

Carbocycle Synthesis via Carbopalladation of Nitriles

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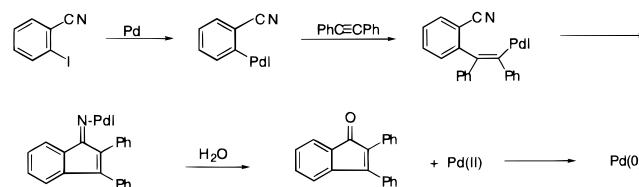
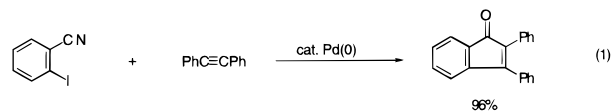
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The extraordinary utility of palladium in organic synthesis in recent years is due in large part to the unique ability of palladium to form carbon–carbon bonds without protecting most important functional groups.¹ Thus, alcohols, amines, aldehydes, ketones, carboxylic acids, and derivatives are generally readily accommodated by organopalladium intermediates under conditions where carbon–carbon bond formation is facile. There are also a number of examples of simple ortho- and para-substituted aromatic nitriles readily undergoing palladium-catalyzed processes without involvement of the nitrile functionality.² In fact, palladium chloride bis-acetonitrile and bis-benzonitrile are widely used reagents and acetonitrile is one of the most commonly employed solvents in organopalladium chemistry. In exploring the scope of the hetero- and carboannulation of alkenes, dienes, and alkynes,³ we have recently observed that simple nitrile groups can actively participate in these annulation processes when the carbopalladation step involved is intramolecular.⁴ We report here our preliminary observations on the synthesis of carbocycles via carbopalladation of nitriles.

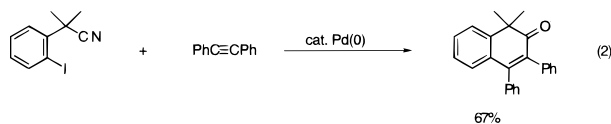
We have recently reported that the carboannulation of internal alkynes by *o*-iodobenzaldehyde provides a useful new synthetic approach to indenones.^{3c} In exploring the palladium chemistry of *o*-iodobenzonitrile, we have made the unusual observation that this substrate will undergo facile carboannulation of diphenylacetylene to afford high yields of the corresponding 2,3-diphenylindenone (eq 1). The best reaction conditions thus far observed employ 10% Pd(dba)₂, 3 equiv of alkyne, 1 equiv of

Scheme 1

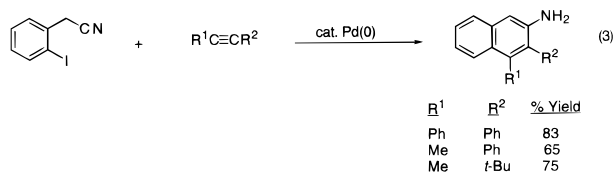
Et₃N, and 9:1 DMF–water as the solvent at 130 °C for 24 h.

This process appears to involve arylpalladium formation and subsequent alkyne insertion to produce a vinylic palladium intermediate, which then adds across the carbon–nitrogen triple bond of the nitrile to produce a palladium imine intermediate, which hydrolyzes to the corresponding ketone (Scheme 1). Subsequent reduction of the palladium(II) salt produced is required to afford a catalytic process. Presumably, the triethylamine employed by us is effecting this reduction.

This chemistry appears to be quite general, since we have found that the analogous chemistry of 2-*o*-iodophenyl-2-methylpropanenitrile and diphenylacetylene affords high yields of the expected six-membered ring aromatic ketone (eq 2), by what is assumed to be an analogous mechanism.

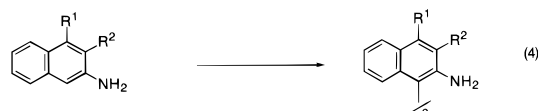


When *o*-iodophenylacetonitrile was employed instead of 2-*o*-iodophenyl-2-methylpropanenitrile, we were surprised to find that high yields of β -naphthylamines were obtained instead (eq 3).



