ORGANIC LETTERS

2004
Vol. 6, No. 17
2837−2840

Palladium-Catalyzed Cyanation of Aryl Bromides Promoted by Low-Level Organotin Compounds

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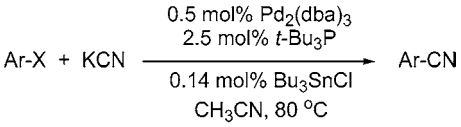
Received March 1, 2004

ABSTRACT



A novel method for palladium-catalyzed cyanation of aryl bromides promoted by low-level tri-*n*-butyltin chloride or cyanide is described. The method features low catalyst loading and mild reaction conditions. KCN is used as the cyanide source. Only trace levels of the tri-*n*-butyltin compound are required to achieve high conversion and yield in the cyanation of aryl bromides, iodides, and triflates.

Cyanation of aryl halides is a common and useful transformation in organic synthesis. Not only are products containing the nitrile group biologically important,[1] but the nitrile is also valuable in installation of functionalities such as aldehydes, amines, amidines, tetrazoles, acids, and acid derivatives.[2] For many years, the only method for cyanation of an aryl halide required stoichiometric CuCN and harsh conditions.[3] Since the discovery that Pd catalyzes the conversion of an aryl halide to a nitrile, methods have been developed that offer milder reaction conditions resulting in fewer side-products.[4−7] It was recognized that cyanide interferes with the prerequisite reaction of Pd(0) with the aryl halide. To make the reactions catalytic in palladium, it was essential to devise a means of delivering cyanide for the reaction with Pd(II) following oxidative insertion while minimizing the exposure of Pd(0) to cyanide. One approach makes use of cyanide salts with poor solubility in the reaction medium. In this way, the oxidative insertion is fast relative to the reaction leading to an inactive form of Pd. The difference in rate is a consequence of the high aryl halide concentration and low cyanide salt concentration. For example, $Zn(CN)_2$[4i,j,l,m] and CuCN,[5] which have limited solubility in the organic solvents used for cyanation, have demonstrated utility in this regard.

While these methods represented significant improvements over earlier procedures, substantial Zn- or Cu-containing waste is produced. As an alternative to transition metal

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10.1021/ol049621d CCC: $27.50 © 2004 American Chemical Society
Published on Web 07/20/2004

cyanides, it was reported that KCN can be used if 0.2 equiv of TMEDA is added.[6] Evidence was presented indicating that the diamine prevents deactivation of the Pd catalyst. Recently, acetone cyanohydrin was used as a cyanide source along with TMEDA; the concentration of cyanide in the reaction was kept low by slow addition of the cyanohydrin using a syringe pump.[7] There remain opportunities for devising milder and more practical methods for general use from bench to manufacturing scales. Here we report a unique Pd-catalyzed cyanation for aryl and heteroaryl bromides promoted by Bu_3SnCl and using KCN as a cyanide source.

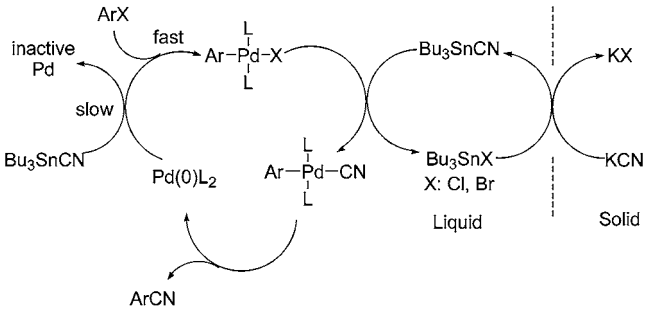
Early attempts to use Me_3SnCN for palladium-catalyzed cyanation of aryl halides, in analogy to the Stille coupling, were not successful.[1b,4c,8] It was found that stoichiometric Pd is required. The catalyzed reaction fails as a result of the rapid reaction of Pd(0) with Me_3SnCN terminating the catalytic cycle. Reaction of Pd(0) with Me_3SnCN is much faster than insertion into the C−I bond of an ArI.[4c] Our own observations using Bu_3SnCN are consistent with the results reported. When we attempted cyanation of 1-bromonaphthalene using 10 mol % tris(dibenzylideneacetone)dipalladium-(0) [$Pd_2(dba)_3$] with *t*-Bu_3P and 1 equiv of Bu_3SnCN, none of the desired product was formed. If, however, we treated 1-bromonaphthalene with 1 equiv of $Pd_2(dba)_3$ with *t*-Bu_3P and then added 1 equiv of Bu_3SnCN, cyanation was completed in less than 10 min at 80 °C. Clearly, Bu_3SnCN interferes with the requisite oxidative insertion but does transfer cyanide to Pd(II) with subsequent reductive elimination to give the nitrile.

