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Ir-Catalyzed Reverse Prenylation of 3-Substituted Indoles: Total Synthesis of (+)-Aszonalenin and (-)-Brevicompanine B

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Ir-Catalyzed Reverse Prenylation of 3-Substituted Indoles: Total Synthesis of (+)-Aszonalenin and (–)-Brevicompanine B

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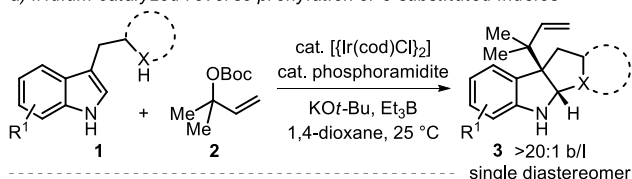
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ABSTRACT: The selective reverse prenylation of 3-substituted-1*H*-indoles at C3 is described. The iridium-catalyzed reaction proceeds with high branched to linear selectivity (>20:1) for a variety of indoles. In addition, a diastereoselective reverse prenylation of tryptophan methyl ester is disclosed and its synthetic utility is demonstrated in the synthesis of (+)-aszonalenin and (–)-brevicompanine B.

Prenylated indole alkaloids from fungi, bryozoans, and cyanobacteria are an important class of natural products encompassing a wide array of unusual structures that display a diverse range of biological activities.¹ A subset of this class of natural products includes hexahydropyrrolo[2,3-*b*]indoles with an embedded 1-(1,1-dimethylallyl) substituent at an indoline C3 quaternary center. The introduction of this characteristic substitution pattern has been referred to as “reverse prenylation” as a means of differentiating it from the less common isomeric prenylation involving the installation of 1-(3,3-dimethylallyl) substituents. The embedded substructures bearing reversed prenyl groups present several key challenges to the design of synthetic strategies en route to the attendant complex natural products. Accordingly, reverse prenylation at a substituted indole carbon must contend with problems involving (1) reactivity, leading to the formation of two vicinal quaternary centers, (2) regioselectivity in the reaction of the dimethyl allyl fragment, divergently leading to prenyl versus reverse prenylation, (3) chemoselectivity, or site selectivity, at the indole, which may furnish *N*-versus *C*-isomers, and (4) stereoselectivity of the transformation. The identification of general catalytic methods for reverse prenylation would provide fresh new strategies for the synthesis of a number of biologically active, natural product targets. Herein, we report a catalytic method for the C3 reverse prenylation of 3-substituted indoles that employs tertiary carbonate **2** and a catalyst generated from a simple phosphoramidite ligand and [Ir(cod)Cl]₂ (Figure 1). The reaction furnishes adducts **3** displaying high regiocontrol (reverse (branched) versus normal (linear) prenylation selectivity b/l >20:1), chemoselectivity for the indole C3, and diastereocontrol in the course of installing two vicinal quaternary centers. Additionally, we also document the implementation of the method in the total synthesis of (+)-aszonalenin and (–)-brevicompanine B.

a) Iridium-catalyzed reverse prenylation of 3-substituted indoles



b) Applications in syntheses

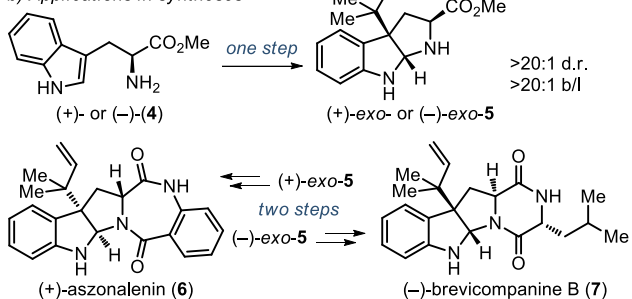


Figure 1. (a) Ir-catalyzed, reverse prenylation of 3-substituted indoles and (b) applications in syntheses.

Metal-catalyzed reverse prenylation of oxindoles,^{2a} isatins^{2b} and C3 unsubstituted indoles^{2c-f} has been reported under a variety of conditions. These can involve the use of electrophilic and nucleophilic dimethyl allyl fragments. Additionally, a large number of substitution reactions of 3-substituted indoles have been described involving simple allyl or monosubstituted allyl fragments and benzylations.³ However, to the best of our knowledge, general methods for the one-step reverse prenylation of 3-substituted indoles at C3 have not been described previously.⁴ Of additional importance, iridium-catalyzed allylations to access products with vicinal quaternary centers is unprecedented.⁵

We began our methodological investigations with *N*-protected tryptamine **1a** as substrate, (Boc)-carbonate **2** as the prenyl source, and a catalyst generated *in situ* from simple phosphoramidite ligands and [Ir(cod)Cl]₂.⁶ The fluoride in **1a** simplifies analysis during the screening and optimization phase of the investigations because of the use of ¹⁹F NMR spectroscopy. The formation of reverse prenylated adduct **3a** was only observed when the reaction was conducted with KOt-Bu and Et₃B as additives, which serve to activate the indole through the generation of the *N*-borylated intermediate.⁷

