Difluorocarbene-Based Cyanation of Aryl Iodides

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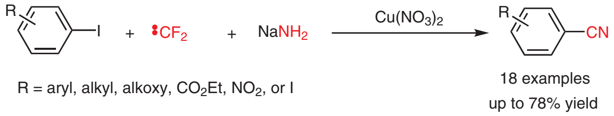

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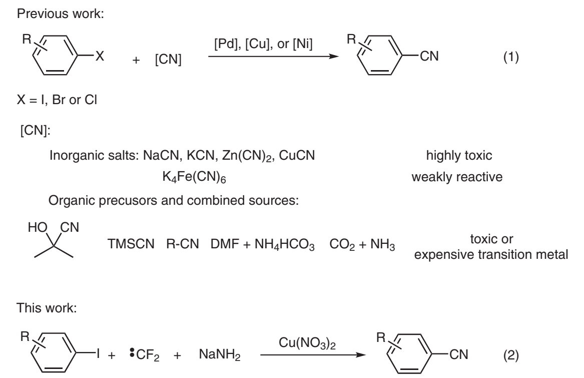
Abstract A large number of efficient cyanation methods have been developed because of the wide range of applications of nitriles, but conventional methods usually suffer from the need for a toxic cyanation reagent. Although difluorocarbene chemistry has received increasing attention, the use of difluorocarbene as a sources of the nitrile carbon for nitrile groups remains largely unexplored. We describe a difluorocarbene-based cyanation of aryl iodides promoted by a cheap copper source, $Cu(NO_3)_2·2.5H_2O$, under an air atmosphere. $Ph_3P^+CF_2CO_2^-$, an easily available and shelf-stable difluorocarbene reagent, and $NaNH_2$ are used as the carbon source and the nitrogen source for the nitrile group, respectively. The cyanation protocol is attractive because no toxic reagent is used and performing the reactions under an air atmosphere is operationally convenient.

Key words difluorocarbene, cyanation, nitriles, copper, aryl iodides

Nitriles are widely present as key structural motifs in natural products, pharmaceuticals, and agrochemicals, and they have emerged as versatile intermediates in organic synthesis.[1] Consequently, the incorporation of a nitrile group into organic molecules has received increasing attention.[2] Cyanation is apparently one of the most straightforward strategies for the installation of a cyano group, and therefore significant efforts have been devoted to the development of efficient cyanation reagents. Commonly used nucleophilic cyanation reagents such as TMSCN,[3] KCN,[4] or CuCN[5] are highly toxic and are prone to undergo hydrolysis with generation of hazardous HCN gas. Electrophilic cyanation can deliver products that cannot be easily obtained by using nucleophilic reagents, and consequently various electrophilic cyanation reagents have been developed, including X–CN (X = Cl, Br),[6] N–CN,[7] I–CN,[8] and S–CN reagents.[9] However, the X–CN (X = Cl, Br) reagents are volatile and highly toxic, and the preparation of the other reagents require the use of poisonous nucleophilic cyanation reagents. Recently, many easily handled cyanation reagents have emerged, such as CH_3CN,[10] DMF alone or in combination with a nitrogen source,[11] or DMSO with a nitrogen source.[12] The emergence of these large numbers of reagents has allowed the development of a variety of cyanation methods for the synthesis of various nitrile-containing molecules.[13]

Because of the wide availability of aryl halides, the cyanation of aryl halides, catalyzed or promoted by a complex of a transition metal such as Pd,[14] Cu,[10c,11c,15] or Ni,[16] serves as an effective protocol for the synthesis of aryl nitriles (Scheme 1, eq 1). However, Pd catalysts are quite expensive and Pd catalysts can be readily deactivated due to the strong binding ability of the CN^- anion.[14a,b] The

