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Protecting-Group-Free Synthesis of 3-*tert*-Prenylated Oxindoles: Contiguous All Carbon Quaternary Centers *via* Tertiary Neopentyl Substitution

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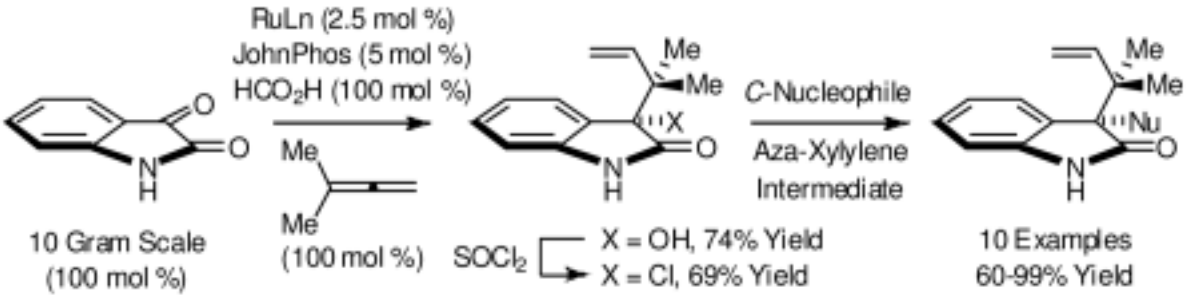
Abstract



Ruthenium catalyzed *tert*-prenylation of isatin 1 occurs efficiently in the absence of *N*-protecting groups under the conditions of C-C bond forming transfer hydrogenation employing 1,1-dimethylallene as the prenyl donor. The prenylated adduct, 3-hydroxy-3-*tert*-prenyl-oxindole 2, is converted to the tertiary neopentyl chloride 3, which participates in nucleophilic substitution by way of an aza-*ortho*-xylylene intermediate to furnish adducts 4a-4i. Through tertiary neopentyl substitution, two contiguous all carbon quaternary centers are established.

Prenylated indole alkaloids have attracted attention due to their remarkable biological effects and challenging structural features. [1] Those incorporating *tert*-prenyl moieties at the 2- or 3-position include the brevianamides, austamides, paraherquamides, marcfortines, echinulins, aspergamides, norgeamides, avrainvillamides, stephacidins, notamides, roquefortines, as well as the amauromine, ardeemin, and flustramine families of natural products. The construction of indole alkaloids that incorporate a 3-*tert*-prenyl moiety requires construction of two contiguous all-carbon quaternary centers. Typically, this substructure is installed through the reaction of *bis*-*N*-protected tryptophan derivatives with *N*-(phenylseleno)phthalimide to form 3-phenylselenio-pyrroloindoline adducts, which are ionized with methyl triflate in the presence of prenyl tributylstannane.[2] Considerable pre-activation attends this method, which requires stoichiometric use of both tin and selenium reagents, as well as protection of the indolic nitrogen.

In the course of studies aimed at the development of C-C bond forming hydrogenations beyond hydroformylation,[3] we recently developed a suite of catalytic methods for carbonyl allylation,[4b,d,e,f,i,j,k] crotylation[4b,c,g,k] and reverse prenylation[4a,b,h,k] in the absence of stoichiometric

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Supporting Information Available. Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single crystal X-ray diffraction data for **4e**. This material is available free of charge *via* the internet at http://pubs.acs.org.

allylmetal reagents. In the specific case of reverse prenylation,[4a,b,h,k] it was found that reductive C-C bond formation is achieved simply upon hydrogenation[4a] or transfer hydrogenation[4b,h,k] of 1,1-dimethylallene in the presence of carbonyl partners, including isatins.[4a,k] Although the synthesis of 3-*tert*-prenylated oxindoles can be achieved through the addition of *n*-prenylindium reagents to isatins [5] or through enolate-Claisen rearrangement, [6] *N*-protected isatins are generally required.[7,8e]

Here, we report that under the mild conditions of transfer hydrogenation, direct *tert*-prenylation of isatin occurs in the absence of *N*-protecting groups. Furthermore, the resulting adduct, 3-hydroxy-3-*tert*-prenyl-oxindole **2**, is readily converted to the chloride **3**, which engages in tertiary neopentyl substitution with *C*-nucleophiles to furnish adducts possessing two contiguous all-carbon quaternary centers, presumably by way of an aza-*ortho*-xylylene intermediate.[8,9] To our knowledge, these studies represent the first general protocol for intermolecular substitution in a tertiary neopentyl system.[10,11]

