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Platinum-Catalyzed Intramolecular Alkylation of Indoles with Unactivated Olefins

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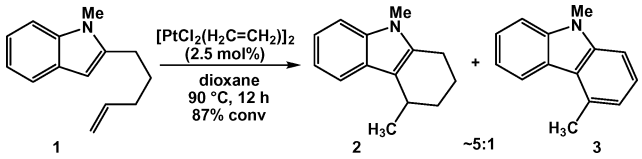
Fused polycyclic indoles including the carbazoles,[1] carbolines,[2] and their partially saturated counterparts represent a prominent class of heterocyclic compounds with varied and often potent biological activity.[3] As a result, considerable effort has been directed to the development of new and efficient methods for the synthesis of polycyclic indoles.[4] Intramolecular alkylation of an alkenyl indole represents an attractive route to the synthesis of polycyclic indoles. Unfortunately, effective alkylation of an indole with an olefin requires either an electron-deficient Michael acceptor[5] or prolonged heating under highly acidic conditions.[6] For these reasons, the development of an effective procedure for the alkylation of an indole with an unactivated olefin under mild conditions would be significant. Here, we report a mild, platinum-catalyzed protocol for the intramolecular alkylation of indoles with unactivated olefins.

Although Pd(II) complexes catalyze the intramolecular alkylation of alkenyl β-diketones and related substrates,[7,8] this catalyst system was ineffective for the alkylation of indoles.[9] We noted with interest a report of Maresca that documented the high reactivity of both Pt(II) olefin complexes toward outer-sphere nucelophilic attack and Pt(II) alkyl complexes toward protonolysis.[10] Because these steps constitute a potential catalytic cycle for the addition of a nucleophile to an unactivated olefin, we targeted simple Pt(II) complexes as catalysts for the alkylation of alkenyl indoles. To this end, treatment of 1-methyl-2-(4-pentenyl)indole (**1**) with a catalytic amount of $[PtCl_2(H_2C{=}CH_2)]_2$ (2.5 mol %) in dioxane at 90 °C for 12 h led to 87% conversion to form a ~5:1 mixture of the tetrahydrocarbazole **2** and carbazole **3** (Scheme 1). In an optimized procedure,[11] reaction of **1** (0.50 M) with a catalytic amount of $PtCl_2$ (2 mol %) in dioxane that contained a trace of HCl (5 mol %) at 60 °C for 24 h led to the formation of **2** as the exclusive product (≥96% by GC) in 92% isolated yield (Table 1, entry 1).[12]

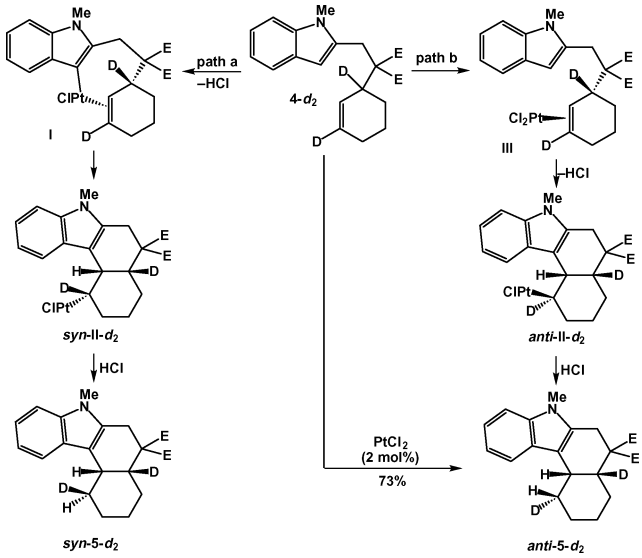
Platinum-catalyzed cyclization of 2-(4-pentenyl)indoles displayed excellent generality and tolerated substitution at each position of the 4-pentenyl chain including the internal and *cis*- and *trans*-terminal olefinic positions (Table 1, entries 1−11). Noteworthy was cyclization of the cyclohexenylethyl indole **4** (E = CO_2Me) to form tetracycle **5** in 82% yield as a single (cis:trans ≥ 50:1) diastereomer (Table 1, entry 9). The protocol was applicable to the synthesis of tetrahydro-β-carbolinones (Table 1, entries 12 and 13) and was effective for cyclization of unprotected indoles (Table 1, entries 8 and 13). Somewhat surprisingly, 2-(3-butenyl)indoles underwent platinum-catalyzed cyclization with exclusive 6-*endo*-trig regioselectivity (Table 1, entries 14 and 15).

