A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
www.angewandte.org

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.201707517
*Angew. Chem.* 10.1002/ange.201707517

**Link to VoR:** http://dx.doi.org/10.1002/anie.201707517
http://dx.doi.org/10.1002/ange.201707517

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# Nickel-Catalyzed Cyanation of Aryl Chlorides and Triflates Using Butyronitrile: Merging Retro-Hydrocyanation with Cross-coupling

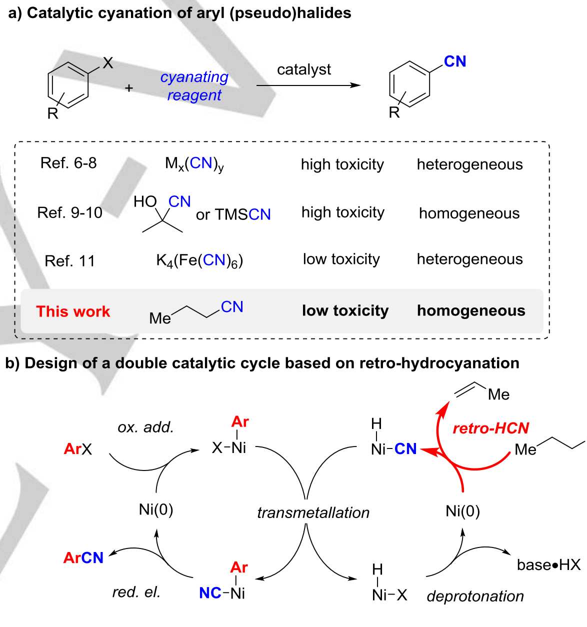
Peng Yu and Bill Morandi*

*Dedicated to Robert H. Grubbs on the occasion of his 75th birthday*

**Abstract:** We describe here a nickel-catalyzed cyanation reaction of aryl (pseudo)halides that employs butyronitrile as a cyanating reagent instead of highly toxic cyanide salts. A dual catalytic cycle merging retro-hydrocyanation and cross-coupling enables the conversion of a broad array of aryl chlorides and aryl/vinyl triflates into their corresponding nitriles. This new reaction provides a strategically distinct approach to the safe preparation of aryl cyanides, which are essential compounds in agrochemistry and medicinal chemistry.

Aromatic nitriles are found in a wide range of pharmaceuticals, agrochemicals, natural products and organic materials.[1] Moreover, aryl nitriles are among the most versatile synthetic intermediates because they can be readily converted to aldehydes, carboxylic acids, ketones, amides, amines, and heterocycles.[2] The development of efficient and practical routes for the synthesis of aryl nitriles has thus been a longstanding goal of organic synthesis. To bypass the limitations of the venerable Sandmeyer[3] and Rosenmund-von Braun reaction[4] that employ stoichiometric amounts of CuCN, the transition-metal catalyzed cyanation of aryl halides has been introduced.[5] While the use of earth-abundant metals as catalysts and less reactive aryl halides as substrates remains challenging, the most severe drawback of the vast majority of the current protocols continues to be the reliance upon highly toxic cyanide salts as reagents.

Traditionally, metal cyanide salts (KCN,[6] NaCN,[7] $Zn(CN)_2$[8]), TMSCN[9] or acetone cyanohydrin[10] have been used in the transition-metal-catalyzed cyanation of aryl halides (scheme 1a). The common feature among all these reagents is the relative ease by which the cyano group can be transferred to the metal catalyst, ensuring a facile cyanation reaction. However, this feature is also often responsible for catalyst deactivation through formation of inactive catalytic species bearing multiple cyanide ligands. More importantly, the facile release of the cyanide anion is responsible for the high toxicity of these reagents, which generates significant safety concerns for both academic and industrial applications. To address these safety concerns, $K_4[Fe(CN)_6]$,[11] a nontoxic food additive, has been introduced as a reagent for the cyanation of aryl halides by the Beller and Weissman group.[11a, c] However, the low solubility of this reagent in organic solvents and its low rate of transmetallation has limited its broader application, in part because of scalability issues due to the heterogeneous nature of the reaction mixture. [10e] Additionally, the use of this reagent leads to the formation of metal wastes. Thus, the discovery of novel, non-toxic reagents addressing these challenges remains of great significance. In particular, a method employing simple, non-hydrolysable alkyl nitriles as benign cyanating reagents would be a complementary tool for the safe preparation of aryl and vinyl cyanides.



