Indole Prenylation

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Diastereodivergent Reverse Prenylation of Indole and Tryptophan Derivatives: Total Synthesis of Amauromine, Novoamauromine, and *epi*-Amauromine**

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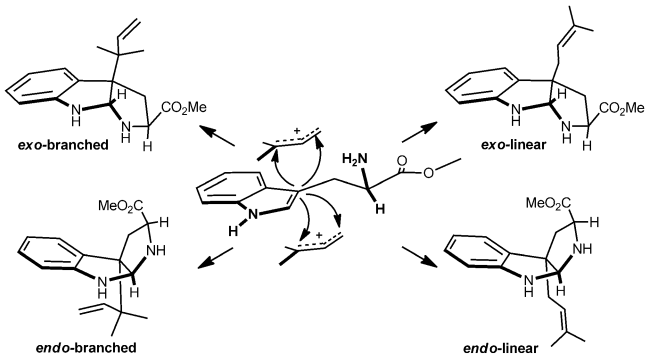
Dedicated to Professor H. Martin R. Hoffmann on the occasion of his birthday

Abstract: *A regio- and stereoselective reverse prenylation of indole and tryptophan derivatives is presented. All four possible stereoisomers are accessible through this iridium-catalyzed reaction. The stereoselectivity is controlled by a chiral phosphoramidite ligand in combination with an achiral borane additive and can be switched by changing the nature of the borane. One enantiomer of the ligand is thus sufficient to prepare all possible isomers. The synthetic potential of this method was demonstrated by a short total synthesis of amauromine and its two natural diastereomers.*

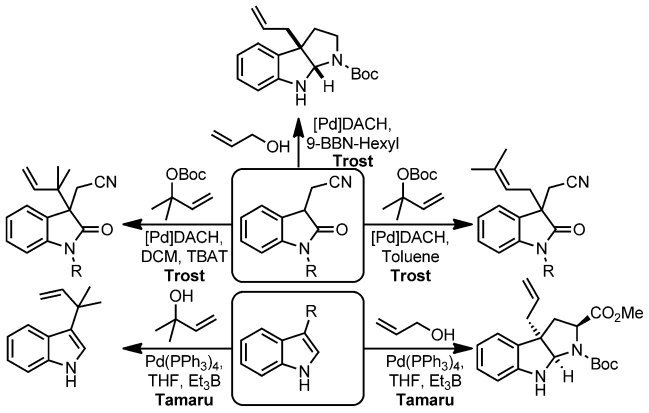
Reverse-prenylated hexahydropyrrolo[2,3]indole natural products are a large and structurally diverse group of tryptophan- and tryptamine-based alkaloids.[1,2] Their broad range of biological activities[3] renders these metabolites interesting targets for total synthesis as well as promising lead structures for medicinal and biological chemistry.[3] Moreover, the role of C3-prenylated tryptophan in the biosynthesis of C4-dimethylallyltryptophan is of significant current interest.[4]

Synthetically, the obvious challenges associated with the C3 prenylation of an indole derivative are a) control of the regioselectivity with respect to the electrophile, with the branched isomer containing two consecutive quaternary carbon centers[5] being the desired isomer, and b) control of the relative and absolute configuration. The respective reaction pathways that lead to the four possible isomeric products from L-tryptophan as the substrate and the corresponding selectivity aspects are summarized in Scheme 1 (C3 prenylation only).

Established synthetic approaches towards this structural motif are often either based on multistep reaction sequences[6] or take advantage of the quasi-aromaticity of the 2-oxindole anion for prenylation in the 3-position (Scheme 2).[7] The latter approach also requires several subsequent steps to construct the hexahydropyrrolo[2,3]indole core from the prenylated oxindole intermediate.



Scheme 1. Regio- and stereoselectivity of the C3 prenylation of L-tryptophan.



Scheme 2. A selection of catalytic C3-selective allylations and prenylations of indoles and 2-oxindoles.

A biomimetic[4] direct chemo-, regio-, and stereoselective addition of a prenyl electrophile to the indole core would obviously present the simplest entry to this class of natural products. A fine-tuned activation of both the electrophile and the nucleophile appears to be necessary to achieve this goal. Recent publications from the groups of Carreira[8] and You[9] prompted us to disclose our own results in this area (Scheme 3).

