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Article

Rh(III)-catalyzed direct C–H cyanation of *N*-methoxybenzamides using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide

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ABSTRACT

A new method has been developed for the mild and efficient Rh(III)-catalyzed direct C–H cyanation of a diverse range of *N*-methoxybenzamides using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide as an environmentally friendly and efficient cyanating reagent. This new reaction proceeded with good regioselectivity to provide direct access to a wide variety of valuable *ortho*-cyanated *N*-methoxybenzamides with broad substrate/functional group tolerance.

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1. Introduction

Cyanoarenes are important structural motifs that form the core structures of numerous compounds, including dyes, herbicides, agrochemicals and natural products, as well as being important pharmacophores and synthetic building blocks [1–5]. Moreover, the cyano functionality of these compounds can be used as a valuable intermediate and effective precursor for the synthesis of various functionalized products such as aldehydes, ketones, amines, amides, amidines, benzoic acid derivatives, and heterocycles [6–10]. Therefore, the development of new mild and efficient methods for facile construction

of aryl-CN bonds has attracted considerable attention in modern organic synthesis [11–18]. Among the many different methods available for the direct synthesis of cyanoarenes, the transition-metal-catalyzed regioselective cyanation of C–H bonds has emerged as one of the most promising and economical [19–46]. Among the various transition-metals available for this reaction, Pd [29–39] and Cu [40–46] catalysts have been investigated extensively with a wide range of both metallic and nonmetallic cyano-group sources, including NaCN, CuCN, Zn(CN)₂, nitromethane, DMF, TMSCN, acetonitrile, isonitrile and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **2**). However, in contrast to the remarkable advances made in this field

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using Pd and Cu catalysts, there have been very few reports pertaining to Rh(III)-catalyzed cyanation reactions. In fact, to the best of our knowledge, only six examples of Rh(III)-catalyzed reactions for the direct construction of cyanoarenes have been reported to date by the groups of Fu [47], Anbarasan [48,49], Gu [50], Zhu [51] and Xu [52] (Scheme 1(a)–(c)). For this reason, further research is still needed to explore and develop new, efficient, selective and practical Rh(III)-catalyzed C–H bond cyanation reactions, because Rh(III)-based catalysts has been proven to perform just as effectively as any other transition metal catalyst in terms of their activity, selectivity, substrate scope and functional group tolerance [53–66].

A suitable directing group (DG) is generally required to achieve Rh(III)-catalyzed C–H activation reactions. Furthermore, the use of a DG can be advantageous in terms of improving the regioselectivity and overall efficiency of the reaction. As a consequence, several versatile DGs have been developed, with the CONHOMe group playing a particularly prominent role [67–83]. Following on from the pioneering work of Yu et al. [67,68] in 2008, significant progress has been made towards the development of a broad range of important synthetic transformations that proceed in a step- and atom-economical fashion using a CONHOMe moiety as part of a DG strategy.

With all of this in mind, it was envisioned that a CONHOMe-mediated C–H bond cyanation could be achieved using a suitable cyanating reagent as the coupling partner. As part of our ongoing interest in the development of Rh(III)-catalyzed and CONHOMe-mediated C–H activation reactions [83], we herein report the development of a Rh(III)-catalyzed reaction for the C–H bond cyanation of *N*-methoxybenzamides using NCTS as the efficient cyanating reagent (Scheme 1(d)).

2. Experimental

2.1. General

All of the chemicals used in the current study were obtained from commercial suppliers and were dried and purified as necessary. The water used in this study was re-distilled and ion-free. Melting points were determined on a WRS-1B digital instrument without correction. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-Plus 400 NMR instruments (^1H 400 MHz; ^{13}C 100 MHz or ^{13}C 125 MHz in CDCl_3). The multiplicities of the peaks have been reported as follows: s, singlet; brs, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. High-resolution mass spectra were measured on an Agilent G6230B mass spectrometer. Thin-layer chromatography was conducted on pre-coated silica gel 60 F254 plates (Merck). Silica gel 60H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. was used for general chromatography.

