ORGANIC LETTERS

2011
Vol. 13, No. 11
2912–2915

Palladium-Catalyzed Decarboxylative Arylation of Potassium Cyanoacetate: Synthesis of α-Diaryl Nitriles from Aryl Halides

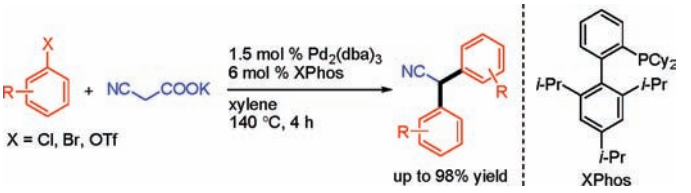
Pui Yee Yeung, Kin Ho Chung, and Fuk Yee Kwong*

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong

bcfyk@inet.polyu.edu.hk

Received April 11, 2011

ABSTRACT



A palladium-catalyzed decarboxylative coupling of potassium cyanoacetate with aryl bromides and chlorides is described. The reaction conditions feature the absence of additional strong inorganic bases and provide ester functional group tolerance. With $Pd(dba)_2$ and XPhos ligand as the catalyst system, α-diaryl nitriles can be obtained in good yields.

α-Arylated nitriles are important substructures in naturally occurring molecules and pharmaceutically useful compounds (Figure 1).[1] The nitrile moiety is a versatile functional group that allows further organic transformations to give the corresponding substituted carboxylic acids, aldehydes, amides, and amines, as well as nitrogen heterocycles.[2] The Friedel–Crafts reactions,[3] dehydration of α-substituted amides,[4] and cyanation of benzyl halides[5] are the traditional methods for synthesizing α-aryl nitriles.

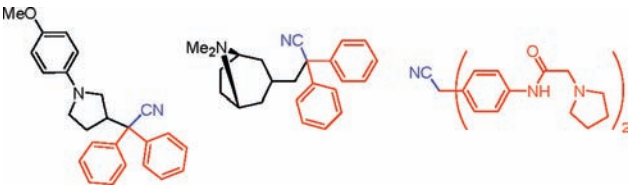


Figure 1. Selected examples of pharmaceutically useful α-diarylated nitriles.

Recently, a palladium-catalyzed α-arylation of nitriles with aryl halides was independently established by Hartwig[6] and Verkade[7] groups. This protocol applied a strong base, $NaN(TMS_3)_2$, and limited the base-sensitive functional group compatibility. A significantly improved method was later reported by Hartwig and co-workers

(1) (a) Onuki, M.; Nishiyama, A. JP Patent, JP2010095453 A20100430. (b) Baker, D.; Burce, M.; Cahn, A.; Thomas, M. *PCT Int. Appl.* WO2010097114, A1 20100902, 2010. (c) Kuwata, K.; Kimura, T.; Muto, J. *PCT Int. Appl.* WO2010131717, A1 20101118, 2010. (d) Tyagi, O. D.; Ray, P. C.; Chauhan, Y. K.; Rao, K. Babu.; Reddy, N. M.; Reddy, D. S. P., *PCT Int. Appl.* WO2009125430, A2 20091015, 2009. (e) Alnabari, M.; Freger, B.; Arad, O.; Zelikovitch, L.; Seryi, Y.; Danon, E.; Davidi, G.; Kaspi, J. U.S. Patent 2006/0035950 A1, 2006. For a review describing the use of coupling technology for preparing pharmaceutically useful compounds, see: (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(2) Friedrich, K.; Wallenfels, K. *The Chemistry of the Cyano Group*; Wiley-Interscience: New York, 1970.

(3) For selected example, see: Kurz, M. E.; Lapin, S. C.; Mariam, A.; Hagen, T. J.; Qian, X. Q. *J. Org. Chem.* **1984**, *49*, 2728.

(4) For selected example, see: Narsaiah, A. V.; Nagaiah, K. *Adv. Synth. Catal.* **2004**, *346*, 1271.

(5) Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573.

(6) For an account, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. For their initial developments, see: (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (c) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641.

(7) (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.

