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# Palladium-Catalyzed Domino Heck-Cyanation Cascade to 3-Cyanomethyl 2,3-Dihydrobenzofuran and 2,3-Dihydroindoles

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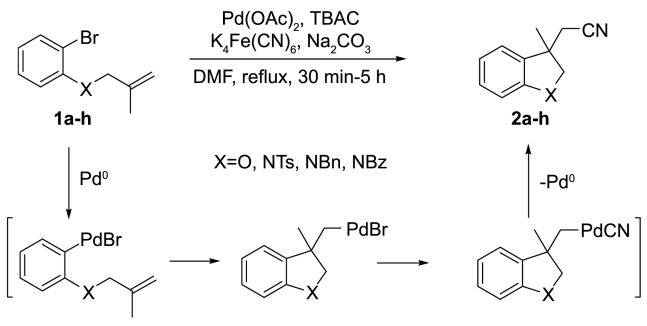
Palladium-catalyzed domino reactions coupled with suitably designed starting materials allow for rapid establishment of complex molecules.[1-3] In particular, a palladium-catalyzed consecutive carbon-carbon bond-formations through a Heck-type cascade cyclization has become one of the most popular methods for the synthesis of multiple ring system.[2] The formation of a σ-alkylpalladium(II) intermediate lacking a suitable β-hydrogen *syn* with respect to the palladium center is essential for the effective cascade bond-formations.[3] In this respect, aryl methallyl ethers and *N*-methallylanilines were the major subject for the Pd-catalyzed domino reactions. The fate of reactive alkylpalladium(II) intermediate formed by the initial Heck-type cyclization is divided largely into two categories: (i) termination by anion capture process by sodium formate,[4a,b] organotin(IV) reagents,[4c,d] arylboronic acid,[4b,d] and cyanide,[5,6] and (ii) termination by C-H activation of either $sp^3$(C)-H[3e-g,7a,b] or $sp^2$(C)-H.[3a,d,7c,d] However, an efficient palladium-catalyzed domino Heck-cyanation reaction was started very recently[5] although the basic concept dates back to the original paper of Grigg in 1993.[6b]

Zhu and co-workers reported an elegant synthesis of 3-alkyl-3-cyanomethyl-2-oxindoles *via* a domino Heck-cyanation from *o*-iodoanilides.[5a,b] Later, Jia and co-workers extended the reaction for the synthesis of various dihydrobenzopyranes.[5c] However, the synthesis of dihydrobenzofuran[8] and dihydroindole[9] derivatives has not been reported. Herein we disclose the first successive domino Heck-cyanation for the synthesis of 3-cyanomethyl dihydrobenzofuran and dihydroindoles, as shown in Scheme 1.

Initially, we prepared *o*-bromophenyl methallyl ether (**1a**) from methallyl chloride and 2-bromophenol ($K_2CO_3$, $CH_3CN$), and examined the reaction conditions of domino Heck-cyanation, as summarized in Table 1. As shown in Table 1, the reaction of **1a** showed the formation of **2a** in trace amounts in the presence of $Pd(OAc)_2$/TBAC/$K_4Fe(CN)_6$/$Na_2CO_3$ in DMF at 120 °C (entry 1). When we run the reaction at refluxing temperature, compound **2a** was isolated in 56%. Increasing the amount of $K_4Fe(CN)_6$ (entry 3) or the use of $Cs_2CO_3$ (entry 4) decreased the yield of **2a**. Without TBAC the yield of **2a** was very low (entry 5). Replacement of DMF to DMA or NMP was not efficient (entries 6 and 7). In addition, the use of excess amounts of TBAC (3.0 equiv) was not beneficial (entry 8).




**Scheme 1**

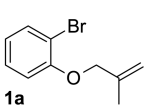
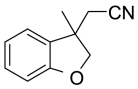
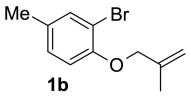
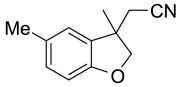
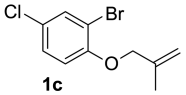
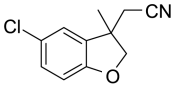
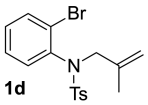
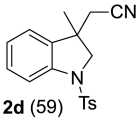
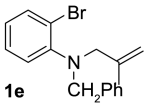
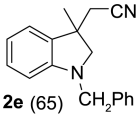
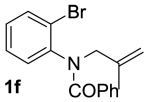
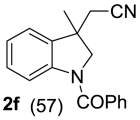
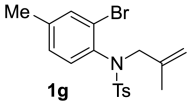
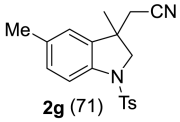
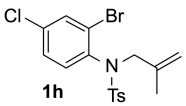
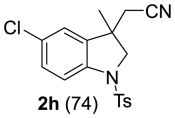
Under the optimized conditions (entry 2 in Table 1), we carried out the synthesis of dihydrobenzofurans **2a-c** and dihydroindole derivatives **2d-h**, as summarized in Table 2. Various aryl methallyl ethers (entries 1-3) and *N*-methallylanilines (entries 4-8) afforded the corresponding dihydrobenzofurans and dihydroindoles in good to moderate yields (56-74%). The yields of dihydroindoles were somewhat higher than those of the 2,3-dihydrobenzofurans. The reason could be ascribed in part to the instability of aryl methallyl ether under the Pd-catalyzed reaction conditions.[4b,7a,10]

