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Rhodium(III)-catalyzed aromatic C–H cyanation with dimethylmalononitrile as a cyanating agent†

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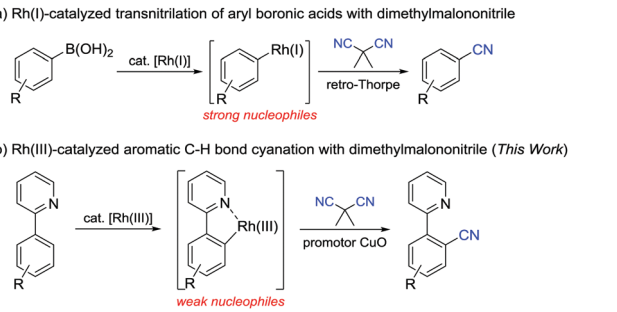
A rhodium-catalyzed aromatic C–H bond direct cyanation with safe, bench-stable, and commercially available dimethylmalononitrile as the cyanating agent has been successfully developed by using copper oxide as a promotor. Pyridine, quinoline, pyrimidine and pyrazole were used as the directing group in this type of C–H bond direct cyanation reaction.

Aryl nitriles are key structural motifs in a variety of natural products, agrochemicals, pharmaceuticals, dyes, *etc.*[1] In addition, the nitrile group can be easily transformed to other functional groups, such as amino, carboxyl, and acylamino groups, through hydrogenation or hydrolysis.[2] Therefore, the development of convenient and efficient methods for the synthesis of aryl nitriles has attracted considerable attention. Over the past decades, many methods have been developed for the preparation of aryl nitriles, including the Sandmeyer reaction of aryl diazonium salts[3] and the Rosenmund–von Braun reaction of aryl halides[4] with a stoichiometric amount of CuCN, the transition metal-catalyzed cyanation of aryl halides or pseudohalides with various cyanide sources,[5] the reaction of aryl organometallics with electrophilic cyanating reagents,[6] and the transition metal-catalyzed aromatic C–H bond direct cyanation with appropriate cyano-group sources.[7] Among the abovementioned methods, the last one has recently attracted considerable attention due to the conciseness of the synthetic procedure. Metallic (*e.g.*, CuCN,[8] NaCN,[9] KCN,[10] and $K_4[Fe(CN)_6]$[11]) and non-metallic (*e.g.*, *tert*-butylisocyanide,[12] *N*-cyanosuccinimide,[13] and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide[14]) cyano-group sources have been successfully employed in the catalytic aromatic C–H bond direct cyanation. Among them, the non-metallic cyano-group source *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide has been demonstrated to be a user-friendly and efficient cyanating reagent by the Fu's group and Anbarasan's group.[15] The use of non-metallic cyano-group sources, namely the organic cyano-group sources, in the catalytic aromatic C–H bond direct cyanation has attracted considerable attention because the poisoning of catalyst can be minimized. However, some organic cyanating reagents are highly toxic, are prepared from highly toxic precursors, or require low temperature storage to avoid decomposition.[16] Moreover, the frequently used organic cyanating reagents with high reactivity are expensive and not commercially available in large scale. Therefore, a new organic cyanating reagent for catalytic aromatic C–H bond direct cyanation is desirable.

Recently, Reeves and co-workers used dimethylmalononitrile (DMMN), a commercially available solid with low toxicity, as an effective organic cyanating reagent for transnitrilation with both Grignard and aryllithium reagents.[17] They also succeeded in the use of DMMN as a cyanating reagent for the Rh(I)-catalyzed transnitrilation of arylboronic acids (Scheme 1a).[18] Quite recently, Fu's group reported copper-catalyzed reagent-controlled regioselective cyanoborylation of vinylarenes using DMMN as the cyano-group source.[19] To the best of our knowledge, the use of DMMN as a cyanating reagent for the catalytic aromatic C–H bond direct cyanation has not been reported. The reasons may



Scheme 1 Synthesis of aryl nitriles with dimethylmalononitrile.