Rosenmund–von Braun reaction is a classic method for the Cu-promoted cyanation of aryl halides,[17] but requires the use of the toxic reagent CuCN in excess. In early studies on transition-metal-catalyzed or -promoted cyanations of aryl halides, toxic inorganic cyanide salts were frequently used.[4,14c] $K_4[Fe(CN)_6]$ is a safe inorganic salt, but its low solubility and its low rate of transmetalation limit its widespread application.[18] Organic cyanide precursors, such as TMSCN,[19] acetone cyanohydrin,[20] or alkyl nitriles,[16a,d] and combined cyanide sources, including DMF/$[NH_4^+ X^-]$,[11c,21] or CO_2/NH_3,[13g] have also proved to be quite effective for the cyanation of aryl halides, but some reagents, such as TMSCN and acetone cyanohydrin are toxic, and the reactions can require an inert atmosphere, the handling of gases, or the use of an expensive catalyst or ligand. It is therefore apparent that it is highly desirable to develop operationally convenient protocols for the cyanation of aryl halides by using easily available reagents.

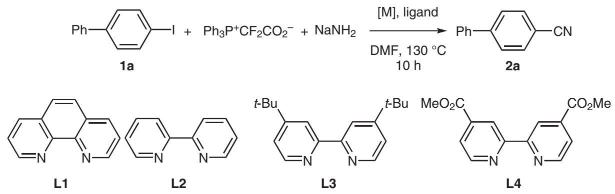


Scheme 1 Cyanation of aryl halides

As an active intermediate, difluorocarbene has found widespread applications in synthetic chemistry.[22] Typical transformations of difluorocarbene include [2+1] cyclization with alkenes or alkynes,[23] insertion into X–H bonds (X = N, O, S),[22a,24] coupling with other carbenes,[25] and transition-metal-catalyzed transfer reactions.[26] We recently developed the mild difluorocarbene reagent $Ph_3P^+CF_2CO_2^-$, which is easily accessible and shelf stable.[27] The use of this reagent as a difluorocarbene source allowed us to discover that difluorocarbene can be captured by a suitable source of sulfur,[28] selenium,[29] or nitrogen[30] to generate thiocarbonyl fluoride (CF_2=S), selenocarbonyl fluoride (CF_2=Se), and cyanide anion (CN^-), respectively, thereby offering new possibilities for difluorocarbene chemistry. The transformation into CN^- was developed into a synthetic tool to enable the incorporation of a nitrile groups into alkanes.[30] These findings prompted us to investigate the installation of cyano groups into arenes to provide aryl nitriles. Here we describe a difluorocarbene-based cyanation of aryl iodides promoted by the cheap copper complex $Cu(NO_3)_2{\cdot}2.5H_2O$, under an air atmosphere by using $Ph_3P^+CF_2CO_2^-$ as the difluorocarbene source (Scheme 1, eq 2).

Our initial attempts at difluorocarbene-based cyanation of 4-iodobiphenyl (**1a**) using sodium amide ($NaNH_2$) as the nitrogen source successfully gave the desired product **2a**, but only in a low yield (Table 1, entry 1). A brief survey of transition-metal compounds, including Cu and Pd complexes (entries 1–6), revealed that $Cu(NO_3)_2{\cdot}2.5H_2O$ was a suitable choice (entry 4). Because the use of a ligand might be favorable, we screened various ligands **L1**–**L4** (entries 7–10). The yield was significantly increased by using **L4** as a ligand (entry 10). Other reaction solvents were found to be inferior to DMF (entries 10–14), although a moderate yield was obtained in hexamethylphosphoramide (HMPA; entry

Table 1 Optimization of the Reaction Conditions[a]



