J|A|C|S
COMMUNICATIONS

Published on Web 11/09/2002

Novel 1,4-Palladium Migration in Organopalladium Intermediates Derived from *o*-Iodobiaryls

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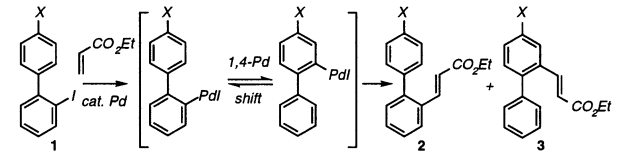
Received July 3, 2002

The extraordinary C−C bond-forming ability of palladium places it among the most versatile and useful metals in organic synthesis. Organopalladium intermediates are often prepared by oxidative addition of an organic halide or triflate to Pd(0), and subsequent C−C bond formation normally occurs at the position originally occupied by the halogen or triflate. Among the most important Pd-catalyzed C−C bond-forming reactions is the Heck reaction for which there are numerous applications in the literature,[1] including a few employing *o*-bromobiaryls.[2]

To our surprise, upon studying the Pd-catalyzed olefination of unsymmetrical *o*-iodobiphenyls with ethyl acrylate, we obtained, under certain modified reaction conditions, the expected *o*-olefinated biphenyl **2** along with the *o*′-olefinated biphenyl **3** (Scheme 1). The observed mixture of Heck products points to the existence of arylpalladium intermediates in which the metal moiety is located in each of the two different ortho positions of the unsymmetrical biphenyl.[3] This through-space relocation of the metal moiety between the ortho positions of biaryls amounts to an overall 1,4-palladium shift, which could possibly involve an intermediate hydridopallada(IV)cycle generated by insertion of palladium into a neighboring C−H bond. The novel palladium migration observed in our *o*-iodobiaryl system is reminiscent of a vinylic-to-aryl palladium rearrangement proposed by us to account for the formation of 9-benzylidene-9*H*-fluorene from diphenylacetylene and iodobenzene.[4]

To obtain a clear picture of how various reaction variables effect the palladium biaryl migration, we have studied the behavior of 2-iodo-4′-methylbiphenyl (X = Me, **1a**) and ethyl acrylate under various reaction conditions (Scheme 2, Table 1). We have found that under the classical reaction conditions described by Jeffrey,[5] the expected ethyl *E*-3-(4′-methylbiphen-2-yl)acrylate (X = Me, **2a**) was obtained exclusively in a quantitative yield (Table 1, entry 1). By simply diluting the reaction mixture 4-fold, we began to observe small amounts of the migration product ethyl *E*-3-(4-methylbiphen-2-yl)acrylate (X = Me, **3a**) (entry 2), and 23% of **3a** was obtained under the more dilute conditions by reducing the number of equivalents of ethyl acrylate from 4 to 1 (entry 3). After exploring a number of organic and inorganic bases, we have obtained nearly equal amounts of the direct olefination product **2a** and the rearranged product **3a** when using CsO_2CCMe_3 (CsPiv) as the base (entry 4). Furthermore, the use of phosphine ligands, such as bis(diphenylphosphino)methane (dppm) and PPh_3, in the reaction further changed the isomer distribution to 50:50 (entries 5 and 6). It is important to note at this point that by manipulating the reaction conditions, we can switch the palladium migration "on" or "off" in this biphenyl system. Thus, our optimal migration conditions for activating palladium migration are those described in entry 5 of Table 1, and the conditions to prevent this process are those described in entry 1.

