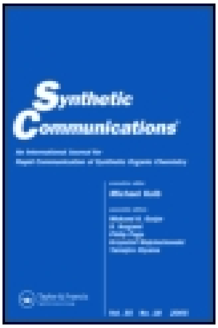

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Yi-Zhong Zhu [a] & Chun Cai [a]

[a] Chemical Engineering College, Nanjing University of Science and Technology, Nanjing, China

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Palladium-Catalyzed Cyanation of Aryl Triflates

Yi-Zhong Zhu and Chun Cai
Chemical Engineering College, Nanjing University of Science and Technology,
Nanjing, China

Abstract: A simple catalyst system comprising $Pd(OAc)_2$ and DPPF was proved to be efficient for the cyanation of aryl triflates with potassium hexacyanoferrate(II) as cyanide source.

Keywords: Aryl nitriles, aryl triflates, cyanation, palladium, potassium hexacyanoferrate(II)

INTRODUCTION

Aryl nitriles are of considerable interest as integral parts of dyes, herbicides, natural products, and pharmaceuticals.[1] In addition, nitriles play a crucial role as they can be easily converted into a variety of functional groups such as acids, ketones, oximes, and amines.[2]

Various methods for the synthesis of aryl nitriles have been reported. In general, aryl nitriles are synthesized from aryl halides and stoichiometric amounts of copper(I) cyanide,[3] from aniline by diazotization and subsequent Sandmeyer reaction,[4] or by ammoxidation.[5] Nevertheless, the most convenient method is based on the transition-metal-mediated displacement of aromatic halides and triflates by the cyanide ion. Until now, a number of successful palladium-[6,7] and nickel-catalyzed[8,9] cyanations have been reported. However, most of the work has concentrated on the inconvenient traditional cyanide sources, which have some severe drawbacks. To avoid these problems, potassium hexacyanoferrate(II) was rediscovered as a nontoxic cyanide

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Address correspondence to Chun Cai, Chemical Engineering College, Nanjing University of Science and Technology, Nanjing, China. E-mail: c.cai@mail.njust.edu.cn

source by Beller in 2004.[10] This procedure provided, for the first time, a generally applicable and relatively nontoxic approach for the synthesis of various aryl nitriles. Since then, several publications have reported on the development of new catalytic systems for the cyanation using potassium hexacyanoferrate(II) as cyanide source.[11] A close look at the literature, however, showed that all these methods explored aryl halides as the substrates. The diversity of available phenols and the simple conversion of phenols to aryl triflates make it clear that the cyanation of aryl triflates as an alternative route to aryl nitriles will have significant synthetic value. Following our interest in the cyanation,[12] herein, we present our studies toward the conversion of aryl triflates to the corresponding aryl nitriles using potassium hexacyanoferrate(II) as cyanide source.

RESULTS AND DISCUSSION

As a starting point for the development of our cyanation system, the reaction of phenyl triflate with $K_4[Fe(CN)_6]$ was investigated (Table 1). $K_4[Fe(CN)_6]\cdot 3H_2O$ was ground to a fine powder and dried under vacuum at 80 °C overnight. First, phenyl triflate was submitted to the ligand-free palladium-mediated cyanation according to literature procedures.[11a,11b] Unfortunately, the yield of our target product, benzonitrile, was low with recovery of significant amounts of unreacted phenyl triflate and the by-product phenol (entry 1). Increasing the amount of $Pd(OAc)_2$ and adding PPh_3 as ligand only led to a slight increase in product yield (entry 2). Fortunately, an excellent yield of 91% was obtained when PPh_3 was changed to 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (entry 3).

Table 1. Evaluation of various reaction conditionsa[a]

Entry	Pd source	Ligand[b]	Yield (%)[c]
1[d]	$Pd(OAc)_2$	—	34
2	$Pd(OAc)_2$	PPh_3	51
3	$Pd(OAc)_2$	DPPF	91
4[e]	$Pd(OAc)_2$	DPPF	23
5	$Pd_2(dba)_3$	DPPF	77
6	$Pd_2(dba)_3$	PPh_3	trace

[a] Reaction conditions: 1 mmol phenyl triflate, 20 mol% dry $K_4[Fe(CN)_6]$, 3 mL DMAc, 5 mol% Pd source, 100 mol% Na_2CO_3, 140 °C, 24 h.

[b] Ligand–Pd source = 2:1.

[c] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

[d] 0.1 mol% $Pd(OAc)_2$ was used.

[e] 2 mol% $Pd(OAc)_2$ was used.

However, reducing the amount of palladium source to 2 mol% had a dramatic effect on the reaction, with the yield being lowered to only 23% (entry 4). Replacing the palladium source with tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] in the presence of DPPF as ligand led to a moderate yield of 77% (entry 5). In contrast, almost no product was obtained when combined with PPh_3 (entry 6).

