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

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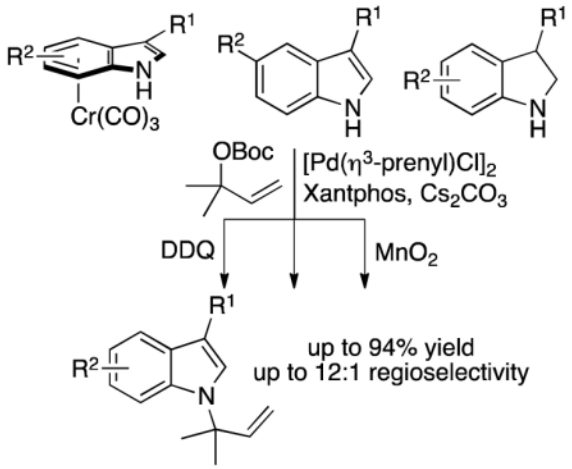
Abstract



Palladium-catalyzed *N-tert*-prenylation 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 carbon-nitrogen bond. *N-tert*-Prenylated indoles and analogs containing oxidized prenyl moieties exhibit an array of medicinal properties including activation of insulin receptors, cytotoxicitiy toward cancer cell lines, as well as antiinflammatory, antimycobacterial, and antifungal activities.[4]

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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.

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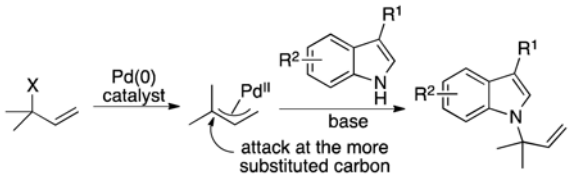
Current synthetic routes to *N-tert*-prenylated indoles involve 1) multiple non-strategic redox steps, 2) the use of pre-functionalized starting materials, or 3) high loadings of a precious metal catalyst and metal co-oxidants (Scheme 1). The traditional, four-step synthetic sequence to generate *N-tert*-prenylated 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 and co-workers 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 arylamination and alkenyl amination (Route B).[6] In 2011, Nishikawa and co-workers 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 and co-workers 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 remains limited because high loadings of the palladium catalyst (20–40 mol %) and a silver 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 non-strategic redox steps and employ practical loadings of catalyst precursors. Here, we report syntheses of *N-tert*-prenylated indoles by a palladium-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 palladium catalyst prepared *in situ* from readily available precursors. These reactions require loadings of the palladium catalyst that are up to ten times less than required for previously reported direct *N-tert*-prenylations of indoles.



(eq 1)

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). We found that palladium 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).

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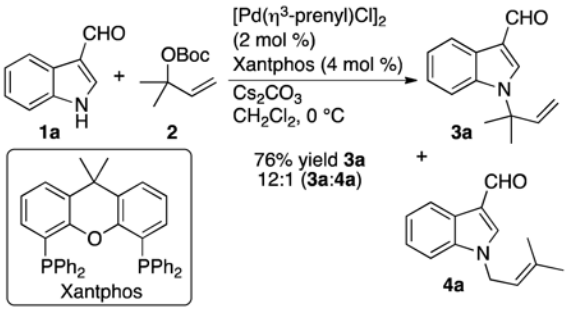

(eq 2)

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-position or the 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 seperable from the *N-n*-prenyl isomers **4c** and **4d**. These products were isolated as 12:1 mixtures of the *N-tert*-prenylindole 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 **3ef** 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.

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 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*-

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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).

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 synthesis of (η^6-indole)Cr(CO)$_3$ complexes formed (η^6-5-bromoindole)Cr(CO)$_3$ in less than 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 = $(CH_2)_2$NPhth), 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 palladium-catalyzed allylic alkylation reactions to generate *N-tert*-prenylindoles. In the presence of the same palladium 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.

