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COMMUNICATION

Direct C–H/C–H Cross-Coupling of Benzimidates with Heteroarenes to Access Biheteroaryl-2-carbonitriles

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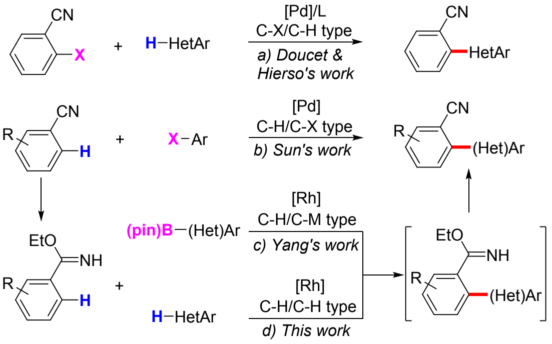
A Rh-catalyzed C–H/C–H oxidative cross-coupling reaction of benzimidates with heteroarenes is developed, yielding biheteroaryl-2-carbonitriles directly after in situ dealcoholization. This protocol features high atom- and step economy, and a broad substrate scope with good functional group tolerance.

Bi(hetero)aryl-2-carbonitriles are useful intermediates widely used in industrial synthesis,[1] as the cyano group can be conveniently converted into various functional groups,[2] such as imidate, aldehyde, carboxylic acid, amide, tetrazolium etc. Moreover, bi(hetero)aryl-2-carbonitriles can also be utilized to construct heteroatom-containing polycyclic aromatics, such as fluorenones, dibenzopyranones, benzoisoquinolines and benzoisoquinolinones.[3] Classical transition-metal catalyzed C–X/C–M cross-coupling reactions[4] between benzonitriles and (hetero)arenes provide reliable synthetic strategy toward these scaffolds, but both substrates need either prehalogenation or premetalation. Especially, site selective *ortho*-activation is required for benzonitrile, but there is no general and straightforward protocol available. During the past decades, the fast development of C–H bond activation strategy has improved the synthetic methodology. For example, Doucet and Hierso et al reported a Pd-catalyzed cross-coupling of 2-chlorobenzonitrile with various heteroarenes in the presence of a special triphosphane ligand (Scheme 1a).[5] Sun et al succeeded in Pd-catalyzed cross-coupling of benzonitriles with iodobenzenes by taking advantage of the π-coordination of the nitrile group (Scheme 1b).[6] Hong et al developed a ligand-promoted C–H arylation of simple arenes with aryl bromides, but only giving 3 examples of biaryl-2-carbonitriles as mixed regioisomers.[7] Very recently, Yang group disclosed that a Rh-catalyzed cross-coupling reaction between benzimidates and arylboronic pinacol esters directly provided bi(hetero)aryl-2-carbonitriles in solvent dimethoxyethane, while the imidate group remained products, bi(hetero)aryl-2-carbimidates were obtained in trifluoroethanol (Scheme 1c).[8] However, these methods still need to preactivate one coupling partner.



Scheme 1. Cross-coupling reactions for the synthesis of bi(hetero)aryl-2-carbonitriles.

No doubt, the direct C–H/C–H cross-coupling of (hetero)arenes is the most efficient strategy to access bi(hetero)aryl-2-carbonitriles in regard to the atom- and step-economy.[9] Due to our continuous interest in this field,[10] preliminary explorations of the cross-coupling between benzonitrile and 2-methylthiophene was conducted. However, no desired products could be detected, which was attributed to the weak π-coordination of the nitrile group. Therefore, a reinforced directing group capable of transforming into the nitrile group after cross-coupling might be necessary.[11] Encouraged by Yang's work, we report herein a C–H/C–H cross-coupling reaction of benzimidates with heteroarenes to directly furnish biheteroaryl-2-carbonitriles under rhodium catalysis.

