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Pd-Catalysis in Cyanide-free Synthesis of Nitriles from Haloarenes via Isoxazolines

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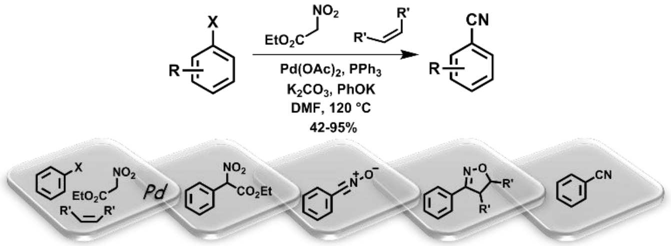
Supporting Information Placeholder



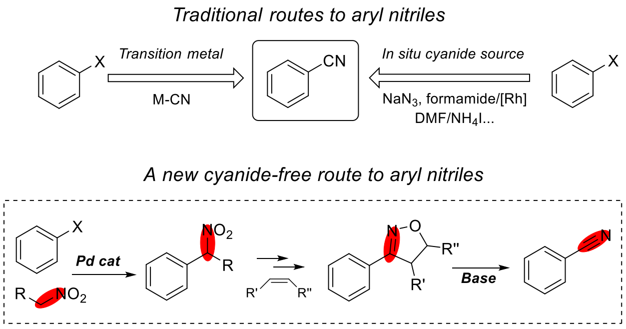
ABSTRACT: A method to obtain aryl nitriles from the corresponding halides by Pd catalysis, in the absence of any cyanide source, is reported. The reaction of an aryl halide, ethyl nitroacetate and an olefin readily delivers an aromatic nitrile. A variety of aryl iodides/bromides has been converted into the corresponding cyanoarenes in fair to excellent yields. The reaction likely involves the following steps: a) Pd-catalyzed α-arylation of ethyl nitroacetate; b) nitrile oxide formation; c) [3+2]-cycloaddition with an olefin to provide an isoxazoline; d) isoxazoline cleavage to benzonitrile formation.

Aryl nitriles are recurrent scaffolds found in both natural and synthetic compounds that are extensively used in the pharmaceutical, agrochemical and materials industries.[1] The nitrile group is also a versatile motif that can be easily converted into a broad range of useful functionalities.[1c]

Transition metal catalyzed cyanations usually involve Pd, Cu and Ni catalysts in combination with inorganic cyanides, (e.g. NaCN or KCN) or organic reagents such as acetone cyanohydrin and Me_3SiCN.[2] These synthetically relevant reactions have long been plagued by catalyst deactivation due to the formation of stable metal-cyanide complexes.[3] During the last decade these limitations were partially overcome both by catalyst design and the use of poorly soluble inorganic cyanides such as $Zn(CN)_2$[4] and $K_4Fe(CN)_6$[5]. Moreover, to avoid the use of hazardous reagents new methodologies have been developed to form the cyano group *in situ*, via tailor-made redox processes employing dimethyl formamide[6], sodium azide[7], formamide/phosphorous oxychloride[8] or dimethylmalononitrile[9].

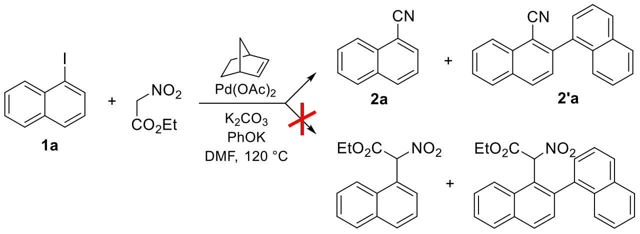
We report herein a complementary approach exploiting Pd catalysis. The method likely involves the sequential Pd-catalyzed α-arylation of ethyl nitroacetate, the temperature and based-induced formation of the corresponding nitrile oxide, the [3+2]-cycloaddition with an olefin to provide an isoxazoline, and its ring cleavage and fragmentation to the desired nitrile under the basic reaction conditions (Scheme 1). This Pd-catalyzed one-pot synthesis of aryl nitriles from the corresponding aryl halides and nitroacetates in the presence of an activated olefin such as dimethyl maleate has, to the best of our knowledge, not been previously observed.[10]