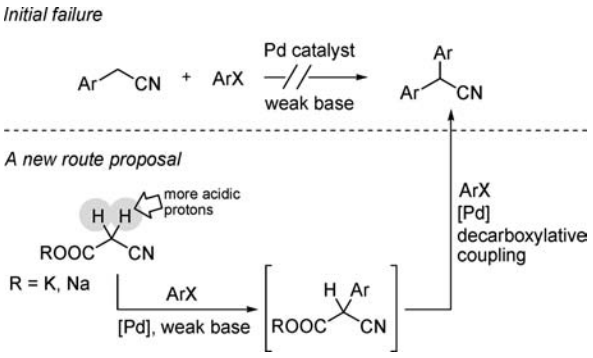
10.1021/ol2009522
Published on Web 05/05/2011

using relatively expensive α-silyl nitriles and zinc cyanoalkyl reagents for coupling of aryl bromides.[8]

Decarboxylative couplings have been successful as an alternative C−C bond construction process to traditional cross-coupling reactions. Recently, Forgione,[9] Glorius,[10] Goossen,[11] Liu,[12] Myers,[13] Tunge,[14] and others[15] made significant advancements of decarboxylative coupling using various electrophiles and nucleophiles. Yet, to the best of our knowledge, there have been very limited literature reports[16] describing the decarboxylative method for accessing 2-arylacetonitrile-related skeletons. Inspired by the advantages of using decarboxylative coupling (in the absence of transmetallating agent, e.g., B, Zn, Mg, Si, etc.)[17] and our continuing progress in nitrile synthesis,[18] we were attracted to developing a decarboxylative protocol for preparing α-substituted nitriles. Herein, we report our exploration on decarboxylative coupling of potassium cyanoacetates with aryl halides for synthesizing the α-diarylated nitriles. This protocol features both coupling partners that are readily available.

We embarked on this investigation from our initial failure in the arylation of benzylic nitrile using weak bases under palladium catalysis (Scheme 1). This reaction did not proceed, possibly because of the inefficient basicity of the weak base for assisting α-deprotonation of nitriles. Thus, if the acidity of the α-proton is increased by an additional neighboring activating group, this process would likely be viable.[19] Hence, we chose cyanoacetate as the substrate for the attempted diarylation process (Scheme 1). Having the additional carboxylic group, this type of substrate offers both the feasibility of α-deprotonation/arylation and a subsequent decarboxylative arylation step.

Scheme 1. Investigations on the Protocol for α-Diaryl Nitrile Synthesis



We began to examine the proposed study by using potassium cyanoacetate and 4-chlorotoluene as the coupling partners (Table 1). A scanning of commercially available palladium precursors revealed that $Pd(dba)_2$ and $Pd(OAc)_2$ were the best choice (entries 1−6). Commonly used phosphine ligands for aryl chloride coupling reactions were screened. XPhos[20] gave the best results, while SPhos[21] and CM-phos[22] provided slightly lower product yield (entries 6−8). CataXium A,[23] CataXium PCy, and CataXium PInCy[24] did not promote this reaction well (entries 9−11). Xylene and mesitylene solvents gave excellent yield, while DMF solvent afforded low substrate conversion (entries 12−14). This decarboxylative coupling did not proceed at 100 °C (entry 15).

(8) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(9) Forgione, P.; Brochu, M. C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.

(10) (a) Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006. (b) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.

(11) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (c) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103. (d) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (e) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (f) Goossen, L. J.; Rodriguez, N.; Lange, P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111.

(12) (a) Shang, R.; Yang, Z. W.; Wang, Y.; Zhang, S. L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391. (b) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638. (c) Shang, R.; Fu, Y.; Li, J. B.; Zhang, S. L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (d) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350.

(13) (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

(14) (a) Weaver, J. D.; Ka, B. J.; Morris, D. K.; Thompson, W.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *13*, 12179. (b) Recio, A., III; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5630. (c) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138. (d) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002.

(15) For other recent selected references, see: (a) Fang, P.; Li, M.; Ge, H. *J. Am. Chem. Soc.* **2010**, *132*, 11898. (b) Lindh, J.; Sjoberg, P. J. R.; Larhed, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7733. (c) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun* **2008**, 6312. (d) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

(16) During the completion of the manuscript, a Pd-catalyzed mono-α-arylation of nitriles appeared (April 7, 2011); see: Shang, R.; Ji, D.-S.; Chu, L.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, Early View.

(17) For research books of traditional cross-couplings using transmetallating agents, see: (a) de Meijere, A.; Diederich, F., Ed. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1−2. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis, Building Blocks and Fine Chemicals*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1−2. (c) Negishi, E., Ed. *Handbook of Organopalladium for Organic Synthesis*; Wiley-Interscience: New York, 2002; Vols. 1−2. (d) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004.

(18) (a) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918. (b) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 648.

(19) For a recent review on Pd-catalyzed α-arylation of the activated methylene group, see: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. For our previous investigation on α-arylation of 1,3-dicarbonyl compounds, see: Yip, S. F.; Cheung, H. Y.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469.

