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Synthesis of Biphenyl-2-carbonitrile Derivatives via a Palladium-Catalyzed sp^2 C−H Bond Activation Using Cyano as a Directing Group

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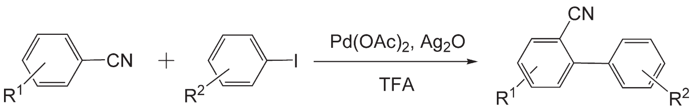
ABSTRACT



Pd^{II}-catalyzed aromatic C−H bond activation using cyano as a directing group was carried out in TFA medium. Biphenyl-2-carbonitrile derivatives were therefore synthesized from aryl nitriles and aryl halides in moderate to good yields.

Aromatic nitriles possess versatile utilities and are indispensible not only in organic synthesis but also in the chemical industry.[1] In fact, the nitrile group is an important precursor for various functional groups such as aldehydes, amines, amidines, tetrazoles, amides, and their carboxyl derivatives.[2] In addition, biphenyls represent a key structural motif in a large number of compounds used as pharmaceuticals, agrochemicals, dyes, chiral ligands for metal catalysts, liquid crystals, organic semiconductors, and materials for molecular recognition devices. Furthermore, the biaryl subunit is present in an extensive range of natural products.[3] Considering the importance of the compounds with these structural units, the development of an efficient approach for the synthesis of biphenyl nitriles is therefore desirable.

In recent years, transition-metal-catalyzed C−H functionalization has emerged as a powerful tool to transform otherwise unreactive C−H bonds into carbon−carbon or carbon−heteroatom bonds.[4] In particular, C−H arylation has become an attractive alternative to traditional C−C cross-coupling reactions due to the minimization of stoichiometric metallic waste and the costs associated with the preparation of starting materials,[5] and many reactions

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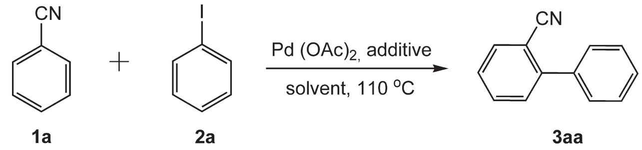
involving directing-group-assisted activation of sp^2 C−H bonds of ortho aromatic C−H bonds have been extensively investigated. Many directing groups, such as acetyl, acetamino, carboxylic acid, oxazolyl, pyridyl, nitro, hydroxyl, and imino moieties have been used for C−H bond activation. Mechanistic studies indicated that aromatic C−H bonds can be activated via five-membered metallacycles.[5,6] A few methods were used to obtain biphenyl nitriles via a directed C−H functionalization, for example, a magnesiation or zincation to arenes with magnesium bis(amide) or zinc bis(amide) and then quenching with aryl iodide, and [7] a palladium-catalyzed benzamide *ortho*-arylation that is then treated with trifluoroacetic anhydride.[8] To the best of our knowledge, no benzonitrile *ortho*-arylation directed by a cyano group has been reported. Herein, we wish to report a new synthesis of biphenyl-2-carbonitrile derivatives from aryl nitriles and aryl halides via a palladium-catalyzed aromatic C−H bond activation using cyano as a directing group.