**Table 1.** Optimization of reaction conditions with **1a**

| Entry | Conditions[a] | **2a** (%) |
|---|---|---|
| 1 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMF, 120 °C, 15 h | < 5 |
| 2 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMF, reflux, 3 h | 56[b] |
| 3 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (1.0 equiv), $Na_2CO_3$ (1.3 equiv), DMF, reflux, 3 h | < 10 |
| 4 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Cs_2CO_3$ (1.3 equiv), DMF, reflux, 3 h | 26[b] |
| 5 | $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMF, reflux, 3 h | < 10 |
| 6 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMA, 150-160 °C, 3 h | 35[b] |
| 7 | TBAC (1.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), NMP, 150-160 °C, 3 h | < 10 |
| 8 | TBAC (3.0 equiv), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMF, reflux, 3 h | 39[b] |

[a]$Pd(OAc)_2$ (10 mol %) is common. [b]Isolated yield and the yields in other entries were estimated based on TLC observation.

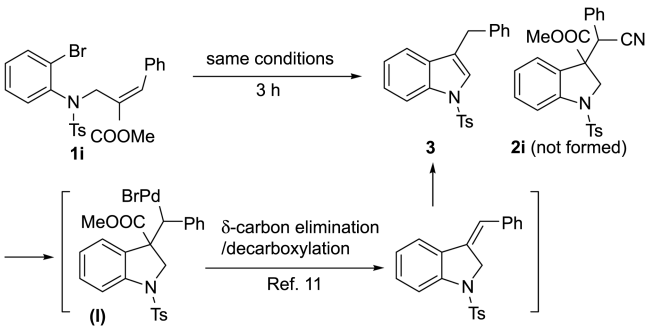
**Table 2.** Pd-catalyzed domino Heck-cyanation

| Entry | Substrate | Time (h) | Product (%) |
|---|---|---|---|
| 1 |  **1a** | 3 |  **2a** (56) |
| 2 |  **1b** | 5 |  **2b** (59) |
| 3 |  **1c** | 3 |  **2c** (66) |
| 4 |  **1d** | 0.5 |  **2d** (59) |
| 5 |  **1e** | 0.5 |  **2e** (65) |
| 6 |  **1f** | 0.5 |  **2f** (57) |
| 7 |  **1g** | 0.5 |  **2g** (71) |
| 8 |  **1h** | 0.5 |  **2h** (74) |

[a]Conditions: Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), TBAC (0.5 mmol), $K_4Fe(CN)_6$ (0.25 equiv), $Na_2CO_3$ (1.3 equiv), DMF, reflux.

Usually, allyl aryl ether and its derivatives undergo many side reactions under the Pd-catalyzed reaction conditions including the formation of π-allylpalladium intermediate and subsequent decomposition to phenol.[10]

As a next entry, we examined the reaction of **1i** under the same conditions, as shown in Scheme 2. However, the expected compound **2i** was not formed in any trace amount, instead 3-benzyl-*N*-tosylindole (**3**) was isolated as the major product (58%).[11] As reported previously in our group,[11] the alkylpalladium intermediate (**I**) underwent preferentially a concomitant δ-carbon elimination/decarboxylation process to form **3** instead of cyanation to **2i**.




**Scheme 2**

In summary, we disclosed an efficient synthesis of 3-methyl-3-cyanomethyl-2,3-dihydrobenzofuran and 2,3-dihydroindole derivatives *via* a domino Heck-cyanation process in moderate yields.