(20) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

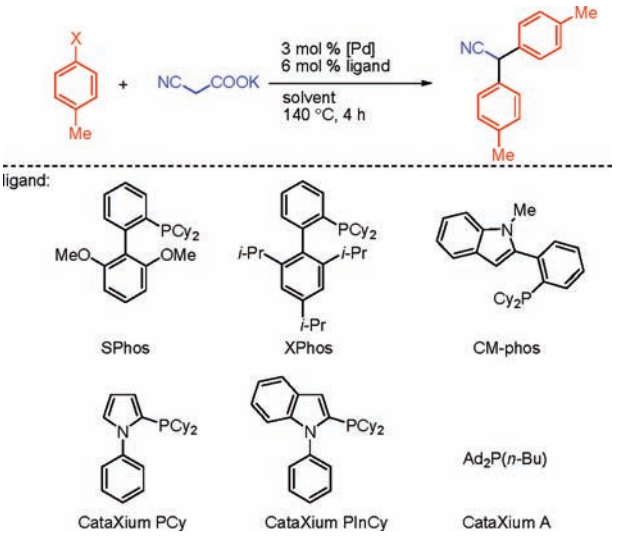
(21) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(22) (a) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402. (b) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. (c) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731.

(23) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153.

(24) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.

Table 1. Screening of Reaction Conditions[a]

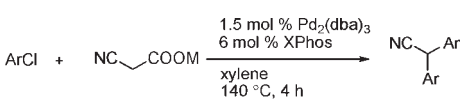


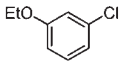
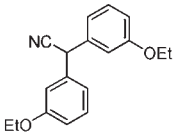
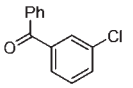
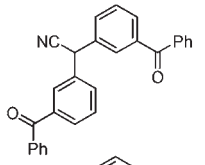
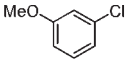
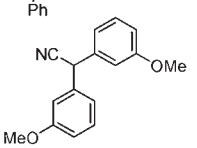
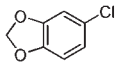
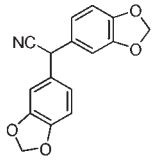
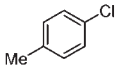
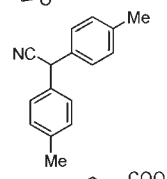
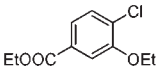
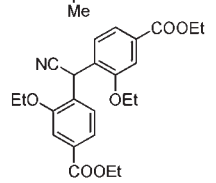
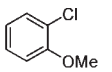
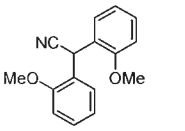
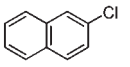
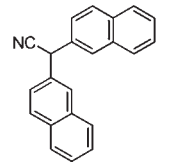
entry	Pd precursor	ligand	yield[b] (%)
1	$PdCl_2$	XPhos	77
2	$Pd(MeCN)_2Cl_2$	XPhos	46
3	$Pd(COD)Cl_2$	XPhos	30
4	$Pd(OAc)_2$	XPhos	92
5	$[Pd(allyl)Cl]_2$	XPhos	66
6	$Pd_2(dba)_3$	XPhos	96 (92)[c]
7	$Pd_2(dba)_3$	SPhos	81
8	$Pd_2(dba)_3$	CM-phos	87
9	$Pd_2(dba)_3$	CataXium A	31
10	$Pd_2(dba)_3$	CataXium PCy	0
11	$Pd_2(dba)_3$	CataXium PInCy	54
12[d]	$Pd_2(dba)_3$	XPhos	57
13[e]	$Pd_2(dba)_3$	XPhos	12
14[f]	$Pd_2(dba)_3$	XPhos	92
15[g]	$Pd_2(dba)_3$	XPhos	4

[a] Reaction conditions: 4-chlorotoluene (0.5 mmol), palladium precursor (3.0 mol % or 1.5 mol % for Pd dimer), ligand (6.0 mol %), potassium cyanoacetate (0.5 mmol), xylene (1.0 mL) were stirred at 140 °C for 4 h under nitrogen. [b] Calibrated GC yields were reported using dodecane as the internal standard. [c] Isolated yield in parentheses. [d] Reaction was conducted with $Pd(dba)_2$ (1.0 mol %). [e] Reaction was conducted in DMF instead of xylene. [f] Reaction was conducted in mesitylene instead of xylene. [g] Reaction was conducted at 100 °C for 24 h.

Having the optimized reaction conditions in hand, we next tested a series of substituted aryl chlorides in this decarboxylative coupling (Table 2). Ortho-, meta-, and para-substituted aryl chlorides coupled smoothly with cyanoacetates to generate α-diaryl nitriles. Keto and ester functional groups were found to be compatible under these reaction conditions (entries 3, 4, 11, and 12). Sterically hindered aryl chlorides showed applicability in this decarboxylative coupling (entries 11–14). Naphthyl chloride gave a moderate product yield, associated with naphthalene side product (entries 15 and 16). In general, potassium cyanoacetate performed better than sodium cyanoacetate in this reaction, except for the naphthyl- and keto-substituted coupling partners.