Scheme 1. Catalytic synthesis of aryl nitriles



We came across this unique transformation (Scheme 2) serendipitously during our studies aimed at the α-arylation of nitroacetates[11] by biarylpalladium complexes via Pd/norbornene catalysis.[12] We were surprised to find that the reaction of 1-iodonaphthalene **1a** with ethyl nitroacetate[13] in the presence of norbornene and $Pd(OAc)_2$ as catalyst, K_2CO_3 and

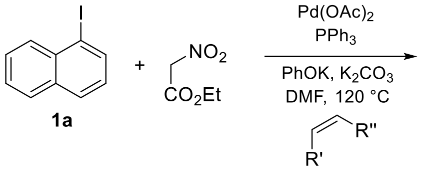
Scheme 2. Unexpected formation of nitriles 2a and 2’a



PhOK as bases,[12d] in DMF at 120 °C gave nitriles **2a** and **2’a**[14] in ca. 5% and 30% yield, respectively, in place of the expected arylated and biarylated ethyl nitroacetates.[11]

To our further surprise, when a control experiment was carried out in the absence of norbornene no traces of **2a** and **2’a** were detected by GC (Table 1, entry 1). The negative result clearly indicated the involvement of norbornene not only in the biaryl construction[12] but also in the transformation of the CH_2NO_2 group into a CN. The requirement of an olefin for the formation of the nitrile group was readily confirmed by addition of cyclohexene to the reaction mixture (Table 1, entry 2) which gave a small but significant amount of naphthonitrile (**2a**, ca. 5% yield) together with 55% of the arylated olefin (Heck product). The addition of an activated alkene such as methyl cinnamate afforded **2a** in 55% yield and 17% of the corresponding Heck product (Table 1, entry 3). Switching to dimethyl maleate, a disubstituted olefin that does not readily undergo a Heck reaction, proved beneficial to the selectivity of the reaction and delivered 37% of **2a** at 55% conversion (Table 1, entry 4). The addition of 5 mol % PPh_3 boosted the conversion and yield to 90% and 74%, respectively (Table 1, entry 5). Further increasing the amount of PPh_3 up to 20 mol %, gave **2a** in good to excellent yield (81 and 88% respectively) (Table 1, entries 6 and 7). Under these conditions, other electron-poor disubstituted olefins performed much worse (Table 1, entries 8–10). The nitroacetate can be replaced by nitromethane although at the expense of yield (55 %) (Table 1, entry 11), while another commercially available nitromethylene derivative (benzoylnitromethane) has a comparable efficiency (87%) (Table 1, entry 12). Lower yields were observed on reducing the amount of the nitro-derivative, the olefin or one of the two bases. In all the cases, conversion of the halide stopped upon formation of Pd black. Compound **2a** did not form in the absence of a Pd salt, the nitro-derivative or the olefin.

