JOC Article

# $P(i\text{-}BuNCH_2CH_2)_3N$: An Efficient Ligand for the Direct α-Arylation of Nitriles with Aryl Bromides

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A new catalyst system for the synthesis of α-aryl-substituted nitriles is reported. The bicyclic triaminophosphine $P(i\text{-}BuNCH_2CH_2)_3N$ (**1b**) serves as an efficient and versatile ligand for the palladium-catalyzed direct α-arylation of nitriles with aryl bromides. Using ligand **1b**, ethyl cyanoacetate and primary as well as secondary nitriles are efficiently coupled with a wide variety of aryl bromides possessing electron-rich, electron-poor, electron-neutral, and sterically hindered groups.

α-Aryl-substituted nitriles are very important building blocks for synthesizing pyridines, carboxylic acids, primary amines, bicyclic amidines, lactones, aldehydes and esters.[1] Such nitriles are also valuable for constructing biologically active compounds such as verapamil and related compounds containing a tertiary benzylic nitrile which act as slow-acting calcium channel antagonists.[2] Usually, such compounds are synthesized by displacement of an activated benzylic alcohol or halide with cyanide, followed by α-alkylation. In sharp contrast to α-alkylation of nitriles with alkyl halides, however, direct α-arylation of nitriles appears to be quite difficult to accomplish, and consequently, chemistry related to this transformation is much less developed. It has been reported for uncatalyzed α-arylations of nitriles that the corresponding anions of diphenylacetonitrile, phenylacetonitrile, and ethyl cyanoacetate can couple with aryl fluorides possessing another electron-withdrawing group.[3] Interestingly, Caron and co-workers recently achieved uncatalyzed coupling of nitrile anions with aryl fluorides lacking an additional electron-withdrawing group.[4] However, limitations were encountered with the structures of the nitriles that underwent addition. For example, the anion of ethyl cyanoacetate was unreactive, primary nitriles did not undergo substitution, and reactions using either phenyl acetonitrile or isovaleronitrile with 2-fluoroanisole led to decomposition.[4]

Palladium-catalyzed α-arylations of enolates and other stabilized carbanions have undergone significant development in recent years.[5] Although alkyl nitriles are less acidic than ketones, a cyano group is more electron-withdrawing than an acyl group.[6] In principle, the anion of a nitrile in the presence of a transition metal catalyst could couple with an aryl halide, but only a few reports of such reactions have appeared. For example, arylations of cyanoacetates, which are considerably more acidic than

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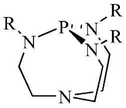
alkyl nitriles, were reported in 1993 to occur in moderate yields using catalytic amounts of copper, although the reaction was limited to aryl iodides.[7] Very recently, cross-coupling products of aryl bromides or chlorides with cyanoacetates were achieved in good yields under mild conditions in the presence of a palladium/$P(t\text{-}Bu)_3$ or $(Ph_5C_5)Fe(C_5H_4)P(t\text{-}Bu)_2$ catalyst system.[8] For alkyl nitriles, the Miura group reported in 1998 that the palladium-catalyzed α-arylation of phenylacetonitrile gave a moderate product yield at high temperature, even though the electronic properties of phenylacetonitrile are similar to those of ketones (which couple easily with aryl halides). Unfortunately, other alkyl nitriles that were tried did not take part in this reaction.[9] Very recently, Hartwig and co-workers reported that BINAP or $P(t\text{-}Bu)_3$-ligated palladium was effective for the monoarylation of secondary alkyl nitriles and for the diarylation of acetonitrile (as well as other unhindered primary nitriles) with aryl bromides giving moderate to good yields.[10]

