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Palladium-Catalyzed Direct α-Arylation of Arylacetonitriles with Aryl Tosylates and Mesylates

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Dedication ((optional))

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Abstract: The first general palladium-catalyzed α-arylation of arylacetonitriles with aryl and heteroaryl sulfonates are reported. $Pd(OAc)_2$ associated with XPhos serves as the effective catalyst to facilitate this reaction. A broad range of electron-rich, -neutral, -deficient, and sterically hindered aryl/heteroaryl tosylates and mesylates are coupled with arylacetonitriles bearing different substituents to give the corresponding products in good to excellent yields. Catalyst loading down to 0.1 mol% Pd was achieved, and 22 unprecedented compounds were synthesized from 43 demonstrated examples using this method. Its applicability with the modification of biological phenolic compounds was successfully demonstrated. The Pd/XPhos system catalyzed the α-arylation and followed by alkylation in one-pot sequential conditions, resulting in the direct synthesis of compounds containing quaternary center- and deuterium-containing compounds in good to excellent yields.

Diarylacetonitriles are important motifs in many natural products and pharmaceutically active molecules (Figure 1).[1] The nitrile moiety is a versatile functional group that allows further organic transformations that afford corresponding substituted benzoic acids/esters, amides, amines, aldehydes, and nitrogen-containing heterocycles[2] and offer the diarylmethane unit for natural products synthesis[3]. Traditional methods for preparing α-aryl nitriles include the Friedel-Crafts reactions,[4] dehydration of α-substituted amides,[5] cyanation of benzyl alcohols and halides,[6] and decarboxylative arylation of potassium cyanoacetate.[7] Among these methods, palladium-catalyzed α-arylation of nitriles with aryl halides is an efficient method to synthesize α-aryl nitriles,[8] which was independently developed by the Hartwig,[9] Verkade[10] and other[11] research groups. Nambo reported the selective synthesis of multi-arylated acetonitriles via sequential palladium-catalyzed arylations of chloroacetonitrile.[12]

Despite the fact that aryl halides are prevalent electrophiles in α-arylation of nitriles because of their ease of oxidative addition and non-sensitive towards strong basic condition, halogenated compounds are not common in view of medicinal chemistry. Lengthy synthetic pathways and functional group manipulations are required to perform the halogenation of specific sites in natural products or pharmaceuticals. Aryl electrophiles generated from phenolic compounds are highly desirable because of their easy preparation and unique substitution pattern. Phenolic moieties are also commonly presented in biologically active compounds.[13] The usage of these phenolic moieties enables the rapid modification and derivatization which greatly facilitate the structure refinement and structure-activity relationship study. However, the reaction conditions such as strong base and high temperature employed in palladium-catalyzed direct arylation reactions with aryl halides are too harsh for frequently used phenolic derivatives. A strong base, such as NaHMDS[10a] or KO*t*-Bu,[10b] is generally required for the direct deprotonation of the benzylic CH_2 proton. To the best of our knowledge, the general palladium-catalyzed α-arylation of arylacetonitriles with aryl sulfonates even for most common aryl triflates has not been reported.

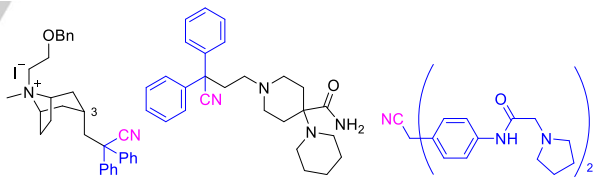
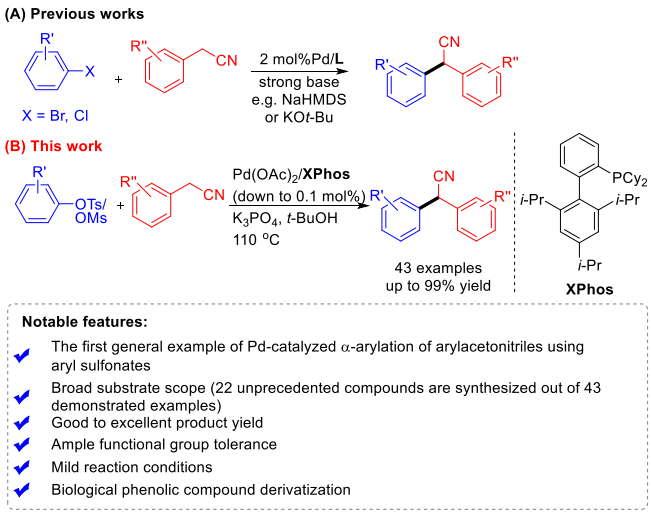


