Synthetic Methods

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

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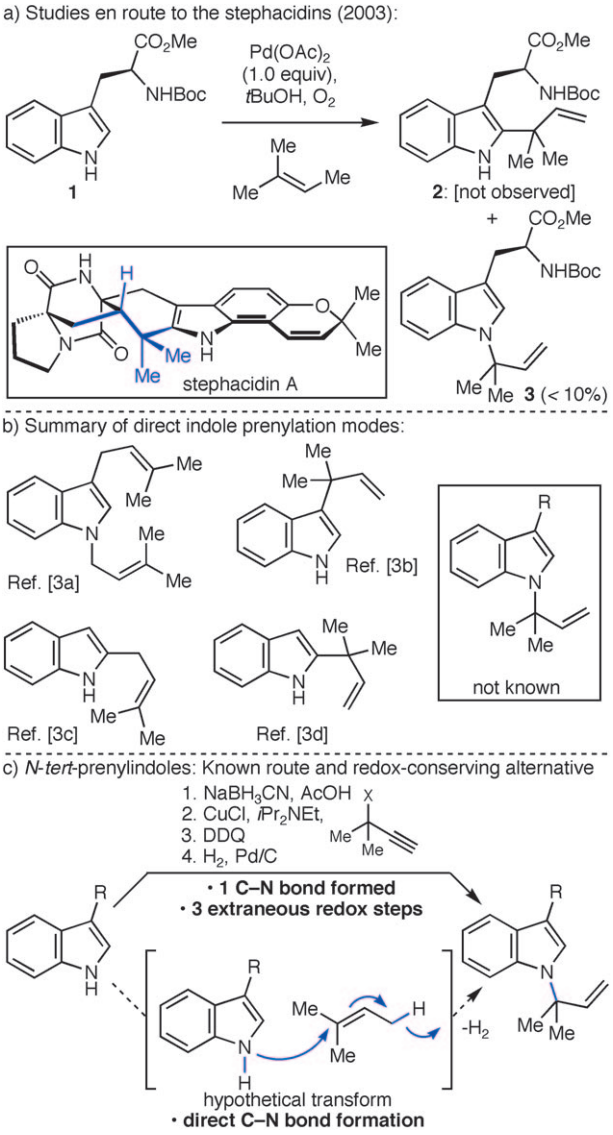
Prenylated indole alkaloids have long been targets for total synthesis, since they possess a broad range of medicinal properties and intriguing architectures.[1] Our interest in this family began with the stephacidin family of indole alkaloids,[2] during which the fortuitous finding shown in Scheme 1a was made. Thus, in 2003, during an attempt to convert *N*-Boc-tryptophan methyl ester (**1**) into the C-2 prenylated tryptophan **2** directly using 2-methyl-2-butene by electrophilic palladation[3] and olefin capture, we instead observed small amounts (<10%) of a nonpolar compound which was 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 (Scheme 1b).[8] Inspired by our initial findings, we herein delineate a mild, highly chemoselective, scalable, and one-step route to these biologically relevant motifs by C–H functionalization.

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

Building on our initial observations (Scheme 1a), we envisioned a direct, one-step procedure to synthesize *N*-*tert*-prenylated indoles without the use of prefunctionalized 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, which in this case would not be applicable.[11] Specifically, C–H activation of indoles is known to occur at C-2 or C-3, and involves the direct coupling of arenes[12] and electron-deficient olefins[13] and annulations,[2,9,14] even in the presence of free N–H indoles.[15] Palladium-catalyzed intramolecular allylic C–H aminations[16] 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 Scarborough and Stahl[18] as well as of Wasa and Yu[19] were



Scheme 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*-prenylindoles compared to the C–H functionalization alternative (C). Boc = *tert*-butoxycarbonyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

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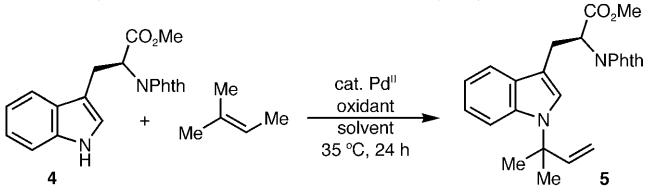
instrumental in transforming our esoteric observations in 2003 into a useful method for synthesis.

Selected results of extensive optimization with the *N*-Phth-tryptophan methyl ester **4** are outlined in Table 1 (see the Supporting Information for a more comprehensive listing). The work of Scarborough and Stahl pointed us to the use of CH_3CN as a solvent, while the research from Wasa and Yu 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% $[Pd_2(dba)_3]\cdot CHCl_3$) with 30 equivalents of 2-methyl-2-butene in the presence of $Cu(OAc)_2$ and an Ag^I source (AgOTf or AgTFA) as the cooxidants in CH_3CN was optimal for this transformation.

