Intramolecular Oxycyanation of Alkenes by Cooperative Pd/BPh₃ Catalysis

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Ⓢ *Supporting Information*

ABSTRACT: The cooperative catalysis by palladium and triphenylborane effects the intramolecular oxycyanation of alkenes through the cleavage of O−CN bonds and the subsequent insertion of double bonds. The use of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) as a ligand for palladium is essential for allowing the transformation to proceed with high chemo- and regioselectivity. Variously substituted dihydrobenzofurans with both a tetra-substituted carbon and cyano functionality are accessed by the newly developed methodology.

Nitriles are an important class of organic compounds, which are found in a number of pharmaceuticals, agrochemicals, and optoelectronic materials. They also serve as versatile synthetic intermediates for carboxylic acids, esters, amides, and amines. Accordingly, the development of novel and efficient synthetic methods for nitriles has been a major topic in synthetic organic chemistry.[1] Metal-catalyzed cyanation reactions of unsaturated compounds such as alkenes and alkynes to access a variety of nitriles in highly chemo- and stereoselective manners have thus gained much interest. Hydrocyanation typically represents the utility of such cyanation reactions and has been performed on an industrial scale, as demonstrated in DuPont's adiponitrile process.[2] In addition to the production of such bulk chemicals, cyanation reactions should be of great synthetic potential to access fine chemicals with defined functionalities and stereochemistry. In particular, metal-catalyzed cyanofunctionalization reactions, in which both cyano and other functional groups are installed simultaneously, have gained increasing attention in the past decade (eq 1).
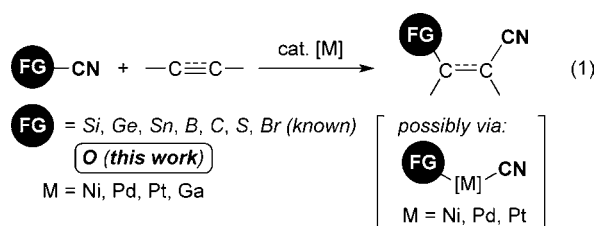
These transformations include silylcyanation,[3] germylcyanation,[4] stannylcyanation,[5] borylcyanation,[6] carbocyanation,[7] thiocyanation,[8] and bromocyanation.[9]

Most cyanofunctionalization reactions rely on the cleavage of FG−CN bonds by electron-rich late transition metal complexes such as nickel(0), palladium(0), and platinum(0) through oxidative addition as a key step in their proposed catalytic cycles. We have demonstrated that the use of Lewis acid cocatalysts significantly affects the rate of nickel-catalyzed carbocyanation reactions,[10] possibly by promoting the oxidative addition of C−CN bonds[11] through coordination of a cyano group to a Lewis acid catalyst in an η^1-fashion, which allows the oxidative addition of C−CN bonds to nickel(0) to proceed smoothly.[12] We envisaged that cooperative catalysis for C−CN activation may be key to further develop other cyanofunctionalization reactions through the cleavage of unreactive FG−CN bonds. We therefore focused our attention particularly on the oxycyanation reaction of unsaturated compounds, which should be a useful synthetic transformation to access functionalized nitriles because both oxygen and cyano functionalities can be installed simultaneously.[13] O−CN bonds of cyanates can be considered strong based on their bond lengths, which lie between those of O−C single bonds and O═C double bonds.[14] Indeed, the catalytic cleavage of O−CN bonds has never been reported until very recently,[15] whereas some nucleophiles are known to react with cyanates through the cleavage of O−CN bonds in a stepwise manner.[16] We report herein that cooperative Pd/BPh₃ catalysis allows chemo- and regioselective intramolecular oxycyanation of alkenes, a novel entry to cyanofunctionalization reactions, to proceed for the first time to afford substituted dihydrobenzofurans having both a tetra-substituted carbon and cyano functionality.

To prove the viability of the oxycyanation reaction through O−CN bond activation by cooperative catalysis, we first examined the reaction of 1-cyanato-2-(2-methylallyl)benzene (**1a**), which is readily available from phenol via *O*-methallylation followed by the Claisen rearrangement and subsequent cyanation of the resulting phenolic oxygen.[17] After screening several combinations of metal complexes, ligands, and Lewis acids, we found that the use of Pd₂(dba)₃ (5 mol % Pd), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos)[18] (5 mol %), and BPh₃ (10 mol %) allowed the expected transformation to proceed in a 5-*exo*-trig manner for affording 2-(cyanomethyl)-2-methyl-2,3-dihydrobenzofuran (**2a**) in 85% yield after 3 h in THF at 50 °C (entry 1 of Table 1). The Pd/Xantphos catalyst is exceptionally effective for this reaction; neither Ni(cod)₂, the catalyst of choice for the

Table 1. Intramolecular Oxycyanation of Alkenes Catalyzed by Pd/BPh$_3$

entry	substrate	time (h)	product	yield (%)[a]
1[b,c,d]	1a	3	2a	85
2[b,c,d]	1b	3	2b	88
3[b,c,d,e]	1c	1	2c	71
4[b,f]	1d	1	2d	79
5	1e	2	2e	51
6	1f	2	2f	43
7[g,h,i]	1g	2.5	2g	44
8[b]	1h	1	2h	78
9	1i	2	2i	90
10[c]	1j	16	2j	64
11[c,e]	1k	2	2k	71
12[j]	1l	2	2l	60
13[h]	1m	3	2m	60

