

Palladium-Catalyzed Carbonylative Cyclization of Unsaturated Aryl Iodides and Dienyl Triflates, Iodides, and Bromides to Indanones and 2-Cyclopentenones

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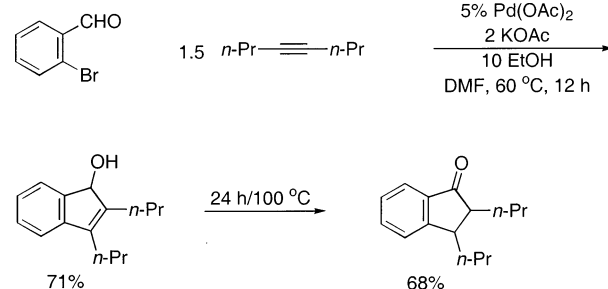
Abstract: Indanones and 2-cyclopentenones have been successfully prepared in good to excellent yields by the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides, respectively. The best results are obtained by employing 10 mol % of Pd(OAc)₂, 2 equiv of pyridine, 1 equiv of *n*-Bu₄NCl, 1 atm of CO, a reaction temperature of 100 °C, and DMF as the solvent. This carbonylative cyclization is particularly effective on substrates that contain a terminal olefin. The proposed mechanism for this annulation includes (1) Pd(OAc)₂ reduction to the active palladium(0) catalyst, (2) oxidative addition of the organic halide or triflate to Pd(0), (3) coordination and insertion of carbon monoxide to produce an acylpalladium intermediate, (4) acylpalladation of the neighboring carbon-carbon double bond, (5) reversible palladium β-hydride elimination and re-addition to form a palladium enolate, and (6) protonation by H₂O to produce the indanone or 2-cyclopentenone.

Introduction

2-Cyclopentenones are found in many natural products or used as building blocks for the development of other biologically active compounds. For instance, tetrahydrodicranenone **B** has shown antimicrobial and antihypertensive properties,¹ while indanocine has been identified as having antiproliferative activity.² Because of the importance of 2-cyclopentenones³ and indanones,⁴ numerous synthetic methods for their preparation have been developed.

A number of palladium-catalyzed annulation processes have been reported for the synthesis of carbo- and heterocycles.⁵ Yamamoto et al. have synthesized indenols and indanones through a palladium-catalyzed annulation of internal alkynes by aromatic aldehydes (Scheme 1).⁶ A number of substituted indenol derivatives have been prepared by treating *o*-bromobenzaldehydes with various internal alkynes in the presence of a palladium catalyst. Upon further heating, these indenol deriva-

Scheme 1



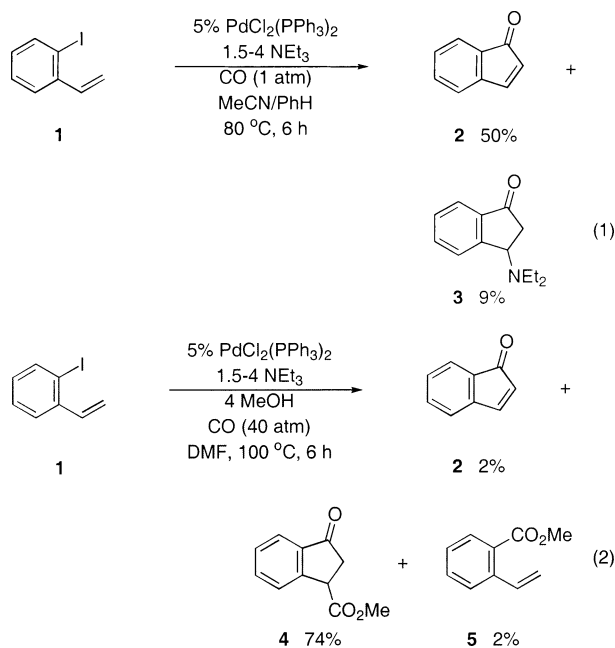
tives isomerize to the corresponding indanones. We have also reported the synthesis of indenones using similar starting materials and slightly modified palladium conditions.⁷

Negishi and co-workers have extensively explored palladium-catalyzed carbonylative cyclization reactions which produce a variety of cyclic ketones. They were able to produce 2-cyclopentenones and indanones through the palladium-catalyzed carbonylation of 1-iodo-1,4-alkadienes and *o*-iodostyrene derivatives.⁸ When *o*-iodostyrene (**1**) was reacted under their palladium conditions without MeOH present, indenone **2** and indanone **3** were produced in 50 and 9% yields, respectively (eq 1). When MeOH was added to the reaction and the amount of CO was increased to 40 atm, **2** was produced in a 2% yield along with a 74% yield of indanone **4** and a 2% yield of ester **5** (eq 2).