2.2. General procedure for the synthesis of products 3

A mixture of *N*-methoxybenzamide (**1**, 0.20 mmol), NCTS (**2**, 49.0 mg, 0.22 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol, 2.5 mol %) and Ag_2CO_3 (54 mg, 0.2 mmol, 1.0 equiv.) in dioxane (1.0 mL) was stirred at 80 °C for 8 h. The mixture was then cooled to room temperature and the solvent removed under reduced pressure to give a residue, which was purified by column chromatography over silica gel to give the desired product **3**.

2.3. Spectral data for products

2-Cyano-*N*-methoxybenzamide (**3a**). 75% yield as a white solid. M.p. 72–73 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, J = 7.0 Hz, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.75–7.69 (m, 2H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.2, 153.8, 133.8, 132.8, 131.0, 128.4, 123.4, 122.2, 65.4; HRMS (ESI) calcd. for 177.0664 ($[\text{M}+\text{H}]^+$), found 177.0663 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*-methoxy-6-methylbenzamide (**3b**). 80% yield as a white solid. M.p. 67–68 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.78 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 4.07 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.2, 154.0, 138.0, 135.0, 133.2, 131.4, 125.2, 119.8, 65.4, 17.4; HRMS (ESI) calcd. for 191.0821 ($[\text{M}+\text{H}]^+$), found 191.0820 ($[\text{M}+\text{H}]^+$).

2-Chloro-6-cyano-*N*-methoxybenzamide (**3c**). 48% yield as a white solid. M.p. 126–126 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, J = 6.8 Hz, 1H), 7.70–7.61 (m, 2H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.0, 134.6, 134.4, 131.6, 124.4, 120.8, 65.4; HRMS (ESI) calcd. for 211.0274, 213.0245 ($[\text{M}+\text{H}]^+$), found 211.0273, 213.0244 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*-methoxy-5-methylbenzamide (**3d**). 75% yield as a white solid. M.p. 87–88 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.91 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 4.10 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.4, 154.0, 143.8, 134.4, 128.4, 128.2, 1234.0, 122.2, 65.4, 22.0; HRMS (ESI) calcd. for 191.0821 ($[\text{M}+\text{H}]^+$), found 191.0821 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*,5-dimethoxybenzamide (**3e-1**) and 2-cyano-*N*,3-

Scheme 1. Evolution of the Rh(III)-catalyzed C–H cyanation of arenes.

dimethoxybenzamide (**3e-2**). These two compounds were obtained as an inseparable mixture of regioisomers in a combined yield of 81% [mixture of **3e-1/3e-2** (4:1)] as a white solid. M.p. 90–91 °C; **3e-1**: ^1H NMR (400 MHz, CDCl_3): δ 7.82 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.19 (dd, J = 8.4, 2.0 Hz, 1H), 4.06 (s, 3H), 3.91 (s, 3H); **3e-2**: ^1H NMR (400 MHz, CDCl_3): δ 7.67–7.56 (m, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.22 (m, 1H), 4.09 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.6, 162.2, 156.4, 153.6, 134.2, 130.4, 129.8, 123.8, 123.0, 120.2, 116.4, 115.6, 107.6, 65.4, 56.0; HRMS (ESI) calcd. for 207.0770 ($[\text{M}+\text{H}]^+$), found 207.0769 ($[\text{M}+\text{H}]^+$).

