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Direct, Chemoselective *N*-*tert*-Prenylation of Indoles via C–H Functionalization

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Prenylated indole alkaloids have long been targets for total synthesis, possessing a broad range of medicinal properties and intriguing architectures.¹ Our interest in this family began with the stephacidin family of indole alkaloids² during which the fortuitous finding shown in Figure 1A was made. Thus, in 2003, during an attempt to convert *N*-Boc-tryptophan methyl ester (**1**) to the C-2 prenylated tryptophan **2** directly using 2-methyl-2-butene *via* electrophilic palladation³ and olefin capture, we instead observed small amounts (<10%) of a non-polar compound identified as *N*-*tert*-prenylated indole **3**. Whereas many elegant methods have been invented for accomplishing the direct prenylation of indoles,^{4–7} no methods currently exist for the direct *N*-*tert*-prenylation of indoles (Figure 1B).⁸ Inspired by our initial findings (Figure 1A), this communication delineates a mild, highly chemoselective, scalable, and one-step route to these biologically relevant motifs *via* C–H functionalization.

The only known route to *N*-*tert*-prenylated indoles requires a four step sequence, three of which involve non-strategic redox-fluctuations⁹ (Figure 1C): 1) reduction of the indole to the indoline, 2) propargyl substitution *via* Cu^I-catalysis, 3) oxidation back to the indole, 4) and finally Lindlar reduction of the alkyne to the olefin. This chemistry has been successfully incorporated into a number of total syntheses.⁹

Building off of our initial observations (Figure 1A), we envisioned a direct, one-step procedure to synthesize *N*-*tert*-prenylated indoles without the use of pre-functionalized starting materials and superfluous redox steps – well known tenets of C–H functionalization logic.¹⁰ Such a strategy would be orthogonal to routes that involve nucleophilic prenylation that in this case would not be applicable.¹¹ Specifically, C–H activation of indoles are known to occur at C-2 or C-3, involving the direct coupling of arenes¹² and electron-deficient olefins¹³ and annulations,^{2,9,14} even in the presence of free N-H indoles.¹⁵ Pd-catalyzed allylic C–H aminations¹⁶ have been accomplished; however, there have been only a few reports involving the intermolecular coupling of amines and allylic olefins.¹⁷ The fundamental mechanistic insights and reaction designs of Stahl^{18a} and Yu¹⁹ were instrumental in transforming our esoteric 2003 observations into a useful method for synthesis.

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Selected results of extensive optimization with the *N*-Phth-tryptophan methyl ester **4** are outlined in Table 1. The work of Stahl pointed us to the use of CH₃CN as a solvent while research from the Yu lab inspired the use of Cu(OAc)₂ and AgOTf in concert. Ultimately, we found that 40 mol% of a Pd source (either 40 mol% Pd(OAc)₂ or 20 mol% Pd₂dba₃•CHCl₃) with 30 eq of 2-methyl-2-butene in the presence of Cu(OAc)₂ and an Ag^I source (AgOTf or AgTFA) as the co-oxidants in CH₃CN was optimal for this transformation.

With these conditions in hand, the synthetic utility could be immediately demonstrated by applying it to known intermediates in total synthesis (Figure 2). For example, compound **3**, an intermediate in the okaramine N synthesis^{9c} requiring the aforementioned four step sequence (50% overall yield), could be obtained in 66% yield on a gram-scale and in a single step with no other regioisomers observed under these conditions. Similarly, *N*-Cbz-tryptophan methyl ester (**6**) was converted to **7**, an intermediate towards the synthesis of the rufomycins,^{9b} in 61% yield (gram-scale) as compared to 60% over 4 steps. Indole 3-carboxaldehyde (**8**) was prenylated to give **9** on a gram-scale, an intermediate in a cyclomarin synthesis,^{9d} in 68% yield versus 70% (4-step sequence from indoline). The use of methyl acrylate^{18a} and 3-NO₂-pyridine^{12b,14} (possibly as stabilizing ligands of Pd⁰) was needed when an electron-withdrawing group was occupied at C-3. The natural product **11**, isolated from *Aporpium caryae*,²⁰ has been synthesized previously starting from indoline^{9a} and indole^{9e} in 60% yield over 5 steps and 34% over 7 steps, respectively. The current approach starts from commercially available methyl indole 3-carboxylate (**10**) and leads to **11** in a single step in 83% yield (gram-scale).

