

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

Giovanni Maestri,^{†,‡,§} Tatiana Cañeque,[‡] Nicola Della Ca',[†] Etienne Derat,[§] Marta Catellani,^{*,†,§} Gian Paolo Chiusoli,^{†,||} and Max Malacria^{*,‡,§,||}

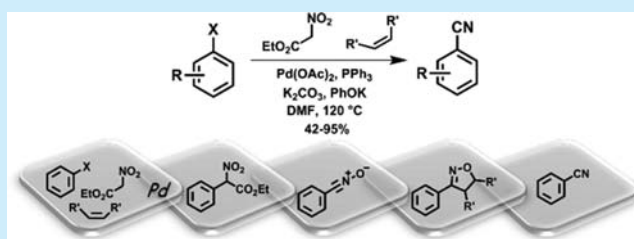
[†]Dipartimento di Chimica and CIRCC, Università di Parma, Parco Area delle Scienze, 17/A, 43124 Parma, Italy

[‡]Institut de Chimie des Substances Naturelles, ICSN-CNRS UPR 2301, Gif/Yvette Cedex 91198, France

[§]Institut Parisien de Chimie Moléculaire, UPMC Université Paris 06, IPCM-UMR 8232, Paris 75005 Cedex, France

S Supporting Information

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 have 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.



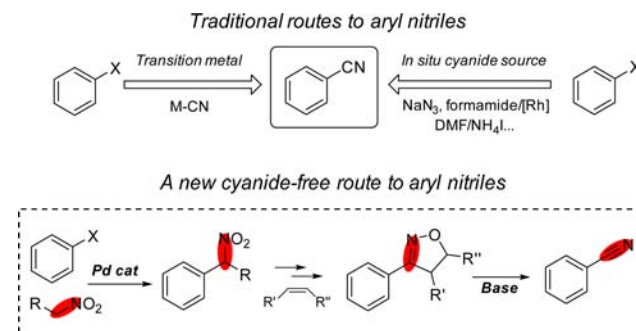
Aryl nitriles are recurrent scaffolds found in both natural and synthetic compounds that are extensively used in the pharmaceutical, agrochemical, and materials industries.¹ The nitrile group is also a versatile motif that can be easily converted into a broad range of useful functionalities.^{1c}

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 Me₃SiCN.² These synthetically relevant reactions have long been plagued by catalyst deactivation due to the formation of stable metal–cyanide complexes.³ During the past decade, these limitations were partially overcome both by catalyst design and the use of poorly soluble inorganic cyanides such as Zn(CN)₂⁴ and K₄Fe(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 dimethylformamide,⁶ sodium azide,⁷ formamide/phosphorus oxychloride,⁸ or dimethylmalononitrile.⁹

We report herein a complementary approach exploiting Pd catalysis. The method likely involves sequential Pd-catalyzed α -arylation of ethyl nitroacetate, temperature- and base-induced formation of the corresponding nitrile oxide, [3 + 2]-cycloaddition with an olefin to provide an isoxazoline, and 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

We came across this unique transformation (Scheme 2) serendipitously during our studies aimed at the α -arylation of

Scheme 1. Catalytic Synthesis of Aryl Nitriles



Scheme 2. Unexpected Formation of Nitriles 2a and 2'a



nitroacetates¹¹ by biarylpalladium complexes via Pd/norbornene catalysis.¹² We were surprised to find that the reaction of 1-iodonaphthalene **1a** with ethyl nitroacetate¹³ in the presence of norbornene and Pd(OAc)₂ as catalyst and K₂CO₃ and PhOK

Received: October 15, 2016

Published: November 14, 2016

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 biarylized 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

Table 1. Screening of Additives and Reaction Conditions^a

entry	olefin	time (h)	PPh ₃ (mol %)	conv 1a ^b (%)	yield 2a ^c (%)
1				5	
2	cyclohexene	20		100	5 ^d
3	methyl cinnamate	24		100	55 ^e
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 ^f	dimethyl maleate	24	20	70	55
12 ^g	dimethyl maleate	24	20	100	87

^aReaction 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), K₂CO₃ (3 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N₂ or Ar at 120 °C. ^bBy GC. ^cBy ¹H NMR. ^d55% yield of Heck product. ^e17% yield of Heck product. ^fNitromethane in place of ethyl nitroacetate. ^gBenzoylnitromethane in place of ethyl nitroacetate.

result clearly indicated the involvement of norbornene not only in the biaryl construction¹² but also in the transformation of the CH₂NO₂ 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 % of PPh₃ boosted the conversion and yield to 90% and 74%, respectively (Table 1, entry 5). Further increasing the amount of PPh₃ 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 upon reducing the amount of the nitro derivative, the olefin, or one of the two bases. In all 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.