2-Cyano-5-fluoro-*N*-methoxybenzamide (**3f-1**) and 2-cyano-3-fluoro-*N*-methoxybenzamide (**3f-2**). White solids in 20% (**3f-1**) and 56% (**3f-2**) yields. **3f-1**: M.p. 108–109 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.01 (dd, J = 8.2, 4.4 Hz, 1H), 7.56 (dd, J = 7.0, 2.2 Hz, 1H), 7.43 (td, J = 8.7, 2.2 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.6 (d, J = 255.6 Hz), 161.0, 153.0, 130.8 (d, J = 9.1 Hz), 125.0 (d, J = 9.0 Hz), 121.0 (d, J = 23.6 Hz), 111.2 (d, J = 24.8 Hz), 65.6; HRMS (ESI) calcd. for 195.0570 ($[\text{M}+\text{H}]^+$), found 195.0569 ($[\text{M}+\text{H}]^+$). **3f-2**: M.p. 81–82 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.69 (m, 2H), 7.42 (m, 1H), 4.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.4, 157.8 (d, J = 261.0 Hz), 151.8, 134.8 (d, J = 7.6 Hz), 130.6, 121.8 (d, J = 19.6 Hz), 119.8 (d, J = 3.6 Hz), 65.38; HRMS (ESI) calcd. for 195.0570 ($[\text{M}+\text{H}]^+$), found 195.0567 ($[\text{M}+\text{H}]^+$).

5-Chloro-2-cyano-*N*-methoxybenzamide (**3g**). 46% yield as a white solid. M.p. 57–58 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.73 (dd, J = 8.1, 1.6 Hz, 1H), 4.13 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.0, 139.2, 133.8, 130.0, 123.8, 123.6, 65.4; HRMS (ESI) calcd. for 211.0274, 213.0245 ($[\text{M}+\text{H}]^+$), found 211.0273, 213.0243 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*-methoxy-4-methylbenzamide (**3h**). 66% yield as a white solid. M.p. 47–48 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.73 (m, 2H), 7.48 (d, J = 7.6 Hz, 1H), 4.07 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.6, 154.0, 145.0, 133.4, 131.2, 125.8, 123.4, 122.6, 65.2, 22.2; HRMS (ESI) calcd. for 191.0821 ($[\text{M}+\text{H}]^+$), found 191.0821 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*,4-dimethoxybenzamide (**3i**). 77% yield as a white solid. M.p. 95–96 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.15 (dd, J = 8.4, 2.0 Hz, 1H), 4.07 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.4, 162.4, 125.2, 120.4, 119.27, 106.8, 65.4, 56.0; HRMS (ESI) calcd. for 207.0770 ($[\text{M}+\text{H}]^+$), found 207.0769 ($[\text{M}+\text{H}]^+$).

2-Cyano-4-fluoro-*N*-methoxybenzamide (**3j**). 55% yield as a white solid. M.p. 102–103 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.87 (dd, J = 8.2, 4.8 Hz, 1H), 7.65 (dd, J = 7.5, 2.2 Hz, 1H), 7.37 (m, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.2 (d, J = 255.9 Hz), 161.4, 152.6, 134.0, 126.0 (d, J = 9.5 Hz), 124.4, 120.0 (d, J = 23.6 Hz), 110.2 (d, J = 25.2 Hz), 65.4; HRMS (ESI) calcd. for 195.0570 ($[\text{M}+\text{H}]^+$), found 195.0568 ($[\text{M}+\text{H}]^+$).

4-Chloro-2-cyano-*N*-methoxybenzamide (**3k**). 30% yield as a white solid. M.p. 109–110 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, J = 1.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 8.0, 1.8 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.4, 152.4, 140.4, 133.0, 126.6, 124.8, 122.8, 65.4; HRMS (ESI) calcd. for 211.0274, 213.0245 ($[\text{M}+\text{H}]^+$), found 211.0273, 213.0241

($[\text{M}+\text{H}]^+$).

4-Bromo-2-cyano-*N*-methoxybenzamide (**3l**). 35% yield as a white solid. M.p. 132–133 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.10 (s, 1H), 7.83 (dd, J = 8.0, 1.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 161.6, 136.8, 135.8, 128.6, 127.0, 125.6, 124.8, 65.4; HRMS (ESI) calcd. for 254.9769, 256.9749 ($[\text{M}+\text{H}]^+$), found 254.9767, 256.9745 ($[\text{M}+\text{H}]^+$).

Methyl 3-cyano-4-(methoxycarbonyl)benzoate (**3m**). 73% yield as a white solid. M.p. 160–161 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.61 (s, 1H), 8.38 (dd, J = 7.8, 1.0 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 4.11 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.4, 161.2, 135.2, 1334.0, 132.0, 123.6, 123.4, 65.4, 52.8; HRMS (ESI) calcd. for 235.0719 ($[\text{M}+\text{H}]^+$), found 235.0717 ($[\text{M}+\text{H}]^+$).

