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Palladium-Catalyzed Cyanation of Aryl Perfluorooctylsulfonates

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Cyanation of aryl perfluorooctylsulfonates with potassium hexacyanoferrate(II) catalyzed by an efficient catalyst system comprising $Pd(OAc)_2$, CuI and PPh₃ or 1,1'-bis(diphenylphosphino)ferrocene (dppf) is described.

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Aryl nitriles are important compounds not only for their interesting biological properties, but also because of their use as versatile starting materials for many important aromatic compounds, including acids, ketones, oximes, and amines.^[1,2] Various methods for the synthesis of aryl nitriles have been reported. In general, the most direct and versatile method is based on the transition metal-mediated displacement of aromatic halides and triflates by the cyanide ion. Since the discovery of transition metal-catalyzed cross-coupling reactions, much interest has been shown in the development of a practical version of this transformation. Until now, several successful palladium-^[3,4] and nickel-catalyzed^[5,6] displacements of aryl halides and triflates with the cyanide ion to afford the corresponding aryl nitriles have been reported. However, most of the work concentrated on the inconvenient traditional cyanide sources, which have some severe drawbacks. To avoid these problems, potassium hexacyanoferrate(II) was rediscovered as a non-toxic cyanide source by Beller in 2004.^[7] This procedure provided, for the first time, a generally applicable and relatively non-toxic approach for the synthesis of various aryl nitriles. Since then, several publications have reported the development of new catalytic systems for cyanation using potassium hexacyanoferrate(II) as the cyanide source.[8]

Aryl perfluoroalkanesulfonates are well-known aryl halide equivalents for palladium-catalyzed coupling reactions owing to the diversity of available phenols and the simple conversion of phenols to aryl perfluoroalkanesulfonates,^[9] making it clear that the cyanation of aryl perfluoroalkanesulfonates as an alternative route to aryl nitriles will have significant synthetic value. However, most accounts of cyanations focussed on the use of aryl triflate rather than other aryl perfluoroalkanesulfonates.^[4,6] In a close look at the literature, the only other report that deals with the cyanation of 3-(methoxycarbonyl)-1,2,3,4tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate catalyzed by Pd(OAc)₂ using potassium hexacyanoferrate(II) as the cyanide source was shown by Torrado and coworkers.^[10] However, the yield of the corresponding product was moderate (43%). Aryl perfluorooctylsulfonates are an attractive alternative to triflates because of the following reasons: (1) aryl

perfluorooctylsulfonates can easily be prepared from commercially available phenols and are stable to chromatography and storage at room temperature;^[11] (2) aryl perfluorooctylsulfonates have been shown to have reactivity similar to aryl triflates in cross-coupling reactions such as Suzuki,^[11b] amination,^[11e] and reduction,^[11c] and are more stable toward hydrolysis; and (3) it is also noteworthy that perfluorooctylsulfonates containing a light C₈F₁₇ chain can be used as a fluorous tag for the fluorous solid-phase extraction (F-SPE) separation to simplify reaction mixture purifications in multistep synthesis.^[11] However, no detailed study of palladium-catalyzed cyanation of aryl perfluorooctylsulfonates has been reported. Following our interest in the cyanation,^[12] herein we present our studies toward the conversion of phenols via their corresponding aryl perfluorooctylsulfonates^[13] to aryl nitriles using potassium hexacyanoferrate(II) as the cyanide source.

Our goal was to find an efficient approach to synthesize aryl nitriles from phenols via their corresponding aryl perfluorooctylsulfonates using potassium hexacyanoferrate(II). As indicated in Table 1, we chose the reaction of phenyl perfluorooctylsulfonate with $K_4[Fe(CN)_6]$, which was ground to a fine powder and dried under a high vacuum at 80°C overnight, as a model for exploring optimized reaction conditions. Because the perfluoroalkanesulfonate group is an excellent leaving group,[9] conversion of phenyl perfluorooctylsulfonate into benzonitrile was initially tried using standard conditions for the cyanation of aromatic halides (Pd(OAc)₂ only),^[8a,8b] but the yield of our target product, benzonitrile, was low, with recovery of significant amounts of unreacted phenyl perfluorooctylsulfonate (entry 1). Increasing the amount of Pd(OAc)₂ and adding PPh₃ as ligand only led to a slight increase in product yields (entries 2, 3). After switching from PPh₃ to 1,1'-bis(diphenylphosphino)ferrocene (dppf), the yield was enhanced to 73% (entry 4). Cyanation of phenyl perfluorooctylsulfonate under the catalysis of Pd(dppf)Cl₂, a good catalyst in some cross-coupling reactions using aryl perfluorooctylsulfonates as substrates,[11a-11d] provided the corresponding product in 76% yield (entry 5). As addition of copper salts has recently been shown to increase reaction rates in palladium-catalyzed cyanation,^[8k,14] we attempted