Table 2. Palladium-Catalyzed Diarylation of Potassium/Sodium Cyanoacetates with Aryl Chlorides[a]

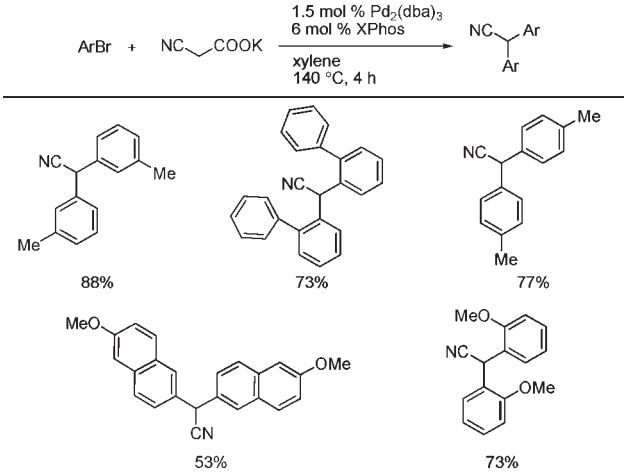


entry	ArCl	cyanoacetate	product	yield %[b]
1		NC COOK		87
2		NC COONa		53
3		NC COOK		58
4		NC COONa		62
5		NC COOK		83
6		NC COONa		85
7		NC COOK		72
8		NC COONa		42
9		NC COOK		92
10		NC COONa		78
11		NC COOK		98
12		NC COONa		88
13[c]		NC COOK		90
14[c]		NC COONa		58
15		NC COOK		58
16		NC COONa		82

[a] Reaction conditions: ArCl (0.5 mmol), $Pd_2(dba)_3$ (1.5 mol %), XPhos (6.0 mol %), potassium/sodium cyanoacetate (0.5 mmol), xylene (1.0 mL) were stirred at 140 °C for 4 h under nitrogen (reaction times were not optimized for each substrate). [b] Isolated yields. [c] $[Pd(allyl)Cl]_2$ was used instead of $Pd_2(dba)_3$.

Scheme 2 illustrates the arylation of potassium cyanoacetate using aryl bromides. No coupling products were found when the reaction temperature was lowered to 110 °C. Substituted aryl bromides were coupled smoothly to furnish desired products. Notably, a highly sterically

Scheme 2. Palladium-Catalyzed Diarylation of Potassium Cyanoacetates with Aryl Bromides[a]

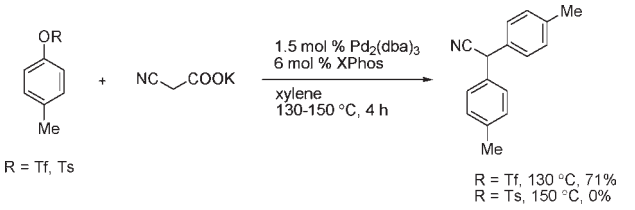


[a] Reaction conditions: ArBr (0.5 mmol), $Pd(dba)_2$ (3.0 mol %), XPhos (6.0 mol %), potassium cyanoacetate (0.5 mmol), and xylene (1.0 mL) were stirred at 140 °C for 4 h under nitrogen (reaction times were not optimized for each substrate). Isolated yields were reported.

hindered 2-bromobiphenyl was found to be a feasible coupling partner in this reaction.

To expand the substrate scope further, we next investigated the possibility of using phenol-derived electrophiles as the coupling partners (Scheme 3). It should be noted that previous α-arylations of nitriles applied strong bases and were incompatible with base-sensitive aryl triflates.[6,7] Under our new reaction conditions, *p*-tolyl triflate was found to couple well with potassium cyanoacetate (Scheme 3).

Scheme 3. Palladium-Catalyzed Diarylation of Potassium Cyanoacetates with Aryl Sulfonates



However, the arylation did not proceed when aryl tosylate was used.

In summary, we have developed a simple decarboxylative arylation of cyanoacetates using aryl chlorides, bromides, and sulfonates as the coupling partners. We believe this Pd system will be useful for α-diaryl nitrile synthesis. Further mechanistic studies are in progress.

Acknowledgment. We thank the Research Grants Council of Hong Kong (GRF: PolyU5008/08P) and PolyU Internal Competitive Research Grant (A-PG13) for financial support. A UGC special large equipment grant (SEG PolyU01) is gratefully acknowledged.

Supporting Information Available. Detailed experimental procedures, compound characterization data, and copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.