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Reductive cyclization of halo-ketones to form 3-hydroxy-2-oxindoles via palladium catalyzed hydrogenation: a hydrogen-mediated Grignard addition

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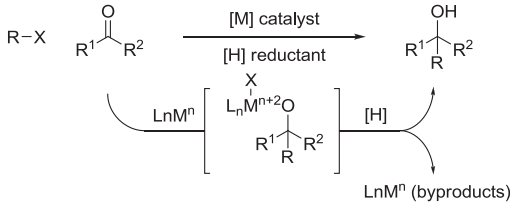
ABSTRACT

The reductive cyclization of *N*-oxoacyl *ortho*-bromoanilides to form 3-hydroxy-2-oxindoles under the conditions of palladium catalyzed hydrogenation is described. This work may be viewed as a prelude to intermolecular hydrogen-mediated Grignard-type reductive couplings of organic halides with carbonyl compounds.

1. Introduction

Carbonyl addition is a cornerstone of chemical synthesis.[1] The Grignard reaction,[2] the magnesium mediated reductive coupling of organic halides and carbonyl compounds, persists as one of the most broadly utilized methods for carbonyl addition. Despite its broad scope, operational simplicity and cost-effective nature, the Grignard reaction requires organomagnesium reagents, which are highly basic and, hence, moisture sensitive, and which generate stoichiometric quantities of metallic byproducts, posing challenges for use on scale.[3–5] Additionally, enantioselective variants of the Grignard addition have proven elusive.[6] These limitations are potentially addressed through the development of metal catalyzed organic halide-carbonyl reductive couplings, especially those employing non-metallic low molecular weight terminal reductants (Scheme 1).[7] The Nozaki-Hiyama-Kishi (NHK) reaction is perhaps the most notable metal catalyzed reaction of this type.[8] While enantioselective variants of the NHK reaction have been developed,[8] this process employs toxic chromium base catalysts and, as elemental manganese is used as terminal reductant, it does not circumvent generation of stoichiometric metallic byproducts.



Scheme 1. Transition metal catalyzed reductive carbonyl addition.

We have developed the first 'C–C bond forming hydrogenations' beyond hydroformylation, the largest volume application of homogeneous catalysis.[9] In these processes, π-unsaturated reactants are hydrogenated in the presence of carbonyl compounds or imines to furnish products of reductive coupling.[10] As catalytic hydrogenation is used routinely for the reduction of organic halides to form the corresponding C–H compounds,[11] we became attracted to the prospect of capturing the intervening organometallic species via carbonyl addition. Such hydrogen-mediated organic halide-carbonyl reductive couplings would bypass the generation of stoichiometric metallic byproducts and potentially provide a conduit to enantiomerically enriched adducts. The feasibility of hydrogen-mediated Grignard-type reactions is supported by reports of related halo-ketone reductive cyclizations under the conditions of transfer hydrogenation, wherein alcohols[12] or tertiary amines[13–15] are utilized as terminal reductants (Scheme 2, Eq. 1–3).[16,17] Here, we demonstrate palladium catalyzed hydrogenation of *N*-oxoacyl

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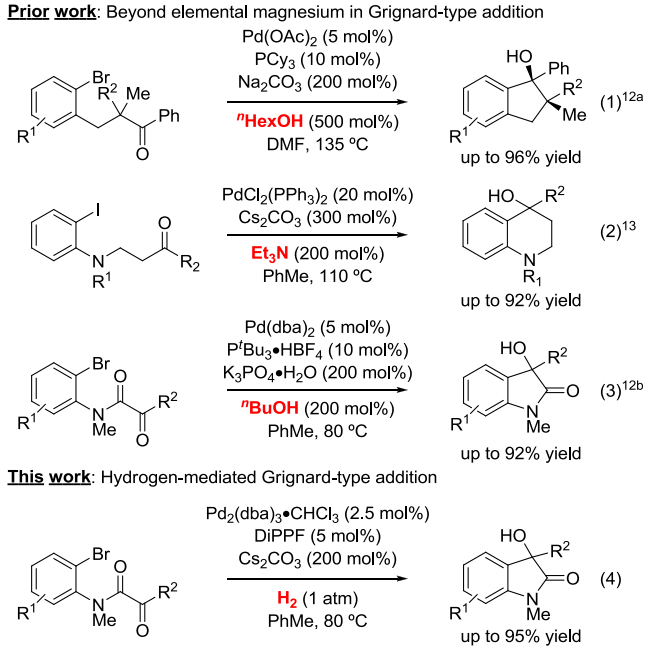
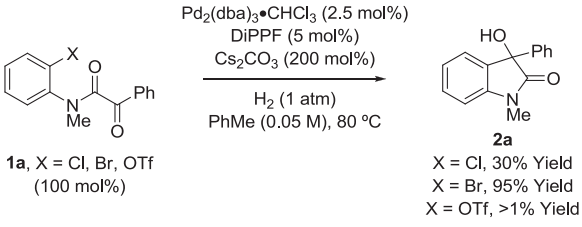
ortho-bromoanilides promotes reductive cyclization to form 3-hydroxy-2-oxindoles in good to excellent yield with complete suppression of conventional aryl halide hydrogenolysis pathways (Scheme 2, Eq. 4).