The influences of bases and solvents on the cyanation of phenyl triflate were also investigated (Table 2). Except for the catalysts, the bases also played very important roles in obtaining the corresponding product. Note that 20% yield was obtained under the base-free condition (entry 1). Na_2CO_3 was proved to be the most efficient (entry 2). Interestingly, the use of K_2CO_3 and Cs_2CO_3, which are very efficient bases in many cross-coupling reactions, resulted in little corresponding product with only a large amount of by-product phenol being formed (entries 3, 4). Employing the bases, $C_4H_4O_6KNa{\cdot}4H_2O$ and NaOAc, could give moderate yields (entries 5, 6). Other bases such as Bu_3N, potassium fluoride (KF), C_2H_5ONa, KOH, NaOH, *t*-BuOK, $HCOONa{\cdot}2H_2O$, and

Table 2. Cyanation of phenyl triflate in the presence of different bases and solvents[a]

Entry	Base	Solvent	Yield (%)[b]
1	—	DMAc	20
2	Na_2CO_3	DMAc	91
3[c]	K_2CO_3	DMAc	<3
4[c]	Cs_2CO_3	DMAc	8
5[d]	$C_4H_4O_6KNa{\cdot}4H_2O$	DMAc	72
6	NaOAc	DMAc	61
7	Bu_3N	DMAc	19
8	KF	DMAc	24
9	C_2H_5ONa	DMAc	25
10	KOH	DMAc	5
11	NaOH	DMAc	36
12	*t*-BuOK	DMAc	2
13	$HCOONa{\cdot}2H_2O$	DMAc	0
14	$K_3PO_4{\cdot}3H_2O$	DMAc	30
15	Na_2CO_3	DMF	90
16	Na_2CO_3	NMP	12

[a] Reaction conditions: 1 mmol phenyl triflate, 20 mol% dry $K_4[Fe(CN)_6]$, 5 mol% $Pd(OAc)_2$, 10 mol% DPPF, 3 mL solvent, 100 mol% base, 140 °C, 24 h.

[b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard.

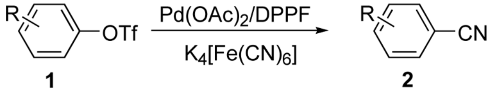
[c] A large amount of phenol was obtained.

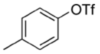
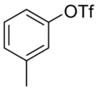
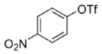
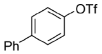
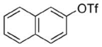
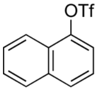
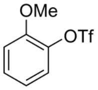
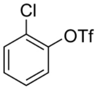
[d] $C_4H_4O_6KNa{\cdot}4H_2O$–potassium sodium tartrate tetrahydrate.

$K_3PO_4{\cdot}3H_2O$ were less effective (entries 7–14). Solvent other than DMAc, such as N,N-dimethylformamide (DMF) (entry 15), gave almost the same result, but N-methyl-2-pyrroolidone (NMP) afforded benzonitrile only in a poor yield of 12% (entry 16). These results showed that the selection of base and solvent was very important for obtaining high activity.

To evaluate the scope and limitation of this procedure, the reactions of a wide variety of aryl triflates were examined (Table 3). Very efficient

Table 3. Pd-catalyzed cyanation of various aryl triflates[a]



Entry	Aryl triflates	Aryl nitriles	Yield (%)[b,c]
1		2a	83
2		2b	85
3		2c	81
4		2d	80
5		2e	88
6		2f	71
7		2g	66 (62)
8		2h	68

[a] Reaction conditions: 1 mmol aryl triflate, 20 mol% dry $K_4[Fe(CN)_6]$, 3 mL DMAc, 5 mol% $Pd(OAc)_2$, 10 mol% DPPF, 100 mol% Na_2CO_3, 140 °C, 24 h.

[b] Yields were determined by GC with 1,3-dimethoxybenzene as the internal standard. All prepared benzonitriles are commercially available.

transformation of *meta*-substituted and *para*-substituted aryl triflates (entries 1–4) were observed under the reaction conditions. On the other hand, 2-naphthyl triflate also afforded the desired product in good yield (entry 5). However, the hindered aryl triflates were converted into the nitriles in moderate yields (entries 6–8). Because slow addition of the aryl triflates could prevent cleavage of the triflates and generation of phenols,[13] the yield however, of the desired product did not improve when performing the reaction using that method.

To conclude, a simple catalyst system comprising $Pd(OAc)_2$ and DPPF was effective for the cyanation of various aryl triflates with potassium hexacyanoferrate(II) as cyanide source. The diversity of available phenols and the simple conversion of phenols to aryl triflates and the notoxic cyanide source make this catalytic reaction attractive as a synthetic method of aryl nitriles.

EXPERIMENTAL

Typical Procedure for the Cyanation of Aryl Triflates

After standard cycles of evacuation and filling with dry and pure nitrogen, an oven-dried tube was charged with 1 mmol of aryl triflate, 20 mol% of $K_4[Fe(CN)_6]$, 5 mol% of $Pd(OAc)_2$, 10 mol% of DPPF, 100 mol% of Na_2CO_3, and 3 mL of DMAc. The tube was evacuated and filled with nitrogen. Then the tube was sealed, and the mixture was stirred at 140 °C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered. Then 1,3-dimethoxybenzene (130μL) was added as the internal standard. The filtrate was washed with water (3 × 10 mL) and analyzed by gas chromatography. The GC yields were determined by obtaining correction factors using authentic samples of the expected products. For isolating products: After the reaction was completed, the mixture was diluted with ethyl acetate (30 mL) and filtered. The filtrate was washed with water (3 × 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Finally, the product was isolated by flash chromatography on silica gel with EtOAc–petroleum ether as the eluent. All prepared benzonitriles are known compounds and identified by gas chromatography-mass spectrometric (GC-MS).

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