It had been proposed that the relative rates in the reaction of Pd(0) with ArI and Me_3SnCN could be made favorable for the desired reaction if the concentration of the tin cyanide were sufficiently low throughout the reaction. It was reported that slow addition of Me_3SnCN using a syringe pump afforded a modest yield (40%) in the cyanation of an aryl iodide. We found that slow addition of Bu_3SnCN to a reaction containing 0.25 mol % $Pd_2(dba)_3$ with *t*-Bu_3P as a ligand gave 12% conversion of 1-bromonaphthalene to the nitrile.

These results validated the premise, but we felt that there would be problems inherent in this approach. Although optimization of the addition time might improve conversion, the addition time affording complete conversion would be highly dependent on the substrate. For use at production scale, the reaction would depend on the tight control of integral parameters (time, temperature, addition rate), making consistent performance difficult to achieve. Finally, a stoichiometric amount of the tin compound is required.

Formation of Bu_3SnCN in the reaction of a tri-*n*-butyltin halide with KCN[9] suggested an alternate means of controlling the level of Bu_3SnCN while reducing the amount of tin compound needed. Using KCN as the stoichiometric cyanide source, we could control the level of Bu_3SnCN in the reaction by charging a relatively small amount of a tri-*n*-butyltin halide. In the cyanation reaction of an aryl bromide, Bu_3SnBr would be generated, which would then react with solid KCN to return Bu_3SnCN to the catalytic cycle. Direct inhibition of the catalyst by KCN would be minimized by using a solvent that does not appreciably dissolve the salt. Our thinking is illustrated in Scheme 1.

Scheme 1. Proposal for Pd-Catalyzed Cyanation of Aryl Halides



With 0.5 mol % $Pd_2(dba)_3$ with (*t*-Bu_3P), 0.5 mol % Bu_3SnCl or Bu_3SnCN, and 1.5 equiv of KCN in acetonitrile at 80 °C, 1-bromonaphthalene was efficiently converted to the corresponding nitrile. A series of experiments were performed to determine the optimum charges. The ratio of Bu_3SnCl to Pd catalyst had a dramatic effect on reaction conversion. It was found that very little Bu_3SnCl is required to improve both the rate and the conversion. The optimum molar ratio of Bu_3SnCl to $Pd_2(dba)_3$ was about 1:3.7; at higher and lower ratios, the reaction was slower and did not go to completion.

Under optimal conditions (0.25 mol % $Pd_2(dba)_3$, 1.25 mol % *t*-Bu_3P, and 0.07 mol % Bu_3SnCl in acetonitrile at 80 °C), the conversion for 1-bromonaphthalene was 54% in 1 h with complete conversion achieved in 6 h. In a control experiment without Bu_3SnCl, only 2% conversion was observed after 1 h with 54% conversion after 17 h.

In this reaction, we found *t*-Bu_3P[10] to be superior to racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 9,9-dimethyl-4,5-bis(diphenyl-phosphino) xanthene (Xantphos), 1,1-bis(diphenylphosphino)ferrocene (dppf), P(*o*-Tol)$_3$, P(*o*-furyl)$_3$, and PPh_3. With a ratio of Pd to *t*-Bu_3P between 1:1 and 1:2.5, complete conversion was observed in cyanation of 1-bromonaphthalene, but when the ratio of Pd to *t*-Bu_3P was 1:3, the conversion was only 40%. With *t*-Bu_3P as a ligand, aryl bromides were generally converted to the nitrile at 50 °C. With other ligands, a somewhat higher temperature (80 °C) was required.

