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# Highly Regio- and Stereoselective Synthesis of Indene and Benzo[*b*]furan Derivatives via a Pd-Catalyzed Carboannulation of Propargyl Carbonates with Nucleophiles

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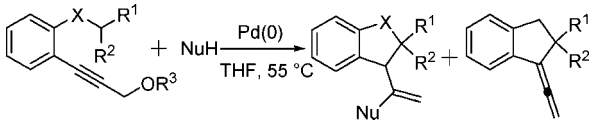



A new and efficient synthesis of indene and benzo[*b*]furan derivatives has been achieved via Pd-catalyzed carboannulation of propargyl carbonates with nucleophiles in good to excellent yields with high regio- and stereoselectivity. A novel sequence of nucleophilic attack is observed, and a possible mechanism is proposed.

The formation of carbon−carbon and carbon−heteroatom bonds via Pd-catalyzed reactions of propargyl compounds with nucleophiles has attracted much interest in the past a few decades.[1] The key step in these reactions is the formation of an allenyl- or $\pi$-propargylpalladium complex (an equilibrium process) by facile decarboxylation, which undergoes double nucleophilic attack to form products. Recently, Yoshida[2] and Cacchi[3] et al. reported Pd-catalyzed reactions of propargyl carbonates with nucleophiles for the synthesis of substituted 2,3-dihydrofurans, benzofurans, and functionalized indoles (Figure 1a). Very recently, we also reported a convenient method for the preparation of indene derivatives via a regioselective nucleophilic attack at different sites of propargyl carbonates catalyzed by palladium (Figure 1b).[4] In these processes,

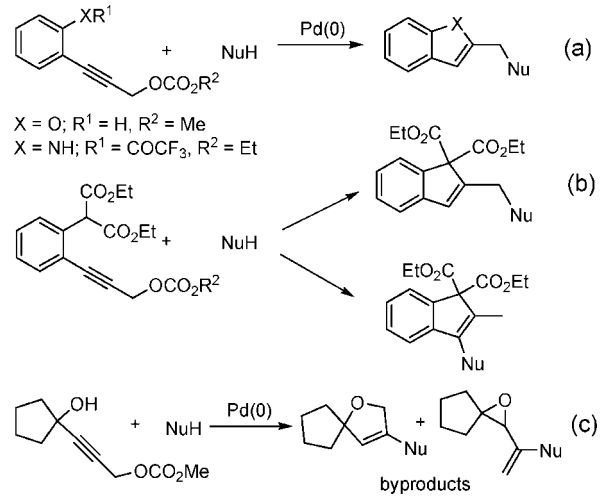
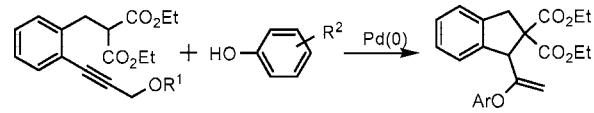



**FIGURE 1.** Palladium-catalyzed double addition of nucleophiles to propargylic substrates.

intramolecular nucleophilic attack is prior to the intermolecular reaction. In 2003, Yoshida et al. accomplished the cyclization of 4-methoxycarbonyloxy-2-butyn-1-ols, but dihydrofuran and epoxide were formed as the side products via a prior intermolecular reaction (Figure 1c).[5]

Very recently, we have developed methods for the synthesis of indene derivatives by carboannulation.[4,6] Encouraged by reported results,[7] we herein report a novel Pd-catalyzed cyclization of propargyl carbonates with phenol nucleophiles for the synthesis of indene derivatives with high regioselectivity. In this process, intermolecular nucleophilic attack happened prior to intramolecular reaction (Scheme 1).

**SCHEME 1**




Initially, we started our investigation of the reaction by using 1.0 equiv of propargyl carbonate (**1a**; 0.2 mmol) and 1.2 equiv of phenol (**2a**) in the presence of 5 mol % of $Pd_2(dba)_3$ and 20 mol % dppf in THF under argon at 55 °C for 3 h; the desired

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(1) For reviews of Pd-catalyzed reactions of propargyl carbonates see: (a) De Meijere, A., Diederich, F. Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Chapter 10; Wiley-VCH: New York, 2004. (b) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (d) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (e) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

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(7) The $\pi$-propargylpalladium complex is formed in a more stable manner in the presence of a bidentate ligand than in the presence of a monodentate ligand, see: (a) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938. (b) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687.