Our study commenced with the coupling of benzimidate **1a** with 2-methylthiophene **2a** under different transition metal catalysts. Fortunately, the desired 2-(5-methylthiophen-2-yl)benzonitrile, **3aa**, was detected in 14% yield in a Rh-catalyzed system in the presence of silver fluoride as the oxidant, and sodium acetate as the additive in 1,2-dichloroethane (DCE) at

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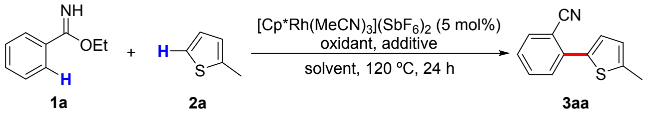
120 °C for 24 h, as determined by ^{1}H NMR analysis (Table 1, entry 1), while iridium and ruthenium catalysts were ineffective (Table S1 entries 2-3). It is noted that **3aa** was obtained directly and no extra step to dealcoholize the imidate group to the cyano group was needed. The solvent screening showed that ^{t}BuOH gave the best yield of 43% (Table 1, entry 1-6 and Table S1, entries 4-14). Interestingly, the optimal solvents for the C–H arylation of benzimidates with arylboronic pinacol esters were inferior: dimethoxyethane (DME) and trifluoroethanol (TFE) gave lower yields of 25% and 12, respectively (Table 1, entries 3-4). The oxidant screening indicated that silver fluoride was the most efficient (Table 1, entries 6-8, and Table S1, entries 16-21). Other silver salts provided lower yields while copper salts did not work at all. Increasing the amount of AgF to 3.0 equiv led to a 50% yield of **3aa** (Table 1, entry 9). After testing different additives, 0.4 equiv of KOAc increased the yield to 55% (Table 1, entry 10, and Table S1, entries 23-28). Significant improvement was achieved after Increasing the amount of **2a** to 3.0 equiv, and **3aa** was detected in 72% yield (Table 1, entry 11). Finally, lowering the reaction temperature to 100 °C promoted the yield to 80%, and **3aa** was isolated in 75% yield after workup (Table 1, entry 12).

Table 1. Optimization of the reaction conditions^a

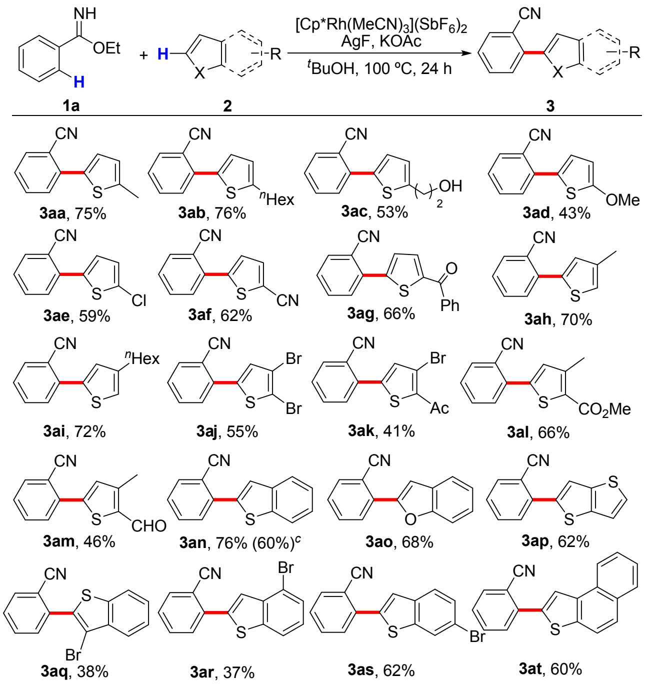


Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Yield^b (%)
1	AgF/2.0	NaOAc/0.2	DCE	14
2	AgF/2.0	NaOAc/0.2	toluene	20
3	AgF/2.0	NaOAc/0.2	DME	25
4	AgF/2.0	NaOAc/0.2	TFE	12
5	AgF/2.0	NaOAc/0.2	DMSO	0
6	AgF/2.0	NaOAc/0.2	^{t}BuOH	43
7	AgOAc/2.0	NaOAc/0.2	^{t}BuOH	18
8	CuF_2/1.0	NaOAc/0.2	^{t}BuOH	0
9	AgF/3.0	NaOAc/0.2	^{t}BuOH	50
10	AgF/3.0	KOAc/0.4	^{t}BuOH	55
11^c	AgF/3.0	KOAc/0.4	^{t}BuOH	72
12^{c,d}	AgF/3.0	KOAc/0.4	^{t}BuOH	80 (75^e)

^{a}Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 mol%), oxidant, additive and solvent (1.0 mL) at 120 °C for 24 h under ambient atmosphere. ^{b}NMR yields calculated by using CH_2Br_2 as the internal standard. ^{c}3.0 equiv **2a** was used. ^{d}The reaction was carried out at 100 °C. ^{e}Isolated yield.