Table 1. Screening of additives and reaction conditions

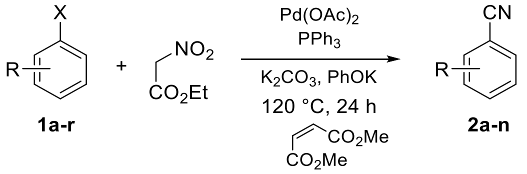


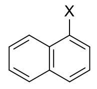
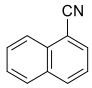
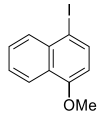
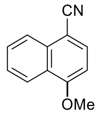
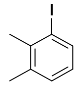
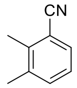
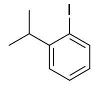
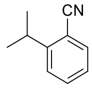
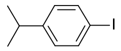
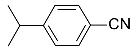
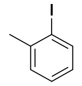
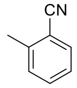
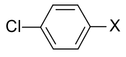
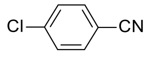
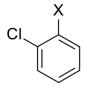
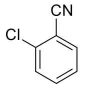
entry	olefin	*t* (h)	PPh_3 (mol %)	conv **1a** (%)[a]	yield **2a** (%)[b]
1	-		-	5	-
2	cyclohexene	20	-	100	5[c]
3	methyl cinnamate	24	-	100	55[d]
4	dimethyl maleate	24	-	55	37
5	dimethyl maleate	24	5	90	74
6	dimethyl maleate	22	10	95	81
7	dimethyl maleate	24	20	100	88
8	stilbene	40	20	95	30
9	dimethyl fumarate	47	20	60	48
10	fumaronitrile	24	20	5	-
11[e]	dimethyl maleate	24	20	70	55
12[f]	dimethyl maleate	24	20	100	87

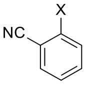
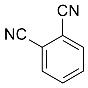
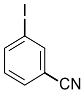
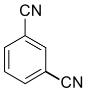
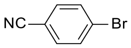
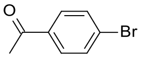
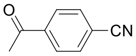
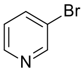
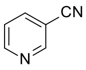
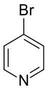
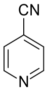
Reaction conditions: 1-iodonaphthalene (0.4 mmol, 1 equiv), ethyl nitroacetate (5 equiv), olefin (2.5 equiv), Pd(OAc)$_2$ (2.5 mol %, 0.002 M), K_2CO_3 (3 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N_2 or Ar at 120 °C; [a] by GC; [b] by ^{1}H NMR; [c] 55% yield of Heck product; [d] 17% yield of Heck product; [e] nitromethane in place of ethyl nitroacetate; [f] benzoylnitromethane in place of ethyl nitroacetate.

With these conditions in hand, we evaluated the scope of the reaction by employing differently substituted aryl halides as summarized in Table 2.

Table 2. Catalytic access to aryl nitriles



entry	substrate, **1**		product, **2**	yield (%)[a]
1		**1a**, X = I		**2a**, 88
2		**1b**, X = Br		**2a**, 71
3		**1c**		**2b**, 42
4		**1d**		**2c**, 81
5		**1e**		**2d**, 75
6		**1f**		**2e**, 71
7		**1g**		**2f**, 56
8		**1h**, X = I		**2g**, 86
9		**1i**, X = Br		**2g**, 76
10		**1j**, X = I		**2h**, 94
11		**1k**, X = Br		**2h**, 78

12 13		**1l**, X = I **1m**, X= Br		**2i**, 95 **2i**, 86
14		**1n**		**2j**, 61
15		**1o**		**2k**, 85
16		**1p**		**2l**, 87
17		**1q**		**2m**, 80
18		**1r**		**2n**, 72

Reaction conditions: **1** (0.4 mmol, 1 equiv), ethyl nitroacetate (5 equiv), dimethyl maleate (2.5 equiv), $Pd(OAc)_2$ (2.5 mol %, 0.002 M), PPh_3 (20 mol %), K_2CO_3 (3 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N_2 or Ar at 120 °C for 24 h. [a]Isolated yields based on the average of two runs.

Good results were obtained with 1-iodo- and 1-bromonaphthalene (88 and 71%) (Table 2, entries 1–2), while an electron donating methoxy substituent proved to be detrimental (42 %) (Table 2, entry 3). Aryl halides bearing alkyl groups, whether in ortho-, meta- or para- positions were usually well tolerated (56–81 %) (Table 2, entries 4–7). The presence of electron withdrawing groups had a positive effect and provided excellent yields with iodides and good ones with bromides (Table 2, entries 8–16). Interestingly, the reaction proved to tolerate the presence of the chloride substituent (Table 2, entries 8–11), useful for further functionalization. The formal cyanation of 3- and 4-bromopyridine occurred smoothly delivering the 3- and 4-cyanopyridine in 80 and 72% yield, respectively (Table 2, entries 17-18).