With these encouraging results in hand, we applied this new protocol to a range of substrates, including aryl

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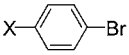
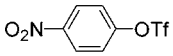
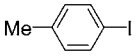
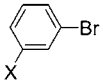
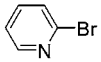
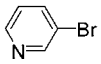
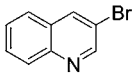
bromides, heteroaryl bromides, an aryl iodide, and aryl triflate. To ensure good performance with a wide range of substrates, we increased the catalyst loading to 0.5 mol % and the corresponding Bu_3SnCl charge to 0.14 mol %. The reactions were conducted at 80 °C and stopped after 17 h. Table 1 shows that a variety of cyanation substrates are converted to the corresponding nitriles using these conditions.

Table 1. Pd-Catalyzed Cyanation Results

entry	ArX	conversion % (isolated yield %)
1[a]		100 (97)
2[a]	 X = H	100 (90)
3[a]	X = Me	94 (90)
4[a]	X = Ph	98 (93)
5[a]	X = F	84 (54)
6[a]	X = CF_3	86 (81)
7[a]	X = CH_3CO	97 (93)
8[a]	X = EtOCO	97 (91)
9[a]	X = CH_3O	62 (50)
10[b]	X = NO_2	78 (78)
11[b]		100 (88)
12[a,c]		100 (96)
13[a]	 X = Cl	100 (92)
14[a]	X = $HOCH_2$	92 (89)
15	X = CH_3O	55 (50)[a] 98 (90)[d]
16		48 (42)[b] 100 (96)[e]
17[b]		97 (93)
18[b,c]		100 (95)
19[b]		100 (96)

[a] Reaction conditions: 1.0 equiv of 1-aryl bromide, 1.5 equiv of KCN, acetonitrile (0.94 mL/mmol), 0.0014 equiv of Bu_3SnCl, 0.005 equiv of $Pd_2(dba)_3$, 0.025 equiv of *t*-Bu_3P, 80 °C, 17 h. [b] Reaction conditions: 1.0 equiv of heteroaryl bromide, 1.5 equiv of KCN, acetonitrile (0.94 mL/mmol), 0.0027 equiv of Bu_3SnCl, 0.005 equiv of $Pd_2(dba)_3$, 0.005 equiv of Xantphos, 80 °C, 17 h. [c] Reaction conditions: 22 °C, 3 h. [d] Performed with 0.0007 equiv of Bu_3SnCl. [e] Performed with 0.0014 equiv of Bu_3SnCl and 0.005 equiv of dppf.

Excellent yields were observed for aryl bromides and methyl- or phenyl-substituted aryl bromides (entries 1−4), which are considered deactivated or slightly deactivated substrates for cyanation. Good conversion was achieved with substrates containing fluoride, trifluoromethyl, methyl ketone, ester, chloride, and hydroxymethyl (entries 5−8, 13−14) functionality. Aryl bromides substituted with a deactivating methoxyl group (entries 9, 15) provided moderate yields. To improve the yield for 3-bromoanisole, we adjusted the amount of tributyltin chloride and found that the yield improved dramatically (entry 15). It will be necessary to fine-tune the amount Bu_3SnCl for some substrates. Cyanation of an aryl iodide (entry 12) was completed at ambient temperature in less than 3 h. Even after tuning the amount of ligand and Bu_3SnCl for cyanation of 3-bromopyridine, the yield was only 46%. For heteroaryl bromides, the chelating ligand Xantphos afforded higher yields. With 3-bromopyridine as a substrate, we further optimized the amount of ligand and Bu_3SnCl.