With the optimized conditions in hand (Table 1, entry 12), we next investigated the substrate scope of heteroarenes **2** (Scheme 2). Benzimidate **1a** coupled with a variety of thiophenes bearing electron-donating or electron-withdrawing substituents to furnish 2-(thiophen-2-yl)benzonitrile **3aa**-**am** in moderate to excellent yields. The functionalities such as alkyl, hydroxyalkyl, methoxy, cyano, acetyl, benzoyl, formyl, ester and halide groups were all compatible. **1a** coupled at the C5 position of 2,3-dibromothiophene **2j** to afford **3aj** in 55% yield. Other heteroarenes such as benzothiophenes and benzofuran were also applicable, but *N*-protected indoles resulted in complicated reaction mixtures without any product. Thieno[3,2-*b*]thiophene **2p**, an important heterocyclic unit in organic functional materials, could successfully couple with **1a** to give the corresponding product **3ap** in 62% yield. Various bromo-substituted benzothiophenes (**2q**-**s**) could couple with **1a** to provide the desired products (**3aq**-**3as**) with opportunity for further modification at different positions. To demonstrate the synthetic practicability of this reaction, a gram-scale reaction of **1a** with **2n** was also carried out, provding **3an** in a slightly lower yield of 60%.

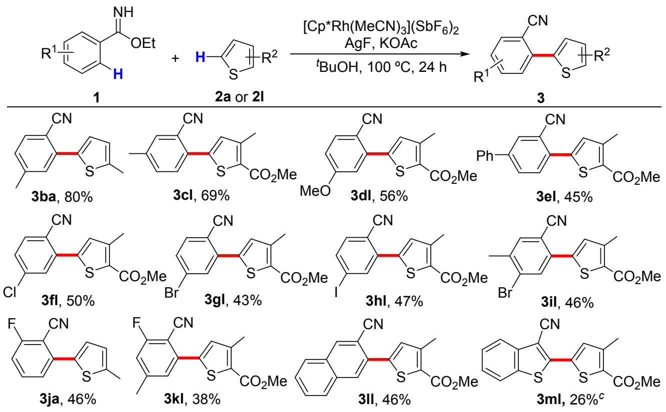
Scheme 2. Scope of heteroarenes^{a,b}



^{a}Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 mol %), AgF (3.0 equiv), KOAc (0.4 equiv) and *t*BuOH (1.0 mL) at 100 °C for 24 h under ambient atmosphere. ^{b}Isolated yields. ^{c}Yield for a gram-scale reaction (2 mmol).

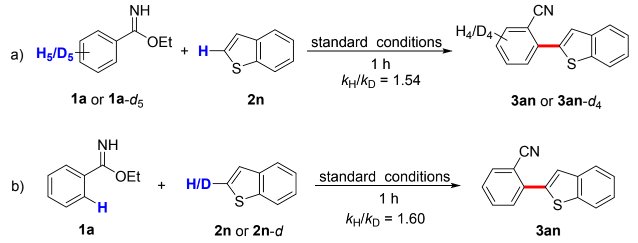
Subsequently, an investigation on the scope of the ethyl imidates **1** was carried out (Scheme 3). A set of benzimidates provided the desired coupled products in moderate to good yields. The functionalities on the phenyl ring affected significantly on the stabilities of benzimidates in the catalytic system, which caused dealcoholization of **1** to release benzonitriles, and thus diminished the coupling reaction. except the reactions of **1b** and **1c**, we observed significant amount of benzonitriles along with the desired products after reactions. For example, ethyl 2-naphthimidate **1l** coupled with **2l** to afford **3ll** in 46% yield, while 2-naphthonitrile was obtained in 36%. Moreover, *ortho*-substituted benzimidates are too labile to be prepared, and only *ortho*-fluorinated benzimidates **1j** and **1k** were obtained. The coupling reactions of them with **2a** and **2l** furnished the corresponding products **3ja** and **3kl** in 46% and 38% yields, respectively. Finally, the coupling between two heteroaryls, **1m** and **2l** was conducted, giving no desired product but benzothiophene-3-carbonitrile. To balance the dealcolization and cross coupling processes, **1m** was slowly added into the reaction mixture with **2l** over 2 h. The targeted product **3ml** was obtained in 26% yield, but a significant amount of benzothiophene-3-carbonitrile was still detected.

