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Palladium-Catalyzed Synthesis of *N-tert*-Prenylindoles

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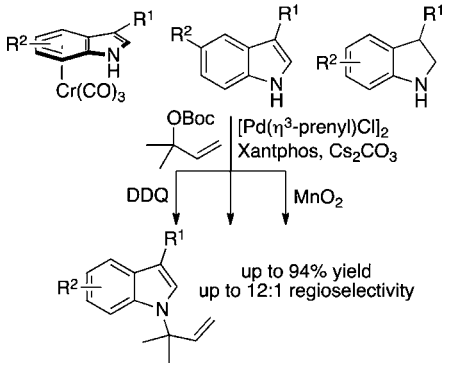
ABSTRACT



Palladium-catalyzed *N-tert*-prenylations of indoles, tricarbonylchromium-activated indoles, and indolines that occur in high yields (up to 94%) with high *tert*-prenyl-to-*n*-prenyl selectivity (up to 12:1) are reported.

Prenylated indoles are found in structurally diverse fungal, plant, and bacterial natural products[1] and have been the focus of many recent synthetic[2] and biosynthetic studies.[3] The diversity of these natural products stems from nature's ability to incorporate the prenyl group throughout the indole core as either an *n*-prenyl (prenyl) or *tert*-prenyl (reverse prenyl) moiety. Synthetic chemists have developed a variety of methods to prepare both prenylated and *tert*-prenylated indoles that exhibit promising medicinal properties.[1−3] Despite these efforts, the synthetic methodology necessary to access certain classes of *tert*-prenylated indoles remains underdeveloped.

N-tert-Prenylated indoles (Figure 1) are a unique class of prenylated indoles in which the prenyl group is linked to the indole core through a C−N bond. *N-tert*-Prenylated indoles and analogs containing oxidized prenyl moieties exhibit an array of medicinal properties including activation of insulin receptors and cytotoxicitiy toward cancer cell lines, as well as antiinflammatory, antimycobacterial, and antifungal activities.[4]

Current synthetic routes to *N-tert*-prenylated indoles involve (1) multiple nonstrategic redox steps, (2) the use

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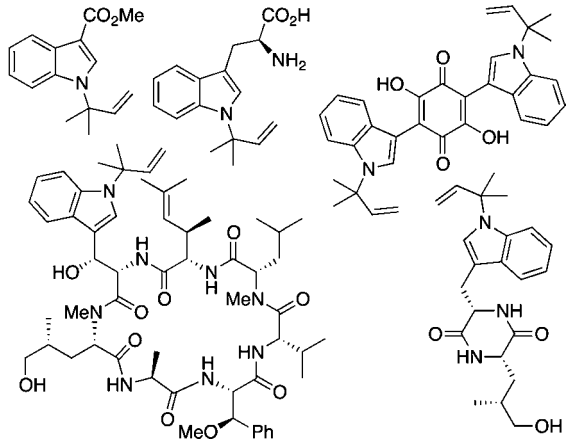


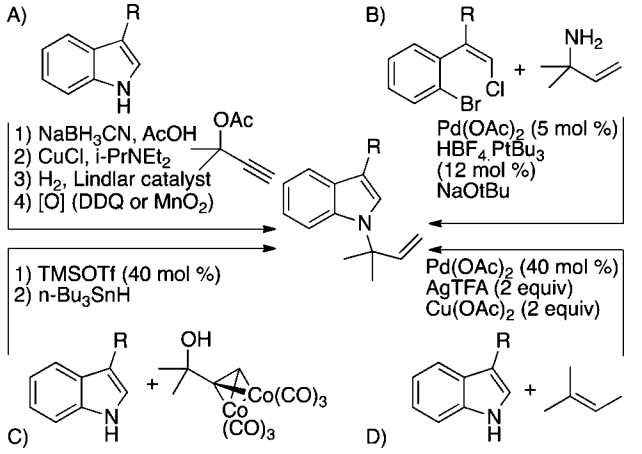
Figure 1. Examples of *N-tert*-prenylindole natural products.