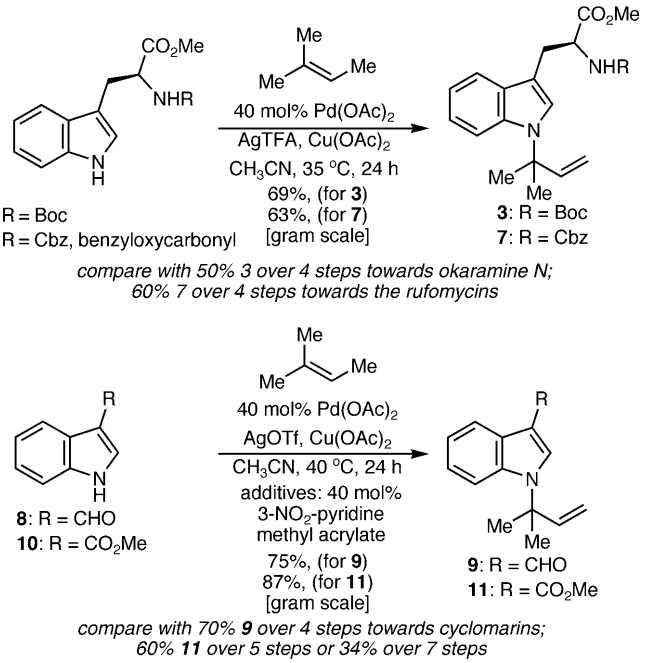
Table 1: Optimization of the direct indole *N-tert*-prenylation.



Entry	Catalyst (loading, mol%)	Oxidant	Solvent	Yield [%][a]
1	$Pd(OAc)_2$ (25)	O_2, pyridine	THF	NR
2	$[PdCl_2(CH_3CN)_2]$ (25)	$CuSO_4$	THF	5
3	$Pd(OAc)_2$ (25)	$Cu(OAc)_2$, air	THF	10
4	$Pd(TFA)_2$ (30)	BQ, Ph_3P	CH_3CN	37
5	$Pd(TFA)_2$ (30)	BQ, *t*BuOOH	CH_3CN	NR
6	$Pd(OAc)_2$ (40)	$Cu(OAc)_2$	CH_3CN	31
7	$Pd(OAc)_2$ (40)	AgOTf	CH_3CN	22
8	**$Pd(OAc)_2$ (40)**	**$Cu(OAc)_2$, AgOTf**	**CH_3CN**	**70**

[a] Yield of isolated pure compound. The conditions giving the highest yield are highlighted in bold. Phth = phthalimide, TFA = trifluoroacetate, BQ = *p*-benzoquinone, Tf = trifluoromethanesulfonyl, NR = no reaction.

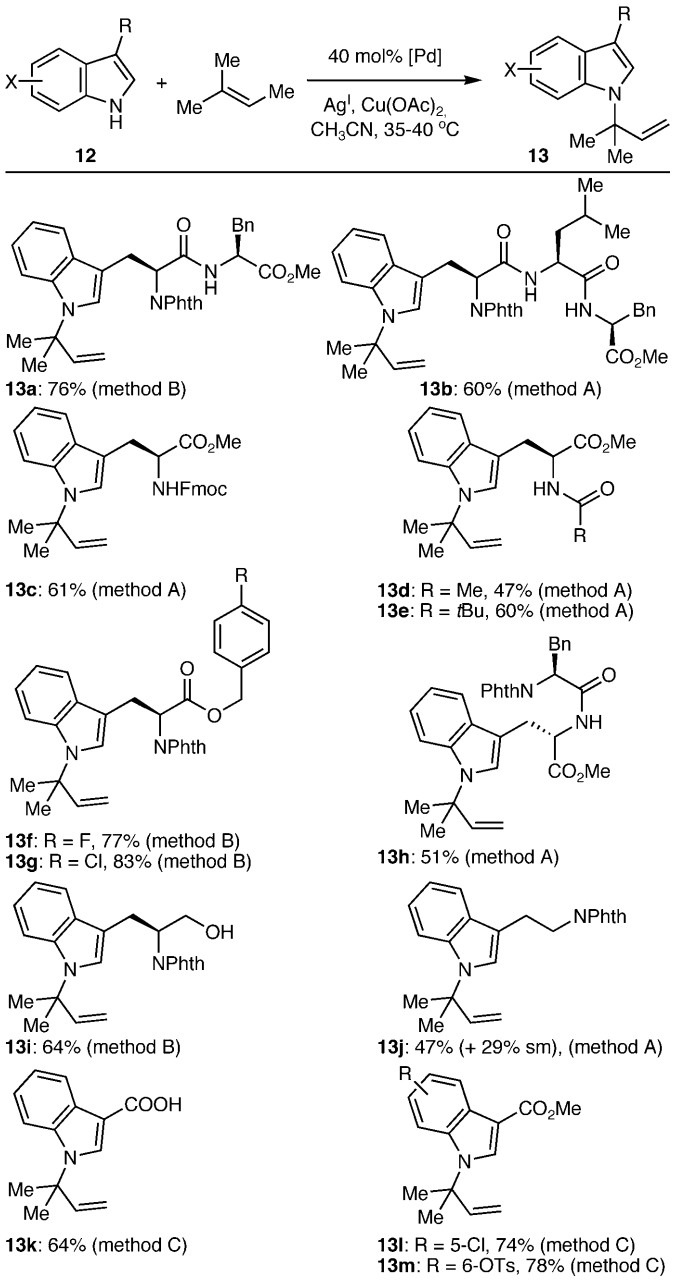
With these conditions in hand, the synthetic utility could be immediately demonstrated by applying it to known intermediates in total synthesis (Scheme 2). For example, compound **3**, an intermediate in the okaramine N synthesis[9c] that required the aforementioned four-step sequence (50% overall yield), 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 into **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**, an intermediate in a cyclomarin synthesis,[9d] on a gram scale and in 68% yield versus 70% for the 4-step sequence from indoline. The use of methyl acrylate[18] and 3-NO_2-pyridine[12b,14] (possibly as stabilizing ligands for Pd^0) was needed when an electron-withdrawing group was present at C-3. The natural product **11**, isolated from *Aporpium caryae*,[20] has been previously synthesized 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 methylindole 3-carboxylate (**10**) and leads to **11** in a single step in 83% yield (gram scale).