Scheme 3. Scope of ethyl benzimidates[a,b]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** or **2l** (0.6 mmol, 3.0 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 mol %), AgF (3.0 equiv), KOAc (0.4 equiv) and *t*BuOH (1.0 mL) at 100 °C for 24 h under ambient atmosphere. [b]Isolated yields. [c]**1m** was added over 2 h.

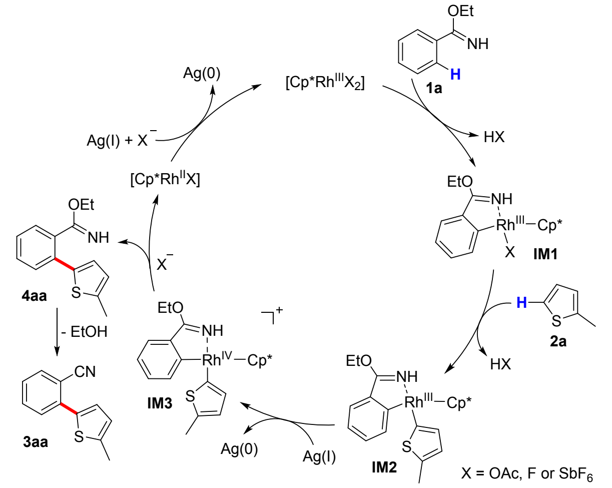
To shed light on the reaction mechanism, kinetic isotopic effect (KIE) experiments were conducted. Under the standard conditions, the parallel competitive reactions of **1a** and **1a**-d_5 with **2o** were carried out, providing a KIE value of 1.54 (Scheme 4a). Meanwhile, the parallel reactions of **1a** with **2n** and **2n**-*d* gave a similar KIE value of 1.60 (Scheme 4b). These results suggested that both C–H bond activation processes might not be involved in the turnover-limiting step in this cross-coupling reaction.



Scheme 4. Kinetic isotopic effect study.

Based on our results and the previous reports,[8,11-15] a plausible mechanism is proposed in Scheme 5. The coordination of the imidate group with $[Cp^*Rh(MeCN)_3](SbF_6)_2$ initiates the *ortho*-C–H cleavage of **1a**, giving a five-membered rhodacycle species **IM1**.[12] **IM1** reacts with **2a** to form **IM2** via either an S_EAr or CMD mechanism.[13] At this stage, **IM2**, a Rh(III) species, is oxidized by Ag(I) to generate a Rh(IV) species, **IM3**.[8,15] The subsequent reductive elimination releases bi(hetero)aryl-2-carbimidate **4aa** and a Rh(II) species.[16] Finally, dealcoholisation of **4aa** provides the targeted product **3aa**,[8,11] and the Rh(II) species is oxidized by Ag(I) to revive the Rh(III) species for the next catalytic cycle. It needs to point out that **4aa** was only detected by HRMS analysis (See ESI) and could not be isolated due to its easy dealcoholisation in reaction system.

In conclusion, we have developed a Rh-catalyzed C–H/C–H oxidative coupling and dealcoholization reaction of benzimidates with heteroarenes to directly furnish biheteroaryl-2-carbonitriles. A variety of functionalities could be tolerant in this reaction, Moreover, this reaction was run under ambient atmosphere and no inert gas protection was needed. The simple operation, high atom- and step-economy of this reaction make this protocol highly attractive for the synthesis of biheteroaryl-2-carbonitriles.



Scheme 5. Proposed pathway.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) Z. Rappoport, *The Chemistry of the Cyano Group*, Interscience Publishers: London, 1970; (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, Germany, 2001.

2 (a) B. E.Huff, M. A.Staszak, *Tetrahedron Letters* 1993, **34**, 8011; (b) D.-W. Gao, E. V. Vinogradova, S. K. Nimmagadda, J. M. Medina, Y. Xiao, R. M. Suciu, B. F. Cravatt, K. M. Engle, *J. Am. Chem. Soc.* 2018, **140**, 8069.

