Iridium-Catalyzed Regio- and Enantioselective N-Allylation of Indoles[**]

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Keywords

allylation; asymmetric catalysis; heterocycles; iridium; synthetic methods

Chiral indole architectures are present in a wide variety of natural products and have been identified as promising lead compounds in medicinal chemistry.[1] Therefore, extensive effort has been dedicated to synthesizing enantioenriched indole derivatives by catalytic, enantioselective reactions,[2] such as 1,2-additions to carbonyl compounds and imines,[3] additions to electron-deficient alkenes,[4] and allylation reactions.[5] However, the indole acts as a carbon nucleophile in each of these reactions; catalytic, enantioselective reactions at the nitrogen atom of an indole are rare, but would provide access to an array of enantioenriched, heterocyclic architectures.
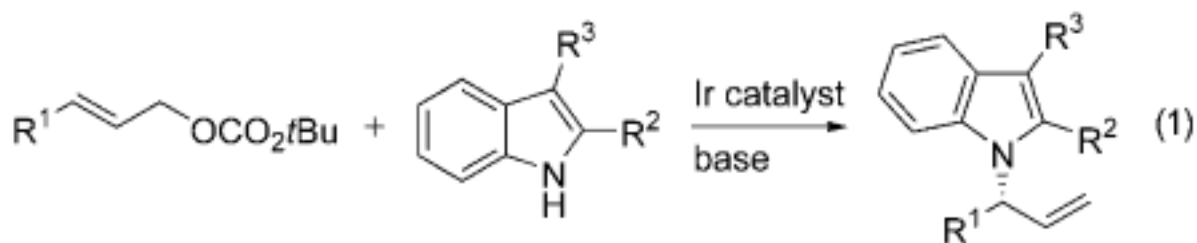
One approach to overcome the greater nucleophilicity of the C3-position of indole, relative to that of N1, is to install an electron-withdrawing substituent at C2. Such a substituent tempers the nucleophilicity at C3, increases the acidity of the N–H bond, and can be used either for additional transformations or removed after reaction at the nitrogen center. Even by following this approach, catalytic, enantioselective reactions of indoles at the nitrogen center are rare. Recent reports by Bandani et al.[6] and Chen et al.[7] have shown that asymmetric alkylation of the indole nitrogen atom occurs with modified cinchona alkaloids, but just one report of enantioselective reactions catalyzed by a transition-metal complex that occur at an indole nitrogen atom has been published. In this work, N-substituted indolopyrrolocarbazole derivatives were synthesized by palladium-catalyzed asymmetric allylic alkylation of bis (indole) lactam pro-aglycons.[8]

The potential of enantioselective N-allylation of indoles to create an entry into biologically active indole derivatives, particularly with catalysts that preferentially form chiral, branched products from linear allylic esters, led us to investigate iridium-catalyzed, asymmetric, N-allylation of indoles. We report herein the synthesis of enantioenriched, branched *N*-allylindoles from the reactions of 2-subsituted, 3-substituted, and 2,3-disubstituted indoles with achiral linear allylic carbonates in the presence of a single-component iridium catalyst [Eq. (1)]. The enantioenriched products are readily converted into monoamine reuptake inhibitors, [9] the indole core of integrin $\alpha_v\beta_3$ inhibitors,[10] and highly substituted dihydropyrrolo[1,2-*a*]indoles.

$$R^1 \diagdown\!\!\diagup\!\!\diagdown OCO_2tBu \; + \; \text{(indole with } R^3, R^2\text{)} \xrightarrow[\text{base}]{\text{Ir catalyst}} \text{(N-allylindole with } R^3, R^2, R^1\text{)} \quad (1)$$

