Cross-Coupling

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Synthesis of α-Aryl Nitriles through Palladium-Catalyzed Decarboxylative Coupling of Cyanoacetate Salts with Aryl Halides and Triflates**

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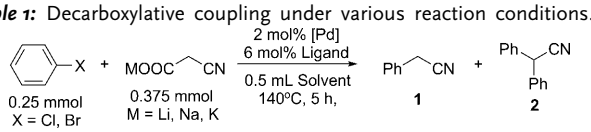
α-Aryl nitriles are versatile intermediates for the synthesis of carboxylic acids, amides, primary amines, aldehydes, and heterocycles.[1] They can also have biological activity as exemplified by medicinal compounds such as anastrozole.[2] Traditional methods for the synthesis of α-aryl nitriles include cyanation of benzylic halides or alcohols,[3] Friedel–Crafts reactions,[4] and dehydration of α-aryl amides.[5] Recently, the groups of Hartwig[6] and Verkade[7] developed new methods that involve palladium-catalyzed α-arylation of nitriles (and also 2-cyanoacetate esters) with aryl chlorides and bromides. The requirement of a strong base (e.g., $NaN(SiMe_3)_2$) in these palladium-catalyzed α-arylation reactions limits the functional group tolerance, and monoarylation is difficult to achieve for acetonitrile and primary nitriles. To solve these two problems, Hartwig et al. described improved methods that use relatively expensive α-silyl nitriles and zinc cyanoalkyl reagents to couple with aryl bromides (but not chlorides).[8] Herein we report a new synthetic strategy for α-monoarylated nitriles through palladium-catalyzed decarboxylative coupling of aryl bromides, chlorides, and even triflates with readily accessible cyanoacetate salts.[9] This new reaction expands the scope and synthetic utility of the catalytic decarboxylative coupling reactions previously developed by the groups of Myers,[10] Forgione,[11] Goossen,[12] and others.[13–15] This work also shows that for some synthetic purposes the decarboxylative coupling not only provides a conceptually alternative method, but also can be practically favored in terms of both reagent accessibility and reaction scope.

Our study began by testing the coupling of chlorobenzene with sodium or potassium cyanoacetate (Table 1). A series of palladium salts, phosphine ligands, and solvents were examined. Under the optimal reaction conditions and using $[Pd_2Cl_2(allyl)_2]$/S-Phos as the catalyst (entry 9), the desired monoarylated product was selectively obtained in 86% yield without the use of any extra base. The same conditions can also be used to achieve the coupling with bromobenzene to produce the monoarylated product selectively (entry 15). Notably, without adding chlorobenzene we observed the formation of acetonitrile as a result of the decarboxylation of cyanoacetate (see the Supporting Information). Also, in a control experiment in which palladium was not added, sodium cyanoacetate did not decompose at 150 °C, thus indicating the essential role of palladium for the decarboxylation process. Moreover, a competition reaction (Scheme 1) was conducted in which 2-phenylacetonitrile was added to the reaction mixture containing 4-bromoanisole and potassium cyanoacetate. The major product of the competition reaction corresponds to the decarboxylative monoarylation of cyanoacetate,

Table 1: Decarboxylative coupling under various reaction conditions.[a]



0.25 mmol, X = Cl, Br; 0.375 mmol, M = Li, Na, K; **1**; **2**

Entry	X, M	[Pd]	Ligand	Solvent	Yield [%] **1**	**2**
1	Cl, K	$[Pd_2(dba)_3]$	$P(Cy)_3$	mesitylene	trace	16
2	Cl, K	$[Pd_2(dba)_3]$	$P(tBu)_3$	mesitylene	trace	trace
3	Cl, K	$[Pd_2(dba)_3]$	X-Phos	mesitylene	10	28
4	Cl, K	$[Pd_2(dba)_3]$	Cy-JohnPhos	mesitylene	trace	21
5	Cl, K	$[Pd_2(dba)_3]$	DavePhos	mesitylene	33	18
6	Cl, K	$[Pd_2(dba)_3]$	Ru-Phos	mesitylene	65	7
7	Cl, K	$[Pd_2(dba)_3]$	*t*BuX-Phos	mesitylene	18	8
8	Cl, K	$[Pd_2(dba)_3]$	S-Phos	mesitylene	69	10
9[b]	**Cl, Na**	**$[Pd_2Cl_2(allyl)_2]$**	**S-Phos**	**mesitylene**	**86**	**trace**
10	Cl, Li	$[Pd_2(dba)_3]$	S-Phos	mesitylene	trace	trace
11	Cl, Na	$[Pd_2(dba)_3]$	S-Phos	DMA	9	23
12	Cl, Na	$[Pd_2(dba)_3]$	S-Phos	diglyme	80	6
13[c]	Cl, Na	$Pd(OAc)_2$	S-Phos	mesitylene	57	13
14[c]	Cl, Na	$Pd(TFA)_2$	S-Phos	mesitylene	63	4
15	**Br, Na**	**$[Pd_2Cl_2(allyl)_2]$**	**S-Phos**	**mesitylene**	**88**	**2**