3 (a) L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* 2010, **12**, 3682; (b) E. Dubost, R. Magnelli, T. Cailly, R. Legay, F. Fabis, S. Rault, *Tetrahedron*, 2010, **66**, 5008; (c) J.-C. Wan, J.-M. Huang, Y.-H. Jhan, J.-C. Hsieh, *Org. Lett.* 2013, **15**, 2742.

4 (a) N. Miyaura, A. Suzuki, *Chem. Rev.* 1995, **95**, 2457; (b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* 2008, **41**, 1461; (c) C.

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DOI: 10.1039/C9CC05314J

Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya, P. Espinet, *ACS Catal.* 2015, **5**, 3040; (d) C. Liu, C. Liu, X.-M. Li, Z.-M. Gao, Z.-L. Jin, *Chin. Chem. Lett.*, 2016, **27**, 631.

5 D. Roy, S. Mom, M. Beaupérin, H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* 2010, **49**, 6650.

6 W. Li, Z. Xu, P. Sun, X. Jiang, M. Fang, *Org. Lett.* 2011, **13**, 1286.

7 J. Kim, S. H. Hong, *ACS Catal*. 2017, **7**, 3336.

8 B. Jiang, S. Wu, J. Zeng, X. Yang, *Org. Lett.* 2018, **20**, 6573.

9 (a) J. A. Ashenhurst, *Chem. Soc. Rev.* 2010, **39**, 540; (b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* 2011, **111**, 1780; (c) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* 2015, **115**, 12138; (d) Y. Yang, J. Lan, J. You, *Chem. Rev.* 2017, **117**, 8787.

10 (a) D. Qin, J. Wang, X. Qin, C. Wang, G. Gao, J. You, *Chem. Commun.,* 2015, **51**, 6190; (b) Y. Cheng, G. Li, Y. Liu, Y. Shi, G. Gao, D. Wu, J. Lan, J. You, *J. Am. Chem. Soc.* 2016, **138**, 4730; (c) Z. She, Y. Wang, D. Wang, Y. Zhao, T. Wang, X. Zheng, Z.-X. Yu, G. Gao, J. You, *J. Am. Chem. Soc.* 2018, **140**, 12566; (d) X. Zheng, R. Su, Z. Wang, T. Wang, Z. Bin, Z. She, G. Gao, J. You, *Org. Lett*. 2019, **21**, 797; (e) T. Zhao, D. Qin, W. Han, S. Yang, B. Feng, G. Gao, J. You, *Chem. Commun.*, 2019, **55**, 6118.

11 X. Yang, X. Jin, C. Wang, *Adv. Syn. Catal.* 2016, **358**, 2436.

12 (a) S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan, X. Li, *Angew. Chem., Int. Ed.* 2016, **55**, 8696; (b) X. Wang, N. Jiao, *Org. Lett.* 2016, **18**, 2150; (c) N. Lv, Z. Chen, Y. Liu, Z. Liu, Y. Zhang, *Org. Lett.* 2017, **19**, 2588.

13 (a) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu, J. You, *J. Am. Chem. Soc.* 2010, **132**, 1822; (b) N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 8230; (c) J. Dong, Z. Long, F. Song, N. Wu, Q. Guo, J. Lan, J. You, *Angew. Chem. Int. Ed.* 2013, **52**, 580.

14 (a) J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 2247; (b) G. Song, X. Li, *Acc. Chem. Res.* 2015, **48**, 1007; (c) H. Deng, H. Li, L. Wang, *Org. Lett.* 2016, **18**, 3110; (d) F. Xie, X. Li in *Rhodium Catalysis in Organic Synthesis: Methods and Reactions* (Ed.: K. Tanaka), Wiley-VCH, Weinheim, 2019, p. 521.

15 J. Kim, K. Shin, S. Jin, D. Kim, S. Chang, *J. Am. Chem. Soc.* 2019, **141**, 4137.

16 A reaction of **1a** and **2a** was conducted by using a stoichiometric amount of Rh(III) catalyst without the oxidant AgF and gave no product **3aa**, excluding the direct reductive elimination of **IM2**. See ESI.