Initial studies to develop catalytic, enantioselective N-allylations of indoles were guided by work from our laboratory on the N-allylation of more acidic and nucleophilic benzimidazoles, imidazoles, and purines catalyzed by the metallacyclic iridium–phosphoramidite complexes [Ir(cod)-(κ^2-**L1**)(ethylene)] (**1**)[11] and [Ir(cod)(κ^2-**L2**)(ethylene)] (**2**).[12] To test whether iridium-catalyzed N-allylation of indoles could occur, we studied the reaction of ethyl indole-2-carboxylate (**4a**) with allylic carbonates. After conducting reactions under various conditions with different catalysts and different carbonate derivatives (see Table S1 in the Supporting Information for details), we found that the allylation of **4a** with *tert*-butylcinnamyl carbonate in the presence of 2 mol% of metallacycle **2** and 10 mol% Cs_2CO_3 occurred exclusively at N1 with excellent branched-to-linear selectivity (**5a/6a** = 97:3). This reaction was conducted with the single-component iridium catalyst **2** to eliminate potential complications that would arise from the generation of the metallacyclic catalyst by base[13] in a system containing a weakly basic nucleophile and carbonate base. The branched *N*-allylindole (*R*)-**5a** was isolated in 89% yield and 99% *ee* [Eq. (2) and Table 1, entry 1]. The absolute configuration of the *N*-allylindole **5a** parallels that of the products from the addition of other nucleophiles that appear to react by backside attack onto the allyl ligand of the intermediate allyliridium complex.[14]
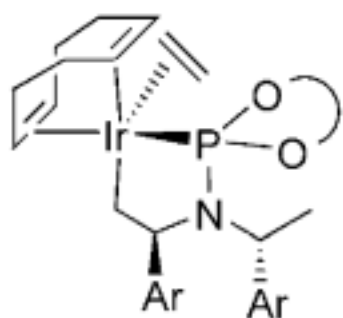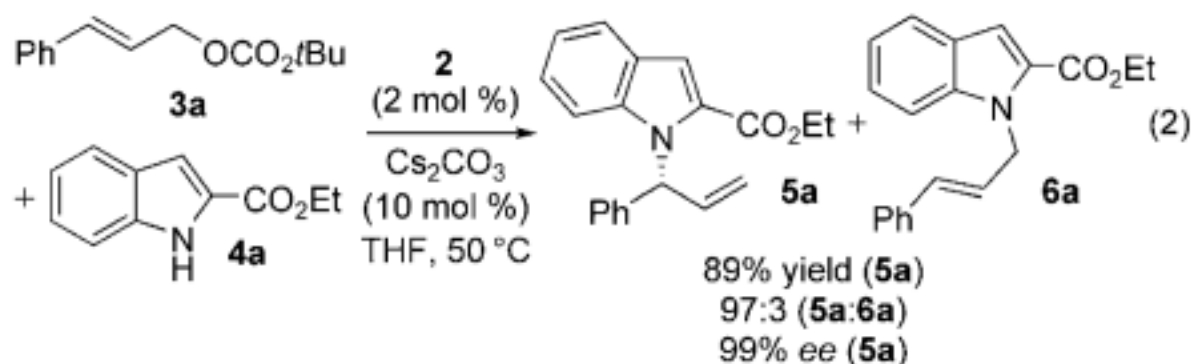

[Ir(cod)(κ^2-**L1**)(ethylene)] (**1**)
[Ir(cod)(κ^2-**L2**)(ethylene)] (**2**)
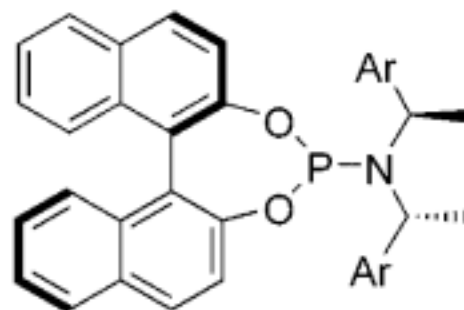
(R_a,R_c,R_c)-**L1**: Ar = Ph
(R_a,R_c,R_c)-**L2**: Ar = 2-MeOC$_6$H$_4$