Figure 1. Examples of useful intermediates and products containing diarylacetonitriles motifs.

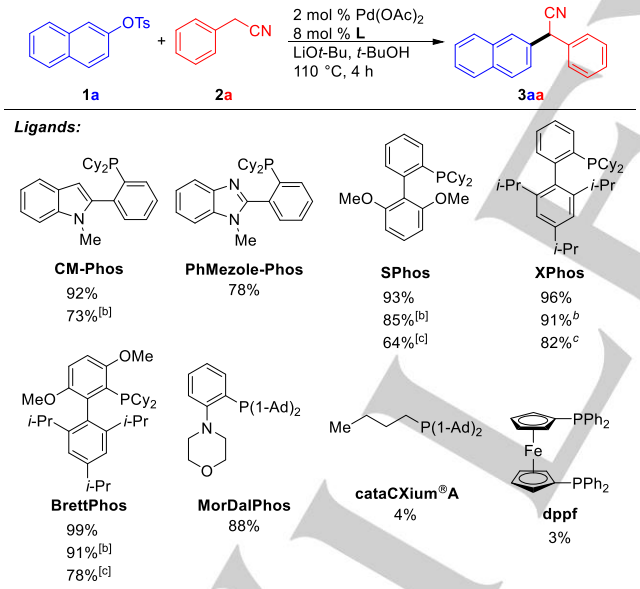
We envisioned that using relatively stable, easily accessible, and inexpensive aryl mesylates and tosylates could be used as the attractive electrophiles for the arylation reaction.[14] However, several challenging issues associated with the reaction have to be resolved: (1) phenolic derivatives and cyano group suffer from severe hydrolysis under the strong alkaline reaction conditions; (2) base-sensitive functional groups are not compatible; (3) further arylation may occur due to the increased acidity of the remaining α-C-H bonds after the first step of arylation of arylacetonitriles, resulting in undesirable mixtures; (4) the competitive coordination of the cyano group may retard the desired reaction; (5) the oxidative addition of relatively inert aryl mesylates and tosylates required electron-rich phosphine, yet it may significantly increase the difficulty of completing reductive

elimination step in the α-arylation reaction.[15] Given our research group's persistent interest in palladium-catalyzed direct C-H arylation with challenging electrophiles,[15c, 16] we herein report our effort in the first general palladium-catalyzed α-arylation of arylacetonitriles with aryl tosylates and mesylates (Scheme 1).



Scheme 1. Palladium-catalyzed α-arylation of arylacetonitriles.

Table 1. Evaluation of Ligand Efficacy[a]

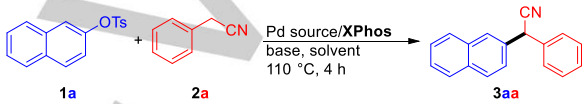


[a] Reaction conditions: 2-naphthyl tosylate (0.5 mmol), benzyl cyanide (0.6 mmol), $Pd(OAc)_2$, (2 mol%), L (8 mol%), LiO*t*-Bu (1.0 mmol) and *t*-BuOH (1.5 ml) were stirred at 110 °C under N_2 for 4 h. Calibrated GC yields were reported using dodecane as the internal standard. [b] 0.5 mol% Pd. [c] 0.1 mol% Pd were used.

