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Palladium-Catalyzed Carboannulation of Propargylic Carbonates and Nucleophiles to 2-Substituted Indenes

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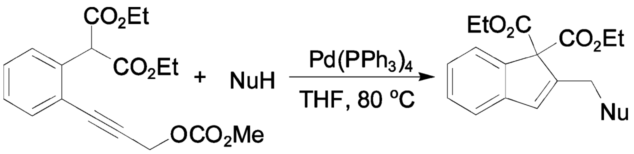
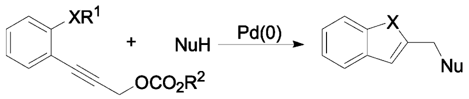
Received November 17, 2006



A new and efficient synthesis of 2-substituted indenes has been achieved via palladium-catalyzed carboannulation of propargylic carbonates with nucleophiles in good to excellent yields. A variety of nucleophiles were tolerated in this reaction.

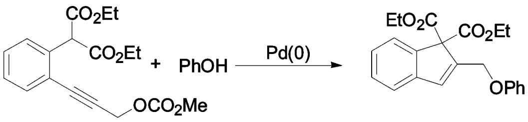
Palladium-catalyzed reactions of propargylic compounds with nucleophiles have been shown to be extremely effective for the construction of carbon−carbon and carbon−heteroatom bonds.[1] The key step in these reactions is the formation of a π-allyl- or π-allenylpalladium complex by facile decarboxylation, which undergoes a variety of further transformations under neutral conditions. Since the first report by Tsuji in 1985,[2] a wide variety of reactions in this family have been developed and applied in the preparation of various organic substances.[1,3] Recently, Yoshida et al. reported palladium-catalyzed reactions of propargylic carbonates with nucleophiles for the synthesis of substituted 2,3-dihydrofurans and benzofurans,[4] and very recently, Cacchi et al. reported a convenient method for the preparation of functionalized indoles by the palladium-catalyzed reaction of ethyl-3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate with piperazines (Scheme 1).[5]

SCHEME 1



X = O; R^1 = H, R^2 = Me
X = NH; R^1 = $COCF_3$, R^2 = Et

SCHEME 2



1 **2a** **3a**

In connection with our ongoing project on the carboannulation reaction via palladium catalysis,[6] we expected that a phenol could react as a nucleophile with 3-(2-(di(ethoxycarbonyl)-methyl)phenyl)prop-2-ynyl methyl carbonate (**1**) under palladium catalysis to give the 2-substituted indene (Scheme 2).[7,8]

To realize this goal, the catalytic activity of palladium catalysts was examined for the cyclization of propargylic carbonate **1** and phenol. $Pd(PPh_3)_4$ has proved to be the best catalyst. Other palladium catalysts such as $Pd_2(dba)_3 \cdot CHCl_3$ and $Pd(OAc)_2/PPh_3$ were less effective. THF was an excellent solvent.

Subsequently, the reaction was examined on various substrates. Typical results of the palladium-catalyzed cyclization of propargylic carbonates and phenols are shown in Table 1. The reaction of propargylic carbonate **1** (0.2 mmol) with 1.2 equiv of phenol in the presence of 5 mol % of $Pd(PPh_3)_4$ in THF under argon at 80 °C for 1 h gave the desired 2-substituted indene **3a** in 96% isolated yield (Table 1, entry 1). Phenols bearing an electron-donating group or an electron-withdrawing group in the para, ortho, and meta positions afforded the corresponding 2-substituted indenes in good to high yields (entries 2−9). Phenols bearing an electron-donating group in the para position usually led to high yields of the 2-substituted indenes (entries 2−4). When 4-chlorophenol (**2e**) and 4-nitrophenol (**2f)** were employed in the reaction with substrate **1**, the

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(1) For reviews on the palladium-catalyzed reactions of propargylic compounds, see: (a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144. (b) Tsuji, J.; Mandai. T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

(2) (a) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225.

(3) For recent examples of similar types of palladium-catalyzed reactions of propargylic carbonates with nucleophiles, see: (a) Geng, L.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1992**, 17. (b) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, 553. (c) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583. (d) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (e) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616. (f) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **2001**, *66*, 6634. (g) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (h) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874. (i) Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2005**, *70*, 6980.