Scheme 2. Reductive cyclization of aromatic halo-ketones in the absence of stoichiometric metals.

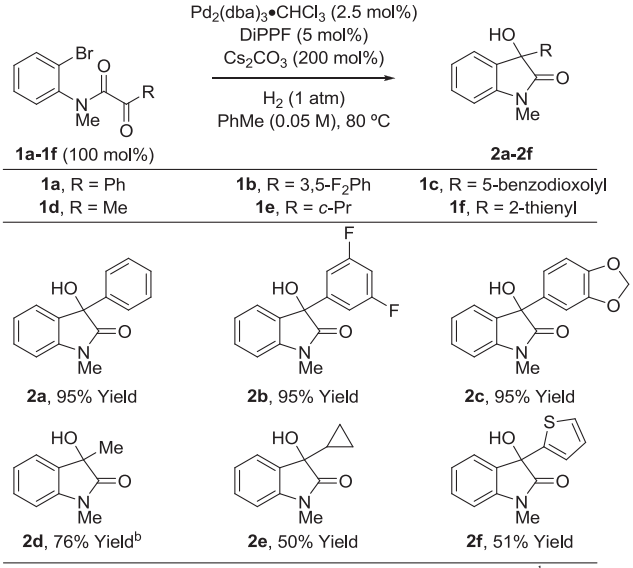
2. Results and discussion

Initial experiments focused on the reductive cyclization of α-ketoamides **1a** (X=Br) under hydrogenation conditions using $Pd_2(dba)_3$•$CHCl_3$ as precatalyst in combination with various phosphine ligands (Eq. 5). Gaseous hydrogen was introduced simply using balloons. Several phosphine ligands were tested for this transformation, for example, 1,1′-bis(di-*tert*-butylphosphino)ferrocene (DtBPF, 55% yield), XPhos (64% yield), and 1,2-bis(dicyclohexylphosphino)ethane (DCyPE, 68% yield). The palladium catalyst modified by the chelating phosphine ligand 1,1′-bis(di-*iso*-propylphosphino)ferrocene (DiPPF) provided the best results, enabling formation of 3-hydroxy-2-oxindole **2a** in 95% yield after isolation by silica gel flash column chromatography. The use of Cs_2CO_3 as base is important, as substantially diminished isolated yields were observed in reactions using Na_2CO_3 (trace conversion), K_2CO_3 (47% yield) or K_3PO_4 (20% yield) under otherwise identical conditions, which may, in part, be due to solubility. Under the indicated conditions (Eq. 5), the corresponding *ortho*-chloro ketoamide **1a** (X=Cl) provided **2a** in 30% yield due to a combination of incomplete conversion and hydrogenolysis of the chloride. The triflyl derivative of ketoamide **1a** (X=OTf) did not convert to oxindoles **2a** under these conditions due to hydrolysis to form the phenol.[14]