Our best present reaction conditions for this process involve 5 mol % Pd(OAc)₂, 3 equiv of alkyne, 2 equiv of Et₃N, and 1 equiv of *n*-Bu₄NCl in DMF at 100 °C for 48 h. This afforded an 83% yield of 2-amino-3,4-diphenylindole from diphenylacetylene. 1-Phenylpropyne and 3,3-dimethyl-2-butyne (5 equiv of alkyne and 2 equiv of water were added) afforded 65 and 75% yields, respectively, of the corresponding β -naphthylamines in which the bulkier substituent of the alkyne resides exclusively in the 3-position, as noted in all of our previous annulation chemistry.³

This particularly convenient synthesis of hindered β -naphthylamines affords readily available starting materials for the synthesis of 2,2'-diamino-1,1'-binaphthyls, substrates proving increasingly useful as ligands in organic chemistry (eq 4).⁵



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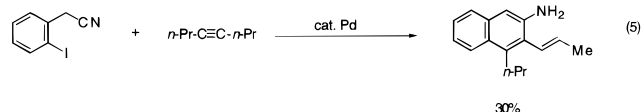
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It appears that a similar alkyne/nitrile carbopalladation process is involved in this synthesis of β -naphthylamines but that the intermediate palladium imine is undergoing tautomerization before hydrolysis, resulting in the amine products, rather than ketones. Presumably, tautomerization and reduction of the palladium(II) salt are again being effected by the triethylamine present in the reaction. It is noteworthy, however, that the yields of β -naphthylamines are substantially lower if the solvent DMF is replaced by other polar solvents, such as DMA, DMSO, or acetonitrile. Thus, the solvent may also be playing a key role in reducing the palladium.

When 4-octyne (5 equiv) was employed as the acetylene, the yield of product dropped substantially, but to our surprise, the major product obtained in 30% yield was 2-amino-3-(1-propenyl)-4-*n*-propylphthalene (eq 5). The precise mechanism by which



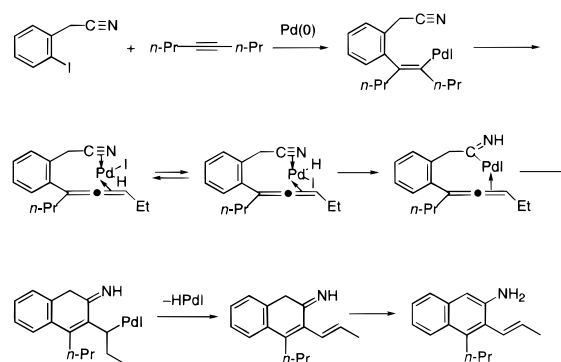
this product is formed remains uncertain, but it appears that some kind of allene intermediate may be involved as shown in Scheme 2. This process may be related mechanistically to Trost's palladium-catalyzed cyclization of 1,6-enynes.⁵

In our preliminary studies of the scope of this nitrile annulation chemistry, we have found that bicyclic alkenes also undergo facile carboannulation by *o*-iodobenzonitrile. For example, norbornene affords a 93% yield of the bicyclic aryl ketone, and bicyclo[2.2.2]oct-2-ene produces the anticipated product in 82% yield (eq 6). This is the first example of this type of carboannulation of a bicyclic alkene. In this case, palladium hydride elimination in the bicyclic palladium intermediate is prevented by the inability

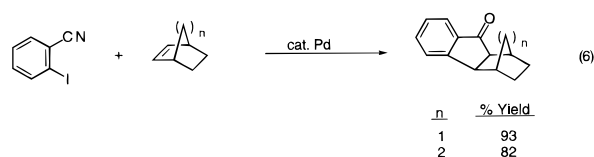
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Scheme 2



of the palladium and the bridgehead hydrogen to align in a *cis* fashion and, if elimination were to occur, would produce a very strained bridgehead olefin.



In conclusion, the carbon–nitrogen triple bond of simple aryl nitriles has been observed to readily participate in organopalladium annulation reactions. 2-Iodobenzonitrile and 2-iodophenylacetone nitriles react with internal alkynes and bicyclic alkenes to form indenones, naphthenones, 2-aminonaphthalenes, and bicyclic aryl ketones in good yields. This chemistry suggests that there may be many other organopalladium processes which will occur intramolecularly that normally will not occur by intermolecular processes.

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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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