Initially, benzonitrile **1a** and iodobenzene **2a** were chosen as model substrates for surveying the reaction parameters (Table 1). Pd(OAc)$_2$ was selected as a catalyst for the cross-coupling. We at first performed the reaction under basic or neutral conditions. Unfortunately, no desired cross-coupling product biphenyl-2-carbonitrile **3aa** was observed. An acidic medium appeared possible for this transformation. AcOH, AcOH/toluene (1:1), and TFA were tested as the solvent. The result showed that TFA was the best one in which **3aa** was obtained in 70% yield in 9 h. No reaction took place without a catalyst in this acidic system. Pd(OAc)$_2$ has the dual role of electrophilic activation of the arene and intramolecular deprotonation, as reported previously. Other palladium species, such as PdCl$_2$, Pd(PPh$_3$)$_4$, Pd(dba)$_2$, and Pd nanoparticles (NPs), were substantially less effective (Table 1, entries 13−16). It was found that the nature of the additive plays a critical role on the reaction efficiency. Several silver compounds and oxidants as additive were tested; the best result was obtained by the use of Ag$_2$O (Table 1, entry 6), while Ag$_2$CO$_3$, AgOAc, AgNO$_3$, BQ, K$_2$S$_2$O$_8$, and O$_2$ showed poor reactivity (Table 1, entries 7−12). Increasing reaction temperature led to higher conversion (Table 1, entry 6). When the reaction temperature was raised to 110 °C, it reached the highest yield. Thus, the optimized reaction proceeded using 10 mol % of Pd(OAc)$_2$ as a catalyst with Ag$_2$O as an additive in TFA at 110 °C.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	additive	yield (%)[b]
1	Pd(OAc)$_2$	NMP	Ag$_2$O	0
2	Pd(OAc)$_2$	DMF	Ag$_2$O	0
3	Pd(OAc)$_2$	Toluene	Ag$_2$O	0
4	Pd(OAc)$_2$	AcOH	Ag$_2$O	22
5	Pd(OAc)$_2$	AcOH/toluene	Ag$_2$O	20
6	Pd(OAc)$_2$	TFA	Ag$_2$O	70 (58, 71)[c]
7	Pd(OAc)$_2$	TFA	Ag$_2$CO$_3$	45
8	Pd(OAc)$_2$	TFA	AgOAc	trace
9	Pd(OAc)$_2$	TFA	AgNO$_3$	36
10	Pd(OAc)$_2$	TFA	BQ	trace
11	Pd(OAc)$_2$	TFA	K$_2$S$_2$O$_8$	trace
12	Pd(OAc)$_2$	TFA	O$_2$	trace
13	PdCl$_2$	TFA	Ag$_2$O	trace
14	Pd(PPh$_3$)$_4$	TFA	Ag$_2$O	trace
15	Pd(dba)$_2$	TFA	Ag$_2$O	trace
16	Pd NPs	TFA	Ag$_2$O	trace

[a] Reaction conditions: benzonitrile (1.0 mmol), iodobenzene (2.0 mmol), catalyst (10 mol %), additive (1.0 mmol), and solvent (2.0 mL) at 110 °C for 9 h. [b] Isolated yields. [c] Reaction proceeded at 90 and 120 °C, respectively.

With identification of the optimal reaction conditions, reactions of benzonitrile with various aryl iodides were studied (Table 2). The experiment showed that aryl iodides with an electron-withdrawing substituent gave higher yields of ortho-arylated products than those with an electron-donating group. For example, benzonitrile reacted smoothly with 1-iodo-4-nitrobenzene or 1-iodo-3-nitrobenzene to give the ortho-arylated products in 91 and 93% isolated yield, respectively (entries 3, 4), while it reacted with iodobenzene or 3-iodo-toluene and gave the corresponding products in 70 and 51% isolated yield, respectively (entries 1, 2). Electron-withdrawing groups weaken C−I bonds, which might explain the increased yields. The reaction can finish in 9 h, and the extension of reaction time was not beneficial for increasing the yield (entry 1).

The reactions of various arylnitrile and aryl iodide derivatives were investigated as shown in Table 3. It can be seen that a range of arylnitriles participate in this reaction efficiently. We can also see that, with increasing Hammett constant σ_m values (−0.07, 0.12, and 0.37 for CH$_3$, OCH$_3$, and Cl, respectively)[9] of para substituents of the cyano group of arylnitriles (they are also at the meta position of activated C−H), the yields of the products decreased. Though the exact reason was not very clear, we presume that it decreases the coordinating ability to palladium with increasing inductive electron-withdrawing abilities of those groups. This is different from the substituent effect on aryl iodides. It is noticeable that the reaction has evident compatibility to some functional groups. The groups existed on the aromatic ring of the reactants with a directing function; whether a group was present on