(4) (a) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381.

(5) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083.

(6) (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325. (b) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 3053.

(7) A new palladium-catalyzed cyclization reaction of propargylic carbonates with carbon nucleophiles to 2,3-disubstituted indenes has been reported by us; see: Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777.

(8) For recent examples of palladium-catalyzed indene synthesis, see: (a) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Fiedler, P. *Tetrahedron* **2002**, *58*, 9007. (b) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963. (c) Furuta, T.; Asakawa, T.; Iinuma, M.; Fujii, S.; Tanaka, K.; Kan, T. *Chem. Commun.* **2006**, 3648. (d) Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406.

10.1021/jo062377e CCC: $37.00

SCHEME 3

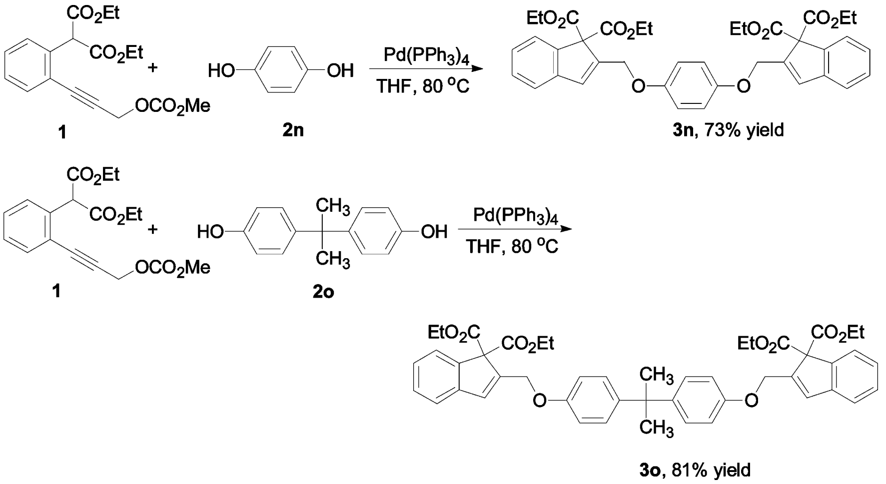
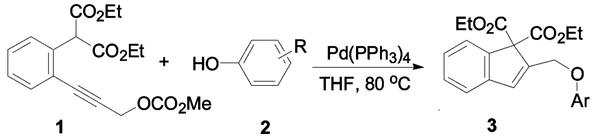


TABLE 1. Palladium-Catalyzed Carboannulation of Propargylic Carbonate 1 with Various Phenols 2[a]

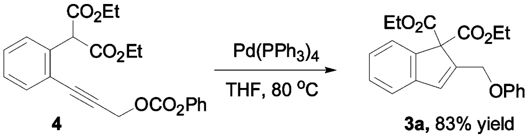


entry	ArOH (**2**)	**3**	isolated yield (%)
1	R = H	**3a**	96
2	R = 4-OMe	**3b**	93
3	R = 4-Me	**3c**	92
4	R = 4-*t*-Bu	**3d**	90
5	R = 4-Cl	**3e**	91
6	R = 4-NO_2	**3f**	76
7	R = 2-Me	**3g**	80
8	R = 2-Br	**3h**	84
9	R = 3-NO_2	**3i**	77
10	R = 2,4-dimethyl	**3j**	80
11	R = 2,4-dichloro	**3k**	81
12	α-naphthol	**3l**	45
13	*β*-naphthol	**3m**	81

[a] All reactions were carried out on a 0.2 mmol scale in 2 mL of THF under argon at 80 °C by using 1.0 equiv of **1**, 1.2 equiv of **2**, and 0.05 equiv of $Pd(PPh_3)_4$; all reactions were run for 1−2 h.

