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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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Abstract

A unique alkene difunctionalization reaction has been developed which allows rapid construction of molecular complexity around the biologically relevant indole framework. The reaction proceeds with up to 87% yield, 99:1 er and >20:1 dr. Evaluation of several of the compounds reveals promising anti-cancer activity against MCF-7 cells.

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

Previously, substrate **1** was found to undergo a Pd-catalyzed highly enantioselective sequential intra-intermolecular alkene difunctionalization using mainly alcohols as exogenous nucleophiles.3 We envisioned a scenario in which Pd-catalyzes an intramolecular nucleopalladation with subsequent proposed formation of a quinone methide intermediate. To this intermediate, addition of electron rich heteroaromatic derivatives can be accomplished via electrophilic aromatic substitution.[4a] However, we were concerned that the indole would not compatible with the Pd(II) catalysis due to the ability of these compounds to undergo C-H activation.[4b] To our delight, combination of substrate **1** and *N*-methylindole under previously reported conditions successfully leads to formation of the desired product. Modest changes were made to these conditions3,[5a] including lowering the concentration of the indole nucleophile (50 to 15 equivalents) resulting in high yield of the desired product (81% isolated yield) with excellent dr (>20:1) and er (97:3).[5] should be noted that a 60% yield can be obtained using five equivalents of *N*-methylindole without any influence on dr or and the remaining nucleophile can be recovered in >95% yield.[5a]

The nature of the phenol was first explored where it was found that electron withdrawing substituents generally give higher yields but in all cases high diastereoselectivity and enantioselectivity are observed (Table 1, Entries **1a**-**1f**). Both tetrahydrofuran and

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

tetrahydropyran ring systems are formed in good yields and 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 wherein it was found that *N*-alkyl protected indoles are 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**-**2e**). The electronic nature of indole substitution has little effect on the reaction outcome (Table 1, Entries **2f**-**2i**). Furthermore, 5-bromoindole was tolerated giving 62% yield and an excellent er of 98:2, which showcases the potential to further functionalize these compounds with Pd(0) catalysis (Table 1, Entry **2g**). The chemistry presented is not limited to only indole nucleophiles, which was 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 electron poor groups (such as Ts or Boc) on the indole nitrogen substantially lower the yield.

To illustrate the utility of this method to rapidly access relatively complex structures, processing of several derivatives was examined. Treatment of **1g** with NBS resulted in rapid oxidative cyclization to give **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 in 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 4 steps.

Considering the ease in which we can access diverse analogs 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 analogs were found to reduce the cell count as compared to a DMSO control including **2c** and **2f** in this whole cell assay. Differential activity was evaluated for these two analogs 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 are quite revealing in that **2c** causes a G1 arrest while **2f** causes a G2 arrest similar to that of Taxol. This finding suggests that the modest structural changes to the indole framework have a significant bearing on the molecular target of these compounds.

