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Synthesis and Preliminary Biological Studies of 3-Substituted Indoles Accessed by a Palladium-Catalyzed Enantioselective Alkene Difunctionalization Reaction

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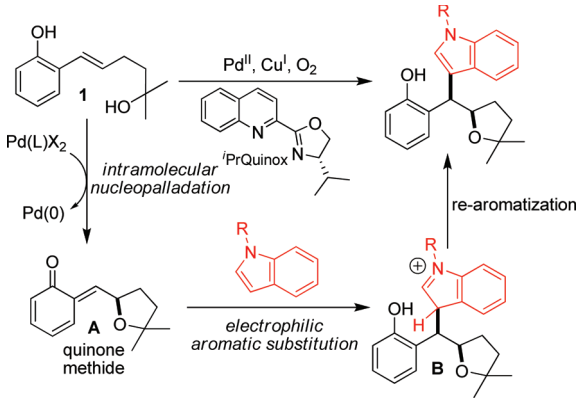
The indole framework represents a "privileged" structural motif commonly found in pharmaceutical drugs and natural products.[1] Therefore, new methods for accessing unique indole derivatives is of importance for drug lead synthesis. For this reason, we became interested in using indoles as nucleophiles in the enantioselective alkene difunctionalization reactions recently disclosed by our laboratory.[2,3] Herein we report the successful development of such a reaction and preliminary biological studies showcasing both the activity toward breast cancer cell lines and differential phenotypes for two related derivatives.

Scheme 1. Proposed Mechanism for the Tandem Oxypalladation/ Electrophilic Aromatic Substitution Process



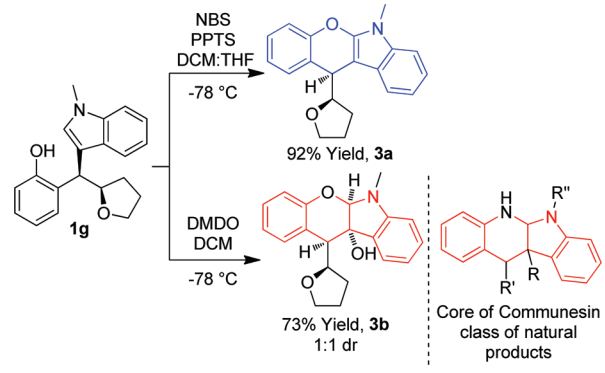
Previously, substrate **1** was found to undergo a highly enantioselective, Pd-catalyzed sequential intra- and intermolecular alkene difunctionalization reaction using mainly alcohols as exogenous nucleophiles.[3] We envisioned a scenario in which Pd would catalyze an intramolecular nucleopalladation, with the proposed subsequent formation of a quinone methide intermediate. To this intermediate, addition of electron-rich heteroaromatic derivatives could be accomplished via electrophilic aromatic substitution (Scheme 1).[4a] However, we were concerned that the indole would not be compatible with the Pd(II) catalysis because of the ability of these compounds to undergo C−H activation.[4b] To our delight, the combination of substrate **1** and *N*-methylindole under previously reported conditions successfully led to the formation of the desired product. Modest changes were made to these conditions,[3,5a] including a decrease in the concentration of the indole nucleophile (from 50 to 15 equiv), resulting in a high yield of the desired product (81% isolated yield) with excellent dr (>20:1) and er (97:3).[5] It should be noted that a 60% yield can be obtained using 5 equiv of *N*-methylindole without any influence on dr or er, with recovery of the remaining nucleophile in >95% yield.[5a]

The nature of the phenol was first explored, and it was found that electron-withdrawing substituents generally gave higher yields; however, high diastereoselectivity and enantioselectivity were observed in all cases (Table 1, entries **1a**−**f**). Both tetrahydrofuran and tetrahydropyran ring systems were formed in good yields with excellent er and dr (Table 1, entries **1g** and **1h**). A substrate containing an ether linkage was cyclized to yield a 1,4-dioxane product, albeit in modest yield (Table 1, entry **1i**).

Various indoles were next submitted to the reaction conditions, and it was found that *N*-alkyl-protected indoles were well-tolerated, including an indole containing a removable protecting group (Table 1, entries **2a** and **2b**). Various 2-substituted indoles with different steric and electronic parameters were also found to be compatible, again leading to good yields and excellent er (Table 1, entries **2c**−**e**). The electronic nature of indole substitution had little effect on the reaction outcome (Table 1, entries **2f**−**i**). Furthermore, 5-bromoindole was tolerated, giving a 62% yield and an excellent er of 98:2 (Table 1, entry **2g**), which showcases the potential for further functionalization of these compounds with Pd(0) catalysis. The chemistry presented is not limited to only indole nucleophiles, as demonstrated by the successful use of *N*-methylpyrrole (Table 1, entry **2j**). However, it should be noted that N-protection of the indole is required and that electron-poor groups (such as Ts or Boc) on the indole nitrogen substantially decrease the yield.

To illustrate the utility of this method to rapidly access relatively complex structures, processing of several derivatives was examined (Scheme 2). Treatment of **1g** with NBS resulted in rapid oxidative cyclization, affording **3a** as the fused tetracyclic product in 92% yield.[6] Additionally, treatment of **1g** with DMDO resulted in the formation of the tertiary alcohol **3b** in good yield, albeit with low dr.[7] Compound **3b**, which has homology with the core structure of the communesin class of natural products,[8] contains four contiguous stereocenters and can be synthesized from salicylaldehyde in just four steps.