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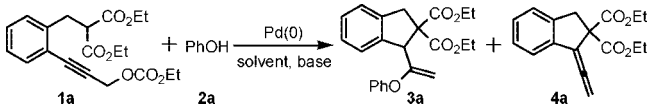
**TABLE 1. Optimization of the Pd-Catalyzed Cyclization of Propargyl Carbonate 1a with Phenol 2a[a]**



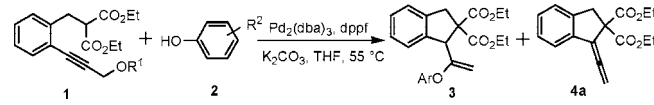

| entry | catalyst | solvent | base | temp (°C) | time (h) | yield of **3a** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$/dppf | THF | | 55 | 3 | 75 (6) |
| 2 | $Pd_2(dba)_3$/dppf | toluene | | 55 | 3 | 63 (10) |
| 3 | $Pd_2(dba)_3$/dppf | DMF | | 55 | 3 | 35 (48) |
| 4 | $Pd_2(dba)_3$/dppf | THF | $K_2CO_3$ | 55 | 3 | 91 (0) |
| 5 | $Pd_2(dba)_3$/dppf | THF | $NEt_3$ | 55 | 3 | 79 (0) |
| 6 | $Pd_2(dba)_3$/dppe | THF | $K_2CO_3$ | 55 | 3 | 84 (0) |
| 7 | $Pd_2(dba)_3$/ $PPh_3$ | THF | $K_2CO_3$ | 55 | 3 | 6 (78) |
| 8 | $Pd_2(dba)_3$ | THF | $K_2CO_3$ | 55 | 2 | 0 (70) |
| 9 | $Pd(PPh_3)_4$ | THF | $K_2CO_3$ | 55 | 2 | 0 (76) |
| 10 | $Pd_2(dba)_3$/dppf | THF | $K_2CO_3$ | 25 | 10 | 14 (8) |
| 11 | $Pd_2(dba)_3$/dppf | THF | $K_2CO_3$ | 80 | 4 | 31 (54) |
| 12 | $Pd(PPh_3)_4$ | THF | | 80 | 4 | 0 (11) |

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent under argon with 1.0 equiv of **1a**, 1.2 equiv of **2a**, 2.0 equiv of base, and 0.05 equiv of [Pd]. [b] Isolated yields, and the numbers in parentheses are the isolated yields of **4a**.

product **3a** was obtained in 75% yield, and the byproduct **4a** was isolated in 6% yield (Table 1, entry 1). Changing the solvent from THF to toluene or DMF did not improve the yield of **3a** nor the selectivity of the product (entries 2 and 3). To our surprise, Using $K_2CO_3$ as a base led to a cleaner reaction, affording the desired product **3a** in 91% yield with none of the side product **4a** (entry 4). $NEt_3$ was less effective (entry 5). Other catalyst systems, such as $Pd_2(dba)_3$/dppe, $Pd_2(dba)_3/PPh_3$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$, were tested, and it was found that the bidentate ligand is important for the selectivity of the two indene products (entries 6−9).[7] Lower or higher temperatures were not beneficial to the reaction (entries 10 and 11). Reaction conditions we have reported before[4b] were also attempt. But only the byproduct **4a** was obtained (entry 12). The optimum reaction conditions thus far developed employ 1.0 equiv of **1a**, 1.2 equiv of phenol, 5 mol % of $Pd_2(dba)_3$, 20 mol % of dppf, and 2.0 equiv of $K_2CO_3$ in THF at 55 °C under argon.