We were intrigued by the unexpected formation of aryl nitriles under these conditions and thus we carried out experimental studies to gain insights into the mechanism of this sequential reaction. Although research is still underway to define the precise pathway, a possible rationale for the observed reactivity is shown in Scheme 3 for benzonitrile formation.

The aryl halide oxidatively adds to Pd(0) to afford arylpalladium(II) complex **I**. Activation of ethyl nitroacetate delivers **II**, which, on reductive elimination, liberates the arylated nitroacetate **3** and Pd(0). The basic medium and thermal activation favor the formation of phenyl nitrile oxide **4**,[15] which can undergo a [3+2]-cycloaddition with the olefin to afford the isoxazoline **5**.[16] Likely through a deprotonation step by the bases present in the reaction medium, species **6** is formed, which eventually delivers benzonitrile **2o** and the enol of ketosuccinate **7** by C–C and N–O bond cleavage. Although the isoxazoline **5** has not been detected, its formation from benzonitrile oxide **4** and dimethyl maleate,[16] and its subsequent fragmentation to benzonitrile have been previously reported.[17] To provide evidence supporting the proposed reaction pathway, isoxazoline **5** was synthetized to ascertain how the species present in the reaction mixture could affect the benzonitrile formation (Table 3). When $Pd(OAc)_2$, PPh_3 and bases were not used, compound 5 was almost completely recovered after 3 hours or longer times at 120 °C (Table 3, entry 1). In the presence of both K_2CO_3 and PhOK as the bases, or equimolar amount of PhOK alone, benzonitrile was obtained in 20 and 32% yield, respectively (Table 3, entries 2-3). While a comparable result was achieved performing the reaction also in the presence of $Pd(OAc)_2$ (25% yield) (Table 3, entry 4), we were pleased to find that the addition of 20 mol % PPh_3 promoted the transformation of isoxazoline 5 to benzonitrile in 78% yield (Table 3, entry 5). We then carried out the same reaction in the absence of $Pd(OAc)_2$ and obtained compound 2o in a similar yield (75%) (Table 3, entry 6). Increasing the amount of PPh_3 up to 80 mol %, gave 2o in 89% yield (Table 3, entry 7). However, when the reaction was carried out in the presence of PPh_3 alone, only traces of benzonitrile were detected even after 24 h at 120 °C (Table 3, entry 8).

Scheme 3. Proposed reaction mechanism

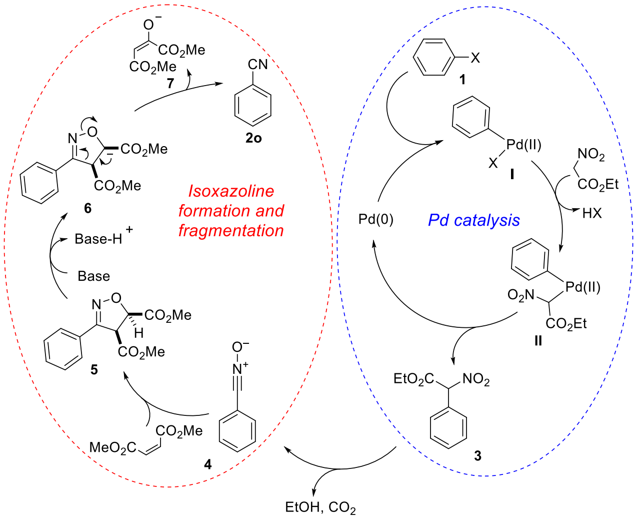
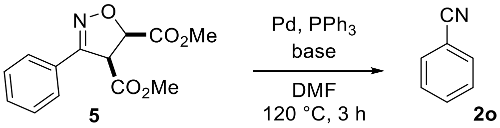