[a] Yields determined by GC methods using benzophenone as the internal standard (average of two runs). [b] 87% yield of isolated product. [c] 4 mol% [Pd] used. Cy = cyclohexyl, dba = dibenzylideneacetone, DMA = dimethylacetamide, DavePhos = 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl, JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl, RuPhos = 2-dicyclohexylphosphanyl-2′,6′-diisopropoxy-1,1′-biphenyl, S-Phos = 2-(2,6-dimethoxybiphenyl)dicyclohexylphosphine, TFA = trifluoroacetic acid, X-Phos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl.

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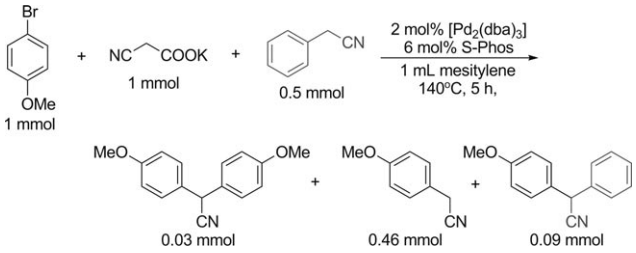
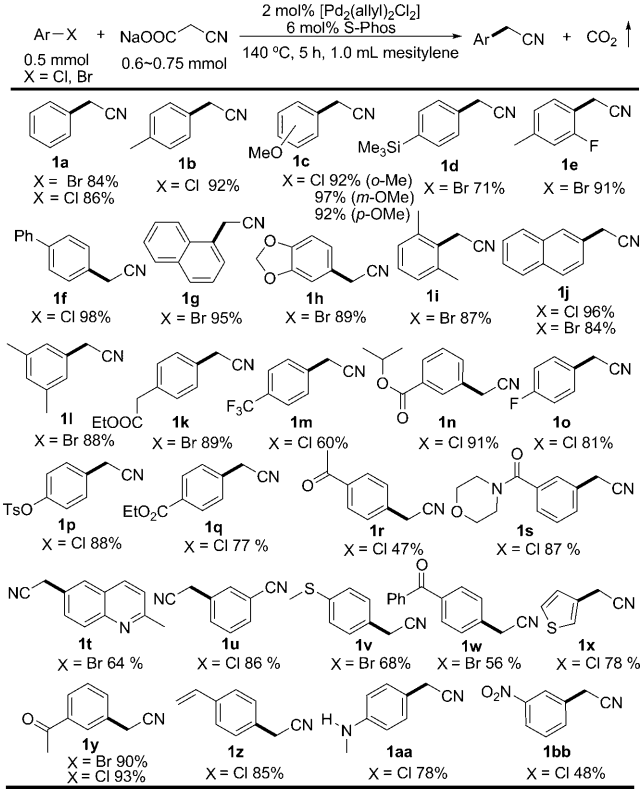


Scheme 1. A competition reaction (amounts of products determined by GC methods; average of two runs).

and a small amount of arylation is observed for 2-phenylacetonitrile. Thus, the diarylated by-product shown in Table 1 may be formed through the deprotonative arylation of the decarboxylative coupling product.