To extend the general applicability of this carboannulation reaction, the reaction of propargyl carbonate **1a** with various phenols was carried out under the above optimized conditions, and the results are summarized in Table 2. Phenols bearing an electron-donating group or an electron-withdrawing group in the para position afforded the corresponding 1-substituted indenes **3** as the sole products in moderate to high yields (entries 1−7). In addition, 2-bromophenol was also applicable and only a very small amount of **4a** was isolated (entry 8). However, when 2-*tert*-butylphenol was used, only the byproduct was obtained (entry 9). Meanwhile, the use of α-naphthol and *β*-naphthol gave the corresponding products **3j** and **3k** in 75% and 89% yields (entries 10 and 11). For phenols bearing an ortho subsituent and α-naphthol, a moderate yield and the byproduct **4a** were obtained, which could be due to the steric effects. We have also investigated the substrates **1**, bearing various leaving groups on the propargyl posotion, and the reactions of propargyl carbonate **1b**, propargyl acetate **1c**, propargyl benzoate **1d**, and propargyl phosphate **1e** with phenol gave **3a** as the sole products in moderate to high yields (entries 12−15). Bisphenols were then employed in this reaction under

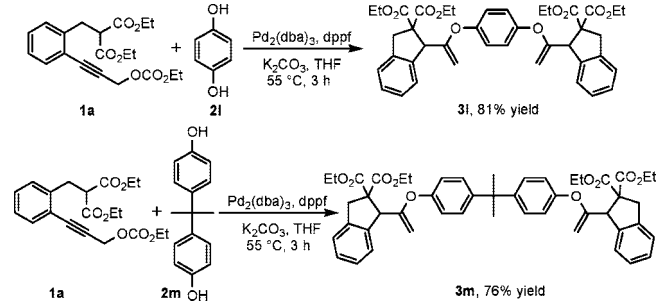
**TABLE 2. Pd-Catalyzed Carboannulation of Propargyl Compounds 1 with Various Phenols 2[a]**




| entry | **1** | ArOH (**2**) | **3** | time (h) | yield of **3** (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a**, $R^1 = CO_2Et$ | $R^2$ = H | **3a** | 3 | 91 (0) |
| 2 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-Me | **3b** | 3 | 90 (0) |
| 3 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-$NO_2$ | **3c** | 3 | 85 (0) |
| 4 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-Ac | **3d** | 3 | 83 (0) |
| 5 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-Ph | **3e** | 3 | 86 (0) |
| 6 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-$CO_2$Et | **3f** | 3 | 80 (0) |
| 7 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 4-Br | **3g** | 3 | 76 (0) |
| 8 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 2-Br | **3h** | 3 | 55 (10) |
| 9 | **1a**, $R^1 = CO_2Et$ | $R^2$ = 2-*t*-Bu | **3i** | 3 | 0 (21) |
| 10 | **1a**, $R^1 = CO_2Et$ | α-naphthol | **3j** | 3 | 75 (<2) |
| 11 | **1a**, $R^1 = CO_2Et$ | *β*-naphthol | **3k** | 3 | 89 (0) |
| 12 | **1b**, $R^1 = CO_2Me$ | $R^2$ = H | **3a** | 3 | 92 (0) |
| 13 | **1c**, $R^1$ = COMe | $R^2$ = H | **3a** | 4 | 84 (0) |
| 14 | **1d**, $R^1$ = COPh | $R^2$ = H | **3a** | 4 | 80 (0) |
| 15 | **1e**, $R^1 = PO(OEt)_2$ | $R^2$ = H | **3a** | 3 | 91 (0) |

[a] All reactions were carried out under the optimal conditions reported in the text. [b] Isolated yields and the numbers in parentheses are the isolated yields of **4a**.

**SCHEME 2**



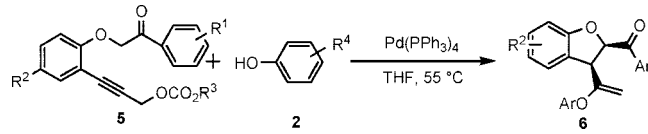

the same conditions by using 0.2 mmol of **1a** and 0.7 equiv of **2**. For hydroquinone **2*l*** and bisphenol **2m**, the reaction proceeded well in both substitution positions and afforded the corresponding disubstituted products **3*l*** and **3m** in 81% and 76% isolated yields, respectively. In these reactions, **4a** was not isolated (Scheme 2).

