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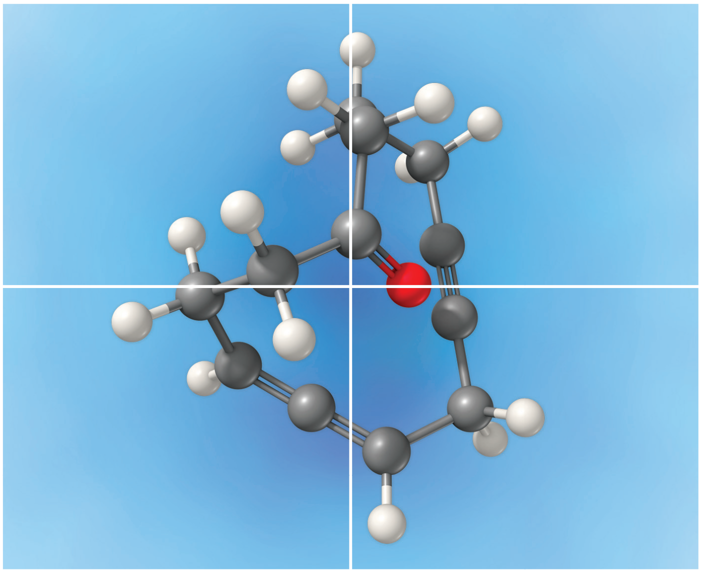

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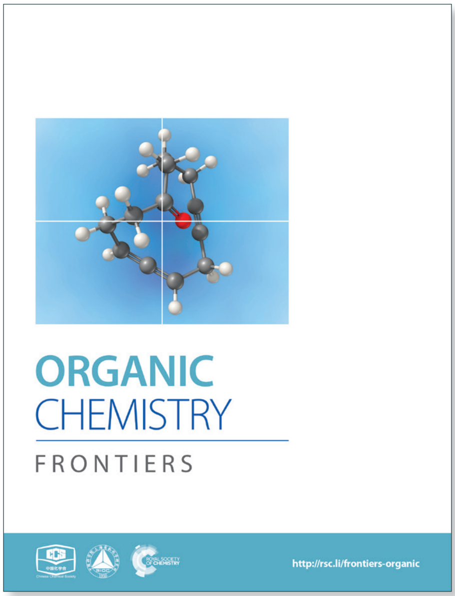

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Sandmeyer Cyanation of Arenediazonium Tetrafluoroborate Using Acetonitrile as Cyanide Source

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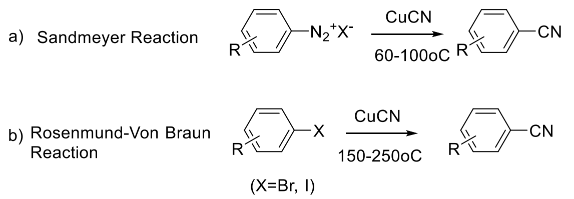
Palladium-catalyzed cyanation of aryldiazonium tetrafluoroborate using acetonitrile as non-metallic cyanide source was achieved in the presence of Ag_2O under ambient air, eliminating the involvement of highly toxic CuCN used in traditional Sandmeyer reaction, in which CN group comes from metallic cyanides. Substrate scope and limitation of this protocol was investigated.

Introduction

The development of methods for the introduction of cyano groups into functionalized arenes is of great interest in organic synthesis because aromatic nitriles not only present widely as a key functional group in various natural products, biologically active molecules and designed functional materials, [1] but also are important precursor to a variety of functional groups, such as aldehydes, amines, amidines, tetrazoles, amides, and other carboxy derivatives. [2] One group of the main method available for the synthesis of aromatic nitriles is the traditional direct cyanation of Ar-X [$X=N_2^+Y^-$, I, Br, Cl, OTf, $B(OR)_2$, etc] with cyano-group originally from metal cyanide (MCN), [3] for which the Sandmeyer reaction of aryldiazonium salts [4] and Rosenmund-Von Braun reaction of aryl halides [5] are two representative methods (**Scheme 1**).