Table 1. Reverse Prenylation of 3-Substituted-1*H*-Indoles^{a,b,c}

substrate	product	yield
		92%
		95%
		79%
		93%
		93%
		90%
		88%
		72%
		62%
		88%

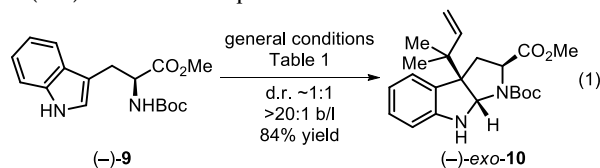
^aStandard procedure: **1a-j** (1.0 mmol, 1.0 equiv), **8** (0.50 mol%), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (0.25 mol%), KOt-Bu (1.1 equiv), Et_3B (1.1 equiv), **2** (1.4 equiv), 1,4-dioxane, 24 °C, 1–5 h. ^bYields of purified products. ^cBranched to linear selectivity determined by ^1H NMR analysis of the unpurified reaction mixture. ^d0.50 equiv KOt-Bu and 0.50 equiv Et_3B . ^eAfter 2 h ethanolamine (2.0 equiv) was added and the reaction was stirred 1 h at 24 °C. ^f1.0 mol% $[\text{Ir}(\text{cod})\text{Cl}]_2$ and 2.0 mol% **8**. ^gReaction conducted at 50 °C.

Examination of various carbonates and phosphoramidite ligands (see Supporting Information for details) revealed **8**⁸ as the optimal ligand, with the reaction reaching full conversion in 1 h at ambient temperature with 0.5 equivalents of Et_3B and KOt-Bu . Chiral ligands were also examined, however while good conversion and regioselectivity was observed with various phosphoramidite ligands, the chiral induction was found to be low (<20% ee) with both a 1:1 and 2:1 ligand to metal ratio. Furthermore, the use of more sterically hindered alkyboranes did not increase the observed enantioselectivity.

The scope of reverse prenylation of 3-substituted-1*H*-indoles was then examined (Table 1). The use of 0.5 equivalents each of Et_3B and KOt-Bu was sufficient for tryptamine derived sulfonamides **1a,b,d,e**; however, a full equivalent of each was needed for **1c,f-j** in order to achieve good levels of conversion. Both electron-rich and electron-deficient 5-substituted indoles were well tolerated (**1b-e**). A 4-substituted indole (**1f**) could be used as substrate without impairing the b/l selectivity. The formation of other *cis*-5,5- or *cis*-5,6-heterocycles was readily achieved from the corresponding 3-substituted indoles **1g-i**. For the synthesis of **3c**, the cyclization of the indole imine intermediate is facilitated by the addition of ethanolamine, which we hypothesize is functioning as an amphoteric mediator, namely both as a mild Brønsted acid and base. In the absence of a pendant nucleophile in the substrate, the indole imine is isolated as product, as demonstrated by the formation of **3j**.⁹

Notable features of the reaction include low catalyst loading (0.5 mol%) and >20:1 b/l selectivity for all products as determined by ^1H NMR analysis of the unpurified reaction mixture. The reaction proceeds with high site selectivity at C3 of the indole and, accordingly, in all cases, no *N*-prenylated products were observed. In line with previous reports, 7-substituted-1*H*-indoles are not suitable substrates when trialkylboranes are used to activate the indole.^{3a,3d,7a}

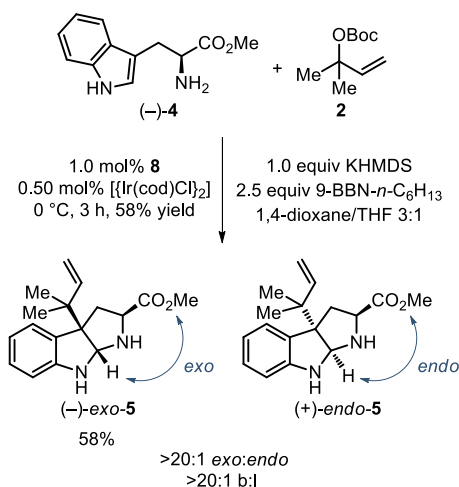
In the various total syntheses that have been reported of natural products incorporating reverse prenyl groups at a substituted indoline C3, introduction of the reverse prenyl group has been implemented through multi-step processes.¹⁰ For example, a common strategy involves oxidative cyclization of a tryptophan derivative with halogen or selenium reagents and subsequent reverse prenylation with an organotin reagent.¹¹ Because of our interest in applying the Ir-catalyzed reverse prenylation method described above to the synthesis of complex targets, we then examined whether the reaction could be carried out with relative stereocontrol, commencing with tryptophan derivatives.¹² In the reaction of *N*-Boc protected tryptophan methyl ester under the reaction conditions described in Table 1, the corresponding pyrroloindole **10** could be isolated, albeit with no diastereocontrol (~1:1) as shown in Equation 1.