Although a variety of triaminophosphines [e.g. $P(NR_2)_3$] are well-known, there have been no reports of the use of such ligands in Pd-catalyzed α-arylations of stabilized carbanions. This may be partly due to the diminished electron-donating capability of acyclic triaminophosphines compared with trialkylphosphines, as was rationalized recently by Woollins et al. on structural grounds.[11] Bicyclic proazaphosphatranes of type **1** (of which **1a**−**c** are commercially available[12]) were first synthesized in our laboratories and they have proven to be versatile, nonionic, very strong, stoichiometric bases and potent catalysts for a variety of useful transformations over the past 10 years.[13] These transformations appear to be quite dependent upon the proven or speculated occurrence of transannulation of the bridgehead nitrogen's lone pair to the phosphorus, which enhances the basicity of these phosphines and the stability of the reaction intermediates they form. In addition, the fairly rigid but strain-free bicyclic (approximately $C_{3v}$) framework of these bases serves to augment the lone pair electron density at phosphorus.[14,15] The electronic and steric properties of these molecules are easily finely tuned by introducing an appropriate organic substituent at each of the $PN_3$ nitrogens.



**1a** R = Me
**1b** R = $CH_2CH(CH_3)_2$
**1c** R = $CH(CH_3)_2$
**1d** R = $CH_2Ph$

**TABLE 1. Catalytic α-Arylation of Ethyl Cyanoacetate with Bromobenzene**[a]

| entry | proazaphosphatrane (mmol) | palladium (mmol) | temp (° C) | yield[b] (%) |
|---|---|---|---|---|
| 1 | | $Pd_2(dba)_3$ (0.02) | 90 | 38 |
| 2 | **1b** (0.08) | | 90 | none |
| 3 | **1b** (0.08) | $Pd_2(dba)_3$ (0.02) | 70 | 98 |
| 4 | **1b** (0.08) | $Pd(OAc)_2$ (0.04) | 90 | 95 |
| 5 | **1b** (0.08) | $\{Pd(allyl)Cl]_2$ (0.02) | 90 | 94 |
| 6 | **1b** (0.04) | $Pd_2(dba)_3$ (0.02) | 70 | 75 |
| 7 | **1a** (0.08) | $Pd_2(dba)_3$ (0.02) | 70 | 44 |
| 8 | **1c** (0.08) | $Pd_2(dba)_3$ (0.02) | 70 | 52 |
| 9 | **1d** (0.08) | $Pd_2(dba)_3$ (0.02) | 70 | 72 |
| 10 | $P(NMe_2)_3$ (0.08) | $Pd_2(dba)_3$ (0.02) | 70 | 43 |

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.1 mmol of ethyl cyanoacetate, 2.0 mmol of KO-*t*-Bu in the presence or absence of triaminophosphine/palladium in 2.0 mL of toluene at 70−90 °C under Ar atmosphere for 5 h. [b] Isolated yields (average of two runs) based on aryl bromide.

Very recently, we reported that the bicyclic $P(i\text{-}BuNCH_2CH_2)_3N$ (**1b**) serves as an effective ligand for palladium-catalyzed Suzuki cross-coupling[16] and for aminations of a wide array of aryl chlorides, bromides, and iodides.[17] Herein we show that **1b** is also an excellent ligand in the palladium-catalyzed direct α-arylation of nitriles with aryl bromides.

## Results and Discussion

Our initial exploration of reaction conditions for the palladium-catalyzed α-arylations of nitriles focused on the coupling of ethyl cyanoacetate with bromobenzene. For this model reaction, three palladium sources were employed at 4 mol % loading in the presence of **1b** as a ligand (Table 1). Although $Pd_2(dba)_3$, $Pd(OAc)_2$, and $[Pd(allyl)Cl]_2$ were all effective precatalysts, $Pd_2(dba)_3$ gave a higher activity (entries 3−5). No reaction was observed in the absence of $Pd_2(dba)_3$ (entry 2), and the yield was only 38% with $Pd_2(dba)_3$ in the absence of ligand **1b** (entry 1). After screening a variety of bases (e.g., $Na_3PO_4$, $K_3PO_4$, $Na_2CO_3$, $Cs_2CO_3$, NaH, $NaN(SiMe_3)_2$, KO-*t*-Bu, and NaO-*t*-Bu), we found that KO-*t*-Bu gave the best results. Reactions with weaker bases, such as $Na_3PO_4$, $K_3PO_4$, $Na_2CO_3$, and $Cs_2CO_3$, provided only poor conversions after 15 h. Toluene and dioxane were the most effective solvents in the presence of KO-*t*-Bu. In an effort to obtain an optimum palladium:ligand ratio, we found that a 1:2 Pd/L ratio gave faster reaction rates and better product yields, while a 1:1 ratio provided only a 75% yield (compare entries 3 and 6).