During the initial investigation, 2-naphthyl tosylate (**1a**) and benzyl cyanide (**2a**) were chosen as the benchmark substrates. A number of previously reported remarkable ancillary ligands were examined for their potential effectiveness in this α-arylation process (Table 1). Preliminary screening employed indolyl (**CM-Phos**), benzimidazoly (**PhMezole-Phos**), Buchwald's biaryl (**SPhos**, **XPhos,** and **BrettPhos**), and Stradiotto's *P*,*N*-type phosphine ligands (**MorDalPhos**), resulting in good product yields (78-99%). **CataCXium®A** and **dppf** were found to be ineffective. **CM-Phos**, **SPhos**, **XPhos,** and **BrettPhos** gave comparable product yields. When catalyst loading was reduced to 0.1 mol% Pd, **XPhos** provided the best product yield (82%).

After identifying the best ligand, we turned our attention to optimizing the reaction conditions (Table 2). Commonly used solvents were screened (Table 2, entries 1-8), and *t*-BuOH was found to be the best solvent in this reaction. Several inorganic bases were also surveyed. Notably, mild bases (e.g., K_3PO_4 and K_2CO_3 vs. LiO*t*-Bu) were able to promote this reaction, which reduced the undesirable reactions such as the formation of multi-arylated mixtures and hydrolyzed side products from nitriles and aryl sulfonates (Table 2, entry 17 vs. entry 18). An organic base (Et_3N) afforded poor product yield (Table 2, entry 16). $Pd(OAc)_2$ exhibited the best performance among the palladium sources examined (Table 2, entries 18-21).

Table 2. Optimization of reaction conditions for palladium-catalyzed α-arylation of benzyl cyanide with 2-naphthyl tosylate[a]



Entry	Pd (mol% Pd)	solvent	base	%yield[b]
1	$Pd(OAc)_2$ (1)	*t*-BuOH	LiO*t*-Bu	92
2	$Pd(OAc)_2$ (1)	MeOH	LiO*t*-Bu	4
3	$Pd(OAc)_2$ (1)	CPME	LiO*t*-Bu	75
4	$Pd(OAc)_2$ (1)	Dioxane	LiO*t*-Bu	59
5	$Pd(OAc)_2$ (1)	THF	LiO*t*-Bu	20
6	$Pd(OAc)_2$ (1)	Toluene	LiO*t*-Bu	64
7	$Pd(OAc)_2$ (1)	DMF	LiO*t*-Bu	42
8	$Pd(OAc)_2$ (1)	CH_3CN	LiO*t*-Bu	0
9	$Pd(OAc)_2$ (1)	*t*-BuOH	K_3PO_4	93
10	$Pd(OAc)_2$ (1)	*t*-BuOH	K_2CO_3	87
11	$Pd(OAc)_2$ (1)	*t*-BuOH	Cs_2CO_3	0
12	$Pd(OAc)_2$ (1)	*t*-BuOH	Na_3PO_4	71
13	$Pd(OAc)_2$ (1)	*t*-BuOH	NaOAc	2
14	$Pd(OAc)_2$ (1)	*t*-BuOH	KOAc	0
15	$Pd(OAc)_2$ (1)	*t*-BuOH	KF	30
16	$Pd(OAc)_2$ (1)	*t*-BuOH	Et_3N	15
17	$Pd(OAc)_2$ (0.1)	*t*-BuOH	LiO*t*-Bu	82
18	$Pd(OAc)_2$ (0.1)	*t*-BuOH	K_3PO_4	89
19	$Pd(TFA)_2$ (0.1)	*t*-BuOH	K_3PO_4	35
20	$Pd(ACN)_2$ (0.1)	*t*-BuOH	K_3PO_4	82
21	$Pd_2(dba)_3$ (0.1)	*t*-BuOH	K_3PO_4	65

[a] Reaction conditions: 2-naphthyl tosylate (0.5 mmol), benzyl cyanide (0.6 mmol), $Pd(OAc)_2$/XPhos = 1:4 (mol % as indicated), base (1.0 mmol), solvent