The use of tryptophan (free) amino ester **4** as substrate¹³ in a reaction gave product **5** in 50% yield and low diastereoselectivity (*exo/endo* 1.3:1). However, the replacement of Et_3B with 9-BBN-*n*- C_6H_{13} ^{3a} led to considerable improvement with

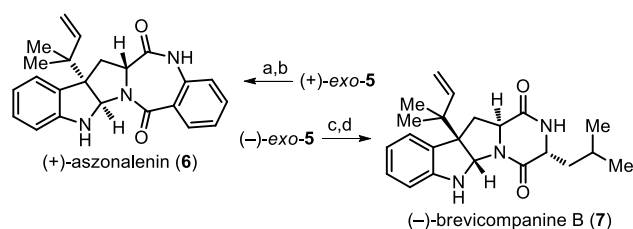
the reaction proceeding with increased diastereoselectivity (*exo/endo* >20:1). The yield could be improved by replacing KOt-Bu with KHMDS and conducting the reaction at 0 °C, whereupon hexahydropyrrolo[2,3-*b*]indole (–)-*exo*-5 was isolated from tryptophan methyl ester (–)-4 (eq 2) in 58% yield and >20:1 d.r. (Scheme 1). Importantly, no racemization was detected over the course of the reaction, as determined by SFC analysis and comparison to an authentic racemic mixture.

Scheme 1. Ir-catalyzed, reverse prenylation of tryptophan methyl ester.



Hexahydropyrrolo[2,3-*b*]indole (–)-*exo*-5 has been previously employed for the syntheses of various ardeemins and amauroamine alkaloids.^{11a-c} As such, its synthesis can be considered formal synthesis of these two alkaloids. However, in order to convincingly illustrate the utility of intermediate *exo*-5, short syntheses of two other indole alkaloids with diverse biological activity were crafted (Scheme 2). Aszonalenin **6**¹⁴ and its derivatives display remarkable activity as substance P inhibitors for the human neurokinin-1 receptor. Brevicompanine **B**¹⁵ is a plant growth regulator isolated from *Penicillium brevicompactum*. (+)-Aszonalenin was accessed in two steps from (+)-*exo*-5 by coupling with 2-aminobenzoic acid and subsequent treatment with AlMe₃. The natural product was obtained as single diastereomer and the structure was confirmed by X-ray crystallographic analysis. In a parallel approach, (–)-brevicompanine **B**^{15a} was readily obtained by coupling (–)-*exo*-5 to (R)-Fmoc-Leu, followed by deprotection and cyclization. The synthesis of **7** we have described is effected in three steps from commercially available (S)-tryptophan methyl ester (39% overall yield), which compares favorably to the only synthesis reported so far (9 steps, 11% overall yield).^{15b}

Scheme 2. Synthesis of (+)-Aszonalenin and (–)-Brevicompanine B^a



^aReagents and conditions: (a) 2-aminobenzoic acid (1.4 equiv), Et₃N (2.0 equiv), HATU (1.4 equiv), CH₂Cl₂ 25 °C, 30 h; (b) AlMe₃ (4.0 equiv), toluene, 0 °C, 1 h, 85% (two steps); (c) (R)-Fmoc-Leu (1.5 equiv), Et₃N (2.0 equiv), HATU (1.1 equiv), CH₂Cl₂, 0 °C to 19 °C, 19 h, 82%; (d) Et₃NH (35 equiv), THF, 0 °C to 22 °C, 14 h, 83%. HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate.

In summary, we have developed the first method for direct, C₃ selective, reverse prenylation of 3-substituted indoles. The reaction employs a readily accessible Ir-catalyst and a simple carbonate as precursor for the prenyl group with a variety of 3-substituted-1*H*-indoles as substrates. All products are obtained in good regioselectivity (>20:1), involving the formation of vicinal quaternary centers. The diastereoselective reaction with tryptophan methyl ester enables access to a versatile hexahydropyrrolo[2,3-*b*]indole intermediate, which we employ as precursor for the stereoselective synthesis of two bioactive natural products, aszonalenin and brevicompanine. Interestingly, the Ir-catalyzed cyclization reactions of these systems were observed to work best with the free (unprotected) amine. The same intermediate and its derivatives are expected to be useful for the streamlined synthesis of other C₃ reverse prenylated indole alkaloids. In a broader context, additional salient and important features of the method described is that it represents the first use of Ir-catalysis to effect reverse prenylation of C₃ substituted indoles. This significantly expands the reaction scope of Ir-catalyzed allylations and suggests additional avenues for investigation.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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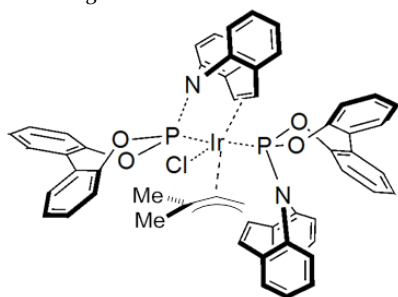
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