Scheme 1



Scheme 2

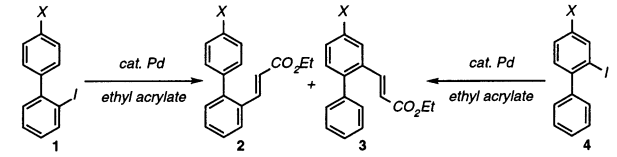


Table 1. Pd-Catalyzed Reaction of 2-Iodo-4′-methylbiphenyl (**1a**) and Ethyl Acrylate (EA)[a]

entry	EA equiv	conditions	time (d)	mol ratio **2a** : **3a**[b]	% yield
1	4	TBAC, $NaHCO_3$[c]	1.0	100:0	100
2	4	TBAC, $NaHCO_3$	1.0	95:5	100
3	1	TBAC, $NaHCO_3$	1.0	77:23	92
4	1	CsPiv	1.5	54:46	93
5	1	5% dppm, CsPiv	1.5	50:50	88
6	1	10% PPh_3, CsPiv	1.5	50:50	87

[a] Reaction was run using 0.25 mmol of the iodobiaryl, ethyl acrylate (EA), 2 equiv of an appropriate base, and 1 equiv of *n*-Bu_4NCl (TBAC) where indicated in 4 mL of DMF at 100 °C unless otherwise indicated. [b] Mol ratio was determined by ^1H NMR spectroscopic analysis. [c] 1 mL of DMF.

An obvious question to answer is whether under our standard reaction conditions 2-iodo-4-methylbiphenyl (X = Me, **4a**) and ethyl acrylate would generate the same distribution of isomers **2a** and **3a** as previously obtained from **1a** and ethyl acrylate. Indeed, substrate **4a** generated a 49:51 mixture of isomers **2a** and **3a** in an 86% yield under our optimized migration conditions (Scheme 2). This interesting result seems to indicate that under our reaction conditions, the arylpalladium intermediates generated from either **1a** or **4a** undergo apparent equilibration prior to olefin-trapping to generate essentially identical mixtures of **2a** and **3a**. Furthermore, under the conditions described by Jeffrey and illustrated in entry 1 of Table 1, 2-iodo-4-methylbiphenyl (**4a**) undergoes the usual Heck reaction with ethyl acrylate to produce exclusively **3a** in 93% yield (Scheme 2).

The palladium-catalyzed reaction of methoxy-substituted iodobiphenyls with ethyl acrylate gave nearly identical results to those obtained with their methyl-substituted counterparts. Again, we can switch "off" the palladium migration by running the reaction under Jeffrey's conditions. Thus, under the reaction conditions described in entry 1 of Table 1, 2-iodo-4′-methoxybiphenyl (X = OMe, **1b**)

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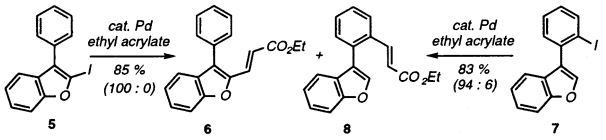
10.1021/ja027548l CCC: $22.00

Scheme 3

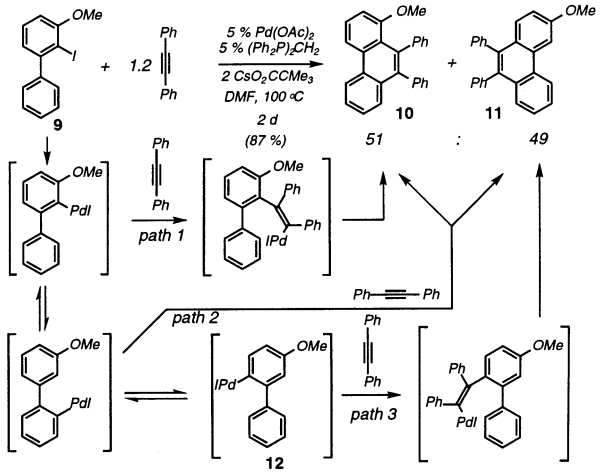


generates exclusively ethyl *E*-3-(4-methoxybiphen-2-yl)acrylate (X = OMe, **2b**) in a quantitative yield, and 2-iodo-4′-methoxybiphenyl (X = OMe, **4b**) produces exclusively ethyl *E*-3-(4-methoxybiphen-2-yl)acrylate (X = OMe, **3b**) in 99% yield. Furthermore, we can switch "on" the palladium migration by running the reaction under our standard migration conditions in which case **1b** produces a 52:48 mixture of isomers **2b** and **3b**, respectively, in a 93% yield. Similarly, substrate **4b** produced a 48:52 mixture of **2b** and **3b**, respectively, in 92% yield (Scheme 2). These results validate the idea that our reaction conditions promote palladium migration between the *o*-positions of these biphenyls. What is perhaps a bit surprising is that there does not seem to be any pronounced electronic effect of a Me or OMe group in these migrations. Currently, we are investigating this reaction using substituted biphenyls bearing electron-withdrawing groups.

