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Rhodium Catalyzed C2-Selective Cyanation of Indoles and Pyrroles

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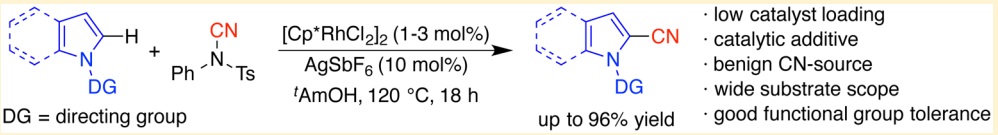
Supporting Information



ABSTRACT: An efficient and general rhodium(III) catalyzed C2-selective cyanation of indoles and pyrroles was accomplished employing easily accessible and environmentally friendly cyanating reagent, NCTS. This methodology tolerates various functional groups, uses readily removable directing groups and allows the synthesis of various 2-cyanoindoles and pyrroles in good to excellent yield.

Cyano heteroarenes, particularly 2-cyanoindoles and pyrroles, are important structural motifs present in various therapeutically important natural products.[1] Also, they are widely used as building blocks for construction of various pharmaceuticals, agrochemicals (Figure 1), and dyes; in addition, incorporation of these moieties in polymers provides them with unique physical properties.[2] Thus, efficient and selective synthesis of 2-cyanoindoles and pyrroles is highly desirable in both organic and medicinal chemistry.

Although traditionally cyano(hetero)arenes were synthesized from corresponding aldehydes and their derivatives or halides,[3] over the past few decades, selective and direct cyanation[4] of highly abundant C−H bonds of (hetero)arenes has emerged as a powerful tool to achieve atom- and step-economy in organic synthesis.[5] In this context, the most documented direct cyanation of indoles is the transition metal mediated/catalyzed C3-selective cyanation,[6] which is probably due to the inherent property of indoles (Scheme 1). Typically, C3-cyanation of indoles can be achieved using isocyanatophosphoric acid dichloride[7] or triphenylthiocyanogen (TPPT)[8] as the cyanating reagent. Recently, these strategies were replaced with transition metal catalyzed cyanation of indoles employing ^{t}BuNC,[9] TMEDA/NH_3,[10] DMF,[11] DMF/NH_4I,[12] DMSO/NH_4HCO_3,[13] metal cyanides,[14] BnCN,[15] 3,5-$(CF_3)_2C_6H_3I(OTf)CN$,[16] and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS).[17] However, the closely related C2-selective cyanation of indoles and related heteroarenes is rather limited.

The known C2-selective cyanation of indoles (pyrroles) includes the directing group assisted palladium-catalyzed cyanation using *tert*-butyl isocyanide[9,18] as "CN" source in combination with 3 equiv of copper salt and the sub-stoichiometric copper catalyzed cyanation employing acetonitrile[19] as "CN" source along with additives such as AgOAc or $(Me_3Si)_2$ (Scheme 2). These reactions suffer from the use of high catalyst loading, super-stoichiometric amounts of expensive additives, harsh reaction conditions, and limited substrate scope. Thus, the efficient catalytic C2-selective cyanation of indoles (pyrroles) is highly warranted. Based on the need for catalytic cyanation and our interest in C−H functionalization[20] and cyanation employing readily accessible and environmentally benign NCTS as a cyanating reagent,[21] we herein reveal the general rhodium catalyzed chelation assisted selective C2-cyanation of indoles and pyrroles with NCTS.

Initially, we investigated the C2-cyanation of indole derivatives. The C2-cyanation of *N*-(2-pyridyl)indole **1a** with NCTS (2 equiv) was performed in the presence of $[Cp^*RhCl_2]_2$ (1 mol %) as a catalyst and $AgSbF_6$ (10 mol %) as an additive in toluene at 100 °C for 36 h.[21] To our delight, 2-cyano-*N*-(2-pyridyl)indole **3a** was observed in 20% isolated yield (Table 1, entry1). No reaction was observed in the absence of either $[Cp^*RhCl_2]_2$ or $AgSbF_6$, which shows that cyanation is catalyzed and promoted by rhodium and silver complex, respectively.[22] Next, a slight improvement in yield was observed with the temperature increasing to 120 °C (Table 1, entry 2). Increasing the ratio of rhodium to silver complex by adding 2 mol % of rhodium complex gave better conversion with 56% isolated yield of **3a**, but the opposite effect was observed when the silver complex was reduced to 5 mol % to increase the ratio of Rh(III)/Ag(I) (Table 1, entries 3 and 4).

Although cyanation in solvents like chlorobenzene and 1,2-DCE was inferior to cyanation in toluene, ^{t}AmOH gave the formation of product **3a** in 82% isolated yield with complete conversion of **1a** in 18 h (Table 1, entres 5−7). Interestingly, decreasing the catalyst loading to 1 mol % in ^{t}AmOH did not affect the reaction. Most importantly, a similar effect was observed when the equivalents of cyanating reagent were reduced to 1 equiv and the product **3a** was isolated in comparable yield (Table 1, entries 8−10). Finally, using 1 equiv of NCTS and 1.2 equiv of **1a** in ^{t}AmOH at 120 °C with

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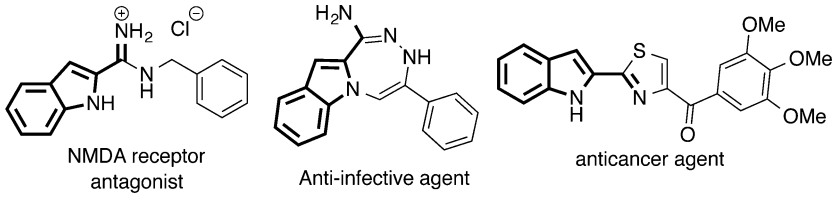


Figure 1. Examples of bioactive molecules synthesized from 2-cyanoindole.