Scheme 1. Traditional Sandmeyer reaction and Rosenmund-Von Braun reaction.

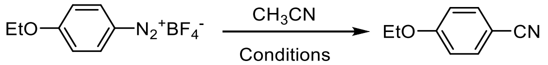
In previous investigations on Sandmeyer reaction and Rosenmund-Von Braun reaction, various kinds of CN sources have been widely explored. [6] Conventional CN sources metal cyanide (MCN) are limited by their toxicity and hazardous handling. Thus in recent years non-metallic CN sources such as aceto cyanohydride, N-cyano-N-phenyl-p-toluenesulfonamide (NCTS), BnSCN, DDQ, tert-butylisocyanide, ethyl cyanoacetate, benzyl cyanide, malononitrile, N-cyanobenzimidazole etc, [7] have been investigated as promising alternatives, particularly along with their contribution to the development of C-H functionalization as well. [8] Special among various CN sources investigated, acetonitrile is very appealing as a potential economic candidate, even though it has rarely been explored as cyanide precursor due to its strong C-CN energy. [9] In 1998, Cheng demonstrated the activation and cleavage of acetonitrile C-CN bond in the cyano-group transfer to aromatic bromides mediated by metal complexes of the palladium and zinc species. [10a] This is the first example of Rosenmund-Von Braun reaction that used acetonitrile as CN sources, even though it was limited to bromoarenes with methyl at *ortho* position and the low yields reported depended strongly on the amount of the phosphine ligand. A few other reports appeared later in regard to C-CN bound activation and cleavage with transition metal as catalyst.[10b~f] Similar to the initial report, in 2012 Li developed a Cu/Ag system for the oxidative cyanation of aryl iodides with acetonitrile. [11] Recently, the economic cyanation of aromatic C-H bond mediated by Cu/Ag and Cu/Si system with inert acetonitrile have been documented by Zhu and Shen respectively. [12, 13] These reports and mechanistic investigations open a new door for transition metal mediated inert alkylnitrile C-CN bond activation and cleavage for the introduction of new aromatic C-CN bond. However there is no report on the utilization of Sandmeyer substrates aryldiazonium salt in this type of transformation.

On the other hand, while a variety of transition-metal catalyzed procedures were developed successfully in Rosenmund von Braun reaction for aryl halides, [14] limited number of investigation has been recorded on Sandmeyer reaction for catalytic cyanation of aryldiazonium salt. [15] In recent years, using aryldiazonium salt as substrate, very useful transition metal (TM) catalyzed protocols for the formation of C-C, C-F, C-CF_3, C-S bond through cross coupling process have been described. [16] These investigations proved the high versatility of aryldiazonium salt. Furthermore, aryldiazonium salts are readily accessible from various aromatic amines through diazotized reaction with $NaNO_2$ or other organic nitriles. Taking into consideration of above mentioned points, we envisioned that TM catalyzed Sandmeyer cyanation of aryldiazonium salt with non-metallic CN sources would be of great interest. Herein, we would like to report the cyanation of aryldiazonium tetrafluoroborates with CH_3CN as the CN source under TM conditions.