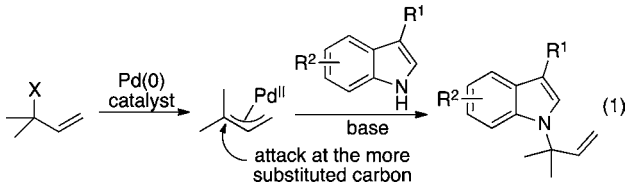
of prefunctionalized starting materials, or (3) high loadings of a precious metal catalyst and metal co-oxidants (Scheme 1). The traditional, four-step synthetic sequence to generate *N-tert*-prenylated indoles includes reduction of the indole to an indoline, Cu(I)-catalyzed propargylic substitution, partial reduction of the alkyne to an alkene, and oxidation of the *N-tert*-prenylated indoline to the corresponding indole (Route A).[5] In 2007, Willis et al. reported a tandem Pd-catalyzed synthesis of *N-tert*-prenylated indoles from 2-methyl-3-butene-2-amine and 2-bromo-β-chlorostyrenes by a sequence of aryl amination and alkenyl amination (Route B).[6] In 2011, Nishikawa et al. reported the *N-tert*-prenylation of methyl indole-3-acetate by alkylation with the dicobalthexacarbonyl complex of 2-methyl-3-butyn-2-ol in the presence of TMSOTf, followed by reduction and decomplexation with *n*-Bu_3SnH (Route C).[7]

To date, only one direct *N-tert*-prenylation of indoles has been reported. In 2009, Baran et al. reported a direct synthesis of *N-tert*-prenylated indoles by Pd-mediated C−H functionalization of 2-methyl-2-butene with indoles (Route D).[8] The direct C−H functionalization 2-methyl-2-butene enables the synthesis of *N-tert*-prenylated indoles from a broad array of readily accessible indoles, but the synthetic utility and practicality of this strategy remain limited because high loadings of the Pd catalyst (20−40 mol %) and a Ag co-oxidant (2.0−2.5 equiv) are required.

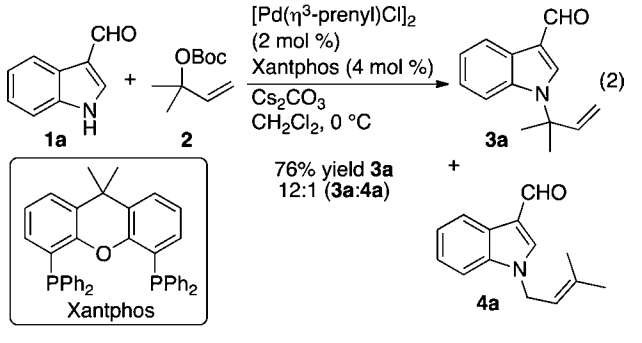
At the outset of this project, we sought to develop strategies to form *N-tert*-prenylindoles with a range of electronic properties that minimize the number of nonstrategic redox steps and employ practical loadings of catalyst precursors. Here, we report syntheses of *N-tert*-prenylated indoles by a Pd-catalyzed allylic alkylation approach (eq 1).[9] Three distinct protocols for the synthesis of *N-tert*-prenylindoles are described, using indole, (η^6-indole)-$Cr(CO)_3$, and indoline nucleophiles in the presence of the same Pd catalyst prepared *in situ* from readily available precursors. These reactions require loadings of the Pd catalyst that are up to 10 times less than that required for previously reported direct *N-tert*-prenylations of indoles.