$$89\% \text{ yield (5a)}$$
$$97:3 \text{ (5a:6a)}$$
$$99\% \text{ ee (5a)}$$

The results of reactions of ethyl indole-2-carboxylate with a series of achiral, linear allylic carbonates under these reaction conditions are shown in Table 1. The reactions of **4a** with electron-rich, electron-neutral, and electron-deficient substituted cinnamyl carbonates gave the corresponding *N*-allylindole products **5b–f** in high yields with a range of 91:9 to 99:1 branched-to-linear selectivity and 96–99% enantiomeric excess (Table 1, entries 2–6). The reaction of 4-(trifluoromethyl)cinnamyl *tert*-butyl carbonate **3d** with **4a** required a higher loading of catalyst **2** (4 mol%), but gave product **5d** in 85% yield with a 91:9 branched-to-linear ratio and 99% *ee* (Table 1, entry 4). Furthermore, this reaction occurred without isomerization of the chiral 1-arylallyl product into the corresponding achiral 1-arylprop-1-enyl product; an analogous isomerization was observed during the allylation of benzimidazoles and purines with electron-deficient cinnamyl carbonates.[12]

Reactions of **4a** with heteroaryl and aliphatic allylic carbonates, as well as a dienyl carbonate, also occurred with moderate to high regioselectivity (**5**/**6**=77:23 to 99:1) and excellent enantioselectivity (98–99% *ee*) (Table 1, entries 7–10). These reactions occurred at room temperature and gave the corresponding *N*-allylindoles in higher yields with higher regioselectivities at room temperature than at 50°C. The reaction of the benzyloxy-substituted allylic carbonate **3j** (R=CH₂OBn) occurred with somewhat lower branched-to-linear selectivity, but nevertheless provides a route to hydroxyalkyl-substituted indoles (Table 1, entry 10). The reaction of **4a** with the aliphatic carbonate **3k** containing branching alpha to the allyl unit (R=cyclohexyl) required more forcing reaction conditions. Although the branched-to-linear ratio was only 87:13, the allylation product **5k** was isolated as a single regioisomer in 54% yield and with 99% *ee* when the reaction was conducted at 50°C in the presence of 4 mol% **2** (Table 1, entry 11).

The range of indoles that undergo the enantioselective N-allylation in the presence of catalyst **2** is summarized in Table 2. Various ethyl indole-2-carboxylates containing electron-donating and electron-withdrawing organic substituents, as well as halogens at the 5-position, were suitable nucleophiles for the allylation reaction with *tert*-butyl cinnamyl carbonate (Table 2, entries 1–4). The reactions of 5-subsituted ethyl indole-2-carboxylates (**4b–e**) occurred with high branched-to-linear selectivity (94:6 to 97:3) and enantioselectivity (99% *ee*), and products **5l–o** were isolated in high yields (84–91%). In addition, indole-2-carboxaldehyde (**4f**) reacted with **3a** to form indole **5p** in 89% yield with 99% *ee* (Table 2, entry 5).

3-Substituted indoles also reacted to give *N*-allylindoles in high yields with excellent selectivities. The reactions of indoles **4g–4j** containing a variety of electron-withdrawing substituents at the 3-position (Table 2, entries 6–9) occurred with high branched-to-linear selectivity (94:6 to 98:2) and excellent enantioselectivity (96–97% *ee*) to form *N*-allylindoles **5q–t** in high yields (84–93%). The reaction of 3-phenylindole (**4k**) with *tert*-butyl cinnamyl

carbonate (Table 2, entry 10) occurred with excellent selectivities, but low conversion because of deactivation of the catalyst.

Indoles containing substituents in both the 2- and 3-positions also underwent selective iridium-catalyzed N-allylation reactions (Table 2, entries 11–15). For example, reactions of **3a** with 2,3-substituted indoles containing an electron-withdrawing substituent at either the 2- or 3-position, such as 3-methylindole-2-carboxaldehyde (**4l**) or 2-phenylindole-3-carboxaldehyde (**4m**), gave the corresponding N-allylated products in high yields with excellent regio- and enantioselectivities (Table 2, entries 11 and 12). The presence of a strong electron-withdrawing group at either the 2- or 3-position of a 2,3-disubstituted indole was not even required for N-allylation. The reactions of 2,3-dipheylindole (**4n**), 3-methyl-2-phenylindole (**4o**), and carbazole (**4p**) with **3a** occurred with 98:2 branched-to-linear ratio in each case and gave *N*-allylindoles **5x**–**z** in 88–95% yield with 98–99% *ee* (Table 2, entries 13–15).