To examine the feasibility of the proposed reaction, we started with *p*-ethoxybenzenediazonium fluoroborate **1a** as the model substrate. The combination of one equivalent of $Cu(OAc)_2$ and Ag_2O have been shown to be effective in catalyzing cyantion of arylhalide with CH_3CN as the CN source, [11, 12] we started with this combination in our initial exploration of the condition. As shown in **Table 1**, the $Cu(OAc)_2/Ag_2O$ combination turned out to be ineffective in promoting the cyanation of *p*-ethoxybenzenediazonium salts by CH_3CN (entry 1). With arylhalide, the reference reported elevated temperature to drive the reaction; in our case the Arenediazonium fluoroborate substrates are not stable at elevated temperature. However it was pleasing to find out that switching to catalytic amount of $Pd(OAc)_2$ coupled with one equivalent of Ag_2O at 55℃ for 24 h gave fair amount of expected product (entry 2). Replacing $Pd(OAc)_2$ with $PdCl_2$ further improved the yield modestly (entry 3). In an attempt to determine the role of each component of this combination, we tested with either catalytic amount of $PdCl_2$ or one equivalent of Ag_2O alone, not any cyanation product was observed in both cases (entries 4 and 5). Therefore $PdCl_2$ was utilized as the catalyst of choice in the current study, and a series of experiments were then carried out to screen the other additives. The results indicated that $PdCl_2$ in company with Cu (II) species such as $Cu(OAc)_2$, CuO or $Cu(OTf)_2$ were mostly ineffective in this reaction (entries 6-8). However Cu_2O did promote the formation of cyanation product, although the yield was inferior to that of Ag_2O (entry 9 *vs* 3), which suggested the presence of Ag_2O was important to the transformation. Other silver salts such as Ag_2CO_3, AgOAc and $AgNO_3$ were also examined and they demonstrated similar effect on the product yield compared to Ag_2O (entry 13–15). Surprisingly AgOTf didn't exhibit similar reactivity as the other silver salts did in this reaction (entry 10). Slightly increasing either the amount of $PdCl_2$ or Ag_2O didn't significantly affect the yields (entries 11 and 12) and thus the equivalence of $PdCl_2$ or Ag_2O were kept to be 0.1 and 1.0 respectively in related to starting aryldiazonium fluoroborate.

Further studies on the reaction temperature and time suggested high temperature or long reaction time did not improve the cyanation of arenediazonium salts (entries 16–23). Other experiments were also carried out with PPh_3, Et_3N and 2, 9-Dimethyl-1, 10-phenanthroline as additives or under oxygen atmosphere (entry 20–22). The presence of pure oxygen and addition of ligands didn't seem to affect the formation of cyanation product (entry 23). Similar phenomenon was observed previously in palladium-catalyzed coupling reactions with diazonium salts. [16a, 17] Therefore, the optimal reaction condition was chosen as the following in further experiment with other substrates: $PdCl_2$ 0.1 equiv., Ag_2O 1.0 equiv., 55℃, the reaction time is 24 h, under ambient air.

Table 1 Optimization of the reaction conditions [a]

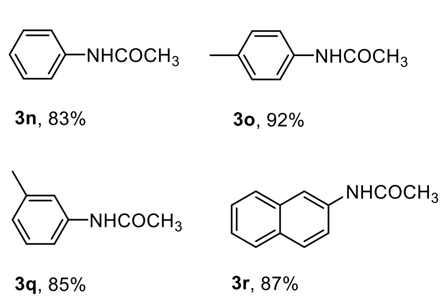


1a **2a**

No	Catalyst (equiv)	Additives (equiv)	Temp (℃)	Yield[b] (%)
1	$Cu(OAc)_2$ (1.0)	Ag_2O (1.0)	55	n.r.
2	$Pd(OAc)_2$ (0.1)	Ag_2O (1.0)	55	39
3	**$PdCl_2$ (0.1)**	**Ag_2O (1.0)**	**55**	**64**
4	-	Ag_2O (1.0)	55	n.r.
5	$PdCl_2$ (0.1)	-	55	n.r.
6	$PdCl_2$ (0.1)	$Cu(OAc)_2$ (1.0)	55	trace
7	$PdCl_2$ (0.1)	CuO (1.0)	55	n.r.
8	$PdCl_2$ (0.1)	$Cu(OTf)_2$ (0.1)	55	trace
9	$PdCl_2$ (0.1)	Cu_2O (1.0)	55	29
10	$PdCl_2$ (0.1)	AgOTf (1.0)	55	n.r.
11	$PdCl_2$ (0.1)	Ag_2O (1.5)	55	65
12	$PdCl_2$ (0.15	Ag_2O (1.0)	55	65
13	$PdCl_2$ (0.10)	Ag_2CO_3 (1.0)	55	64
14	$PdCl_2$ (0.10)	AgOAc	55	59
15	$PdCl_2$ (0.10)	$AgNO_3$	55	56
16	$PdCl_2$ (0.1)	Ag_2O (1.0)	Reflux	59
17	$PdCl_2$ (0.1)	Ag_2O (1.0)	RT	10
18	$PdCl_2$ (0.1)	Ag_2O (1.0)	Sealed tube	59
19[c]	$PdCl_2$ (0.1)	Ag_2O (1.0)	55	59
20	$PdCl_2$ (0.1)	Ag_2O (1.0) PPh_3 (1.0)	55	62
21	$PdCl_2$ (0.1)	Ag_2O (1.0) TEA(1.0)	55	34
22	$PdCl_2$ (0.1)	Ag_2O (1.0)[d]	55	62
23	$PdCl_2$ (0.1)	Ag_2O (1.0) O_2	55	60

