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SHORT COMMUNICATION

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Metal-Free Directed *ortho* C–H Iodination: Synthesis of 2′-Iodobiaryl-2-carbonitriles[‡]

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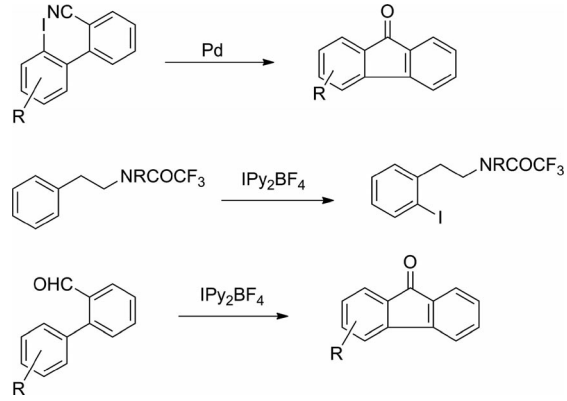
Metal-free directed *ortho* C–H iodination of biaryl-2-carbonitriles was developed. A series of 2′-iodobiaryl-2-carbonitriles were synthesized from substituted biphenyl carbonitriles and naphthylbenzonitriles in reasonably good yields by using bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4, Barluenga's reagent) and HBF_4·OEt_2. The biaryl-2-carbonitriles are useful precursors for the synthesis of benzocyclic ketones.

Introduction

C–H bond activation is a major strategy used in the construction of C–heteroatom (C–X) and C–C bonds, and it has drawn great interest.[1] Organic chemists are focusing on C–H bond activation owing to its cost effectiveness, common nature, and atom economy. Major challenges in this area are chemoselectivity, regioselectivity, *ortho* selectivity, and choice of metal catalyst and additives. Directed *ortho* C–H functionalization requires proper modification of molecular scaffolds. Over the past few years, novel strategies have been developed for directed *ortho* functionalization of sp^2 and sp^3 C–H bonds.[2] In this context, methods for directed *ortho* C–H halogenation[3] through C–H bond activation have grown intensively as a result of the number of approaches that have been developed for directed *ortho* C–H iodination.[4] Joshi et al.[5] reported selective *ortho* C–H iodination of phenol, anisole, and anilines by using silver salts as iodination reagents. Buchwald et al.[6] developed metal-free directed *ortho* C–H iodination and demonstrated its application in the synthesis of naturally occurring carbazoles. Metal-free directed iodination of arenes with bis(pyridine)iodonium tetrafluoroborate (Scheme 1) was also developed recently by Barluenga et al.[7]

The development of new approaches for directed *ortho* C–H iodination is in high demand and quite challenging. Directed *ortho* C–H iodination of biaryl-2-carbonitriles has so far not been used for the synthesis of 2′-iodobiaryl-2-carbonitriles, which are useful intermediates in the synthesis of benzocyclic ketones (Scheme 1). For example, Larock et al.[8] reported the palladium-catalyzed cyclization of 2′-iodobipheny-2-carbonitrile for the synthesis of 9-benzofluorenone (Scheme 1). Similarly, Barluenga et al.[9] reported easy access to benzocyclic ketones by using iodonium chemistry (Scheme 1).



Scheme 1. Pd-catalyzed cyclization of 2′-iodobiaryl-2-carbonitriles, bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4, Barluenga's reagent) mediated *ortho*-iodination, and access to benzocyclic ketones.

2′-Iodobiphenyl-2-carbonitrile was first synthesized by Grinham et al.,[10] and the Grinham procedure was later modified by Larock et al.[8] through cyanation of 2,2′-diiodobiphenyl by using copper cyanide in pyridine under reflux; however, this process required complex starting materials, metal cyanide, and high temperatures. Therefore, an easy and efficient process is required for the modular construction of these molecules. As part of our ongoing synthetic program on biaryl scaffolds,[11] we intended to synthesize 2′-iodobiaryl-2-carbonitriles by metal-free directed *ortho* C–H iodination (Scheme 2).

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[‡] This is CDRI communication no. 8514.
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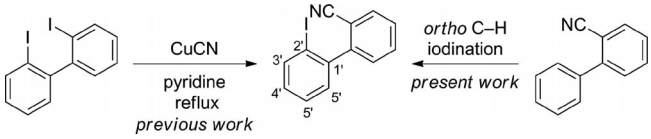


Scheme 2. Strategy towards the synthesis of 2′-iodobiphenyl-2-carbonitrile.