The parent indole and certain indoles containing one phenyl or solely alkyl substituents did not undergo N-allylation, but 7-azaindole did undergo productive N-allylation. Allylations of indole, 2-methylindole, and 2-phenylindole with **3a** catalyzed by **1** or **2** and Cs_2CO_3 at 50°C occurred selectively at the 3-position, whereas no allylation products formed from the analogous reactions of 3-methylindole and 2,3-dimethylindole. However, the reaction of 7-azaindole **7** with *tert*-butyl cinnamyl carbonate (**3a**) occurred with greater than 90:10 N1-to-C3 selectivity and 91:9 branched-to-linear selectivity, and the branched *N*-allylazaindole **8** was isolated from this reaction in 79% yield and 99% *ee* (Scheme 1).

Within the past five years, molecular scaffolds containing 3-(1*H*-indol-1-yl)-3-arylpropan-1-amine and 3-(1*H*-indol-1-yl)-propanoic acid substructures have been identified as promising lead compounds for medicinal chemistry. 3-(1*H*-Indol-1-yl)-*N*-methyl-3-arylpropan-1-amines are potent dual-acting norephinephrine and serotonin reuptake inhibitors,[9a] while 3-(1*H*-indol-1-yl)-3-arylpropanoic acids and 3-(1*H*-indol-1-yl)-3-alkylpropanoic acids are constituents of potent inhibitors of the integrin $\alpha_v\beta_3$.[10] All of these structures contain a stereocenter at the 3-position of the arylpropanamine, arylpropanoic acid, or alkylpropanoic acid subunit that could be formed with control of absolute stereochemistry by iridium-catalyzed allylic substitution. Furthermore, the allyl moieties of the *N*-allylindole products provide a suitable handle for straightforward elaboration into the requisite propanamine or propanoic acid units.

The syntheses of 3-(1*H*-indol-1-yl)-*N*-methyl-3-arylpropan-1-amines **11** and **12a**–**c** are presented in Scheme 2. The known monoamine reuptake inhibitor (*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (**11**) was prepared from **5q** by a sequence including removal of the 3-alkoxycarbonyl group by hydrolysis and decarboxylation, and standard conversion of the alkene unit into an aminoethyl group by hydroboration, oxidation, then conversion of the alcohol into the chloride, and finally substitution with methylamine. However, we also developed a more direct route using hydrozirconation. Hydrozirconation of *N*-allylindoles **5x**–**z** and subsequent reaction of the alkylzirconium intermediate with *N*-methyl hydroxylamine-*O*-sulfonic acid gave 3-(1*H*-indol-1-yl)-*N*-methyl-3-arylpropan-1-amines **12a**–**c** in a two-step, one-pot sequence from the allylation product in 63–73% yield.

We also showed that highly substituted and enantioenriched dihydropyrrolo[1,2-*a*]indoles, which occur in natural products and other biologically active molecules,[15] are readily synthesized from appropriately substituted *N*-allylindoles. For example, the reaction of (*R*)-1-(1-phenylallyl)-1*H*-indole-2-carboxaldehyde (**5p**) with *N*-methylhydroxylamine forms a transient nitrone that undergoes an intramolecular dipolar cycloaddition with the allyl moiety of **5p** to form a tricyclic cycloadduct in 83% yield with excellent regio- and diastereoselectivity. [16] Reductive cleavage of the N–O bond contained in the cycloadduct gave the highly

substituted dihydropyrrolo[1,2-*a*]indole **13**, a ring-constrained analogue of the 3-(1*H*-indol-1-yl)-*N*-methyl-3-arylpropan-1-amines, in 87% yield.

Enantioenriched *N*-allylindoles are also precursors to indolyl-1-yl propanoic acids, which are key subunits in a class of integrin $\alpha_v\beta_3$ inhibitors.[10] Sequential hydroboration and oxidation of *N*-allylindole **5q** and then oxidation of the alcohol with iodobenzene diacetate, TEMPO, and sodium bicarbonate led to (*R*)-3-(3-(methoxycarbonyl)-1*H*-indol-1-yl)-3-phenylpropanoic acid (**14**) in 79% yield over two steps.