a Reactions were carried out with **1a** (0.5 mmol) in CH_3CN (3.0 mL) for 24 h, under air, unless otherwise indicated., *b* Isolated yield. n.r. no reaction. *c* 48 h. *d* 2,9-Dimethyl-1,10-phenanthroline (1.0 equiv) was added.

With the optimized reaction conditions in hand, the substrate scope and limitations of the protocol were examined subsequently (**Table** 2). In general, there are some noticeable trend and observations. Among those substrates that afforded aromatic nitriles in the products mixture, those bearing a strong *para*-electro-donating group proceeded most efficiently to give aromatic nitriles in moderate yields 50%-64% (**2a**–**2f**). When the starting aryldiazonium fluoroborates contain halide substitutions (**2g**–**2j**), the yield of corresponding aromatic nitriles were usually lower, likely due to the interference of halides, which may also undergo oxidative addition with the palladium catalyst, facilitating coupling process at the position of halides to complicate the product matrix. Other electron-withdrawing groups (C=O, NO_2, CO_2Et etc) decreased the yields of aromatic nitriles even lower after column chromatography (**2k**–**2m**). It is worth mention that for all those substrates that gave moderate or low yield of cyanation products from the starting aryldiazonium salts in acetonitrile, there is either a lone pair *p* electron or *π* electrons conjugating with the phenyl ring (**2a**–**2m**). On the other hand, substrates without such a structural feature didn't afford the corresponding aromatic nitriles and the products were acetanilides in excellent yield (**Scheme** 2). Due to the high reactivity of $ArN_2^+BF_4^-$ to CH_3CN, likely the nitrilium ion were formed and subsequently hydrolyzed to give acetanilides **3n**–**3r**. [18] Moreover, aryldiazonium fluoroborate with substituents at the *meta* and *ortho* positions could be smoothly transformed into the corresponding aromatic nitriles, which indicated that the steric hindrance did not significantly affect the reactivity (**2d**–**2g**, **2i**). In some cases the *ortho* substitution may even have beneficiary effect that increased the yields of the corresponding aromatic nitriles (**2i** *vs* **2g** and **2j**), however such effect was not obvious when the *ortho* substitution is methoxy group (**2e** *vs* **2b** and **2f**).