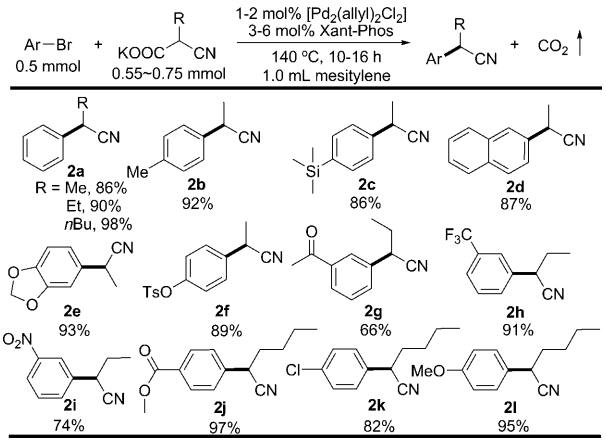
By using the optimized protocol, we explored the scope of this reaction with various aryl halides (Scheme 2). Both electron-rich and electron-poor aryl chlorides as well as bromides can be successfully converted across a wide range of functional groups including ether, thioether, fluoro, ketone, amide, silyl, nitro, tosyl, nitrile, ester, olefin, and amine groups. Substitution at the *ortho* positions (**1c** and **1i**) can be well tolerated. Heterocyclic halides (**1t** and **1x**) are also good substrates. Most significantly, base-sensitive functional groups (e.g., ketones and esters with enolizable hydrogen atoms) can



Scheme 2. Decarboxylative coupling of sodium cyanoacetate. Yields are of isolated products. The low yields for some substrates (e.g. **1m**) are due to the formation of the diarylation by-product. See the Supporting Information for more details.

be tolerated in the present reaction (**1k**, **1r**, **1y**). Finally, it is interesting to observe that olefins that may undergo Heck coupling reaction first (**1z**) and amines that have a free protic functionality (**1aa**,) can survive the present reaction conditions.

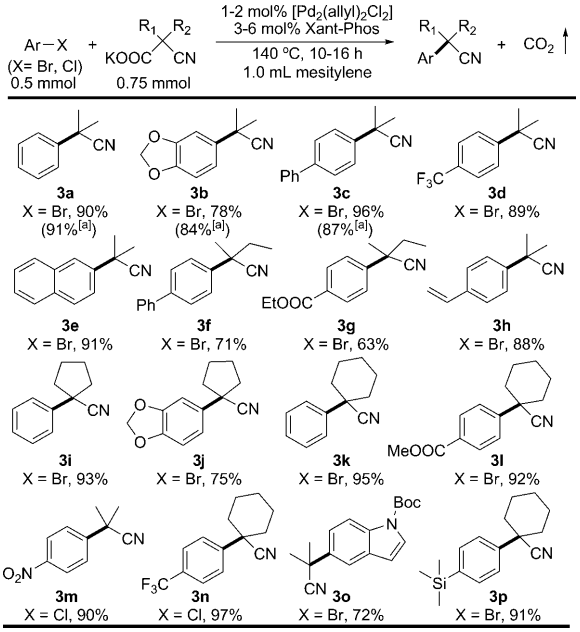
However, use of the above protocol, decarboxylative coupling of the 2-cyanopropanoate salt with 4-bromobiphenyl gave the desired product, 2-(biphenyl-4-yl)propanenitrile, in a relatively low yield (47%). Careful analysis of the reaction mixture reveals the formation of biphenyl (40%), thus suggesting the possible occurrence of a β-hydride elimination. To solve this problem we changed the ligand to Xant-Phos, which has been shown to effectively inhibit β-hydride elimination.[16] To our gratification, the modified protocol can be used to accomplish decarboxylative coupling of tertiary and even quaternary (including cyclic) cyanoacetate salts in good to excellent yields (Schemes 3 and 4). Selective monoarylation is successfully achieved for tertiary cyanoace-



Scheme 3. Decarboxylative coupling of tertiary cyanoacetates. Yields are of isolated products. See the Supporting Information for more details. Note that the potassium salts were used for the reactions, because some sodium salts of tertiary cyanoacetates are hygroscopic and difficult to prepare as a solid. Xant-Phos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

