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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Intramolecular Oxidative C−H Coupling for Medium-Ring Synthesis

Didier G. Pintori and Michael F. Greaney*

EastChem, School of Chemistry, University of Edinburgh, King's Buildings, West Mains Rd, Edinburgh EH9 3JJ, U.K.

Supporting Information

ABSTRACT: An oxidative C−H coupling is described for medium-ring synthesis.

Transition-metal-catalyzed oxidative C−H coupling offers a highly efficient approach to biaryl synthesis.[1] Using two C−H bonds as coupling partners, no pre-functionalization is required and the reaction can, in principle, afford minimal waste products. The field has undergone rapid growth in recent years, with a number of impressive intermolecular cross-couplings being developed.[2] The intramolecular variant, by contrast, has not been widely investigated. Seminal work in the 1970s established the reaction for five-membered, fully aromatic systems such as carbazoles and dibenzofurans,[3,4] but applications to alternative ring systems are rare (Figure 1). We reasoned that dehydrogenative coupling for the synthesis of medium-ring-containing biaryls would represent a powerful approach to these compounds, which are often difficult to access by classical routes. These challenges are particularly relevant to medicinal chemistry; despite the plethora of medium-ring structures found in biologically active natural products, seven-, eight-, and nine-membered rings remain rare in drug molecules (Figure 1).[5]

We chose to study the indole system, given its widespread occurrence in biologically active compounds.[6] A screen of *N*-alkylated indoles identified compounds of general structure **1**, containing an electron-withdrawing group (EWG) at the indole 3-position, as potential substrates for dehydrogenative seven-membered ring formation. A catalyst optimization study (Supporting Information) established that catalytic $Pd(OAc)_2$ in the presence of excess $Cu(OAc)_2$, using DMA as solvent, was effective for C−C bond formation, with the parent structure **2a** being formed in 77% yield (Chart 1). With these conditions in hand, we examined their generality for seven-membered ring formation. A range of indole substrates corresponding to general structure **1** were prepared, whereby the substituent pattern, heteroatom substitution, and EWG at the indole 3-position were all varied.

We were pleased to see that the reaction conditions proved general, delivering a variety of medium-ring annulated indoles in good to excellent yield.[7] Aromatic rings containing *p*-MeO and *p*-CF_3 groups were good substrates for the reaction, affording indoles **2b** and **2c** in 60 and 80% yields, respectively. A substrate containing a *m*-fluoro aromatic ring was prepared to gain some insight into the mechanism of the reaction. Medium-ring biaryl **2d** was formed as the major regioisomer (63% overall yield, 4:1 dr), i.e., the more acidic hydrogen atom[8] underwent reaction, suggesting a base-assisted palladation pathway was operating in the reaction mechanism (*vide infra*). Incorporation of heteroatoms into the tethering chain was possible, with the three oxazapane derivatives **2e**, **2f**, and **2g** all formed in good yield.

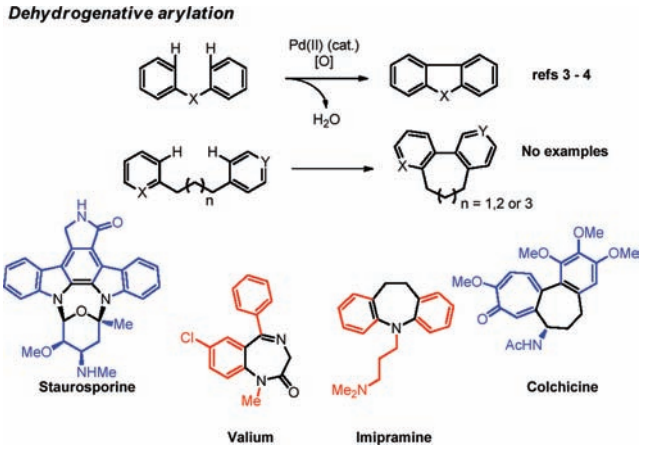


Figure 1. Dehydrogenative coupling for medium-ring biaryl synthesis. Examples of biologically active medium-ring containing biaryls from Nature (blue) and pharmaceuticals (red).

Interestingly, no five-membered ring products from C−H activation at the benzylic position were observed for substrates **2e** and **2f**, despite the susceptibility of benzyl ethers to oxidation.[9] sp^2 C−H activation to form the medium ring is evidently favored under these reaction conditions. Nitrogen substitution into the medium ring was likewise possible, with the diazapane analogues **2h** (NMe) and **2i** (NMs) being formed in very good yield. A good EWG at the indole C3 was necessary for reaction, with esters and ketones producing low yields of medium-ring product (Supporting Information). The cyano group was proficient, however, affording annulated indole **2j** and the azaindole **2k** in high yield. The nitro group proved the most effective of all, enabling the azaindole **2l** to oxidatively couple in an excellent 95% yield.