Scheme 1. Strategies To Form *N-tert*-Prenylated Indoles





To establish the viability of our allylic substitution approach, we conducted reactions of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate with indole-3-carboxaldehyde in the presence of Cs_2CO_3 and catalysts generated from a variety of Pd precursors and bisphosphine ligands (Supporting Information (SI)). We found that Pd complexes of bisphosphine ligands with wide natural bite angles catalyze the *N*-prenylation of indole-3-carboxaldehyde **1a** with high *tert*-prenyl/*n*-prenyl selectivity (9:1 to 13:1). The reaction of **1a** with *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2** in the presence of a catalyst generated from [Pd(η^3-prenyl)Cl]$_2$ and Xantphos occurred with the best combination of yield (76% isolated yield of **3a**) and *tert*-prenyl/*n*-prenyl selectivity (12:1) (eq 2).

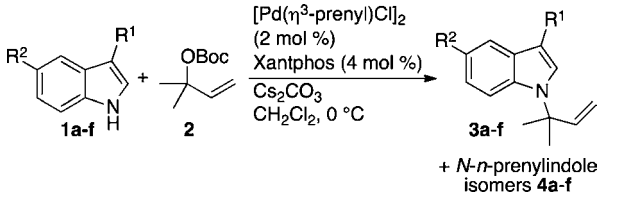


We then evaluated these conditions for palladium-catalyzed *N-tert*-prenylation in reactions of a series of indoles containing electron-withdrawing groups at either the 3- or 5-position with carbonate **2**. The data from these experiments are summarized in Table 1. As shown in entries 1−4, 3-substituted indoles **1a**−**1d** (R^1 = CHO,

C(O)Me, CO_2Me, or CN) reacted with carbonate **2** to form *N-tert*-prenylindoles **3a**–**3d** in good-to-excellent yield with 10:1 or greater regioselectivity (**3:4**). *N-tert*-Prenylindoles **3a** and **3b** were isolated in 76% and 65% yield as single constitutional isomers. In contrast, *N-tert*-prenylindoles **3c** and **3d** were not readily separable from the *N-n*-prenyl isomers **4c** and **4d**. These products were isolated as 12:1 mixtures of the *N-tert*- and *N-n*-prenylindole isomers.

The presence of electron-withdrawing substitution at the 3-position of the indole core is not a strict requirement under our reaction conditions. Reactions of 5-cyanoindole **1e** and 5-nitroindole **1f** with carbonate **2** occurred to form mixtures of *N*-prenylindole products **3e**–**f** and **4e**–**f** in 40% and 62% yield with 7:1 *tert*-prenyl/*n*-prenyl selectivity (entries 5 and 6). However, reactions of indoles lacking electron-withdrawing substitutents and reactions of 2-substituted indoles did not form *N*-prenylindole products.

Table 1. Scope of Pd-Catalyzed *N-tert*-Prenylation of Indoles[a]



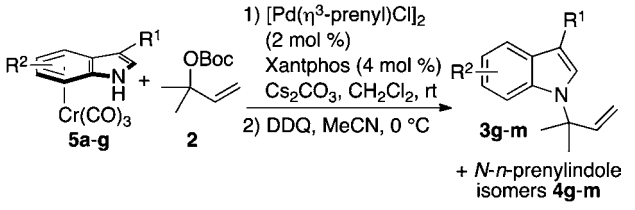
entry	1	R^1	R^2	3	yield 3 + 4 (%)[b]	3:4[c]
1	**1a**	CHO	H	**3a**	76[d]	12:1
2	**1b**	C(O)Me	H	**3b**	65[d]	10:1
3	**1c**	CO_2Me	H	**3c**	90	12:1
4	**1d**	CN	H	**3d**	94	12:1
5[e]	**1e**	H	CN	**3e**	40	7:1
6[e]	**1f**	H	NO_2	**3f**	62	7:1

[a] For detailed reaction conditions, see SI. [b] Isolated yield of **3** + **4**. [c] Determined by ^1H NMR spectroscopy. [d] Isolated yield of **3**. [e] Reactions run at rt.

