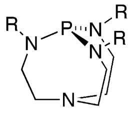
Arylation of Nitriles

A General Method for the Direct α-Arylation of Nitriles with Aryl Chlorides**

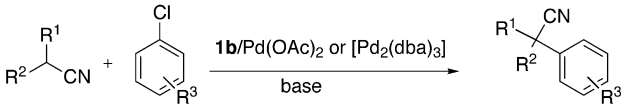
*Jingsong You and John G. Verkade**

α-Aryl-substituted nitriles are not only important building blocks for constructing pyridines, carboxylic acids, primary amines, bicyclic amidines, lactones, aldehydes, and esters,[1] but also for synthesizing biologically active compounds.[2] However, the synthesis of α-aryl nitriles by direct α-arylation of nitriles has been sufficiently difficult, that the development of chemistry that could emanate from a successful method for such a process has been seriously inhibited. Only a few reports have appeared describing uncatalyzed couplings of nitrile carbanions with aryl halides possessing another electron-withdrawing group,[3] or with unactivated aryl fluorides,[4] or for transition-metal-catalyzed α-arylations with aryl iodides[5] or bromides.[6] Although aryl chlorides are both more abundant and less expensive than their corresponding iodides, bromides, and fluorides, they are much less reactive, and to date the addition of a nitrile anion to an aryl chloride has been achieved only with relatively acidic cyanoacetates in the presence of a palladium/P(tBu)$_3$ or Ph$_5$C$_5$FeC$_5$H$_4$P(tBu)$_2$ catalytic systems.[6b,c]

Herein, we describe a general solution to this long-standing challenge by employing bicyclic **1b** as a ligand for palladium in Equation (1) (dba = dibenzylideneacetone) which leads to efficient coupling of an array of nitriles with a broad range of aryl chlorides.



1a R = Me
1b R = CH$_2$CH(CH$_3$)$_2$
1c R = CH(CH$_3$)$_2$
1d R = CH$_2$Ph



(1)

Ever since the bicyclic proazaphosphatranes **1** (of which **1a–c** are commercially available[7]) were first synthesized in our laboratories, they have continued to find uses as versatile nonionic very strong bases and potent catalysts for a variety of useful transformations.[8] These reactions appear to be quite dependent upon the occurrence (and in many cases the postulated occurrence) of transannulation of the bridgehead nitrogen center‘s lone pair to the phosphorus, which enhances the basicity of these proazaphosphatranes and also the stability of reaction intermediates formed with them. Moreover, the frameworks of compounds such as **1a–d** are fairly rigid but strain-free in a bicyclic (approximately C_{3v}) structure, thus favoring augmentation of the lone-pair electron density at phosphorus.[9,10] Additionally, the electronic and steric properties of these molecules can be easily fine tuned by introducing suitable organic substituents at each PN$_3$ nitrogen center. Very recently, we discovered that **1b** serves as a particularly effective ligand for palladium-catalyzed Suzuki-type cross-coupling[11] and aryl aminations[12] with a wide array of aryl chlorides, bromides and iodides. Those results prompted us to examine the use of **1** in α-arylations of nitriles with aryl chlorides.[13]

Our initial exploration of reaction conditions for the palladium-catalyzed α-arylation of nitriles focused on the coupling of isobutyronitrile with chlorobenzene (Table 1, entries 1–5). After screening **1a**–**1d** and P(NMe$_2$)$_3$, the more bulky **1b** was found to be a particularly effective ligand, while **1a** and **1c** provided only trace amounts of the cross-coupling product and **1d** gave only a moderate yield.[11,12,14] As expected, non-cyclic P(NMe$_2$)$_3$ did not afford the anticipated α-arylated product (Table 1, entry 5). The best results were obtained with α-arylations of isobutyronitrile at 90 °C in toluene using NaN(SiMe$_3$)$_2$[15] as a base, and a catalyst system generated in situ from 2 mol% of Pd(OAc)$_2$ and 4 mol% of **1b**.[16] Under our optimized reaction conditions, α-arylations of isobutyronitrile in high yields were accomplished with a wide array of aryl chlorides including electron-rich, electron-poor, electron-neutral, and sterically hindered examples (Table 1, entries 2 and 6–8).