Supplementary Material

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References

1. For recent reviews, see: Li SM. Nat Prod Rep. 2010; 27:57. [PubMed: 20024094] Lindel T, Marsch N, Adla SK. Top Curr Chem. 2012; 309:67. [PubMed: 21915778]
2. For a recent review, see: Miller K, Williams RM. Chem Soc Rev. 2009; 38:3160. [PubMed: 19847349] For selected recent examples, see: Scheerer JR, Laws SW. J Org Chem. 2013; 78:2422. [PubMed: 23360221] Trost BM, Malhotra S, Chan WH. J Am Chem Soc. 2001; 133:7328. [PubMed: 21520958] Finefield JM, Sherman DH, Tsukamoto S, Williams RM. J Org Chem. 2011; 76:5954. [PubMed: 21504234] Ignatenko VA, Zhang P, Viswanathan R. Tetrahedron Lett. 2011; 52:1269.Finefield JM, Williams RM. J Org Chem. 2010; 75:2785. [PubMed: 20359229] Grant CD, Krische MJ. Org Lett. 2009; 11:4485. [PubMed: 19764718] Miller KA, Tsukamoto S, Williams RM. Nature Chem. 2009; 1:63. [PubMed: 20300443] Baran PS, Guerrero CS, Corey EJ. J Am Chem Soc. 2003; 125:5628. [PubMed: 12733890]
3. For selected recent examples, see: Haynes SW, Gao X, Tang Y, Walsh CT. ACS Chem Biol. 2013; 8:741. [PubMed: 23330675] Rudolf JD, Wang H, Poulter CD. J Am Chem Soc. 2013; 135:1895. [PubMed: 23301871] Chen J, Morita H, Wakimoto T, Mori T, Noguchi H, Abe I. Org Lett. 2012; 14:3080. [PubMed: 22642693] Yin S, Yu X, Wang Q, Liu XQ, Li SM. Appl Microbiol Biotechnol. 2013; 97:1649. [PubMed: 22660767] Li S, Finefield JM, Sunderhaus JD, McAfoos TJ, Williams RM, Sherman DH. J Am Chem Soc. 2012; 134:788. [PubMed: 22188465] Yin W-B, Xie X-L, Matuschek M, Li S-M. Org Biomol Chem. 2010; 8:1133. [PubMed: 20165805]
4. For activity as insulin receptor modulators see: Webster NJG, Park K, Pirrung MC. ChemBioChem. 2003; 4:379. [PubMed: 12740809] For a report of activity against cancer cell lines: Yamamoto Y, Nishimura KI, Kiriyama N. Chem Pharm Bull. 1976; 24:1853.For anti-inflammatory activity, see: Renner MK, Shen YC, Cheng XC, Jensen PR, Frankmoelle W, Kauffman CA, Fenical W, Lobkovsky E, Clardy J. J Am Chem Soc. 1999; 121:11273.For antimycobacterial activity, see: Schmitt EK, Riwanto M, Sambandamurthy V, Roggo S, Miault C, Zwingelstein C, Krastel P, Noble C, Beer D, Rao SPS, Au M, Niyomrattanakit P, Lim V, Zheng J, Jeffery D, Pethe K, Camacho LR. Angew Chem Int Ed. 2011; 50:5889.For antifungal activity, see: Levy LM, Cabrera GM, Wright JE, Seldes AM. Phytochem. 2000; 54:941.
5. a) Sugiyama H, Yokokawa F, Aoyama T, Shioiri T. Tetrahedron Lett. 2001; 42:7277.b) Sugiyama H, Shioiri T, Yokokawa F. Tetrahedron Lett. 2002; 43:3489.c) Della Salla G, Capozzo D, Izzo I, Giordano A, Iommazzo A, Spinella A. Tetrahedron Lett. 2002; 43:8839.d) Yokokawa F, Sugiyama H, Aoyama T, Shioiri T. Synthesis. 2004; 9:1476.
6. Fletcher AJ, Bax MN, Willis MC. Chem Commun. 2007:4764.
7. Isaji H, Nakazaki A, Isobe M, Nishikawa T. Chem Lett. 2011; 40:1079.
8. Luzung MR, Lewis CA, Baran PS. Angew Chem Int Ed. 2009; 48:7025.
9. For a related synthesis of N-tert-prenylindole by Rh-catalyzed amination of tertiary allylic trichloroacetimidates, see: Arnold JS, Cizio GT, Nguyen HM. Org Lett. 2011; 13:5576–5579. [PubMed: 21958228] For related palladium-catalyzed tert-prenylations of nitrogen nucleophiles, see: Johns AM, Liu Z, Hartwig JF. Angew Chem Int Ed. 2007; 46:7259.
10. For similar trends in reactivity of indoles, see: Stanley LM, Hartwig JF. Angew Chem Int Ed. 2009; 48:7841.
11. For books, see: Hartwig JF. Organotransition Metal Chemistry: From Bonding to Catalysis. University Science BooksSausalito, CA2010EP. Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis; Kündig. Springer-VerlagBerlin2004For reviews, see: Rosillo M, Dominguez G, Perez-Castells J. Chem Soc Rev. 2007; 36:1589. [PubMed: 17721584] Kalinin VN. Russ Chem Rev. 1987; 56:682.For selected examples, see: McGrew GI, Stanciu C, Shang J, Carroll PJ, Dreher SD, Walsh PJ. Angew Chem Int Ed. 2012; 51:11510.Zhang J, Stanciu C, Wang B, Hussain MM, Da CS, Carroll PJ, Dreher SD, Walsh PJ. J Am Chem Soc. 2011; 133:20552. [PubMed: 22047504] Castaldi MP, Gibson SE, Rudd M, White AJP. Chem Eur J. 2006; 12:138.