In summary, we have developed a method for highly regioselective and enantioselective N-allylation of indoles with achiral, acyclic allylic electrophiles in the presence of a metallacyclic iridium catalyst. These reactions encompass a broad range of indole nucleophiles, as well as a variety of unsymmetrical aryl, heteroaryl, and aliphatic allylic carbonates and a dienyl carbonate. The enantioenriched N-allylindole products are formed with consistently high enantioselectivity (96–99% *ee*) and are readily transformed into 3-(1*H*-indol-1-yl)-*N*-methyl-3-arylpropan-1-amines, dihydropyrrolo-[1,2-*a*]indoles, and indol-1-yl propanoic acids. The use of this reaction to prepare libraries of enantioenriched indole derivatives to identify lead compounds for medicinal chemistry will be the subject of future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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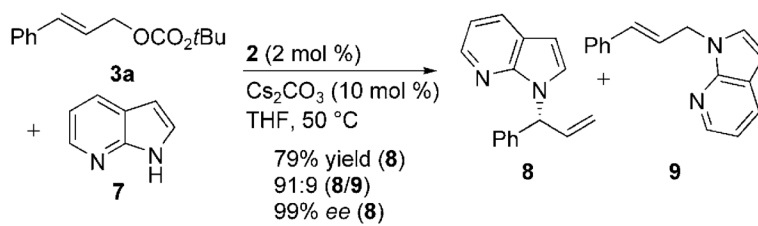
Scheme 1.
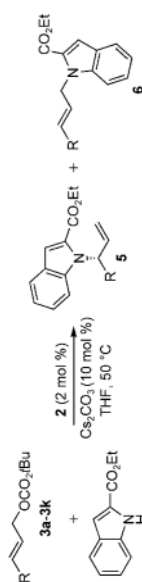Regioselective and enantioselective N-allylation of 7-azaindole **7** with **3a** in the presence of catalyst **2**.
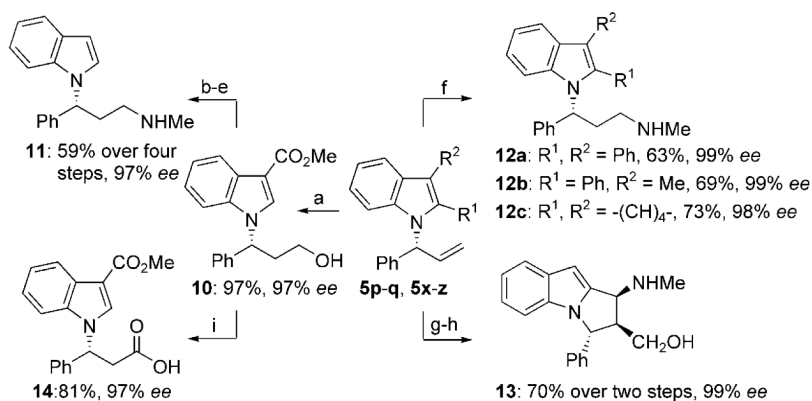
Scheme 2.
Syntheses of enantioenriched 3-(1H-indol-1-yl)-*N*-methyl-3-arylpropan-1-amines **11** and **12a-c**, dihydropyrrolo[1,2-*a*]indole **13**, and indol-1-yl propanonic acid **14** from *N*-allylindoles. *N*-Allylindoles: **5p**, R^1=CHO, R^2=H, 99% *ee*; **5q**, R^1=H, R^2=CO$_2$Me, 97% *ee*; **5x**, R^1, R^2=Ph, 99% *ee*; **5y**, R^1=Ph, R^2=Me, 99% *ee*; **5z**, R^1, R^2=-(CH)$_4$-, 98% *ee*. Reaction conditions: a) **5q**, 9-BBN, THF, −78°C to RT, then H$_2$O$_2$, 3$_M$ NaOH, EtOH, 0°C to RT, 97%, 97% *ee*; b) KOH, MeOH, reflux; c) PhBr, reflux, 68% over two steps; d) PPh$_3$, CCl$_4$, 0°C→RT, 91%; e) MeNH$_2$, EtOH, 90°C, 95%, 97% *ee*; f) **5x–z,** [Cp$_2$Zr(H)Cl], THF, RT, then CH$_3$NHOSO$_3$H, 60°C (see Scheme 2 for results); g) **5p**, MeNHOH·HCl, NaOAc, THF, reflux, 83%, 9:1 regioselectivity, >99:1 d.r.; h) Zn, AcOH, H$_2$O, 60°C, 87%, 99% *ee*; i) PhI(OAc)$_2$, TEMPO, NaHCO$_3$, MeCN/H$_2$O (1:1), 81%, 97% *ee*. 9-BBN=9-borabicyclo[3.3.1]nonane, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical.