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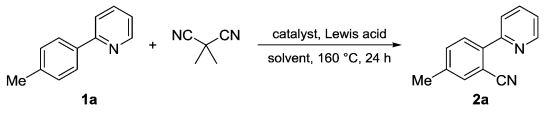
be as follows: the chelation of DMMN to metal catalyst may lead to deactivation of catalyst; the low nucleophilic reactivity of organometallic intermediate generated *in situ via* C–H activation. To solve these issues, we conducted a detailed study. Herein, we report the first example of rhodium-catalyzed aromatic C–H bond direct cyanation with DMMN as the cyanating reagent using copper oxide as a promotor to activate DMMN (Scheme 1b).

In our initial studies, the reaction of 2-(*p*-tolyl)pyridine (**1a**) with DMMN was chosen as a model to optimize the reaction conditions, and the results are summarized in Table 1. The catalyst was firstly screened in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 160 °C (entry 1 *vs.* Table S1 (ESI†), entries 1–7 in the ESI†). The desired cyanation product, 5-methyl-2-(pyridin-2-yl)-benzonitrile (**2a**), was obtained in 38% yield when $[RhCp^*(MeCN)_3](SbF_6)_2$ was applied (entry 1). This result suggested that the DMMN can be used as a cyanating reagent in the aromatic C–H bond direct cyanation, even though the yield is unsatisfactory. The solvent was subsequently screened using $[RhCp^*(MeCN)_3](SbF_6)_2$ as the catalyst. Among the solvents [HFIP, 2,2,2-trifluoroethanol (TFE), chlorobenzene (PhCl), 1,2-dichloroethane (DCE), and 1,4-dioxane], HFIP proved to be the best solvent (entry 1 *vs.* entries 2–5). The nucleophilic reactivity of aryl-Rh(III) intermediate is lower than that of aryl-Rh(I) analogue in the reaction with DMMN (Scheme 1). Therefore, a Lewis acid may be required to activate DMMN to improve the yield of **2a**. Unexpectedly, the use of $Cu(OAc)_2$, a soluble salt in HFIP, leads to the complete inhibition of the target reaction (entry 6).[20] However, the yield of **2a** is dramatically improved to 85% by just changing the Lewis acid from $Cu(OAc)_2$ to CuO, an insoluble salt in HFIP (entry 7). The use of other insoluble salt, such as Ag_2O and CoO also increase the yield of **2a**, but not as better as that with the use of CuO (entries 8 and 9). The results obtained from the study on the effect of rhodium catalyst loading indicate that 5 mol% of $[RhCp^*(MeCN)_3](SbF_6)_2$ is enough to obtain high yield (entry 10 *vs.* entries 7 and 11). The yield of **2a** decreases along with the decrease in CuO loading and temperature (entries 12 and 13). No reaction was observed when the model reaction was conducted in the absence of a rhodium catalyst (entry 14). Therefore, the subsequent aromatic C–H bond direct cyanation reactions of various substrates with DMMN were conducted in the presence of $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol%) and CuO (4.0 eq.) in HFIP at 160 °C for 24 h.

The scope and limitation of this type of aromatic C–H bond direct cyanation reaction were determined under the optimal reaction conditions. Scheme 2 shows the results obtained from the reactions of aromatic substrates bearing a simple pyridine ring as the directing group. Similarly, the reactions of 2-phenylpyridine (**1b**) and 2-(*m*-tolyl)pyridine (**1c**) proceeded also smoothly as the reaction of **1a** to produce the cyanated products **2b** and **2c** in good yields (79% and 88%, respectively). Products **2d** and **2e** were obtained in moderate yields (58% and 56%, respectively). These relatively low yields were attributed to the steric hindrance caused from one or two methyl (Me) groups linked on *ortho*- or *meta*-positions of benzene ring. The 2-phenylpyridine substrates **1f–1i** bearing an alkyl (Et, ^{n}Pr, and ^{t}Bu) or a phenyl (Ph) group on the *para*-position of benzene ring proceeded with the target reaction smoothly to give the desired products **2f–2i** in satisfactory yields (60–68%). Good yields of **2j** and **2k** (70% and 88%, respectively) were obtained in the reactions of 2-phenylpyridine substrates **1j** and **1k** bearing methoxyl (MeO), a stronger electron-donating group, on *meta*- or *para*-positions of benzene ring. In the case of the