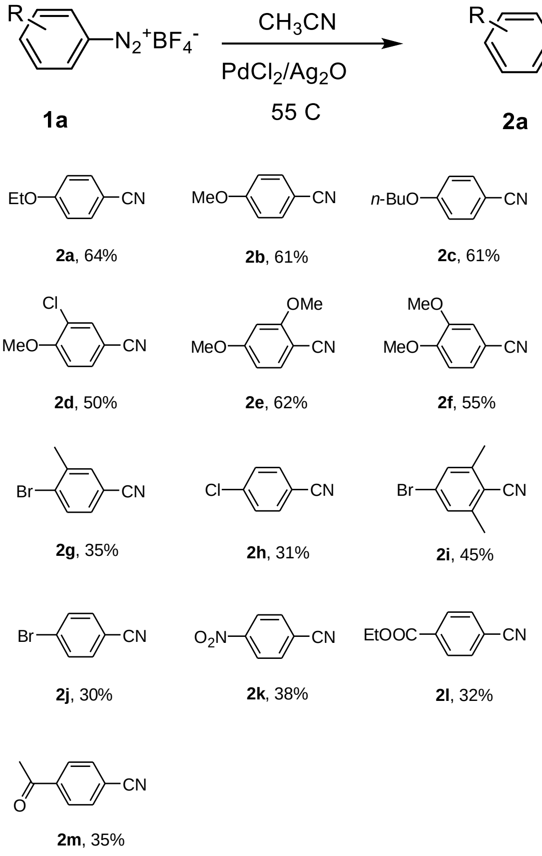
3n, 83% **3o**, 92% **3p**, 92%

3q, 85% **3r**, 87%

Scheme 2. Acetanilides formed in excellent yields from arenediazonium salts under the standard conditions..

It is worth noting that, the formation of bisaryl byproduct derived from $PdCl_2$-catalyzed homocoupling of arenediazonium salts were obvious (eg: 28% yield of 4,4'-dibromobiphenyl starting with **1j** and 12% yield of 4,4'- dimethoxy-biphenyl starting with **1b**). Such product has also been reported in other cases as the major products in refluxing methanol catalyzed by $Pd(OAc)_2$. [19] Expectedly in this protocol, the homocoupling aryldiazonium salts and cyanation with CH_3CN are two competitive reactions, probably accompanied by simple reduction as well. As a result, different catalysis system such as Pd/Ag species in CH_3CN or Pd species alone in CH_3OH [19] affected the formation of different major products from the same arenediazonium fluoroborates. So, it is concluded that the relative yields of aromatic nitriles, byproducts of biaryls and acetanilides, depended on and varied with the type of substitution in aryldiazonium tetrafluoroborates in our protocol here. Complete product distribution of each substrate is listed in supporting information; we tabulated the yields for those products that can be isolated pure and characterized properly.

Table 2 Pd-Catalyzed Sandmeyer cyanation of aryldiazonium tetrafluoroborate in acetonitrile.



1a **2a**

2a, 64% **2b**, 61% **2c**, 61%

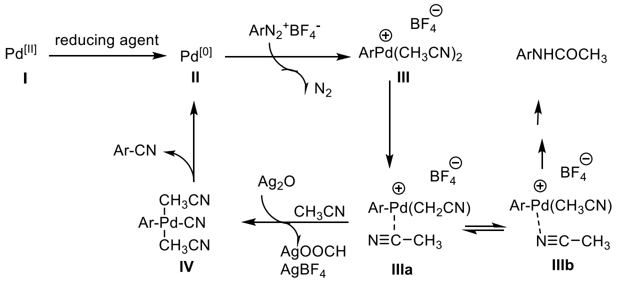
2d, 50% **2e**, 62% **2f**, 55%

2g, 35% **2h**, 31% **2i**, 45%

2j, 30% **2k**, 38% **2l**, 32%

2m, 35%

Even though the mechanism is not clear in detail at current stage, based on the experiments and previous reports, we proposed a possible general mechanism outlined in **Scheme 3**.[10-13, 16a, 18] Initially, divalent palladium is reduced to zero-valent palladium **II**. Oxidative addition of **II** to $ArN_2^+BF_4^-$ gives Ar-Pd species **III** upon releasing of nitrogen and complexing with CH_3CN. Subsequently the cleavage of CH_3-CN bond likely occurred in presence of Ag_2O to provide the intermediate Ⅳ. Finally, reductive elimination of intermediate **IV** gave aromatic nitriles along with the regeneration of Pd species **II** to complete the catalytic cycle.