As delineated in Table 1, this mild reaction exhibits broad functional group tolerance. For example, tryptophan derivatives with various protecting groups can be prenylated (Table 2, **13a–i**). Peptides containing tryptophan also undergo prenylation (**13a**, **13h**), including a tripeptide (**13b**). The presence of amides, particularly at the tryptophan nitrogen (**13d**, **13h**), reduces the reactivity, possibly due to ligation of the amides onto electrophilic Pd^{II}. However, a sterically hindered amide substrate does lead to an increased yield (**13e**) compared to other amide substrates. A tryptamine derivative (**13j**) is also prenylated, albeit in lower yield, but starting material can be recovered. Free alcohol, acid, and protected phenols substrates are well tolerated under the reaction conditions (**13i**, **13k**, and **13m** respectively). Halogenated substrates (**13f–g**), including those incorporated in the indole ring (**13l**) work well, and are not oxidatively cleaved under these conditions.

To gain insight into the mechanism of this transformation, we studied the interactions that Pd may have with both the indole and the olefin. We initially believed that the indole was being palladated at C-2, thus providing proximal delivery of the prenyl group to nitrogen.^{3,13} When a methyl group occupied the C-2 position, there was less than 5% conversion to the desired product (Figure 3A). However, when deuterium was placed on C-2 (**16**), we found that the deuterium was fully incorporated in product **17**. We also found that 1,1,1-*d*₃-3-methyl-2-butene reacted at the same rate as its protio isomer with Pd^{II}, consistent with Bercaw's mechanistic studies of allylic C–H activation (the C–H activation step is not rate-determining).²¹

Based on these results, we have proposed the following mechanism (Figure 3B). First, C–H activation of the olefin with Pd^{II} gives intermediate **18**. The palladated olefin reacts with indole in three possible modes. The first involves direct coordination of the indole nitrogen to Pd leading to **19**. Alternatively, indole palladation at C-3 takes place to give **20** which rearranges to the product by a metallo-Claisen rearrangement.²² Finally, a Wacker-type mechanism (**21**) may also be operative.^{16a} All three intermediates are plausible, although intermediate **20** may explain the regioselectivity more convincingly. The Pd⁰ species then undergoes oxidation with Ag^I and Cu^{II} to close the cycle. In order to rule out initial allylic oxidation of the olefin to prenyl acetate a control experiment was performed using prenyl acetate in place of 2-methyl-2-

butene (following Method A). The reaction did not provide the desired product, but rather produced 22 in *ca.* 10% yield (tentative assignment).

The use of *cis*-butene substituted for 2-methyl-2-butene did afford desired products in decent yield (**23**, **24**). This method is obviously not without limitations. For example, terminal olefins provided only enamine products. Lowering the loading of palladium to 10–20% or reducing the equivalents of olefin added (5 equiv.) led to diminished yields (<30%). With regard to indole substrate scope, substitution at C–3 is required, diketopiperazine ring systems give lower yields of product, and pyrroles are too reactive under these conditions. While the current method is by no means atom-economic, it is direct, scalable, and selective even on complex substrates. It compares favorably to the only other method known for the synthesis of these compounds.²³ Finally, our attempts to utilize prenyl acetate (or similar derivatives) in concert with various transition metals has not led to indole *N*-*tert*-prenylation.²⁴

In conclusion, a simplified, redox-conserving route to *N*-*tert*-prenylated indoles using Pd^{II}-mediated C–H functionalization has been developed. Contrary to the known reactivity of indoles, prenylation occurs exclusively at N-1. Although substitution at C-2 hindered reactivity and the use of stoichiometric Ag^I and Cu^{II} salts are required, this method is amenable to gram-scale synthesis using a variety of indoles, including formal syntheses of a number of natural products and the synthesis of antifungal natural product **11** in a single step. The high level of chemoselectivity exhibited in this reaction bodes well for further applications in both the early and advanced stages of prenylated indole total synthesis endeavors.

Experimental Section

General

Method A—To a flame-dried flask or vial charged with a stirbar was added indole (1g, 1 equiv.), Cu(OAc)₂ (2 equiv.), and AgTFA (2 equiv.). Acetonitrile (CH₃CN) was added followed by the addition of Pd(OAc)₂ (10 mol%) and 2-methyl-2-butene (30 equiv.). The mixture was heated to 35 °C, followed by 3 sequential additions of Pd(OAc)₂ (10 mol% after each hour × 3). The mixture was allowed to stir for 24 hr total. The solvent was then evaporated and the mixture was loaded directly onto silica gel for purification.

Method B—Similar to method A using Pd₂dba₃•CHCl₃ (5 mol% × 4).

