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Synthesis of heterocycles via ligand-free palladium catalyzed reductive Heck cyclization

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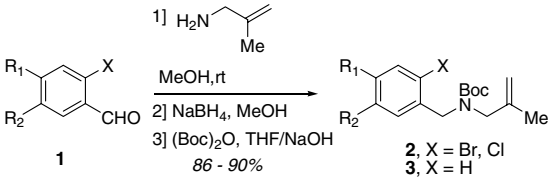
Abstract—Synthesis of five and six membered heterocycles, indolines, 2,3-dihydrobenzofurans, chromans, isochromans, 1,2,3,4-tetrahydroquinolines, and 1,2,3,4-tetrahydroisoquinolines, in 70–99% yield by a ligand-free palladium catalyzed reductive Heck cyclization of phenyl bromides and chlorides, under mild conditions, is reported. Water was found to be essential for these reactions.

The presence of indoline, 2,3-dihydrobenzofuran, isochroman, chroman, isochromene, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline in a variety of natural products and therapeutic agents has resulted in the development of several strategies for their preparation.[1] The most common synthetic methods include[2] Bronsted or Lewis acid catalyzed electrophilic cyclizations on electronic rich aromatic rings,[3] radical cyclization,[4] olefin metathesis,[5] tetrahydrothiophene catalyzed sulfonium ylide annulation,[6] and metal catalyzed cyclization.[7] However, no general method to access all these heterocycles is available, particularly those containing quaternary carbon centers.

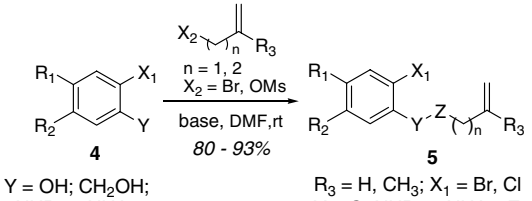
Phenyl iodides are generally employed in the palladium catalyzed Heck and reductive Heck cyclization reaction.[8] The use of readily available phenyl bromides or chlorides to construct heterocyclic compounds by a reductive Heck cyclization protocol would be attractive.[9] In this manuscript, we report a practical, ligand-free palladium catalyzed reductive cyclization reaction on phenyl bromides and chlorides for the synthesis of indoline, 2,3-dihydrobenzofuran, isochroman, chroman, isochromene, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline heterocycles. The reaction was robust in the presence of water, and was successful with electron-neutral, electron-donating and electron-deficient groups on the aromatic ring.

Synthesis of the cyclization precursors to prepare 1,2,3,4-tetrahydroisoquinolines is represented in Eq. 1. Reductive amination[10] of aldehyde **1** with 2-methylallylamine, in MeOH, followed by protection of the secondary amine with *tert*-butyl dicarboxylate afforded Boc protected amines **2** in 86–90% overall yield.



(1)

Synthesis of cyclization precursors to prepare indolines, 2,3-dihydrobenzofurans, isochromans, chromans, 1,2,3,4-tetrahydroquinolines, and isochromene is represented in Eq. 2. Deprotonation of a carbamate, acetate, phenol, benzenethiol, or benzyl alcohol **4** with base (NaH, *t*-BuOK), followed by alkylation with an alkenyl bromide or mesylate in DMF afforded **5** in 80–93% yield.



(2)

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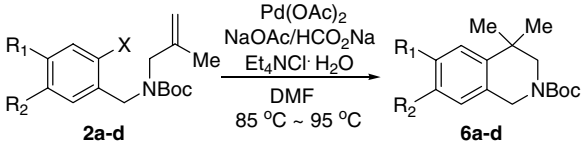
The reductive cyclization reaction was initially evaluated with olefin **2a** (Eq. 3, Table 1, entry 1) using Jeffery's conditions[9a] and HCO_2Na as reducing agent. Treatment of **2a** with $Pd(OAc)_2$ (0.5 mol %),[11] NaOAc (2.5 equiv), HCO_2Na (1.2 equiv), and $Et_4NCl{\cdot}H_2O$ (1.2 equiv) in *N*,*N*-dimethylformamide at 85–95 °C under nitrogen for 1–4 h provided *tert*-butyl 4,4-dimethyl-3,4-dihydro-iso-quinoline-2(1*H*)-carboxylate **6a** in 95% isolated yield. $Et_4NCl{\cdot}H_2O$ was better than *n*-Bu_4NCl and *n*-Bu_4NBr. In the absence of $Et_4NCl{\cdot}H_2O$, the reaction afforded <10% **6a**. Water was essential for the reaction and up to 5% water in DMF was tolerated. Excess water was detrimental to the cyclization. Using 25% water in DMF the reaction was sluggish and unknown impurities were generated. Under anhydrous conditions, the major product was the reductive dehalogenation compound **3**. $Pd(OAc)_2$ 0.5 mol % proved optimal, since with high palladium loading (10 mol %) the reaction sometimes stalled and palladium black precipitated from the reaction mixture. These results are in accordance with generation of palladium nano-particles that are the actual palladium pre-catalysts for the reductive Heck reaction.[12] Ammonium salts are reported as palladium nano-particle stabilizing agents.[13]