Scheme 1. Direct Cyanation of Indoles and Pyrroles

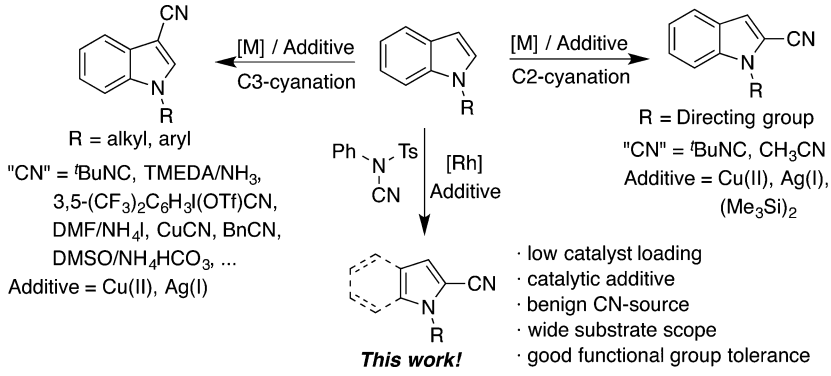
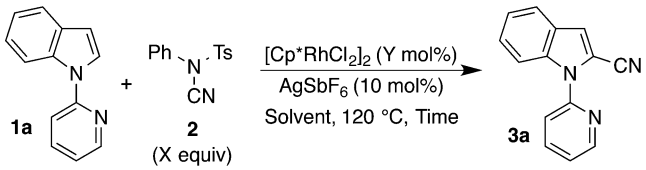


Table 1. Rhodium Catalyzed C2-Selective Cyanation of *N*-(2-Pyridyl)indole 1a: Optimization[a]



entry	X	Y	solvent	time (h)	conversion[b] (%)	yield[c] (%)
1[d]	2	1	toluene	36	-	20
2	2	1	toluene	36	60	32
3	2	2	toluene	36	81	56
4[e]	2	2	toluene	36	35	<10
5	2	2	C_6H_5Cl	36	72	33
6	2	2	1,2-DCE	36	62	18
7	2	2	^{t}AmOH	18	100	82
8	2	1	^{t}AmOH	18	100	84
9	1.5	1	^{t}AmOH	18	100	82
10	1.2	1	^{t}AmOH	18	100	82
11[f]	1	1	^{t}AmOH	18	100	92

[a]Reaction conditions: *N*-(2-pyridyl)indole **1a** (1 equiv), NCTS **2** (X equiv), $[Cp^*RhCl_2]_2$ (Y mol %), $AgSbF_6$ (10 mol %), solvent (1.5 mL), 120 °C, time. [b]Based on the recovered starting material. [c]Isolated yield. [d]100 °C. [e]5 mol % of $AgSbF_6$. [f]1.2 equiv of **1a** and the yield is based on cyanating reagent.

1 mol % of $[Cp^*RhCl_2]_2$ and 10 mol % of $AgSbF_6$ afforded the product **3a** in the best isolated yield of 92%.

After identifying the optimal reaction conditions, we studied the scope and generality of the Rh(III)-catalyzed C2-cyanation with various substituted indoles. As shown in Scheme 2, the optimized conditions tolerate functional groups at various position (C3, C4, and C5) of *N*-(2-pyridyl)indoles to afford the corresponding product in good to excellent yield. Simple aryl and readily functionalizable bromo-substituted cyanoindoles (**3b** and **3c**) were achieved in 76% and 77% yield, respectively. Interestingly, the reaction tolerates both electron donating (methoxy and benzyloxy) and electron-withdrawing groups (tosyloxy and cyano) on the indole moiety and led to the formation of corresponding 2-cyanoindoles (**3d**–**3h**) in good yields. Sterically demanding C–H possessing 3-methyl and 3-(carbomethoxy)methyl substituted indoles were also readily converted to corresponding cyanated product (**3i** and **3j**) in 96% and 82% yield, respectively. Similarly, substitutions on the directing group were also examined. All the pyridine derivatives that were examined helped the chelation-assisted cyanation and led to the formation of cyanated product (**3k**–**3m**) in good yield. Instead of pyridine, other chelating groups like quinoline and pyrimidine were also studied. *N*-(2-Quinolyl)indole and *N*-(2-pyrimidyl)indole underwent smooth reaction to afford the products **3n** and **3o** in 71% and 46% yield, respectively. However, substrate with an additional coordination site gave comparatively lower yields.

Subsequently, we extended the optimized conditions to pyrrole-based derivatives. Initial attempts with *N*-(pyridyl)-pyrrole **4a** afforded only moderate yield of 2-cyano-*N*-(pyridyl)pyrrole **5a**. By changing the catalyst loading, the reaction conditions were optimized to afford the product **5a** in 81% yield, with 3 mol % of rhodium catalyst and 10 mol % of $AgSbF_6$ in *tert*-amyl alcohol at 120 °C (Scheme 3 and see Supporting Information).

