A Facile Approach to the Construction of 1*H*-Inden-1-one

Bo Chen,[a] Xingang Xie,[a] Jiangping Lu,[a] Qiaoling Wang,[a] Jiyong Zhang,[a] Shouchu Tang,[a] Xuegong She,*[a,b] Xinfu Pan*[a]

[a] State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou, 730000, P. R. of China

[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou, 730000, P. R. of China
Fax +86(931)8912582; E-mail: shexg@lzu.edu.cn panxf@lzu.edu.cn

Received 8 October 2005

Abstract: The one-pot synthesis of 1*H*-inden-1-one from 1-(2-bromoaryl)prop-2-en-1-ol was described. The reaction involved a sequential intramolecular Heck reaction followed by an aerial oxidation of allylic alcohol.

Key words: 1*H*-inden-1-one, Heck reaction, aerial oxidation, Pd-catalyzed, one-pot

The palladium-catalyzed vinylic substitution reaction (Heck reaction) enjoys considerable popularity as a reliable and general method for carbon–carbon bond formation.[1] It has been widely applied as a strategy to the synthesis of complex natural products.[2] In the past decades, the scope of the reaction has been extended to many substrates including vinyl iodides, vinyl bromides and enol triflates. Moreover, the intramolecular variants have also become one of most important reactions in the construction of optically active polycyclic skeletons.[3]

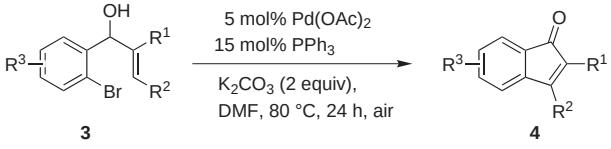
We were interested in constructing multiple chiral centers in one step using intramolecular Heck reaction. Initially, a substrate **1**[4] possessing both an aryl bromide and an allylic alcohol moiety was selected in our study. However, an unanticipated result was obtained when we tried the reaction. Hence, when compound **1** was treated with catalytic amount of $Pd(OAc)_2$ in the presence of air, an oxidation product, 1*H*-inden-1-one **2** was obtained exclusively (Scheme 1).[4,5] This process was believed to involve firstly the Heck reaction followed by aerial oxidation of allylic alcohol. This unexpected result prompted us to further investigate the scope and general applicability of this reaction.

Upon further examination, we found that the reaction did not proceed under argon atmosphere (Table 1, entry 1). However, if argon was replaced by air, the indenone **2** was produced exclusively in moderate yield (Table 1, entry 2). A few experiments were performed to examine the effect of each key reagent on the yield. Finally, we found that DMF was the best solvent and K_2CO_3 was the best base to effect the reaction. The optimal reaction conditions were found to be at 80 °C for 24 hours using 5 mol% of $Pd(OAc)_2$ and 15 mol% of PPh_3.

Table 1 Optimization of Reaction Conditions

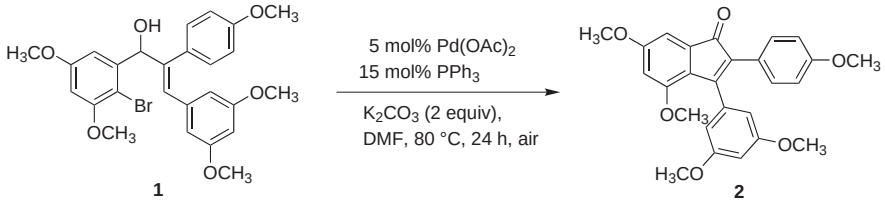
Entry	Base	Solvent	Yield (%)[a]
1	K_2CO_3	Toluene	0[b]
2	K_2CO_3	Toluene	44
3	K_2CO_3	MeCN	30
4	K_2CO_3	DMF	62
5	*i*-Pr_2NEt	DMF	36
6	Et_3N	DMF	55

[a] Isolated yield.
[b] Reaction was run under argon atmosphere.



