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Access to Biaryl Sulfonamides by Palladium-Catalyzed Intramolecular Oxidative Coupling and Subsequent Nucleophilic Ring Opening of Heterobiaryl Sultams with Amines

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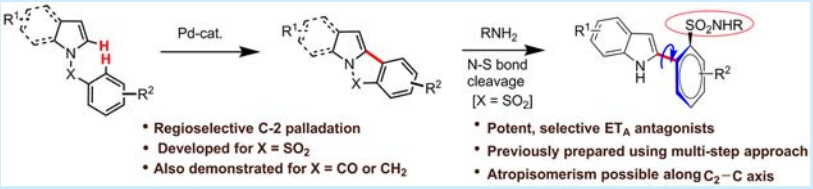
Supporting Information



ABSTRACT: The installation of sulfonamide pharmacophores on heterobiaryls has successfully been executed by a previously unknown palladium-catalyzed intramolecular oxidative coupling in *N*-arylsulfonyl heterocycles followed by novel ring opening of heterobiaryl sultams with amine nucleophiles. The protocol has a wide scope of substrates warranting broad applications in the synthesis of heterobiaryls containing an *o*-sulfonyl or carboxyl functional group.

Sulfonamide functional groups have long been acclaimed as important structural motifs in drug discovery since the identification of a series of sulfonamide-containing drugs, such as sulfamethoxazole as an antibacterial agent, azosemide as a diuretic agent, sumatriptan as an antimigraine agent, and celecoxib as a COX-2 specific anti-inflammatory agent.[1] The introduction of a sulfonamide group is often a useful practice in medicinal chemistry for improving pharmacological potency and/or the absorption, distribution, metabolism, and excretion (ADME) properties of the lead compound. Recently, biaryls containing an *o*-sulfonamide group[2] are identified as selective endothelin-A (ET_A) antagonists with potent, broad-ranging activity. BMS-207940 (**I**) is an extremely potent and selective ET_A antagonist (K_i = 10 pm) for the treatment of congestive heart failure (Figure 1).[2b] In addition to serving as pharmacophore, the bulky sulfonamide group at the *ortho*-position restricts the rotation of aryl groups along the biaryl C−C axis resulting in atropisomerism.[3]

2-Arylindoles (heterobiaryls) are privileged molecular scaffolds in therapeutic discovery.[4] The *World Drug Index* contains more than 50 2-arylindoles.[5] A particular subset, 2-(1*H*-indol-2-yl)benzenesulfonamide (**II**), could be promising, although it is largely unexplored in drug discovery. Indeed, an indole−aryl sulfonamide **1** was found to be a potent and selective ET_A antagonist in the early stage of the discovery, although atropisomerism of **1** was uncovered in the investigation.[2a]

Notably, atropisomerism along a C-2(indole)-C(aryl) axis has been the least studied.[6] 2-Arylindoles have been prepared historically by Fischer[7] and Bischler−Mohlau[8] syntheses, later more extensively by Larock indole synthesis,[9] and very recently by Scheidt employing N-heterocylic carbene as a catalyst.[10] Functionalization of indoles with aromatic hydrocarbons by

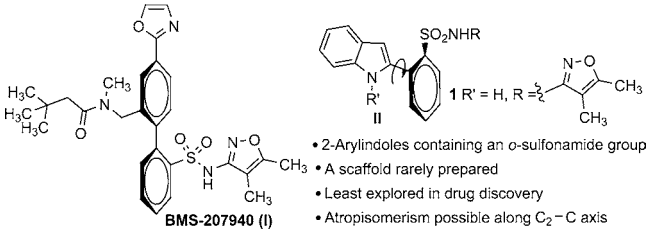


Figure 1. Biaryls containing an *o*-sulfonamide group.

palladium-[11] or copper-catalyzed[12] oxidative coupling was successfully achieved enabling regioselective C-2 arylation of indoles. Although the current literature is quite resourceful warranting broad applications to the preparation of functionalized 2-arylindoles, whether the druglike scaffold **II** could be readily accessible remains a question. Nonetheless, a multistep synthetic strategy including installation of requisite sulfonamide group by a classical approach, preparation of two elaborated prefunctionalized substrates for biaryl formation via a Suzuki reaction, and laborious protection and deprotection is currently a beneficial alternative for preparation of the scaffold **II** (Scheme 1).[2a]

Transition-metal-catalyzed oxidative C−H coupling is a powerful variant of traditional cross-couplings[13] or direct arylations[14] enabling rapid C−C bond formation in biaryls with wide substrate scope.[15] Certainly, transition-metal-catalyzed oxidative coupling is a method of choice over traditional couplings, which obviates the need for the use of prefunction-