Although we initially envisioned a mechanism for the alkylation of alkenyl indoles involving nucleophilic attack of the indole on a platinum-complexed olefin, this mechanism has not been documented for transition metal-catalyzed olefin hydroarylation. Rather, reported examples of olefin hydroarylation occur via initial activation of an aryl C−H bond followed by olefin β-migratory insertion.[9a,13] Given their respective stereochemical requirements, these inner-sphere and outer-sphere pathways can be distinguished by cyclization of **4**-d_2 (Scheme 2). For example, indole C−H bond activation followed by β-migratory insertion of **I** and protonolysis of the Pt−C bond of *syn*-**II**-d_2 with retention of stereochemistry[14] would form exclusively *syn*-**5**-d_2 (Scheme 2, path a). Conversely, attack of indole on the platinum-complexed olefin of **III** to form *anti*-**II**-d_2 followed by stereospecific protonolysis would form exclusively *anti*-**5**-d_2 (Scheme 2, path b). Treatment of **4**-d_2 with a catalytic amount of $PtCl_2$ (2 mol %) in dioxane at 60 °C for 18 h formed *anti*-**5**-d_2 in 73% isolated yield as the exclusive product (Scheme 2), which established a mechanism for indole alkylation involving nucleophilic attack of the indole on a platinum-complexed olefin (Scheme 2, path b).[15]

Scheme 1



Scheme 2



The absence of deuterium scrambling in the conversion of **4**-d_2 to *anti*-**5**-d_2 argued against reversible β-hydride elimination/addition prior to protonolysis. This observation suggested that the stereogenic center generated via C−C bond formation was retained in the product and pointed to the feasibility of asymmetric indole alkylation. In this regard, it was also significant that cationic platinum

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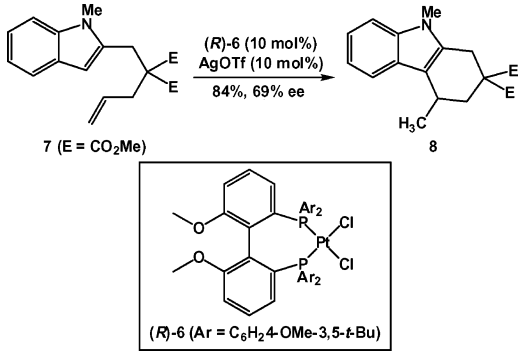
Table 1. Cyclization of 2-Alkenyl Indoles Catalyzed by $PtCl_2$ (2 mol %) in Dioxane That Contained a Trace (5 mol %) of HCl at 60 °C for 18−24 h (E = CO_2Me)

entry	alkenyl indole	polycycle	yield (%)
1	R_1 = H, R_2 = Me (1)	2	92
2	R_1 = H, R_2 = Bn		85
3	R_1 = OMe, R_2 = Me		94
4	cis		80
5	trans		81
6			91
7	R = Me		91
8	R = H		87[a]
9	4	5	82 (≥50:1)
10	R^1 = R^2 = CO_2Me (7)	8	90
11	R^1 = CO_2Me, R^2 = H		98 (2:1)
12	R = Me		80
13	R = H		90
14	R = Me		89[b]
15	R = H		74

[a] Contained a small amount (~3%) of a second isomer. [b] Reaction run at 90 °C for 47 h.

bis(phosphine) complexes catalyzed the cyclization of alkenyl indoles. In a preliminary screen of enantiomerically pure platinum bis(phosphine) catalysts,[11] the hindered platinum BIPHEP complex (*R*)-**6** proved effective for the asymmetric alkylation of alkenyl indoles (Scheme 3). For example, reaction of **7** with a catalytic 1:1 mixture of (*R*)-**6** and AgOTf at 60 °C for 24 h led to the isolation of **8** in 84% yield with 69% ee (Scheme 3).

Scheme 3



In summary, we have developed a mild and effective platinum-catalyzed procedure for the intramolecular alkylation of indoles with unactivated olefins. We have established a mechanism for indole alkylation involving nucleophilic attack on a platinum-complexed olefin, and we have demonstrated the feasibility of asymmetric carbocyclization employing this protocol.

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

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(11) See Supporting Information for details concerning optimization.
(12) Treatment of 1-methyl-2-(4-methyl-4-pentenyl)indole (Table 1, entry 6) with HCl (30 mol %) in dioxane at 60 °C in the absence of platinum formed no detectable amounts of 4,4,9-trimethyl-2,3,4,9-tetrahydro-1*H*-carbazole after 24 h.
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(15) The anti relationship between the indole carbon atom and the secondary proton β- to the indole of *anti*-**5**-d_2 was unambiguously determined by ^{1}H NMR spectroscopy (see Supporting Information).

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