**Scheme 1.** Reaction design.

The installation of a cyano group through transition-metal catalyzed activation of C–CN bonds enables the use of inexpensive and less toxic alkyl nitriles as reagents.[12] This strategy provides a controlled way to generate metal-cyanide intermediates without employing metal cyanide sources, avoiding both catalyst deactivation and exposure to toxic reagents. Recently, our group reported a reversible nickel–catalyzed transfer hydrocyanation through shuttle catalysis[13] that employed a simple alkyl nitrile as a HCN donor to convert alkenes into nitriles.[14]

Inspired by the transfer mechanism of the hydrocyanation process, we hypothesized that simple alkyl nitriles bearing β-hydrogens could possibly be employed as cyanating reagents in transition-metal-catalyzed cyanation of aryl (pseudo)halides (scheme 1b). With regard to the mechanism, we envisaged that a transmetallation event between two independently generated catalytic intermediates, H–Ni–CN (generated through oxidative addition of the C−CN bond followed by β-hydride elimination) and Ar–Ni–X (generated through oxidative addition of Ar–X), could lead to the formation of the desired aryl cyanide after

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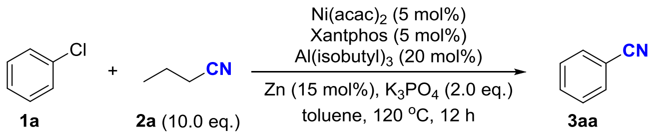
[†] Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.

10.1002/anie.201707517

reductive elimination. Reaction of H–Ni–X with a base could then regenerate the catalytically active Ni(0) species (scheme 1b). However, we anticipated that few challenges would have to be overcome to realize this strategy: (1) a single catalyst must be able to mediate all the elementary steps involved in two distinct catalytic cycles; (2) the rate of both catalytic cycles should be adjusted appropriately to make the transmetallation kinetically accessible.