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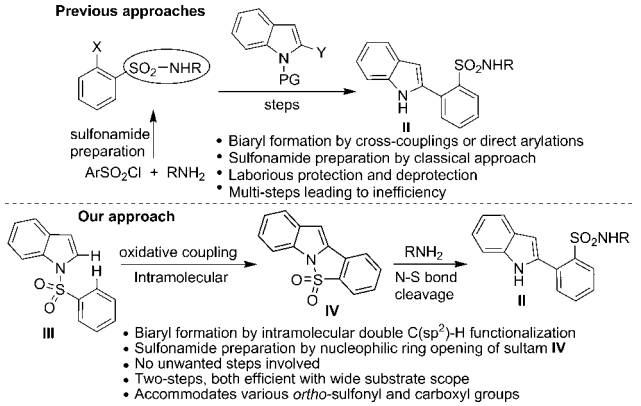
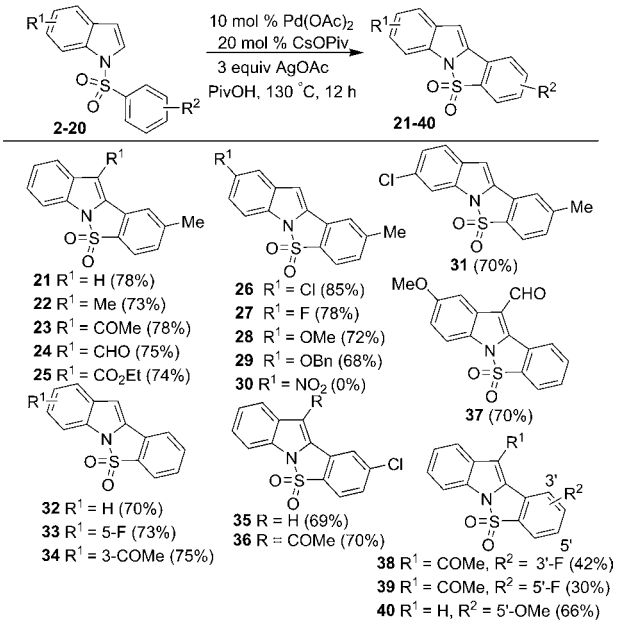
Scheme 1. Approaches to the Synthesis of 2-(1*H*-Indol-2-yl)benzenesulfonamide II



Scheme 2. Synthesis of Various Substituted Indole−Aryl Sultams



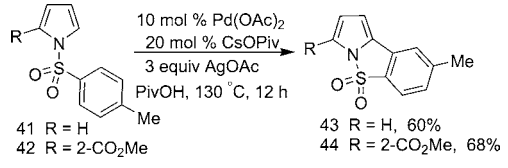
alized substrates and alleviates the generation of salt waste, thereby rendering superior sustainability and environmental compatibility. Despite this magnificent development, the application of transition-metal-catalyzed oxidative coupling is yet to be realized in the synthesis of biaryls containing an *o*-sulfonamide group. Recently, we have developed a palladium-catalyzed intramolecular oxidative coupling involving double C(sp^2)−H bonds in sulfonanilides, providing a workable access to biaryl sultams annulated into a six-membered ring that are otherwise difficult to obtain by literature methods.[16] Based on our previous experiences in the synthesis of nitrogen-containing heterocycles[17] and recent success,[16] we envisaged that installation of sulfonamide pharmacophores on heterobiaryls might be brought to fruition via palladium-catalyzed intramolecular oxidative coupling. Herein, we describe, distinct from our previous report, a novel palladium-catalyzed intramolecular oxidative coupling involving double C(sp^2)−H bonds in *N*-arylsulfonyl indoles to the synthesis of heterobiaryl sultams, which upon subsequent N−S bond cleavage with amines form 2-arylindoles containing an *o*-sulfonamide group. The tactic for the installation of sulfonamide pharmacophore on heterobiaryls reported herein opens a new platform for the synthesis of *ortho*-functionalized biaryls that have invariably been prepared in multiple steps.