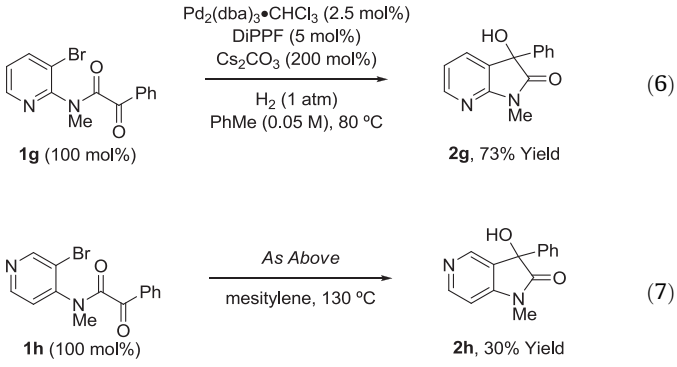
Using the following conditions, $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol %), DiPPF (5 mol %), Cs_2CO_3 (200 mol %) in toluene (0.05 M) at 80 °C in the presence of H_2 (1 atm) the reductive cyclization of α-ketoamides **1a**–**1f** was explored (Table 1). The hydroxy oxindoles **2a**–**2f** were obtained in moderate to excellent yields. Aryl **2a**–**2c**, alkyl **2d**–**2e**, and heteroaryl **2f** groups at the C3 position of the resulting oxindoles **2a**–**2f** were tolerated. Reactants **1a**–**1c** that incorporate aryl substituents gave uniformly better results compared to reactants incorporating alkyl groups (**1d**–**1e**) or heteroaryl groups (**2f**).[18]

Table 1
Reductive cyclization of α-ketoamides **1a**–**1f** under the conditions of palladium catalyzed hydrogenation[a]

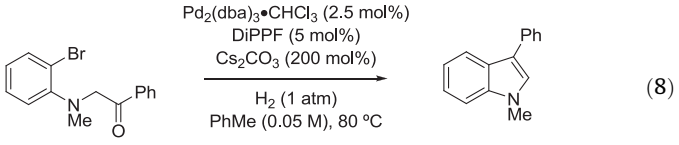


[a]Yields are of material isolated by silica gel chromatography. [b]K_2CO_3 (200 mol%).[18]

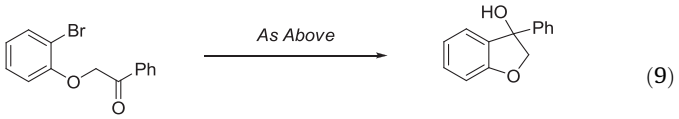
To further probe the scope of this process, compounds **1g** and **1h**, derived from 2-amino-3-bromopyridine and 4-amino-3-bromopyridine, respectively, were subjected to standard conditions for reductive cyclization (Eq. 6,7). Compound **1g** was transformed to 6-aza-3-hydroxy-2-oxindole **2g** in good yield (Eq. 6). For compound **1h**, only trace quantities of the 4-aza-3-hydroxy-2-oxindole **2h** were observed under standard conditions. Elevated temperatures (130 °C) were required to enforce conversion to the 4-aza-3-hydroxy-2-oxindole **2h**, which was isolated in 30% yield along with dehalogenated material (Eq. 7).[18] The diminished reactivity of **1h** may be due to coordination of the less hindered pyridyl nitrogen to the palladium catalyst.



To probe the feasibility of engaging less activated carbonyl partners, compounds **1i** and **1j** were subjected to standard conditions for reductive cyclization (Eq. 8,9). Compound **1i** delivered 3-phenyl indole **2i** due to dehydration-aromatization of the tertiary alcohol derived upon reductive cyclization (Eq. 8).[18] The relatively low isolated yield of **2i** stems from competing dehalogenation of **1i**. For compound **1j**, reductive cyclization to form **2j** occurred in 32% isolated yield (Eq. 9).[18] Dehydration-aromatization to form the corresponding benzofuran was not observed. However, dehalogenation of **1j** again contributed to a relatively low isolated yield of **2j**.

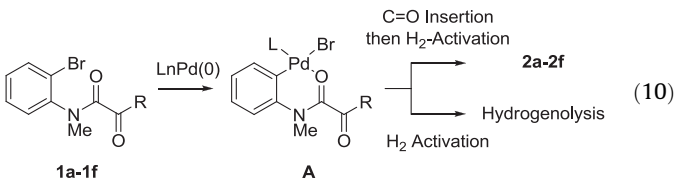


1i (100 mol%) **2i**, 28% Yield (8)



1j (100 mol%) **2j**, 32% Yield (9)

The collective data suggest a catalytic mechanism involving oxidative addition of a palladium(0) complex to *ortho*-haloarenes **1a**–**1f** to form the square planer σ-arylpalladium(II) complex **A** (Eq. 10). Insertion of the tethered carbonyl followed by hydrogen activation delivers products of reductive cyclization **2a**–**2f**. Use of chiral chelating phosphine ligands, Josiphos or Walphos type ligands, DuPhos, and BINAP, did not result in enantiomeric enrichment (>1% ee), suggesting loss of chelating ligand in advance of carbonyl insertion. Competing dehalogenation of **1a**–**1f** presumably stems from the reaction of complex **A** with elemental hydrogen via pathways involving σ-bond metathesis-C–H reductive elimination.[11] The identification of second generation catalysts that promote rapid carbonyl insertion with respect to hydrogen activation is currently under investigation in our laboratory.