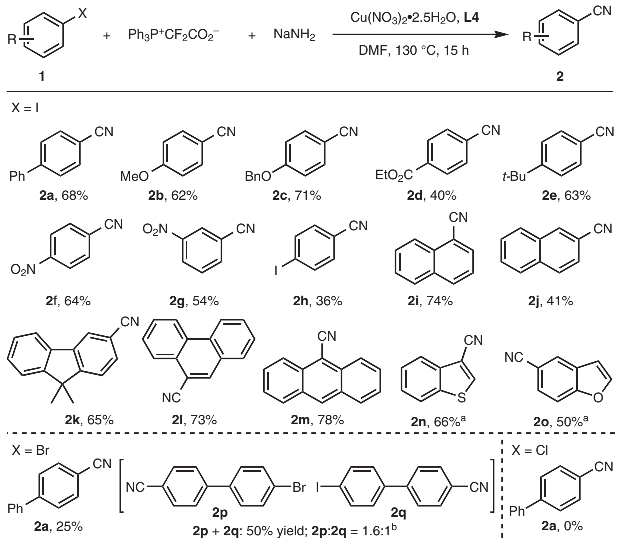
Entry	Metal compound [M]	Ligand (mol%)	Ratio[b]	Yield[c] (%)
1	$Cu(OAc)_2$	–	1:2:3.5:1.8	22
2	CuOAc	–	1:2:3.5:1.8	10
3	CuI	–	1:2:3.5:1.8	30
4	$Cu(NO_3)_2{\cdot}2.5H_2O$	–	1:2:3.5:1.8	44
5	$PdCl_2(PPh_3)_2$	–	1:2:3.5:1.8	13
6	$PdCl_2$(dppf)	–	1:2:3.5:1.8	12
7	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L1** (10)	1:2:3.5:1.8	34
8	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L2** (10)	1:2:3.5:1.8	47
9	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L3** (10)	1:2:3.5:1.8	42
10	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (10)	1:2:3.5:1.8	66
11[d]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (10)	1:2:3.5:1.8	2
12[e]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (10)	1:2:3.5:1.8	ND
13[f]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (10)	1:2:3.5:1.8	22
14[g]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (10)	1:2:3.5:1.8	52
15[h]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (5)	1:1.5:2:1.3	70
16[i]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (5)	1:1.5:2:1.3	34
17[h]	$Cu(NO_3)_2{\cdot}2.5H_2O$	**L4** (5)	1:1.5:2:0.5	12
18[h]	CuI	**L4** (5)	1:1.5:2:1.3	11

[a] Reaction conditions: **1a** (0.2 mmol), $Ph_3P^+CF_2CO_2^-$, metal complex, ligand, $NaNH_2$, anhyd DMF (1.5 mL), under air, 130 °C, 10 h.
[b] Molar ratio **1a**/$Ph_3P^+CF_2CO_2^-$/$NaNH_2$/[M].
[c] Determined by GC/MS analysis. ND = Not Detected
[d] Dimethyl carbonate was used as the reaction solvent.
[e] DME was used as the reaction solvent.
[f] NMP was used as the reaction solvent.
[g] HMPA was used as the reaction solvent.
[h] Reaction time 15 h.
[i] Reaction time 6 h.

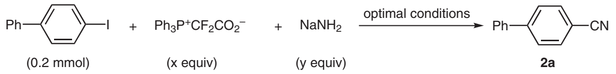
14). Decreasing the loadings of $Ph_3P^+CF_2CO_2^-$, $NaNH_2$, and the Cu complex resulted in slight increases in the yield on prolonging the reaction time to 15 hours (entries 10 and 15). The yield markedly decreased on shortening the reaction time (entry 16). A catalytic amount of the Cu source did not promote this reaction effectively (entry 17). Although a 30% yield was obtained by using CuI (1.8 equiv) as the copper source (entry 3), the yield was not increased by concurrently using **L4** as a ligand with 1.3 equivalents of CuI (entry 18).

With the optimal reaction conditions in hand (Table 1, entry 15), we investigated the substrate scope of the difluorocarbene-based cyanation of aryl halides promoted by $Cu(NO_3)_2·2.5H_2O$ under an air atmosphere (Scheme 2).[31] The process could be extended to a wide range of aryl iodides **1a–o**. Electron-rich, -neutral, and -deficient aryl iodides were all converted into the desire products **2a–o** in moderate to good yields. Various functional groups were tolerated under these conditions, including ether, ester, nitro, and hetaryl groups. Aryl bromides showed a low reactivity, and a low yield (25%) of **2a** was obtained from bromobenzene. When the substrate contained both Br and I atoms, a mixture of the C–I and C–Br cyanation products **2p** and **2q** was produced. In this case, although a dicyanation product was detected by GC/MS analysis, it was produced only in a trace amount and could not be isolated. Aryl chlorides were inert toward this cyanation transformation.