3 4

Scheme 2



1 2

Scheme 1

SYNLETT 2006, No. 2, pp 0259–0262
Advanced online publication: 23.12.2005
DOI: 10.1055/s-2005-923587; Art ID: W10105ST

To explore the generality of this reaction, other substrates were prepared and employed in this study under the optimal reaction conditions (Scheme 2).[6] The results are shown in Table 2. Interestingly, both electron-donating and electron-withdrawing substituents (R^1 and R^2) are tolerated under the reaction conditions, and the product yields were about 34% to 64%. In addition to aryl substituents, alkyl group was also employed in our study (entry 9), and the yield was also satisfactory (69%).[7]

To reveal the reaction mechanism, additional substrates **5**–**7** were prepared (Figure 1). No reaction happened when compound **5** or **6** was employed. On the other hand, compound **7** was smoothly converted into compound **2** under the optimal reaction conditions. The results suggested that the benzylic hydroxyl group played an important role in the reaction. Based on our knowledge and those reported in the literature,[3,8] a plausible mechanism was proposed (Scheme 3). The reaction first involved the reduction of the Pd(II) to the active palladium(0) species, followed by oxidative addition of the aryl bromide to palladium(II). Insertion into the carbon–carbon double bond then produce an organopalladium intermediate which then undergo β-hydride elimination to form the indenol and a palladium(II) salt which can be reduced back to palladium(0). Finally, indenol was oxidated to indenone by air.

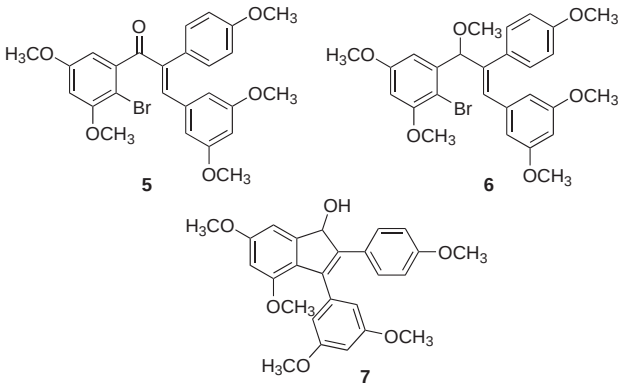
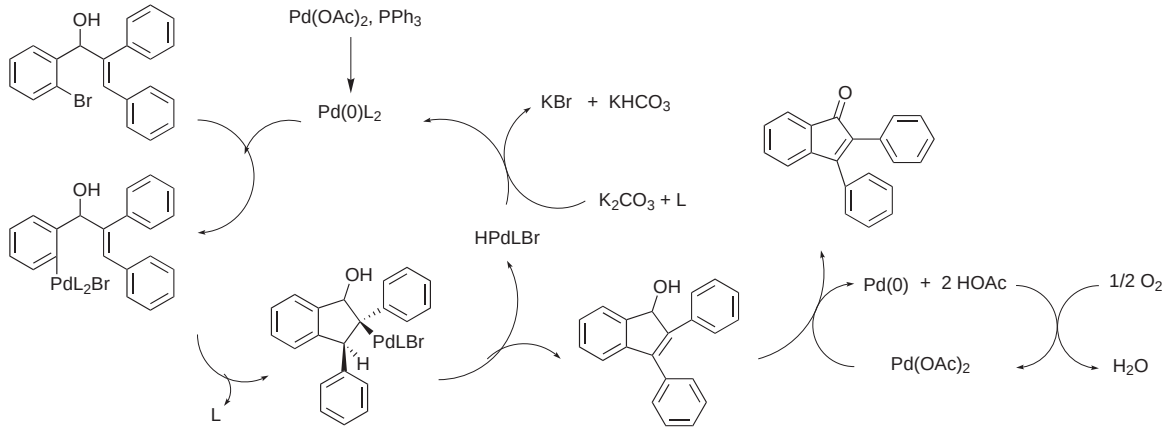


