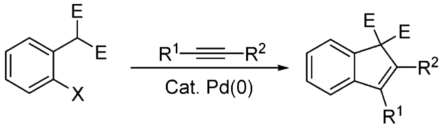


E= CO_2Et, SO_2Ph; R^1= alkyl, aryl, alkenyl

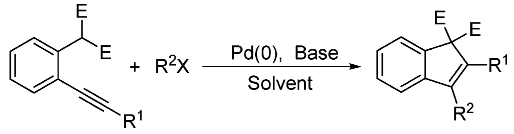
Highly substituted indenes have been prepared in good yields by the palladium-catalyzed carboannulation of diethyl 2-(2-(1-alkynyl)phenyl)malonate with aryl, benzylic, and alkenyl halides. The reaction conditions and the scope of the process were examined, and a possible mechanism is proposed.

Indene derivatives, in particular, multiply-substituted ones, have been attractive, and synthetically useful methods for their synthesis have been developed.[1] Among the most important synthetic routes to such compounds are reduction/dehydration of indanones,[2] the cyclization of phenyl-substituted allylic alcohols,[3] and the ring expansion of substituted cyclopropenes.[4] Recently, Gridnev et al. and Yamamoto et al. have reported Pd-catalyzed or Pt-catalyzed intramolecular carbalkoxylation reactions accompanied by an unprecedented 1,2-alkyl migration to the synthesis of functionalized indenes.[5] Very recently, Larock et al. have reported a convenient method for the preparation of indenes by the palladium-catalyzed carboannulation of internal alkynes with functionally substituted aryl halides (Scheme 1).[6]

SCHEME 1



SCHEME 2



The transition-metal-catalyzed cyclization of alkynes, which possess nucleophilic centers in close proximity to the carbon−carbon triple bond, by *in situ* coupling/cyclization reactions,[7] and reactions promoted by vinylic, aryl, and alkynylpalladium complexes,[8] have also been shown to be extremely effective for the synthesis of a wide variety of carbo- and heterocycles. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation can be effectively employed for the synthesis of furans.[9] Herein, we wish to report that the palladium-catalyzed annulation of diethyl 2-(2-(1-alkynyl)-phenyl)malonate and a variety of organic halides offers an efficient, direct route to highly substituted indenes (Scheme 2).

We started out our investigation of the reaction conditions by using 1.0 equiv of diethyl 2-(2-(2-phenylethynyl)phenyl)-malonate (**1a**; 0.2 mmol), 1.2 equiv of iodobenzene, 5 mol % of $Pd_2(dba)_3$ as the catalyst, and 2.0 equiv of K_2CO_3 in DMF as the solvent at 100 °C for 16 h under argon. The desired product, diethyl 2,3-diphenyl-1*H*-indene-1,1-dicarboxylate (**3aa**) was isolated in 36% yield. While using $Pd(PPh_3)_4$ as the catalyst, the reaction afforded **3aa** in 71% yield. We then screened various bases using **1a** and iodobenzene as the reactants and $Pd(PPh_3)_4$ as the catalyst in DMF (Table 1). We found that K_2CO_3 was the most effective base (Table 1, entry 5). The use of other inorganic bases such as K_3PO_4, KOAc, Cs_2CO_3, and KO*t*-Bu failed to improve the yield of **3aa** (Table 1, entries 3, 4, 6, and 7). Triethylamine and tri-*n*-butylamine were ineffective (Table 1, entries 1 and 2). The optimum reaction conditions thus far developed employ 1.0 equiv of **1a**, 1.2 equiv of the

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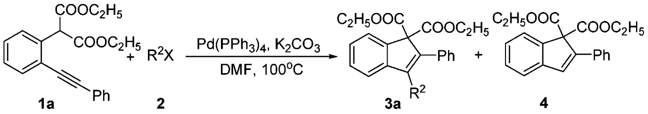
10.1021/jo0601361 CCC: $33.50

TABLE 1. Effect of Base on the Reaction of 1a with Iodobenzene[a]

entry	base	isolated yield of **3aa**[b] (%)
1	Et_3N	no reaction
2	$(n\text{-}Bu)_3N$	no reaction
3	K_3PO_4	15 (<2)
4	KOAc	20 (<2)
5	K_2CO_3	71 (<2)
6	Cs_2CO_3	66 (<2)
7	KO*t*-Bu	68 (<2)

[a] All reactions were carried out using diethyl 2-(2-(2-phenylethynyl)phenyl)malonate (**1a**; 0.2 mmol), 1.2 equiv of iodobenzene, 5 mol % of $Pd(PPh_3)_4$ as the catalyst, and 2.0 equiv of base in DMF as the solvent at 100 °C for 16 h under argon. [b] The numbers in parentheses are the isolated yields of the corresponding 2-substituted indene **4**.