Next, diverse pyrrole derivatives **4** were examined for C2-selective cyanation under the optimized conditions (Scheme 4). Simple alkyl and aryl-substituted pyrrole derivatives were readily converted under the optimized conditions to corresponding cyanated product (**5c** and **5d**) in good yield. 2-Methyl and 2,3-fused pyrroles, sterically demanding pyrrole derivatives, underwent smooth reaction to give the product **5a** and **5e** in 67% and 76% yield, respectively. Interestingly, the optimized reaction tolerates various functional groups, like benzoyl, acetyl, and ester, to afford the corresponding products (**5f**–**5h**) in moderate yield. Furthermore, cyanation of pyrrole containing various chelating pyridines derivatives also furnished the product (**5i**–**5l**) in good to excellent yield.

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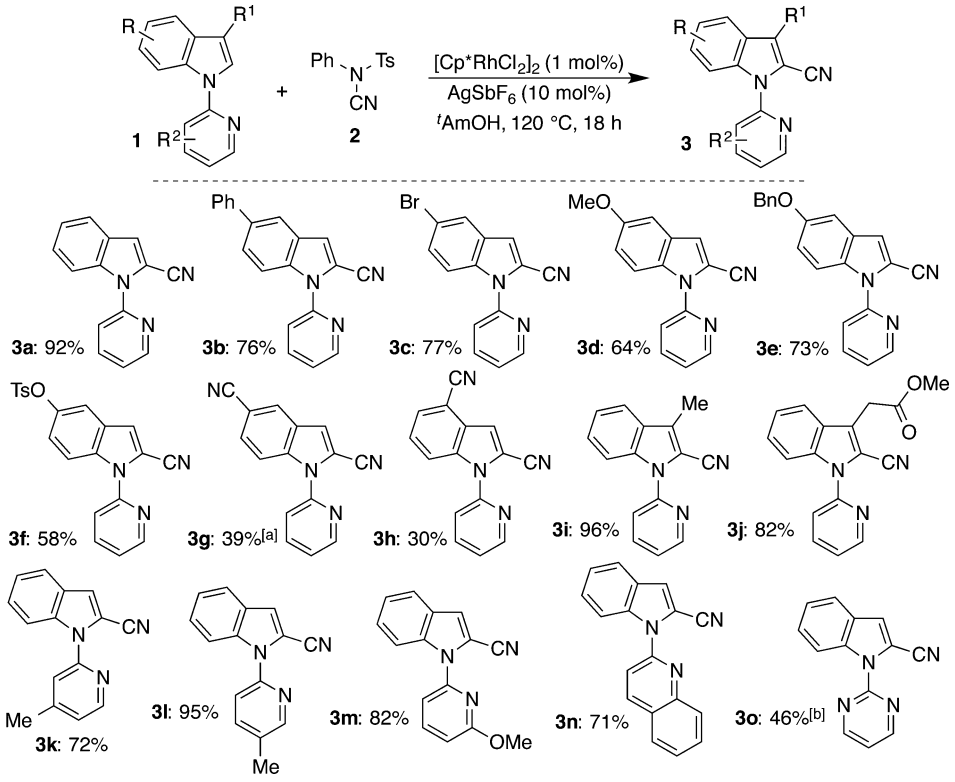
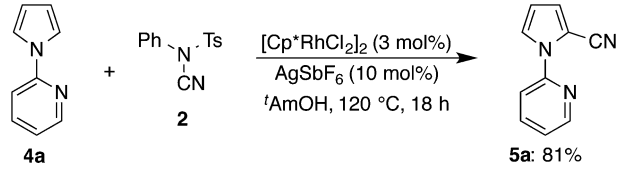
Scheme 2. Rhodium Catalyzed C2-Selective Cyanation of Indoles[a]



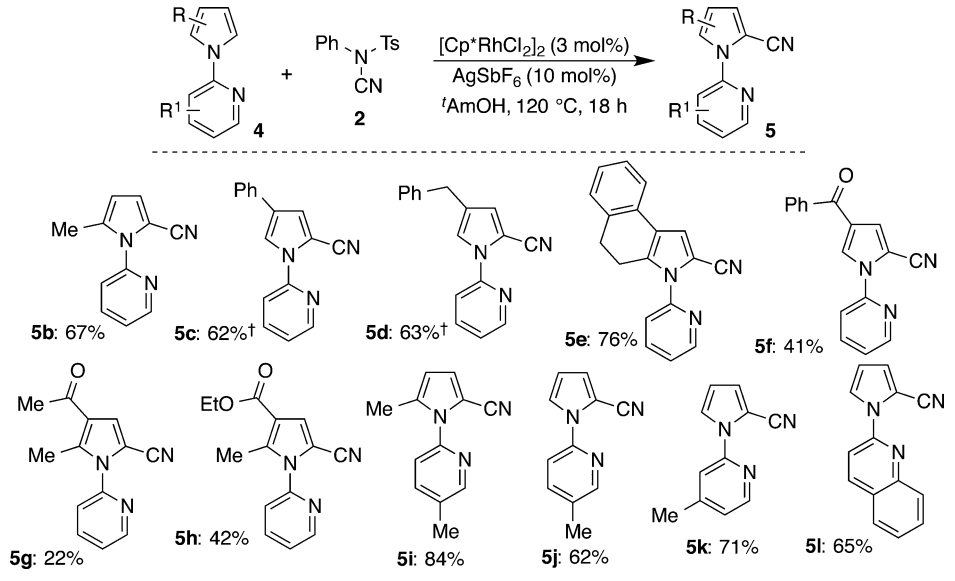
[a][a] 2 mol % $[Cp^*RhCl_2]_2$; [b] 3 mol % $[Cp^*RhCl_2]_2$.