We have determined that not only a broad spectrum of aryl chlorides, but also a diverse set of nitriles (Table 2),

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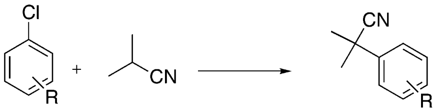
Table 1: Catalytic α-arylation of isobutyronitrile with aryl chlorides by Pd(OAc)$_2$/**1**.[a]

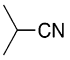
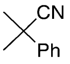
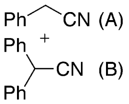
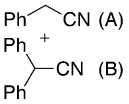
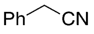
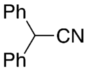
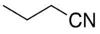
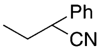
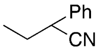
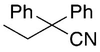
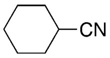
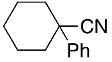


(2)

Entry	Ligand	Aryl chloride	Yield [%][b]
1	**1a**	C_6H_5Cl	10
2	**1b**	C_6H_5Cl	82
3	**1c**	C_6H_5Cl	15
4	**1d**	C_6H_5Cl	40
5	$P(NMe_2)_3$	C_6H_5Cl	0
6	**1b**	2-MeC_6H_5Cl	81
7[c]	**1b**	4-NCC_6H_5Cl	92
8	**1b**	4-MeOC_6H_5Cl	70

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of isobutyronitrile, 1.4 mmol of NaN(SiMe$_3$)$_2$, 0.02 mmol of Pd(OAc)$_2$, and 0.04 mmol of **1** in 2.0 mL of toluene at 90 °C for 8 h under Ar atmosphere. [b] Yields (average of two runs) based on aryl chloride. [c] Reaction time: 2 h.

Table 2: Catalytic α-arylation of nitriles with chlorobenzene by Pd(OAc)$_2$/**1b**.[a]

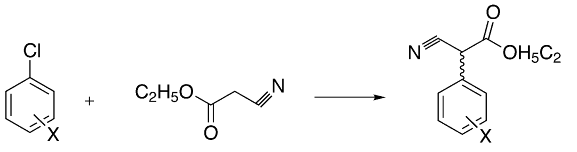
Entry	Nitrile	Product	*t*	Yield [%][b]
1			8 h	82
2	CH_3CN		15 h	50(A) 20(B)
3[c]	CH_3CN		15 h	70(A) 10(B)
4			6 h	91
5[d]			6 h	83
6			3 h	90
7[e]	$PhSO_2CH_2CN$	$PhSO_2CH(Ph)CN$	4 h	96
8			6 h	81

[a] Reaction conditions: 1.0 mmol of chlorobenzene, 1.2 mmol of nitrile, 1.4 mmol of NaN(SiMe$_3$)$_2$, 0.02 mmol of Pd(OAc)$_2$ and 0.04 mmol of **1b** in 2.0 mL of toluene at 90 °C under Ar atmosphere. [b] Yields (average of two runs) based on chlorobenzene. [c] 2.0 mmol of CH_3CN. [d] 0.04 mmol of Pd(OAc)$_2$ and 0.08 mmol of **1b**. [e] Dioxane as a solvent, 1.4 mmol of KO-*t*Bu as a base.

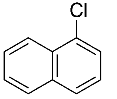
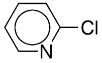
participate efficiently in α-arylations of nitriles in the presence of Pd(OAc)$_2$/**1b**. For these transformations we chose to use chlorobenzene as the aryl chloride. The coupling of primary nitriles, such as benzyl nitrile, *n*-butyronitrile, and $PhSO_2CH_2CN$ with chlorobenzene afforded the corresponding monoarylated product almost exclusively in 91 %, 83 % and 96 % yields, respectively, (entries 4, 5, and 7). The monoarylated product of *n*-butyronitrile was found to couple with a second equivalent of chlorobenzene to form the corresponding diarylated product (entry 6). However, acetonitrile afforded a mixture of di- and monoarylated product under the same conditions (entry 2). By increasing the amount of acetonitrile, however, the yield of the monoarylated product was improved (entry 3). In addition, a cyclic secondary nitrile, such as cyclohexanecarbonitrile, was efficiently coupled with chlorobenzene, affording monoarylated product in good yield (entry 8).

α-Aryl cyanoacetates are useful intermediates in the preparation of amino alcohols, β-amino acids, and arylacetic acids.[17] Thus, it was gratifying to discover that a catalyst system, generated from [Pd$_2$(dba)$_3$]/**1b** in dioxane using KO-*t*Bu as a base, effectively facilitated the α-arylation of ethyl cyanoacetate with a broad range of aryl chlorides (Table 3). Whether the aryl chlorides are electron-rich (entry 7), electron-poor (entries 8–10), electron-neutral (entries 1–6), or sterically hindered (entries 3, 5, and 6), all of them afforded excellent product yields under our conditions.