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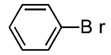
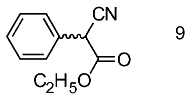
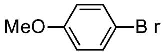
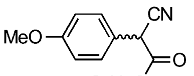
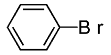
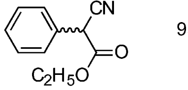
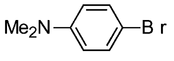
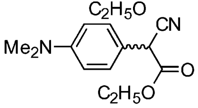
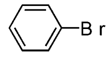
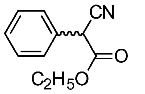
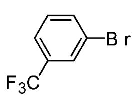
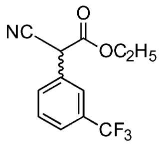
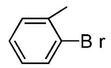
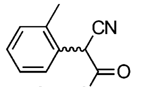
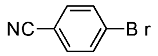
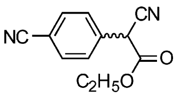
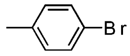
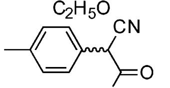
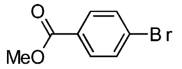
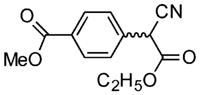
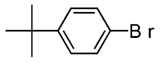
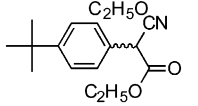
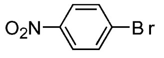
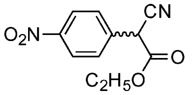
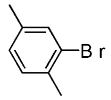
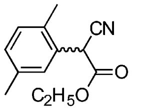
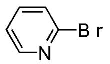
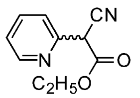
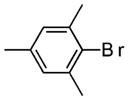
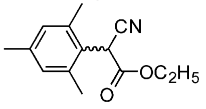
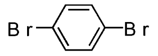
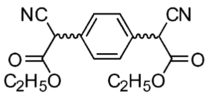
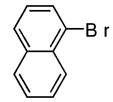
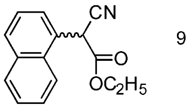
**TABLE 2. α-Arylation of Ethyl Cyanoacetate with Aryl Bromides Catalyzed by P(*i*-BuNCH$_2$CH$_2$)$_3$N (1b)[a]**

| Entry | Aryl Bromide | Product | Yield (%)[b] | Entry | Aryl Bromide | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  |  | 98 | 10 |  |  | 94 |
| 2[c] |  |  | 93 | 11 |  |  | 95 |
| 3[d] |  |  | 91 | 12 |  |  | 96 |
| 4 |  |  | 93 | 13[f] |  |  | 98 |
| 5 |  |  | 95 | 14 |  |  | 93 |
| 6 |  |  | 94 | 15[g] |  |  | none |
| 7 |  |  | 92 | 16 |  |  | 94 |
| 8 |  |  | 88 | 17 |  |  | 92 |
| 9[e] |  |  | 99 | | | | |

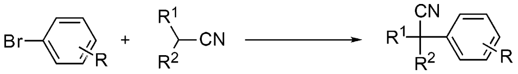
[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.1 mmol of ethyl cyanoacetate, 2.0 mmol of KO-*t*-Bu, 0.02 mmol of Pd$_2$(dba)$_3$, and 0.08 mmol of **1b** in 2.0 mL of toluene at 90 °C under Ar atmosphere for 5 h. [b] Isolated yields (average of two runs) based on aryl bromide. [c] 0.01 mmol of Pd$_2$(dba)$_3$ and 0.04 mmol of **1b**. [d] 0.005 mmol of Pd$_2$(dba)$_3$ and 0.02 mmol of **1b**. [e] Dioxane as a solvent. [f] 70 °C. [g] In the presence of strong base, the substrate decomposed.