Interestingly, when **5a** was subjected to the Pd-catalyzed reaction, benzo[*b*]furan derivative **6a** was obtained in a good yield with high regio- and stereoselectivity (Table 3, entry 1). Similarily, α-naphthol and *β*-naphthol also gave the products **6b** and **6c** in moderate yields (entries 2 and 3). The reactants containing different groups in different positions also gave the desired products in moderate yields (entries 4−7). In this process, the formation of the carbon−carbon bond has proven to be an effective method for preparing benzo[*b*]furan derivatives and only cis-fused benzo[*b*]furan derivatives were obtained.

To clarify the mechanism of this process, we examined the reaction of purified **4a**with phenol (**2a**) and no reaction was observed (Scheme 3). This result confirmed that the formation of **3a** was not attributed to addition of phenol to diethyl 1-vinylidene-1*H*-indene-2,2(3*H*)-dicarboxylate (**4a**).

The mechanism shown in Scheme 4 is proposed for this process. It consists of the following key steps: (a) palladium(0) reacted with the carbanion of propargyl carbonate **1** through

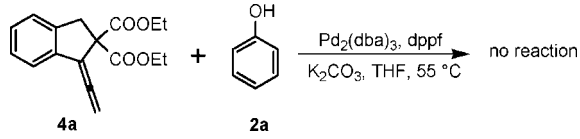
**TABLE 3. Pd-Catalyzed Carboannulation of Propargylic Compounds 5 with Various Phenols 2**[a]



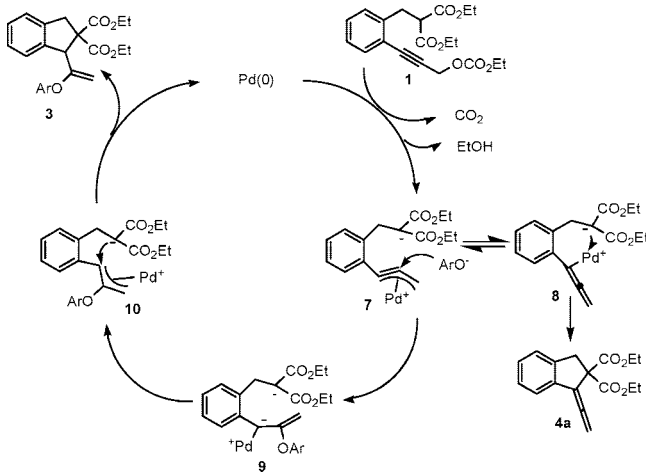

| entry | 5 | ArOH (2) | 6 | time (h) | yield of 6 (%)[b] |
|---|---|---|---|---|---|
| 1 | **5a**, $R^1$ = H, $R^2$ = H $R^3$ = Me | $R^4$ = 4-Ac | **6a** | 4 | 75 |
| 2 | **5a**, $R^1$ = H, $R^2$ = H $R^3$ = Me | α-naphthol | **6b** | 4 | 70 |
| 3 | **5a**, $R^1$ = H, $R^2$ = H $R^3$ = Me | β-naphthol | **6c** | 4 | 68 |
| 4 | **5b**, $R^1$ = H, $R^2$ = Me $R^3$ = Me | $R^4$ = 4-Ac | **6d** | 4 | 64 |
| 5 | **5c**, $R^1$ = H, $R^2$ = *t*-Bu $R^3$ = Me | $R^4$ = 4-Ac | **6e** | 4 | 71 |
| 6 | **5d**, $R^1$ = H, $R^2$ = Cl $R^3$ = Me | $R^4$ = 4-Ac | **6f** | 4 | 58 |
| 7 | **5e**, $R^1$ = 2,4-dimethyl, $R^2$ = Cl, $R^3$ = Et | $R^4$ = 4-Ac | **6g** | 4 | 61 |

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.20 mmol of **5**, 1.2 equiv of **2**, and 0.05 equiv of $Pd(PPh_3)_4$ in 2 mL of THF were stirred at 55 °C under argon for the specified period of time. [b] Isolated yields.