Our initial studies focused on the reaction of isatin **1** with 1,1-dimethylallene under the conditions of ruthenium catalyzed transfer hydrogenation. Our prior work on allene couplings of this type took advantage of a catalyst derived from $RuBr(CO)_3(\eta^3\text{-}C_3H_5)$ and *t*-$BuPPh_2$ in combination with isopropanol as terminal reductant.[12] For the present study, a process better suited to gram scale synthesis was sought. Hence, our optimization focused on the use of commercially available $RuHCl(CO)(PPh_3)_3$ as pre-catalyst. For this catalyst precursor, formic acid was found to be superior to isopropanol as terminal reductant. Additionally, the choice of ligand proved to be crucial. Use of $RuHCl(CO)(PPh_3)_3$ in the absence of added ligand did not result in product formation. However, use of $RuHCl(CO)(PPh_3)_3$ in the presence of more electron rich phosphines, such as tris(4-methoxyphenyl)phosphine or JohnPhos, provided the desired product of *tert*-prenylation **2** in isolated yields of 61% and 74%, respectively, at catalyst loadings of 2.5 mol % employing equimolar quantities of isatin **1**, 1,1-dimethylallene and formic acid at 65°C. The latter conditions employing JohnPhos as ligand were employed on 10 gram scale with isolation of the product *via* crystallization from ethyl acetate-hexane (Scheme 1).

With gram quantities of alcohol **2** in hand, methods for the synthesis of tertiary neopentyl chloride **3** were explored. Standard conditions employing thionyl chloride and a tertiary amine base led to isolated yields ranging between 30%-90%. However, the desired chloride **3** was contaminated with substantial quantities of Wagner-Meerwein product. It was postulated that Wagner-Meerwein rearrangement occurs upon ionization of the transient chlorosulfite to form the protonated aza-*ortho*-xylylene. Based on this interpretation, irreversible dianion formation followed by the addition of thionyl chloride should generate a transient chlorosulfite that should eliminate to furnish a neutral aza-*ortho*-xylylene, which should be less susceptible to Wagner-Meerwein shift. Indeed, treatment of alcohol **2** with 2.2 equivalents of LHMDS followed by thionyl chloride provided the tertiary neopentyl chloride **3** in 69% yield as a single constitutional isomer (Scheme 1).

Acquisition of chloride **3** set the stage for tertiary neopentyl substitution. Upon exposure of chloride **3** to dimethyl malonate in the presence of potassium carbonate in dichloromethane solvent,[8] the desired product of tertiary neopentyl substitution **4a** was obtained in 84% isolated yield. These conditions were applied to a range of *C*-nucleophiles. As demonstrated by the formation of adducts **4a-4i**, active methylene compounds, cyanide and electron rich arenes engage in efficient tertiary neopentyl substitution with chloride **3** (Scheme 2). Finally, borohydride reduction of chloride **3** also is possible, as demonstrated by the formation of **4j** (Scheme 3).

In summary, we report a protecting group-free method for the gram-scale synthesis of 3-hydroxy-3-*tert*-prenyl-oxindole **2** *via* ruthenium catalyzed C-C bond forming transfer hydrogenation. Conditions were identified for the conversion of tertiary neopentyl alcohol **2** to the corresponding chloride **3** in the absence of Wagner-Meerwein shift. Finally, chloride **3** engages in tertiary neopentyl substitution by way of an aza-*ortho*-xylylene intermediate to furnish the *tert*-prenylated oxindoles **4a**-**4i**. Future studies will focus on the development of related asymmetric neopentyl substitutions and application of these methods toward the synthesis of naturally occurring 3-*tert*-prenylated indoles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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7. As described in reference 8e, treatment of 3-methyl-3-bromooxindole with *n*-prenyl tributylstannane delivers the 3-methyl-3-*tert*-prenyl-oxindole in the absence of an *N*-protecting group. However, stoichiometric quantities of tin byproducts are generated.