3-Cyano-*N*-methoxy-[1,1'-biphenyl]-4-carboxamide (**3n**). 86% yield as a white solid. M.p. 112–113 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.44 (s, 1H), 7.95 (m, 2H), 7.72–7.67 (m, 2H), 7.53 (t, J = 7.2 Hz, 2H), 7.50–7.46 (m, 1H), 4.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 147.6, 139.0, 1312.0, 129.2, 129.0, 127.4, 126.2, 124.4, 122.0, 65.8; HRMS (ESI) calcd. for 253.0977 ($[\text{M}+\text{H}]^+$), found 253.0976 ($[\text{M}+\text{H}]^+$).

3-Cyano-*N*-methoxy-2-naphthamide (**3o**). 35% yield as a white solid. M.p. 135–136 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.43 (s, 1H), 8.37 (s, 1H), 8.05 (m, 2H), 7.75–7.65 (m, 2H), 4.14 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 135.4, 134.8, 130.0, 129.8, 129.0, 128.6, 124.8, 122.0, 65.2; HRMS (ESI) calcd. for 227.0821 ($[\text{M}+\text{H}]^+$), found 227.0820 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*-methoxy-1-naphthamide (**3p**). 74% yield as a white solid. M.p. 135–136 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.96 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.69 (m, 2H), 4.14 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 154.2, 135.6, 134.6, 129.2, 128.6, 128.2, 124.6, 123.4, 117.8, 65.4; HRMS (ESI) calcd. for 227.0821 ($[\text{M}+\text{H}]^+$), found 227.0821 ($[\text{M}+\text{H}]^+$).

2-Cyano-*N*-methoxycyclohex-1-enecarboxamide (**3q**). 51% yield as a white solid. M.p. 131–132 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.96 (m, 3H), 2.43 (m, 2H), 2.32 (m, 2H), 1.83–1.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.0, 157.4, 141.0, 136.0, 65.2, 21.4, 20.2, 19.8; HRMS (ESI) calcd. for 181.0977 ($[\text{M}+\text{H}]^+$), found 181.0978 ($[\text{M}+\text{H}]^+$).

3. Results and discussion

Given that the results of several previous studies have shown that NCTS, which is non-toxic, easy to prepare and handle and bench-stable, can be used as a highly efficient cyanating reagent for Rh(III)-catalyzed C–H activation reactions [47–51], we commenced our study by investigating the reaction of *N*-methoxybenzamide (**1a**) with NCTS (**2**) in presence of several well-known Rh(III) catalysts to allow for the optimization of the reaction conditions (Table 1). Pleasingly, when $[\text{Cp}^*\text{Rh}(\text{Cl})_2]_2$ and CsOAc were employed as the catalyst and the additive, respectively (Table 1, entry 2), the reaction of **1a** with **2** proceeded successfully in dioxane to deliver the expected cyanation product **3a** in 46% yield. Furthermore, the replacement of CsOAc with Ag_2CO_3 gave an improved yield of 62%

Table 1

Optimization of the reaction conditions.

Entry	Catalyst (mol%)	Additive (mol%)	Solvent	T (°C)	Isolated yield (%)
1	[Cp*Rh(MeCN) ₃] (SbF ₆) ₂ (2.5)	—	Dioxane	100	0
2	[Cp*RhCl ₂] ₂ (2.5)	CsOAc (100)	Dioxane	100	46
3	[Cp*RhCl ₂] ₂ (2.5)	Cu(OAc) ₂ (100)	Dioxane	100	0
4	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	Dioxane	100	62
5	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	Dioxane	120	45
6	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	Dioxane	80	75
7 ^a	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	Dioxane	50	20
8	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	DCE	80	57
9	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	THF	80	10
10	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	MeCN	80	25
11	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (20)	Dioxane	80	36
12 ^b	[Cp*RhCl ₂] ₂ (2.5)	Ag ₂ CO ₃ (100)	Dioxane	80	67

Reaction conditions: substrate **1a** (0.20 mmol), **2** (0.22 mmol), catalyst (2.5 mol%), the additive (100 mol%), solvent (1.0 mL), 8 h.^a 24 h, **1a** (20 mg) was recovered. ^b Performed on a 5.0 mmol scale.