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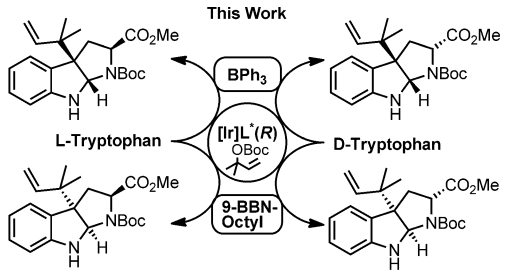
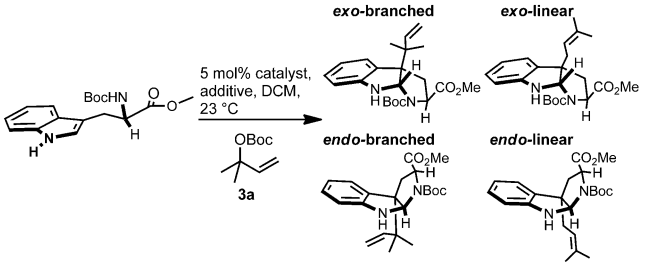


Scheme 3. Diastereodivergent reverse prenylation of L- and D-tryptophan.

As the starting point for our investigation we chose the only catalytic reverse prenylation (using Pd catalysis) of indoles that was, to the best of our knowledge, known at the outset of this project.[10] In an extensive screen of reaction conditions with variations in different reaction parameters, such as the nature of base and solvent as well as the dimethylallyl electrophile precursor (e.g., acetate, carbonate, and phosphate), only the linear rather than the desired branched products were observed (Table 1, entry 1). Changing the palladium catalyst precursor and the ligands (e.g., to DACH-type ligands **L1** and **L2**, Table 1) resulted in moderate yields and selectivities and the formation of inseparable mixtures of regioisomers (branched/linear 3:2–5:2; entries 2 and 3). Other allylic alkylation procedures[12] (see Table 1, entry 4 for an example) led to no improvement.[11] However, the use of $[Ir(COD)Cl]_2$ together with ligand **L3**,[13,14] DBU, and Et_3B yielded the desired branched isomer exclusively, albeit in low yield and with a poor diastereoselectivity of 3:2 (entry 5). The use of other phosphoramidite ligands such as (*R*)-**L4**[15] in DCM resulted in substantially increased yields of over 90%, but a still unsatisfactory d.r. of 1:1 (entry 7). Further systematic variation of the ligands and the ligand/metal stoichiometry (entries 8 and 14) did not lead to any further improvement. Similarly, the type and amount of added base did not have any influence on the diastereoselectivity. With respect to conversion, 20 mol% of DBU proved to be optimal. Eventually, we noticed the interesting and crucial role of the borane additive (entries 9 and 10). Starting from L-tryptophan, the use of 9-BBN-octyl[16] leads to the *endo* isomer with good selectivity (*exo/endo* = 1:9), whereas the addition of triphenylborane (Ph_3B) yields the *exo* diastereomer (*exo/endo* > 20:1). Both reactions proceed with good to excellent, but opposite selectivity, leading to enantiomerically pure *endo*-**2a** and *exo*-**2a**, respectively. The initially modest conversion observed when using Ph_3B was significantly improved by utilizing 10 mol% of TBD and replacing one equivalent of the ligand (*R*)-**L4** with the carbene precursor 1-benzyl-3-methylimidazolium chloride in the presence of five equivalents of carbonate **3a** (entry 11).[11] Upon switching to mirror-image ligand (*S*)-**L4**, the situation turned around: Now the trialkyl borane (9-BBN-octyl) leads to *exo*-**2a** (entry 12) whereas the triaryl borane (BPh_3) delivers *endo*-**2a** (entry 13).

Accordingly, a given enantiomer of the ligand (*R*)- or (*S*)-**L4** reacts in a diastereodivergent fashion with respect to the (achiral!) borane employed. Likewise, a given borane reacts in a diastereodivergent fashion with respect to the ligand chosen (Scheme 3). This finding implies that even though a small matched/mismatched effect[17] is observed (see Table 1, entries 9 and 11–13), for a particular borane–ligand combination, the indole moiety is always prenylated from the same prochiral face irrespective of whether L- or D-tryptophan is used as the starting material (Scheme 3; for the use of D-tryptophan as the starting material, see Table 2). For the synthesis of all four possible stereoisomers, only one enantiomer of the ligand is thus required (e.g., the (*R*)-ligand in Scheme 3).

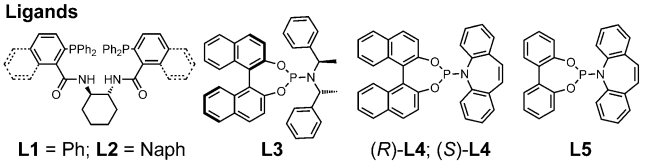
Table 1: Optimization of the catalyst and additives used for the reverse prenylation of protected L-tryptophan.