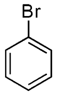
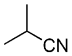
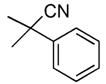
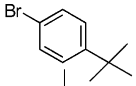
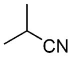
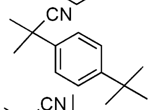
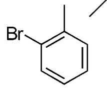
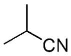
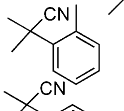
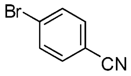
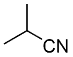
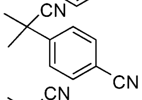
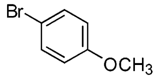
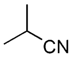
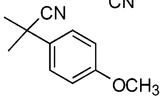
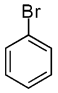
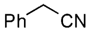
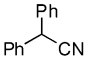
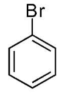
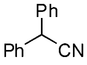
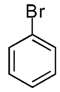
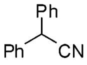
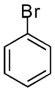
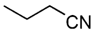
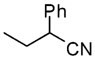
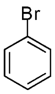
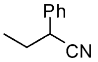
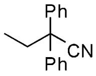
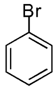
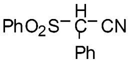
While **1a** as a ligand was disappointing, providing only a 44% product yield in the reaction in Table 1 (entry 7), the more bulky **1b** delighted us with a 98% yield (entry 3), whereas **1c** was not as efficient (entry 8). As described earlier by us, the latter result could arise from the fact that **1c** does not provide sufficient bulk, since the methyl groups on the *i*-Pr substituents are probably turned outward and away from the phosphorus lone pair when it coordinates to the Pd, a conformation that is also present in the solid-state structures of **1c** as well as in its protonated form.[15,17] While a similar conformation of the isobutyl groups could occur in ligand **1b**, the greater flexibility of these substituents and the larger cone angle they can sweep out as they rotate around the C−N bonds in **1b** effectively increases their steric requirements over that of an isopropyl group, thus conferring on this ligand a unique balance of steric and electronic inductive influences that optimize the activity of the **1b**/Pd catalyst system. Interestingly, the further increase in nitrogen substituent cone angles provided in ligand **1d** was not beneficial (entry 9).

After optimization of the reaction conditions, we investigated various aryl bromides that could be coupled with ethyl cyanoacetate (Table 2). The best results were obtained between 70 and 90 °C in toluene using KO-*t*-Bu as a base in the presence of a catalyst system generated in situ from 2 mol % Pd$_2$(dba)$_3$ and 8 mol %**1b**. Under these conditions, a broad range of aryl bromides, including electron-rich, electron-poor, electron-neutral, sterically hindered, and heteroaryl bromides, were smoothly coupled. Electron-poor substrates such as those in entries 12−14 of Table 2 led to very high yields, except for 4-bromonitrobenzene, which did not afford the desired product, although conversion of starting material was complete (entry 15). Deactivated aryl bromides afforded the expected coupling products in excellent yields. Thus, the reaction of *p*-methyoxybromobenzene with ethyl cyanoacetate gave a 94% yield of product (Table 2, entry 10). Substrates with an ortho or pseudo-ortho substituent also reacted to afford excellent product yields (entries 4 and 7−9). Our protocol was equally effective for aryl bromides possessing substituents at other positions (entries 4 and 5). The reaction of *p*-(dialkylamino)-bromobenzene gave a 95% product yield (entry 11). The arylation of ethyl cyanoacetate with *p*-dibromobenzene afforded exclusively the para-coupled aromatic product in excellent yield (entry 17) and no monocoupled aromatic product was observed, even when a 1:1.1 ratio of *p*-dibromobenzene to ethyl cyanoacetate was employed.

