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Palladium(II)-Catalyzed Synthesis of Functionalized Indenes from *o*-Alkynylbenzylidene Ketones

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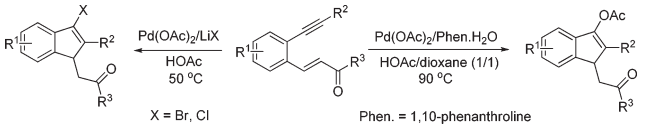
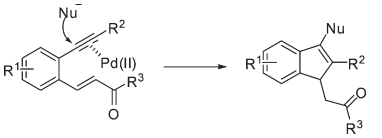


An efficient method for the synthesis of functionalized indenes from *o*-alkynylbenzylidene ketones under palladium(II) catalysis was developed. The reaction is initiated by *trans*-nucleopalladation of alkynes, followed by conjugate addition and quenched by protonolysis of the carbon−palladium bond. With acetate and halide ions as nucleophiles, 3-acetoxy- and 3-halogen-substituted indenes could be obtained in high yields.

Molecules containing the indene core have been attractive as drug candidates possessing remarkable biological activities,[1] and show great interest as functional materials[2] as well as precursors of metallocene complexes[3] for catalysts of polymerization processes. Consequently, some approaches to the synthesis of the indene ring system have been developed, embodying the annulation of phenyl-substituted allylic alcohols,[4] the ring expansion of substituted cyclopropenes,[5] and the reduction/dehydration of the indanones.[6] Although the methods mentioned above are quite effective in synthesizing simple indenes, certain drawbacks are unavoidable in the preparation of highly substituted indenes, namely lengthy reaction sequences, strong acid conditions, and the low tolerance for sensitive organic functionality. Tandem cyclization reactions catalyzed by transition metals have been proven highly useful especially when the highly substituted indene derivatives and their yields are concerned,[7,8] whereas there are only limited reports for the synthesis of acetoxyindenes or haloindenes.[9] On the basis of the advancement of acetoxypalladation and halopalladation chemistry,[10] we conceived if 3-functionalized indenes could be obtained via the tandem reaction of *o*-alkynylbenzylidene ketone initiated by nucleopalladation of the triple bond (Scheme 1). Herein we report our results of the successful synthesis of this class of indene compounds.

SCHEME 1. Cyclization of *o*-Alkynylbenzylidene Ketones Catalyzed by Pd(II)



With the hypothesis mentioned above, initial studies were focused on using *o*-alkynylbenzylidene ketone **1a** as a model substrate. Gratifyingly, the tandem cyclized product **2a** was formed in 85% yield in HOAc (Table 1, entry 1). Other solvents such as HOAc/CH_3CN (1/1), HOAc/DCE (1/1),

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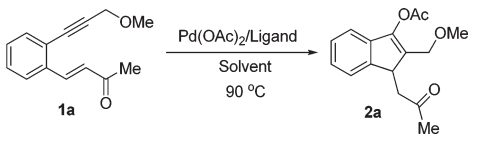
TABLE 1. Optimization of the Palladium-Catalyzed Synthesis of 3-Acetoxy Indene from 1a[a]



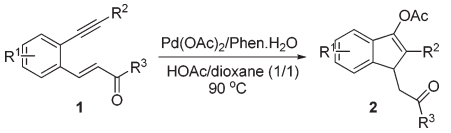
entry	ligand	solvent (v/v)	time (h)	yield (%)[b]
1	bpy[c]	HOAc	30	85
2	bpy	HOAc/CH_3CN (1/1)	40	53
3	bpy	HOAc/DCE (1/1)	40	36
4	bpy	HOAc/toluene (1/1)	30	85
5	bpy	HOAc/dioxane (1/1)	20	85
6	—	HOAc/dioxane (1/1)	24	0
7[d]	bpy	HOAc/dioxane (1/1)	24	0
8[e]	bpy	HOAc/dioxane (1/1)	20	83
9[f]	NO_2-bpy[c]	HOAc/dioxane (1/1)	36	29
10	MeO-bpy[c]	HOAc/dioxane (1/1)	36	87
11	Phen.H_2O[c]	HOAc/dioxane (1/1)	24	92
12	Phen[c]	HOAc/dioxane (1/1)	36	78
13	PPh_3	HOAc/dioxane (1/1)	24	0
14	bpy/H_2O[g]	HOAc/dioxane (1/1)	50	87
15[h]	bpy	HOAc/dioxane (1/1)	24	73

