Cross-Coupling

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A Mild and Efficient Palladium-Catalyzed Cyanation of Aryl Mesylates in Water or *t*BuOH/Water**

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Dedicated to Professor Albert S. C. Chan on the occasion of his 60th birthday

Aryl nitriles are structural motifs that frequently occur in agrochemically useful and pharmaceutically active compounds.[1] Their widespread synthetic utility is highlighted by a myriad of possible nitrile transformations,[2] including the synthesis of benzoic acids/esters, amides, amines, aldehydes, and nitrogen-containing heterocycles.[3] Traditional methods for preparing aromatic nitriles from the corresponding aryl iodides/bromides or aryl diazonium salts are the Rosenmund–von Braun[4] and Sandmeyer reaction,[5] respectively. These reactions require a stoichiometric amount of CuCN at an elevated temperature (typically 150–250 °C), and involve complicated workup procedures. The other industrial method of choice is ammoxidation, whereby the corresponding toluene derivatives are treated with oxygen and ammonia at 330–550 °C in the presence of a heterogeneous catalyst under high pressure.[6]

A versatile alternative for the preparation of benzonitrile derivatives with more complex substitution patterns is the transition-metal-catalyzed cyanation of readily available aryl halides.[7] Nickel, palladium, and recently copper catalysts have been shown to be effective for this purpose.[8–18] Nickel catalysts are more air- and moisture-sensitive, as well as less functional-group-compatible than palladium complexes. Copper-catalyzed cyanation has been successful with aryl iodides and bromides, yet inferior with aryl chlorides. In 1973, Takagi et al. reported the palladium-catalyzed cyanation of aryl iodides/bromides in the presence of KCN and the catalyst $Pd(CN)_2$ at 140 °C or above.[8] Since this pioneering study, palladium-based methods have garnered most of the attention as a result of their better functional-group tolerance, air stability, and high catalytic activity.[7a] The palladium-catalyzed cyanation has mostly been explored with relatively straightforward aryl bromide substrates in the presence of cyanides M–CN (M = alkali metal,[9] trimethylsilyl,[10] Cu,[11] Zn[12]), acetone cyanohydrin,[13] potassium ferrocyanide(II),[14] and other cyanating agents.[15] The palladium-catalyzed cyanation of aryl chlorides remains problematic and is generally only possible at high temperature (120–160 °C).[13,16] In 2007, Littke et al. reported milder cyanation conditions for aryl chlorides with the Buchwald-type ligand *rac*-2-di-*tert*-butylphosphanyl-1,1′-binaphthyl.[17]

Although the cyanation of aryl halides (mainly ArBr) is quite well established, the popularity of pseudohalides (aryl triflates) in cyanation reactions is limited.[18] Possible constraints of this process may the high cost of the triflating agent (e.g. Tf_2O; Tf = trifluoromethanesulfonyl), and the ease of decomposition of aryl triflates under basic reaction conditions, especially at higher reaction temperatures (120–160 °C). However, the development of phenolic derivatives for use as electrophilic reaction partners is worthwhile, since they may offer different or unique substitution of the aromatic ring. The corresponding aryl halides may not be commonly available or may require additional synthetic steps to manipulate the substitution pattern. Thus, the use of aryl mesylates or arenesulfonates, which are less expensive and more stable than aryl triflates, as cyanation substrates could be highly favorable.[19] Nickel-mediated catalytic processes with aryl mesylates were reported by Percec and co-workers in 1995.[20] Although aryl mesylates have several beneficial features, no palladium-catalyzed cyanation has been reported previously. Herein, we report the first general palladium-catalyzed cyanation of aryl mesylates. The reaction temperature of 80 °C is the mildest ever reported for the cross-coupling of aryl mesylates. Moreover, this cyanation reaction was carried out in an environmentally benign solvent: water or a water/*t*BuOH solvent mixture.

We initially investigated the palladium-catalyzed cyanation of electronically neutral 4-*tert*-butylphenyl mesylate as the benchmark substrate in the presence of a series of commercially available ligands, as well as our previously developed indolylphosphines (Scheme 1). Poor conversion of the aryl mesylate was observed with the phosphine ligands Xphos,[21] Brettphos,[22] and Sphos,[23] whereas the ligands Catacxium A[24] and Catacxium PCy[25] did not promote the cyanation reaction. The aminophosphine **L1** and the C–P-type phosphines **L2** and **L3** with a phosphanyl group at the 3-position of the indole were also found to be inferior ligands for the desired reaction.[26] However, with the ligand CM-phos,[27] in which the phosphanyl unit is attached to the non-indolyl ring, the desired product was formed in 90% yield.