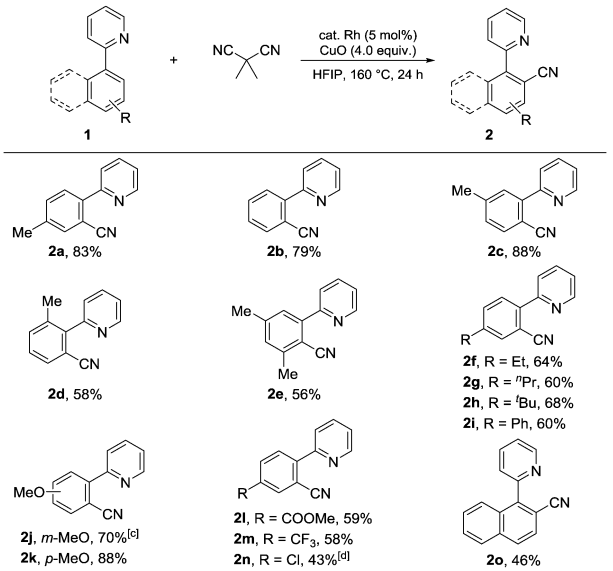
Table 1 Screening of reaction conditions[a]



1a 2a

Entry	Catalyst	Lewis acid	Solvent	Yield[b] (%)
1	$[RhCp^*(MeCN)_3](SbF_6)_2$	None	HFIP	38
2	$[RhCp^*(MeCN)_3](SbF_6)_2$	None	TFE	20
3	$[RhCp^*(MeCN)_3](SbF_6)_2$	None	PhCl	16
4	$[RhCp^*(MeCN)_3](SbF_6)_2$	None	DCE	NR[c]
5	$[RhCp^*(MeCN)_3](SbF_6)_2$	None	Dioxane	NR[c]
6	$[RhCp^*(MeCN)_3](SbF_6)_2$	$Cu(OAc)_2$	HFIP	NR[c]
7	$[RhCp^*(MeCN)_3](SbF_6)_2$	CuO	HFIP	85
8	$[RhCp^*(MeCN)_3](SbF_6)_2$	Ag_2O	HFIP	43
9	$[RhCp^*(MeCN)_3](SbF_6)_2$	CoO	HFIP	60
10[d]	$[RhCp^*(MeCN)_3](SbF_6)_2$	CuO	HFIP	87
11[e]	$[RhCp^*(MeCN)_3](SbF_6)_2$	CuO	HFIP	70
12[f]	$[RhCp^*(MeCN)_3](SbF_6)_2$	CuO	HFIP	73
13[g]	$[RhCp^*(MeCN)_3](SbF_6)_2$	CuO	HFIP	67
14	None	CuO	HFIP	NR[c]

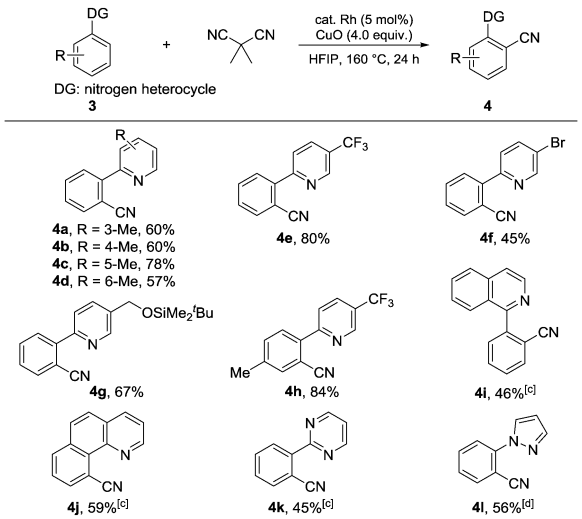
[a] Reaction conditions: 2-(*p*-tolyl)pyridine (**1a**, 0.2 mmol, 33.8 mg), dimethylmalononitrile (DMMN, 0.4 mmol, 37.6 mg), catalyst (10 mol%) and Lewis acid (4.0 eq.) in solvent (1.0 mL) at 160 °C for 24 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as an internal standard. [c] No reaction was observed, and starting materials were recovered. [d] $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol%) was used. [e] $[RhCp^*(MeCN)_3](SbF_6)_2$ (2.5 mol%) was used. [f] CuO (3.0 eq.) was used. [g] The reaction was performed at 130 °C.