We wish to report at this time a novel palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl

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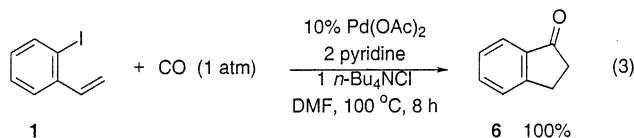
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triflates, iodides, and bromides which provides a highly efficient new route to indanones and 2-cyclopentenones, respectively.

Results and Discussion

Our initial work was aimed at developing a set of palladium conditions that would work well for a variety of substrates to produce 2-cyclopentenones and indanones. The original set of palladium conditions used included 10 mol % Pd(OAc)₂, 2 equiv of pyridine, 1 equiv of *n*-Bu₄NCl, 1 atm of CO, DMF as the solvent, and a reaction temperature of 100 °C. These carbonylative palladium conditions were developed within the Larock group for the synthesis of coumarins.⁹ Using *o*-iodostyrene as the model system, we discovered that indanone (**6**) was produced in a quantitative yield after 8 h (eq 3). A few experiments were



performed to examine the effect of each key reagent on the yield, beginning with the chloride source. When *n*-Bu₄NCl was removed from the reaction mixture, the reaction time increased to 18 h, and the yield of indanone decreased to 66%. In a second experiment, the amount of pyridine was lowered to 1 equiv, which lowered the yield of **6** to 93%. Also, when the pyridine base was replaced by NEt₃, only a trace of indanone was observed, with no evidence of any other products. Last, the palladium catalyst was reduced to 5 mol %, which increased the reaction time to 18 h and lowered the yield of **6** to 76%. Therefore, the standard conditions for this palladium transformation are those employed in eq 3 (henceforth identified as procedure A).

This palladium-catalyzed carboannulation has been extended to other aryl systems to explore the generality of this reaction and produce substituted indanone derivatives (Table 1). Styryl derivatives that are substituted next to the aromatic ring by either

Table 1. Synthesis of Cyclic Ketones^a

entry	organic substrate	ketone	procedure	time (h)	% yield ^b
1			A	8	100
2			A	12	100
3			A	72	60
4			A	72	0
	3:1 <i>E/Z</i>				
5			A	24	82
6			A	24	45
7			A	24	61
8			A	24	89
9			A	12	95
10			B	72	87
11			A	72	86
12			A	72	85
13			A	72	98
14			B	48	98
15			A	24	70

^a Procedure A includes 10 mol % of Pd(OAc)₂, 2 equiv of pyridine, 1 equiv of *n*-Bu₄NCl, 1 atm of CO, a reaction temperature of 100 °C, and DMF as the solvent. In procedure B, the 10 mol % of Pd(OAc)₂ in procedure A is replaced with 10 mol % pf Pd(dba)₂. ^b All reported yields are for isolated products.

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an aryl or an alkyl group work well (entries 2 and 3). Aryl iodides **7** and **9** both reacted under the standard palladium conditions to provide the desired indanone products **8** and **10** in 100 and 60% yields, respectively. Unfavorable steric interactions between the phenyl group and the organopalladium intermediate may occur during the cyclization, accounting for the lower yield with starting material **9** (see the later mechanistic discussion). Styryl derivative **11**, which contains an internal carbon-carbon double bond, failed to cyclize to the desired indanone (entry 4). Presumably, steric interactions between the aryl- or acylpalladium intermediate and the methyl group do not allow the palladium to add across the carbon-carbon double bond. Starting materials, which contain electron-donating methoxy groups on the arene, cyclize to the desired indanones (entries 5 and 6). However, when a methoxy group is placed *ortho* to the iodide, the yield drops substantially, presumably due to steric hindrance to oxidative addition (entry 6).

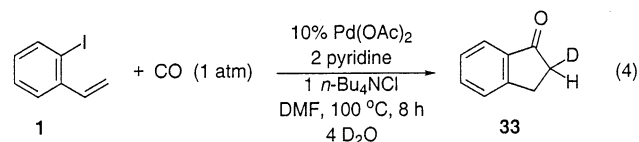
In addition to reactions which form 5,6 ring-fused ketones, a few examples have been attempted which would lead to a 5,5 ring-fused system. However, both heterocyclic iodide **17** and vinylic triflate **19** produced simple carboxylic acid derivatives, rather than the desired cyclic ketones (entries 7 and 8). The failure of these substrates to cyclize to the ketones can be attributed to the ring strain introduced in trying to form a 5,5 ring-fused system. The anticipated acylpalladium intermediate may not be able to properly coordinate to the nearby olefin and subsequently add across the carbon-carbon double bond. Instead, the corresponding hydrolysis products **18** and **20** are produced.