8. While many substitution reactions involving *C*-nucleophiles and 3-substituted-3-halo-oxindoles are reported, examples of tertiary neopentyl substitution are absent. While in earlier literature aza-xylylene intermediates are not proposed as intermediates (e.g. refs. a-c), their intervention is possible and highly likely: (a)Labroo RB, Labroo VM, King MM, Cohen LA. J Org Chem 1991;56:3637.(b)Kobayashi M, Aoki S, Gato K, Matsunami K, Kurosu M, Kitagawa I. Chem Pharm Bull 1994;42:2449. [PubMed: 7697760](c)Rajeswaran WG, Labroo RB, Cohen LA. J Org Chem 1999;64:1369.(d)Fuchs JR, Funk RL. J Am Chem Soc 2004;126:5068. [PubMed: 15099080](e)Fuchs JR, Funk RL. Org Lett 2005;7:677. [PubMed: 15704923](f)England DB, Merey G, Padwa A. Org Lett 2007;9:3805. [PubMed: 17711291](g)England DB, Merey G, Padwa A. Heterocycles 2007;74:491.(h)Krishnan S, Stoltz BM. Tetrahedron Lett 2007;48:7571.

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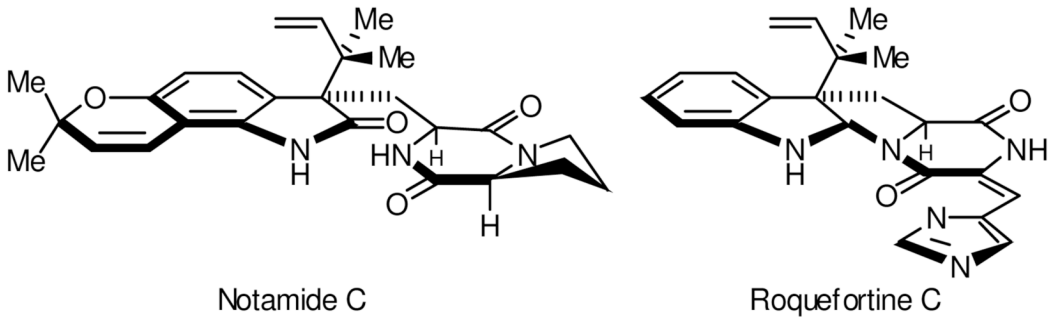
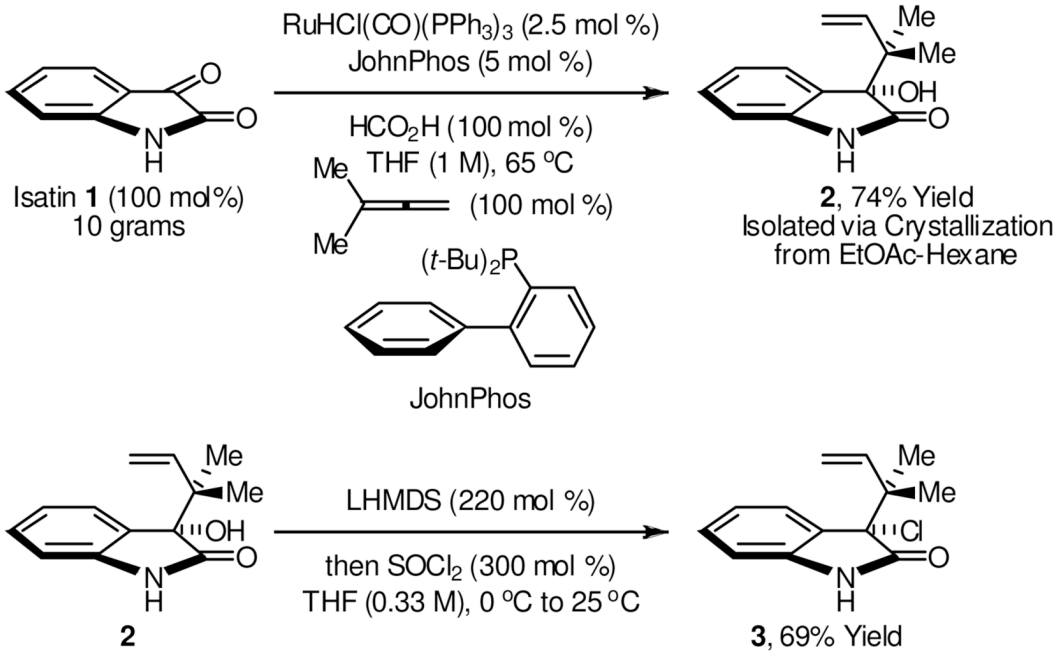


