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Regio- and Enantioselective Iridium-Catalyzed *N*-Allylation of Indoles and Related Azoles with Racemic Branched Allylic Acetates

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Graphical Abstract

Rough, Ready and Regioselective. Stable to air, water and SiO₂, cyclometallated π -allyliridium *C,O*-benzoates modified by (*S*)-tol-BINAP catalyze highly enantioselective *N*-allylations of indoles and related azoles. Complementing the scope of all previously reported metal-catalyzed indole allylations, complete levels of *N* vs C3 and branched vs linear regioselectivity are observed.

Keywords

Enantioselective; Amination; C-N Bond Formation; Iridium; Allylic Alkylation

Iridium-catalyzed allylic amination has emerged as an important method for enantioselective C-N bond formation.^[1–9] Pursuant to the pioneering work of Takeuchi,^{1,2} studies from the laboratories of Helmchen,^{3,4} Hartwig,^{5,6} Carreira⁷ and You^{8,9} have shown that chiral phosphoramidite-modified iridium complexes are especially effective in this regard (Figure 1). Like the parent palladium-catalyzed Tsuji-Trost reactions,^[10] the iridium-phosphoramidite-catalyzed allylic alkylations occur by way of cationic π -allylmetal intermediates. Recently, we found that π -allyliridium-*C,O*-benzoates, which are well-known to promote *nucleophilic* allylation of carbonyl compounds,^[11,12] are also effective catalysts for highly regio- and enantioselective *electrophilic* allylation of amines.^[13] These π -allyliridium-*C,O*-benzoates react by way of neutral π -allylmetal intermediates, which may account for their amphiphilic character. One advantage of the π -allyliridium-*C,O*-benzoate catalysts relates to their facile preparation and remarkable stability toward air, water and

SiO₂.^[14] Using SEGPHOS-modified π -allyliridium-*C,O*-benzoate catalysts, allylic aminations mediated by aliphatic amine nucleophiles occur with high levels of regio- and enantioselectivity.^[13a] It was later found that the tol-BINAP-modified π -allyliridium-*C,O*-benzoate (*S*)-Ir-**I** is a superior catalyst, enabling highly regio- and enantioselective allylation of electronically diverse primary and secondary (hetero)aryl amines.^[13b]

In the latter study, it was shown that 5-amino-indole (5-*N*)-**1a** undergoes allylic alkylation at the 5-amino moiety to furnish (5-*N*)-**3a** with complete site-selectivity (eq. 1), suggesting indoles may not be subject to π -allyliridium-*C,O*-benzoate-catalyzed *N*-allylation. To challenge this assumption, the parent indole **1a** was exposed to essentially identical conditions for allylic alkylation (eq. 2). To our delight, the product **3a** was obtained in excellent yield as a single regioisomer in 93% enantiomeric excess. These results were deemed significant, as indoles and related azoles are prevalent structural motifs in clinical candidates and FDA approved drugs (Figure 1),^[15,16] and allylation at C3 is the major product observed in the intermolecular allylation of structurally and electronically unbiased indoles using palladium,^[17] ruthenium^[18] or iridium^[19] catalysts. For example, to enforce *N*-allylation, use of electron deficient indoles^[17j,19c] or heteroatom substituted π -allylmetal species (from alkoxyallenes) is required.^[17o] These limitations have necessitated the development of indirect methods for the synthesis of enantiomerically enriched *N*-allyl indoles (Figure 1).^[20] As the development of enantioselective methods for intermolecular indole allylation that are completely *N*-selective and display exclusive branched regioselectivity remains an unmet challenge,^[17–20] an effort to assess the scope the π -allyliridium-*C,O*-benzoate-catalyzed indole allylation was undertaken. Here, we show that the tol-BINAP-modified iridium complex (*S*)-Ir-**I** catalyzes highly enantioselective allylation of diverse indoles and azoles with complete *N*-regioselectivity and complete branched regioselectivity.

To assess the generality of indole allylation catalyzed by (*S*)-Ir-**I**, the reaction conditions utilized in equation 2 were applied to structural diverse indoles and azoles **1a–1p** (Table 1).

Beyond the parent indole **1a**, electronically diverse indoles substituted at the 2-position (**1b**), 4-position (**1e**), 5-position (**1f**), 6-position (**1g**, **1h**) and 7-position (**1i–1k**) each underwent efficient allylation to deliver the respective adducts (**3b**, **3e–3k**) with complete *N*-regioselectivity, complete branched regioselectivity and uniformly high levels of enantioselectivity. The structurally related azoles tetrahydro-carbazole **1c**, the “homo-tetrahydro-carbazole” **1d**, 3-methyl-indazole **1l**, 2-ethyl-benzimidazole **1m**, 6-azaindole **1n**,

7-azaindole **1o**, carbazole **1p** and 2-methyl-3-carboxypyrrole ethyl ester **1q** also underwent efficient *N*-allylation to form adducts **3c**, **3d** and **3l–3q**, respectively, as single constitutional isomers with high levels of enantiomeric enrichment. Of relevance to medicinal chemistry applications, the formation of adduct **3o** demonstrates tolerance of a pinacol boronate moiety under the conditions of asymmetric *N*-allylation. Additionally, to further test the limits of our method, catalyst-directed diastereoselectivity was explored in the allylation of the structurally complex chiral azole **1r**, which is related to AZD-9496, a clinical stage non-steroidal oral estrogen receptor inhibitor.^[21] Remarkably, the enantiomeric iridium catalysts (*S*)-Ir-**I** and (*R*)-Ir-**I** deliver the diastereomeric adducts **3r** and **3s** in >95% yield with complete levels of catalyst-directed stereoinduction.

