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Pd-Catalyzed Dehydrogenative Aryl−Aryl Bond Formation via Double C(sp^2)−H Bond Activation: Efficient Synthesis of [3,4]-Fused Oxindoles

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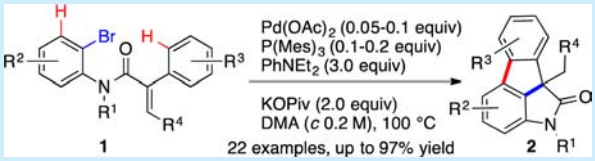
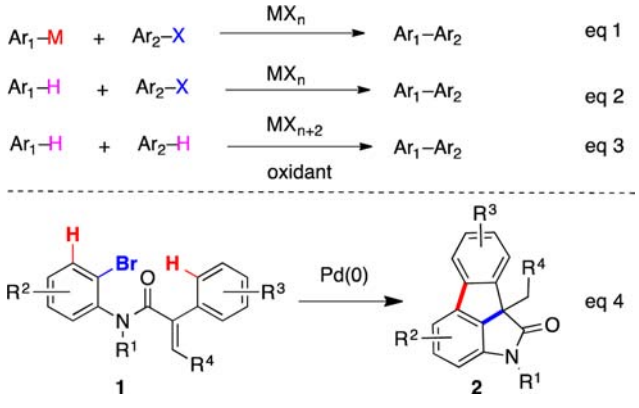
Supporting Information

ABSTRACT: A Pd(0)-catalyzed double cyclization of easily available *o*-bromoanilides leading to strained [3,4]-fused oxindoles was developed. The reaction proceeded through a highly ordered sequence involving key carbopalladation, 1,4-Pd migration, and C(sp^2)−H functionalization steps.



Biaryls are important structural units found in many bioactive natural products, marketed drugs, and advanced materials.[1] Among many different synthetic approaches, transition-metal-catalyzed cross-couplings of organometallics (Ar-M) with aryl(pseudo)halides Ar-X (e.g., Suzuki−Miyaura, Stille, Neigishi, and Hiyama couplings) have met with great success (eq 1, Scheme 1).[2] To avoid the use of organometallics

Scheme 1. Transition-Metal-Catalyzed Synthesis of Biaryls



(Ar-M), two alternatives have emerged, namely direct cross-coupling between Ar-H and Ar-X (eq 2) and cross-dehydrogenative coupling (CDC).[3] Both routes involve a C(sp^2)−H functionalization step.[4] Inherent to the CDC reaction mechanism, an external oxidant is generally required to regenerate the active catalytic species.

In continuation with our current research interest in the area of palladium-catalyzed C−H functionalization reaction,[5] we report herein a palladium-catalyzed double cyclization of easily available *o*-bromoanilides **1** for the synthesis of strained [3,4]-fused oxindoles **2** (eq 4, Scheme 1). In this transformation, an appropriately positioned internal aryl bromide served both as an oxidant and a trigger to initiate the domino process leading to the formation of one C(sp^2)−C(sp^3) and one C(sp^2)−C(sp^2) bond with concurrent creation of a quaternary carbon center. Although many efficient methods have been developed allowing the rapid access to diversely functionalized oxindoles as well as spirooxindoles,[6] there are only few methods available for the direct synthesis of [3,4]-fused oxindoles from simple linear precursors.[7,8] Structurally, compound **2** is a hybrid between oxindole and fluorene motifs. The latter is also an important motif in organic dyes,[9] molecular superconducting materials,[10] and organic light-emitting diodes[11] and is found in the structure of antiviral[12] and antimalarial drugs.[13] Since both oxindole and fluorene are important pharmacophores, a hybrid structure could be of potential interest in medicinal chemistry.[14]

We began our investigation using the easily accessible (*E*)-*N*-(2-bromophenyl)-*N*-methyl-2,3-diphenylacrylamide (**1a**) as a model substrate.[15] Applying the conditions we developed previously in the related studies [[$Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, $CsOPiv/PhNEt_2$ (1/1), DMA, 140 °C],[8] the expected [3,4]-fused oxindole **2a** was formed in 39% yield together with 1-methyl-3,4-diphenylquinolin-2(1*H*)-one (**3a**) in a 1:1 ratio (entry 1, Table 1). The formation of quinolinone **3a** could be accounted for by a sequence involving 6-*endo*-*trig* cyclization/β-hydride elimination, although this cyclization mode is generally considered to be less favorable relative to the alternative 5-*exo*-*trig* cyclization.[16,17] Using potassium pivalate as a base improved the selectivity (2.5/1) in favor of the desired tetracycle **2a** (entry 3). When P(*o*-tolyl)$_3$ was used as a ligand instead of PCy_3, **2a** was isolated in 81% yield (entry 4, Table 1). Using bulky $PMes_3$ in combination with potassium pivalate (KOPiv), the yield of **2a** was further increased (84% at 90% conversion, entry 5). Interestingly, by adding *N*,*N*-diethylaniline (2.0 equiv) to the reaction mixture, the reaction reached completion furnishing the desired [3,4]-fused oxindoles in 97%