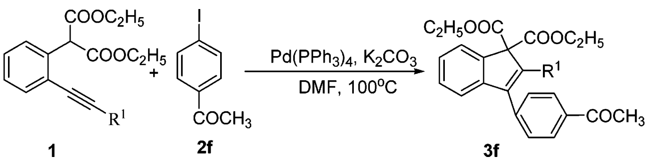
TABLE 2. Pd-Catalyzed Reaction of Diethyl 2-(2-(2-Phenylethynyl)phenyl)malonate and Organic Halides[a]



entry	R^2X (**2**)	time (h)	R^2 (**3a**)	isolated yield[b] (%)
1	PhI	16	Ph (**3aa**)	71 (<2)
2	*p*-$CH_3C_6H_4I$	16	*p*-$CH_3C_6H_4$ (**3ab**)	67 (3)
3	*p*-$CH_3OC_6H_4I$	24	*p*-$CH_3OC_6H_4$ (**3ac**)	26 (5)
4	*p*-ClC_6H_4I	10	*p*-ClC_6H_4 (**3ad**)	85 (0)
5	*p*-CNC_6H_4I	6	*p*-CNC_6H_4 (**3ae**)	78 (0)
6	*p*-$CH_3OCC_6H_4I$	6	*p*-$CH_3OCC_6H_4$ (**3af**)	82 (0)
7	*p*-$CH_3O_2CC_6H_4I$	6	*p*-$CH_3O_2CC_6H_4$ (**3ag**)	75 (<2)
8	*p*-$NO_2C_6H_4I$	6	*p*-$NO_2C_6H_4$ (**3ah**)	82 (0)
9	*p*-$CF_3C_6H_4I$	6	*p*-$CF_3C_6H_4$ (**3ai**)	87 (0)
10	*o*-$CH_3OCC_6H_4I$	8	*o*-$CH_3OCC_6H_4$ (**3aj**)	65 (<2)
11	*o*-$NO_2C_6H_4I$	8	*o*-$NO_2C_6H_4$ (**3ak**)	66 (<2)
12	*o*-$CH_3O_2CC_6H_4I$	8	*o*-$CH_3O_2CC_6H_4$ (**3al**)	72 (<2)
13	*o*-$CH_3C_6H_4I$	12	*o*-$CH_3C_6H_4$ (**3am**)	73 (0)
14	2-iodothiophene	12	2-thienyl (**3an**)	72 (<2)
15	PhBr	24	Ph (**3aa**)	67 (<2)
16	*p*-$CH_3C_6H_4Br$	24	*p*-$CH_3C_6H_4$ (**3ab**)	63 (<2)
17	*p*-$CH_3OCC_6H_4Br$	12	*p*-$CH_3OCC_6H_4$ (**3af**)	77 (0)
18	*p*-$NO_2C_6H_4Br$	12	*p*-$NO_2C_6H_4$ (**3ah**)	80 (0)
19	benzyl chloride	12	benzyl (**3ao**)	85 (0)
20	β-bromostyrene ($E/Z > 95{:}5$)	16	β-styryl (**3ap**) ($E/Z > 99{:}1$)[c]	70 (<2)
21	β-bromostyrene ($Z/E > 99{:}1$)	16	β-styryl (**3aq**) ($Z/E > 99{:}1$)[c]	73 (<2)

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 2-substituted indene **4**. [c] The ratio was determined by ^1H NMR analysis of the product.

TABLE 3. Pd-Catalyzed Reaction of Diethyl 2-(2-(1-alkynyl)phenyl)malonate and Organic Halides[a]



entry	R^1	time (h)	**3f**	isolated yield[b] (%)
1	*p*-BrC_6H_4 (**1b**)	12	**3bf**	60 (0)
2	1-cyclohexenyl (**1c**)	8	**3cf**	67 (0)
3	*n*-pentyl (**1d**)	8	**3df**	70 (0)

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 1,2-disubstituted indenes.

organic halide, 5 mol % of $Pd(PPh_3)_4$, and 2.0 equiv of K_2CO_3 in DMF at 100 °C.