Results and Discussion

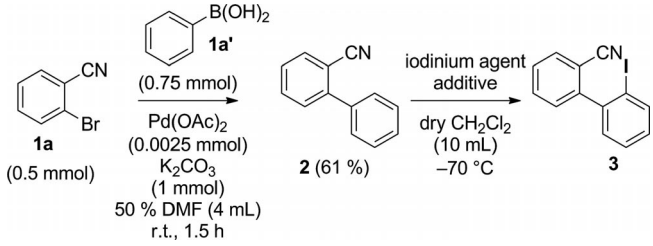
We started with the synthesis of the key intermediate, biphenyl-2-carbonitrile (**2**), by using a reported Suzuki coupling reaction.[12] We anticipated that the iodonium ion generated in situ from bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4, Barluenga's reagent) could recognize and coordinate through the nitrile group of **2** and assist in the delivery of the iodonium ion to the *ortho* position through a chelation-assisted process. The weak coordination of the iodonium ion to the nitrile moiety is the key step for this process. By selecting **2** as a model substrate, screening of experimental conditions with various iodonium agents and additives was completed, and the results are summarized in Table 1. The use of HBF_4 (4 equiv.) and Barluenga's reagent (2 equiv.) produced good yields of the product (Table 1, entries 1–4). The conversion of **2** was unchanged with an increase in the reaction time and was also unaffected with an increase in the number of equivalents of Barluenga's reagent and HBF_4 (Table 1, entries 5–7). No product was obtained regardless of whether the reaction was performed at low temperature or at room temperature with *N*-iodosuccinimide (NIS) as the iodonium agent in the absence and in the presence of HBF_4 (Table 1, entries 8–10). If triflic acid (TfOH)[13] was used instead of HBF_4, the formation of the product was not observed (Table 1, entry 11). Furthermore, no product was formed if the reaction was performed at room temperature with HBF_4 (4 equiv.) and Barluenga's reagent (2 equiv.; Table 1, entry 12).

After successful screening of the experimental conditions with various iodonium agents and additives, we determined the optimized conditions for the directed *ortho* C–H iodination (Table 1, entry 4). The moderate conversions of **2** and the low yields of **3** might be attributed to the poor electronic nature of the phenyl ring. Under these optimized conditions, to further investigate the directed *ortho* C–H iodination, we prepared biaryl-2-carbonitriles **4**–**18** (Scheme 3) by using the same reported Suzuki coupling reaction.[12]

With the use of biaryl-2-carbonitriles **4**–**17**, we explored the scope of this metal-free directed *ortho* C–H iodination process. The structures of 2′-iodobiaryl-2-carbonitriles **18**–**31** obtained in the metal-free directed *ortho* C–H iodination process, the reaction times, and the yields of the isolated products are depicted in Table 2.

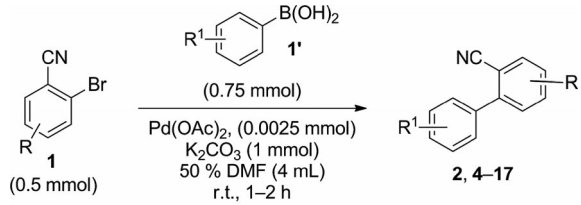
Compounds **18**–**25** were obtained in moderate yields (45–59%) upon reaction of **4**–**10**. It appears that electron-donating groups in the *para* position weekly activate the C–H bond (Table 2, entry 6), whereas electron-donating groups in the *meta* position strongly activate the C–H bond (Table 2, entry 13). We did not observe the formation of other iodinated side products, which might be due to steric interactions between the iodonium ion and the substituents. 2′-Iodobiaryl-2-carbonitriles **25** and **26** were obtained in good yields, whereas **27** and **28** were obtained in low yields, because the iodonium ion might have been trapped by the

Table 1. Optimization of the reaction conditions for the formation of **3** from **2**.[a]