Table 3: Catalytic α-arylation of ethyl cyanoacetate with aryl chlorides by [Pd$_2$(dba)$_3$]/**1b**.[a]



(3)

Entry	Aryl chloride	Yield [%][b]
1	C_6H_5Cl	93
2[c]	C_6H_5Cl	91
3	2-MeC_6H_5Cl	92
4	4-MeC_6H_5Cl	93
5	2,5-Me$_2C_6H_5Cl$	90
6		92
7	4-MeOC_6H_5Cl	90
8	4-$F_3CC_6H_5Cl$	92
9[d]	4-NCC_6H_5Cl	96
10	4-$CH_3OCOC_6H_5Cl$	87
11		91

[a] Reaction conditions: 1.0 mmol of aryl chloride, 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 dioxane at 90 °C under Ar atmosphere for 5 h. [b] Yields (average of two runs) based on aryl chloride. [c] 0.005 mmol of [Pd$_2$(dba)$_3$] and 0.02 mmol of **1b**. [d] Temperature: 80 °C.

Limitations on the structures of aryl halides were encountered when Pd/$Ph_5C_5FeC_5H_4P(t\text{Bu})_2$ or Pd/P(*t*Bu)$_3$ catalyst systems were employed.[6c] For example, cyanoacetate esters did not couple with pyridyl halides or with aryl halides possessing electron-withdrawing groups, such as esters or nitriles.[6c] In contrast, our catalytic system tolerates a broad variety of aryl halides. Thus the arylation of ethyl cyanoacetate with 4-chlorobenzonitrile, methyl-4-chlorobenzoate, and 2-chloropyridine gave the desired products in 96, 87, and 91 % yields, respectively, (entries 9–11).

Although not yet investigated in detail, α-arylations of ethyl cyanoacetate also occurred with substantially lower catalyst loading than with our standard condition of 2 mol% of [Pd$_2$(dba)$_3$]. As shown in entry 2 of Table 3, the reaction of ethyl cyanoacetate with chlorobenzene occurred in 91% yield with 1 mol% of palladium precursor at 90°C.

In summary, we have described a solution to the long-standing challenge of developing a general method for the direct α-arylation of nitriles with aryl chlorides. With the catalytic system generated from palladium and commercially available **1b**, it is now possible to effect direct α-arylation of a wide variety of nitriles with a broad range of aryl chlorides.

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Keywords: α-arylation · homogeneous catalysis · nitriles · P ligands · palladium

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[10] An X-ray structural study of **1c** showed that the bonding environment around the PN$_3$ nitrogen center is rather planar, the sum of angles being 354.9, 356.6, and 357.5°: A. E. Wroblewski, J. Pinkas, J. G. Verkade, *Main Group Chem.* **1995**, *1*, 69–79.

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[13] General experimental: A dried Schlenk flask equipped with a magnetic stirring bar was charged with Pd(OAc)$_2$ or [Pd$_2$(dba)$_3$] (0.02–0.04 mmol) and KO-*t*Bu (2.0 mmol) or NaN(SiMe$_3$)$_2$ (1.4 mmol) inside a nitrogen-filled glove box. The flask was capped with a rubber septum and removed from the glove box. Toluene or dioxane (2 mL), **1b** (0.04–0.08 mmol in toluene or dioxane (0.5–0.7 mL)) and aryl halide (1.0 mmol) were then added successively. After stirring for 20 min at room temperature, a nitrile (1.1 or 1.2 mmol) was added and the reaction mixture was stirred under the conditions indicated in Tables 1–3. The mixture was then quenched by addition of aqueous 1N HCl and extracted with diethyl ether. The isolated organic phase was dried over Na$_2$SO$_4$, filtered, concentrated in vacuo, and purified by column chromatography on silica gel eluting with ethl acetate/hexane or dichloromethane/hexane.

[14] Control experiments showed that either in the absence of a Pd source or in the absence of proazaphosphatrane, no reaction was observed.

[15] After screening a variety of bases (i.e., Na$_3$PO$_4$, K$_3$PO$_4$, Na$_2$CO$_3$, Cs$_2$CO$_3$, NaH, NaN(SiMe$_3$)$_2$, KO-*t*Bu, and NaO-*t*Bu), we found that NaN(SiMe$_3$)$_2$ gave the best results. In the presence of a weaker base, such as Na$_3$PO$_4$, K$_3$PO$_4$, Na$_2$CO$_3$ or Cs$_2$CO$_3$, no reaction was observed.

[16] A 1:2 palladium-to-ligand ratio gave faster reaction rates and better product yields than a 1:1 ratio.

[17] a) C. Cativiela, M. D. Diaz-de-Villegas, J. A. Galvez, *J. Org. Chem.* **1994**, *59*, 2497–2505; b) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1–15; c) H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, 2119–2133.