

Palladium-Catalyzed Cyclization/Carboalkoxylation of Alkenyl Indoles

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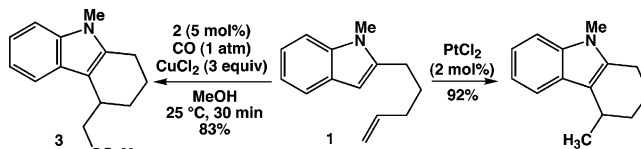
The transition metal-catalyzed addition of a carbonyl group to an olefin is a transformation of considerable importance that has been applied to the synthesis of both complex organic molecules¹ and commodity chemicals.² Industrial processes, most notably, olefin hydroformylation, typically involve the addition of a hydrogen atom and a carbonyl group across the C=C bond of the olefin.^{2,3} However, the catalytic addition of a carbon or heteroatom nucleophile and a carbonyl group across the C=C bond of an olefin represents a more desirable transformation for the synthesis of complex organic molecules. Indeed, effective palladium-catalyzed protocols for the alkoxylation/carboalkoxylation⁴ and amination/carboalkoxylation⁵ of unactivated olefins have been developed and applied to the synthesis of functionalized heterocycles. In contrast, the catalytic addition of a carbon nucleophile and a carbonyl group across the C=C bond of an olefin has not been realized.^{6,7} Here we report the palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles, which represents the first effective protocol for the catalytic addition of a carbon nucleophile and a carbonyl group across the C=C bond of an olefin.

We have recently reported the platinum(II)-catalyzed cyclization of 2-alkenyl indoles to form tetrahydrocarbazoles and related derivatives (Scheme 1).⁸ Although Pt(II) complexes catalyze the carbonylation of vinyl arenes,⁹ all our efforts to realize the platinum-catalyzed cyclization/carbonylation of 2-alkenyl indoles have been unsuccessful. Because Pd(II) alkyl complexes are reactive toward CO insertion^{1–7} and because Pd(II) complexes catalyze the oxidative cyclization of alkenyl indoles,^{10,11} we considered that Pd(II) complexes might catalyze the cyclization/carbonylation of 2-alkenyl indoles. Indeed, in an optimized procedure,¹² treatment of 1-methyl-2-(4-pentenyl)indole (**1**) with a catalytic amount of PdCl₂(CH₃CN)₂ (**2**) (5 mol %) and a stoichiometric amount of CuCl₂ (3 equiv) in methanol under CO (1 atm) at room temperature for 30 min led to the isolation of tetrahydrocarbazole **3** in 83% yield as a single regioisomer (Scheme 1).

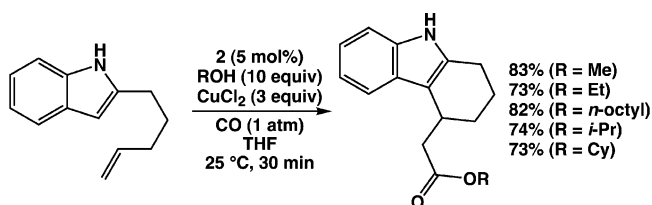
Unprotected, electron-rich, and electron-poor 2-(4-pentenyl)indoles underwent efficient palladium-catalyzed cyclization/carboalkoxylation (Table 1, entries 1–3). Palladium-catalyzed cyclization/carboalkoxylation of 2-(4-alkenyl)indoles tolerated substitution along the alkenyl chain and at the internal and cis-terminal olefinic positions (Table 1, entries 4–9). 2-(3-Alkenyl)indoles also underwent efficient, regioselective, and, in the case of 2-(3-alkenyl)indoles that possessed terminal olefinic substitution, highly stereospecific palladium-catalyzed cyclization/carboalkoxylation (Table 1, entries 10–12). In addition to 2-(4-alkenyl)- and 2-(3-alkenyl)indoles, 2-(5-hexenyl)-, 3-(3-butenyl)-, and 3-(4-pentenyl)indoles also underwent palladium-catalyzed cyclization/carboalkoxylation to form the corresponding tricyclic indole derivatives in moderate to good yield with excellent regioselectivity (Table 1, entries 13–15).