Entry	Iodonium agent (equiv.)	Additive (equiv.)	*t* [h]	Conv.[b] [%]	Yield[c] [%]
1	IPy_2BF_4 (1)	–	24	–	–
2	IPy_2BF_4 (1)	HBF_4 (1)	24	6	–
3	IPy_2BF_4 (1)	HBF_4 (2)	24	22	15
4	IPy_2BF_4 (2)	HBF_4 (4)	24	56	44
5	IPy_2BF_4 (2)	HBF_4 (4)	30	56	44
6	IPy_2BF_4 (3)	HBF_4 (6)	24	56	44
7	IPy_2BF_4 (3)	HBF_4 (6)	30	56	44
8	NIS (2)	–	24	–	–
9	NIS (2)	HBF_4 (4)	24	–	–
10[d]	NIS (2)	HBF_4 (4)	24	–	–
11	IPy_2BF_4 (2)	TfOH (4)	30	–	–
12[d]	IPy_2BF_4 (2)	HBF_4 (4)	30	–	–

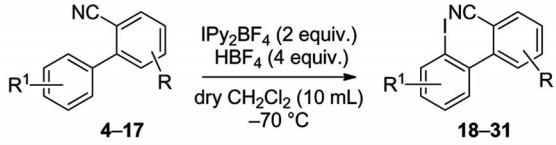
[a] The reaction was conducted with **2** (1 mmol or 1 equiv.) and the iodonium agent and the additive (amounts with respect to **2**; see the Supporting Information), unless otherwise noted. [b] Determined on the basis of the percent yield of recovered **2**. [c] Yield of isolated **3** with respect to **2**. [d] Reaction was performed at r.t.

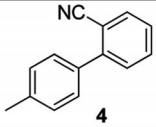
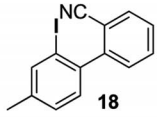
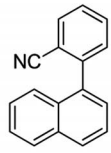
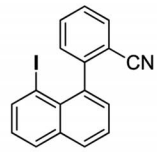
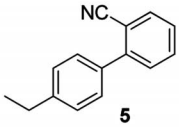
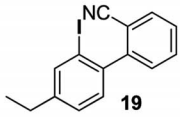
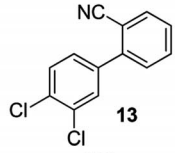
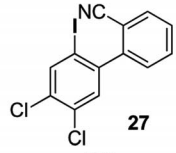
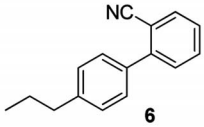
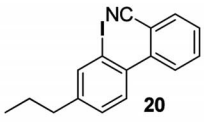
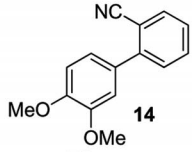
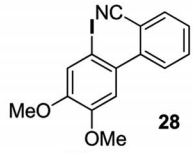
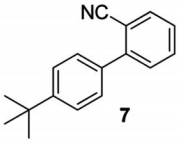
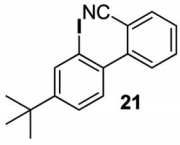
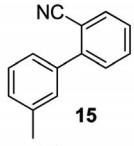
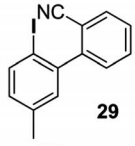
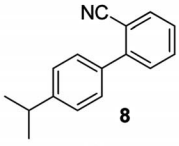
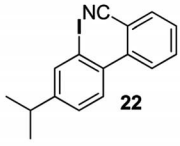
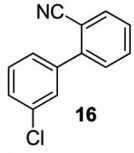
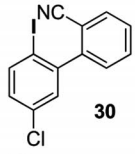
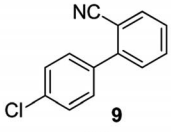
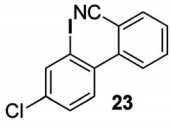
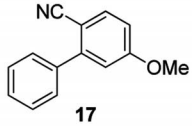
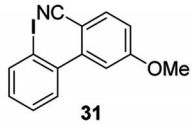
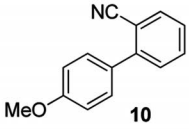
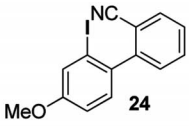
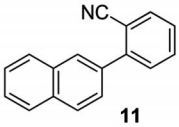
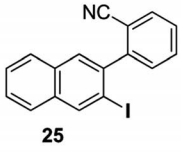