The same reaction conditions were successfully applied to the synthesis of substituted 1,2,3,4-tetrahydroisoquinolines **6b–d** in 72–92% yield (Table 1, entries 2–4). Interestingly under the ligand-free reductive cyclization conditions, electron-neutral (entry 1), electron-donating (entry 2), and electron-deficient (entries 3 and 4) substrates, all gave good to excellent yields of the desired products **6**. Incorporation of a *p*-NO_2 group on the aromatic ring, substrate **2d** afforded **6d** in 92% yield (entry 4). This reaction has been reproduced on a 10 g scale.



(3)

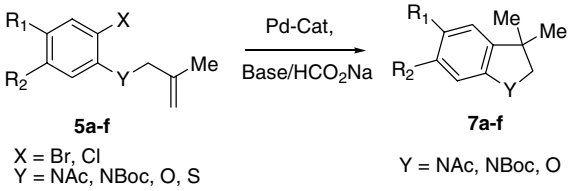
Table 1. Synthesis of 1,2,3,4-tetrahydroisoquinoline **6** (Eq. 3)[a]

Entry	**2**	X	R_1, R_2	Yield **6**[b] (%)
1	**a**	Br	H, H	95
2	**b**	Br	–$O(CH_2)_2O$–	72
3	**c**	Br	H, F	83
4	**d**	Cl	H, NO_2	92

[a] Reactions were performed with 0.5–2.0 g of substrate in 5–20 mL DMF [0.1 g/mL] under nitrogen. All products exhibit satisfactory spectroscopic and physical properties.
[b] Isolated yield of purified products.

Indolines and 2,3-dihydrobenzofurans were also prepared using similar conditions (Eq. 4, Table 2). The NBoc derivative **5a** afforded **7a** in 90% yield (entry 1). Similarly the *N*-acetyl analog **5b**, derived from 2-bromo-nitro aniline, afforded **7b** in 94% yield (entry 2). As observed with **2d**, this reaction was also successful with the corresponding chloro analog **5c**, affording **7c** in 92% yield (entry 3).[14] The high reactivity observed with substrates **2d** and **5c** was presumably due to the strong electron-withdrawing effect of the *p*-nitro group on the Ar–Cl bond that accelerates the rate of palladium oxidative insertion, since reaction of **5d**, the nitro free analog of **5c**, only gave ca. 6% conversion to **7d** (entry 4).

To address the low reactivity of phenyl chlorides under reductive Heck conditions in the absence of an activating group on the aromatic ring, we evaluated the phosphine free catalyst system reported by Buchwald that has proved effective in coupling activated olefins with both electron-donating and electron-deficient phenyl iodides and bromides.[15] Application of these conditions to **5d**, provided **7d** in 87% yield (Table 2, entry 5). Upon further development of this chemistry we found that the palladium-phosphinous acid complexes $[(t\text{-Bu})_2P(OH)]_2$-$PdCl_2$, $[(t\text{-Bu})_2P(OH)(t\text{-Bu})]_2PdCl_2$, and $[(t\text{-Bu})_2P(OH)$-$PdCl_2]_2$,[16,17] developed by Li, afforded a 99% yield of **7d** (entry 6). This chemistry was also successful in preparation of 2,3-dihydrobenzofuran **7e** in 70% yield from **5e** (entry 7). Attempts to prepare benzo[*b*]thiophene **7f** failed, presumably due to poisoning of palladium by sulfur (entry 8).[18]



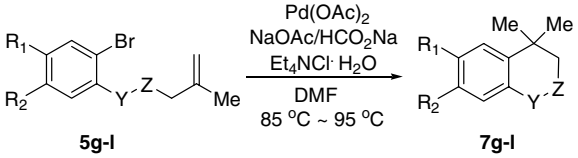
(4)

Table 2. Synthesis of indolines and 2,3-dihydrobenzofuran **7** (Eq. 4)[a]

Entry	**5**	X	Y	R_1, R_2	Yield **7**[b] (%)
1	**a**	Br	NBoc	H, H	90
2	**b**	Br	NAc	H, NO_2	94
3	**c**	Cl	NAc	H, NO_2	92
4	**d**	Cl	NAc	H, H	6
5	**d**	Cl	NAc	H, H	87[c]
6	**d**	Cl	NAc	H, H	99[d]
7	**e**	Br	O	H, H	70
8	**f**	Br	S	H, H	Mixture

[a] Reactions were performed with 0.5–2.0 g of substrates in 5–20 mL DMF [0.1 g/mL] under nitrogen. All products exhibit satisfactory spectroscopic and physical properties.
[b] Isolated yield of purified products.
[c] Reaction performed using $Pd(OAc)_2$, Cy_2NMe, Et_4NCl, HCO_2Na, DMAc, 100 °C, 2 h.
[d] Reaction performed using $[(t\text{-Bu})_2P(OH)PdCl_2]_2$, Cs_2CO_3, HCO_2Na, DMAc, 100 °C, 4 h.