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

Good results were obtained with 1-iodo- and 1-bromonaphthalene (88 and 71%) (Table 2, entries 1 and 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 yields 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 and 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 maleate¹⁶ and its subsequent fragmentation to benzonitrile have been previously reported.¹⁷ To provide evidence supporting the proposed reaction pathway, isoxazoline **5** was synthesized to ascertain how the species present in the reaction mixture could affect the benzonitrile formation (Table 3). When Pd(OAc)₂, PPh₃ and bases were not used, compound **5** was almost completely recovered after 3 h or longer at 120 °C (Table 3, entry 1). In the presence of both K₂CO₃ and PhOK as the bases, or an equimolar amount of PhOK alone, benzonitrile was obtained in 20 and 32% yield, respectively (Table 3, entries 2 and 3). While a comparable result was achieved in the presence of Pd(OAc)₂ (25% yield) (Table 3, entry 4), we were pleased to find that the addition of 20 mol % of PPh₃ 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 PPh₃ up to 80 mol % gave **2o** in 89% yield (Table 3, entry 7). However, when the reaction was carried out in the presence of PPh₃ alone, only traces of benzonitrile were detected even after 24 h at 120 °C (Table 3, entry 8).

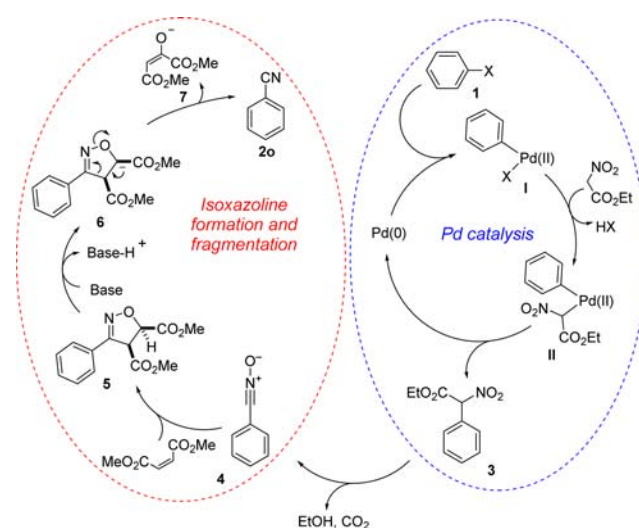
Thus, the fragmentation of isoxazoline **5** to benzonitrile is strongly promoted by the inorganic bases in combination with PPh₃; the latter, however, does not show any substantial activity in the absence of the bases.

Table 2. Catalytic Access to Aryl Nitriles*

entry	substrate, 1	product, 2	yield (%) ^a
1			2a , 88
2			2a , 71
3			2b , 42
4			2c , 81
5			2d , 75
6			2e , 71
7			2f , 56
8			2g , 86
9			2g , 76
10			2h , 94
11			2h , 78
12			2i , 95
13			2i , 86
14			2j , 61
15			2k , 85
16			2l , 87
17			2m , 80
18			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), PPh₃ (20 mol %), K₂CO₃ (3 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N₂ or Ar at 120 °C for 24 h. ^aIsolated yields based on the average of two runs.

Scheme 3. Proposed Reaction Mechanism

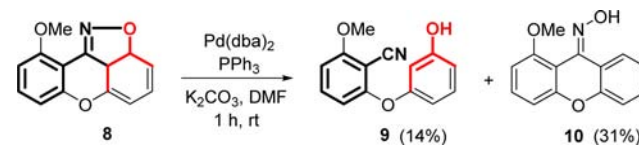
Table 3. Effect of Pd(OAc)₂, PPh₃, and Bases on Yield of 2o^a

entry	Pd(OAc) ₂ (mol %)	PPh ₃ (mol %)	K ₂ CO ₃ (equiv)	PhOK (equiv)	2o , yield ^b (%)
1					^c
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 ^c

^aReaction conditions: isoxazoline **5** (0.21 mmol, 1 equiv) in DMF (4 mL) under N₂ at 120 °C for 3 h. ^bGC yield. ^cThe GC conversion of isoxazoline **5** after 3 and 24 h at 120 °C was less than 5%.

Moreover, efforts to identify the expected aliphatic coproducts proved fruitless, likely owing to the thermal instability of ketosuccinates. We reasoned that synthesizing an isoxazoline bearing a suitable tether would intramolecularly trap the coproduct 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**

Scheme 4. Ring Opening of Isoxazoline 8



even at room temperature in basic medium.¹⁸ The expected aryl nitrile **9** features a stable, tethered phenol fragment isolobal to the unstable and elusive ketosuccinate, and its formation would further substantiate our proposal.

Not surprisingly, isoxazoline **8** in DMF in the presence of K₂CO₃ quantitatively delivered compound **10** in 1 h 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 PPh₃ (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 at DOI: 10.1021/acs.orglett.6b03103.

Detailed experimental procedures and spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: marta.catellani@unipr.it.

*E-mail: max.malacria@upmc.fr.

ORCID

Giovanni Maestri: 0000-0002-0244-8605

Etienne Derat: 0000-0002-8637-2707

Marta Catellani: 0000-0002-6145-0211

Max Malacria: 0000-0002-3563-3508

Notes

The authors declare no competing financial interest.

[†]Deceased February 2, 2013.

■ ACKNOWLEDGMENTS

We thank MIUR, UNIPR, CNRS, and UPMC for funding.

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