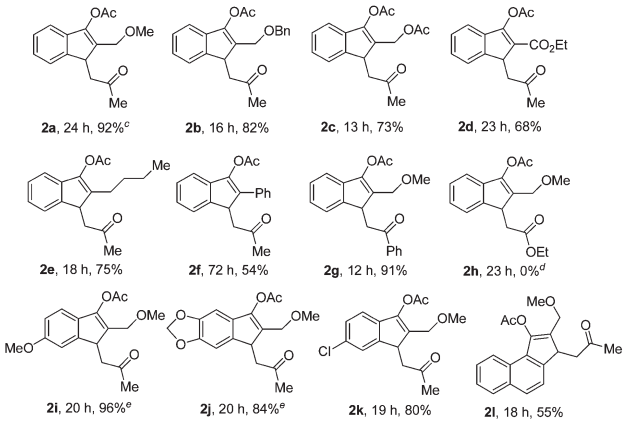
[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), ligand (12 mol %), solvent (2 mL), 90 °C. [b]Isolated yield. [c]bpy = 2,2′-bipyridine; NO_2-bpy = 4,4′-dinitro-2,2′-bipyridine; MeO-bpy = 4,4′-dimethoxy-2,2′-bipyridine; Phen = 1,10-phenanthroline. [d]No $Pd(OAc)_2$ was used. [e]$Pd(OAc)_2$/ligand (1/2). [f]53% of **1a** was recovered. [g]H_2O (12 mol %) was added. [h]1 equiv of LiOAc was added.

HOAc/toluene (1/1), and HOAc/dioxane (1/1) were also examined (Table 1, entries 2−5). Finally, the HOAc/dioxane (1/1) system was chosen as the solvent because of the highest yield obtained and the shortest time required. Control experiments demonstrated that no reaction occurred in the absence of the palladium catalyst or the ligand (Table 1, entries 6 and 7). When the ratio of catalyst and ligand was changed from 1/1.2 to 1/2, the yield slightly declined to 83% (Table 1, entry 8). Next, several ligands including nitrogen-containing ligands with electron-withdrawing or -donating group and triphenylphosphine were screened. 1,10-Phenanthroline monohydrate gave the best yield (92%), while a lower yield was obtained by using 1,10-phenanthroline (Table 1, entries 9−13). The reaction yield incredibly reduced to 73% with the addition of LiOAc (Table 1, entry 15). Thus, **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), 1,10-phenanthroline monohydrate (12 mol %), and HOAc/dioxane (1/1) at 90 °C were chosen as the optimized conditions.

Under these optimized reaction conditions, the scope of the tandem reaction was investigated. The results are shown in Table 2. The substrates, **1a**−**c** and **1e** with an alkoxy or alkyl group on one side of the alkyne, reacted smoothly to give corresponding cyclized products in good to excellent yields (Table 2, **2a**−**c** and **2e**). The reaction of **1d** with an electron-withdrawing group on one side of the alkyne could also proceed successfully to give the product with the yield of 68% (Table 2, **2d**). In the case of phenyl-substituted alkyne **1f**, the reaction was completed in 72 h and the yield was declined dramatically to 54% (Table 2, **2f**). Similar reactivity was observed in the ketones with different substituents (Table 2, **2a** and **2g**). When the ketone group in **1a** was changed to an ester group **1h**, no annulation product was detected (Table 2, **2h**). The effect of the substituents on the aromatic ring of the *o*-alkynylbenzylidene ketone was also

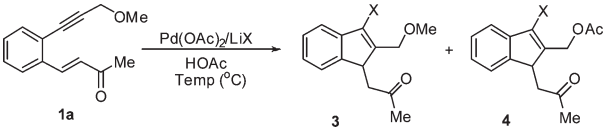
TABLE 2. Palladium-Catalyzed Synthesis of 3-Acetoxy Indenes[a,b]





[a]Reactions were carried out at 90 °C with **1** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), Phen·H_2O (12 mol %) in HOAc/dioxane (1/1, 2 mL). [b]Isolated yield. [c]The reaction was carried out at 80 °C. [d]No cyclized product was obtained. [e]The reaction was carried out at 60 °C.