Figure 1



Scheme 3

Table 2 One-Pot Synthesis of 1*H*-Inden-1-one from Compound **3**

Entry	R^1	R^2	R^3	Yield of **4** (%)[a]
1	4-$MeOC_6H_4$	3,5-$(MeO)_2C_6H_3$	3,5-Dimethoxy	62 (**2**)
2	C_6H_5	C_6H_5	H	55 (**4a**)
3	H	4-$MeOC_6H_4$	H	34 (**4b**)
4	4-$MeOC_6H_4$	C_6H_5	H	60 (**4c**)
5	C_6H_5	4-$MeOC_6H_4$	H	64 (**4d**)
6	C_6H_5	4-$NO_2C_6H_4$	H	61 (**4e**)
7	H	C_6H_5	3,5-Dimethoxy	52 (**4f**)
8	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	H	38 (**4g**)
9	*n*-C_3H_7	4-$MeOC_6H_4$	3,5-Dimethoxy	69 (**4h**)

[a] All products were characterized by ^1H NMR, ^{13}C NMR, and MS.

In summary, a novel approach to construct 1*H*-inden-1-one was described. The indenone/indanone skeleton is a fairly common benzannulated motif in many natural products.[9] Because of their exciting pharmacological properties, e.g., cytotoxic,[10,11] anti-HIV,[11] and antibacterial activies,[12] much attention has been paid to the synthesis of these molecules and several synthetic methods have been developed to construct their skeleton.[13] Further applications of this methodology in natural product synthesis are being pursued in our laboratory.

Acknowledgment

The authors are grateful for the generous financial support by the Special Doctorial Program Funds of the Ministry of Education of China (20040730008), A Hundred Talents Program of CAS, NSFC (QT program, No.20372026) and the Key Grant Project of Chinese Ministry of Education (No.105169).

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(6) **General Reaction Procedure.**
Compound **3** (1 mmol) was dissolved in DMF (5 mL); K_2CO_3 (200 mol%), $Pd(OAc)_2$ (5 mol%) and PPh_3 (15 mol%) were added in turn. The reaction was heated to 80 °C and stirred for 24 h. The reaction mixture was extracted with Et_2O (3 × 20 mL), washed with brine, dried with Na_2SO_4, filtered and evaporated under reduced pressure. The product **4** was purified by column chromatography on silica gel using PE–EtOAc as eluent.