Scheme 3. Rhodium Catalyzed C2-Selective Cyanation of *N*-Pyridylpyrrole 4a



After the successful development of rhodium catalyzed C2-selective cyanation of indoles and pyrroles, the utility of the synthesized 2-cyanoheteroarenes was demonstrated through the conversion into synthetically useful building blocks. First, we envisioned the removal of directing group form the 2-cyanoindole moiety. Thus, the reaction of **3o** and sodium methoxide in DMSO at 110 °C furnished the simple 2-cyanoindole **7**, an important building block for the synthesis

Scheme 4. Rhodium Catalyzed C2-Selective Cyanation of Pyrroles.[†]



[†]^{1}H NMR yield.

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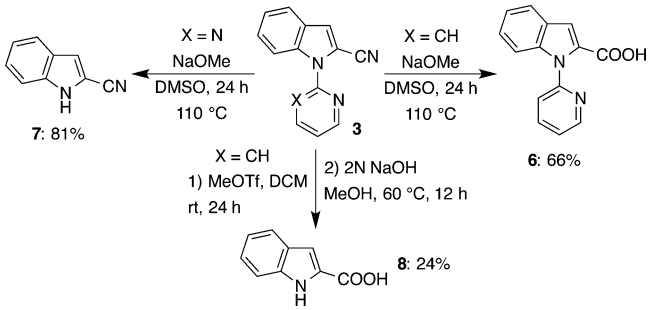
of bioactive molecules shown in Scheme 1, in 81% yield. Similarly, the treatment of **3a** with sodium methoxide afforded the hydrolyzed product **6** in good yield. The combined deprotection and hydrolysis of cyano compound **3a** to indole-2-carboxylic acid **8** was achieved through the initial reaction with methyltriflate followed by treatment with sodium hydroxide.

Scheme 5. Representative Reaction of 2-Cyanoindoles 3



In conclusion, we have developed an efficient and direct rhodium catalyzed C2-cyanation of indoles and pyrroles employing readily available and environmentally benign *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **2**) as a cyanating reagent. The developed reaction tolerated various functional groups and allowed the synthesis of diverse 2-cyanoindoles and pyrroles in good to excellent yield. Additionally, the reaction utilizes the readily modifiable chelating groups like pyridine, pyrimidine, and quinoline. Furthermore, the potential of the synthesized cyano compounds was successfully demonstrated by converting into highly important building blocks.

EXPERIMENTAL SECTION

General Procedure for Rhodium Catalyzed C2 Cyanation *N*-Pyridyl Indole (3). A dry reaction tube (10 mL) was charged with heteroarene **1** (0.24 mmol), *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide **2** (54 mg, 0.2 mmol), $[Cp^*RhCl_2]_2$ (1.2 mg, 0.002 mmol, 1 mol %), $AgSbF_6$ (6.8 mg, 0.02 mmol, 10 mol %), and dry ^{t}AmOH (1.5 mL) under nitrogen atmosphere. The reaction tube was sealed under nitrogen atmosphere and the reaction mixture was stirred at 120 °C for 18 h. After the completion of the reaction, as monitored by TLC analysis, the reaction mixture was cooled to room temperature and purified by column chromatography using a mixture of hexane and ethyl acetate as eluent to afford the pure cyanated product **3**.

3a:[9] 49 mg, 92% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.69−8.67 (m, 1H), 7.96−7.91 (m, 1H), 7.76 (dd, 1H, J = 8.72, 0.64 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.58 (d, 1H, J = 8.2 Hz), 7.43−7.35 (m, 3H), 7.29−7.25 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.7 (CH), 149.6 (C), 138.9 (CH), 137.1 (C), 127.0 (CH), 126.9 (C), 122.9 (CH), 122.8 (CH), 124.4 (CH), 118.8 (CH), 117.4 (CH), 113.8 (C), 112.3 (CH), 109.1 (C); HRMS: calcd. for $C_{14}H_9N_3$+H: 220.0875; found: 220.0886.

3b: 54 mg, 76% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.72−8.70 (m, 1H), 7.99−7.94 (m, 1H), 7.90 (d, 1H, J = 1.09 Hz), 7.85 (d, 1H, J = 8.76 Hz), 7.69−7.62 (m, 4H), 7.48−7.45 (m, 3H), 7.41−7.34 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.8 (CH), 141.1 (C), 139 (CH), 136.6 (C), 136.4 (C), 129 (C), 128.9 (CH), 127.5 (C), 127.4 (CH), 127.2 (CH), 126 0.9 (CH), 122.9 (CH), 120.5 (CH), 118.7 (CH), 117.7 (CH), 113.7 (C), 112.7 (CH), 109.7 (C); HRMS: calcd. for $C_{20}H_{13}N_3$+H: 296.1188; found: 296.1199.

3c:[9] 55 mg, 77% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.69−8.67 (m, 1H), 7.96 (m, 1H), 7.84 (d, 1H, J = 1.57 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.57 (d, 1H, J = 8.18 Hz), 7.49−7.47 (m, 1H), 7.42−7.38 (m, 1H), 7.32 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.8 (CH), 149.4 (C), 139.1 (CH), 135.7 (C),129.9 (CH), 128.4 (C), 124.7 (CH), 123.2 (CH), 118.8 (CH), 116.3 (CH), 116 (C), 114.1 (CH), 113.2 (C), 110 (C); HRMS: calcd. for $C_{14}H_8N_3Br$+H: 297.9980; found: 297.9969.