The disparate reactivity of indoles with and without electron-withdrawing substituents suggested that indolate anions of the electron-deficient indoles were primarily responsible for nucleophilic attack on a prenylpalladium(II) intermediate. Thus, the difference in the relative acidity of the indole N–H is likely responsible for the difference in reactivity between more acidic, electron-deficient indoles and less acidic, electron-rich indoles.[10] Since η^6-coordination of metal carbonyl complexes to arenes is known to increase the acidity of benzylic C–H bonds,[11] we hypothesized that η^6-coordination of a metal carbonyl complex to the indole core would similarly increase the acidity of the indole N–H bond by reducing the electron density in the indole π-system.

We prepared a series of (η^6-indole)$Cr(CO)_3$ complexes of electron-rich indoles and evaluated their reactivity as nucleophiles in Pd-catalyzed prenylation reactions. Reactions of (η^6-indole)$Cr(CO)_3$ complexes of indoles **5a**–**g** with carbonate **2** are summarized in Table 2. As shown in entries 1–3, (η^6-indole)$Cr(CO)_3$ complexes prepared from indole, 3-methylindole, and methyl indole-3-acetate (**5a**–**c**) reacted with carbonate **2** to form *N-tert*-prenylindoles **3g**–**3i** after oxidative decomplexation with DDQ. These one-pot, two-step transformations gave the *N-tert*-prenylindoles **3g**–**i** and *N-n*-prenylindoles **4g**–**i** in 62–86% yield with 6:1 to 9:1 *tert*-prenyl/*n*-prenyl selectivity. Reactions of (η^6-indole)$Cr(CO)_3$ complexes prepared from 4-MeO-, 5-MeO-, and 6-MeO-indole also occurred in moderate to good yields with high *tert*-prenyl/*n*-prenyl selectivities (entries 4–6). The reactions of (η^6-indole)$Cr(CO)_3$ complexes **5d**–**f** with **2** and subsequent decomplexation formed *N-tert*-prenylindoles **3j**–**l** and *N-n*-prenylindoles **4j**–**l** in 51–78% yield and 7–8:1 *tert*-prenyl/*n*-prenyl selectivity. In contrast, the prenylation of (η^6-7-MeO-indole)$Cr(CO)_3$ **5g** with **2** occurred with >20:1 selectivity favoring the *N-n*-prenylindole isomer **4m** (entry 7).

Table 2. Scope of Pd-Catalyzed *N-tert*-Prenylation of (η^6-Indole)$Cr(CO)_3$ Complexes[a]



entry	5	R^1	R^2	3	yield 3 + 4 (%)[b]	3:4[c]
1	**5a**	H	H	**3g**	86	8:1
2	**5b**	Me	H	**3h**	75	8:1
3	**5c**	CH_2CO_2Me	H	**3i**	78	9:1
4	**5d**	H	4-MeO	**3j**	78	7:1
5	**5e**	H	5-MeO	**3k**	51	8:1
6	**5f**	H	6-MeO	**3l**	72	7:1
7	**5g**	H	7-MeO	**3m**	46	<1:20

[a] For detailed reaction conditions, see SI. [b] Isolated yield of **3** + **4**. [c] Determined by ^1H NMR spectroscopy.

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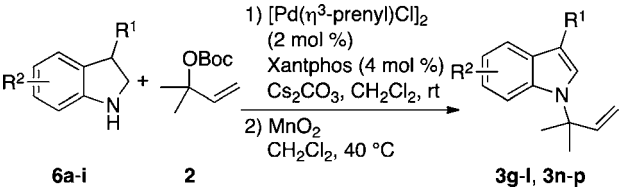
The synthesis of *N-tert*-prenylindoles from electron-rich indole precursors is enabled by the markedly different electronic properties of the corresponding (η^6-indole)Cr-$(CO)_3$ complexes. The utility of these complexes is, however, inherently limited by the need for stoichiometric quantities of chromium. In addition, the synthesis of (η^6-indole)Cr-$(CO)_3$ complexes from indoles containing even weakly deactivating groups is challenging. For example, standard procedures for the synthesis of (η^6-indole)Cr$(CO)_3$ complexes formed (η^6-5-bromoindole)Cr$(CO)_3$ in $< 5\%$ yield.