1a-1f **A** (10)

3. Conclusions

In summary, we report that palladium catalyzed hydrogenation of *ortho*-bromoaryl α-ketoamides **1a**–**1f** results in reductive cyclization to form 3-substituted-3-hydroxy-2-oxindoles **2a**–**2f** in good to excellent isolated yields. Additionally, as illustrated in the conversion of 2-amino-3-bromopyridine derived α-ketoamides **1g** and 4-amino-3-bromopyridine derived α-ketoamides **1h** to compounds **2g** and **2h**, respectively, this method also provides access to aza-3-hydroxy-2-oxindoles. These results may be viewed as proof-of-concept with respect to the long term objective of developing general intermolecular hydrogen-mediated Grignard type additions of organic halides and carbonyl partners. The observation of competing aryl halide hydrogenolysis in the present transformations foreshadows the principal challenge associated with this endeavor.

4. Experimental

4.1. General experimental

Tetrahydrofuran (THF) and toluene (PhMe) were distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) and mesitylene were distilled from calcium hydride under a nitrogen atmosphere. Unless otherwise stated, commercially obtained reagents were used as received. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz with a Varian Gemini spectrometer. Chemical shifts are reported as parts per million (ppm) from tetramethylsilane (TMS) or ppm relative to the deuteriochloroform ($CDCl_3$), 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR, respectively. Melting points (°C) are uncorrected. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Analytical thin layer chromatography (TLC) was performed on TLC silica gel plates (250 μm) precoated with a fluorescent indicator. Standard flash column chromatography procedures were followed using 40–63 μm silica gel. Visualization was effected with *p*-anisaldehyde, potassium permanganate, and iodine stains.

4.2. General experimental procedure for palladium catalyzed reductive cyclization

To a flask charged with $Pd_2(dba)_3$•$CHCl_3$ (2.6 mg, 0.0025 mmol, 2.5 mol%), DiPPF (2.1 mg, 0.005 mmol, 5 mol%), and Cs_2CO_3 (65.2 mg, 0.2 mmol, 200 mol%) under an argon atmosphere was added freshly distilled toluene (2 mL, 0.05 M). The mixture was allowed to stir at 80 °C for 1 h, during which time the color of the solution changed from purple to orange or brown. *N*-Acyl *ortho*-bromoanilides **1** (0.1 mmol, 100 mol%) was added in one portion to the flask, then an argon balloon was switched to H_2 balloon, and the reaction mixture was allowed to stir at 80 °C for 20 h. The reaction mixture was evaporated and the residue was subjected to flash silica gel column chromatography to furnish the title compound **2**.

*4.2.1. 3-Hydroxy-1-methyl-3-phenylindolin-2-one (**2a**).* According to general procedure for palladium catalyzed reductive cyclization with **1a** (31.8 mg, 0.1 mmol, 100 mol%), the title product **2a** was obtained as a white solid in 95% yield (22.7 mg, 0.095 mmol) after flash column chromatography (hexanes/EtOAc=1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.18 (m, 7H), 7.01 (td, J=7.6, 1.0 Hz, 1H), 6.84 (dt, J=7.8, 0.8 Hz, 1H), 3.46 (br s, 1H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 143.5, 140.0, 131.5, 129.8, 128.5, 128.2, 125.3, 124.9, 123.5, 108.6, 77.9, 26.5. Data is consistent with reported literature.[12b]