corresponding products **3e** and **3f** were isolated in 91 and 76% yields (entries 5 and 6). Phenols containing an electron-donating group or an electron-withdrawing group in the ortho position have also proven successful. For example, the reaction of 2-methylphenol and 2-bromophenol produced 80 and 84% yields of the desired products, respectively (entries 7 and 8). The reactions of **1** and phenols with an electron-withdrawing group, such as the NO_2 group in the meta position, afforded the desired product **3i** in good yield (entry 9). The disubstituted phenols such as 2,4-dimethylphenol and 2,4-dichlorophenol with **1** also worked well to give products **3j** and **3k** in 80 and 81% yields, respectively (entries 10 and 11). Meanwhile, the use of α-naphthol and *β*-naphthol also afforded the corresponding products **3l** and **3m** in 45 and 81% yields (entries 12 and 13). For α-naphthol, a moderate yield was obtained, which could be due to the involvement of steric effects. In addition, propargylic carbonate with different electron-withdrawing groups such as ethyl-2-[2-{3-(methoxycarbonyloxy)prop-1-ynyl}phenyl]-2-(phenylsulfonyl)acetate was also employed as a substrate, but no reaction was observed.

SCHEME 4



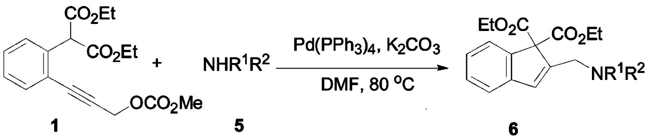
Bisphenols were then employed in this reaction under the same conditions by using 0.2 mmol of **2** and 2.0 equiv of **1**. For hydroquinone and bisphenol A, the reactions proceeded well in both substitution positions and afforded the corresponding disubstituted products **3n** and **3o** in 73 and 81% isolated yields, respectively (Scheme 3).

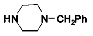
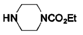
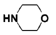
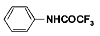
Furthermore, the reaction of **4**, containing a latent nucleophilic phenolic moiety as a part of the carbonate leaving group, was also examined (Scheme 4). When **4** was subjected to the palladium-catalyzed reaction, the corresponding 2-substituted indene **3a** was isolated in 83% yield. In this reaction, the substrate initially releases the phenoxide, which then acts as a nucleophile for the cyclized *π*-allyl complex to produce the product.

To further explore the scope of this cyclization reaction, nitrogen nucleophiles were also investigated. Based on optimization efforts, the combination of 0.2 mmol of **1**, 1.2 equiv of nucleophile, 2.0 equiv of K_2CO_3, 5 mol % of $Pd(PPh_3)_4$, and the use of DMF as the solvent at 80 °C gave the best results. In this reaction, base is essential. To our delight, various secondary amines could react with **1** to give the desired products (Table 2). Yields are usually moderate to good with secondary amines (entries 1−6). Aryl secondary amines such as trifluoroacetophenylamine also afforded the corresponding product **6g** in 62% yield (entry 7).

A plausible mechanism accounting for the formation of the 2-substituted indenes is depicted in Scheme 5. In this process, a palladium catalyst initially promotes decarboxylation of propargylic carbonate **1** to generate an allenylpalladium complex **7**, which would be in equilibrium with *π*-propargylpalladium intermediate **8**.[4,5] Palladium complex **8** undergoes intramolecular nucleophilic attack of the carbanion at the central carbon of the allenyl/propargylpalladium complex to form the carbene complex **9**,[5] which abstracts an active hydrogen from the nucleophile moiety to give the *π*-allylpalladium intermediate **10**.[3−5] Finally,

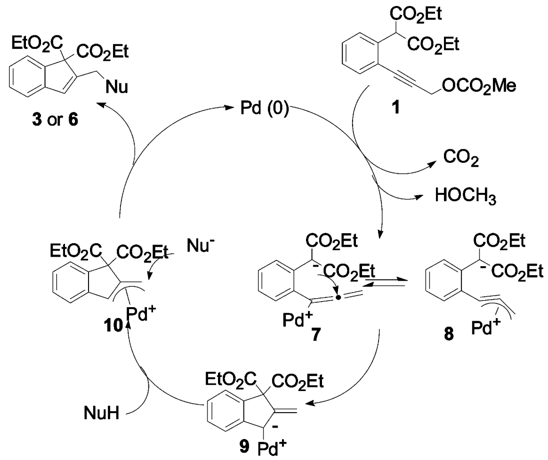
TABLE 2. Palladium-Catalyzed Carboannulation of Propargylic Carbonate 1 with Various Amines 5[a]



entry	amine (**5**)	**6**	isolated yield (%)
1		**6a**	62
2		**6b**	75
3		**6c**	71
4		**6d**	78
5		**6e**	73
6	Et_2NH	**6f**	52
7		**6g**	62[b]