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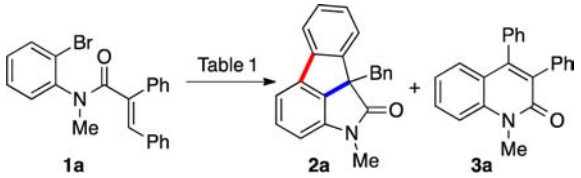
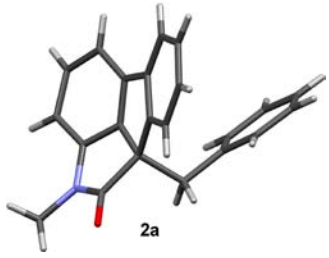
Table 1. Synthesis of [3,4]-Fused Oxindoles: A Survey of Reaction Conditions[a]



entry	ligand	base(s)	ratio **2a**/**3a**[b]	yield[c] (%)
1	$PCy_3{\cdot}HBF_4$	CsOPiv/$PhNEt_2$ (1/1)	1.0	38
2	$PCy_3{\cdot}HBF_4$	CsOPiv	1.1	42[b]
3	$PCy_3{\cdot}HBF_4$	KOPiv	2.5	65[b]
4	P(*o*-tolyl)$_3$	KOPiv	9	81
5[d]	$PMes_3$	KOPiv	>20	84
6	$PMes_3$	KOPiv/$PhNEt_2$ (1/1)		93
7[e]	$PMes_3$	KOPiv/$PhNEt_2$ (1/1)		97
8[e,f]	$PMes_3$	KOPiv/$PhNEt_2$ (2/3)		93

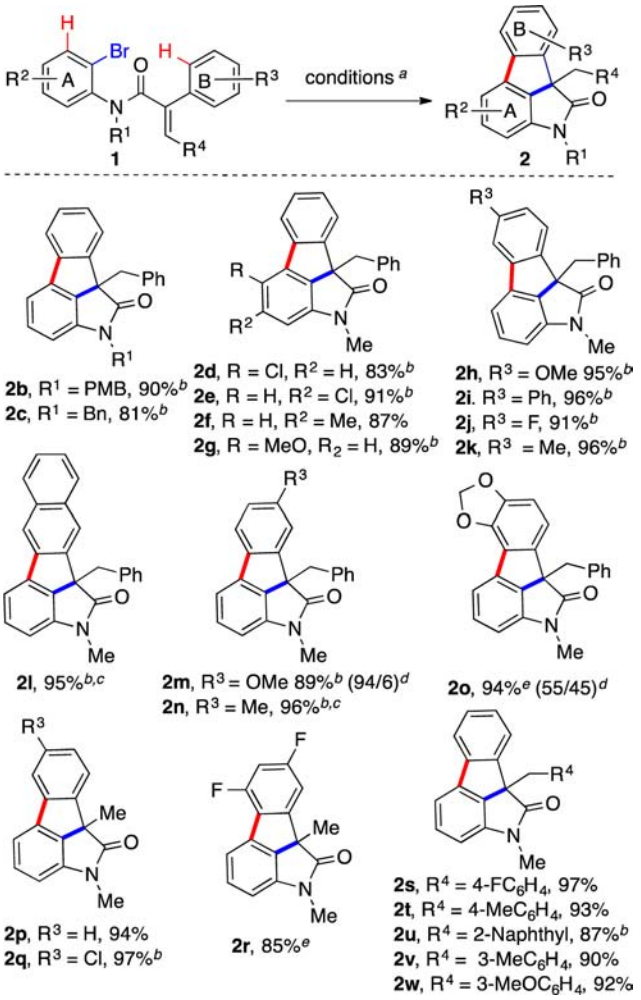
[a]All reactions were carried out under nitrogen atmosphere using **1a** (0.05 mmol), $Pd(OAc)_2$ (0.1 equiv), ligand (0.2 equiv), and base (2.0 equiv) in DMA (*c* 0.1 M) at 140 °C. [b]Determined by ^1H NMR. [c]Isolated yield. [d]Conversion = 90% (^1H NMR). [e]Reaction temperature 100 °C. [f]$Pd(OAc)_2$ (0.05 equiv), $PMes_3$ (0.1 equiv), *c* 0.2 M.

isolated yield. Similar efficiency was observed when the loading of Pd was reduced from 10 to 5 mol % (entry 8, Table 1). Overall, the optimized conditions consisted of heating a DMA solution of **1a** (*c* 0.2 M) at 100 °C in the presence of $Pd(OAc)_2$ (0.05 equiv), $PMes_3$ (0.1 equiv), KOPiv (2.0 equiv) and $PhNEt_2$ (3.0 equiv). Under these conditions, tetracycle **2a** was isolated in 93% yield (entry 8). The structure of **2a** was confirmed by single-crystal X-ray structural analysis.