*4.2.2. 3-(3,5-Difluorophenyl)-3-hydroxy-1-methylindolin-2-one (**2b**).* According to general procedure for palladium catalyzed reductive cyclization with **1b** (35.4 mg, 0.1 mmol, 100 mol%), the title product **2b** was obtained as a white solid in 95% yield (26.1 mg, 0.095 mmol) after flash column chromatography (hexanes/EtOAc=1:1). Mp: 45 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (td, J=7.7, 1.3 Hz, 1H), 7.26 (ddd, J=7.4, 1.4, 0.6 Hz, 1H), 7.12 (td, J=7.6, 1.0 Hz, 1H), 6.96–6.93 (m, 1H), 6.93–6.87 (m, 2H), 6.74 (tt, J=8.7, 2.3 Hz, 1H), 3.27 (s, 3H), 3.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 163.9 (d, J=12.6 Hz), 162.2 (d, J=12.6 Hz), 144.1 (t, J=8.6 Hz), 143.3, 130.7, 130.4, 129.1, 124.8, 123.9, 109.0, 108.7 (dd, J=21.1, 5.6 Hz), 103.7 (t, J=25.4 Hz), 77.4 (t, J=2.2 Hz), 26.7; IR (neat) 3410, 1701, 1610, 1595, 1450, 1111 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{11}F_2NO_2Na$ $[M+Na]^+$ 298.0650, found 298.0649.

*4.2.3. 3-(Benzo[d][1,3]dioxol-5-yl)-3-hydroxy-1-methylindolin-2-one (**2c**).* According to general procedure for palladium catalyzed

reductive cyclization with **1c** (36.2 mg, 0.1 mmol, 100 mol %), the title product **2c** was obtained as a colorless oil in 72% yield (19.8 mg, 0.072 mmol) after flash column chromatography (hexanes/EtOAc=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, J=7.8, 1.3, 1H), 7.29 (ddd, J=7.4, 1.3, 0.6 Hz, 1H), 7.10 (td, J=7.5, 1.0 Hz, 1H), 6.91–6.89 (m, 2H), 6.83 (dd, J=8.1, 1.8 Hz, 1H), 6.73 (dd, J=8.1, 0.5 Hz, 1H), 5.93 (q, J=1.4 Hz, 2H), 3.35 (s, 3H), 3.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.2, 147.9, 147.7, 143.1, 133.8, 131.3, 129.9, 124.8, 123.5, 118.9, 108.7, 108.1, 106.3, 101.2, 29.6, 26.5. Data is consistent with reported literature.[12b]

*4.2.4. 3-Hydroxy-1,3-dimethylindolin-2-one (**2d**).* According to general procedure for palladium catalyzed reductive cyclization with **1d** (25.6 mg, 0.1 mmol, 100 mol %), the title product **2d** was obtained as a white solid in 76% yield (13.5 mg, 0.076 mmol) after flash column chromatography (hexanes/EtOAc=1:1). Mp: 141–143 °C (lit.: 141–143 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=7.5 Hz, 1H), 7.34 (td, J=8.0 Hz, 1.5 Hz, 1H), 7.12 (t, J=7.5 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 3.23 (s, 1H), 3.21 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 143.0, 131.4, 129.6, 123.4, 123.0, 108.0, 74.0, 26.1, 25.0. Data is consistent with reported literature.[19]

*4.2.5. 3-Cyclopropyl-3-hydroxy-1-methylindolin-2-one (**2e**).* According to general procedure for palladium catalyzed reductive cyclization with **1e** (28.2 mg, 0.1 mmol, 100 mol %), the title product **2e** was obtained as a white solid in 50% yield (10.2 mg, 0.050 mmol) after flash column chromatography (hexanes/EtOAc=15:1 to 2:1). Mp: 179–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 2H), 7.11–7.04 (m, 1H), 6.83 (d, J=7.8 Hz, 1H), 3.18 (s, 3H), 2.70 (br s, 1H), 1.39–1.31 (m, 1H), 0.66–0.53 (m, 2H), 0.48–0.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 143.2, 129.5, 129.3, 123.8, 122.8, 108.2, 75.6, 29.6, 26.1, 17.9; IR (neat) 3331, 2922, 1699, 1615, 1467, 1260, 1090, 1021 cm^{-1}; HRMS (ESI+) calcd for $C_{12}H_{13}NO_2Na$ [M+Na]$^+$ 226.0838, found 226.0836.