TABLE 3. Optimization of the Palladium-Catalyzed Synthesis of 3-Halogen-Substituted Indenes[a]



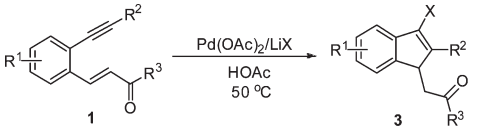
				yield (%)[b]	
entry	LiX	temp (°C)	time (h)	**3**	**4**
1	LiBr	80	4.5	**3a** (52)	**4a** (39)
2	LiBr	60	6.0	**3a** (70)	**4a** (8)
3	LiBr	50	8.5	**3a** (75)	**4a** (0)
4	LiCl	50	7.0	**3m** (80)	**4m** (0)

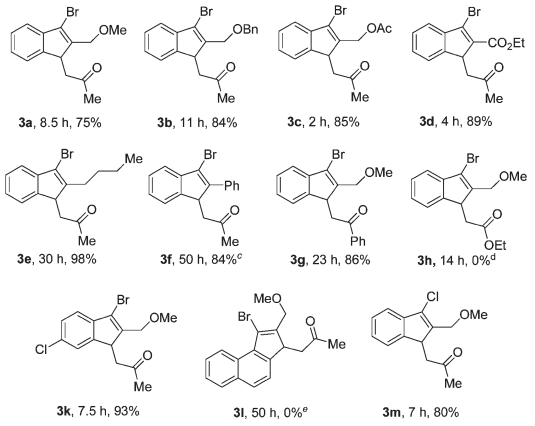
[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), LiX (4.0 equiv), HOAc (2 mL). [b]Isolated yield.

examined. The reactions gave good to excellent yields (Table 2, **2i**−**k**). However, only a 55% yield of the product was obtained with the naphthalene ring as a substitute for the benzene ring (Table 2, **2l**).

After the reaction initiated by acetoxypalladation was well developed, the halide ion was chosen as the nucleophile instead of the acetoxy anion to perform the reaction. First, **1a** was still chosen as the model substrate. On the basis of our previous works,[10d] the reaction was initially conducted at 80 °C by using $Pd(OAc)_2$ as the catalyst in the presence of LiBr and HOAc. The desired 3-bromoindene derivative **3a** was generated in 52% yield together with a byproduct **4a** (Table 3, entry 1). Comparing **3a** with **4a**, it is obvious that the group OMe in **3a** was replaced by the group OAc in **4a**. Control experiments revealed that **4a** could be formed by only heating **3a** in the presence of LiBr/HOAc at 80 °C, indicating that the byproduct **4a** might be formed from the

TABLE 4. Palladium-Catalyzed Synthesis of 3-Halogen-Substituted Indenes[a,b]





[a]Reactions were carried out at 50 °C with **1** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), LiX (4 equiv), and HOAc (1 mL). [b]Isolated yield. [c]The reaction was carried out at 70 °C. [d]No cyclized product was obtained. [e]The reaction was carried out at 90 °C.

product **3a**. It was proposed in literature[11] that the reaction involves the formation of an oxonium intermediate by the coordination of the oxygen atom of the ether in product **3a** to the lithium ion. The reaction is then driven to completion by nucleophilic attack of the acetate ion in the presence of acetic acid. Then it was observed that a higher yield of **3a** (70%) could be obtained at a lower temperature (60 °C) (Table 3, entry 2). When the temperature was further lowered to 50 °C, the reaction afforded **3a** in 75% isolated yield without the formation of **4a** (Table 3, entry 3). Moreover, the yield could be increased to 80% when LiCl was used as the nucleophile instead of LiBr (Table 3, entry 4). Then, LiBr was chosen as the nucleophile for easier transformation to other derivatives.