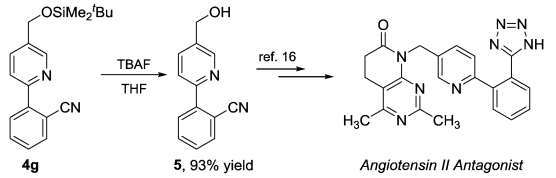
Scheme 2 Rhodium-catalyzed aromatic C–H bond cyanation of 2-arylpyridines with dimethylmalononitrile.[a,b] [a] Reaction conditions: 2-arylpyridine derivatives (**1**, 0.2 mmol), dimethylmalononitrile (DMMN, 0.4 mmol, 37.6 mg), $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol%, 8.3 mg), CuO (0.8 mmol, 63.6 mg) in HFIP (1.0 mL) at 160 °C for 24 h. [b] Isolated yield. [c] An isomer 2-methoxy-6-(pyridin-2-yl)benzonitrile (**2j′**) was isorated in 12% yield. [d] The reaction was performed for 36 h.

reaction of **1j**, an isomer, 2-methoxy-6-(pyridin-2-yl)benzonitrile (**2j′**), was also separated in 12% yield; this result was considered that due to the chelation effect of nitrogen and oxygen atoms to rhodium catalyst. However, moderate yields (43–59%) of **2l–2n** were achieved when the substrates **1l–1n** bearing an electron-withdrawing group (COOMe, CF_3 or Cl) on *para*-position of benzene ring. These results clearly indicated that this type of cyanation reaction was influenced by the electron density of benzene ring. The naphthalene ring-containing substrate **1o** was finally examined, and the corresponding cyanated product **2o** was obtained in 46% yield.

Scheme 3 shows the results obtained from the reactions of aromatic substrates bearing a substituted pyridine ring or other nitrogen heterocycle as the directing group. Moderate to satisfactory yields (57–78%) of products **4a–4d** were obtained from the reactions of substrates **3a–3d** bearing a methyl group on the pyridine ring; these results suggested that the methyl group did not influence on the reactivity of substrate even when linked on different positions. Reactions of substrates **3e–3g** having a substituent (CF_3, Br or $CH_2OSiMe_2{}^tBu$) linked on the 5-position of pyridine ring proceeded smoothly to offer the products **4e–4g** in 80%, 45%, and 67% yields, respectively. These aforementioned results indicated that the electron property of substituent linked on pyridine ring did not exert a significant influence on the reactivity of substrate. Br and $CH_2OSiMe_2{}^tBu$ linked to the pyridine ring were notably maintained in the structures of products **4f** and **4g**, suggesting that further manipulation may produce more useful compounds. As expected, **4h** was obtained in good yield (84%) from the reaction of substrate **3h** having a methyl, which is an electron-donating group, on the benzene ring. Other nitrogen heterocycles such as quinoline, pyrimidine,



Scheme 3 Rhodium-catalyzed C–H bond cyanation of arenes having various directing groups with dimethylmalononitrile.[a,b] [a] Reaction conditions: 2-arylpyridine derivatives (**3**, 0.2 mmol), dimethylmalononitrile (DMMN, 0.4 mmol, 37.6 mg), $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol%, 8.3 mg), CuO (0.8 mmol, 63.6 mg) in HFIP (1.0 mL) at 160 °C for 24 h. [b] Isolated products. [c] 10 mol% of $[RhCp^*(MeCN)_3](SbF_6)_2$ was used. [d] PhCl (1 mL) was used as solvent.



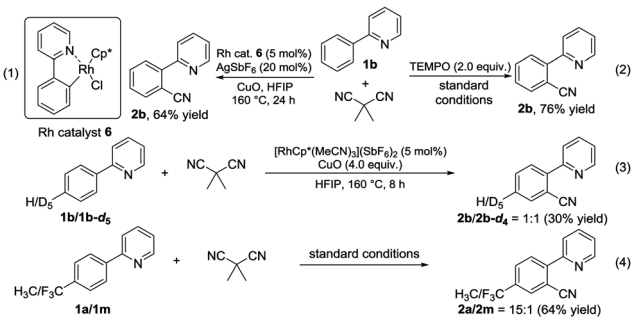
Scheme 4 Synthesis of Angiotensin II Antagonist from product **4g**.

and pyrazole were successfully used as the directing group in the further investigation on the catalytic aromatic C–H bond direct cyanation reaction. The desired products **4i–4l** were obtained in moderate yields (45–59%).