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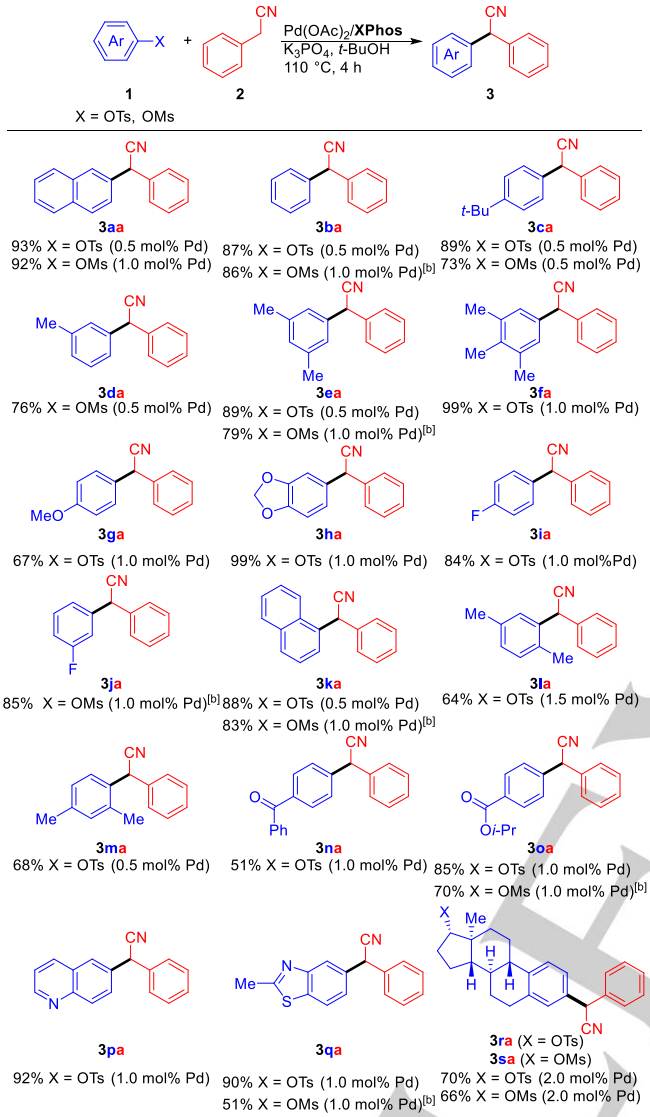
(1.5 ml) were stirred at 110 °C under N_2 for 4 h. Calibrated GC yields were reported using dodecane as the internal standard.

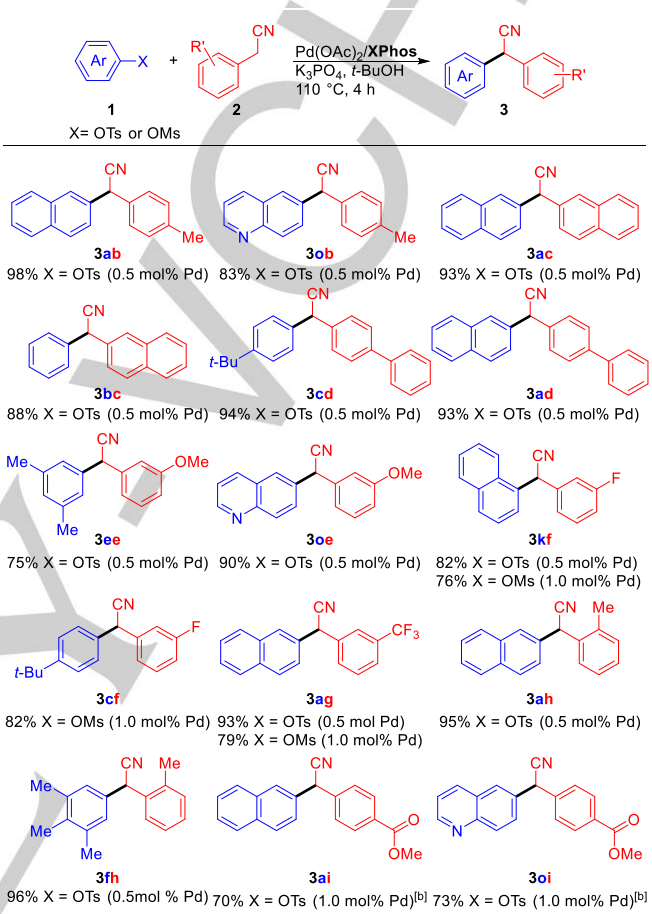
Table 3. Palladium-catalyzed α-arylation of benzyl cyanide with aryl tosylates and mesylates[a]