We carried out a series of screening experiments to optimize the reaction parameters (Table 1). A control experi-

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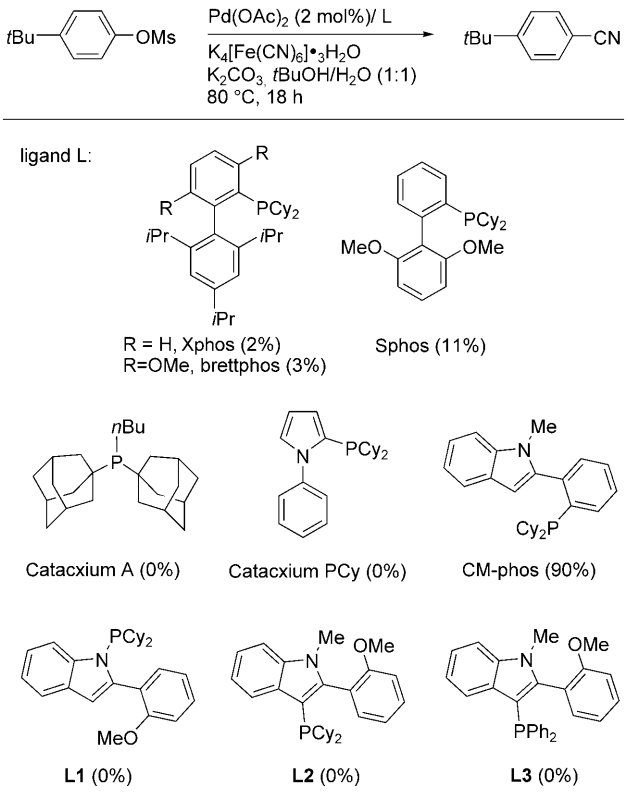


Scheme 1. Ligand screening for the palladium-catalyzed cyanation of 4-*tert*-butylphenyl mesylate. Reaction conditions: aryl mesylate (1.0 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol, 2 mol%), L (8 mol%; Pd/L 1:4), K_2CO_3 (0.125 mmol), water/*t*BuOH (1:1, 4 mL total), 80°C, 18 h. Yields were determined by GC with dodecane as the internal standard. Cy = cyclohexyl.

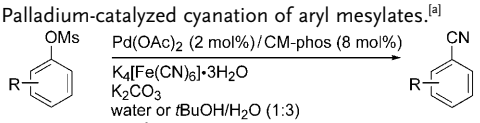
Table 1: Initial screening of the palladium-catalyzed cyanation of a non-activated aryl mesylate.[a]

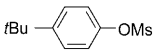
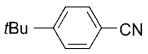
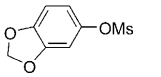
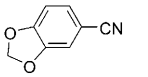
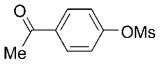
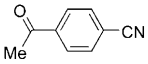
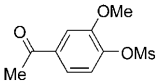
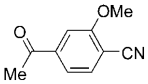
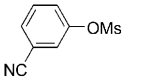
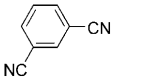
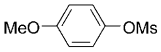
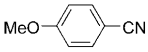
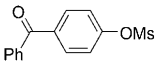
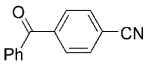
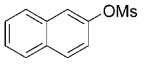
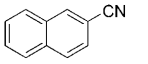
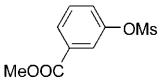
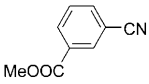
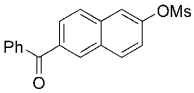
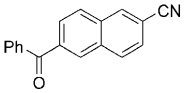
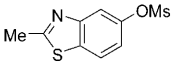
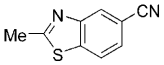
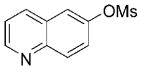
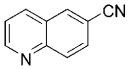
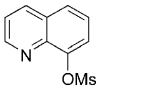
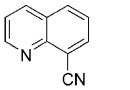
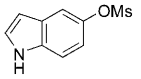
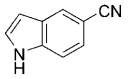
Entry	Base	"CN" source	Solvent	Yield [%][b]
1	K_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	90
2	Na_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	86
3	Cs_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	88
4	NaO*t*Bu	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	10
5	KO*t*Bu	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	52
6	K_3PO_4	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH/H_2O (1:1)	90
7	K_2CO_3	NaCN	*t*BuOH/H_2O (1:1)	0
8	K_2CO_3	CuCN	*t*BuOH/H_2O (1:1)	0
9	K_2CO_3	$Zn(CN)_2$	*t*BuOH/H_2O (1:1)	2
10	K_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	*t*BuOH	3
11	K_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	MeCN/H_2O (1:1)	89
12	K_2CO_3	$K_4[Fe(CN)_6]\cdot 3H_2O$	dioxane/H_2O (1:1)	88