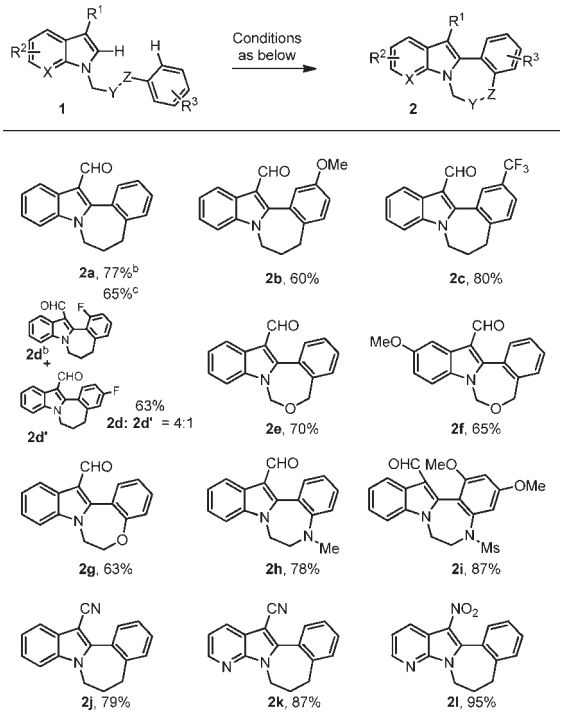
We extended the work to encompass heteroaromatic ring systems, with the aim of synthesizing novel heterobiaryls annulated in a seven-membered ring (Chart 2). The reaction was very effective for the synthesis of symmetrical bisindole **4a**, synthesized in 91% yield from C2 oxidative coupling of the symmetrical precursor. We could likewise use both benzimidazole and pyrazole C−H bonds as participants in the reaction to form the highly functionalized biheteroaryls **4b**, **4c**, and **4d** in good yields.

Following the success of the reaction for seven-membered ring synthesis, we applied the same approach to the more challenging

Received: October 9, 2010
Published: December 31, 2010

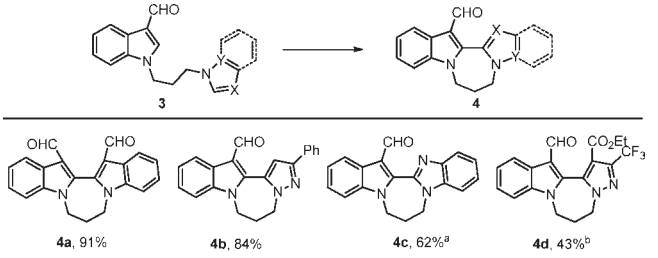
dx.doi.org/10.1021/ja1090854 | *J. Am. Chem. Soc.* 2011, 133, 1209–1211

Chart 1. Scope of Oxidative Coupling of Indole with Arenes To Form Annulated Seven-Membered Rings[a]



[a] Reaction conditions: 0.2 mmol of the substrate, 10 mol % $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.2 mmol), $Cu(OAc)_2$ (0.6 mmol) in 1 mL of DMA at 90 °C for 16 h. Isolated yields throughout.
[b] Crystallographic data available.
[c] Reaction conditions: 2.0 mmol of **1a**, 10 mol % $Pd(OAc)_2$ (0.2 mmol), K_2CO_3 (2.0 mmol), $Cu(OAc)_2$ (6.0 mmol) in 10 mL of DMA at 90 °C for 16 h.

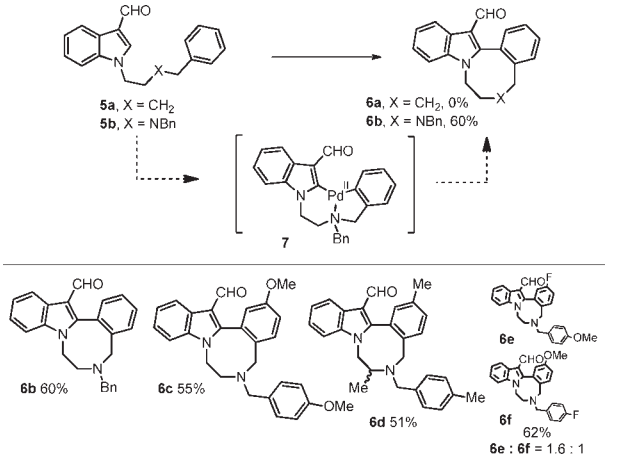
Chart 2. Intramolecular Oxidative Coupling of Indole and Heteroarenes[a]



[a] Reaction conditions: 0.2 mmol of the substrate, 10 mol % $Pd(OAc)_2$, K_2CO_3 (0.2 mmol), $Cu(OAc)_2$ (0.6 mmol) in 1 mL of DMA at 120 °C for 8 h. Isolated yields throughout. Exceptions: [a]140 °C for 3 h. [b]120 °C for 24 h.