At the outset, we explored the intramolecular oxidative coupling in *N*-arylsulfonyl indoles **III** with a goal of finding an atom-economical green approach to the synthesis of heterobiaryl sultam **IV**. The synthesis of sultam **IV** is limited to intramolecular direct arylations of prefunctionalized *N*-arylsulfonyl indoles[18] and the only example of direct arylation in 3-iodo-*N*-Ts indole producing 3-norbornene-substituted sultam.[19] A detailed investigation toward finding an optimized condition for the intramolecular oxidative coupling of *N*-Ts indole **2** ultimately secured a reagent blend consisting of $Pd(OAc)_2$ (10 mol %), CsOPiv (20 mol %), AgOAc (3 equiv), and PivOH (200 mM) at 130 °C for 12 h, which afforded sultam **21** in 78% yield (Scheme 2). Next, we investigated the scope of other readily accessible substrates **3**−**20**[20] that could participate in the intramolecular oxidative coupling. The substrates with an electron-donating or -withdrawing group at the 3-, 5-, or 6-position of the indole ring with the exception of 5-nitro-*N*-Ts indole underwent oxidative coupling eventfully, affording sultams **22**−**31** in 68−85% yield. Interestingly, the chloro group at the 5- or 6-position of indole displays distinct reactivity. A methyl group on the benzene ring is not crucial for effective cyclization as reflected in the synthesis of sultams **32**−**34**. A chloro group at the 4-position in the benzene ring has slightly deleterious effect in delivering the sultam **35**. Substrates with disubstitution in one or both rings are also competent, affording cyclized products **36** and **37**. *N*-3-Fluorobenzenesulfonyl indole displays similar reactivity under the optimized conditions, resulting in the formation of regioisomeric sultams **38** and **39** which are easily separable by chromatography. Notably, the major sultam **38** was obtained from the cyclization at the *ortho*-position of the fluoro group. However, *N*-(3-methoxybenzenesulfonyl)indole yielded only one regioisomer **40** resulting from cyclization at the *para*-position to the methoxy group. The double C(sp^2)−H functionalization in *N*-arylsulfonyl indoles to the synthesis of sultams, a long-standing sought yet elusive transformation, has been achieved that overcomes the limitations of protocols currently available in literature.

Central to this study was demonstrating the general applicability of the double C−H functionalizations in other nitrogen heterocycles and novel synthetic applications of the heterobiaryl sultams. Pleasingly, we found that the optimized conditions can also be extended to the synthesis of arylpyrrole sultams (Scheme 3). Thus, *N*-Ts-pyrrole **41** or methyl *N*-Ts-pyrrole-2-carboxylate **42** gave novel arylpyrrole sultams **43** and **44** in 60 and 68% yields, respectively.

To explore further the scope of substrates, we performed the cyclization using *N*-benzoylindoles **45**−**48**[21] and *N*-benzylindole **49** under the optimized conditions (Scheme 4). While *N*-benzoylindoles underwent cyclization to give 6-oxo-6*H*-

Scheme 3. Intramolecular Oxidative Coupling in *N*-Tosylpyrroles



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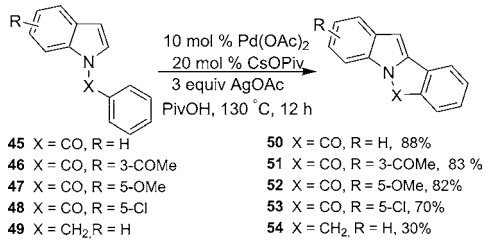
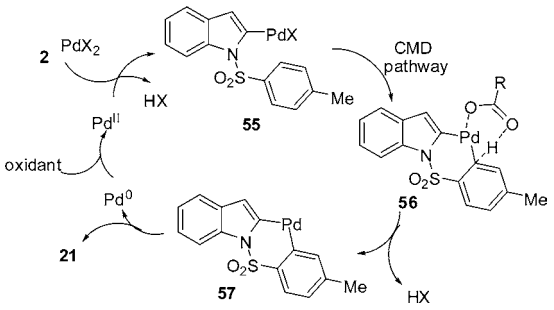
Scheme 4. Intramolecular Oxidative Coupling in *N*-Benzoyl- or *N*-Benzylindoles



isoindolo[2,1-*a*]indoles **50**–**53**[15c,22] in 70–88% yield, compound **49** gave 6*H*-isoindolo[2,1-*a*]indole **54**[17g] *albeit* in moderate yield. Nonetheless, the optimized conditions developed in our current study have the broader scope of substrates.

In line with the mechanism proposed for intramolecular oxidative couplings in indoles,[11a,15d] a Pd(0)/Pd(II) catalytic cycle, consistent with mild a oxidant AgOAc,[11c,15f] is proposed in Scheme 5. Regioselective palladation occurs at the C-2 position