## Experimental Section

**Typical Procedure for the Synthesis of 2-Bromophenyl Methallyl Ether (1a).** A stirred mixture of 2-bromophenol (173 mg, 1.0 mmol), methallyl chloride (135 mg, 1.5 mmol), and $K_2CO_3$ (207 mg, 1.5 mmol) in $CH_3CN$ (2.0 mL) was heated to reflux for 4 h. After aqueous workup and column chromatographic purification process (hexanes/ether, 20:1), **1a** was obtained as colorless oil, 213 mg (94%).[7c] Other starting materials were prepared similarly and the spectroscopic data of unknown compounds **1f-h** are as follows.

**Compound 1f:** 94%; colorless oil; IR (film) 1651, 1474, 1377 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.87 (s, 3H), 3.75 (d, $J$ = 15.0 Hz, 1H), 4.81 (s, 1H), 4.88 (s, 1H), 5.14 (d, $J$ = 15.0 Hz, 1H), 7.01-7.23 (m, 6H), 7.35 (d, $J$ = 6.9 Hz, 2H), 7.48 (d, $J$ = 7.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 20.79, 54.27, 113.99, 123.17, 127.52, 127.80, 127.91, 128.98, 129.59, 131.62, 133.61, 135.97, 140.45, 141.75, 170.57; ESIMS *m/z* 330 ($M^+$+H), 332 ($M^+$+H+2).

**Compound 1g:** 74%; colorless oil; IR (film) 1488, 1350, 1163 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H), 2.29 (s, 3H), 2.42 (s, 3H), 4.08 (d, $J$ = 14.1 Hz, 1H), 4.16 (d, $J$ = 14.1 Hz, 1H), 4.66 (s, 1H), 4.74 (s, 1H), 6.98 (d, $J$ = 8.1 Hz, 1H), 7.04 (dd, $J$ = 8.1 and 1.8 Hz, 1H), 7.25 (d, $J$ = 8.1 Hz, 2H), 7.37 (d, $J$ = 1.8 Hz, 1H), 7.60 (d, $J$ = 8.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 20.39, 20.66, 21.47, 57.02, 115.70, 124.69, 127.84, 128.45, 129.33, 131.55, 134.34, 134.77, 136.43, 139.86, 139.92, 143.40; ESIMS *m/z* 394 ($M^+$+H), 396 ($M^+$+H+2).

**Compound 1h:** 67%; colorless oil; IR (film) 1470, 1353, 1164 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 2.44 (s, 3H), 4.12 (s, 2H), 4.65 (s, 1H), 4.76 (s, 1H), 7.06 (d, $J$ = 8.4 Hz, 1H), 7.24 (dd, $J$ = 8.4 and 2.4 Hz, 1H), 7.28 (d, $J$ = 8.4 Hz, 2H), 7.57 (d, $J$ = 2.4 Hz, 1H), 7.60 (d, $J$ = 8.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 20.43, 21.58, 57.01, 116.23, 125.75, 127.90, 128.01, 129.55, 132.92, 133.67, 134.70, 136.22, 136.35, 139.59, 143.80.

**Typical Procedure for the Synthesis of 3-Methyl-3-Cyanomethyl-2,3-Dihydrobenzofuran (2a).** A stirred mixture of **1a** (114 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%), TBAC (139 mg, 1.0 equiv), $K_4Fe(CN)_6$ (55 mg, 0.25 equiv), and $Na_2CO_3$ (69 mg, 1.3 equiv) in DMF (1.0 mL) was heated to reflux for 3 h under nitrogen atmosphere. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 5:1), **2a** was obtained as colorless oil, 49 mg (56%).[8e] Other compounds were prepared similarly and the spectroscopic data of unknown compounds **2b-h** are as follows.

**Compound 2b:** 59%; colorless oil; IR (film) 2248, 1491, 1227, 1201 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 2.30 (s, 3H), 2.58 (s, 2H), 4.20 (d, $J$ = 9.0 Hz, 1H), 4.40 (d, $J$ = 9.0 Hz, 1H), 6.72 (d, $J$ = 8.1 Hz, 1H), 7.00 (d, $J$ = 8.1 Hz, 1H), 7.02 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 20.78, 23.48, 29.15, 43.75, 81.66, 109.84, 117.34, 123.14, 129.85, 130.60, 131.61, 156.96; ESIMS *m/z* 188 ($M^+$+H). Anal. Calcd. For $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.15; H, 7.11; N, 7.23.

**Compound 2c:** 66%; colorless oil; IR (film) 2249, 1480, 1258, 1089 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 2.61 (s, 2H), 4.26 (d, $J$ = 9.3 Hz, 1H), 4.46 (d, $J$ = 9.3 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 7.14-7.19 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 23.53, 29.03, 43.94, 81.98, 111.37, 116.89, 122.97, 125.85, 129.39, 133.42, 157.72; ESIMS *m/z* 208 ($M^+$+H), 210 ($M^+$+H+2). Anal. Calcd. For $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.87; H, 5.01; N, 6.64.