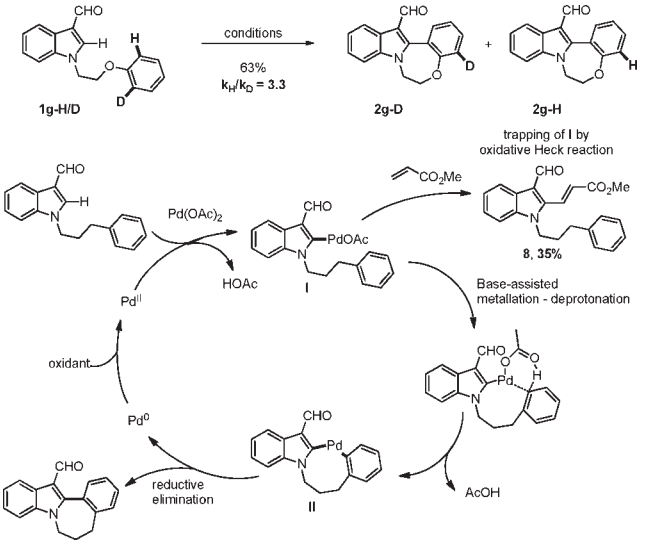
eight-membered -ring targets (Chart 3). Eight-membered rings are generally the most difficult of the medium rings to form, due to energetically unfavorable transannular and torsional strain effects in ring-closing reactions.[10] These difficulties were manifest in our initial attempts at oxidative cyclization of substrate **5a**, which were unsuccessful under a range of conditions. We reasoned that the replacement of a methylene in the tethering chain with a heteroatom might serve to both reduce transannular strain and provide a stabilizing interaction with the presumed

Chart 3. Formation of Eight-Membered Rings by Dehydrogenative Coupling[a]



[a] Reaction conditions: 0.2 mmol of the substrate, 10 mol % $Pd(OAc)_2$, K_2CO_3 (0.2 mmol), $Cu(OAc)_2$ (0.6 mmol) in 1 mL of DMA at 120 °C for 16 h.

Scheme 1. Mechanistic Studies[a]



[a] Reaction conditions for KIE study: indole (0.225 mmol), K_2CO_3 (0.225 mmol), $Pd(OAc)_2$ (0.0225 mmol), $Cu(OAc)_2$ (0.675 mmol) in 1.5 mL of DMA at 90 °C for 16 h. k_H/k_D determined by ^1H NMR and LRMS.

Pd(II) intermediate in the reaction (structure **7**).[11] We were pleased to see that incorporation of a dibenzylamine group (**5b**) into the substrate proved a success, providing eight-membered diazocane derivative **6b** in 60% yield. This reaction was extended to a small range of examples: Products **6b** and **6c** arise from dibenzylamine derivatives containing four identical sites for aromatic C−H activation. Interestingly, **6d** was isolated as a 1:1 mixture of diastereoisomers, suggesting hindered rotation around the biaryl axis. The dibenzyl motif allowed us to set up a competition experiment to probe the mechanism, using electron-rich (*p*-OMe) and electron-poor (*p*-F) benzyl groups in the same substrate. Compounds **6e** and **6f** were isolated in 62% combined

dx.doi.org/10.1021/ja1090854 |*J. Am. Chem. Soc.* 2011, 133, 1209–1211

yield in the ratio 1.6:1. The more acidic C−H bond on the fluoro-substituted arene is preferentially activated, although the selectivity is reduced relative to that seen with the previous seven-membered systems (Chart 1, **2d** and **2d′**).

A preliminary picture of the reaction mechanism is set out in Scheme 1. Palladation of the indole at C2 forms complex I, an intermediate that could be successfully trapped with methyl acrylate in a Fujiwara−Moritani-type process[12] to give ester **8** (Supporting Information). In the normal course of reaction, I then undergoes a concerted metalation−deprotonation (CMD)[13] step to afford intermediate II. An alternative electrophilic palladation mechanism is unlikely here due to the observed selectivities for electron-poor sites in competition experiments (**2d** in Chart 1 and **6g**/**6f** in Chart 3).[14] In addition, an intramolecular kinetic isotope effect (KIE) study on substrate **1g**-H/D gave a value of k_H/k_D = 3.3, in line with literature reports of C−H activation via CMD mechanisms.[4c,15,16] Reductive elimination then produces the medium-ring products, along with Pd(0) which is reoxidized by the excess Cu(II) in the reaction.

In conclusion, we have shown for the first time that intramolecular oxidative C−H coupling is an effective strategy for synthesizing medium-ring compounds. The reaction is tolerant of a rich array of functional groups, forming annulated heterocycles for application as versatile scaffolds in medicinal chemistry[17,18] Previous routes to these medium-ring-containing indoles have featured lengthy, multistep routes; our approach is rapid, using a simple catalyst system, and should be amenable to a broad range of further applications in medium-ring heterocycle synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
Michael.Greaney@ed.ac.uk

■ ACKNOWLEDGMENT

We thank the EPSRC and the University of Edinburgh for funding (Leadership fellowship to M.F.G. and studentship to D.G.P.) and the EPSRC mass spectrometry service at Swansea. Dr. Fraser White is thanked for X-ray crystallography.

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