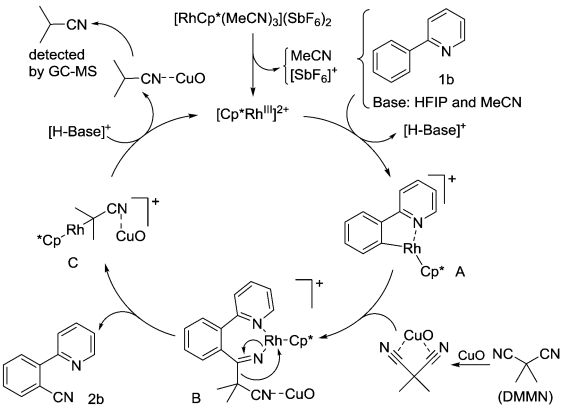
To prove the practicality of the present method, a deprotection reaction of product **4g** was performed in the presence of tetrabutylammonium fluoride (TBAF) (Scheme 4). The product 2-[5-(hydroxymethyl)pyridin-2-yl]benzonitrile (**5**) having a free hydroxyl group was obtained in 93% yield, which was previously used as a key intermediate for the development of Angiotensin II Antagonist.[21]

Control experiments were conducted to gain insight into the mechanism of the cyanation reaction (Scheme 5). The aromatic C–H bond direct cyanation reaction of **1b** with DMMN also proceeded smoothly in the presence of a well-defined rhodium(III) complex and $AgSbF_6$ to produce the desired product **2b** in 64% yield (eqn (1)). The rhodium(III) complex **6** would react with $AgSbF_6$ *in situ* to generate a cationic rhodium(III) complex, which was considered to be the catalytic species. The desired product **2b** was still obtained in 76% yield even though the C–H bond cyanation reaction of **1b** was performed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger (eqn (2)). This result indicates that a radical process is not involved in the target reaction. The deuterium kinetic isotope effect was investigated by conducting an intermolecular competition reaction between **1b** and **1b-d_5**; a 1 : 1 ratio of **2b** to **2b-d_4** demonstrated that the cleavage of the aromatic C–H bond in **1b** is not involved in the rate-determining step (eqn (3)). A 15 : 1 ratio of **2a** to **2m** was observed in the intermolecular reaction between **1b** and **1m** (eqn (4)), indicating electron-rich arenes to be preferentially converted.

On the basis of our experimental outcomes and previous reports,[22] a catalytic cycle is proposed to account for the present



Scheme 5 Control experiments.



Scheme 6 Proposed mechanism for the Rh-catalyzed aromatic C–H bond cyanation.

catalytic C–H bond cyanation reaction (Scheme 6). The catalytic cycle starts from $[Cp^*Rh(III)]^{2+}$, which is generated *in situ* from the precatalyst $[RhCp^*(MeCN)_3](SbF_6)_2$. Coordination of the nitrogen atom of **1b** to rhodium catalyst species and subsequent *ortho* C–H bond activation would generate a cationic five-membered rhodacyclic intermediate **A**. Then, the insertion of C≡N moiety in DMMN activated by CuO into the Rh–C bond would produce the intermediate **B**, which would subsequently undergo C–C(N) bond cleavage to afford product **2b** and generate intermediate **C**. Protodemetalation of **C** would proceed to generate isopropylnitrile and regenerate catalytic species $[Cp^*Rh(III)]^{2+}$. The formation of isopropylnitrile was detected by gas chromatography–mass spectrometry.

In summary, we developed a rhodium-catalyzed aromatic C–H bond direct cyanation by using safe, bench-stable, and commercially available DMMN as a cyanating reagent for the synthesis of aryl nitriles. The cyanation reaction of 2-phenylpyridine and its derivatives with DMMN proceeded smoothly in the presence of rhodium(III) complex and copper oxide as the catalyst and promotor, respectively, to produce the corresponding aryl nitriles in moderate to good yields. Synthetically useful functional groups, namely, MeO(O)C, Cl, Br, and $CH_2OSiMe_2{}^tBu$, remained intact during the C–H bond direct cyanation. Further studies on the extensive use of the DMMN as a cyanating reagent for C–H bond direct cyanation are ongoing.

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Conflicts of interest

There are no conflicts to declare.

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