Vinylic derivatives, which contain a triflate, bromide, or iodide, are able to cyclize to 5,6 ring-fused cyclopentenones efficiently (entries 9–11). Vinylic triflate **21** reacted under the standard palladium conditions to produce cyclopentenone **22** in a 95% yield after 12 h (entry 9). The corresponding vinylic bromide **23** and vinylic iodide **24** also gave high 87 and 86% yields, respectively, of cyclopentenone **22** (entries 10 and 11). However, the reaction times for both **23** and **24** increased to 72 h. It should also be noted that vinylic bromide **23** required 10 mol % of Pd(*dba*)₂, instead of 10 mol % Pd(OAc)₂, as the palladium catalyst (procedure B). When **23** was allowed to react using Pd(OAc)₂ as the catalyst, palladium black precipitated out of solution after only 1 h, and only a trace of indanone **22** was detected after 72 h. Precipitated palladium black was only found when reacting vinylic bromides and no other starting materials. Vinylic iodides **25** and **27**, which were synthesized from α - and β -tetralone, respectively, also produced high 85 and 98% yields, respectively, of the corresponding cyclopentenones (entries 12 and 13).

A 5,7 ring-fused cyclopentenone has also been prepared from vinylic bromide **29** in a 98% yield (entry 14). Finally, acyclic vinylic iodide **31** afforded cyclopentenone **32** in a 70% yield after 24 h (entry 15).

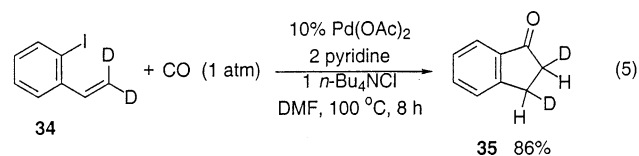
The mechanism for this process was not clearly understood initially, because the products differed significantly from those reported in Negishi's earlier work.^{8,10} Negishi's products (see eq 2) are presumably derived from the β -hydride elimination of an organopalladium intermediate to form indenones or insertion of a second CO under high pressures to form ester

derivatives. In our system, a proton is incorporated into the product to form the indanone or 2-cyclopentenone. One possible source of this proton might be the solvent DMF. Therefore, an experiment was carried out replacing DMF with DMA under the standard palladium conditions and employing **1** as the starting material. It was discovered that indanone (**6**) was still produced in a near quantitative yield in the same 8 h reaction time. A second possible proton source is water. Water could be introduced into the system by either *n*-Bu₄NCl or DMF, because both of these materials are hygroscopic. Another experiment was carried out with **1**, in which 4 equiv of D₂O was added (eq 4).



The indanone product recovered in a 95% yield contained 55% deuterium in the 2-position, and no deuterium incorporation was found in the 3-position. In a separate experiment, it was found that indanone itself will incorporate 55% deuterium at the 2-position under the standard palladium conditions when 4 equiv of D₂O is added. Therefore, the results from the experiment in eq 4 only suggest that the palladium intermediate formed after addition across the carbon-carbon double bond does not directly incorporate a proton from water. The deuterium is apparently only introduced later, after the indanone product has been formed.

In another mechanistic reaction, styryl derivative **34**, which contains two deuteria at the terminal positions of the olefin, was allowed to react under the standard palladium conditions (eq 5). Indanone was obtained in an overall 86% yield. It was

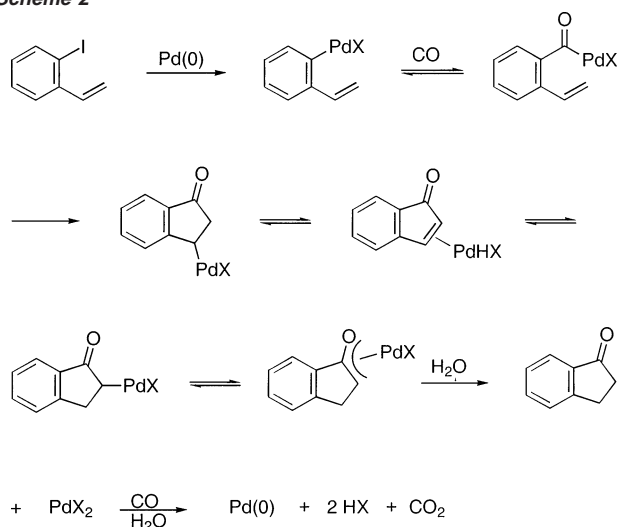


found that 35% deuterium was incorporated into the 3-position and 12% deuterium was incorporated into the 2-position. The deuterium incorporation in the 3-position suggests that a deuterium is migrating from the 2-position. The relatively low percentage of deuterium at the 2-position can be explained by deuterium-proton exchange occurring with the H₂O present under the reaction conditions, after the 2,3-dideuterioindanone is formed. From these mechanistic studies, the following mechanism for this transformation is proposed (Scheme 2): (1) Pd(OAc)₂ reduction to the active palladium(0) catalyst; (2) oxidative addition of the aryl iodide to Pd(0); (3) coordination and insertion of carbon monoxide to produce an acylpalladium intermediate; (4) acylpalladation of the neighboring carbon-carbon double bond; (5) reversible palladium β -hydride elimination and re-addition to form a palladium enolate; and (6) protonation by H₂O to produce the indanone and a Pd(II) salt, which is once again reduced to Pd(0).