[a] Reaction conditions: 4-*tert*-butylphenyl mesylate (1.0 mmol), cyanide source ($K_4[Fe(CN)_6]\cdot 3H_2O$: 0.5 mmol; NaCN, CuCN, $Zn(CN)_2$: 2.0 mmol), Pd source (0.02 mmol, 2 mol%), CM-phos (8 mol%, Pd/CM-phos 1:4), base (0.125 mmol), solvent (4.0 mL total), 80°C, 18 h. [b] The yield was determined by GC with dodecane as the internal standard.

ment revealed that no cyanation product was formed in the absence of either the palladium catalyst or CM-phos. Inorganic bases were found to assist the cyanation. Carbonated bases and K_3PO_4 were superior, whereas the reactions

Table 2: Palladium-catalyzed cyanation of aryl mesylates.[a]



Entry	ArOMs	ArCN	Solvent	Yield[b] [%]
1			water	90
2[c]			*t*BuOH/H_2O	88
3			water	96
4			water	84
5			water	84
6			water	72
7			*t*BuOH/H_2O	91
8			*t*BuOH/H_2O	82
9			*t*BuOH/H_2O	72
10			*t*BuOH/H_2O	67
11			*t*BuOH/H_2O	81
12			*t*BuOH/H_2O	95
13			*t*BuOH/H_2O	86
14			*t*BuOH/H_2O	87
15			*t*BuOH/H_2O	93

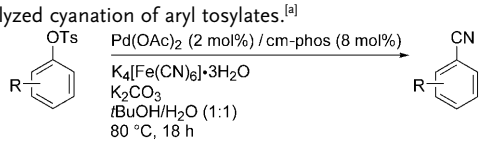
[a] Reaction conditions: ArOMs (1.0 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol, 2 mol%), Pd/CM-phos (1:4), K_2CO_3 (0.125 mmol), water (2.0 mL) or water/*t*BuOH (3:1, 4.0 mL total), 80°C, 18 h (the reaction time was not optimized for each substrate). [b] Yield of the isolated product. [c] The reaction was carried out at 65°C for 24 h.

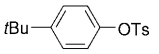
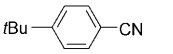
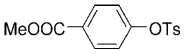
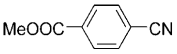
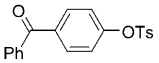
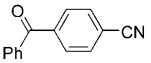
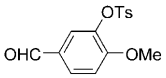
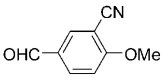
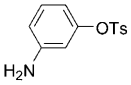
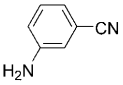
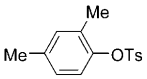
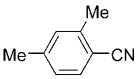
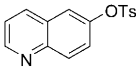
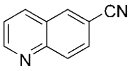
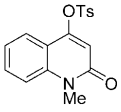
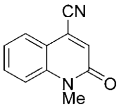
with NaO*t*Bu and KO*t*Bu provided the product in poorer yield (Table 1, entries 1–6). The cyanide sources NaCN, CuCN, and $Zn(CN)_2$ did not promote the reaction (Table 1, entries 1 versus 7–9). We initially attempted the cyanation with *t*BuOH as the solvent. However, essentially no conversion of the aryl mesylate was observed under our cyanation conditions (Table 1, entry 10). We considered that these poor results might be attributed to low solubility of the cyanide source. Therefore, we added water as a cosolvent to the reaction system in attempt to improve the solubility of the

hydrated $K_4[Fe(CN)_6]$ reagent. Under these conditions, the yield of the aryl nitrile increased dramatically to 90% (Table 1, entry 1). Inspired by these results, we conducted further experiments to determine the best solvent ratio (see the Supporting Information). Surprisingly, the reaction even proceeded in water without a cosolvent.