We have previously reported that $Ph_3P^+CF_2CO_2^-$ and $NaNH_2$ can act as sources of carbon and nitrogen for a nitrile group, respectively.[30] Indeed, in this aryl halide cyanation process, the desired conversion was almost completely suppressed without their presence (Scheme 3). Almost no product **2a** was observed when $NaNH_2$ was not used, further indicating that $NaNH_2$ is the nitrogen source. In the absence of $Ph_3P^+CF_2CO_2^-$, product **2a** was obtained in low yield, suggesting that the predominant carbon source is $Ph_3P^+CF_2CO_2^-$. DMF might also serve as a nonnegligible source of carbon,[11b,c,21] A 52% yield was obtained by using HMPA as the reaction solvent instead of DMF (Table 1, entry 14), further confirming that $Ph_3P^+CF_2CO_2^-$ and $NaNH_2$ are, respectively, the sources of the C and N atoms of the CN group.



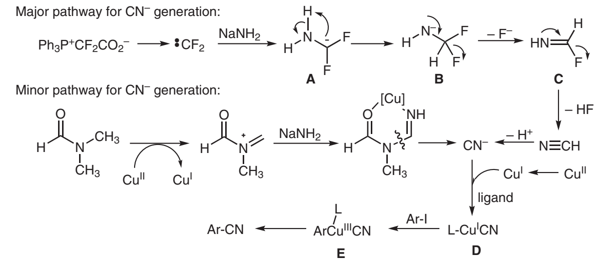
Scheme 2 Difluorocarbene-based cyanation of aryl halides. *Reagents and conditions*: **1** (0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (1.5 equiv), $Cu(NO_3)_2·2.5H_2O$ (1.3 equiv), **L4** (5 mol%), $NaNH_2$ (2 equiv), dry DMF (4 mL), under air, 130 °C, 15 h. Isolated yields are reported.
[a] For products **2n** and **2o**, the reaction time was 20 h. [b] Both **2p** and **2q** were obtained from the conversion of 4-bromo-4′-iodobiphenyl; the molar ratio (1.6:1) was determined by ^1H NMR spectroscopy.



x	y	Yield[a] (%)
0	0	trace
1.5	0	trace
0	2	17

Scheme 3 The identification of the carbon source and the nitrogen source for the CN group. The optimal conditions were those shown in Table 1, entry 15. [a] Determined by GC/MS analysis.

On the basis of the above results and our previous studies on difluorocarbene-based cyanation of alkenes,[30] we propose the plausible mechanism shown Scheme 4. Difluorocarbene generated from $Ph_3P^+CF_2CO_2^-$ reacts with $NaNH_2$ to produce a CN^- anion through sequential formation of intermediates **A**, **B**, and **C** (major pathway).[30] The generation of CN^- from the DMF/$NaNH_2$ system cannot be excluded (minor pathway).[11b,c] Because of its strong oxidizing power, Cu^{II} can be readily reduced to Cu^I in the reaction system.[32] The coordination of a ligand and CN^- gives the Cu^ICN complex **D**. Oxidative insertion of CuI into the Ar–I bond delivers $ArCu^{III}CN$ (intermediate **E**), reductive elimination from which affords the final product. Although the last reductive elimination also releases the catalyst Cu^I, a stoichiometric amount of the Cu^{II} source is still necessary, probably because the reductive elimination proceeds quite slowly and/or the Cu^I is deactivated by coordinating ligands.



Scheme 4 The proposed mechanism

In summary, we have described a difluorocarbene-based cyanation of aryl iodides promoted by a cheap copper source, $Cu(NO_3)_2·2.5H_2O$, under an air atmosphere.