**Table 1:** Optimization of reaction conditions.[a]

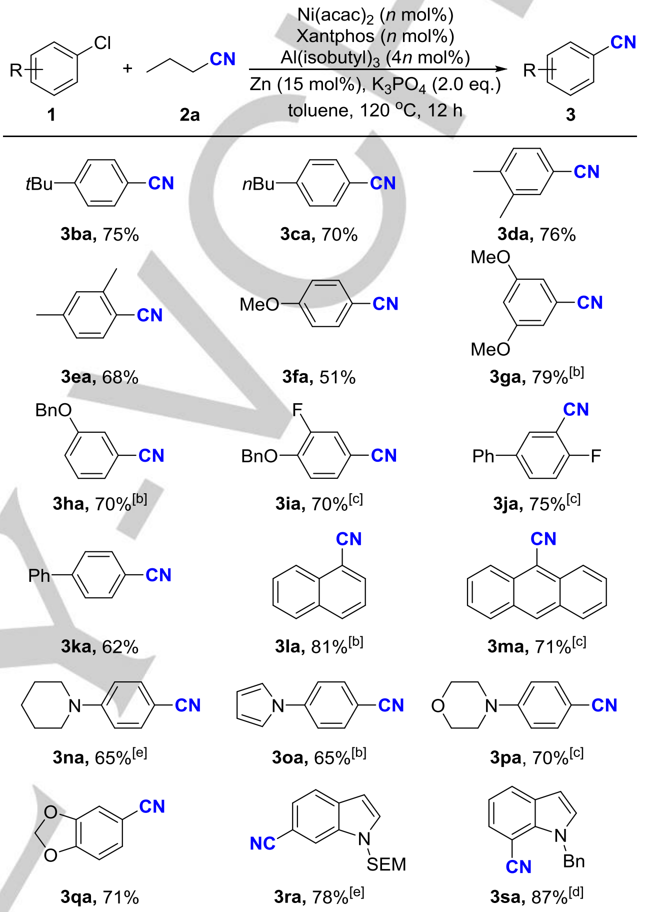


| Entry | Deviation from standard conditions | **3aa** (%)[b] |
|---|---|---|
| 1 | none | 88 |
| 2 | DPEPhos instead of Xantphos | <5 |
| 3 | PPhCy$_2$ instead of Xantphos | 0 |
| 4 | NiCl$_2$·glyme instead of Ni(acac)$_2$ | 32 |
| 5 | NiBr$_2$·glyme instead of Ni(acac)$_2$ | 37 |
| 6 | Ni(COD)$_2$ instead of Ni(acac)$_2$ | 25 |
| 7 | AlMe$_2$Cl instead of Al(isobutyl)$_3$ | 27 |
| 8 | AlMe$_3$ instead of Al(isobutyl)$_3$ | 71 |
| 9 | AlCl$_3$ instead of Al(isobutyl)$_3$ | 0 |
| 10 | K$_2$CO$_3$ instead of K$_3$PO$_4$ | 21 |
| 11 | Et$_3$N instead of K$_3$PO$_4$ | 59 |
| 12 | Mn instead of Zn | 27 |
| 13 | 2.0 equivalent of **2a** | 22 (52[c]) |

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), Ni(acac)$_2$ (5 mol%), Xantphos (5 mol%), Al(isobutyl)$_3$ (20 mol%), Zn (15 mol%), K$_3$PO$_4$ (2.0 eq.), toluene (0.5 mL) at 120 °C, 12 h. [b] GC yields. [c] **2a** (6.0 eq.).

To test our hypothesis, we selected butyronitrile **2a** as an inexpensive reagent (~80€/L) to cyanate aryl chloride **1a** (Table 1). The choice of **2a** as cyanating agent is accounted for its low price, low-molecular weight and high volatility of the corresponding alkene by-product. After careful evaluation of reaction parameters,[15] we found that a combination of inexpensive and bench-stable Ni(acac)$_2$, Xantphos, Al(isobutyl)$_3$ as co-catalyst, Zn as reducing agent to generate Ni(0) and K$_3$PO$_4$ as base in toluene at 120°C gave the best result within 12 hours, delivering **3aa** in 88% GC yield (entry 1). It is noteworthy that undesired homodimerization or Heck-type reactions were not observed under the reaction conditions. The use of a bidentate ligand with a smaller bite angle hampered the reactivity of this cyanation reaction, and no product was detected when the reaction was treated with a monodentate phosphine ligand (entries 2 and 3). As shown in entries 4-9, the use of other precatalysts or co-catalysts resulted either in lower yields of **3aa** or no product formation, indicating that an aluminium Lewis acid plays a critical role in the activation of the C–CN bond. Likewise, other bases or reducing agent had a deleterious effect on the outcome of the reaction (entries 10-12). Lower yields of **3aa** were obtained when the reaction was treated with fewer equivalents of **2a** (entry 13), probably reflecting the slower rate of retro-hydrocyanation relative to the oxidative addition of the aryl chloride.

**Table 2:** Scope of nickel-catalyzed transfer cyanation of aryl chlorides.[a]

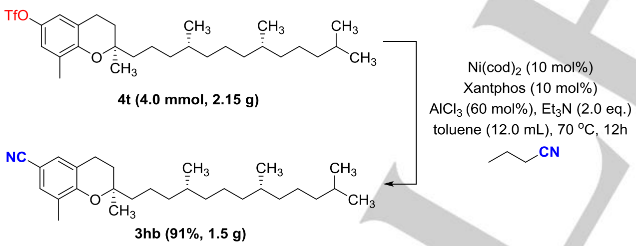


[a] Yields of isolated products. [b] n = 7.5. [c] n = 10. [d] n = 12.5. [e] n = 15.

As shown in table 2, substrates bearing electron donating or withdrawing substituents, whether they were at the *para*, *meta* or even *ortho* position, reacted well (**3ba-3ja**), revealing a good tolerance to steric and electronic effects. Naphthyl and 9-phenanthryl chlorides can also be converted to the corresponding aryl nitriles in good yields (**3la**, **3ma**). Several nitrogen and oxygen heterocycles relevant to the drug discovery processcould be efficiently tolerated by the catalytic system (**3oa-3sa**).