**Compound 2d:** 59%; colorless oil; IR (film) 2249, 1478, 1356, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 2.23 (d, $J$ = 16.8 Hz, 1H), 2.34 (d, $J$ = 16.8 Hz, 1H), 2.39 (s, 3H), 3.60 (d, $J$ = 11.1 Hz, 1H), 3.90 (d, $J$ = 11.1 Hz, 1H), 7.05 (t, $J$ = 7.5 Hz, 1H), 7.38 (d, $J$ = 7.5 Hz, 1H), 7.27 (d, $J$ = 8.1 Hz, 2H), 7.26-7.32 (m, 1H), 7.67 (d, $J$ = 7.8 Hz, 1H), 7.72 (d, $J$ = 8.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 21.52, 24.13, 29.42, 41.90, 61.14, 114.90, 116.92, 122.88, 124.14, 127.23, 129.39, 129.87, 133.54, 135.49, 140.79, 144.60; ESIMS *m/z* 327 ($M^+$+H). Anal. Calcd. For $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.83; N, 8.53.

**Compound 2e:**[9a] 65%; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 3H), 2.55 (s, 2H), 3.07 (d, $J$ = 9.6 Hz, 1H), 3.26 (d, $J$ = 9.6 Hz, 1H), 4.14 (d, $J$ = 14.7 Hz, 1H), 4.38 (d, $J$ = 14.7 Hz, 1H), 6.55 (d, $J$ = 7.5 Hz, 1H), 6.75 (t, $J$ = 7.5 Hz, 1H), 7.10-7.16 (m, 2H), 7.25-7.35 (m, 5H).

**Compound 2f:** 57%; colorless oil; IR (film) 2247, 1646, 1481, 1393 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 2.60 (s, 2H), 3.90 (d, $J$ = 11.7 Hz, 1H), 4.04 (d, $J$ = 11.7 Hz, 1H), 7.07-7.58 (m, 9H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 24.39, 29.41, 41.72, 62.09, 117.06, 122.49, 124.43, 127.14, 128.69 (2C), 128.81, 130.75, 136.01, 136.26, 141.50, 168.75; ESIMS *m/z* 277 ($M^+$+H). Anal. Calcd. For $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.01; H, 5.97; N, 9.98.

**Compound 2g:** 71%; colorless oil; IR (film) 2249, 1486, 1355, 1166 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 2.19 (d, $J$ = 16.5 Hz, 1H), 2.29 (s, 3H), 2.31 (d, $J$ = 16.5 Hz, 1H), 2.37 (s, 3H), 3.58 (d, $J$ = 11.1 Hz, 1H), 3.88 (d, $J$ = 11.1 Hz, 1H), 6.94 (s, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 7.26 (d, $J$ = 8.1 Hz, 2H), 7.55 (d, $J$ = 8.4 Hz, 1H), 7.70 (d, $J$ = 8.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 20.87, 21.45, 24.13, 29.29, 41.84, 61.24, 114.76, 116.96, 123.37, 127.20, 129.78, 129.88, 133.41, 133.98, 135.64, 138.37, 144.44; ESIMS *m/z* 341 ($M^+$+H). Anal. Calcd. For $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.32; H, 5.96; N, 8.03.

**Compound 2h:** 74%; white solid, mp 42-44 °C; IR (KBr) 2249, 1474, 1357, 1167 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 2.24 (d, $J$ = 16.8 Hz, 1H), 2.34 (d, $J$ = 16.8 Hz, 1H), 2.40 (s, 3H), 3.62 (d, $J$ = 11.1 Hz, 1H), 3.91 (d, $J$ = 11.1 Hz, 1H), 7.10 (d, $J$ = 2.1 Hz, 1H), 7.25 (dd, $J$ = 8.7 and 2.1 Hz, 1H), 7.29 (d, $J$ = 8.1 Hz, 2H), 7.61 (d, $J$ = 8.7 Hz, 1H), 7.70 (d, $J$ = 8.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 21.50, 24.16, 29.18, 41.94, 61.24, 115.98, 116.51, 123.26, 127.16, 129.34, 129.40, 129.97, 133.16, 137.36, 139.50, 144.88; ESIMS *m/z* 361 ($M^+$+H), 363 ($M^+$+H+2). Anal. Calcd. For $C_{18}H_{17}ClN_2O_2S$: C, 59.91; H, 4.75; N, 7.76. Found: C, 60.14; H, 4.87; N, 7.71.

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## References and Notes

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