Ph$_3$P$^+$CF$_2$CO$_2^-$, an easily available and shelf-stable reagent, and NaNH$_2$ act as the sources of carbon and nitrogen, respectively, for the CN group. This convenient cyanation process, which does not use any toxic cyanation reagent, might find application in the synthesis of aryl nitriles.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691590.

References and Notes

(1) (a) *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Wiley Interscience: London, **1970**. (b) Fatiadi, A. In *Triple-Bonded Functional Groups, Vol. 2*; Patai, P.; Rappoport, Z., Ed.; Wiley: Chichester, **1983**, 1057. (c) Jones, L. H.; Summerhill, N. W.; Swain, N. A.; Mills, J. E. *MedChemComm* **2010**, *1*, 309.

(2) (a) Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014**, *55*, 1271. (b) Pellissier, H. *Adv. Synth. Catal.* **2015**, *357*, 857. (c) Kurono, N.; Ohkuma, T. *ACS Catal.* **2016**, *6*, 989. (d) Schörgenhumer, J.; Waser, M. *Org. Chem. Front.* **2016**, *3*, 1535. (e) Yu, J.-T.; Teng, F.; Cheng, J. *Adv. Synth. Catal.* **2017**, *359*, 26. (f) Yan, G.; Zhang, Y.; Wang, J. *Adv. Synth. Catal.* **2017**, *359*, 4068. (g) Chaitanya, M.; Anbarasan, P. *Org. Biomol. Chem.* **2018**, *16*, 7084. (h) Cui, J.; Song, J.; Liu, Q.; Liu, H.; Dong, Y. *Chem. Asian J.* **2018**, *13*, 482.

(3) (a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014. (b) Wang, D.; Zhu, N.; Chen, P.; Lin, Z.; Liu, G. *J. Am. Chem. Soc.* **2017**, *139*, 15632. (c) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. *Nature* **2019**, *574*, 516.

(4) (a) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (b) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837.

(5) (a) Hoffmann, H. M. R.; Iranshahi, L. *J. Org. Chem.* **1984**, *49*, 1174. (b) Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323.

(6) (a) Kaupp, G.; Schmeyers, J.; Boy, J. *Chem. Eur. J.* **1998**, *4*, 2467. (b) Okamoto, K.; Watanabe, M.; Murai, M.; Hatano, R.; Ohe, K. *Chem. Commun.* **2012**, *48*, 3127.

(7) (a) Hughes, T. V.; Hammond, S. D.; Cava, M. P. *J. Org. Chem.* **1998**, *63*, 401. (b) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 4217. (c) Cai, Y.; Qian, X.; Rérat, A.; Auffrant, A.; Gosmini, C. *Adv. Synth. Catal.* **2015**, *357*, 3419. (d) Kiyokawa, K.; Nagata, T.; Minakata, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 10458.

(8) (a) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975. (b) Ma, B.; Lin, X.; Lin, L.; Feng, X.; Liu, X. *J. Org. Chem.* **2017**, *82*, 701. (c) Nagata, T.; Matsubara, H.; Kiyokawa, K.; Minakata, S. *Org. Lett.* **2017**, *19*, 4672. (d) Le Vaillant, F.; Wodrich, M. D.; Waser, J. *Chem. Sci.* **2017**, *8*, 1790. (e) Declas, N.; Le Vaillant, F.; Waser, J. *Org. Lett.* **2019**, *21*, 524.

(9) (a) Talavera, G.; Peña, J.; Alcarazo, M. *J. Am. Chem. Soc.* **2015**, *137*, 8704. (b) Barrado, A. G.; Zieliński, A.; Goddard, R.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 13401. (c) Li, X.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 9496.

(10) (a) Kou, X.; Zhao, M.; Qiao, X.; Zhu, Y.; Tong, X.; Shen, Z. *Chem. Eur. J.* **2013**, *19*, 16880. (b) Zhu, Y.; Li, L.; Shen, Z. *Chem. Eur. J.* **2015**, *21*, 13246. (c) Zhu, Y.; Zhao, M.; Lu, W.; Li, L.; Shen, Z. *Org. Lett.* **2015**, *17*, 2602.