Table 3. Effect of $Pd(OAc)_2$, PPh_3 and bases on 2o yield



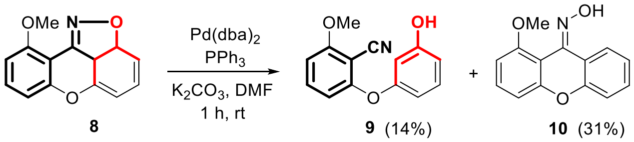
entry	$Pd(OAc)_2$ (mol %)	PPh_3 (mol %)	K_2CO_3 (equiv)	PhOK (equiv)	**2o**, yield (%)[a]
1	-	-	-	-	-[b]
2	-	-	2	0.3	20
3	-	-	-	1	32
4	2.5	-	2	0.3	25
5	2.5	20	2	0.3	78
6	-	20	2	0.3	75
7	-	80	2	0.3	89
8	-	80	-	-	traces[b]

Reaction conditions: isoxazoline **5** (0.21 mmol, 1 equiv) in DMF (4 mL) under N_2 at 120 °C for 3 h; [a] GC yield. [b] The GC conversion of isoxazoline **5** after 3 and 24 h at 120 °C was less than 5%.

Thus, the fragmentation of isoxazoline **5** to benzonitrile is strongly promoted by the inorganic bases in combination with PPh_3, the latter, however, appears unable of any substantial activity in the absence of the bases.

Moreover, efforts to identify the expected aliphatic co-products proved fruitless, likely owing to the thermal instability of ketosuccinates. We reasoned to synthesize an isoxazoline bearing a suitable tether in order to trap intramolecularly the co-product and thus corroborate our rationale. The candidate of choice appeared to be polycyclic isoxazoline **8** (Scheme 4) despite its propensity to readily deliver oxime **10** even at room temperature in basic medium.[18] The expected arylnitrile **9** features a stable, tethered phenol fragment isolobal to the unstable and elusive ketosuccinate and its formation would further substantiate our proposal.

Scheme 4. Ring opening of isoxazoline 8



Not surprisingly, isoxazoline **8** in DMF in the presence of K_2CO_3 quantitatively delivered compound **10** in 1 hour at room temperature. We were delighted, however, to observe formation of nitrile **9** in 14% yield upon addition of a catalytic amount of $Pd(dba)_2$ (2.5 mol %) and PPh_3 (5 mol %).

In conclusion, we have developed a catalytic method to obtain aryl nitriles from the corresponding halides in the absence of any cyanide source. Aryl nitriles are formed in fair to excellent yields making this formal cyanation a viable synthetic method complementary to existing cyanide-free alternatives. The reaction proceeds through a sequential process that consists of four consecutive transformations. Under the adopted conditions, each transformation spontaneously occurs with high efficiency, eventually delivering the stable target molecule. Notably, dimethyl maleate enables the construction of isoxazolines suitable for fragmentation to benzonitriles, without interfering with the Pd cycle. Further detailed mechanistic studies and synthetic applications of this reaction are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures and spectra of all compounds.

AUTHOR INFORMATION

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REFERENCES

[1] (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. Pharmaceutical Substances: Syntheses, Patents, Applications, 4th ed.; Thieme: Stuttgart, 2001. (b) Pollak, P., Romeder, G., Hagedorn, F., Gelbke, H.-P. Nitriles. In Ullmann's Encyclopedia of Industrial Chemistry; Wiley-VCH: Weinheim, Germany, 2012. (c) Srimani, D.; Feller, M.; Ben-David, Y.; Milstein, D. *Chem. Commun*. **2012**, *48*, 11853.

[2] (a) Anbarasan, P., Schareina, T., Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (b) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 8918. (c) Chen, J.; Sun, Y.; Liu, B.; Liu, D.; Cheng, J. *Chem. Commun.* **2012**, *48*, 449. (d) Zhang, D.; Sun, H.; Zhang, L.; Zhou, Y.; Li, C.; Jiang, H.; Chen, K.; Liu, H. *Chem. Commun*. **2012**, *48*, 2909. (e) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed*. **2003**, *42*, 1661. (f) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2010**, *12*, 2517. (g) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389. (h) Ushkov, A. V.; Grushin, V. V. *J. Am. Chem. Soc*. **2011**, *133*, 10999.