[a] Reaction conditions: ArOTs or ArOMs (0.5 mmol), benzyl cyanide (0.6 mmol), $Pd(OAc)_2$/XPhos = 1:4 (mol % as indicated), K_3PO_4 (1.0 mmol) and *t*-BuOH (1.5 ml) were stirred at 110 °C under N_2 for 4 h. Isolated yields were reported. [b] K_2CO_3 was used instead of K_3PO_4.

Once the optimized reaction conditions were established, the efficacy of the catalyst system in α-arylation of benzyl cyanide was then evaluated with a wide range of aryl tosylates and mesylates (Table 3). In general, 0.5-2.0 mol% Pd completed the cross-couplings of benzyl cyanide. Electron-neutral and -rich arenes were converted to the corresponding products in good to excellent product yields (Table 3, compounds **3aa**-**3ha**). Electron-deficient arenes, which proved to be difficult substrates in *a*-arylation, gave good product yields (Table 3, compounds **3ia** and **3ja**). Sterically hindered substrates were also found to be applicable in our system (Table 3, compounds **3ka**-**3ma**). Common functional groups such as ketone and ester were compatible under these mild basic reaction conditions (Table 3, compounds **3na** and **3oa**), and heteroaryl tosylates and mesylates were also used as the coupling partners to give excellent product yields (Table 3, compounds **3pa** and **3qa**). In addition, our protocol allowed for modification of the human sex hormone 17β-estradiol. Tosylated and mesylated 17β-estradiol were smoothly coupled with benzyl cyanide to produce the corresponding products (Table 3, compounds **3ra** and **3sa**).

Table 4. Palladium-catalyzed α-arylation of arylacetonitriles with aryl tosylates and mesylates[a]



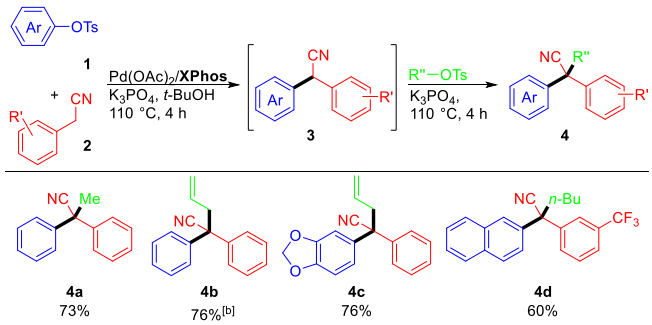
[a] Reaction conditions: ArOTs or ArOMs (0.5 mmol), benzyl nitrile derivatives (0.6 mmol), $Pd(OAc)_2$/XPhos = 1:4 (mol % as indicated), K_3PO_4 (1.0 mmol) and *t*-BuOH (1.5 ml) were stirred at 110 °C under N_2 for 4 h. Isolated yields were reported. [b] K_2CO_3 was used instead of K_3PO_4.

To further expand the substrate scope, we next investigated whether other arylacetonitriles could act as the cross-coupling partners (Table 4). 4-Me, 4-Ph, 3-OMe substituted arylacetonitriles were found to be applicable substrates (Table 4, compounds **3ab**, **3ob**, **3ac**, **3ac**, **3bc**, **3cd**, **3ad**, **3ee,** and **3oe**). Electron-poor arylacetonitriles were suitable counterparts and afforded the corresponding products in good to excellent yields (76-93% yield) (Table 4, compounds **3kf**, **3cf,** and **3ag**). Our system was also capable of handling sterically hindered arylacetonitriles and exhibited good reactivity (Table 4, compounds **3ah** and **3fh**). Arylacetonitriles containing C(O)OMe group was also found to be compatible under these mild reaction conditions (Table 4, compounds **3ai** and **3oi**).