(11) (a) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374. (b) Kim, J.; Choi, J.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 2528. (c) Pawar, A. B.; Chang, S. *Chem. Commun.* **2014**, *50*, 448.

(12) (a) Ren, X.; Chen, J.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 6725. (b) Zheng, K.; Liu, B.; Chen, S.; Chen, F. *Tetrahedron Lett.* **2013**, *54*, 5250.

(13) (a) Bag, S.; Jayarajan, R.; Dutta, U.; Chowdhury, R.; Mondal, R.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 12538. (b) McManus, J. B.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 2880. (c) Wang, L.; Wang, G.; Zhang, J.; Bian, C.; Meng, X.; Xiao, F.-S. *Nat. Commun.* **2017**, *8*, 15240. (d) Gao, D.-W.; Vinogradova, E. V.; Nimmagadda, S. K.; Medina, J. M.; Xiao, Y.; Suciu, R. M.; Cravatt, B. F.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 8069. (e) Lennox, A. J. J.; Goes, S. L.; Webster, M. P.; Koolman, H. F.; Djuric, S. W.; Stahl, S. S. *J. Am. Chem. Soc.* **2018**, *140*, 11227. (f) Wang, X.; Studer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 11792. (g) Wang, H.; Dong, Y.; Zheng, C.; Sandoval, C. A.; Wang, X.; Makha, M.; Li, Y. *Chem* **2018**, *4*, 2883. (h) Lu, F.-D.; Liu, D.; Zhu, L.; Lu, L.-Q.; Yang, Q.; Zhou, Q.-Q.; Wei, Y.; Lan, Y.; Xiao, W.-J. *J. Am. Chem. Soc.* **2019**, *141*, 6167. (i) Zhao, D.; Xu, P.; Ritter, T. *Chem* **2019**, *5*, 97.

(14) (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (b) Vafaeezadeh, M.; Hashemi, M. M.; Karbalaie-Reza, M. *Inorg. Chem. Commun.* **2016**, *72*, 86. (c) Ushkov, A. V.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 10999. (d) Senecal, T. D.; Shu, W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 10035. (e) Kristensen, S. K.; Eikeland, E. Z.; Taarning, E.; Lindhardt, A. T.; Skrydstrup, T. *Chem. Sci.* **2017**, *8*, 8094.

(15) (a) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (b) Jiang, Z.; Huang, Q.; Chen, S.; Long, L.; Zhou, X. *Adv. Synth. Catal.* **2012**, *354*, 589. (c) Kim, K.; Hong, S. H. *Adv. Synth. Catal.* **2017**, *359*, 2345.

(16) (a) Yu, P.; Morandi, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 15693. (b) Zhang, X.; Xia, A.; Chen, H.; Liu, Y. *Org. Lett.* **2017**, *19*, 2118. (c) Yang, L.; Liu, Y.-T.; Park, Y.; Park, S.-W.; Chang, S. *ACS Catal.* **2019**, *9*, 3360. (d) Ueda, Y.; Tsujimoto, N.; Yurino, T.; Tsurugi, H.; Mashima, K. *Chem. Sci.* **2019**, *10*, 994.

(17) (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges. A* **1919**, *52*, 1749. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.

(18) (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (b) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189.

(19) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714.

(20) Schareina, T.; Zapf, A.; Cotte, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 777.

(21) Zhang, G.; Ren, X.; Chen, J.; Hu, M.; Cheng, J. *Org. Lett.* **2011**, *13*, 5004.

(22) (a) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842. (b) Dilman, A. D.; Levin, V. V. *Acc. Chem. Res.* **2018**, *51*, 1272.

(23) (a) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411. (b) Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7153. (c) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12390.

(24) (a) Thomoson, C. S.; Dolbier, W. R. Jr. *J. Org. Chem.* **2013**, *78*, 8904. (b) Xie, Q.; Ni, C.; Zhang, R.; Li, L.; Rong, J.; Hu, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3206.