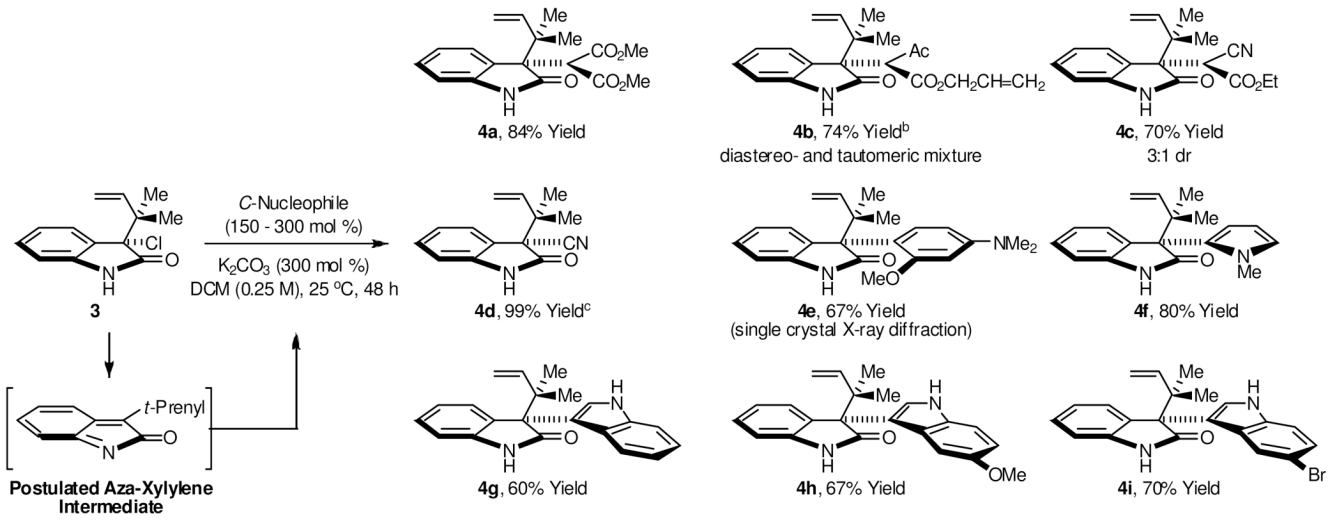
Figure 1.
Examples of indole alkaloids that incorporate a *tert*-prenyl moiety at the indole 3-position.



Scheme 1.

Reverse prenylation of isatin **1** and conversion to 3-chloro-3-*tert*-prenyl oxindole **3**.[a]

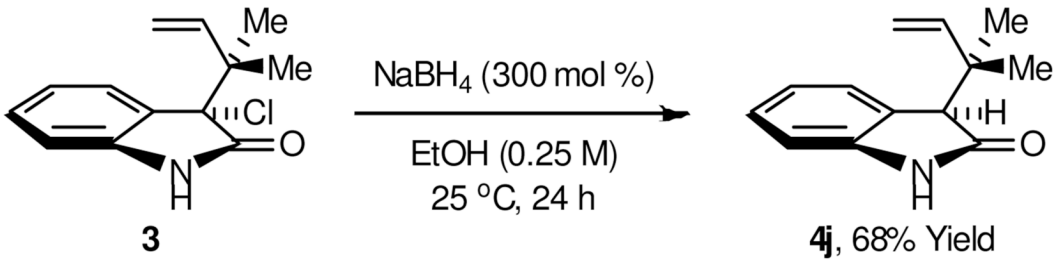
[a]Compound **2** was isolated by crystallization from ethyl acetate-hexane. Compound **3** was isolated by silica gel chromatography. See Supporting Information for experimental details.



Scheme 2.

Tertiary neopentyl substitution of chloride **3** to furnish adducts **4a-4i** possessing contiguous all-carbon quaternary centers.[a]

[a]For adducts **4a**-**4f**, 300 mol % of NuH was employed. For adducts **4g**-**4i**, 150 mol % of NuH was employed. Cited yields are of material isolated by silica gel chromatography. See Supporting Information for experimental details. [b]Obtained as a mixture of diastereomers and keto-enol tautomers. [c]For the formation of **4d**, 10 mol % Bu_4NI, THF-H_2O (1:3) was used as solvent and the reaction was run for 24 h.



Scheme 3.
Dehalogenation of chloride **3** mediated by $NaBH_4$.
[a]As described in Scheme 2.