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[PubMed: 16278918] Koide H, Hata T, Uemura M. J Org Chem. 2002; 67:1929. [PubMed: 11895413] Kalinin VN, Cherepanov IA, Moiseev SK. J Organomet Chem. 1997; 536–537:437.Kalinin VN, Cherepanov IA, Moiseev SK. Metalloorg Khim. 1991; 4:177.Organomet Chem USSR. 1991; 4:94.

12. For Ir-catalyzed N-allylation of indolines and oxidation to the corresponding N-allylindoles, see: Liu W-B, Zhang X, Dai L-X, You S-L. Angew Chem Int Ed. 2012; 51:5183.

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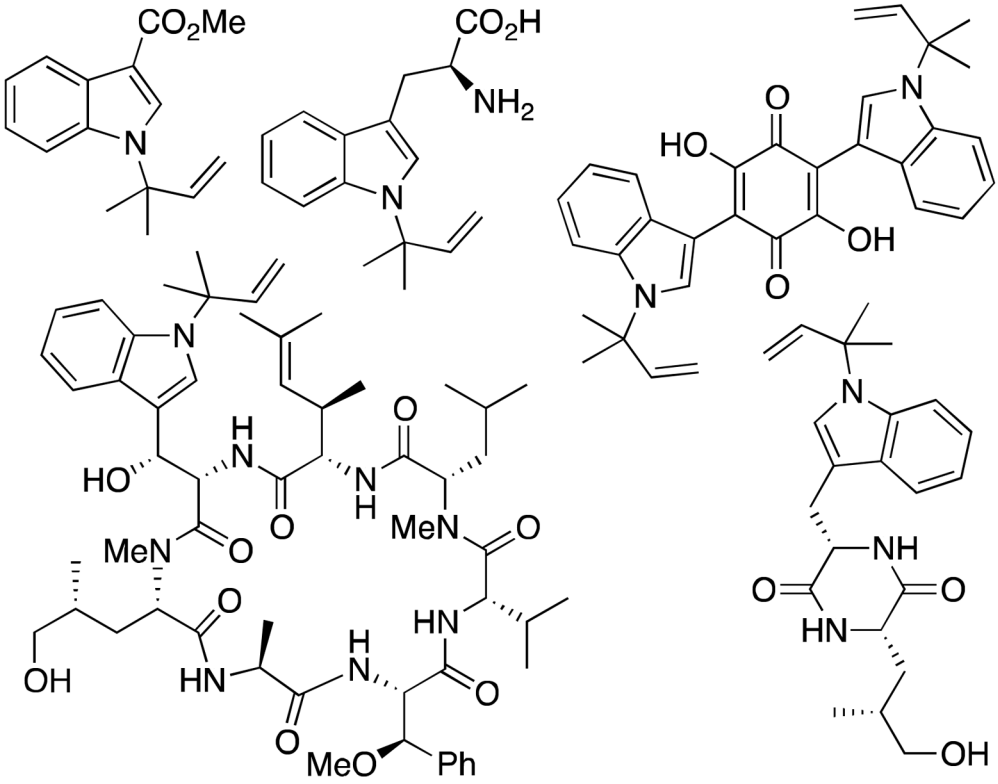