Table 1. Evaluation of various reaction conditions

Reaction conditions: 1 mmol phenyl perfluorooctylsulfonate, 2 mol-% Pd(OAc)₂, 20 mol-% dry K₄[Fe(CN)₆], 3 mL DMF, 100 mol-% Na₂CO₃, 10 mol-% additive, 140°C, N2 atmosphere

| Entry | Ligand ^A | Additive [10 mol-%] | Time [h] | Yield [%] ^B |
|-------|---------------------|------------------------|-------------|---------------------------|
| 1 | _ | _ | 24 | 33 ^C |
| 2 | PPh ₃ | _ | 24 | 38 |
| 3 | PPh ₃ | _ | 24 | 46 ^D |
| 4 | dppf | _ | 24 | 73 ^D |
| 5 | - | _ | 24 | 76 ^E |
| 6 | PPh ₃ | CuI | 5 | 95 |
| 7 | PPh ₃ | $Cu(OAc)_2$ | 5 | 12 |
| 8 | PPh ₃ | CuI | 5 | 0^{F} |
| 9 | PPh ₃ | CuI | 5 | 54 ^G |
| 10 | PPh ₃ | CuI | 5 | 11^{H} |

^ALigand:Pd = 2/1.

^BYields were determined by gas chromatography with 1,3-dimethoxybenzene as the internal standard.

^C0.1 mol-% Pd(OAc)₂ was used.

^D5 mol-% Pd(OAc)₂ was used.

^E5 mol-% Pd(dppf)Cl₂ was used.

FNo Pd(OAc)₂.

^GSolvent: DMAc.

^HSolvent: NMP.

to add simple copper salts to improve the yield. As we expected, a higher yield and shorter time were obtained by adding 10 mol-% CuI (entry 6). In contrast to what has been previously observed $[\tilde{k}_k]$ the reaction afforded benzonitrile only in a poor yield of 12% when adding Cu(OAc)₂ (entry 7). A blank test using CuI without Pd(OAc)₂ gave no corresponding product (entry 8). The beneficial effect of CuI as an additive prompted us to examine other copper salts and iodine salts in the cyanation of phenyl perfluorooctylsulfonate. In agreement with our previous results on the cyanation of aryl triflates, other salts such as CuBr, CuCl, CuCl₂, CuBr₂, CuO, AgI, KI, and ZnI₂ were far less effective than CuI. In addition, a switch in the solvent to N,N-dimethylacetamide (DMAc) or N-methylpyrolidone (NMP) gave inferior results (entries 9, 10). This is opposite to that noticed in the cyanation of aryl triflates, in which DMAc as a solvent gives the best result.

After optimized reaction conditions were obtained, the reaction scope was explored with various aryl perfluorooctylsulfonates. The results are summarized in Table 2. It was found that meta-substituted and para-substituted aryl perfluorooctylsulfonates were suitable for the reaction conditions, giving the desired products in good to excellent yields (entries 1-7). When 4-chlorophenyl perfluorooctylsulfonate was used as the substrate, only the product reacted at the C-O bond was isolated in 84% yield (entry 7), which implies that there existed great selectivity between aryl perfluorooctylsulfonates and aryl chlorides under the present reaction conditions. Also, extension to synthetic access to naphthyl derivatives was also achieved in good yields with lower catalyst loading (entries 8, 9). Conversion of ortho-substituted aryl perfluorooctylsulfonate was affected by the steric environment around the reaction site, as 2-methoxyphenyl perfluorooctylsulfonate, an electron-rich aryl perfluorooctylsulfonate, gave a considerably lower yield in comparison with that of less hindered 4-methoxyphenyl perfluorooctylsulfonate, even adding more catalyst and prolonging the