*4.2.6. 1-methyl-3-(thiophen-2-yl)indolin-2-one (**2f**).* According to general procedure for palladium catalyzed reductive cyclization with **1f** (32.4 mg, 0.1 mmol, 100 mol %), the title product **2f** was obtained as a yellow solid in 51% yield (12.5 mg, 0.051 mmol) after flash column chromatography (hexanes/EtOAc=6:1 to 2:1). Mp: 119–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=7.4 Hz, 1H), 7.38 (dd, J=7.6, 7.6 Hz, 1H), 7.31 (d, J=4.9 Hz, 1H), 7.15 (dd, J=7.4, 7.4 Hz, 1H), 7.01–6.96 (m, 1H), 6.96–6.91 (m, 1H), 6.89 (d, J=7.8 Hz, 1H), 3.50 (br s, 1H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 143.4, 143.3, 130.5, 126.9, 126.1, 125.1, 123.6, 109.0, 75.5, 26.7 (one carbon was not detected); IR (neat) 3346, 1702, 612, 1469, 1373, 1347, 1093, 1018 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_{11}NO_2SNa$ [M+Na]$^+$ 268.0403, found 268.0405.

*4.2.7. 3-Hydroxy-1-methyl-3-phenyl-1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one (**2g**).* According to general procedure for palladium catalyzed reductive cyclization with **1g** (31.9 mg, 0.1 mmol, 100 mol %), the title product **2g** was obtained as a colorless oil in 73% yield (17.6 mg, 0.073 mmol) after flash column chromatography (hexanes/EtOAc=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J=5.3, 1.6 Hz, 1H), 7.47 (dd, J=7.3, 1.6 Hz, 1H), 7.38–7.23 (m, 5H), 6.93 (dd, J=7.3, 5.3, 1H), 3.29 (s, 3H), 3.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 157.0, 148.7, 139.2, 132.4, 128.8, 127.7, 125.9, 125.2, 118.9, 77.6, 25.6; IR (neat) 3340, 1635, 1467, 1351 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{12}N_2O_2Na$ [M+Na]$^+$ 263.0791, found 263.0792.

*4.2.8. 3-Hydroxy-1-methyl-3-phenyl-1,3-dihydro-2H-pyrrolo[3,2-c]pyridin-2-one (**2h**).* According to general procedure for palladium catalyzed reductive cyclization with **1h** (31.9 mg, 0.1 mmol, 100 mol %) in mesitylene at 130 °C, the title product **2h** was obtained as a colorless oil in 30% yield (7.2 mg, 0.03 mmol) after flash column chromatography (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J=5.4 Hz, 1H), 8.26 (d, J=0.9 Hz, 1H), 7.42–7.31 (m, 5H), 6.83 (dd, J=5.4, 0.8 Hz, 1H), 3.22 (s, 3H), 1.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 151.4, 151.2, 145.1, 139.0, 131.1, 129.0, 127.5, 125.5, 123.4, 104.5, 26.7; IR (neat) 3350, 1630, 1466, 1359 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{12}N_2O_2Na$ [M+Na]$^+$ 263.0791, found 263.0789.

*4.2.9. 1-Methyl-3-phenyl-1H-indole (**2i**).* According to general procedure for palladium catalyzed reductive cyclization with **1i** (30.4 mg, 0.1 mmol, 100 mol %), the title product **2i** was obtained as a yellow oil in 28% yield (5.8 mg, 0.028 mmol) after flash column chromatography (hexanes/EtOAc=3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dt, J=8.0, 1.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.41–7.34 (m, 2H), 7.30 (dt, J=8.3, 1.0 Hz, 1H), 7.24–7.17 (m, 3H), 7.12 (ddd, J=8.0, 7.0, 1.1 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.6, 127.8, 127.9, 126.1, 125.6, 121.8, 120.0, 119.9, 117.0, 109.1, 32.9. Data is consistent with reported literature.[20]

*4.2.10. 3-Phenyl-2,3-dihydrobenzofuran-3-ol (**2j**).* According to general procedure for palladium catalyzed reductive cyclization with **1j** (29.1 mg, 0.1 mmol, 100 mol %), the title product **2j** was obtained as a light yellow oil in 32% yield (6.8 mg, 0.032 mmol) after flash column chromatography (hexanes/EtOAc=25:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.33–7.27 (m, 2H), 7.27–7.20 (m, 2H), 7.05–7.02 (m, 1H), 6.93–6.83 (m, 2H), 4.64 (d, J=10.2 Hz, 1H), 4.44 (d, J=10.2 Hz, 1H), 2.23 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 142.7, 132.3, 130.8, 128.4, 127.7, 126.2, 124.5, 121.6, 110.9, 86.3, 82.7. Data is consistent with that reported in the literature.[21]

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all new compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.085.

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