3d:[9] 38 mg, 64% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.67−8.66 (m, 1H), 7.95−7.91 (m, 1H), 7.70 (dd, 1H, J = 9.88, 0.54 Hz), 7.58 (m, 1H), 7.34 (ddd, 1H, J = 7.50, 4.88, 0.89 Hz), 7.31 (d, 1H, J = 0.6 Hz), 7.08−7.05 (m, 2H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 156.0 (C), 149.8 (C), 149.6 (CH), 139 (CH),132.4 (C), 127.5 (C), 122.7 (CH), 118.5 (CH), 118.2 (CH), 117 (CH), 113.9 (C), 113.5 (CH), 109 (C), 102.3 (CH), 55.8 (CH_3); HRMS: calcd. for $C_{15}H_{11}N_3O$+H: 250.0980; found: 250.0981.

3e: 57 mg, 73% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.67−8.65 (m, 1H), 7.94−7.90 (m, 1H), 7.71 (d, 1H, J = 9.97 Hz), 7.7 (d, 1H, J = 8.04 Hz), 7.45 (d, 2H, J = 7.07 Hz), 7.40−7.32 (m, 4H), 7.29 (s, 1H), 7.17−7.14 (m, 2H), 5.1 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 155.1 (C), 149.8 (C), 149.6 (CH), 139 (CH),136.9 (C), 132.5 (C), 128.7 (CH), 128.1 (CH), 127.6 (CH), 127.4 (C), 122.7 (CH), 118.7 (CH), 118.5 (CH), 117 (CH), 113.9 (C), 113.5 (CH), 109 (C), 103.9 (CH), 70.6 (OCH_2); HRMS: calcd. for $C_{21}H_{15}N_3O$+H: 326.1293; found: 326.1279.

3f: 54 mg, 58% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.59 (d, 1H, J = 4.58 Hz), 7.90−7.86 (m, 1H), 7.64−7.60 (m, 3H), 7.49 (d, 1H, J = 7.95 Hz), 7.34−7.31 (m, 1H), 7.26−7.18 (m, 4H), 6.97 (d, 1H, J = 9.15 Hz), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.8 (CH), 149.4 (C), 145.5 (C), 145.3 (CH), 139.2 (CH),135.4 (C), 132.3 (C), 130.9 (C), 129.9 (CH), 128.7 (CH), 126.9 (C), 123.3 (CH), 121.9 (CH), 118.9 (CH), 117.1 (CH), 115.5 (CH), 113.1 (C), 110.7 (C), 21.8 (CH_3); HRMS: calcd. for $C_{21}H_{15}N_3O_3S$+H: 390.0912; found: 390.0926.

3g:[9] 23 mg, 39% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.72−8.71 (m, 1H), 8.10−8.09 (m, 1H), 8.03−7.99 (m, 1H), 7.88−7.86 (m, 1H), 7.64−7.60 (m, 2H), 7.48−7.45 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 150.0 (CH), 148.9 (C), 139.4 (CH), 138.4 (C), 129.2 (CH), 128.0 (CH), 126.6 (C), 123.8 (CH), 119.2 (C), 119.2 (CH), 117.1 (CH), 113.9 (CH), 112.6 (C), 111.8 (C), 106.6 (C); HRMS: calcd. for $C_{15}H_8N_4$+H: 245.0827; found: 245.0832.

3h: 18 mg, 30% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.72−8.71 (m, 1H), 8.06−7.99 (m, 2H), 7.66 (dd, 1H, J = 7.28, 0.72 Hz), 7.63−7.61 (m, 1H), 7.59 (d, 1H, J = 0.72 Hz), 7.51−7.45 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 150.0 (CH), 149.0 (C), 139.4 (CH), 136.7 (C), 128.3 (CH), 127.7 (C), 126.6 (CH), 123.8 (CH), 119.2 (CH), 117.7 (CH), 117.2 (C), 114.9 (CH), 112.6 (C), 111.6 (C), 105.4 (C); HRMS: calcd. for $C_{15}H_8N_4$+H: 245.0827; found: 245.0836.

3i:[9] 54 mg, 96% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.56 (s, 1H), 7.83−7.80 (m, 1H), 7.70 (d, 1H, J = 8.34 Hz), 7.56 (d, 1H, J = 7.94 Hz), 7.47 (d, 1H, J = 7.94 Hz), 7.32−7.31 (m, 1H), 7.23−7.16 (m, 2H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 150.0 (C), 149.5 (CH), 138.8 (CH), 137.0 (C), 128.6 (C), 127.5 (C), 127.2 (CH), 122.3 (CH), 122.1 (CH), 120.6 (CH), 118.3 (CH), 113.7 (C), 112.3 (CH), 107.6 (C), 9.9 (CH_3); HRMS: calcd. for $C_{15}H_{11}N_3$+H: 234.1031; found: 234.1033.

3j: 57 mg, 82% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.69−8.67 (m, 1H), 7.96−7.92 (m, 1H), 7.79−7.76 (m, 1H), 7.71−7.69 (m, 1H), 7.61−7.59 (m, 1H), 7.45−7.41 (m, 1H), 7.37 (ddd, 1H, J = 7.49, 4.88, 0.95 Hz), 7.31−7.27 (m, 1H), 4.02 (s, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 170.1 (C), 149.7 (CH), 139.0 (CH), 137.0 (C), 127.4 (CH), 126.8 (C), 124.0 (C), 122.8 (CH), 122.7 (CH), 120.9 (C), 120.8 (CH), 118.7 (CH), 113.0 (C), 112.4 (CH), 108.9 (C), 52.5 (OCH_3), 31.1 (CH_2); HRMS: calcd. for $C_{17}H_{13}N_3O_2$+H: 292.1086; found: 292.1079.