Under the optimized reaction conditions above, the reactions of **1a** with a variety of aryl iodides afforded the corresponding multiply-substituted indenes **3a** in moderate to good yields (Table 2, entries 1−13). Aryl iodides bearing an electron-withdrawing group in the para position usually led to good to high yields of the 2,3-disubstituted indenes (Table 2, entries 4−9). When 4-methyl-iodobenzene and 4-iodoanisole were employed in the reaction with substrate **1a** (Table 2, entries 2 and 3), the corresponding products **3ab** and **3ac** were isolated in 67 and 26% yields along with low yields of the side product diethyl 2-phenyl-1*H*-indene-1,1-dicarboxylate (**4**). Thus, strong electron-rich aryl iodides gave poor results in this cyclization chemistry. The 2-substituted indene **4** is believed to be formed by the Pd(II)-catalyzed cyclization of the diethyl malonate alkynes **1a**.[10] Interestingly, the reactions of substrate **1a** and aryl iodides bearing an electron-withdrawing group or an electron-donating group in the ortho position also led to good yields of the desired 2,3-disubstituted indenes (Table 2, entries 10−13). Accordingly, steric hindrance did not appear to be a major problem. 2-Iodothiophene also gave the indene **3an** in 72% yield (Table 2, entry 14). In addition, the use of aryl bromides also afforded desired products in good yields (Table 2, entries 15−18). But the reaction of aryl bromides were slower than their corresponding aryl iodide counterparts. Benzylic halides have also proven successful. For example, the reaction of benzyl chloride produced a high 85% yield of the indene product **3ao** (Table 2, entry 19). Surprisingly, when a mixture of β-bromostyrene ($E/Z > 95{:}5$) was employed in the reaction with substrate **1a**, no detectable amount of the *Z*-diethyl 2-phenyl-3-styryl-1*H*-indene-1,1-dicarboxylate (**3aq**) was afforded, but the *E*-styryl product was afforded in 70% yield (Table 2, entry 20). We assumed that this was due to the isomerization of the *Z*-styryl product to the corresponding trans isomer. To prove this result, using β-bromostyrene ($Z/E > 99{:}1$) as substrate, only the product containing the *Z*-styryl moiety was isolated (Table 2, entry 21). The reason for this remained unclear.[11] However, when chlorobenzene was used as the reactant, no desired product was observed.

We have also investigated the reactions of diethyl malonate alkynes containing different R^1 groups at the end of the triple bond with an aryl iodide. With 4-iodoacetophenone, diethyl malonate alkyne **1b** was employed in the reaction (Table 3, entry 1), and the corresponding product, **3bf**, was isolated in 60% yield. Diethyl malonate alkyne **1c** bearing a 1-cyclohexenyl group afforded the corresponding 2,3-disubstituted indene **3cf** in a good yield of 67% (Table 3, entry 2). Diethyl malonate alkyne **1d** containing an *n*-pentyl group afforded the desired product **3df** in a 70% yield (Table 3, entry 3).

Meanwhile, diethyl malonate alkyne with different electron-withdrawing groups, such as ethyl 2-(2-(2-phenylethynyl)-phenyl)-2-(phenylsulfonyl)acetate (**1e**), has also been allowed to react with 4-iodoacetophenone to afford a moderate yield of the desired product **3ef** (Scheme 3).

The mechanism shown in Scheme 4 is proposed for this process. It consists of the following key steps: (1) oxidative

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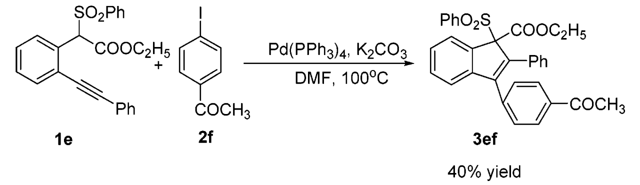
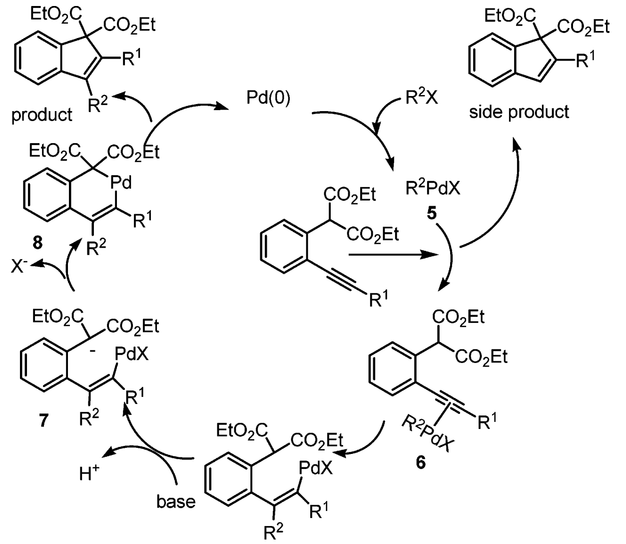
(10) Similar results were observed in a Pd-catalyzed coupling reaction, see: ref 8d and ref 8e.