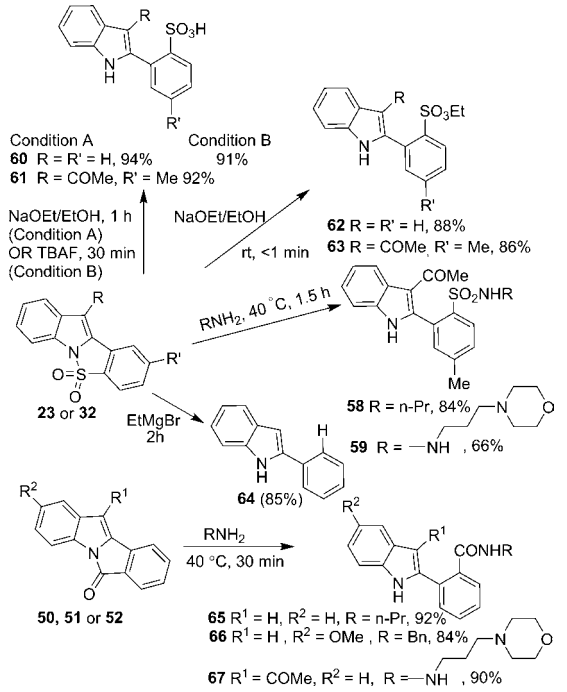
Scheme 5. Proposed Mechanism of Intramolecular Oxidative Coupling



of the indole followed by a second palladation that occurs at the *ortho*-position of the sulfonyl group in the benzene ring to form **57**. The intermediate **55** was successfully trapped in the presence of benzene to obtain *N*-Ts-2-phenylindole. As pivalic acid is essential for this cyclization, a concerted metalation–deprotonation (CMD) pathway[14f,g] may be followed for the second palladation. An alternate electrophilic palladation mechanism is unlikely here due to the observed regioselectivities for electron-poor sites (**38** and **39**). Finally, **57** would reductively eliminate to give the observed product **21** and regenerate the catalyst.

Subsequently, we investigated previously unexplored ring opening of heterobiaryl sultams with nucleophiles for the synthesis of heterobiaryls containing an *ortho*-functional group. It is worth noting that cyclobutyl β-sultams are reported to undergo ring cleavage under alkaline conditions to yield acyclic β-amino sulfonic acids.[23] When sultam **23** was exposed to amines at 40 °C for 1.5 h, a smooth N–S bond cleavage was observed yielding the corresponding indole–aryl sulfonamides **58** and **59** (Scheme 6). Treatment of sultam **32** or **23** with NaOEt in ethanol for 1 h resulted in ring cleavage with the formation of sulfonic acid **60** or **61** in 94 and 92% yields, respectively. However, a controlled reaction time (<1 min) results in the formation of sulfonate ester **62** or **63** in 88 and 86% yields, respectively. A fluoride ion assisted cleavage of sultam **32** occurred in 30 min to afford aryl sulfonic acid **60** in 91% yield. Interestingly, a Grignard reagent efficiently cleaved the sultam **32** ultimately to form **64** with concomitant release of SO_2. Importantly, treatment of lactams **50**–**52** with amines at 40 °C

Scheme 6. Cleavage of N–S/N–C Bonds in Heterobiaryl Sultams and Lactams



for 30 min gave heterobiaryls **65**–**67** with an *o*-carboxamide group,[24] which demonstrates further synthetic potential of the current protocol.

Pivotal to this study was the realization of mild reaction conditions and shorter reaction time required for the N–S/N–C bond cleavages in heterobiaryl sultams or lactams. A comparative reactivity of sultam **23** and lactam **50** with propylamine at 40 °C indicates that the most reactive lactam **50** undergoes N–C bond cleavage completely in 30 min, whereas the least reactive sultam **23** undergoes slow ring cleavage. Notably, cleavage of β-sultams is much faster than the corresponding β-lactams.[23] In contrast, ring opening of heterobiaryl sultams in our study is slower than the corresponding lactams. While a stepwise bond-breaking and bond-making mechanism is indicated for the cleavage of β-sultams,[23] the cleavage of heterobiaryl sultams with amines in terms of mechanism is a subject of further investigation.

In conclusion, we have developed a new protocol for the installation of sulfonamide pharmacophores on heterobiaryls. For comparison, the biaryl linkage in heterobiaryl sulfonamides is formed by cross-couplings or direct arylations using prefunctionalized substrates, whereas a novel palladium-catalyzed double C(sp^2)–H functionalization strategy was utilized in our protocol. Invariably, a classical approach for the preparation of sulfonamide has been adopted in the literature. The novel ring opening of heterobiaryl sultams with amines under mild conditions unveils a new tactic for the preparation of sulfonamides that provides a unique platform for the installation of an *o*-sulfonamide pharmacophore in 2-arylindoles. Our protocol is quite resourceful, warranting broad applications to the synthesis of biaryls containing an *ortho*-functional group other than sulfonamides. Furthermore, atropisomerism in 2-arylindoles containing an *o*-sulfonamide group, which could explore new opportunities in drug discovery, is currently under investigation.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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