Entry	Catalyst and ligand	Additive[a]	Branched/linear	*exo*/*endo*[g]	Yield [%]
1	$[Pd(PPh_3)_4]$	Et_3B, DBU	< 1:20	1:1	87
2	[Pd], **L1**[b]	Et_3B, DBU	3:2	n.d.	45
3	[Pd], **L2**[b]	Et_3B, DBU	5:2	n.d.	32
4	$[Rh(COD)Cl]_2$, $P(OPh)_3$	Et_3B, LiHMDS	–	n.d.	–
5	$[Ir(COD)Cl]_2$, **L3**[c]	Et_3B, DBU	> 20:1	3:2	37
6	$[Ir(COD)Cl]_2$, (*R*)-**L4**[d]	Et_3B	> 20:1	1:1	23
7	$[Ir(COD)Cl]_2$, (*R*)-**L4**	Et_3B, DBU	> 20:1	1:1	91
8	$[Ir(COD)Cl]_2$, (*R*)-**L4** [c]	Et_3B, DBU	> 20:1	n.d.	< 5
9	$[Ir(COD)Cl]_2$, (*R*)-**L4**[d]	9-BBN-Octyl, DBU	> 20:1	1:9	94
10	$[Ir(COD)Cl]_2$, (*R*)-**L4**[d]	Ph_3B, DBU	> 20:1	> 20:1	34
11	$[Ir(COD)Cl]_2$, (*R*)-**L4**[e]	Ph_3B, TBD[f]	> 20:1	> 20:1	83
12	$[Ir(COD)Cl]_2$, (*S*)-**L4**[d]	9-BBN-Octyl, DBU	> 20:1	7:1[g]	n.d.
13	$[Ir(COD)Cl]_2$, (*S*)-**L4**[e]	Ph_3B, TBD[f]	> 20:1	< 1:20[g]	n.d.
14	$[Ir(COD)Cl]_2$, **L5**[d]	Et_3B, DBU	> 20:1	1:1	67

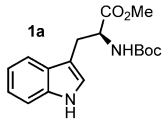
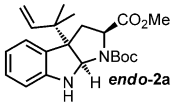
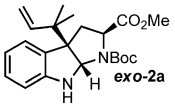
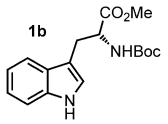
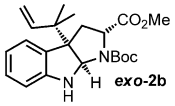
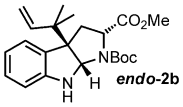
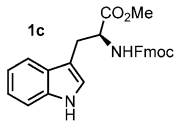
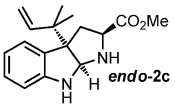
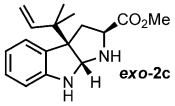
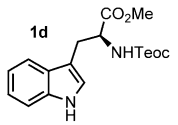
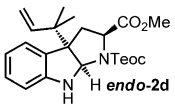
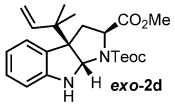
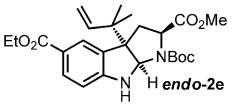
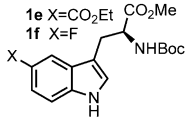
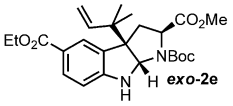
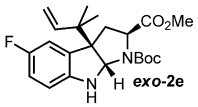
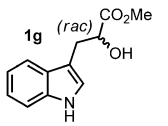
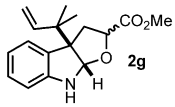
[a] Unless otherwise stated, 130 mol% of the borane and 20 mol% of the base were used. [b] Pd(Cp)allyl (5 mol%), **L1** or **L2** (5 mol%). [c] $[Ir(COD)Cl]_2$ (2.5 mol%), **L3** (5 mol%). [d] $[Ir(COD)Cl]_2$ (2.5 mol%), **L4** (10 mol%). [e] $[Ir(COD)Cl]_2$ (2.5 mol%), **L4** (5 mol%), 1-benzyl-3-methylimidazolium chloride (5 mol%). [f] Base (10 mol%). [g] Determined by ^1H NMR spectroscopy of the crude reaction mixtures. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene. n.d. = not determined.

Ligands



L1 = Ph; **L2** = Naph **L3** (*R*)-**L4**; (*S*)-**L4** **L5**

Table 2: Substrate scope of the iridium-catalyzed reverse prenylation.