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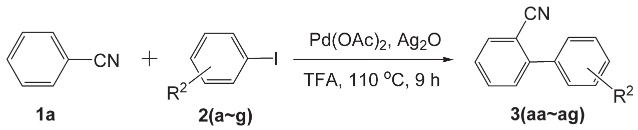
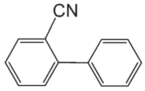
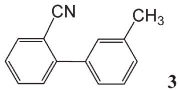
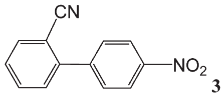
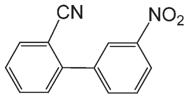
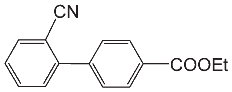
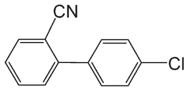
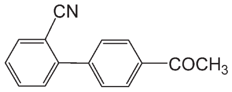
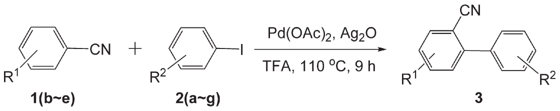
Table 2. Reaction Results of Benzonitrile with Aryl Iodides[a]

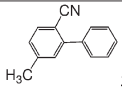
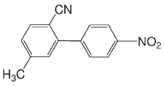
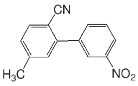
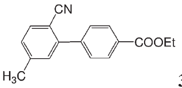
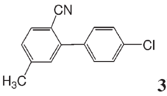
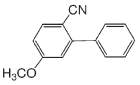
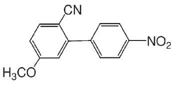
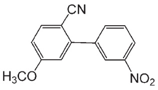
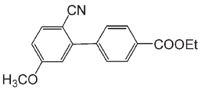
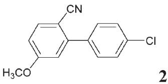
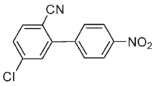
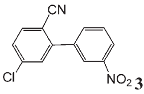
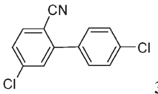
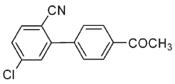
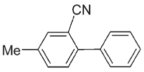
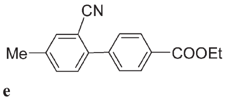
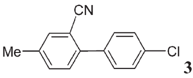


entry	R^2	product	yield (%)[b]
1	H (**2a**)	 **3aa**	70 (55, 70)[c]
2	*m*-CH_3 (**2b**)	 **3ab**	51
3	*p*-NO_2 (**2c**)	 **3ac**	91
4	*m*-NO_2 (**2d**)	 **3ad**	93
5	*p*-COOEt (**2e**)	 **3ae**	83
6	*p*-Cl (**2f**)	 **3af**	73
7	*p*-$COCH_3$ (**2g**)	 **3a** **g**	87

[a] Unless otherwise mentioned, all the reactions were carried out using nitrile **1a** (1.0 mmol), aryl iodide **2** (2.0 mmol), Pd(OAc)$_2$ (10 mol %), and Ag$_2$O (1.0 mmol) in TFA (2.0 mL) at 110 °C for 9 h. [b] Isolated yields. [c] The reaction time was 6 and 12 h, respectively.

Table 3. Reaction Results of Arylnitrile with Aryl Iodides[a]