3k: 40 mg, 72% yield; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.45 (d, 1H, J = 5.17 Hz), 7.66 (dd, 1H, J = 8.61,

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0.86 Hz), 7.63−7.61 (m, 1H), 7.35−7.30 (m, 3H), 7.20−7.16 (m, 1H), 7.12−7.11 (m, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 150.7 (C), 149.8 (C), 149.3 (CH), 137.2 (C), 128.5 (C), 126.9 (CH), 124.0 (CH), 122.7 (CH), 122.3 (CH), 119.7 (CH), 117.2 (CH), 113.8 (C), 112.4 (CH), 109.2 (C), 21.34 (CH_3); HRMS: calcd. for $C_{15}H_{11}N_3$+H: 234.1031; found: 234.1029.

3l: 53 mg, 95% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.40 (m, 1H), 7.65−7.59 (m, 3H), 7.38−7.36 (m, 1H), 7.33−7.28 (m, 2H), 7.18−7.14 (m, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.9 (CH), 147.4 (C), 139.4 (CH), 137.2 (C), 132.9 (C), 128.4 (C), 126.8 (CH), 122.5 (CH), 122.3 (CH), 118.5 (CH), 116.8 (CH), 113.8 (C), 112.2 (CH), 109.1 (C), 18.13 (CH_3); HRMS: calcd. for $C_{15}H_{11}N_3$+H: 234.1031; found: 234.1041.

3m: 49 mg, 82% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.79−7.75 (m, 2H), 7.71−7.69 (m, 1H), 7.43−7.38 (m, 2H,), 7.29−7.25 (m, 1H), 7.13 (d, 1H, *J* = 7.44 Hz), 6.78 (d, 1H, *J* = 8.33 Hz), 4.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 164.0 (C), 147.1 (C), 140.7 (CH), 136.7 (C), 127.0 (C), 126.8 (CH), 122.6 (CH), 122.4 (CH), 117.3 (CH), 114.1 (C), 112.2 (CH), 112.2 (CH), 109.9 (CH), 109.3 (C), 54.3 (OCH_3); HRMS: calcd. for $C_{15}H_{11}N_3O$+H: 250.0980; found: 250.0983.

3n: 46 mg, 71% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.40 (d, 1H, *J* = 8.68 Hz), 8.17 (d, 1H, *J* = 8.35 Hz), 7.96−7.91 (m, 2H), 7.83−7.79 (m, 1H), 7.76−7.73 (m, 2H), 7.64−7.60 (m, 1H), 7.48−7.44 (m, 2H), 7.33−7.29 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 148.6 (C), 147.4 (C), 139.5 (CH), 137.2 (C), 130.9 (CH), 129.1 (CH), 127.8 (CH), 127.3 (CH), 127.2 (C), 127.2 (CH), 127.2 (C), 123 (CH), 122.5 (CH), 118.0 (CH), 117.0 (CH), 113.9 (C), 112.7 (CH), 109.2 (C); HRMS: calcd. for $C_{18}H_{11}N_3$+H: 270.1031; found: 270.1033.

3o:[9] 24 mg, 46% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.83 (d, 2H, *J* = 4.67 Hz), 8.69 (d, 1H, *J* = 8.57 Hz), 7.68 (d, 1H, *J* = 8.01 Hz), 7.52−7.47 (m, 2H), 7.34−7.31 (m, 1H), 7.23 (t, 1H, *J* = 4.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 158.4 (CH), 156.7 (C), 136.7 (C), 127.9 (C), 127.6 (CH), 123.6 (CH), 122.1 (CH), 121.1 (CH), 118.1 (CH), 116.2 (CH), 114.3 (C), 109.1 (C); HRMS: calcd. for $C_{13}H_8N_4$+H: 221.0827; found: 221.0830.

General Procedure for Rhodium Catalyzed C2 Cyanation of *N*-Pyridyl Pyrrole (5). A dry reaction tube (10 mL) was charged with heteroarene **4** (0.24 mmol), *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide **2** (54 mg, 0.2 mmol), $[Cp^*RhCl_2]_2$ (3.7 mg, 0.006 mmol, 3 mol %), $AgSbF_6$ (6.8 mg, 0.02 mmol, 10 mol %), and dry ^{t}AmOH (1.5 mL) under nitrogen atmosphere. The reaction tube was sealed under nitrogen atmosphere and the reaction mixture was stirred at 120 °C for 18 h. After the completion of the reaction, as monitored by TLC analysis, the reaction mixture was cooled to room temperature and purified by column chromatography using mixture of hexane and ethyl acetate as eluent to afford the pure cyanated product **5**.

5a:[9] 33 mg, 81% yield, colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.46−8.44 (m, 1H), 7.79−7.75 (m, 1H), 7.54−7.52 (m, 1H), 7.50 (dd, 1H, *J* = 2.95, 1.65 Hz), 7.22−7.19 (m, 1H), 6.96 (dd, 1H, *J* = 3.79, 1.64 Hz), 6.29−6.28 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.8 (C), 149.2 (CH), 139.1 (CH), 125.5 (CH), 124.4 (CH), 122.6 (CH), 114.9 (CH), 114.2 (C), 111.2 (CH), 102.4 (C); HRMS: calcd. for $C_{10}H_7N_3$+H: 170.0718; found: 170.0720.