Indenone was also prepared and reacted under the standard palladium conditions to see if it can be reduced to indanone. After 12 h, the only material found in the reaction mixture was indenone itself, which was recovered in an 80% yield. This

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Scheme 2



reaction supports the idea that after the palladium β -hydride elimination, the palladium hydride never dissociates completely from the indenone, but rather adds back to the C–C double bond, eventually forming a palladium enolate. It has been suggested that Hofmann elimination of the *n*-Bu₄NCl salt by pyridine provides the proton which appears in the final product, but omission of the *n*-Bu₄NCl still affords a 66% yield of indenone, ruling out this process as the sole source of protons appearing in the final product. Water present in the reaction mixture appears to be the most likely source of these protons.

Conclusion

Indanones and 2-cyclopentenones have been successfully prepared by the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides in moderate to excellent yields. A number of ketone derivatives have been prepared. However, it has been observed that a terminal olefin is required to obtain high yields; presumably this is due to steric hindrance to alkene insertion by the more hindered olefin. Several bicyclic cyclopentenones containing 5,6 and 5,7 fused-rings have been prepared in excellent yields. However, 5,5 ring-fused products cannot be obtained.

Several mechanistic experiments employing D₂O have been performed which help explain the mechanism for this process. It is likely that this palladium transformation is forming an indenone intermediate, which is coordinated to a palladium hydride species. This palladium hydride adds back across the carbon–carbon double bond to form a palladium enolate, which is protonated by H₂O.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and

visualization was effected with short wavelength UV light (254 nm) and a basic KMnO₄ solution (3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5%) + 300 mL of H₂O). All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High-resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents and Starting Materials. All reagents were used directly as obtained commercially unless otherwise noted. Pyridine, DMF, DMA, THF, hexanes, ethyl acetate, and ethyl ether were purchased from Fisher Scientific Co. *n*-Bu₄NCl was purchased from Lancaster Synthesis, Inc. 1-Indanone, 3,4,5-trimethoxybenzyl alcohol, 3,4-dimethoxybenzaldehyde, cyclohexanone, α -tetralone, β -tetralone, cycloheptanone, ethyl 2-cyclohexanonecarboxylate, ethyl 2-cyclopentanonecarboxylate, 4-octyne, methyltriphenylphosphonium bromide, iodomethane-*d*₃, and *n*-BuLi were purchased from Aldrich Chemical Co., Inc. 2-Iodobenzaldehyde,¹¹ 1-iodo-2-vinylbenzene, 1-iodo-2-isopropenylbenzene,¹⁰ 1-iodo-2-propenylbenzene,¹⁰ 4,5-dimethoxy-2-iodobenzaldehyde,¹² 2-iodo-3,4,5-trimethoxybenzaldehyde,¹³ 4-iodo-3-*n*-propylhepta-1,3-diene,¹⁴ indenone,¹⁵ and (methyl-*d*₃)triphenylphosphonium iodide¹⁶ were prepared according to previous literature procedures.

General Procedure for the Palladium-Catalyzed Carbonylative Cyclization of Unsaturated Aryl Iodides and Dienyl Triflates, Iodides, and Bromides. The appropriate aryl iodide, dienyl triflate, dienyl bromide or dienyl iodide (0.5 mmol), Pd(OAc)₂ (0.05 mmol), pyridine (1.0 mmol), *n*-Bu₄NCl (0.5 mmol), and DMF (5 mL) were placed in a 4 dram vial. The reaction mixture was placed under a CO atmosphere provided by a balloon and allowed to stir at 100 °C for the designated time. The reaction was diluted with saturated aqueous NH₄-Cl (50 mL), extracted with diethyl ether (3 × 25 mL), and dried (Na₂SO₄). The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography.

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Supporting Information Available: Characterization, including ¹H and ¹³C NMR spectra, for all indanones and 2-cyclopentenones in Table 1 and preparative procedures and characterization for compounds **9**, **13**, **15**, **17**, **19**, **21**, **23**, **24**, **25**, **27**, **29**, and **34** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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