To test the effectiveness of our catalytic system, we examined the transformation of a variety of aryl mesylates under the optimized reaction conditions (Table 2). Water was used as the only solvent when the substrates were soluble at 80°C (Table 2, entries 1 and 3–6). When the reaction temperature was lowered to 65°C, the reaction still proceeded well and gave the desired product in good yield (Table 2, entry 2). However, in that case a *t*BuOH/water mixture was necessary as the reaction medium. Common functional groups, such as keto, ester, and nitrile groups, were compatible with the reaction conditions (Table 2, entries 3–11). Deactivated *para*-methoxyphenyl mesylate was a suitable coupling partner (Table 2, entry 7). The cyanation of benzothiazolyl and quinolyl mesylates furnished the corresponding products in excellent yields (Table 2, entries 12–14). Notably, the cyanation of an unprotected indole afforded the nitrile product in 93% yield (Table 2, entry 15).

Table 3: Palladium-catalyzed cyanation of aryl tosylates.[a]



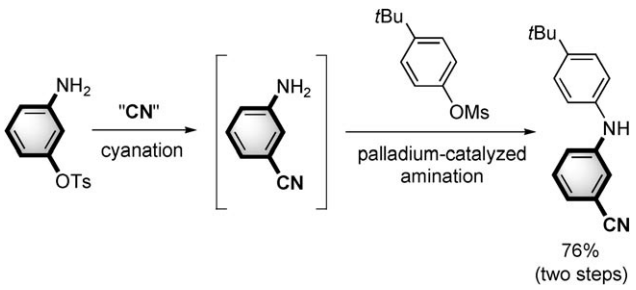
Entry	ArOTs	ArCN	Solvent	Yield[b] [%]
1			water	trace
2			*t*BuOH/H_2O	94
3			*t*BuOH/H_2O	69
4			*t*BuOH/H_2O	84
5			*t*BuOH/H_2O	89
6			*t*BuOH/H_2O	85
7			*t*BuOH/H_2O	43
8			*t*BuOH/H_2O	92
9			*t*BuOH/H_2O	96
10			*t*BuOH/H_2O	87
11[c]			*t*BuOH/H_2O	71

[a] Reaction conditions: ArOTs (1.0 mmol), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol, 2 mol%), Pd/CM-phos (1:4), K_2CO_3 (0.125 mmol), *t*BuOH/H_2O (1:1, 2.0 mL total), 80°C, 18 h (the reaction time was not optimized for each substrate). [b] Yield of the isolated product. [c] $Pd(OAc)_2$: 5 mol%. Ts = *p*-toluenesulfonyl.

To further extend our catalytic system, we also tested an array of aryl tosylates (Table 3). Interestingly, the reaction did not proceed when water was used as the only solvent (Table 3, entry 1 versus Table 2, entry 1) owing to the low solubility of the aryl tosylates. Hence, we used an organic cosolvent and finally identified the optimal reaction medium as a 1:3 *t*BuOH/water mixture. The yield was significantly improved (Table 3, entry 2). Ester, keto, aldehyde, and free amino groups were compatible with the reaction conditions (Table 3, entries 3–6). Not only aryl tosylates, but also an alkenyl tosylate was a suitable substrate for the cyanation reaction (Table 3, entry 11).

The manipulation of functionalized intermediates in a reaction sequence is crucial in organic synthesis.[28] Under the reaction conditions for cyanation, common functional groups were tolerated well. Thus, it is possible to incorporate other functional groups, such as an NH_2 moiety, in the substrate for a further coupling reaction. To demonstrate the feasibility of this approach, we carried out a one-pot sequential synthesis of an *N*-aryl aminobenzonitrile from the tosylate derived from 3-aminophenol by cyanation of the aryl tosylate and subsequent N-arylation of the amino group (Scheme 2).

In summary, we have demonstrated the palladium-catalyzed cyanation of aryl mesylates. The reaction temperature



Scheme 2. One-pot sequential cyanation–amination reaction. After the cyanation reaction (conditions in Table 2, 18 h), 4-*t*BuC_6H_4OMs (1.2 mmol) and K_2CO_3 (2.5 mmol) were added under N_2, and the reaction mixture was stirred at 110°C for an additional 24 h.

of 80 °C is the mildest ever reported for the coupling of aryl mesylates. Interestingly, the use of water as the solvent or a cosolvent was found to be essential. This palladium catalyst system exhibits excellent functional-group tolerance: nitrile, ester, keto, aldehyde, free amine, and heterocyclic groups remained intact during the course of reaction. Moreover, this system is also applicable to the cyanation of aryl and alkenyl tosylates. A one-pot cyanation–amination sequence demonstrated the suitability of this reaction for the introduction of a nitrile group and manipulation of a further functional group in a synthetic pathway without isolation of the initial nitrile-substituted intermediate. Given the practical advantages of these sulfonating agents and the favorable cyanation conditions, we believe that this method will find widespread use in organic synthesis.

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