It may be noted that cyanoacetate esters did not couple with aryl bromides possessing electron-withdrawing groups such as esters, ketones, and nitriles in the

**TABLE 3. Catalytic α-Arylation of Nitriles with Aryl Bromides**[a]



| Entry | ArBr | Nitriles | Product | Ligand **1b** (mmol) | Pd(OAc)$_2$ (mmol) | Conditions (Temp/Time) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  |  |  | 0.02 | 0.01 | 100 °C/4 h | 95 |
| 2 |  |  |  | 0.02 | 0.01 | 100 °C/3 h | 92 |
| 3 |  |  |  | 0.02 | 0.01 | 100 °C/5 h | 89 |
| 4 |  |  |  | 0.02 | 0.01 | 100 °C/2 h | 98 |
| 5 |  |  |  | 0.02 | 0.01 | 100 °C/8 h | 88 |
| 6 |  |  |  | 0.04 | 0.02 | 100 °C/6 h | 93 |
| 7 |  | $CH_3CN$ |  | 0.08 | 0.04 | 100 °C/16 h | 81 |
| 8[c] |  | $CH_3CN$ |  | 0.08 | 0.04 | 100 °C/16 h | 74 |
| 9[d] |  |  |  | 0.08 | 0.04 | 90 °C/6 h | 85 |
| 10 |  |  |  | 0.04 | 0.02 | 70 °C/3 h | 91 |
| 11[e] |  | $PhSO_2CH_2CN$ |  $PhO_2S-CH(Ph)-CN$ | 0.04 | 0.02 | 90 °C/5 h | 96 |

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.2 mmol of nitrile, 1.4 mmol of NaN(SiMe$_3$)$_2$, 0.01–0.04 mmol of Pd(OAc)$_2$ and 0.02–0.08 mmol of **1b** in 2.0 mL of toluene at 70–100 °C under Ar atmosphere. [b] Isolated yields (average of two runs) based on aryl bromide. [c] $CH_3CN$: 2.0 mmol. [d] 1.05 mmol of NaN(SiMe$_3$)$_2$. [e] Dioxane as a solvent.

presence of the Pd/(Ph$_5$C$_5$)-Fe(C$_5$H$_4$)P(t-Bu)$_2$ or Pd/P(t-Bu)$_3$ catalyst systems.[8b] Moreover, pyridyl halides were unreactive with ethyl cyanoacetate, and coupling of very hindered aryl halides such as bromomesitylene with ethyl cyanoacetate also did not take place.[8b] By contrast, our catalytic system allows for a broad scope of substrates, and it functions very well for aryl bromides of the aforementioned types. Thus, the arylation of ethyl cyanoacetate with 2-bromopyridine, methyl 4-bromobenzoate, 4-bromobenzonitrile, and 2-bromomesitylene gave the desired products in 94%, 93%, 98%, and 88% yields (Table 2; entries 16, 14, 13, and 8, respectively).

Although not investigated in detail, the α-arylation of ethyl cyanoacetate also proceeded with substantially lower catalyst loadings than with the 2 mol % Pd$_2$(dba)$_3$ used under our standard conditions. As shown in entries 2 and 3 of Table 2, the reaction of ethyl cyanoacetate with bromobenzene at 70 °C still gave a high yield with 2 mol % or even with 1 mol % of the palladium precursor.