Scheme 3. Proposed possible mechanism for Pd-catalyzed cyanation of arenediazonium fluoroborate with CH_3CN as cyanide source

Conclusions

In summary, we have discovered a novel approach to form aromatic nitriles from aryldiazonium tetrafluoroborates with cheap organic solvent acetonitrile as the non-metal cyanide source.[20] In such case, the "CN" group could be installed regiospecifically in the position of aryldiazonium. This strategy involves $PdCl_2$ catalyzed cyanation process via the cleavage of inert acetonitrile C-CN bond in the presence of Ag_2O under ambient air. Even though this approach has a limited substrate scope with moderate yields at its current stage, but it eliminates the involvement of toxic CuCN, in comparison with the traditional Sandmeyer reaction and it is an example of preparative cyanation of arenediazonium tetrafluoroborates with simple acetonitrile. Further studies are ongoing to expand the reaction scope, simplify the reaction procedure, increase the yield, and study the reaction mechanism in detail in our lab.

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Notes and references

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Electronic Supplementary Information (ESI) available: Detailed experimental procedure, ^{1}HNMR, ^{13}CNMR, IR and MS are available in Supplementary data file.

1 For examples, see: (a) A. Kleemann, J. Engel, B. Kutschner, D. Reichert, *Pharmaceutical substances: Syntheses, Patents, Applications*, 4th Edition. Thieme, Stuttgart, New York, **2001** (b) Review: J. S. Miller, J. L. Manson, *Acc. Chem. Res*. **2001**, *34*, 563.

2 Z. Rappoport, *The Chemistry of the Cyano Group*, Interscience Publishers, New York, **1970.** b) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd Edition. Wiley-VCH, New York, **1999**.

3 For examples, see: (a) P. Y. Yeung, C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem*. **2010**, *122*, 9102. (b) T. Schareina, A. Zapf, M. J. Beller, *Organomet. Chem*. **2004**, *689*, 4576. (c) G. Ishii, K. Moriyama, H. Togo, *Tetrahedron Lett*. **2011**, *52*, 2404. (d) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 958. (e) Z. H. Zhang, L. S. Liebeskind, *Org. Lett*. **2006**, *8*, 4331. (f) G. Y. Zhang, L. L. Zhang, M. L. Hu, J. Cheng, *Adv. Synth. Catal*. **2011**, *353*, 291.

4 a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. b) J. K. Kochi, *J. Am. Chem. Soc.* **1957**, *79*, 2942. c) J. Lindley, *Tetrahedron* **1984**, *40*, 1433. d) See review: H. H. Hodgson, *Chem. Rev*. **1947**, *40*, 251.

5 (a) K. W. Rosenmund, E. Struck, *Chem. Ber*. **1919**, *52*, 1749. (b) C. F. Koelsch, A. G. Whitney, *J. Org. Chem*. **1941**, *6*, 795 (c) Review: C. Galli, *Chem. Rev*. **1988**, *88*, 765. (d) Review: E. B. Merkushev, *Syhthesis* **1988**, *12*, 923.

6 For recent examples, see: (a) J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc*. **2003**, *125*, 2890. (b) H. J. Cristau, A. Ouali, J. F. Spindler, M. Taillefer, *Chem. Eur. J.* **2005**, *11*, 2483.

7 For recent examples using "non-metallic" CN sources for the cyanation reaction, see: (a) Review: J. kim. H. J. Kim. S. Chang, *Angew. Chem. Int. Ed*. **2012**, *51*, 11948 and references therein (b) T. J. Gong, B. Xiao, W. M. Cheng, W. Su, J. Xu, Z. J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc*. **2013**, *135*, 10630. (c) Y. Yang, S. L. Buchwald, *Angew. Chem. Int. Ed*. **2014**, *53*, 8677.

8 For examples, see: (a)Review: T. Wang, N. Jiao, *Acc. Chem. Res*. **2014**, *47*, 1137 and references therein (b) H. Xu, P. T. Liu, Y. H. Li, F. S. Han, *Org. Lett.* **2013**, *15*, 3354.

9 (a) See recent minireview: C. Najera, J. M. Sansano, *Angew. Chem. Int. Ed.* **2009**, *48*, 2452 and refrences therein. (b) P. Hanson, A. B. Taylor, P. H. Walton, A. W. Timms, *Org. Biomol. Chem.*, **2007**, *5*, 679.