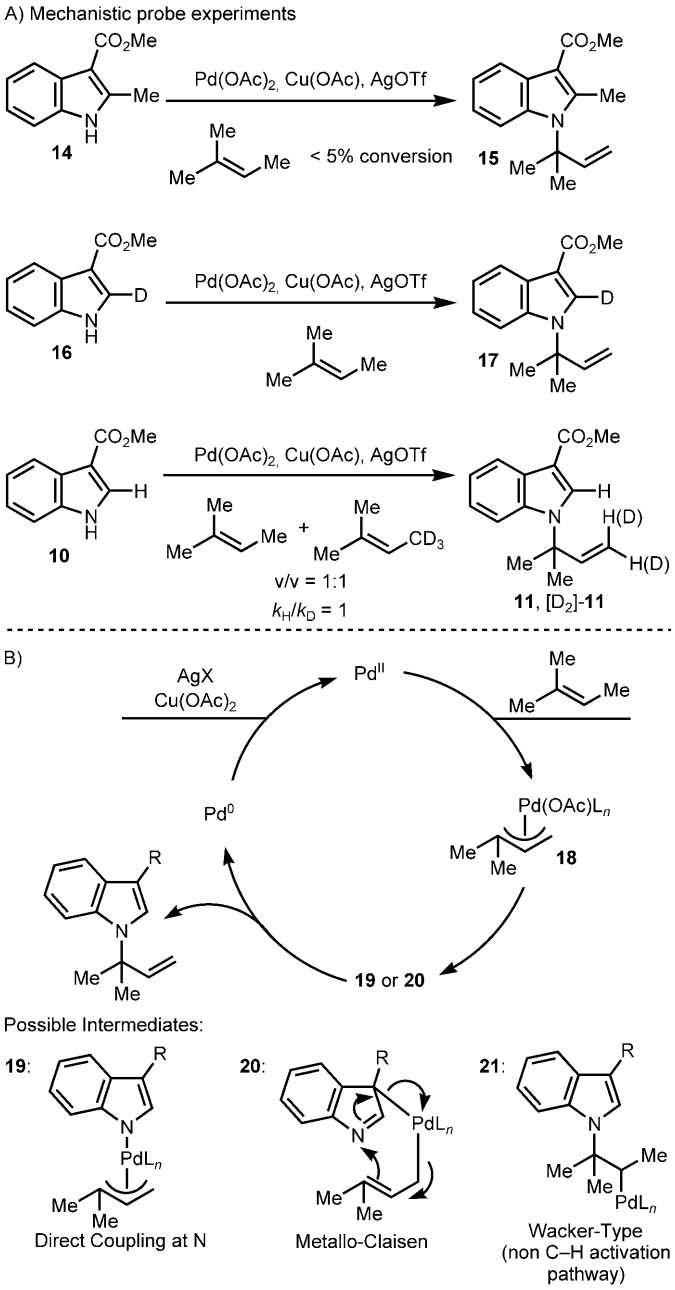
Scheme 2. Scalable, one-step routes to previously employed *N-tert*-prenylindole intermediates.