Method C—To a flame-dried flask charged with a stirbar was added indole (1g, 1 equiv.), Pd(OAc)₂ (40 mol%), Cu(OAc)₂ (2.5 equiv.), AgOTf (2.5 equiv.), and 3-NO₂-pyridine (40 mol %). The flask was evacuated and backfilled with argon (3X). Acetonitrile (CH₃CN) was added followed by the addition of 2-methyl-2-butene (30 equiv.) and methyl acrylate (1 equiv.). The mixture was heated to 40 °C and allowed to stir for 24 hr. The solvent was then evaporated and the mixture was loaded directly onto silica gel for purification.

Method D—Similar to method A using *cis*-butene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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23. That four-step sequence generally involves the following reagents (ref 9c): NaBH_3CN (1000 mol%, a toxic expensive reagent that releases HCN), CuCl (10 mol%), 2-acetoxy-2-methyl-3-butyne (110 mol%), DDQ (105 mol%), and Pd (10 mol%). It also requires four separate purifications (silica gel) and the associated cost of time, labor, and solvent.
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(A) Studies en route to the stephacidins (2003):

(B) Summary of direct indole prenylation modes:

(C) *N*-*tert*-prenylindoles: Known route and redox-conserving alternative **Figure 1.**

Inspiration from a failed campaign in the stephacidin total synthesis (A), currently known direct prenylation modalities (B), and the known route to *N*-*tert*-prenyl indoles compared to the C-H functionalization alternative (C). Boc = *tert*-butoxycarbonyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

compare with 50% **3** over 4 steps towards okaramine N;
60% **7** over 4 steps towards the rufomycins

compare with 70% **9** over 4 steps towards cyclomarins;
60% **11** over 5 steps or 34% over 7 steps

Figure 2.

Scalable, one-step routes to previously employed *N*-*tert*-prenyl indole intermediates.

Figure 3.
Mechanistic probe experiments (A), and postulated mechanism (B).

Figure 4.
Informative products using prenyl acetate or *cis*-2-butene as olefin source.

Table 1Optimization of the direct indole *N*-*tert*-prenylation.

Entry	Catalyst (loading)	Oxidant	Solvent	Yield (%) ^a
1	Pd(OAc) ₂ (25 mol%)	O ₂ , pyridine	THF	NR
2	(CH ₃ CN) ₂ PdCl ₂ (25 mol%)	CuSO ₄	THF	5
3	Pd(OAc) ₂ (25 mol%)	Cu(OAc) ₂ , air	THF	10
4	Pd(TFA) ₂ (30 mol%)	BQ, Ph ₃ P	CH ₃ CN	37%
5	Pd(TFA) ₂ (30 mol%)	BQ, <i>t</i> -BuOOH	CH ₃ CN	NR
6	Pd(OAc) ₂ (40 mol%)	Cu(OAc) ₂	CH ₃ CN	31%
7	Pd(OAc) ₂ (40 mol%)	AgOTf	CH ₃ CN	22%
8	Pd(OAc)₂ (40 mol%)	Cu(OAc)₂, AgOTf	CH₃CN	70%

^a isolated yield of pure compound. Phth = phthalimide, TFA = trifluoroacetate, BQ = *p*-benzoquinone, Tf = trifluoromethanesulfonyl.

Table 2

Scope of *N*-tert-prenylation.

13i: 64% (method B)

13j: 47% (+ 29% sm), (method A)

13l: R = 5-Cl, 74%, (method C)

13m: R = 6-OTs, 78%, (method C)

^aReaction conditions **A**: (10 mol% X 4) $\text{Pd}(\text{OAc})_2$, 2 eq AgTFA , 2 eq $\text{Cu}(\text{OAc})_2$, CH_3CN (0.1M), 35 °C, air, 24 hr. **B**: (5 mol% X 4) $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$, 2 eq AgTFA , 2 eq $\text{Cu}(\text{OAc})_2$, CH_3CN (0.1M), 35 °C, air, 24 hr. **C**: 40 mol% $\text{Pd}(\text{OAc})_2$, 40 mol% 3-NO₂-pyridine, 1 eq methyl acrylate, 2.5 eq AgOTf , 2.5 $\text{Cu}(\text{OAc})_2$, CH_3CN (0.08M), 40 °C, Ar.

^bIsolated yield. Fmoc = 9-fluorenylmethyloxy carbonyl, dba = dibenzylideneacetone, Ts = *p*-toluenesulfonyl.