Finally the reaction scope was expanded to the synthesis of chromans, isochromans, and 1,2,3,4-tetrahydroquinolines in 91–97% yield (Eq. 5, Table 3, entries 1–6). Again, the reductive cyclization of **5** afforded the desired product **7** regardless of whether the substrate was electron-neutral, electron-donating or electron-deficient.[19]



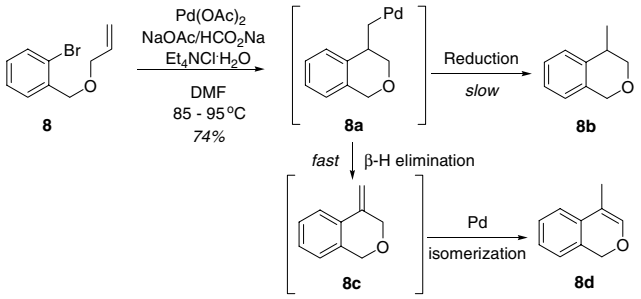
(5)

Table 3. Synthesis of chromans and 1,2,3,4-tetrahydroquinolines **7** (Eq. 5)[a]

Entry	5	Y	Z	R_1, R_2	Yield 7[b] (%)
1	**g**	NHBoc	CH_2	H, H	96
2	**h**	O	CH_2	H, H	91
3	**i**	O	CH_2	CN, H	96
4	**j**	CH_2	O	H, H	91
5	**k**	CH_2	O	$-O(CH_2)_2O-$	97
6	**l**	CH_2	O	H, F	97

[a] Reactions were performed with 0.5 g of substrate in 5 mL of DMF [0.1 g/mL] under nitrogen. All products exhibit satisfactory spectroscopic and physical properties.

[b] Yield refers to isolated yield of purified products.



Scheme 1.

Interestingly, substrate **8** provided Heck product **8d**, rather than the reductive cyclization product **8b**, even with HCO_2Na as reducing agent (Scheme 1).[20] Product **8b** could not be detected in the reaction mixture. We speculated that **8** first underwent palladium catalyzed oxidative addition and subsequently palladium migratory insertion to afford **8a**; the β-hydride elimination of **8a** to provide **8c** was faster than competing hydride reduction of **8a**–**8b**. The exo-alkene intermediate **8c** isomerized under the reaction conditions to give the thermodynamically more stable **8d** as the final product in 74% isolated yield. Without HCO_2Na, palladium catalyzed Heck cyclization of **8** afforded **8d** but with a slower reaction rate. We speculate that HCO_2Na might serve as the reducing agent facilitating the generation of palladium(0) nano-particles from $Pd(OAc)_2$ under the reaction conditions.

In summary, we have developed a general ligand-free palladium catalyzed reductive Heck reaction that can be applied to the synthesis of a variety five and six membered heterocycles in 70–99% yield. The chemistry is robust and easy to perform on scale.

Acknowledgments

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19. Typical reductive Heck cyclization procedure: A mixture of 3-bromo-4-(3-methylbut-enyloxy)benzene **5h** (0.5 g, 1.9 mmol), NaOAc (0.43 g, 5.0 mmol), HCO_2Na (0.15 g, 2.4 mmol), $Et_4NCl{\cdot}H_2O$ (0.41 g, 2.4 mmol), and $Pd(OAc)_2$ (4.7 mg, 0.02 mmol) in DMF (5 mL) was degassed and refilled with nitrogen three times. The mixture was heated to 85–95 °C (oil bath) for 1–4 h. Completion of the reductive cyclization was monitored by HPLC and GC. After completion, the reaction mixture was cooled to room temperature. Water (15 mL) was added and the mixture filtered through a Celite bed and washed with *tert*-butyl methyl ether (25 mL). The organic phase was separated and concentrated to give an oily residue that was filtered through silica gel with eluent (EtOAc/hexane 1/20) to give the desired product 3,4-dimethyl-3,4-dihydro-2*H*-chromene **7h** as colorless oil (0.31 g, 91%). ^1H NMR (400 MHz, $CDCl_3$, δ): 1.33, (s, 6H); 1.83, (t, $J = 5.5$ Hz, 2H); 4.19 (t, $J = 5.5$ Hz, 2H); 6.75–6.80 (m, 1H); 6.83–6.91 (m, 1H); 7.02–7.10 (m, 1H); 7.23–7.28 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$, δ): 30.56, 31.10, 37.70, 64.04, 116.89, 120.40, 126.91, 131.64, 153.59. Exact mass (M+H): 163.11174. Found: 163.11242.
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