We conducted the reactions of indolines with carbonate **2** under the assumption that the increased nucleophilicity of the indoline nitrogen would enable us to synthesize *N-tert*-prenylindoles with a greater range of electronic character after oxidation (Table 3).[12] Indoline, 3-methylindoline, methyl indoline-3-acetate, and 3-phenylindoline react with carbonate **2** to form **3g**–**i** and **3n** after oxidation of the intermediate *N-tert*-prenylindolines with MnO_2 (entries 1–4). The reactions occur with 5–6:1 *tert*-prenyl/*n*-prenyl selectivity, and the *N-tert*-prenylindolines are readily separated. *N-tert*-Prenylindoles **3g**–**i** and **3n** were isolated in 43–80% yield over two steps as single constitutional isomers. Reactions of 4-MeO-, 5-MeO-, and 6-MeO-indolines with **2** occurred with 2–4:1 selectivity, and subsequent oxidation gave *N-tert*-prenylindoles **3j**–**l** in 25–60% yield (entries 6–8) as single constitutional isomers.

The sequence of *N*-prenylation of indolines followed by oxidation to the corresponding indoles allowed us to form *N-tert*-prenylindoles that were not accessible via the approaches shown in Tables 1 and 2. Reactions of protected tryptamine derivatives, 3-phenylindole, and 5-bromoindole with carbonate **2** either did not occur in high yields or the corresponding (η^6-indole)Cr$(CO)_3$ complexes were difficult to isolate. However, reactions of 3-phenylindoline **6d**, indoline **6e** ($R^1 = (CH_2)_2NPhth$), and 5-bromoindoline **6i** with **2** occurred with 4–5.5:1 *tert*-prenyl/*n*-prenyl selectivity (entries 4, 5, and 9). After oxidation of the intermediate *N-tert*-prenylindolines, the *N-tert*-prenylindoles **3n**–**p** were isolated in 47–64% yield over two steps.

In summary, we have developed three strategies based on Pd-catalyzed allylic alkylation reactions to generate *N-tert*-prenylindoles. In the presence of the same Pd catalyst, good yields and high regioselectivity are observed for three distinct classes of nucleophiles. Direct *N-tert*-prenylations of electron-deficient indoles and indolines occur readily, while *N-tert*-prenylations of electron-rich indoles are facilitated by complexation with chromium. Straightforward procedures for oxidative decomplexation of the chromium carbonyl fragment from the (η^6-*N-tert*-prenylindole)Cr-$(CO)_3$ intermediates and oxidation of the *N-tert*-prenylindolines provide access to electron-rich *N-tert*-prenylindoles in moderate to good yields. Thus, *N-tert*-prenylindoles with a broad range of substitution and electronic character can be accessed through these complementary approaches. Efforts to extend these *tert*-prenylation methods to additional heterocyclic nucleophiles are ongoing.

Table 3. Scope of Pd-Catalyzed *N-tert*-Prenylation of Indolines[a]



entry	**6**	R^1	R^2	**3**	yield **3** (%)[b]	*tert*-/*n*-prenyl[c]
1	**6a**	H	H	**3g**	80	6:1
2	**6b**	Me	H	**3h**	57	5:1
3	**6c**	CH_2CO_2Me	H	**3i**	43	5:1
4	**6d**	Ph	H	**3n**	47	5:1
5	**6e**	$(CH_2)_2NPhth$	H	**3o**	47	4:1
6	**6f**	H	4-MeO	**3j**	54	4:1
7	**6g**	H	5-MeO	**3k**	26	2:1
8	**6h**	H	6-MeO	**3l**	60	5:1
9	**6i**	H	5-Br	**3p**	64	5.5:1

[a] For detailed reaction conditions, see SI. [b] Isolated yield of **3** over two steps. [c] Ratio of *N-tert*-prenylindoline/*N-n*-prenylindoline determined by ^1H NMR spectroscopy.

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Supporting Information Available. Experimental procedures, supporting tables, and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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