(11) A similar result was observed in a Pd-catalyzed coupling/cyclization reaction, see: Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813.

SCHEME 3



SCHEME 4



addition of the organic halide to the Pd(0) catalyst, (2) coordination of the resulting palladium intermediate **5** to the alkyne triple bond to form complex **6**,[8] (3) generation of a carbanion by the base, (4) intramolecular nucleophilic attack of the carbanion on the vinylic palladium intermediate to afford a palladacyclic intermediate, **8**,[6] and (5) reductive elimination of the intermediate to furnish the indene and regenerate the Pd(0) catalyst. If the diethyl malonate alkyne does not coordinate well to the palladium(II) intermediate, **5**, cyclization by Pd(II) catalysis to the monosubstituted indene can occur.[10] Therefore, the selectivity between the mono- and disubstituted indenes is determined by whether the triple bond of the diethyl malonate alkyne coordinates the $R^2Pd^{II}X$ intermediate, **5**.

In conclusion, an efficient, palladium-catalyzed synthesis of substituted indenes has been developed. A variety of aryl, benzylic, and alkenyl halides undergo this process, giving the desired products in moderate to good yields, particularly aryl iodides with a substituted group in the ortho position, which also produce the desired indenes.

Experimental Section

All reactions were performed under an argon atmosphere. Unless otherwise stated, all aryl halides were purchased from commercial suppliers and used without further purification. The preparation and characterization of the starting material **1a**−**1e** is described in the Supporting Information. The preparation and characterization of the other highly substituted indenes are included in Supporting Information.

General Procedure for the Preparation of Substituted Indenes. To a solution of diethyl 2-(2-(2-phenylethynyl)phenyl)malonate **1a** (67.2 mg, 0.20 mmol) in DMF (2.0 mL) was added K_2CO_3 (44.2 mg, 0.40 mmol). The mixture was stirred for 10 min and $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol, 5 mol %) and organic halides (0.24 mmol) was added. The resulting mixture was then heated under an argon atmosphere at 100 °C. When the reaction was considered complete, as determined by TLC analysis, the reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of ammonium chloride, and extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding 2,3-disubstituted indenes.

Diethyl 3-(4-methoxyphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate, 3ac. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 22.9 mg (26%) of the indicated compound as a solid: mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.68 (d, J = 6.9 Hz, 1H), 7.37−7.17 (m, 10H), 6.87−6.84 (d, J = 8.7 Hz, 2H), 4.20−4.08 (m, 4H), 3.80 (s, 3H), 1.10−1.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 159.0, 145.1, 144.3, 140.8, 139.7, 135.2, 130.8, 130.3, 128.6, 127.5, 127.1, 126.5, 126.4, 124.5, 121.2, 113.8, 72.6, 61.8, 55.1, 13.7; IR (KBr, cm^{-1}) 3450, 2927, 1730, 1511, 1464, 1247, 1041; HRMS (ESI) calcd for $C_{28}H_{26}O_5$ Na $[M^+ + Na]$, 465.1672; found, 465.1668. Anal. Calcd for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 75.98; H, 6.08.

Diethyl 3-(4-acetylphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate, 3af. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 74.5 mg (82%) of the indicated compound as a solid: mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94−7.91 (d, J = 9.0 Hz, 2H), 7.73−7.70 (m, 1H), 7.45−7.43 (d, J = 8.1 Hz, 2H), 7.39−7.34 (m, 2H), 7.29−7.26 (m, 1H), 7.23−7.20 (m, 5H), 4.22−4.10 (m, 4H), 2.60 (s, 3H), 1.11−1.07 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 167.9, 144.3, 143.8, 141.8, 140.8, 139.3, 136.1, 134.5, 130.2, 129.8, 128.7, 128.4, 127.6, 127.5, 126.9, 124.7, 120.9, 72.9, 62.0, 26.6, 13.7; IR (KBr, cm^{-1}) 3451, 3351, 2983, 1730, 1684, 1464, 1362, 1248, 1046; HRMS calcd for $C_{29}H_{27}O_5$ $[M + H]^+$, 455.1853; found, 455.1847. Anal. Calcd for $C_{29}H_{26}O_5$: C, 76.63; H, 5.77. Found: C, 76.47; H, 5.77. For the characterization of the rest of the 2,3-disubstituted indenes, see Supporting Information.

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Supporting Information Available: Typical experimental procedures and characterizations for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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