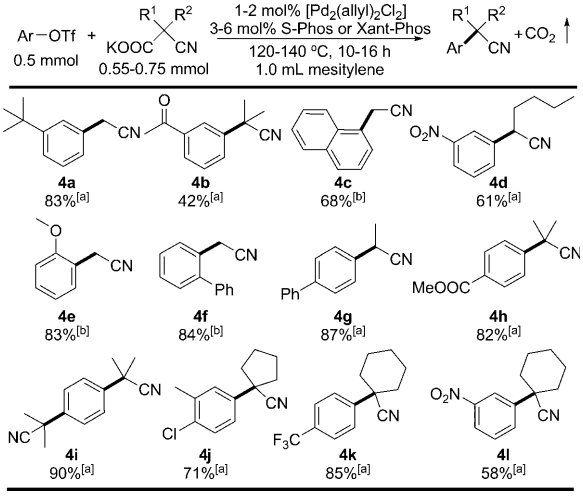
tate salts, which compares favorably with palladium-catalyzed α-arylation of nitriles under highly basic conditions. Also, base-sensitive groups such as ketones with enolizable hydrogen atoms can survive the reaction conditions. In addition, all the functional groups that were previously shown to be compatible in the arylation of zinc and silicon cyanoalkyl reagents[8] are tolerated in the present reactions. It is important to point out that the tertiary and quaternary cyanoacetate salts can be easily prepared from ethyl cyanoacetate, whereas the corresponding zinc and silicon cyanoalkyl reagents are relatively more expensive to obtain.[8] Furthermore, for the quaternary cyanoacetate salts it is impossible to involve any deprotonative arylation. This feature distinguishes the present decarboxylative coupling reaction from the palladium-catalyzed arylation of ethyl cyanoacetate.[6–7]

Notably, the previous palladium-catalyzed α-arylation reactions of nitriles[6,7] or coupling reactions with α-silyl



Scheme 4. Decarboxylative coupling of quaternary cyanoacetates. Yields are of isolated products. See the Supporting Information for more details. Note that the potassium salts were used for the reactions, because some sodium salts of quaternary cyanoacetates are hygroscopic and difficult to prepare as a solid. [a] $NaOOCCMe_2CN$ was used.

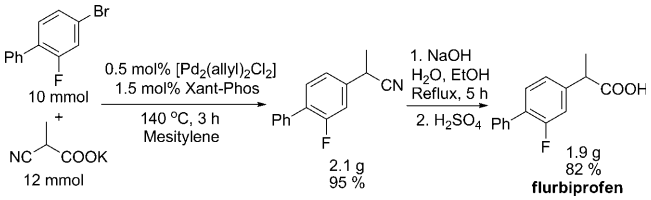
nitriles and zinc cyanoalkyl reagents[8] only used aryl bromides and chlorides as substrates. In the present decarboxylative coupling, we are delighted to find that aryl triflates can also be used as the arylation reagents (Scheme 5). This feature additionally expands the utility of the new reaction for α-aryl nitrile synthesis, because aryl triflates are more readily accessible from phenols. Interestingly, a slightly lower temperature (120 °C) can be used for the decarboxylative coupling with aryl triflates. The reaction tolerates *ortho* substitution (**4e** and **4f**) and base-sensitive groups (**4b**). Both



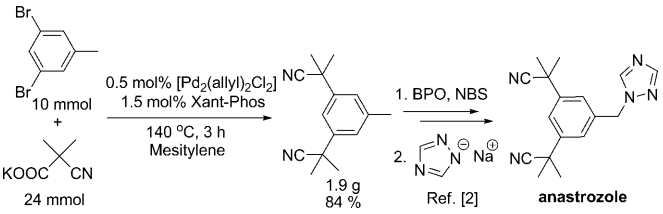
Scheme 5. Decarboxylative coupling with aryl triflates. Yields are of isolated products. See the Supporting Information for more details. [a] Xant-Phos was used. [b] S-Phos was used.

electron-rich and electron-poor aryl triflates are good substrates, whereas secondary, tertiary, and quaternary cyanoacetate salts are all acceptable coupling partners. In addition, the chloro substitution can be tolerated in the transformation (**4j**), making possible to accomplish selective sequential cross-coupling reactions.

Application of the new decarboxylative coupling on a gram-scale synthesis was tested for the preparation of flurbiprofen,[17] which is a nonsteroidal anti-inflammatory drug (Scheme 6), and anastrozole,[2] which is a drug used to treat breast cancer (Scheme 7). For flurbiprofen, the decar-



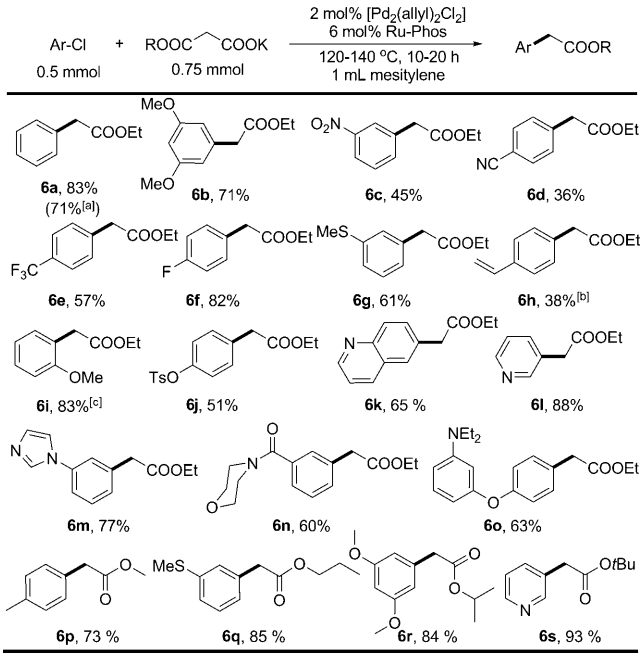
Scheme 6. Synthesis of flurbiprofen.