(25) (a) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14496. (b) Zheng, J.; Lin, J.-H.; Yu, L.-Y.; Wei, Y.; Zheng, X.; Xiao, J.-C. *Org. Lett.* **2015**, *17*, 6150. (c) Zhang, Z.; Yu, W.; Wu, C.; Wang, C.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 273.

(26) (a) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. *Org. Lett.* **2016**, *18*, 4384. (b) Feng, Z.; Min, Q.-Q.; Zhang, X. *Org. Lett.* **2016**, *18*, 44. (c) Feng, Z.; Min, Q. Q.; Fu, X. P.; An, L.; Zhang, X. *Nat. Chem.* **2017**, *9*, 918. (d) Fu, X.-P.; Xue, X.-S.; Zhang, X.-Y.; Xiao, Y.-L.; Zhang, S.; Guo, Y.-L.; Leng, X.; Houk, K. N.; Zhang, X. *Nat. Chem.* **2019**, *11*, 948.

(27) (a) Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C. *Chem. Commun.* **2013**, *49*, 7513. (b) Deng, X.-Y.; Lin, J.-H.; Zheng, J.; Xiao, J.-C. *Chem. Commun.* **2015**, *51*, 8805.

(28) (a) Zheng, J.; Wang, L.; Lin, J.-H.; Xiao, J.-C.; Liang, S. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 13236. (b) Zheng, J.; Cheng, R.; Lin, J.-H.; Yu, D. H.; Ma, L.; Jia, L.; Zhang, L.; Wang, L.; Xiao, J.-C.; Liang, S. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 3196. (c) Yu, J.; Lin, J.-H.; Xiao, J.-C. *Angew. Chem. Int. Ed.* **2017**, *56*, 16669.

(29) Chen, X.-L.; Zhou, S.-H.; Lin, J.-H.; Deng, Q.-H.; Xiao, J.-C. *Chem. Commun.* **2019**, *55*, 1410.

(30) Zhang, M.; Lin, J.-H.; Xiao, J.-C. *Angew. Chem. Int. Ed.* **2019**, *58*, 6079.

(31) **Cyanation of Aryl Iodides 1; General Procedure**
Under air atmosphere, a reaction tube was charged with the appropriate aryl iodide **1** (0.5 mmol), $Ph_3P^+CF_2CO_2^-$ (268 mg, 0.75 mmol, 1.5 equiv), ligand **L4** (6.3 mg, 5 mol%), $Cu(NO_3)_2{\cdot}2.5\,H_2O$ (143 mg, 0.65 mmol, 1.3 equiv), $NaNH_2$ (39 mg, 1.0 mmol, 2.0 equiv), and anhyd DMF (4 mL). The mixture was stirred at 130 °C for 15 h, then cooled to rt and filtered through a pad of Celite that was washed with CH_2Cl_2. The combined organic phase was washed with H_2O (3 × 15 mL), and the organic layer was further washed with sat. aq Na_2SO_3 and sat. brine, then dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash column chromatography.
9,9-Dimethyl-9*H*-fluorene-3-carbonitrile (2k)
The reaction was performed on a 0.6 mmol scale. Yellow oil; yield: 85 mg (65%). IR (neat): 3062, 2962, 2924, 2866, 2223, 1609, 1485, 1471, 1447, 1416, 1302, 1283, 1219, 1077, 1023, 893, 835, 783, 759, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.72 (m, 2 H), 7.69 (s, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 7.1 Hz, 1 H), 7.43–7.34 (m, 2 H), 1.48 (s, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.19, 154.16, 143.8, 137.2, 131.4, 129.1, 127.5, 126.4, 122.9, 121.1, 120.5, 119.7, 110.1, 47.1, 26.8. HRMS (EI); *m/z* $[M]^+$ calcd for $C_{16}H_{13}N$: 219.1048; found: 219.1054.

(32) Shi, R.; Zhang, H.; Lu, L.; Gan, P.; Sha, Y.; Zhang, H.; Liu, Q.; Beller, M.; Lei, A. *Chem. Commun.* **2015**, *51*, 3247.