Then a variety of other substrates are readily accessed with this methodology as outlined in Table 4. The substrates **1a**−**c** and **1e** with an alkoxy or alkyl group on one side of the alkyne reacted smoothly to give corresponding cyclized products in good to excellent yields (Table 4, **3a**−**c** and **3e**). Cyclization of **1d** with an electron-withdrawing group occurred providing **3d** with a yield of 89%, which was higher than the yield of the corresponding 3-acetoxy product **2d**. The annulation of substrate **1f** was completed in 50 h with a 84% yield of the product (Table 4, **3f**). Similar results were achieved in the ketones with different substituents (Table 4, **3a** and **3g**). In the case of an ester group (**1h**), no cyclized product was found (Table 4, **3h**). It is worth noting that the reaction of the substrates **1i** and **1j** with electron-donating groups in the benzene ring gave the products **4i** and **4j**, in which the group OMe was completely replaced by the group OAc as shown in Scheme 2, probably due to the further

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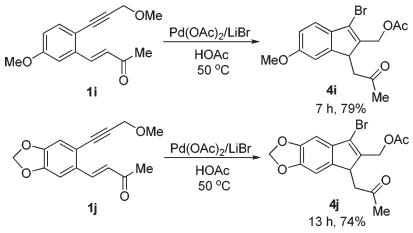
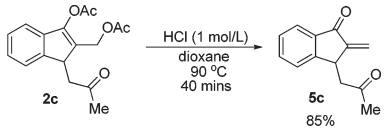
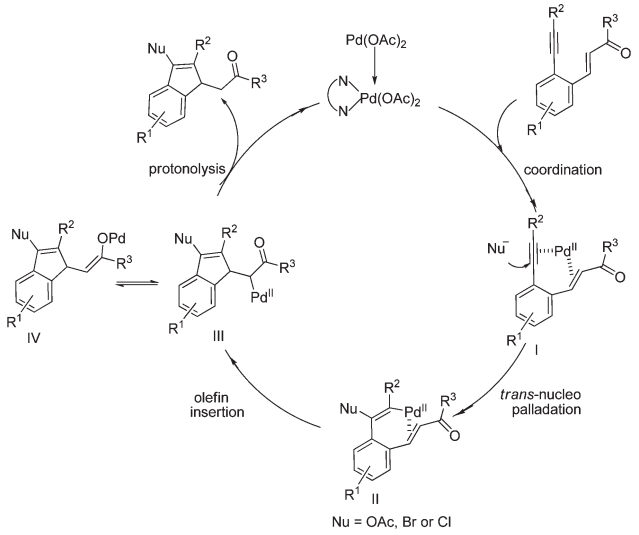
SCHEME 2



SCHEME 3. Hydrolysis of 3-Acetoxy Indene



SCHEME 4. Proposed Mechanism for the Annulation Reaction



conversion of the initial products similar to the transformation of **3a** to **4a**. On the other hand, the reaction of **1k** with a chlorine atom in the benzene ring provided **3k** in 93% yield in a normal way (Table 4, **3k**). Surprisingly, no product was detected when the benzene ring was changed to the naphthalene ring even at 90 °C with the extension of the reaction time to 50 h (Table 4, **3l**).

The possibility of further conversion of the 3-acetoxy indenes to other products was studied. Treatment of **2c** with HCl (1 mol/L) in dioxane at 90 °C afforded the hydrolysis product **5c** in 85% yield with the formation of exocyclic double bond (Scheme 3). Compound **5c** could be transferred further to the spirocyclic skeletons,[12] which occurred widely in a large number of natural products.[13]

A plausible mechanism involving *trans*-nucleopalladation and conjugate addition is proposed as shown in Scheme 4. The first step involves π-coordination of the carbon−carbon

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multiple bond of **1** to the Pd(II) species followed by *trans*-nucleopalladation of the carbon−carbon triple bond of **I** to afford vinylpalladium species **II**. Then, conjugate addition of the vinylpalladium species to the double bond of the benzylidene ketone occurs to yield **III** or **IV**. Protonolysis of **IV** gives the products **2** in the presence of an acid with regeneration of the palladium(II) species to complete the catalytic cycle.[10a] It is also worth mentioning that the bidentate nitrogen-containing ligands or halide ions play a crucial role in inhibiting the β-H elimination of intermediate **III** and promoting the protonolysis of the carbon−palladium bond making the catalytic cycles possible.[10a,d,g,h]