Effective palladium-catalyzed cyclization/carboalkoxylation of alkenyl indoles did not require methanol as solvent. For example, treatment of 2-(4-pentenyl)indole with a catalytic amount of **2** and

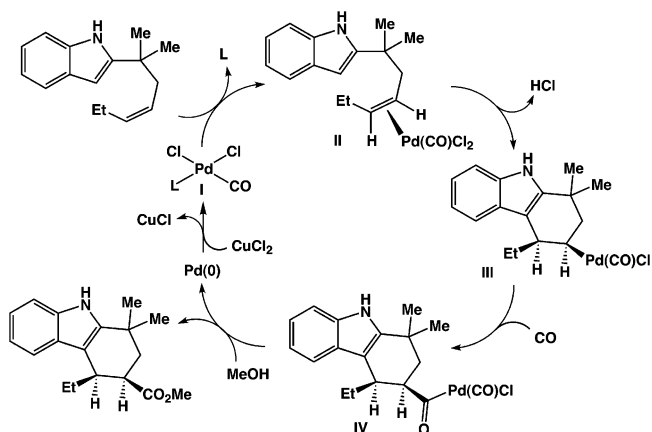
Scheme 1



Scheme 2



Scheme 3



a stoichiometric amount of CuCl₂ in THF that contained methanol (10 equiv) led to the isolation of the corresponding tetrahydrocarbazole in 83% yield (Scheme 2).¹² By employing this procedure, efficient palladium-catalyzed cyclization/carboalkoxylation of 2-(4-pentenyl)indole with ethanol, *n*-octanol, 2-propanol, and cyclohexanol was achieved (Scheme 2).

Because the migratory insertion of CO into an M–C bond occurs with retention of stereochemistry at the metal-bound carbon atom,¹³ the stereospecific cyclization of (*E*)- and (*Z*)-2-(3-hexenyl)indole (Table 1, entries 11 and 12) established the anti addition of the indole and palladium across the C=C bond of the olefin. This stereochemical outcome directly implicates a mechanism for palladium-catalyzed cyclization/carboalkoxylation involving attack of the indole on the palladium-complexed olefin of **II** (Scheme 3); subsequent loss of HCl would form the palladium alkyl intermediate **III**. α -Migratory insertion of CO into the Pd–C bond of **III** would form the palladium acyl complex **IV**, which could undergo methanolysis to release the tetrahydrocarbazole and form a palladium(0) complex. Oxidation of Pd(0) with Cu(II) would then regenerate the Pd(II) carbonyl complex **I** (Scheme 3).¹⁴ The 6-endo-

Table 1. Cyclization/Carboalkoxylation of Alkenyl Indoles Catalyzed by $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (**2**) (5 mol %) in the Presence of CuCl_2 (3 equiv) in Methanol at Room Temperature

entry	alkenyl indole	product	time (h)	yield (%) ^a
1			0.5	83
2	$\text{R}^1 = \text{OMe}, \text{R}^2 = \text{Me}$		0.5	86
3	$\text{R}^1 = \text{F}, \text{R}^2 = \text{H}$		0.5	74
4			0.5	84
5	$\text{X} = \text{CH}_2, \text{Y} = \text{C}(\text{CO}_2\text{Me})_2$		0.5	87
6	$\text{X} = \text{CO}, \text{Y} = \text{NMe}$		12	91
7			2.5	87
8			3.5	62 (≥50:1)
9			24	45 (≥50:1) ^b
10			0.5	76
11			2.5	92 (≥50:1)
12			3.0	84 (≥50:1)
13			24	74
14			42	58
15			3	85

^a Isolated material of >95% purity. ^b 10 mol % **2** employed.

trig cyclization of 1-methyl-3-(3-butenyl)indole (Table 1, entry 14) suggests that an analogous outer-sphere pathway is operative for the Pd(II)-catalyzed cyclization/carboalkoxylation of 3-alkenyl indoles.¹⁵

In summary, we have developed a mild and effective Pd(II)-catalyzed protocol for the cyclization/carboalkoxylation of alkenyl indoles. These transformations represent both the first examples of the catalytic addition of a carbon nucleophile and a carbonyl group across the C=C bond of an olefin and an efficient and selective route to the synthesis of functionalized polycyclic indole derivatives from simple precursors.

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Supporting Information Available: Experimental procedures and spectroscopic data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- ¹H NMR analysis of **2** in CD₃OD under CO (1 atm) revealed complete displacement of acetonitrile by CO. Therefore, **I** likely exists either as a dicarbonyl monomer (L = CO) or as a chloride-bridged dimer (L = PdCl₂-CO).
- Noteworthy is that the stereochemistry and mechanism of ring closure for the palladium-catalyzed cyclization/carboalkoxylation of 2-alkenyl indoles differs from the stereochemistry and mechanism observed for the Pd(OAc)₂-catalyzed oxidative cyclization of 3-alkenyl indoles.^{10a} This latter transformation proceeds with net syn addition of the indole and palladium to the olefin, presumably via C-H bond activation followed by β-migratory insertion of the olefin into the resulting Pd-C bond.^{10a}

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