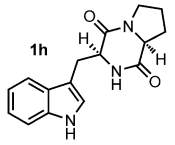
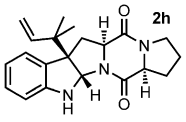
Entry	Substrate	Cond.	Product	Yield [%]	*exo*/*endo*[a]
1		A		95	1:9
2		B		72	20:1
3		A		not isol.	7:1[b]
4		B		not isol.	1:20[b]
5		A		87	1:9[c]
6		B		77	20:1[c]
7		A		91	1:9
8		B		81	20:1
9		A		69	1:9
10		B		57	9:1
11		B		83	20:1
12		C		91	2:3[d]

Encouraged by these findings, we next investigated the scope and limitations of these two diastereodivergent procedures (Table 2). Differently protected L- and D-tryptophan derivatives were smoothly converted into the desired products (entries 1–11). Irrespective of the protecting groups and further functional groups on the tryptophan backbone, the same "stereochemical switch" as for model substrate **1a** was observed when changing from the bulky trialkyl to the triaryl borane additive. Despite the presence of 20 mol% DBU, even the Fmoc protecting group proved to be stable under the reaction conditions (entries 5 and 6; the products were deprotected prior to isolation). A hydroxy group (instead of the amine) also readily acts as the internal nucleophile, furnishing N,O-acetal **2g** (entry 12). With respect to biomimetic[4] applications, tryptophan-based dipeptides represent particularly interesting substrates. Pleasingly, L-Trp-L-Pro derived diketopiperazine[18] **1h** underwent a highly regio- and stereoselective prenylation/cyclization process to yield the desired hexahydropyrrolo-[2,3]indole **2h** (entry 13).

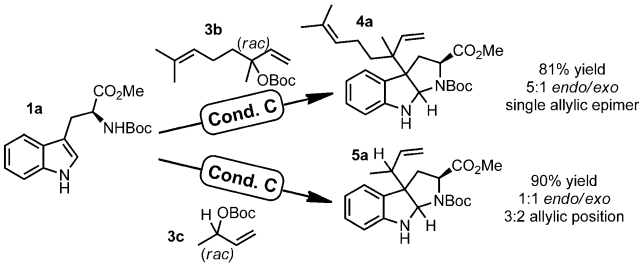
Other O-Boc-protected allylic alcohols as electrophile precursors follow the same reaction pathway (Scheme 4). Therefore, carbonates **3b** and **3c** produce the alkylated products in high yields (Scheme 4). Again, the observed regioselectivity with regard to the C electrophile is high. For the racemic secondary electrophile precursor **3c**, low stereoselectivity (3:2) regarding the allylic stereocenter was observed.

Finally, we investigated the applicability of this method in stereoselective natural product synthesis. Amauromine[19a] and its two natural diastereomers *epi*-amauromine[19b] and novoamauromine[19c] were chosen as the target molecules (Scheme 5).[20] To achieve a short and elegant synthesis, we choose a homo- and heterodimerization strategy employing the diastereomerically and enantiomerically pure building blocks *endo*-**2c** and *exo*-**2c** (see Table 2 and Scheme 5), respectively. Starting from *exo*-**2c**, hydrolysis of the methyl ester (CsOH) followed by double amide-bond formation (excess HBTU) led to the dimeric C_2-symmetric natural product amauromine (**7**; Scheme 5). Novoamauromine (**8**) was prepared in analogous manner starting from *endo*-**2c**. The products of both four-step sequences were isolated in reasonable overall yields. Next, the expectedly more complicated synthesis of the unsymmetric natural product *epi*-amauromine (**9**) was studied. Surprisingly, the application of the same dimerization conditions to a 1:1 mixture of diastereomeric *exo*-**2c** and *endo*-**2c** led to selective formation of *epi*-amauromine (**9**), with only traces of the two other possible isomers (**7** and **8**) detectable. The 1,3-*syn*-oriented prenyl group sterically shields the carboxylate group of *exo*-**6c** compared with that in *endo*-**6c**. On the other hand, the pyrrolidine nitrogen atom in *endo*-**6c** is deactivated through an $n_N \rightarrow \sigma_{C-N^*}$ interaction compared with that in *exo*-**6c**. Hence, the secondary amine (of the aminal) in diastereomer *exo*-**6c** is more nucleophilic. This stereoelectronic model provides a possible explanation for the observed preferential hetero-