Scheme 7. Synthesis of anastrozole. BPO = benzoyl peroxide, NBS = *N*-bromosuccinimide.

boxylative coupling of potassium 2-cyanopropanoate with commercially available 4-bromo-2-fluorobiphenyl affords the nitrile intermediate in 95% yield. Hydrolysis of this nitrile intermediate gives the target compound in 82% yield.[17] As for anastrozole, the decarboxylative coupling of potassium 2-cyano-2-methylpropanoate with commercially available 3,5-dibromotoluene affords the key nitrile intermediate in 84% yield. This intermediate can be readily converted into the target compound through previously established benzylic bromination and substitution reactions.[2]

Finally, it is important to point out that the concept of decarboxylative coupling at the α-carbon atom is not limited to nitriles, but can be extended to carbonyl compounds.[18] For instance, in Scheme 8 we show the decarboxylative coupling of malonate monoester salts with aryl chlorides. This new reaction provides an alternative approach for the synthesis of α-arylated esters that complements the previous palladium-catalyzed α-arylation of esters.[19] The functional group tolerance of the transformation is fairly good and encompasses ether, thioether, fluoro, amide, nitro, tosyl, nitrile, olefin, amine, and heterocyclic groups. Again, the decarboxylative coupling does not need to use any of the strong bases (e.g., $LiN(SiMe_3)_2$ or $LiNCy_2$) that were previously required in the palladium-catalyzed α-arylation of esters.[19] More detailed studies on the decarboxylative coupling of esters and



Scheme 8. Decarboxylative coupling of malonate monoesters. Yields are of isolated products. See the Supporting Information for the optimization studies and detailed procedures. [a] 6 mol% S-Phos was used as ligand. [b] 0.6 mmol potassium 3-ethoxy-3-oxopropanoate was used. [c] 1.5 mmol potassium 3-ethoxy-3-oxopropanoate was used; 36 h.

other types of carbonyl compounds are ongoing in our laboratory.

In summary, we present the palladium-catalyzed decarboxylative coupling of a cyanoacetate salt and its substituted derivatives with aryl chlorides, bromides, and even triflates. The new reaction is potentially useful for the preparation of diverse α-aryl nitriles from readily accessible reactants under relatively convenient reaction conditions. In comparison to the previous methods that use either nitriles or zinc and silicon cyanoalkyl reagents, there are several important advantages of the new reaction including good selectivity towards monoarylation, good functional group tolerance, and good availability of the reactants. Moreover, the concept of α-carbon decarboxylative coupling was extended to carbonyl compounds as an alternative approach for the synthesis of, for instance, α-arylated esters.

Experimental Section

A typical procedure for the decarboxylative coupling of sodium cyanoacetate (**1b** in Table 1): A 10 mL oven-dried Schlenk tube was charged with $[Pd_2(allyl)_2Cl_2]$ (2 mol%, 3.7 mg, 0.01 mmol), S-Phos (6 mol%, 12.3 mg, 0.03 mmol), and sodium cyanoacetate (79.5 mg, 0.75 mmol). The tube was evacuated and filled with argon (this procedure was repeated three times). Then 1-chloro-4-methylbenzene (63 mg, 0.50 mmol) and mesitylene (1.0 mL) were added with a syringe under a counter flow of argon. The tube was sealed with a screw cap, stirred at RT for 10 min, and connected to the Schlenk line which was full of argon. The reaction was stirred in a preheated oil bath (140 °C) for 5 h. Upon completion of the reaction, the mixture was cooled to RT. Purification of the residue by column chromatography (silica gel, ethyl acetate/hexane gradient) yielded 2-p-tolylacetonitrile (**1b**) as a colorless liquid (60 mg, 92%). Spectroscopic data matched those described in the literature.

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