1a: R = H	**1b'**: R^1 = 4-Me	**4**: 72 %, 1 h
1a: R = H	**1c'**: R^1 = 4-Et	**5**: 72 %, 1 h
1a: R = H	**1d'**: R^1 = 4-*n*Pr	**6**: 75 %, 1 h
1a: R = H	**1e'**: R^1 = 4-*t*Bu	**7**: 67 %, 1 h
1a: R = H	**1f'**: R^1 = 4-*i*Pr	**8**: 69 %, 1 h
1a: R = H	**1g'**: R^1 = 4-Cl	**9**: 74 %, 1 h
1a: R = H	**1h'**: R^1 = 4-MeO	**10**: 68 %, 1 h
1a: R = H	**1i'**: R^1 = Ph	**11**: 60 %, 2 h
1a: R = H	**1j'**: R^1 = Ph	**12**: 58 %, 2 h
1a: R = H	**1k'**: R^1 = 3,4-Cl_2	**13**: 63 %, 2 h
1a: R = H	**1l'**: R^1 = 3,4-$(MeO)_2$	**14**: 65 %, 2 h
1a: R = H	**1m'**: R^1 = 3-Me	**15**: 64 %, 1 h
1a: R = H	**1n'**: R^1 = 3-Cl	**16**: 64 %, 1 h
1b: R = 4-MeO	**1p'**: R^1 = H	**18**: 66 %, 1.5 h

Scheme 3. Synthesis of biaryl-2-carbonitriles **2** and **4**–**17** through Suzuki coupling of 2-bromobenzonitriles **1**, reaction times, and yields of the isolated products.

Table 2. 2′-Iodobiaryl-2-carbonitriles **17**–**29** obtained in the metal-free directed *ortho* C–H iodination of biaryl-2-carbonitrile **4**–**16**, reaction times, and yields of isolated products.

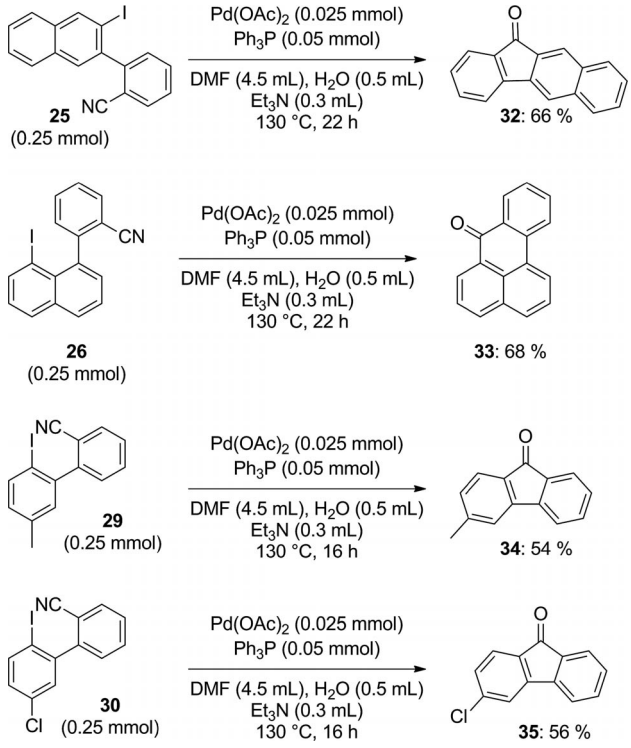


Entry	Biaryl-2-carbonitrile	2'-Iodobiaryl-2-carbonitrile	Time [h]	Yield [%]	Entry	Biaryl-2-carbonitrile	2'-Iodobiaryl-2-carbonitrile	Time [h]	Yield [%]
1	 **4**	 **18**	24	56	9	 **12**	 **26**	24	68
2	 **5**	 **19**	24	59	10	 **13**	 **27**	24	41
3	 **6**	 **20**	24	52	11	 **14**	 **28**	24	35
4	 **7**	 **21**	24	57	12	 **15**	 **29**	24	71
5	 **8**	 **22**	24	58	13	 **16**	 **30**	24	64
6	 **9**	 **23**	24	49	14	 **17**	 **31**	24	56
7	 **10**	 **24**	24	45					
8	 **11**	 **25**	24	66					