5b: 30 mg, 67% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.56−8.54 (m, 1H), 7.83 (td, 1H, *J* = 7.81, 1.89 Hz), 7.35−7.30 (m, 2H), 6.83 (d, 1H, *J* = 3.84 Hz), 6.01 (dd, 1H, *J* = 3.78, 0.73 Hz), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.7 (C), 149.5 (CH), 138.8 (CH), 136.4 (C), 123.7 (CH), 121.8 (CH), 120.7 (CH), 114.3 (C), 110.1 (CH), 103.4 (C), 13.59 (CH_3); HRMS: calcd. for $C_{11}H_9N_3$+H: 184.0875; found: 184.0871.

5e: 49 mg, 76% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.64−8.62 (m, 1H), 7.94−7.90 (m, 1H), 7.46 (dt, 1H, *J* = 7.99, 0.79 Hz), 7.43−7.37 (m, 2H), 7.26 (s, 1H), 7.25−7.19 (m, 2H), 7.16−7.12 (m, 1H), 3.02−2.93 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.5 (CH), 149.2 (C), 138.9 (CH), 136.5 (C), 133.5 (C), 130.8 (C), 128.2 (CH), 127.1 (CH), 126.4 (CH), 123.5 (CH), 122.4 (CH), 121.3 (C), 119.6 (CH), 117.1 (CH), 114.4 (C), 103.6 (C), 29.1 (CH_2), 22.0 (CH_2); HRMS: calcd. for $C_{18}H_{13}N_3$+H: 272.1188; found: 272.1178.

5f: 27 mg, 41% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.60−8.58 (m, 1H), 8.12 (d, 1H, *J* = 1.81 Hz), 7.95−7.91 (m, 1H), 7.88−7.86 (m, 2H), 7.72−7.70 (m, 1H), 7.62−7.58 (m, 1H), 7.53−7.49 (m, 3H), 7.41−7.38 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 189.1 (C), 149.6 (CH), 149.1 (C), 139.5 (CH), 138.4 (C), 132.6 (CH), 130.0 (CH), 129.1 (CH), 128.7 (CH), 125.8 (C), 125.1 (CH), 123.8 (CH), 115.5 (CH), 113.0 (C), 104.3 (C); HRMS: calcd. for $C_{17}H_{11}N_3O$+H: 274.0980; found: 274.0989.

5g: 12 mg, 22% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.69−8.67 (m, 1H), 7.99−7.94 (m, 1H), 7.49 (ddd, 1H, *J* = 7.56, 4.91, 0.88 Hz), 7.40 (d, 1H, *J* = 7.96 Hz), 7.31 (s, 1H), 2.53 (s, 3H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 193.9 (C), 150.1 (CH), 148.6 (C), 141.0 (C), 139.1 (CH), 124.8 (CH), 122.6 (CH), 122.5 (C), 121.5 (CH), 112.9 (C), 103.8 (C), 28.8 (CH_3), 13.3 (CH_3); HRMS: calcd. for $C_{13}H_{11}N_3O$+H: 226.0980; found: 226.0989.

5h: 26 mg, 42% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.68−8.66 (m, 1H), 7.95 (td, 1H, *J* = 7.72, 2.01 Hz), 7.48−7.45 (m, 1H), 7.40 (m, 1H), 7.36 (s, 1H), 4.31 (q, 2H, *J* = 7.11 Hz), 2.53 (s, 3H), 1.36 (t, 3H, *J* = 7.22 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 163.7 (C), 150.0 (CH), 148.9 (C), 141.6 (C), 139.1 (CH), 124.6 (CH), 122.8 (CH), 121.4 (C), 114.8 (CH), 113.0 (C), 103.9 (C), 60.3 (CH_2), 14.5 (CH_3), 12.7 (CH_3); HRMS: calcd. for $C_{14}H_{13}N_3O_2$+H: 256.1086; found: 256.1075.

5i: 40 mg, 84% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.43−8.42 (m, 1H), 7.70−7.67 (m, 1H), 7.28 (d, 1H, *J* = 8.17 Hz), 6.87 (d, 1H, *J* = 3.83 Hz), 6.06 (dd, 1H, *J* = 3.84, 0.77 Hz), 2.41 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.8 (CH), 147.5 (C), 139.2 (CH), 136.3 (C), 133.7 (C), 121.4 (CH), 120.2 (CH), 114.4 (C), 109.8 (CH), 103.5 (C), 18.1 (CH_3), 13.4 (CH_3); HRMS: calcd. for $C_{12}H_{11}N_3$+H: 198.1031; found: 198.1025.

5j: 27 mg, 62% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.352−8.350 (m, 1H), 7.67−7.64 (m, 1H), 7.53−7.49 (m, 2H), 7.03−7.02 (m, 1H), 6.35 (dd, 1H, *J* = 3.77, 3.02 Hz), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 149.3 (CH), 147.9 (C), 139.5 (CH), 132.6 (C), 125.6 (CH), 124.0 (CH), 114.8 (CH), 114.3 (C), 111.0 (CH), 102.5 (C), 18.0 (CH_3); HRMS: calcd. for $C_{11}H_9N_3$+H: 184.0875; found: 184.0877.