In contrast to our results obtained with KO-*t*-Bu as a base in the α-arylation of ethyl cyanoacetate, NaN(SiMe$_3$)$_2$ was the most effective base for the arylation of alkyl nitriles. Reactions involving KO-*t*-Bu failed to go to completion, even after extended periods of heating. Moreover, Pd(OAc)$_2$ proved to be more effective in the α-arylation of ethyl cyanoacetate than Pd$_2$(dba)$_3$. As shown in Table 3, secondary nitriles were effectively coupled to afford monoarylation products with aryl bromides possessing electron-rich, electron-poor, electron-neutral, and sterically hindered groups in high yields, even with palladium loadings as low as 1.0 mol %. For example, cross-coupling of isobutyronitrile with bromobenzene, 1-bromo-4-*tert*-butylbenzene, 2-bromotoluene, and 4-bromobenzonitrile gave the corresponding tertiary α-arylnitriles in 2–5 h in 95%, 92%, 89%, and 98% yield, respectively (entries 1–4). The reaction of isobutyronitrile with electron-rich 4-bromoanisole needed a somewhat longer reaction time to obtain a good yield (entry 5). The **1b**/Pd(OAc)$_2$ catalyst system was also effective for primary nitriles, although these reactions required higher catalyst loadings. Thus, the coupling of primary nitriles, such as benzyl nitrile and *n*-butyronitrile, with bromobenzene gave the corresponding monoarylated product as the major one in 93% and 85% yields, (entries 6 and 9, respectively). The monoarylated product of *n*-butyronitrile was easily coupled with a second equivalent of bromobenzene to form the corresponding diarylated product (entry 10). Interestingly, diarylation of acetonitrile occurred preferentially over monoarylation (entry 7), and monoarylated product was not observed, even in the presence of 2.0 equiv of $CH_3CN$, presumably because the monoarylated species is readily deprotonated and is sufficiently unhindered to bind to palladium during the reaction pathway (entry 8). Apparently, arylation of acetonitrile beyond the disubstituted stage is prevented by steric hindrance of the deprotonated disubstituted species to coordination to palladium. Interestingly, the reaction of $PhSO_2CH_2CN$ with bromobenzene conducted in dioxane gave a higher product yield than in toluene, possibly because the poor solubility of the sodium salt of (phenylsulfonyl)acetate in toluene, as was suggested by precipitate formation observed when NaN(SiMe$_3$)$_2$ was added (entry 11).

In summary, we have developed an efficient and versatile catalytic system for the synthesis of α-aryl-substituted nitriles that is of broad scope. Bicyclic **1b** is the first member of a new class of triaminophosphines that has been demonstrated to be an advantageous ligand in palladium-catalyzed α-arylations of stabilized carbanions. Particularly noteworthy are the generally better product yields and the broader reaction scope facilitated by our catalytic systems compared with *rac*-BINAP, (Ph$_5$C$_5$)Fe(C$_5$H$_4$)P(*t*-Bu)$_2$, and P(*t*-Bu)$_3$. Further development of our synthetic methodology is in progress, including direct α-arylations of nitriles with aryl chlorides.

## Experimental Section

**Typical Procedure for α-Arylation of Ethyl Cyanoacetate with Aryl Bromides.** A dried Schlenk flask equipped with a magnetic stirring bar was charged with Pd$_2$(dba)$_3$ (0.02 mmol) and KO-*t*-Bu (2.0 mmol) inside a nitrogen-filled drybox. The flask was capped with a rubber septum followed by removal from the drybox. Toluene or dioxane (2 mL), P(*i*-BuNCH$_2$CH$_2$)$_3$N (**1b**) (0.08 mmol), and aryl bromide (1.0 mmol) were then added successively. After stirring for 20 min at room temperature, ethyl cyanoacetate (1.1 mmol) was added and stirring was continued under the conditions indicated in Table 2. The mixture was then quenched by adding aqueous 1 N HCl, followed by extraction with ethyl acetate. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

**Typical Procedure for α-Arylation of Alkyl Nitriles with Aryl Bromides.** An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with Pd(OAc)$_2$ (0.01−0.04 mmol) and NaN(SiMe$_3$)$_2$ (1.4 mmol) inside a nitrogen-filled drybox. The flask was capped with a rubber septum followed by removal from the drybox. Toluene (2 mL), P(*i*-BuNCH$_2$CH$_2$)$_3$N (**1b**) (0.02−0.08 mmol), and aryl bromide (1.0 mmol) were then added successively. After stirring for 20 min at room temperature, an alkyl nitrile (1.2 mmol) was added. The reaction mixture was stirred under the conditions indicated in Table 3. The mixture was then quenched by adding aqueous 1 N HCl followed by extraction with ether. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

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**Note Added after ASAP Posting.** The aryl bromide structure in entry 17, Table 2, was incorrect in the version posted September 26, 2003; the correct version was posted September 30, 2003.

**Supporting Information Available:** General experimental methods used, characterizational NMR spectral data ($^1$H and $^{13}$C), and chromatography conditions for product purification. This material is available free of charge via the Internet at http://pubs.acs.org.

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