A more marked effect on the product distribution was observed in the reaction of 2-iodo-3-phenylbenzofuran (**5**) and ethyl acrylate, which under our standard migration conditions gives exclusively ethyl *E*-3-(3-phenylbenzofuran-2-yl)acrylate (**6**) in 85% yield (Scheme 3). This unexpected result showing no apparent 1,4-Pd shift suggested one of two things in this biaryl system. Either palladium has a strong preference for the more electron-rich 2-position of the benzofuran moiety, or the two possible arylpalladium intermediates generated by palladium migration have different reactivities toward the olefin. In either case, olefination occurs on the 2-position of the benzofuran moiety exclusively. When 3-(2-iodophenyl)benzofuran (**7**) was allowed to react with ethyl acrylate under our standard migration conditions, **6** was produced in a 78% yield alongside only ~5% of isomer **8** (Scheme 3), clearly indicating a preference for palladium migration from the phenyl to the benzofuran ring. Furthermore, ethyl *E*-3-[2-(benzofuran-3-yl)phenyl]acrylate (**8**) was obtained exclusively in a 75% yield from **7** when using the reaction conditions described by Jeffrey at 80 °C for 1 d.

To further explore the scope of this migration process, we have carried out the palladium-catalyzed reaction of diphenylacetylene and 2-iodo-3-methoxybiphenyl (**9**) in the hope that the arylpalladium intermediates generated by a 1,4-Pd shift could be trapped by way of alkyne insertion−annulation chemistry described earlier by us.[6] First, the reaction was carried out under the conditions described previously by us employing 1.2 equiv of the acetylene, 5 mol % $Pd(OAc)_2$, 1 equiv of LiCl, and 2 equiv of NaOAc in DMF at 100 °C for 2 d, and we obtained the expected 1-methoxy-9,10-diphenylphenanthrene (**10**) in 90% yield (Scheme 4, path 1). We then switched "on" the palladium migration by allowing **9** to react with 1.2 equiv of diphenylacetylene under our standard migration conditions to obtain a 51:49 mixture of phenanthrenes **10** and **11**, respectively, in 87% overall yield (Scheme 4). The mechanism for the formation of phenanthrenes **10** and **11** is described in Scheme 4. It is important to note that in these alkyne reactions the formation of product **11** cannot arise directly from the intermediacy of a simple bridged pallada(II)cycle,[7] but instead its formation requires complete migration of the palladium moiety from the methoxy-bearing ring to the other aromatic ring. These interesting migration results with

Scheme 4



alkenes and alkynes suggest that there is the exciting possibility of trapping aryl- and other organopalladium intermediates generated by 1,4-Pd shifts by many other synthetically useful palladium methodologies. We are currently examining this possibility.

In conclusion, we have been able to establish a novel 1,4-palladium shift in arylpalladium intermediates generated from *o*-iodobiaryls. This migration of palladium has been established by trapping the arylpalladium intermediates generated by this process by way of a Heck reaction, as well as alkyne annulation methodology. There appear to be important electronic effects dictating the reactivity and apparent equilibrium between the palladium intermediates, which is reflected in the isomer distribution of the Heck type products. This migration process can be switched "on" and "off" by simply choosing the appropriate reaction conditions. We continue to explore the scope, mechanism, and synthetic utility of this novel palladium migration chemistry.

Acknowledgment. We acknowledge useful discussions of this work with Professor Timothy Gallagher, who has simultaneously observed similar Pd migration chemistry.[3] We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society and the National Science Foundation, for partial support of this research. Thanks are also extended to Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., for donating the $Pd(OAc)_2$ and PPh_3.

Supporting Information Available: General experimental procedures and spectroscopic characterization of all new products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA027548L