In conclusion, we have developed a highly enantioselective and diastereoselective Pd-catalyzed alkene difunctionalization reaction, which 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 be easily processed to relatively complex structures. Several of the new indole compounds were found to have modestly selective activity in MCF-7 tumor cells as compared to MCF-10A normal breast cells. Cell cycle analysis of two of these compounds has revealed distinct phenotypes providing the foundation to further develop the chemical methodology and explore the molecular origin of the antitumor activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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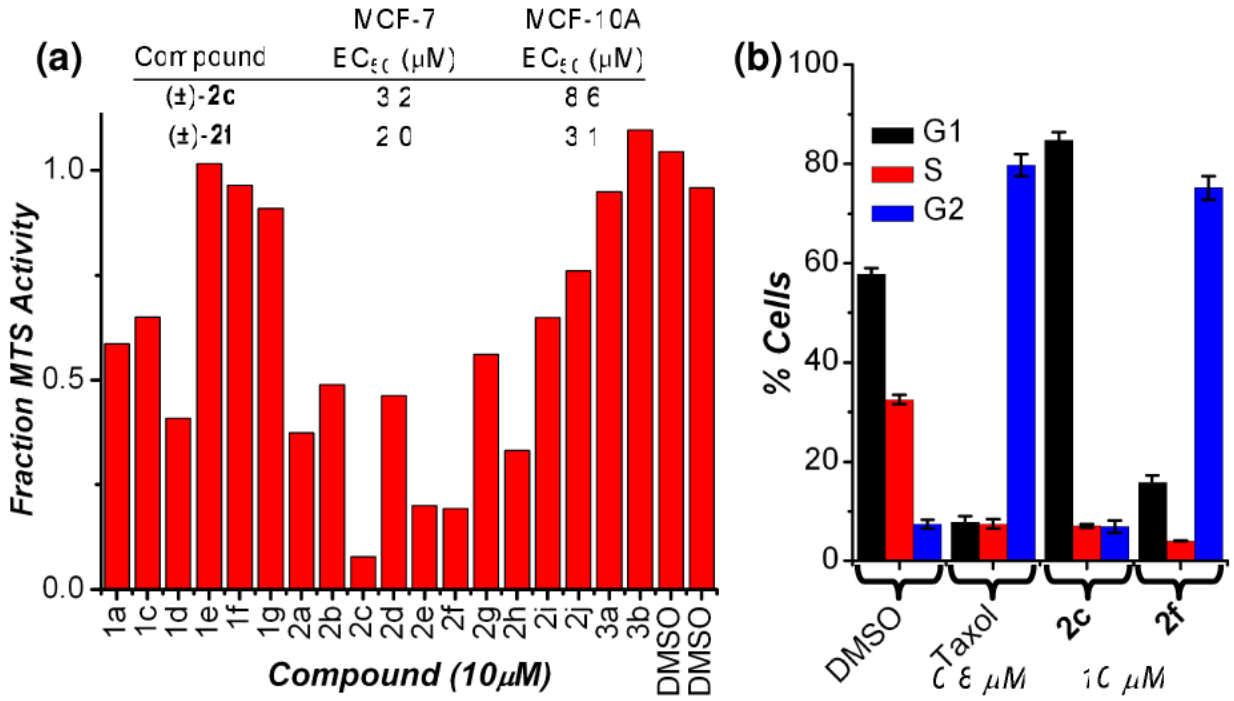
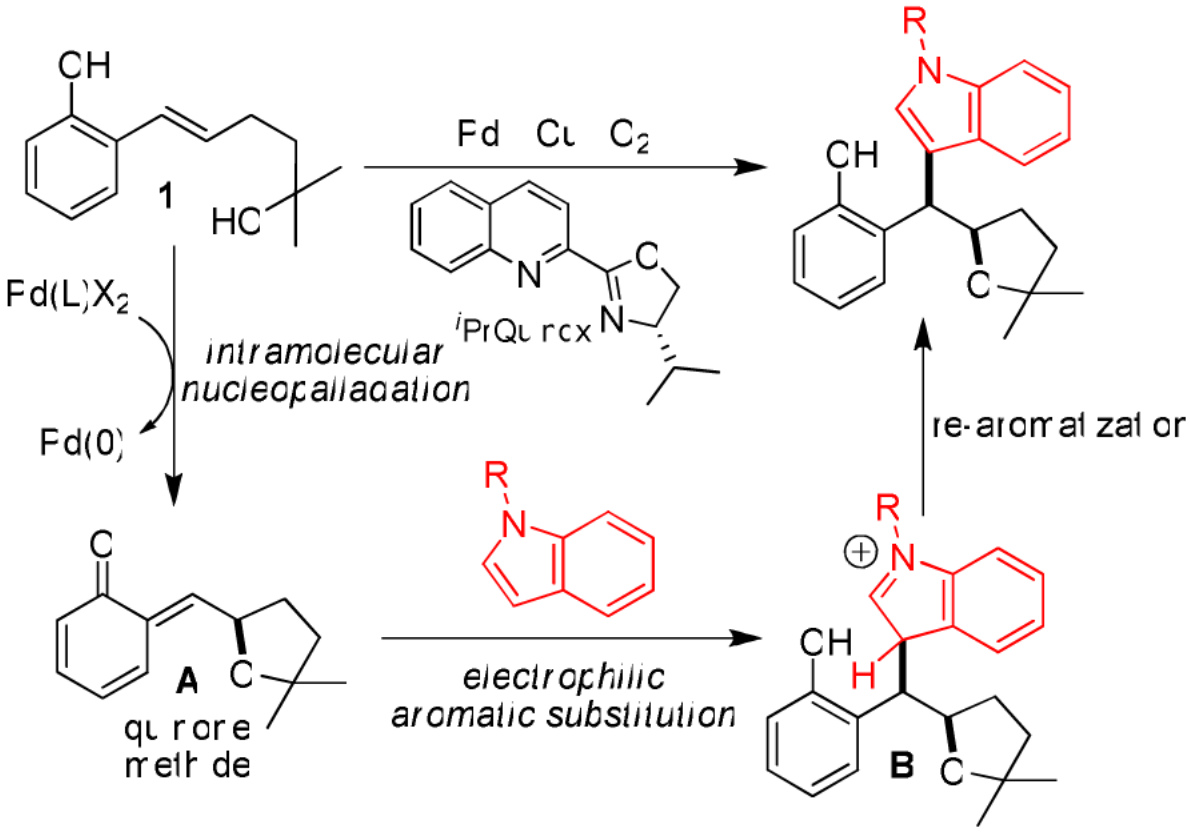
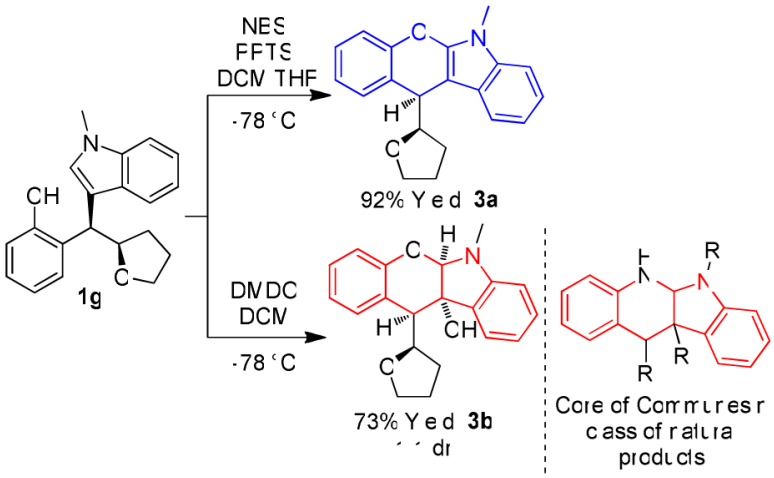


Figure 1.
(a) Relative activity of new compounds in MCF-7 cells. (b) Cell cycle analysis of **2c** and **2f** at 48h.



Scheme 1.
Proposed mechanism for tandem oxypalladation/electrophilic aromatic substitution process.



Scheme 2.
Accessing interesting indole core structures.

Table 1

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