In conclusion, we have developed a palladium-catalyzed synthesis of functionalized indenes from *o*-alkynylbenzylidene ketones. A variety of 3-acetoxy- and 3-halogen-substituted indenes can be easily obtained from this method. Further studies on the asymmetric version and application of this reaction are underway.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Synthesis of 3-Acetoxy Indenes. To a solvent mixture of HOAc/dioxane (1/1, 2 mL) containing $Pd(OAc)_2$ (10 mol %) and 1,10-phenanthroline monohydrate (12 mol %) was added substrate **1a** (0.15 mmol) at 90 °C under nitrogen atmosphere. The mixture was stirred until **1a** disappeared as monitored by TLC. On cooling, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 20:1 to 4:1) to give the product **2a** in 92% yield as an oil. IR (neat) ν 2991, 2937, 2890, 2824, 1770, 1717, 1648, 1464, 1362, 1203, 1162, 1121, 1089, 1012, 949, 896, 755, 538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.2, 0.4 Hz, 1H), 7.29−7.19 (m, 2H), 7.12 (d, J = 6.8 Hz, 1H), 4.20−4.11 (m, 3H), 3.27 (s, 3H), 2.98 (dd, J = 17.6, 6.4 Hz, 1H), 2.70 (dd, J = 17.2, 6.8 Hz, 1H), 2.36 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 168.1, 146.7, 145.0, 137.8, 130.4, 126.8, 126.2, 123.4, 118.4, 65.3, 57.9, 44.4, 42.2, 30.2, 20.5; MS (70 eV, EI) m/z (%) 274 [M^+], 242, 216, 200, 174, 157 (100), 143, 128, 115, 103, 89, 77, 58, 43; HRMS calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1202. Characterization data for other products in Table 2 were shown in the Supporting Information.

Typical Procedure for the Palladium-Catalyzed Synthesis of 3-Halogen-Substituted Indenes. Under nitrogen, a solution of **1a** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), and LiBr (4 equiv) in HOAc (1 mL) was stirred at 50 °C for 2−50 h. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 20:1 to 3:1) to afford the product **3a** in 75% yield as an oil. IR (neat) ν 3070, 2984, 2926, 2893, 2822, 1719, 1610, 1461, 1361, 1261, 1190, 1161, 1093, 1021, 928, 761, 736, 536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.33 (m, 3H), 7.28−7.23 (m, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.30 (d, J = 12.0 Hz, 1H), 4.15 (t, J = 6.3 Hz, 1H), 3.32 (s, 3H), 2.99 (dd, J = 17.4, 6.3 Hz, 1H), 2.65 (dd, J = 17.4, 6.6 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 145.4, 143.3, 141.9, 127.3, 126.7, 122.9, 121.1, 120.6, 68.0, 58.0, 45.6, 44.1, 30.2; MS (70 eV, EI) m/z (%) 296 [M^+, ^{81}Br], 294 [M^+, ^{79}Br], 264, 262, 238, 236, 221 (100), 219, 207, 183, 171, 155, 141, 139, 128, 127, 115, 101, 89, 77, 63, 43; HRMS calcd for $C_{14}H_{15}{}^{79}BrO_2$ 294.0255, found 294.0253. Characterization data for other products in Table 4 were shown in the Supporting Information.

Hydrolysis of 3-Acetoxy Indene 2c. 3-Acetoxy indene **2c** (0.24 mmol) was dissolved in 1 mL of dioxane. Then the HCl (1 mL, 1 mol/L) was added and the mixture was heated at 90 °C for 40 min. The reaction mixture was diluted with diethyl ether (25 mL) and washed with saturated $NaHCO_3$. The aqueous layer was re-extracted with diethyl ether (25 mL) twice. The organic layers were combined, dried (Na_2SO_4), and filtered, and the solvent was removed in *vacuo*. The residue was purified by flash chromatography (petroleum ether:ethyl acetate = 4:1) to give the product **5c** in 85% yield as an oil. IR (neat) ν 2956, 2924, 2852, 1708, 1643, 1607, 1467, 1363, 1302, 1205, 1160, 1099, 985, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.49−7.40 (m, 2H), 6.35 (s, 1H), 5.63 (s, 1H), 4.44 (t, J = 6.3 Hz, 1H), 2.96−2.93 (m, 2H), 2.22 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 206.5, 192.8, 153.2, 147.9, 137.3, 135.3, 128.1, 125.5, 124.4, 120.0, 50.0, 37.1, 30.4; MS (70 eV, EI) m/z (%) 200 [M^+], 191, 169, 158, 143, 128, 115, 99, 86, 84, 57, 49 (100); HRMS calcd for $C_{13}H_{12}O_2$ 200.0837, found 200.0836.

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