[3] (a) Erhardt, S.; Grushin, V. V.; Kilpatrick, A. H.; Macgregor, S. A.; Marshall, W. J.; Roe, C. *J. Am. Chem. Soc.* **2008**, *130*, 4828. (b) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30.

[4] Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177.

[5] (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (b) Senecal, T. D.; Shu, W.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2013**, *52*, 10035. (c) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed*. **2010**, *49*, 8918.

[6] (a) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (b) Ding, S.; Jiao, N. *J. Am. Chem. Soc*. **2011**, *133*, 12374. (c) Pawar, A. B.; Chang, S. *Chem. Commun*. **2014**, *50*, 448.

[7] Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. *Org. Lett*. **2010**, *12*, 2888.

[8] Sawant, D. N.; Wagh, Y. S.; Tambade, P. J.; Bhatte, K. D.; Bhanage, B. M. *Adv. Synth. Catal*. **2011**, *353*, 781.

[9] (a) Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Kanwar, P. S.; Sidhu, K. P.; Marsini, M. A.; Avery Sader, C.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. *J. Am. Chem. Soc*. **2015**, *137*, 9481. (b) Malapit, C. A.; Reeves, J. T.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H. *Angew. Chem., Int. Ed*. **2016**, *55*, 326.

[10] For Cu(II)-mediated cyanation of 2-phenylpyridine using nitromethane as –CN source, see: Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc*. **2006**, *128*, 6790.

[11] (a) Miura, M.; Satoh, T. *Top. Organomet. Chem*. **2005**, *14*, 1. (b) for Pd-catalyzed mono-arylation of nitroalkanes, apart from nitromethane, see: Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002,** *67*, 106. (c) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2009**, *131*, 12898.

[12] (a) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res*. **2016**, *49*, 1389. (b) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res*. **2008**, *41*, 1512. (c) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca', N.; Maestri, G. *Coord. Chem. Rev*. **2010**, *254*, 456. (d) for Pd/norbornene catalysis in arene and ketone C–H bond functionalization, see: G. Maestri, G.; Della Ca', N.; Catellani, M. *Chem. Commun*. **2009**, 4892. (e) Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc*. **2011**, *133*, 8574; (f) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem*. **2010**, *292*, 1. (g) Ye, J.; Lautens, M. *Nat. Chem*. **2015**, *7*, 863.

[13] Ethyl nitroacetate is an energetic material and should be handled carefully and stored away from strong oxidants and bases.

[14] Mariampillai, B.; Alliot, J.; Mengzhou Li. M.; Lautens, M. *J. Am. Chem. Soc*. **2007**, *129*, 15372.

[15] (a) Quilico, A.; Stagno D'Alcontres, G.; Grünanger, P. *Nature* **1950**, *166*, 227. (b) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc*. **1960**, *82*, 5339.

[16] Trogu, E.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2009**, *15*, 7940. The formation of nitrile oxide (**4**) was confirmed employing benzoylnitromethane (Table 1, entry 12) and recovering the desired aryl nitrile and an almost equimolar amount of benzoic acid.

[17] (a) Golebiewski, W. M.; Gucma, M. *J. Heterocyclic Chem.* **2006**, *43*, 509. (b) Baranski, A.; Shvekhgeimer, G. *Polish J. Chem.* **1982**, *56*, 459. (c) Koroleva, E. V.; Bondar, N. F.; Katok, Y. M.; Chekanov, N. A.; Chernikhova T. V. *Chem. Heterocyclic Compd.* **2007**, *43*, 362. (d) Bianchi, G.; Gandolfi, R.; Grünanger, P. *J. Heterocyclic Chem*. **1968**, *5*, 49.

[18] Yonekawa, M.; Koyama, Y.; Kuwata, S.; Takata, T. *Org. Lett.* **2012**, *14*, 1164.