Table 2. Pd-catalyzed cyanation of various aryl perfluorooctylsulfonates

Reaction conditions: 1 mmol aryl perfluorooctylsulfonate, 20 mol-% dry K₄[Fe(CN)₆], 2 mol-% Pd(OAc)₂, 4 mol-% PPh₃, 3 mL DMF, 100 mol-%Na₂CO₃, 10 mol-% CuI, 140°C, N₂ atmosphere, 5 h

| | Pd(OAc) ₂ /Cul/PPh ₃ (or dppf) | |
|--------------|--|---|
| | K ₄ [Fe(CN) ₆] | |
| 1 $Pf = -SC$ | D ₂ (CF ₂) ₇ CF ₃ | 2 |

| Entry | Aryl perfluorooctylsulfonate | Aryl nitriles | Yield [%] ^A |
|--------|------------------------------|---------------|---|
| 1 | OPf | 2a | 91 (82) |
| 2 | OPf | 2ь | 90 (81) |
| 3 | Ph | 2c | 89 (82) |
| 4 | MeO | 2d | 87 (80) |
| 5 | F ₃ C OPf | 2e | 93 (85) |
| 6 | F OPf | 2f | 92 (83) |
| 7 | CI OPf | 2g | 91 (84) |
| 8 | OPf | 2h | 93 (87) ^B |
| 9 | OPf | 2i | 91 (84) ^B |
| 10, 11 | OMe OPf | 2j | 14 (6) ^C 76 (68) ^D |

^AYields were determined by gas chromatography with 1,3dimethoxybenzene as the internal standard. Numbers in parentheses show isolated yields.

^B1 mol-% Pd(OAc)₂ and 2 mol-% PPh₃ were used.

^C4 mol-% Pd(OAc)₂ and 8 mol-% PPh₃ were used with a reaction time of 24 h.

^Ddppf used instead of PPh₃.

reaction time (compare entries 4 and 10). In this case, using dppf as the ligand instead of PPh₃ gave the product in 68% yield (entry 11).

To conclude, we have developed an efficient catalyst system for the cyanation of aryl perfluorooctylsulfonates with K₄[Fe(CN)₆] by using Pd(OAc)₂/CuI as catalyst and PPh₃ or dppf as ligand. An important value of the protocol we describe lies in the use of a readily available and cheap catalyst system based on Pd(OAc)₂, CuI and PPh₃ or dppf. Furthermore, the diversity of available phenols and the simple conversion of phenols to aryl perfluorooctylsulfonates and the non-toxic cyanide source make this catalytic reaction attractive as a synthetic method for aryl nitriles. Application of a fluorous tag for multistep synthesis is currently under investigation in our group.

Experimental

General Procedure for the Cyanation of Aryl Perfluorooctylsulfonates

After standard cycles of evacuation and filling with dry and pure nitrogen, an oven-dried tube was charged with 1 mmol aryl perfluorooctylsulfonate, 20 mol-% K4[Fe(CN)6], 2 mol-% Pd (OAc)₂, 4 mol-% PPh₃, 10 mol-% CuI, 1 mmol Na₂CO₃, and 3 mL of DMF. The tube was evacuated and filled with nitrogen. Then the tube was sealed, and the mixture was stirred at 140°C for 5 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered. Then 1,3-dimethoxybenzene (130 μ L) was added as the internal standard. The filtrate was washed with water $(3 \times 10 \text{ mL})$ and analyzed by gas chromatography (GC). The GC yields were determined by obtaining correction factors using authentic samples of the expected products. For isolating the products: after the reaction was completed, the mixture was diluted with ethyl acetate (30 mL) and filtered. The filtrate was washed with water $(3 \times 10 \text{ mL})$. The organic phase was dried over Na₂SO₄, filtered, and concentrated under vacuum. Finally, the product was isolated by flash chromatography on silica gel with EtOAc/light petroleum as the eluent. All prepared aryl nitriles are known compounds and identified by GC-mass spectrometry.

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