As delineated in Scheme 3, this mild reaction exhibits broad functional-group tolerance. For example, tryptophan derivatives with various protecting groups can be prenylated (Scheme 3, **13a–i**). Peptides containing tryptophan also undergo prenylation (**13a, 13h**), including a tripeptide (**13b**). The presence of amides, particularly at the tryptophan nitrogen atom (**13d**, **13h**), reduces the reactivity, possibly because of 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 phenol substrates are well-tolerated under the reaction conditions (**13i**, **13k**, and **13m** respectively). Halogenated substrates (**13f**, **13g**), 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 the nitrogen atom.[3,13] When a methyl group occupied the C-2 position, there was less than 5% conversion to the desired product (Scheme 4a). 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 the mechanistic studies by Bercaw and co-workers of allylic C–H activation (the C–H activation step is not rate determining).[21]



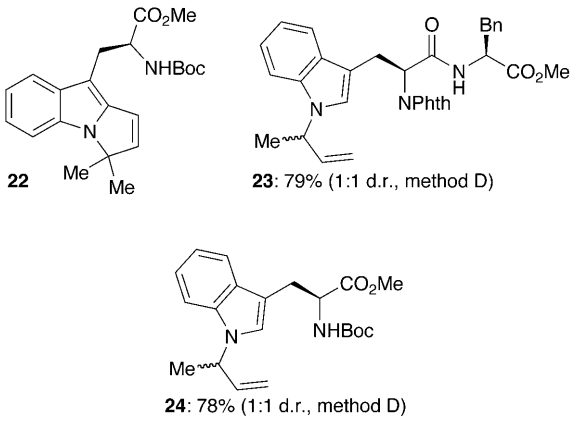
Scheme 3. Scope of *N-tert*-prenylation. [a] Reaction conditions: Method A: $Pd(OAc)_2$ (10 mol% × 4), AgTFA (2 equiv), $Cu(OAc)_2$ (2 equiv), CH_3CN (0.1 M), 35 °C, air, 24 h. Method B: $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol% × 4), AgTFA (2 equiv), $Cu(OAc)_2$ (2 equiv), CH_3CN (0.1 M), 35 °C, air, 24 h. Method C: $Pd(OAc)_2$ (40 mol%), 3-NO_2-pyridine (40 mol%), methyl acrylate (1 equiv), AgOTf (2.5 equiv), $Cu(OAc)_2$ (2.5 equiv), CH_3CN (0.08 M), 40 °C, Ar. [b] Yield of isolated product. Fmoc = 9-fluorenylmethyloxy carbonyl, dba = dibenzylideneacetone, Ts = *p*-toluenesulfonyl.



Scheme 4. Mechanistic probe experiments (A), and postulated mechanism (B).

Based on these results, we have proposed the following mechanism (Scheme 4b). First, C–H activation of the olefin with Pd^{II} gives intermediate **18**. The palladated olefin reacts with indole in two possible modes. The first involves direct coordination of the indole nitrogen atom to the Pd center to give **19**. Alternatively, palladation of the indole at C-3 takes place to give **20**, which rearranges to the product by a metallo-Claisen rearrangement.[22] A Wacker-type mechanism (**21**), not involving C–H activation, may also be operative.[16a,b] The Pd^0 species then undergoes oxidation with Ag^I and Cu^{II} to close the cycle. 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** (Scheme 5) in approximate 10% yield (tentative assignment).

The use of *cis*-butene substituted for 2-methyl-2-butene did afford desired products in respectable yield (**23**, **24**). This method is clearly not without limitations. For example, terminal olefins provided only enamine products. Lowering



Scheme 5. Informative products using prenyl acetate or *cis*-2-butene as the olefin source.

the loading of palladium to 10–20% or reducing the number of 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 with 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 *N-tert*-prenylation of indoles.[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 the reactivity and the use of stoichiometric amounts of Ag^{I} and Cu^{II} salts are required, this method is amenable to gram-scale synthesis using a variety of indoles, including the 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

Method A: Indole (1 g, 1 equiv), $Cu(OAc)_2$ (2 equiv), and AgTFA (2 equiv) were added to a flame-dried flask or vial charged with a stir bar. Acetonitrile (CH_3CN) 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). The mixture was allowed to stir for 24 h in total. The solvent was then evaporated and the mixture was loaded directly onto silica gel for purification.

Method B: Similar to method A, but using $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol% × 4).

Method C: Indole (1 g, 1 equiv), $Pd(OAc)_2$ (40 mol%), $Cu(OAc)_2$ (2.5 equiv), AgOTf (2.5 equiv), and 3-NO_2-pyridine (40 mol%) were added to a flame-dried flask charged with a stir bar. The flask was evacuated and backfilled with argon (3 times). Acetonitrile (CH_3CN) 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 h. The solvent was then evaporated and the mixture was loaded directly onto silica gel for purification.

Method D: Similar to Method A, but using *cis*-butene.

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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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