5k: 31 mg, 71% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.37 (d, 1H, *J* = 5.01 Hz), 7.54−7.53 (m, 1H), 7.40 (s, 1H), 7.10 (d, 1H, *J* = 5.01 Hz), 7.03−7.01 (m, 1H), 6.35−6.33 (m, 1H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 150.8 (C), 150.0 (C), 148.8 (CH), 125.6 (CH), 124.2 (CH), 123.8 (CH), 115.7 (CH), 114.3 (C), 111.0 (CH), 102.4 (C), 21.3 (CH_3); HRMS: calcd. for $C_{11}H_9N_3$+H: 184.0875; found: 184.0880.

5l: 34 mg, 65% yield; colorless liquid; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.32 (d, 1H, *J* = 8.75 Hz), 8.10 (d, 1H, *J* = 8.53 Hz), 7.87−7.85 (m, 1H), 7.79−7.72 (m, 3H), 7.59−7.55 (m, 1H), 7.10 (dd, 1H, *J* = 3.79, 1.63 Hz), 6.43 (dd, 1H, *J* = 3.73, 3.06 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 24 °C): δ 148.4 (C), 147.0 (C), 139.8 (CH), 130.9 (CH), 129.0 (CH), 127.7 (CH), 127.2 (C), 127.0 (CH), 125.6 (CH), 124.8 (CH), 114.3 (C), 113.5 (CH), 111.5 (CH), 102.9 (C); HRMS: calcd. for $C_{14}H_9N_3$+H: 220.0875; found: 220.0877.

Synthesis of 6. A mixture of 1-(pyridin-2-yl)-1*H*-indole-2-carbonitrile **3a** (45 mg, 0.2 mmol) and NaOMe (43 mg, 0.8 mmol) in DMSO (3 mL) was stirred at 110 °C for 24 h. After completion of the reaction as monitored by TLC analysis, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), and extracted with water. The aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layer was

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dried over Na_2SO_4. After filtration and concentration in vacuo, the crude product was purified by column chromatography using a mixture of hexane/ethyl acetate (85:15) as an eluent to afford the pure product **6** as colorless liquid. 32 mg, 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 9.93 (s, 1H), 9.19 (s, 1H), 8.43−8.35 (m, 2H), 7.76−7.73 (m, 1H), 7.65 (d, 1H, J = 8.03 Hz), 7.45−7.43 (m, 1H), 7.31 (t, 1H, J = 7.42 Hz), 7.25−7.22 (m, 1H), 7.17−7.09 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 160.1 (C), 151.4 (C), 147.8 (CH), 138.8 (CH), 137.0 (C), 130.4 (C), 127.7 (C), 125.3 (CH), 122.5 (CH), 121.0 (CH), 120.1 (CH), 114.6 (CH), 112.1 (CH), 104.6 (CH); HRMS: calcd. for $C_{14}H_{10}N_2O_2$+H: 239.0821; found: 239.0824.

Synthesis of 7.[9] A mixture of 1-(pyrimidin-2-yl)-1*H*-indole-2-carbonitrile **3o** (43 mg, 0.2 mmol) and NaOMe (43 mg, 0.8 mmol) in DMSO (3 mL) was stirred at 110 °C for 24 h. After completion of the reaction as monitored by TLC analysis, the reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), and washed with water. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4. After filtration and concentration in vacuo, the crude product was purified by column chromatography using a mixture of hexane/ethyl acetate (95:5) as an eluent to afford the pure product **7** as white solid: 23 mg, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.82 (br, 1H), 7.68 (dd, 1H, J = 8.12, 0.87 Hz), 7.44−7.38 (m, 2H), 7.24−7.20 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 24 °C): δ 137.0 (C), 126.4 (CH), 126.3 (C), 122.2 (CH), 121.8 (CH), 114.5 (CH), 114.4 (C), 111.9 (C), 106.3 (C); HRMS: calcd. for $C_9H_6N_2$+H: 143.0609; found: 143.0610.

Synthesis of 8.[23] Methyl trifluoromethanesulfonate (39 mg, 0.24 mmol) was added dropwise to a solution of 1-(pyridin-2-yl)-1*H*-indole-2-carbonitrile **3a** (45 mg, 0.2 mmol) in dry 1,2-dichloroethane (5 mL) at room temperature, and the reaction mixture was stirred at room temperature for 24 h. Then the solvent was removed under vacuum, and the residue was dissolved in MeOH (2.5 mL). 2 N NaOH (1.2 mL) was added and stirred at 60 °C for 12 h. The solvent was removed and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4. After filtration and concentration in vacuo, the crude product was purified by column chromatography using a mixture of hexane/ethyl acetate (70:30) as an eluent to afford the pure product **8** as a white solid: 10 mg, 24% yield; ^{1}H NMR (400 MHz, DMSO-d_6, 24 °C): δ 12.9 (br, 1H), 11.7 (s, 1H), 7.67 (d, 1H, J = 7.93 Hz), 7.48 (d, 1H, J = 8.26 Hz), 7.27 (t, 1H, J = 7.60 Hz), 7.13−7.07 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, 24 °C): δ 163.7 (C), 138.1 (C), 129.3 (C), 127.8 (C), 125.2 (CH), 122.8 (CH), 120.8 (C), 113.4 (C), 108.2 (C); HRMS: calcd. for $C_9H_7NO_2$+H: 162.0555; found: 162.0557.

■ ASSOCIATED CONTENT

Supporting Information

Optimization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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