Scheme 2. Substrate scope of *N*-methoxybenzamides. Reaction conditions: substrates **1** (0.20 mmol), **2** (0.22 mmol), [Cp*RhCl₂]₂ (2.5 mol %), Ag₂CO₃ (100 mol %), dioxane (1.0 mL), 8 h. *Reacted for 16 h.

(Table 1, entry 4). Encouraged by this finding, we proceeded to investigate the optimization of the reaction using a variety of different temperatures and solvents. As shown in Table 1, de-

creasing the reaction temperature to 80 °C led to an improvement in the yield to 75%, while raising the temperature to 120 °C or lowering to 50 °C resulted in a lower yield (Table 1, en-

tries 5–7). Inferior results were also obtained in several other solvents, including DCE, THF and MeCN (Table 1, entries 8–10). Furthermore, reducing the amount of additive led to a significant decrease in the yield of the reaction (Table 1, entry 11). In summary, the optimal conditions for this reaction were found to include dioxane as the solvent with $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol %) and Ag_2CO_3 (100 mol %) as the catalyst and additive, respectively, at 80 °C for 8 h under air. Finally, the reaction was amenable to scale up and could be readily conducted on a gram scale with the desired product **3a** being isolated in a decent yield (Table 1, entry 12).

With the optimized conditions in hand, we proceeded to examine the substrate scope and limitations of this newly developed reaction using a series of *N*-methoxybenzamides. As demonstrated in Scheme 2, NCTS (**2**) underwent an efficient coupling reaction with a variety of functionalized *N*-methoxybenzamides to afford the corresponding aryl nitriles **3** in moderate to good yields. The presence of an electron-donating or electron-withdrawing group was well tolerated at the *ortho*- (**3b–c**), *meta*- (**3d–g**) or *para*- (**3h–n**) position. Importantly, the reaction also demonstrated good compatibility with a wide range of valuable functional groups, including methyl (**3b**, **3d** and **3h**), chloro (**3c**, **3g** and **3k**), methoxy (**3e** and **3i**), fluoro (**3f** and **3j**), ester (**3m**) and bromo (**3l**)

substituents. Tolerance towards the Br, Cl and ester functional groups is especially noteworthy because these groups are useful intermediates and effective precursors for subsequent cross-coupling reactions. Notably, substrates **1d** and **1g** bearing methyl and Cl groups at the *meta*-position, respectively, afforded the corresponding cyanation products with complete regioselectivity. However, the *meta*-methoxy-substituted substrate **1e** gave a 4:1 mixture of the regioisomeric products **3e-1** and **3e-2**. In contrast, substrate **1f** afforded a 1:3 mixture of the regioisomeric products **3f-1** and **3f-2**, where the CN group was mainly attached at the more-hindered site. Taken together, these results revealed that the nature of the substituent at the *meta*-position played a critical role in determining the outcome of the reaction. Finally, we were pleased to find that this new cyanation reaction could also be applied to polyaromatic naphthalene and cyclohexene substrates, with the corresponding products being obtained in synthetically useful yields (35% for **3o**, 74% for **3p** and 51% for **3q**). The results therefore provide further illustration of the remarkably robust nature of our newly developed Rh(III)-catalyzed system.

Inspired by the results presented above, we conducted a series of additional experiments to develop a deeper understanding of the mechanism of the reaction (Scheme 3). To begin with, we conducted a competition experiment between differ-

Scheme 3. Mechanistic experiments.