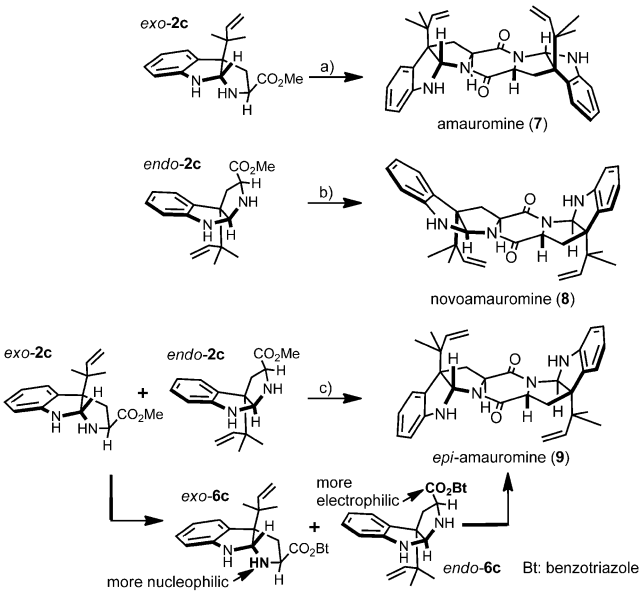
Table 2: (Continued)

Entry	Substrate	Cond.	Product	Yield [%]	*exo*/*endo*[a]
13		C		41	20:1[e]

[a] Determined by ^{1}H NMR spectroscopy of the isolated diastereomeric mixture. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Product isolated after Fmoc deprotection by addition of piperidine (20 equiv). [d] Et_3B (2.5 equiv). [e] $[Ir(COD)Cl]_2$ (5 mol%), (*R*)-**L4** (10 mol%), and 1-benzyl-3-methylimidazolium chloride (10 mol%). Conditions A: $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L4** (10 mol%), 9-BBN-octyl (130 mol%), DBU (20 mol%), prenyl–OBoc (300 mol%), 0.25 M in DCM, 23 °C. Conditions B: $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L4** (5 mol%), 1-benzyl-3-methylimidazolium chloride (5 mol%), Ph_3B (130 mol%), TBD (10 mol%), prenyl–OBoc (500 mol%), 0.25 M in DCM, 23 °C. Conditions C: $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L4** (10 mol%), Et_3B (130 mol%; 1 M in hexane), DBU (20 mol%), prenyl–OBoc (300 mol%), 0.25 M in DCM, 23 °C. Teoc = 2-(trimethylsilyl)ethoxycarbonyl.



Scheme 4. Iridium-catalyzed tryptophan alkylation using different O-Boc-protected electrophile precursors.



Scheme 5. Total synthesis of amauromine, novoamauromine, and *epi*-amauromine using reverse-prenylated tryptophan building blocks. Reagents and conditions: a) $CsOH{\cdot}H_2O$ (3 equiv), THF/MeOH (4:1), RT; then HBTU (3 equiv), 0 °C–RT, 35%; b) $CsOH{\cdot}H_2O$ (3 equiv), THF/MeOH (4:1), RT; then HBTU (3 equiv), 0 °C, 57%; c) *exo*-**6c** (1.0 equiv), *endo*-**6c** (1.0 equiv), $CsOH{\cdot}H_2O$ (4 equiv), THF/MeOH (4:1), RT; then HBTU (3 equiv), RT, 47%. HBTU = 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

dimerization of the amine of *exo*-**6c** and the carbonyl group of *endo*-**6c** (Scheme 5). The natural product is subsequently formed through an intramolecular condensation to the diketopiperazine.[18]

In summary, we have developed a regio- and stereoselective reverse prenylation of indole derivatives. Yields of up to 95% and diastereoselectivities of up to >20:1 were achieved under complete regiocontrol. The iridium catalyst ensures the selective formation of the branched isomer with two consecutive quaternary centers. The stereoselectivity of the process is controlled by a chiral phosphoramidite ligand in combination with an achiral borane additive and can be completely switched to the opposite isomer by changing the nature of the borane. Thus a highly diastereodivergent method to obtain both the *endo* as well as the *exo* isomer irrespective of the absolute configuration of the starting material is presented. For the stereoselective synthesis of all four possible isomers (starting from L- and D-tryptophan), only a single enantiomer of the chiral ligand is required. Finally, the synthetic potential of this method was demonstrated in short syntheses of amauromine and its two natural diastereomers novoamauromine and *epi*-amauromine. Our current investigations focus on further applications of this method and studies on its mechanism and the role of the borane additive, in particular.

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