Figure 1.
Examples of *N-tert*-Prenylindole Natural Products

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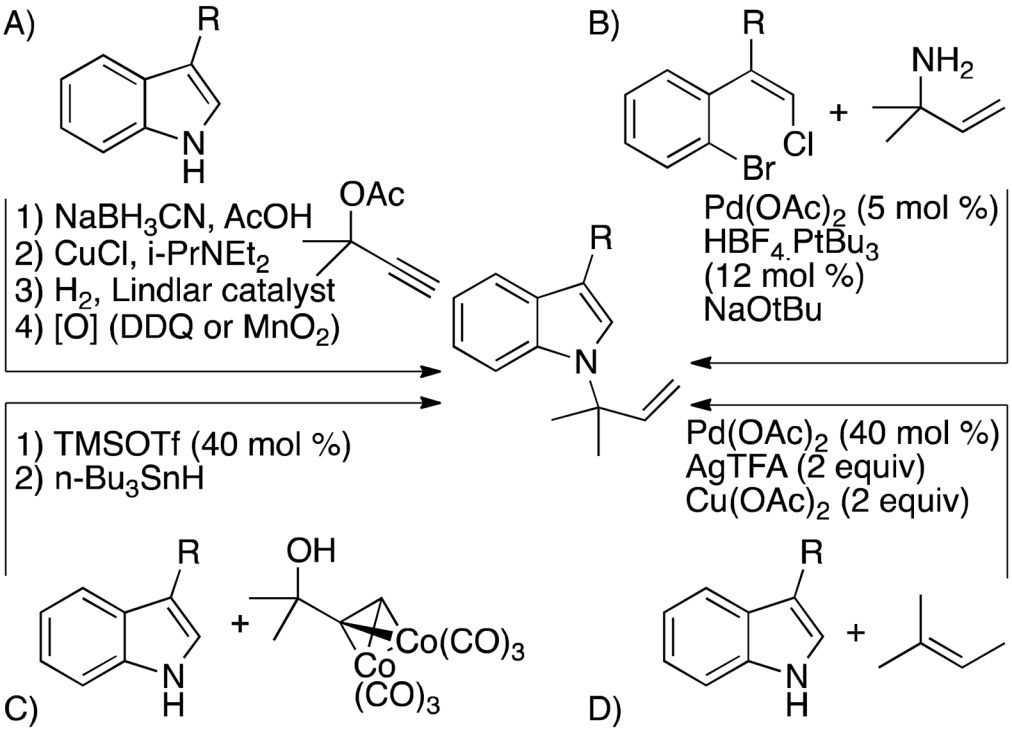

Scheme 1.
Strategies to Form *N-tert*-Prenylated Indoles

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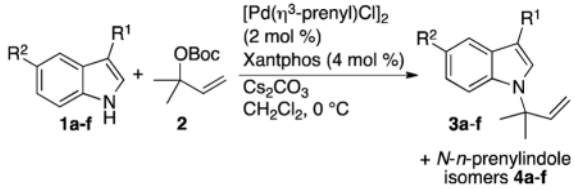
Table 1

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 Supporting Information.

[b]Isolated yield of **3** + **4**.

[c]Determined by ^{1}H NMR spectroscopy.

[d]Isolated yield of **3**.

[e]Reactions run at room temperature.

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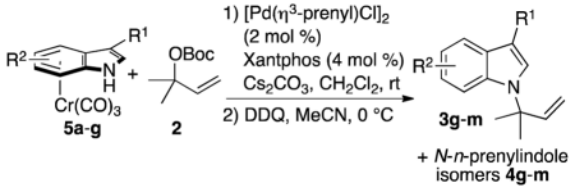
Table 2

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 Supporting Information.

[b]Isolated yield of **3** + **4**.

[c]Determined by ^{1}H NMR spectroscopy.

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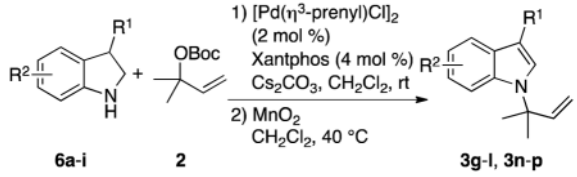
Table 3

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



entry	6	R^1	R^2	3	yield 3 (%)[c]	*tert-*: *n*-prenyl[b]
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 Supporting Information.

[b]Ratio of *N-tert*-prenylindoline:*N-n*-prenyl indoline determined by ^{1}HNMR spectroscopy.

[c]Isolated yield of **3** over two steps.