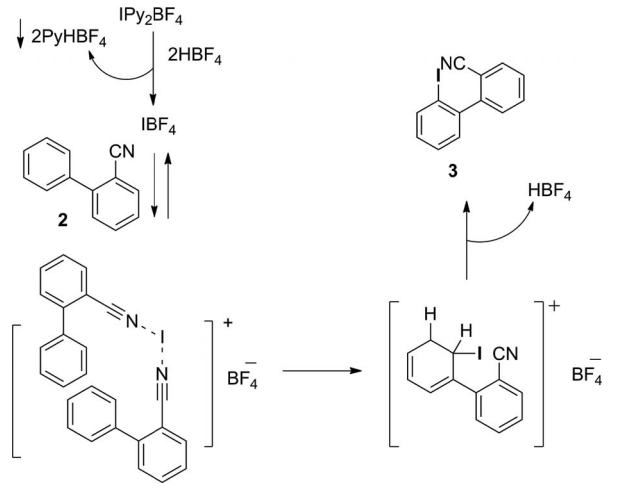
two chloro groups or the two methoxy groups. Interestingly, iodination occurred at the *ortho* position upon performing the iodination reaction with **2**, **15**, and **16**, in which the *para* position is free of substituents. An electron-donating substituent in the cyanophenyl moiety of **17** (Table 2, entry 14) increased the yield of *ortho* iodination product **31**.

To confirm the structures of **25**, **26**, **29**, and **30**, we converted them into known fluorenones and anthracenones through palladium-catalyzed cyclization by using the reported protocol of Larock et al.[8] (Scheme 4).

A possible reaction mechanism for the formation of 2′-iodobiphenyl-2-carbonitriles **3** and **18**–**31** is depicted in Scheme 5. The first step involves the in situ formation of the iodonium ion. The combination of Barluenga's reagent with $HBF_4{\cdot}OEt_2$ and acid protonation of the pyridine molecule results in the generation of the iodonium ion. The resultant iodonium ion coordinates with two molecules biphenyl-2-carbonitrile.[14] In the second step, the nitrile group directs aromatic substitution at the *ortho* position.



Scheme 4. Palladium-catalyzed cyclization to access fluorenones and anthracenones.



Scheme 5. Possible reaction mechanism for the directed *ortho* C–H iodination of biphenyl-2-carbonitrile (**2**).

Conclusions

In conclusion, we have developed an efficient metal-free protocol for the directed *ortho* C–H iodination of biaryl-2-carbonitriles. The formation of 2′-iodobiaryl-2-carbonitriles was achieved in reasonably good yields for the first time from substituted biphenylcarbonitriles and naphthylbenzonitriles through directed *ortho* C–H iodination by using Barluenga's reagent (IPy_2BF_4) and $HBF_4{\cdot}OEt_2$. This efficient process avoids the use of complex starting materials, high temperatures, copper(I) cyanide, transition-metal catalysts, and iodine acetate. Our method also provides 2′-iodobiaryl-2-carbonitriles that are useful precursors for the synthesis of benzocyclic ketones. To the best of our knowledge, we are the first group to report metal-free directed *ortho* C–H iodination for the synthesis of 2′-iodobiaryl-2-carbonitriles. The interaction between the iodonium ion and the nitrile is a crucial finding of our work, which may open some new vistas in metal-free organic transformations.

Experimental Section

General Procedure for the Directed *ortho* C–H Iodination: Bis(pyridine)iodonium tetrafluoroborate (2 mmol or 2 equiv.) was dissolved in dry dichloromethane (10 mL), and the resulting solution was stirred for 10 min at room temperature. The mixture was then cooled to –70 °C and 51–57% HBF_4 in diethyl ether (4 mmol or 4 equiv.) was added. After 15 min, biaryl-2-carbonitrile (1 mmol or 1 equiv.) was added at –70 °C, and the resulting mixture was stirred for 24–30 h. The reaction mixture was poured onto ice and vigorously stirred until the temperature of the mixture had risen to room temperature. The organic layer was washed with a 5% aqueous solution of sodium thiosulfate (50 mL), dried with sodium sulfate, and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (230–400 mesh, ethyl acetate/hexane) to provide the desired product.

General Procedure for the Pd-Catalyzed Cyclization of 2′-Iodobiaryl-2-carbonitriles: Et_3N (0.3 mmol) was added to a solution of the 2′-iodobiaryl-2-carbonitrile (0.25 mmol), $Pd(OAc)_2$ (0.025 mmol), and Ph_3P (0.05 mmol) in DMF (4.5 mL) and water (0.5 mL) under an argon atmosphere. The reaction mixture was stirred at 130 °C for 16–22 h. Then, the reaction mixture was cooled to room temperature and poured into diethyl ether (25 mL). The ether solution was washed with aqueous NH_4Cl and dried with Na_2SO_4. The crude mixture was subjected to column chromatography on silica gel (230–400 mesh, ethyl acetate/hexane) to provide the desired product.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra of the products.

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