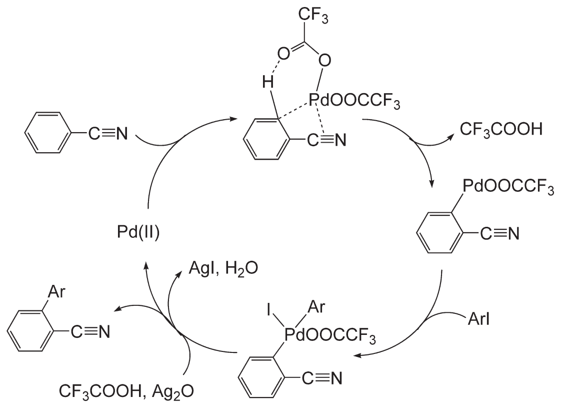
entry	R^1	R^2	product	yield (%)[b]
1	*p*-CH_3 (**1b**)	H (**2a**)	 **3ba**	67
2	*p*-CH_3 (**1b**)	*p*-NO_2 (**2c**)	 **3bc**	91
3	*p*-CH_3 (**1b**)	*m*-NO_2 (**2d**)	 **3bd**	90
4	*p*-CH_3 (**1b**)	*p*-COOEt (**2e**)	 **3be**	83
5	*p*-CH_3 (**1b**)	*p*-Cl (**2f**)	 **3bf**	70
6	*p*-OCH_3 (**1c**)	H (**2a**)	 **3ca**	63
7	*p*-OCH_3 (**1c**)	*p*-NO_2 (**2c**)	 **3cc**	74
8	*p*-OCH_3 (**1c**)	*m*-NO_2 (**2d**)	 **3cd**	81
9	*p*-OCH_3 (**1c**)	*p*-COOEt (**2e**)	 **3ce**	71
10	*p*-OCH_3 (**1c**)	*p*-Cl (**2f**)	 **2cf**	58
11	*p*-Cl (**1d**)	*p*-NO_2 (**2c**)	 **2dc**	62
12	*p*-Cl (**1d**)	*m*-NO_2 (**2d**)	 **3dd**	60
13	*p*-Cl (**1d**)	*p*-Cl (**2f**)	 **3df**	50
14	*p*-Cl (**1d**)	*p*-$COCH_3$ (**2g**)	 **3dg**	55
15	*m*-CH_3 (**1e**)	H (**2a**)	 **3ea**	70
16	*m*-CH_3 (**1e**)	*p*-COOEt (**2e**)	 **3e** **e**	76
17	*m*-CH_3 (**1e**)	*p*-Cl (**2f**)	 **3ef**	85

[a] The reaction conditions were as above. [b] Isolated yields.

arylnitriles, such as methoxyl, or on aryl iodides, such as the acetyl, nitro, and ester group, the directing effect of the cyano group was not overridden. That is to say, no side products were produced in which the substituent on the ortho position of these groups were found, which revealed that the cyano group was more effective in the activation to the ortho C−H bond than the above groups under these reaction conditions.

To account for the present catalytic reaction, a possible mechanism is proposed (Scheme 1). It is different from other directing groups such as acetyl, acetamino, and carboxylic acid assisted activation of sp^2 C−H bonds in which oxygen acts as a coordinating atom; in arylnitriles, the cyano group has a linear configuration, so it will be difficult to form general five-membered metallacycles. For minimizing the ring strain, the coordination of a π-electron between carbon and nitrogen to palladium is possible. Thus, the first step likely involves coordination of arylnitriles to the Pd(II) species followed by ortho C−H activation, in which trifluoroacetate presumably participates in aromatic proton abstraction to form an aryl palladium intermediate. Oxidative addition of aryl iodide to this

Scheme 1. Proposed Reaction Mechanism



intermediate to give a Pd(IV) intermediate followed by reductive elimination affords the product.[5g,j,o,p,10] In fact, as early as 1984, Tremont et al. found that Pd(II) can be oxidized to Pd(IV) by RX.[11] Canty and co-workers showed that diaryliodonium triflates can transfer Ph^+ to Pd(II), leading to the formation of unstable Pd(IV) species that decompose via reductive elimination pathways.[12] Recently, Cheng et al. obtained an aryl palladium intermediate in which C−Pd formed at the ortho position of the directing group.[5o,p] These findings may be relevant to the mechanism of this arylation procedure. Whereas the role of silver oxide in the catalytic reaction is not entirely clear, it likely acts as a halide scavenger to remove iodide and serves to regenerate the Pd catalyst.[5p,13]

In conclusion, we have successfully developed a new method for the synthesis of biphenyl-2-carbonitrile derivatives via a palladium-catalyzed C−H bond activation using cyano as the directing group. To the best of our knowledge, the present reaction is the first example of transition-metal-catalyzed direct arylation of aryl nitrile. Further studies of transition-metal-catalyzed C−H functionalization in the presence of directing groups and detailed mechanistic investigations are in progress in our laboratory.

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Supporting Information Available. Experimental procedures and full characterization for all compounds; copies of ^{1}H and ^{13}C NMR for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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