Scheme 4. Postulated mechanism.

ently substituted *N*-methoxybenzamides (**1h** and **1m**), and the result indicated that electron-rich substrates were preferentially converted to the corresponding cyanated products, which suggested that the C–H activation process could be occurring *via* an internal electrophilic substitution (IES)-type mechanism [84–88] (Scheme 3(a)). An H/D exchange experiment was then performed in the absence of NCTS (Scheme 3(b)). As shown in Scheme 3(b), a remarkable H/D exchange effect was observed for the recovering substrate $[D]_n$ -**1a** when D_2O was added to the reaction mixture, which revealed that the step involving the metallation of the C–H bond was largely reversible [89–92]. The reaction of the *N*-methyl-substituted substrate **1r** was also investigated to evaluate the role of the N–H bond (Scheme 3(c)). As anticipated, the reaction of **1r** and **2** did not proceed, which indicated that the N–H bond was critical to the success of this transformation [93–94]. Finally, a kinetic isotope effect (KIE) experiment [93–95] was carried out using D-labeled *N*-methoxybenzamide **1a-d5**. As shown in Scheme (3d), the treatment of a 1:1 mixture of **1a** and **1a-d5** with NCTS gave a typical KIE value ($k_H/k_D = 2.8$) for a Rh(III)-catalyzed C–H activation process [96–106].

Based on the results presented above and results published elsewhere [47–108], we have proposed a preliminary mechanistic pathway for this reaction, which is shown in Scheme 4. Briefly, the initial coordination of *N*-methoxybenzamide **1** to the Rh(III)-catalyst could be the rate-limiting step for the C–H bond cleavage to form the five-membered rhodacycle A. Compound **2** would then coordinate to the Rh(III) center in A, followed by the insertion of the CN moiety into the C–Rh(III) bond to give intermediate B. Finally, the rearrangement of B would lead to the cyanated product **3** and the Rh species C, which would subsequently release the active Rh catalyst for the next catalytic cycle.

4. Conclusions

We have developed for the first time a Rh(III)-catalyzed method for the direct C–H bond cyanation of various *N*-methoxybenzamides using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as an environmentally friendly and versatile cyanating

reagent. This new reaction boasts many remarkable features, including mild reaction conditions, moderate to good product yields, good regioselectivity, broad substrate scope and excellent functional group tolerance. Furthermore, the experimental results have provided the basis for a plausible reaction mechanism, as well as deepening our understanding of Rh(III)-catalyzed reactions and extending the concept and scope of the Rh-catalyzed C–H cyanation reactions. Considering the valuable structural features of these products, it is envisioned that these reactions will have broad utility in organic synthesis.

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Graphical Abstract

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Rh(III)-catalyzed direct C–H cyanation of *N*-methoxybenzamides using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide

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A new Rh(III)-catalyzed direct C–H cyanation of diverse *N*-methoxybenzamides with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) have been developed. With this method, a variety of valuable *ortho*-cyanated *N*-methoxybenzamides can be easily prepared under mild conditions with broad functional group tolerance.

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Rh(III)催化的*N*-甲氧基苯甲酰胺系列物选择性C–H氰基化反应

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摘要: 采用了最近热门的Rh(III)催化C–H键活化方法, 以*N*-甲氧基苯甲酰胺系列物为反应底物, *N*-氰基-*N*-苯基对甲苯磺酰胺(NCTS)为氰基化试剂, 高效合成了含氰基官能团产物。结果表明, 该反应在碳酸银存在下, 使用二氧六环作为反应溶剂, 于80 °C反应8 h生成的邻位氰基取代的*N*-甲氧基苯甲酰胺的产率较高。进一步研究表明, 该反应具有好的区域选择性和底物/官能团适应性。一系列机理实验研究表明, 该反应可能采用了一个内部的亲电取代机制及使用了C–H键切割步骤作为关键限速步骤。考虑到该反应产物包含有价值的结构单元-*N*-甲氧基甲酰胺和氰基取代基, 因而有望用于现代有机合成中。

关键词: Rh(III)催化剂; C–H键氰基化; *N*-甲氧基苯甲酰胺系列物; *N*-氰基-*N*-苯基对甲苯磺酰胺; 反应机制

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