[a] Isolated yields based on **1**. [b] Run on a 1.0 mmol scale. [c] Run with 5 mol % of the Pd/Xantphos catalyst and 10 mol % of BPh$_3$. [d] Run at 50 °C. [e] Run with Pd[(o-tol)$_3$P]$_2$ instead of Pd$_2$(dba)$_3$. [f] Run at 90 °C. [g] Run at 100 °C. [h] Run with Nixantphos instead of Xantphos. [i] Run with 40 mol % of BPh$_3$. [j] Run on a 0.20 mmol scale.

carbocyanation reactions,[7] nor other mono- and diphosphanes give less than 5% yields at most.[19] In many cases, decyanation of the cyanate moiety was observed to mainly give parent phenols, suggesting that the cleavage of the O−CN bonds may be relatively facile by the cooperative catalysis compared with the subsequent insertion of alkenes (*vide infra*). Among the aluminum- and boron-based Lewis acids examined, BPh$_3$ was particularly effective; AlEt$_3$ gave a modest yield and BEt$_3$ and AlPh$_3$ were futile, whereas the absence of the Lewis acid cocatalyst showed poor conversion of the cyanates under otherwise identical conditions.[19] Various substituents on the benzene ring in **1a** were compatible with the optimized reaction conditions to give the corresponding dihydrobenzofurans in modest to good yields (entries 2−10). Substrates with an electron-donating substituent at the *para*-position of the cyanato group gave better yields than those with an electron-withdrawing substituent; the latter suffered from decyanation, presumably owing to reluctant oxypalladation with less nucleophilic oxygen (*vide infra*). Nevertheless, the chemo-selective activation of O−CN bonds over Ar−Br bonds by palladium catalysis would be worth noting (entry 6).[20] An electron-withdrawing alkoxycarbonyl group at the *meta*-position of the cyanato substituent did not affect the oxycyanation reaction (entry 8). Sterically demanding sub-stituents at the *ortho*-position were also tolerated (entries 9 and 10). Different alkyl substituents on the double bond of **1a** were briefly examined to obtain the corresponding dihydrobenzofur-ans in acceptable yields (entries 11 and 12), whereas simple 1-cyanato-2-allylbenzene (R^1 = R^2 = H) gave only a trace amount of the product (<5% by GC), presumably owing to β-hydride elimination, which may compete with the desired C−CN bond-forming reductive elimination (*vide infra*). Finally, six-membered ring formation was successfully performed using Nixantphos as a ligand, whereas Xantphos gave **2m** in 10% yield at most as estimated by GC (entry 13). A slightly larger bite angle of Nixanthpos (114° vs 111° for Xantphos)[18] may be crucial for the six-membered ring-forming oxypalladation step (vide infra), although the rationale for its effect is yet to be investigated.

Scheme 1. Plausible Catalytic Cycle
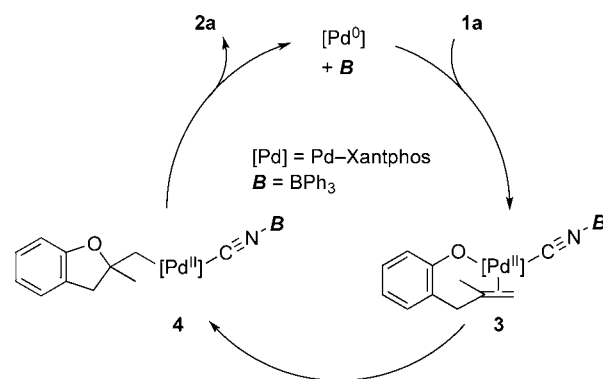
The reaction path is understood in terms of the catalytic cycle shown in Scheme 1 with **1a**. The O−CN bond in **1a** undergoes the oxidative addition to a Pd(0)−Xantphos complex to give **3**, in which the cyano group coordinates to BPh$_3$, as observed with the oxidative addition of C−CN bonds to nickel(0) in the presence of Lewis acids.[12,21] *Syn*-oxypalladation[22] takes place in a 5-*exo*-trig manner to give

(alkyl)(cyano)palladium(II) species **4**, which reductively eliminates **2a**, and the catalytically active palladium and boron complexes are regenerated. The Lewis acid catalyst is crucial for the oxidative addition of O−CN bonds, whereas it has also been shown to promote C(sp³)−CN bond-forming reductive elimination from palladium(II) through coordination of a cyano group to Lewis acid.[23] Bidentate phosphorus ligands with a large bite angle[18] can also affect the reductive elimination[24] and oxypalladation steps, although detailed mechanistic studies have yet to be undertaken for fully understanding the proposed catalytic cycle with exact structures of the suggested intermediates and the roles of palladium and the boron Lewis acid.

In summary, we developed regio- and chemoselective intramolecular oxycyanation of alkenes by palladium/BPh₃ catalysis.[25] The transformation allows simultaneous introduction of a tetra-substituted carbon and cyano group through O−CN bond activation to give dihydrobenzofurans, which are often found in biologically active compounds.[26] Current efforts are directed toward further expansion of the substrate scope,[27] elucidating the catalytic cycle through characterization of some of the reaction intermediates, and developing enantioselective cyclization to access optically active dihydrobenzofuran derivatives.[28]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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