[a] All reactions were carried out on a 0.2 mmol scale in 2 mL of DMF under argon at 80 °C by using 1.0 equiv of **1**, 1.2 equiv of **5**, 2.0 equiv of K_2CO_3, and 0.05 equiv of $Pd(PPh_3)_4$; all reactions were run for 4−5 h. [b] Without K_2CO_3.

SCHEME 5



regioselective intermolecular nucleophilic attack of the nucleophile on **10** at the less-hindered site produces 2-substituted indene.[4,5]

In conclusion, we have developed an efficient and operationally simple cyclization method for the synthesis of 2-substituted indenes. This method accommodates a variety of nucleophiles and affords the anticipated substituted indenes in good to excellent yields.

Experimental Section

General Procedure for the Preparation of 2-Substituted Indenes 3. A mixture of 3-(2-(di(ethoxycarbonyl)methyl)phenyl)-prop-2-ynyl methyl carbonate (**1**; 69.6 mg, 0.20 mmol), phenols (0.24 mmol), $Pd(PPh_3)_4$ (11.5 mg, 5 mol %), and THF (2.0 mL) was placed under an argon atmosphere in a 25 mL flask. The resulting mixture was then heated under an argon atmosphere at 80 °C. When the reaction was considered complete, as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding 2-substituted indenes **3**.

Diethyl-2-(phenoxymethyl)-1*H*-indene-1,1-dicarboxylate (3a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 70.0 mg (96%) of the indicated compound as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, $J = 7.2$ Hz, 1H), 7.34−7.22 (m, 5H), 7.02−7.01 (d, $J = 7.6$ Hz, 2H), 6.97−6.94 (m, 2H), 5.10 (s, 2H), 4.26−4.21 (q, $J = 7.2$ Hz, 4H), 1.27−1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.7, 143.3, 141.7, 140.6, 132.6, 129.4, 128.8, 126.0, 125.2, 121.4, 120.9, 114.8, 70.7, 65.4, 62.3, 13.9; IR (neat, cm^{-1}) 3447, 2982, 1732, 1495, 1242, 1047. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.02; H, 5.94.

General Procedure for the Preparation of 2-Substituted Indenes 6. To a solution of 3-(2-(di(ethoxycarbonyl)methyl)-phenyl)prop-2-ynyl methyl carbonate (**1**; 69.6 mg, 0.20 mmol) in DMF (2.0 mL) were added K_2CO_3 (55.2 mg, 0.40 mmol), amines (0.24 mmol), and $Pd(PPh_3)_4$ (11.5 mg, 5 mol %). The resulting mixture was then heated under an argon atmosphere at 80 °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. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding 2-substituted indenes **6**.

Diethyl-2-((pyrrolidin-1-yl)methyl)-1*H*-indene-1,1-dicarboxylate (6a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 42.5 mg (62%) of the indicated compound as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.0$ Hz, 1H), 7.32−7.24 (m, 2H), 7.21−7.17 (m, 1H), 6.88 (s, 1H), 4.23−4.15 (m, 4H), 3.59 (s, 2H), 2.63−2.60 (t, $J = 6.4$ Hz, 4H), 1.81−1.78 (m, 4H), 1.30−1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.2, 144.0, 140.9, 131.7, 128.5, 125.5, 124.9, 120.9, 71.0, 61.8, 54.5, 54.4, 23.7, 13.9; IR (neat, cm^{-1}) 3402, 2964, 1731, 1463, 1234, 1050. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.85; H, 7.37; N, 3.98.

Acknowledgment. We thank the NSF (NSF-20021001, NSF-20672049) and the "Hundred Scientist Program" from the Chinese Academy of Sciences for financial support.

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.

JO062377E