Using diverse α -substituted allyl acetates **2b–2j**, the scope of the electrophilic partner was subsequently evaluated in *N*-allylations of the parent indole **1a** (Table 2). Branched allylic acetates bearing linear alkyl groups **2b–2d**, which incorporate phenyl, benzyl ether and methyl sulfide moieties, respectively, were efficiently converted to adducts **4b–4d**. As illustrated by the formation adduct **4e**, branched alkyl groups are tolerated. Finally, the preparation of adducts **4f–4j** highlight the tolerance of cycloalkyl substituents. All adducts **4b–4j** were formed as single constitutional isomers and with high levels of enantiomeric enrichment. The absolute stereochemistry of adducts **3a–3s** and **4b–4j** was assigned in analogy to adduct **3a**, which was determined through comparison of its optical rotation to a sample reported in the literature.^[8b]

To further assess the breadth of the present protocol for catalytic enantioselective *N*-allylation, the cyclization of racemic allylic acetate **5a** was explored (eq. 3). The cyclization of **5a** provides an opportunity to test the limits of stereoinduction, as the rate of enantiotopic π -facial interconversion must exceed the rate of 5-membered ring formation.^[22] The cyclization of **5a** also provides another context to evaluate the fidelity of *N*- vs C3-regioselectivity. In the event, exposure of **5a** to (*S*)-Ir-**I** under standard conditions at 50 °C provided the product of *N*-cycloallylation **6a** as single constitutional isomer without competing C3-cycloallylation.

The basicity of the reaction conditions and the acidity of indoles suggest the active nucleophiles in the present protocol for iridium-catalyzed *N*-allylation are *N*-centered anions. In previously reported allylic aminations catalyzed by π -allyliridium-*C,O*-benzoates, significantly less acidic aliphatic and aromatic amines were utilized, which likely serve as neutral *N*-nucleophiles.^[13] Hence, although a mechanism involving outer-sphere addition was established in the previously reported allylic aminations of the less acidic aliphatic and aromatic amines, it was unclear whether inner- or outer-sphere addition pathways were operative in the present indole-mediated asymmetric aminations. To address this question, the enantiomerically enriched (*Z*)-deuterated allylic acetate **2k** was subjected to standard

conditions for allylic amination using indole **1a** (Scheme 1).^[23] Using the enantiomeric catalysts (*S*)-**Ir-I** and (*R*)-**Ir-I** the stereoisomeric products **4k** and *iso*-**4k** are generated, which corroborates C-N bond formation through outer-sphere addition.

In summary, using π -allyliridium-*C,O*-benzoate catalysts in combination with racemic branched alkyl-substituted allylic acetate proelectrophiles, we report the first highly enantioselective intermolecular Tsuji-Trost-type indole *N*-allylations wherein complete *N*-regioselectivity is accompanied by complete branched-regioselectivity. Future work will explore related electrophilic *N*- and *C*-allylations catalyzed by cyclometallated π -allyliridium *C,O*-benzoates. These efforts illustrate the effectiveness of academic-industrial collaboration *vis-à-vis* development of asymmetric methods for unmet challenges in synthetic chemistry of relevance to the drug discovery enterprise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Iridium catalysts for asymmetric allylic amination and chiral indole-containing clinical candidates.

Scheme 1.

Iridium-catalyzed amination of enantiomerically enriched deuterated allylic acetate **2k** with the enantiomeric catalysts $(S)\text{-Ir-I}$ and $(R)\text{-Ir-I}$.^a

Table 1.

Regio- and enantioselective iridium-catalyzed allylic alkylation of indoles and related azoles **1a-1s** using α -methyl allyl acetate **2a**.^a

		3a , 78% Yield 93% ee				3b , 74% Yield 90% ee				3c , 81% Yield 90% ee	
		3d , 83% Yield 90% ee				3e , 83% Yield 91% ee				3f , 79% Yield 92% ee	
		3g , 82% Yield 88% ee				3h , 85% Yield 88% ee				3i , 88% Yield 92% ee	
		3j , 92% Yield 92% ee				3k , 77% Yield 88% ee				3l , 67% Yield 93% ee	
		3m , 85% Yield 90% ee				3n , 71% Yield 90% ee				3o , 76% Yield 92% ee	
		3p , 91% Yield 93% ee				3q , 74% Yield 90% ee				3r , 95% Yield (X-Ray) >20:1 dr, (S)-Ir-I	
		3s , 96% Yield >20:1 dr, (R)-Ir-I									

^aYields are of material isolated by silica gel chromatography. Regio- and diastereoselectivities were determined by ¹H NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Table 2.

Regio- and enantioselective iridium-catalyzed allylic alkylation of indole **1a** using diverse α -substituted allyl acetates **2b-2j**.^a

<div> </div>
4b , 79% Yield 92% ee		4c , 65% Yield 91% ee		4d , 71% Yield 93% ee
4e , 68% Yield 92% ee		4f , 76% Yield 92% ee		4g , 70% Yield 90% ee
4h , 74% Yield 90% ee		4i , 64% Yield 92% ee		4j , 60% Yield 90% ee

^aYields are of material isolated by silica gel chromatography. Regio- and diastereoselectivities were determined by ¹H NMR analysis of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.