(7) **Spectroscopic Data.**
4,6-Dimethoxy-3-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-1*H*-inden-1-one (2).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.7 Hz, 2 H), 6.85 (s, 1 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.49 (d, *J* = 2.1 Hz, 2 H), 6.43 (s, 2 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.69 (s, 6 H), 3.60 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.6, 162.4, 160.1, 158.6, 156.5, 154.6, 136.9, 134.0, 130.9, 130.5, 123.5, 114.2, 108.0, 103.9, 102.6, 100.9, 55.8, 55.6, 55.3, 55.1. ESI-HRMS: *m/z* calcd for $C_{26}H_{25}O_6$ $[M + H]^+$: 433.1646; found: 433.1648.
2,3-Diphenyl-1*H*-inden-1-one (4a).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 6.0 Hz, 1 H), 7.40–7.42 (m, 4 H), 7.35–7.39 (m, 2 H), 7.24–7.26 (m, 6 H), 7.14 (d, *J* = 6.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.5, 155.3, 145.2, 133.4, 132.6, 130.7, 129.9, 129.6, 129.3, 128.9, 128.7, 128.5, 128.0, 127.7, 126.3, 122.9, 121.2. ESI-HRMS: *m/z* calcd for $C_{21}H_{15}O$ $[M + H]^+$: 283.1117; found: 283.1114.
3-(4-Methoxyphenyl)-1*H*-inden-1-one (4b).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.2 Hz, 2 H), 7.76 (d, *J* = 15.6 Hz, 1 H), 7.47–7.61 (m, 3 H), 7.39 (d, *J* = 15.6 Hz, 1 H), 6.92 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.6, 161.6, 144.7, 138.4, 132.5, 130.2, 128.5, 128.3, 127.5, 119.7, 114.3, 55.3. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}O$ $[M + H]^+$: 221.0966; found: 221.0963.
2-(4-Methoxyphenyl)-3-phenyl-1*H*-inden-1-one (4c).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 6.3 Hz, 1 H), 7.41–7.43 (m, 5 H), 7.28–7.41 (m, 3 H), 7.20 (d, *J* = 6.3 Hz, 2 H), 7.09 (d, *J* = 7.2 Hz, 1 H), 6.78 (d, *J* = 6.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 159.1, 153.7, 145.5, 133.4, 132.9, 131.8, 131.2, 130.6, 129.1, 128.7, 128.6, 128.4, 123.0, 122.8, 120.9, 113.6, 55.1. ESI-HRMS: *m/z* calcd for $C_{22}H_{17}O_2$ $[M + H]^+$: 313.1223; found: 313.1225.
3-(4-Methoxyphenyl)-2-phenyl-1*H*-inden-1-one (4d).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.2 Hz, 1 H), 7.19–7.38 (m, 11 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 3.85 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.4, 160.4, 155.2, 145.1, 133.2, 131.6, 131.0, 130.2, 129.9, 128.8, 128.1, 127.5, 126.1, 124.7, 122.7, 121.2, 114.1, 55.2. ESI-HRMS: *m/z* calcd for $C_{22}H_{17}O_2$ $[M + H]^+$: 313.1223; found: 313.1223.
3-(4-Nitrophenyl)-2-phenyl-1*H*-inden-1-one (4e).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.1 Hz, 2 H), 7.60 (d, *J* = 7.2 Hz, 1 H), 7.55 (d, *J* = 8.1 Hz, 2 H), 7.19–7.44 (m, 7 H), 7.07 (d, *J* = 6.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 152.2, 147.9, 144.2, 139.5, 134.0, 133.8, 130.1, 129.8, 129.5, 129.4, 128.3, 124.1, 123.5, 120.8. FAB-MS: *m/z* = 328.1, 307.2.
4,6-Dimethoxy-3-phenyl-1*H*-inden-1-one (4f).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 6.9 Hz, 2 H), 7.42–7.48 (m, 3 H), 6.81 (d, *J* = 1.8 Hz, 1 H), 6.44 (d, *J* = 1.8 Hz, 1 H), 5.69 (s, 1 H), 3.85 (s, 3 H), 3.68 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.5, 166.3, 163.1, 136.1, 134.9, 130.9, 129.7, 127.8, 127.6, 122.1, 107.2, 103.2, 102.6, 55.8, 54.3. ESI-HRMS: *m/z* calcd for $C_{17}H_{14}O_3Na$ $[M + Na]^+$: 289.0835; found: 289.0832.
2-(4-Methoxyphenyl)-3-(4-nitrophenyl)-1*H*-inden-1-one (4g).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.7 Hz, 2 H), 7.56–7.60 (m, 3 H), 7.36–7.41 (m, 1 H), 7.25–7.32 (m, 1 H), 7.15 (d, *J* = 9.0 Hz, 2 H), 7.02 (d, *J* = 6.9 Hz, 1 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 3.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 159.7, 150.6, 147.8, 144.6, 140.0, 133.7, 133.5, 131.2, 130.1, 129.6, 129.0, 124.1, 123.4, 121.9, 120.4, 113.9, 55.2. IR (KBr): 1710, 1602, 1512, 1456, 1343, 1292, 1250, 1177 cm^{-1}. FAB-MS: *m/z* = 356.9, 341.9.
2,3-Dihydro-4,6-dimethoxy-3-(4-methoxyphenyl)-2-propylideneinden-1-one (4h).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 11.7 Hz, 2 H), 6.92 (s, 1 H), 6.73–6.83 (m, 3 H), 6.56 (s, 1 H), 4.92 (s, 1 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.64 (s, 3 H), 1.94–2.15 (m, 2 H), 0.88 (t, *J* = 7.5, 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9, 161.3, 157.8, 157.5, 141.5, 140.4, 139.5, 136.1, 134.1, 129.1, 113.3, 106.1, 96.4, 55.7, 55.5, 55.0, 44.1, 22.4, 12.3. MS (EI): *m/z* (%) = 338 (14) [M^+], 245 (43), 166 (72), 138 (100).

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