Table 1

Iridium-catalyzed enantioselective allylation of ethyl indole-2-carboxylate **4a** with allylic carbonates **3a–k**.[a]

Entry	3 (R)	5	5/6[b]	Yield [%][c]	ee [%][d]
1	3a (Ph)	5a	97:3	89	99
2	3b (4-MeOC$_6$H$_4$)	5b	99:1	88	99
3	3c (4-BrC$_6$H$_4$)	5c	97:3	87	99
4[e]	3d (4-F$_3$CC$_6$H$_4$)	5d	91:9	85	99
5	3e (3-MeOC$_6$H$_4$)	5e	98:2	95	98
6[f]	3 f (2-MeOC$_6$H$_4$)	5 f	95:5	72	96
7[f]	3g (2-furyl)	5g	91:9	85	99
8[f,g]	3h ((E)-CH=CHCH$_3$)	5h	99:1	86	99
9[f]	3i (n-propyl)	5i	94:6	92	99
10[f]	3j (CH$_2$OBn)	5j	77:23	70	98
11[e]	3k (cyclohexyl)	5k	87:13	54	99

[a]See the Supporting Information for experimental details.

[b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

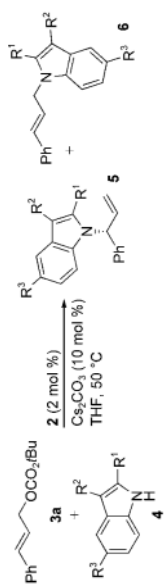[c]Yield of isolated **5**.

[d]Determined by chiral HPLC methods.

[e]Used 4 mol% **2** as the catalyst.

[f]Reaction was run at room temperature.

[g]Enantiomeric excess was determined after reduction with LiAlH4.

Table 2

Iridium-catalyzed N-allylation of 2-substituted, 3-substituted, and 2,3-disubstituted indoles **4b–p** with *tert*-butyl cinnamyl carbonate **3a**.[a]

Entry	4	R[1]	R[2]	R[3]	5	5/6[b]	Yield [%][c]	ee [%][d]
1	**4b**	CO₂Et	H	OMe	**5l**	97:3	88	99
2	**4c**	CO₂Et	H	F	**5m**	94:6	84	99
3	**4d**	CO₂Et	H	Cl	**5n**	95:5	91	99
4	**4e**	CO₂Et	H	NO₂	**5o**	94:6	90	99
5	**4f**	CHO	H	H	**5p**	98:2	89	99
6	**4g**	H	CO₂Me	H	**5q**	96:4	84	97
7	**4h**	H	CHO	H	**5r**	94:6	87	96
8	**4i**	H	C(O)Me	H	**5 s**	98:2	88	96
9	**4j**	H	CN	H	**5t**	96:4	93	96
10	**4k**	H	Ph	H	**5u**	99:1	21	97
11	**4 l**	CHO	Me	H	**5v**	98:2	82	99
12	**4m**	Ph	CHO	H	**5w**	96:4	93	97
13	**4n**	Ph	Ph	H	**5x**	98:2	95	99
14	**4o**	Ph	Me	H	**5y**	98:2	89	99
15	**4p**	-(CH)₄-		H	**5z**	98:2	88	98

[a]See the Supporting Information for experimental details.

[b]Determined by ¹H NMR analysis of the crude reaction mixture.

[c]Yield of isolated **5**.

[d]Determined by chiral HPLC methods.

[e]Methyl cinnamyl carbonate was used as the electrophile.