10 (a) F. H. Luo, C. I. Chu, C. H. Cheng, *Organometallics* **1998**, *17*, 1025. (b) T. A. Ateşin, T. Li, S. Lachaize, W. W. Brennessel, J. J. García, W. D. Jones. *J. Am. Chem. Soc*. **2007**, 129, 7562. (c) F. L. Taw, P. S. White, R. G. Bergman, M. Brookhart. *J. Am. Chem. Soc*. **2002**, 124, 4192. (d) T. Lu, X. Zhuang, Y. Li, Shi Chen. *J. Am. Chem. Soc*. **2004**, 126, 4760. (e) D. S. Marlin, M. M. Olmstead P. K. Mascharak. *Angew. Chem. Int. Ed*. **2001**, 40, 4752. (f) H. Nakazawa, T. Kawasaki, K. Miyoshi, C. H. Suresh, N. Koga. *Organometallics* **2004**, 23, 117.

11 R. J. Song, J. C. Wu, Y. Liu, G. B. Deng, C. Y. Wu, W. T. Wei, J. H. Li, *Synlett* **2012**, *23*, 2491.

12 C. D. Pan, H. M. Jin, P. Xu, X. Liu, Y. X. Cheng, C. J. Zhu, *J. Org. Chem*. **2013**, *78*, 9494.

13 X. Z. Kou, M. D. Zhao, X. X. Qiao, Y. M. Zhu, X. F. Tong, Z. M. Shen, *Chem. Eur. J*. **2013**, *19*, 16880.

14 (a) Review: P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev*. **2011**, *40*, 5049 and references therein (b) S. Zheng, C. Yu, Z. Shen, *Org. Lett*. **2012**, *14*, 3644.

15 (a) W. B. Xu, Q. H Xu, Z. F Zhang, J. Z. Li, *Asian J. Org. Chem*. **2014**, *3*, 1062. (b) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *J. Organomet. Chem*. **2004**, *689*, 3810. (c) A. S. Sigeev, I. P. Beletskaya, P. V. Petrovskii, A. S. Peregudov, *Russ. J. Org. Chem*. **2012**, *48*, 1055. (d) P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *Synthesis* **2007**, *16*, 2534.

16 (a) See review: A. Roglans, A. Pla-Quintana, M. Moreno-Manas, *Chem. Rev*. **2006**, *106*, 4622. (b) See review: F. Y. Mo, G. B. Dong, Y. Zhang, J. B. Wang, *Org. Biomol. Chem*. **2013**, *11*, 1582. (c) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed*. **2013**, *52*, 7972.

17 S. Yasui, M. Fujii, C. Kawano, Y. Nishimura, A. Ohno, *Tetrahedron Lett*. **1991**, *32*, 5601.

18 (a) S. Milanesi, M. Fagnoni, A. Albini, *J. Org. Chem*. **2005**, *70*, 603. (b) S. Milanesi, M. Fagnoni, A. Albini, *Chem. Commun*. **2003**, *2*, 216. (c) V. Cepanec, M. Litvic, J. Udikovic, I. Pogorelic, M. Lovric, *Tetrahedron* **2007**, *63*, 5614. (d) P. C. Buxton, M. Fensome, H. Heaney, *Tetrahedron* **1995**, *51*, 2959. (e) R. Kikukawa, T. Totok, F. Wada, T. Matsuda, *J. Organometallic. Chem*. **1984**, *270*, 283.

19 M. K. Robinsin, V. S. Kochurina, J. M. Hanna, *Tetrahedron Lett.* **2007**, *48*, 7687.

20 **General Procedure.** To a solution of aryldiazonium tetrafluoroborate (0.5 mmol) in CH_3CN (3.0 mL) was added $PdCl_2$ (8.8 mg, 0.05 mmol) and Ag_2O (116 mg, 0.5 mmol). The mixture was stirred at 55℃ for 24 h under air. Then the reaction mixture was cooled to room temperature and filtered through a pad of celite (1.0 g) and rinsed with CH_2Cl_2 (10 mL). The resulting organic solution was concentrated under reduced pressure and further purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate gradient), yielding the corresponding aryl nitriles.