Using 1 mol % Pd and a Pd-to-Xantphos ratio of 1:0.5, with 0.26 mol % Bu_3SnCl, the conversion increased to 97% (entry 17). The results show that conversion is lower when the Bu_3SnCl charge is reduced. It is worth noting that the optimal Pd to Xantphos ratio is 1:0.5, which is unusual for a bidentate ligand. When the ratio of $Pd_2(dba)_3$ to Xantphos is 1:2 (Pd to Xantphos ratio of 1:1), the reaction conversion was lower. It appears that the dba ligand remains associated with the Pd through the catalytic cycle. However, no reaction is observed using $Pd_2(dba)_3$ without a phosphine ligand.

We applied these conditions in the cyanation of 3-bromoquinoline and a quantitative yield was obtained (entry 19). We also used these conditions for a nitro-substituted aryl bromide and aryl triflate. Both the nitroaryl bromide and triflate (entries 10, 11) were converted to the corresponding nitrile smoothly. An aryl triflate, which is considered a difficult substrate in Pd-catalyzed cyanation,[11] performed well. A lower yield was observed using $Pd_2(dba)_3$/*t*-Bu_3P. As with the aryl iodide, a heteroaryl iodide (entry 18) was converted to the nitrile at ambient temperature in 3 h with a quantitative yield. Unfortunately, 2-bromopyridine gave a moderate yield using the general method. We found, however, that dppf is a good ligand for the cyanation of 2-bromopyridine. Using dppf rather than Xantphos with conditions otherwise the same gave 96% yield in the cyanation of 2-bromopyridine (entry 16).

Although it was gratifying to see that our reasoning had led to such a general method, in recognizing the extent of this success, we had to question the validity of our premise. In order for this method to be as general as it proved to be and to work so well at very low catalyst loading, the reaction of Pd(0) with Bu_3SnCN removing Pd from the catalytic cycle must be very slow, inconsistent with what had been reported for Me_3SnCN. It has been reported that Me_3SnCl reacts with KCN in the presence of a crown ether to form an ate complex.[12] If an ate complex were formed on reaction of

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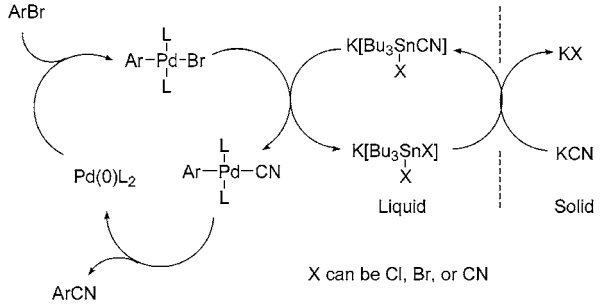
Bu_3SnCl or Bu_3SnCN with KCN, the transfer of cyanide to Pd(II), as required for cyanation, might be favored, and the reactions removing Pd from the catalytic cycle might be suppressed.

NMR experiments provided evidence that ate complexes are formed in the cyanation reaction. On treating Bu_3SnCl with an excess of solid KCN in acetonitrile-d_3 at ambient temperature, the observed ^1H and ^{13}C spectra did not correspond to spectra obtained for commercial Bu_3SnCN. Likewise, treatment of Bu_3SnCN with excess solid KCN resulted in a substantial change in the ^1H and ^{13}C spectra. These results are consistent with the formation of ate complexes. We are working to further characterize these complexes and the equilibria involved. These results will be reported in due course.

On the basis of these observations, we propose the catalytic cycle depicted in Scheme 2.

In conclusion, we have shown that organotin compounds can be used at very low levels to promote the palladium-catalyzed cyanation of aryl bromides. The reaction conditions are mild, and the catalyst loading is 0.5 mol % or lower. KCN is used as a cyanide source in place of Cu and Zn salts with advantages in cost and water solubility for workup. It was found that tin ate complexes are formed under the conditions of the reaction, and these complexes are proposed to be key to the success of the method. With this discovery, other promoters are being explored to further broaden the scope of this method to include aryl chlorides.

Scheme 2. Catalytic Cycle for Pd-Catalyzed Cyanation of Aryl Bromides Promoted by Tin Ate Complexes



Acknowledgment. We would like to acknowledge Professor Barry Trost for useful suggestions and Ms. Lisa DiMichele for NMR support.

Supporting Information Available: General experimental procedure details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049621D