We next aimed to extend the scope to another important class of electrophiles, aryl and vinyl triflates. Despite the fact that triflate electrophiles, which can be easily accessed from phenols or aliphatic ketones, are retrosynthetically complementary to halides, they have not been frequently used in transition-metal catalyzed cyanation reactions.[16] In particular, few examples of nickel-catalyzed cyanation of aryl triflates have been reported,[17] and these protocols all rely on highly toxic KCN as cyanating reagent. After a small modification of the reaction conditions, we found that several aryl and vinyl triflates can be successfully converted to the corresponding cyano products in good to excellent yields (62-97**%**) under mild reaction conditions (Ni(cod)$_2$, Xantphos, AlCl$_3$, Et$_3$N in toluene at 50-110 $^o$C for 3-12 hours). The fact that AlCl$_3$, in contrast to the aryl chloride case, performed best could be explained by the stark influence of the Lewis-acid on the rate of retro-hydrocyanation. As shown in table 3, substrates bearing either electron deficient (**3ta**, **3ua**) or electron donating groups (**3fa**, **3ca**, **3ea**, **3va**) can be efficiently converted to aryl nitriles in excellent yields. Ortho substituted substrates reacted well under our reaction conditions, even though slightly lower yields were obtained (**3ea**, **3xa**). A chemoselective reaction of the triflate electrophile could be realized in the presence of a chloride, furnishing the desired products in good yields (**3ya**, **3za**). Heterocycles such as pyrrolidine, dioxole, carbazole, pyrazole and quinoline were well tolerated under our conditions (**3ab, 3qa, 3bb, 3cb, 3db**). Even unprotected indole and carbazole substrates could be well tolerated (**3eb**, **3fb**). Interestingly, vinyl triflates efficiently afforded synthetically versatile vinyl nitriles in excellent yields (**3gb**). A few natural products, such as *δ*-tocopherol, cholesterol and estrone, were then transformed into the corresponding triflates before being subjected to the transfer cyanation conditions to obtain excellent yields of the desired products (**3hb-3jb**). Notably, the amount of the reagent can be reduced from 10 equiv. to 2 equiv. when the electrophile is slowly added to the reaction mixture (**3aa**).

The method could also be employed on a preparative scale when the reaction was performed in an open system to facilitate the rapid release of the propene side-product (Scheme 2).