Scheme 2. Accessing Interesting Indole Core Structures



In view of the ease with which we were able to access diverse analogues and the unique architecture of the products formed, we decided to evaluate the biological activity of several racemic variants using a luminal-type breast cancer cell line (MCF-7, Figure 1). Excitingly, several of the analogues, including **2c** and **2f**, were found

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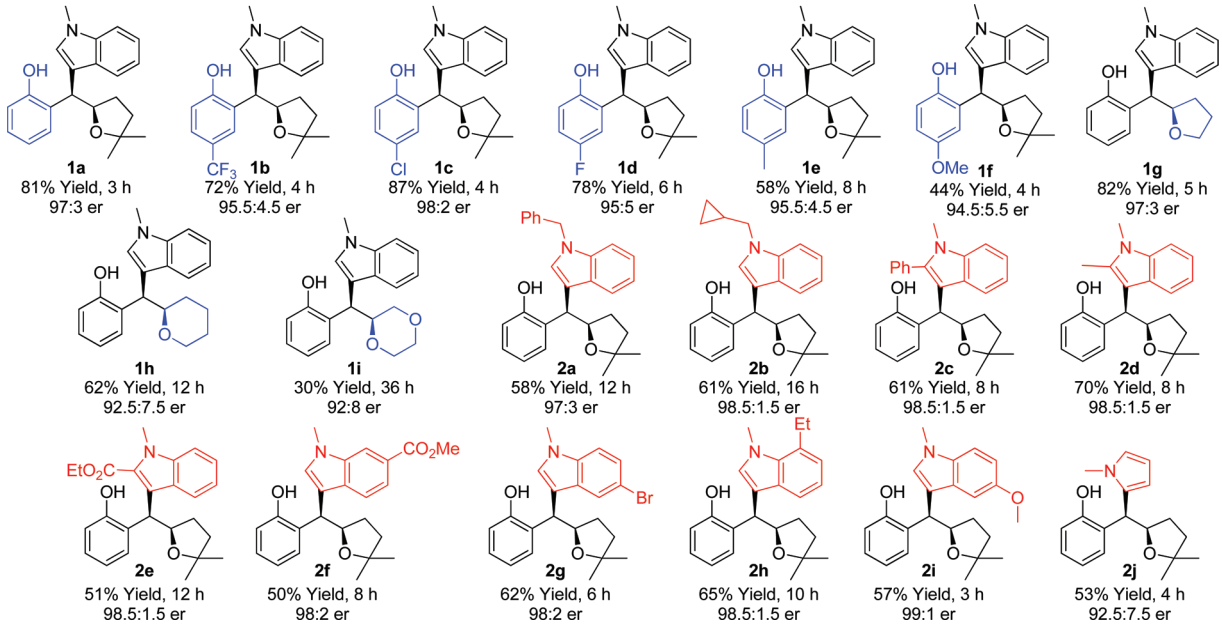
Table 1. 3-Substituted Indoles Formed by the Pd-Catalyzed Enantioselective Alkene Difunctionalization Reaction[a]



[a] Reaction conditions: 4 mol % $Pd(MeCN)_2Cl_2$, 8 mol % CuCl, 14 mol % iPrQuinox, 1 equiv of $KHCO_3$, 15 equiv of NuH, Balloon O_2, r.t., 0.1−0.05 M 4:1 toluene/THF. The er for the major diastereomer was determined by supercritical fluid chromatography using a column equipped with a chiral stationary phase. The dr was >20:1 for all compounds, as determined by ^1H NMR spectroscopy. The major diastereomer was determined by X-ray crystal analysis of entry **2g**. The absolute configuration was assigned by comparison with a previous report.[3]

to reduce the cell count in comparison with a DMSO control in this whole-cell assay. The differential activity was evaluated for these two analogues and their corresponding enantiomers in MCF-7 and MCF-10A (normal breast) cell lines, wherein the compounds were modestly more effective at killing tumor cells.[5a] Of particular interest, cell-cycle analysis was performed using flow cytometry with a bromodeoxyuridine pulse.[5a] The results of this experiment were quite revealing in that **2c** caused a G1 arrest while **2f** caused a G2 arrest similar to that of Taxol. This finding suggests that modest structural changes in the indole framework have a significant bearing on the molecular target of these compounds.

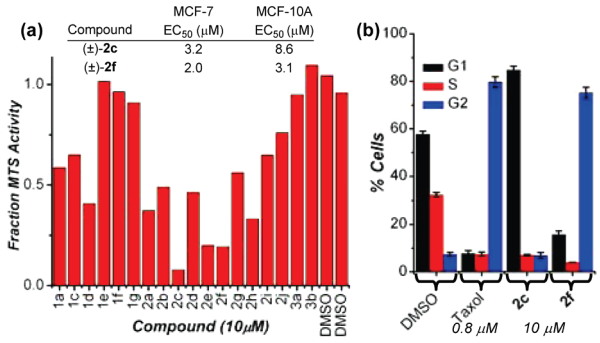


Figure 1. (a) Relative activity of new compounds in MCF-7 cells. (b) Cell-cycle analysis of **2c** and **2f** at 48 h.

In conclusion, we have developed a highly enantioselective and diastereoselective Pd-catalyzed alkene difunctionalization reaction that is proposed to proceed by intramolecular oxypalladation followed by the addition of indole to a quinone methide. The chemistry tolerates a wide range of substitution on both the alkene and indole substrates, and the resulting products can easily be processed to form relatively complex structures. Several of the new indole compounds were found to have modestly selective activity in MCF-7 tumor cells in comparison with MCF-10A normal breast cells. Cell-cycle analysis of two of these compounds revealed distinct phenotypes, providing a foundation for further development of the chemical methodology and exploration of the molecular origin of the antitumor activity.

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Supporting Information Available: Experimental procedures and full spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) See the Supporting Information for more details. (b) See the Table 1 footnote for detailed optimized conditions.

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