Apart from aryl sulfonates, alkyl and allylic tosylates can also be employed as electrophiles for the further construction of quaternary center-containing compounds which can be accessed via a simple one-pot, two-step approach. The two-step reactions were successfully achieved by adding the second electrophilic partner (alkyl or allylic tosylates) after the first step of α-arylation

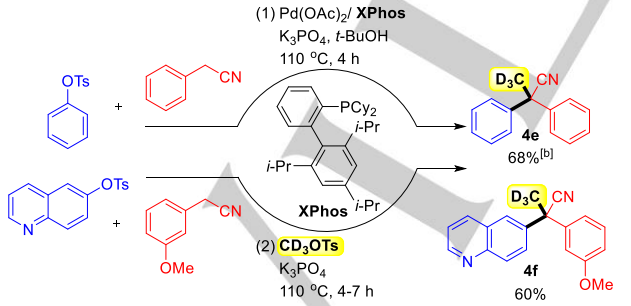
reaction in one-pot (Table 5). Moreover, accessing deuterium compounds in good yields using the deuterated alkyl tosylates is remarkable because it can be easily synthesized using relatively inexpensive deuterated alcohol (Scheme 2). It is particularly noteworthy that no reaction work-up was performed and no additional catalyst was added prior to the second step in the reaction sequence.

Table 5. Synthesis of quaternary center-containing compounds through one-pot, two-step palladium-catalyzed α-arylation of arylacetonitriles with aryl tosylates and alkyl tosylates[a]



[a] 1st-step reaction conditions: ArOTs (0.5 mmol), benzyl nitrile derivatives (0.55 mmol), $Pd(OAc)_2$ (2 mol%), XPhos (8 mol%), K_3PO_4 (1.0 mmol) and *t*-BuOH(1.5 ml) were stirred at 110 °C under N_2 for 4 h. 2nd-step reaction conditions: R''-OTs (0.75 mmol) and K_3PO_4 (1.0 mmol) were stirred at 110 °C under N_2 for 4 h. Isolated yields were reported. [b] 7 h was conducted in 2nd-step.

In conclusion, we report the first general palladium-catalyzed direct α-arylation of arylacetonitriles using aryl/heteroaryl tosylates and mesylate as the electrophilic coupling partners. $Pd(OAc)_2$/**XPhos** catalytic system exhibited excellent compatibility with a wide range of functional groups. Furthermore, this method provided a straightforward modification of biologically active phenolic compounds. The catalyst loading could be achieved with as low as 0.5 mol% of palladium catalyst. α-arylation and α-alkylation in a one-pot sequential manner for the direct synthesis of quaternary center- and deuterium-containing compounds were achieved in good to excellent yields. This general catalyst system offers a convenient synthetic pathway to access versatile diaryl acetonitriles via abundant phenolic compounds.



Scheme 2. Synthesis of deuterium compounds[a] ([a] 1st-step reaction conditions: ArOTs (0.5 mmol), benzyl nitrile derivatives (0.55 mmol), $Pd(OAc)_2$, (2 mol%), XPhos (8 mol%), K_3PO_4 (1.0 mmol) and *t*-BuOH (1.5 ml) were stirred at 110 °C under N_2 for 4 h. 2nd-step reaction conditions: CD_3OTs (0.75 mmol) and K_3PO_4 (1.0 mmol) were stirred at 110 °C under N_2 for 4 h. Isolated yields were reported. [b] 7 h was conducted in 2nd-step.

Acknowledgements

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Keywords: Palladium • Phosphine ligands • α-Arylation• Aryl sulfonates • Nitriles

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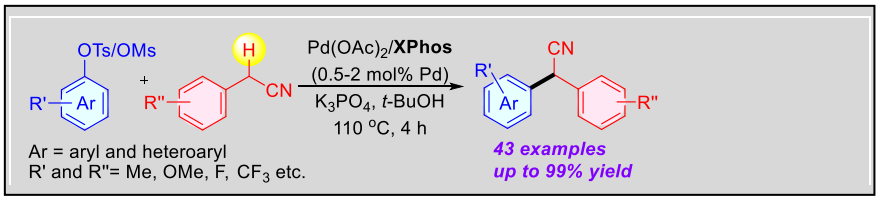
α-Arylation



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