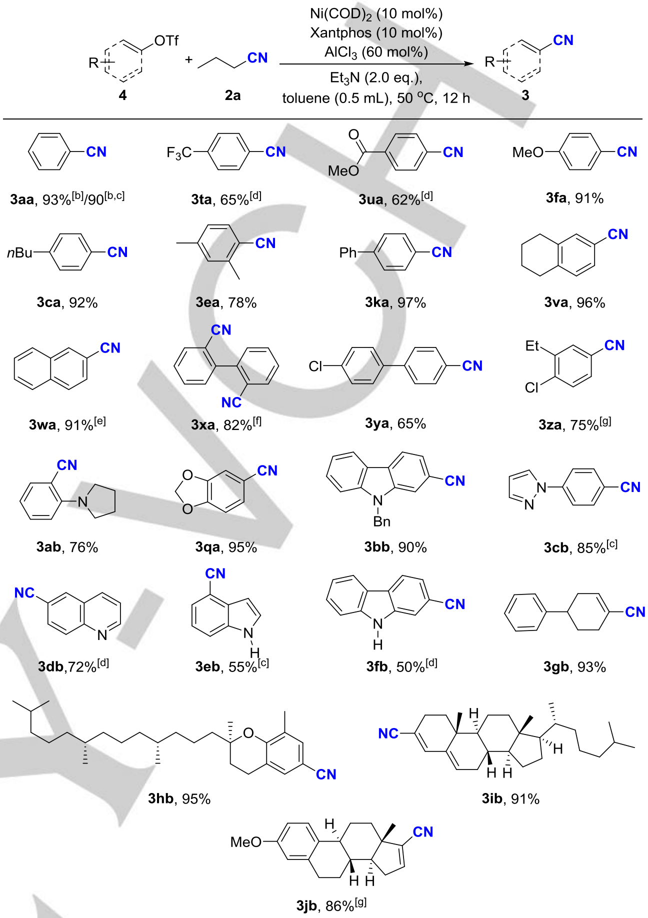


**Scheme 2.** Gram scale experiment.

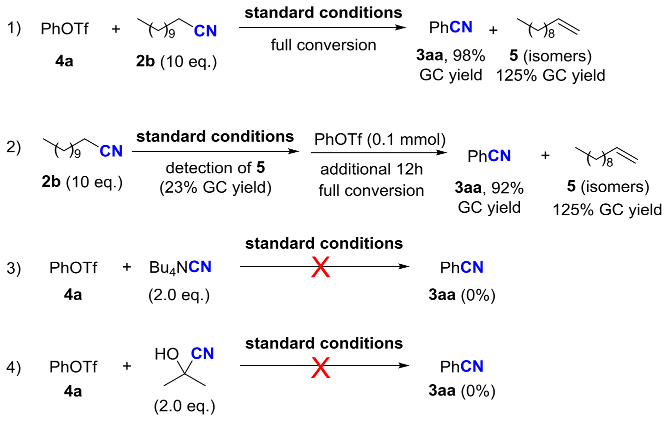
Several control reactions were then performed to gather preliminary information about the mechanism. We demonstrated the occurrence of the proposed retro-hydrocyanation step through the detection of undecene isomers resulting from the retro-hydrocyanation of dodecanitrile (Scheme 3, eq. 1).

We next explored whether retro-hydrocyanation proceeds in the absence of electrophile. In this experiment, only small amounts of alkene isomers were observed, showing that retro-hydrocyanation cannot be performed efficiently in the absence of the electrophile. The normal reaction course resumed after addition of the electrophile, further suggesting that a direct transfer of the cyanide anion between two nickel(II)-species is the main pathway of the reaction (Scheme 3, eq. 2). Additional control experiments using a simple ammonium cyanide salt or acetone cyanohydrin as reagents did not give any conversion, further suggesting that our reaction is not proceeding through the in situ generation of an ammonium cyanide reagent (Scheme 3, eq. 3 and 4). Taken altogether, these experiments are best explained by a double catalytic cycle as presented in Scheme 1b. Within this mechanistic context, the ability to drastically decrease the amount of butyronitrile reagent when the electrophile is slowly added to the reaction mixture (vide supra) highlights the critical importance of matching the rate of retro-hydrocyanation with that of aryl (pseudo)halide oxidative addition.

**Table 3:** nickel-catalyzed transfer cyanation of aryl and vinyl triflates.[a]



[a] Yields of isolated products. [b] GC yields. [c] **4** (0.5 mmol), **2a** (1.0 mmol), toluene (1.5 mL), 50 $^o$C, 3h, triflate added over 2h. [d] **4** (0.5 mmol), **2a** (1.5 mmol), toluene (1.5 mL), 70 $^o$C, 5h, triflate added over 4h. [e] *N*-Xantphos (10 mol%), 110 $^o$C. [f] Ni(COD)$_2$ (20 mol%), Xantphos (20 mol%), AlCl$_3$ (120 mol%), Et$_3$N (4.0 eq.). [g] 80 $^o$C.



**Scheme 3.** Control experiments.

In conclusion, a new nickel-catalyzed cyanation reaction has been developed, enabling the conversion of a broad range of aryl chlorides and aryl/vinyl triflates into aryl/vinyl nitriles. The use of nontoxic and inexpensive butyronitrile as a cyanating agent not only addresses the safety issues encountered with most of the current cyanation reactions, but also overcome other drawbacks by preventing catalyst deactivation and ensuring homogeneity of the reaction mixture. We believe that the new concept delineated in this work, namely the merger of transfer hydrofunctionalization and cross-coupling, will open new avenues in synthetic organic chemistry.

## Acknowledgements

Generous funding from the Max-Planck-Society and the Max-Planck-Institut für Kohlenforschung is acknowledged. We thank Prof. Dr. Benjamin List for sharing analytical equipment. P.Y. thanks the China Scholarship Council for a scholarship.

**Keywords:** Cross-coupling • Cyanation • Aryl chloride • Aryl triflate • Retro-hydrocyanation

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10.1002/anie.201707517

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