**SCHEME 3**




**SCHEME 4**




$S_N2'$ substitution to form a π-propargylpalladium complex **7**, which is in an equilibrium with allenylpalladium intermediate **8**;[2,3,8] (b) regioselective intermolecular nucleophilic attack at the central carbon of the π-propargylpalladium complex forms the palladium complex **9**,[3] which picks up an active hydrogen from the EtOH loosened to give the π-allylpalladium intermediate **10**; (b′) regioselective intramolecular nucleophilic attack of the carbanion forms the side product **4a**; and (c) regioselective intramolecular nucleophilic attack of the carbanion forms product **3**.

In conclusion, we have developed a novel Pd-catalyzed carboannulation of propargyl compounds with high regio- and stereoselectivity under very mild reaction conditions. In these processes, indene and benzo[*b*]furan derivatives are synthesized through the formation of the carbon−carbon bond and intermolecular nucleophilic attack is prior to the intramolecular reaction. It is noteworthy that the bidentate ligand plays an important role in determining the stable manner of intermediates and the sequence of intramolecular and intermolecular nucleophilic attack for the synthesis of indene derivatives.

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## Experimental Section

**General Procedure for the Preparation of Indene Derivatives 3.** To a solution of propargylic compound **1a** (0.20 mmol) in THF (2.0 mL) was added phenols (0.24 mmol) and $K_2CO_3$ (55.2 mg, 0.40 mmol). The mixture was stirred for 1 min and $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 5 mol %) and dppf (22.2 mg, 0.04 mmol, 20 mol %) were added. The resulting mixture was then heated under an argon atmosphere at 55 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, then the mixture was 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. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford indene derivatives **3**.

**3a.** The reaction mixture was chromatographed with 40:1 hexanes/EtOAc to afford 69.2 mg (91%) of the indicated compound as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34−7.20 (m, 6H), 7.07 (t, $J$ = 7.2 Hz, 1H), 6.89 (d, $J$ = 7.5 Hz, 2H), 4.86 (s, 1H), 4.32−4.06 (m, 6H), 3.88 (d, $J$ = 1.5 Hz, 1H), 3.37 (d, $J$ = 16.5 Hz, 1H), 1.23 (t, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.3, 169.3, 162.0, 153.1, 141.1, 140.3, 129.6, 129.4, 127.7, 127.0, 124.5, 124.2, 122.7, 89.9, 64.3, 61.8, 61.4, 55.3, 39.8, 14.0, 13.9; IR (neat, cm$^{-1}$) 1728, 1248, 764. Anal. Calcd for $C_{23}H_{24}O_5$: C 72.61; H 6.36. Found: C 72.44; H 6.34.

**General Procedure for the Preparation of Benzo[*b*]furan Derivatives 6.** To a solution of propargylic compound **5a** (0.20 mmol) in THF (2.0 mL) was added phenols (0.24 mmol). The mixture was stirred for 1 min and $Pd(PPh_3)_4$ (5 mol %) was added. The resulting mixture was then heated under an argon atmosphere at 55 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, then the mixture was 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. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford indene derivatives **6**.

**6a.** The reaction mixture was chromatographed with 40:1 hexanes/EtOAc to afford 57.6 mg (75%) of the indicated compound as an oil: $^1$H NMR (300 MHz, $CDCl_3$); $^1$H NMR (300

MHz, $CDCl_3$) $\delta$ 8.16−8.13 (m, 2H), 7.99−7.96 (m, 2H), 7.64−7.61 (m, 1H), 7.55−7.50 (m, 2H), 7.32−7.21 (m, 2H), 7.14−7.11 (m, 2H), 7.01−6.93 (m, 2H), 6.12 (d, $J$ = 5.7 Hz, 1H), 4.75 (d, $J$ = 6.0 Hz, 1H), 4.52 (d, $J$ = 2.4 Hz, 1H), 4.29 (d, $J$ = 2.7 Hz, 1H), 2.59 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 196.7, 194.3, 160.3, 159.2, 159.0, 134.3, 133.8, 133.4, 130.4, 129.3, 128.7, 125.6, 124.9, 121.4, 120.3, 110.2, 92.9, 85.7, 49.4, 26.5; IR (neat, $cm^{-1}$) 1682, 1597, 1227, 912, 744; HRMS calcd for $C_{25}H_{24}NO_4$ $[M + NH_4]^+$ 402.1700, found 402.1706.

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

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