With the optimized conditions in hand, the scope of the domino process was next studied. When *N*-(*p*-methoxybenzyl)- and *N*-benzyl-substituted anilides were subjected to reaction conditions, the desired compounds **2b** and **2c** were obtained in yields of 90% and 81%, respectively (Scheme 2). Electron-donating (Me, OMe) and electron-withdrawing (Cl) substituents on the ring A were well tolerated as evidenced by the high yield obtained for compounds **2d**–**g**. The influence of substitution on the ring B of anilide was subsequently examined. Substituents at the *para*-position regardless of its electronic nature (methyl, phenyl, methoxy, and fluoro) have a negligible effect on the outcome of the reaction providing tetracyclic [3,4]-fused oxindoles (**2h**–**k**) in excellent yields. In the case of *meta*-substituted substrates, two regioisomers could be formed and the regioselectivity was found to be substituent dependent. With a *m*-methyl substituent, the cyclization occurred exclusively at the less hindered position to afford **2n** in excellent yield. Similarly, 2-naphthyl-substituted substrate afforded **2l** as a single compound. However, the regioselectivity was diminished with a substrate having a dioxolanyl substituent leading to a mixture of two regioisomers (**2o**/**2o**′ = 55/45).

Scheme 2. Synthesis of [3,4]-Fused Oxindoles: Scope



[a]All reactions were carried out under nitrogen atmosphere using **1a** (0.1 mmol), $Pd(OAc)_2$ (0.05 equiv), Mes_3P (0.1 equiv), $PhNEt_2$ (3.0 equiv), and KOPiv (2.0 equiv) in DMA (*c* 0.2 M) at 100 °C. [b]$Pd(OAc)_2$ (0.1 equiv), Mes_3P (0.2 equiv). [c]Single isomer. [d]Only the major regioisomer is represented (the ratio was determined by ^1H NMR analysis). [e]$Pd(OAc)_2$ (0.2 equiv), Mes_3P (0.4 equiv).

Next the effect of substitution on the double bond was evaluated (**2p**–**w**). Terminal unsubstituted double bond furnished the desired compounds in excellent yields (**2p**–**r**). With a trisubstituted double bond (R^4 = Ar), the reaction was insensitive to the electronic nature of the R^4 group providing the desired tetracycles (**2s**–**w**) in excellent yields.

A possible reaction pathway accounting for the conversion of **1** to **2** is depicted in Scheme 3. An oxidative addition of an Ar–Br bond to a Pd(0) species followed by an intramolecular carbopalladation gave intermediate **A** in which the σ-alkyl-Pd(II) function was ideally positioned to activate the neighboring aromatic C(sp^2)–H bond to afford a five membered palladacycle **B**.[18] A formal proton transfer from **B** resulted in a net 1,4-palladium shift from the alkyl to the aryl position.[19] The so-generated Pd(II) species would then activate the neighboring C4 position of oxindole to furnish after reductive elimination the desired tetracyclic oxindole **2** with the concurrent regeneration of the active Pd(0) species. In the case of R^4 = aryl, it is worth noting that formation of spirooxindole **4**

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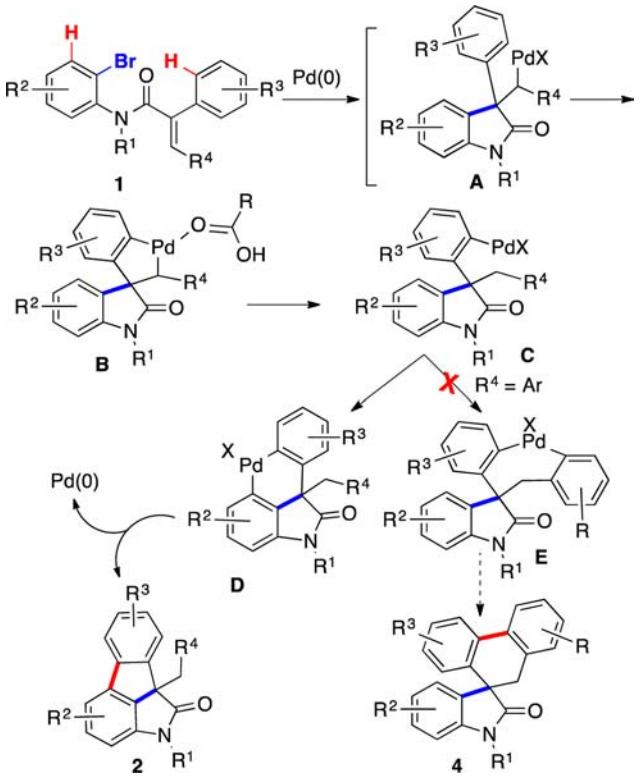
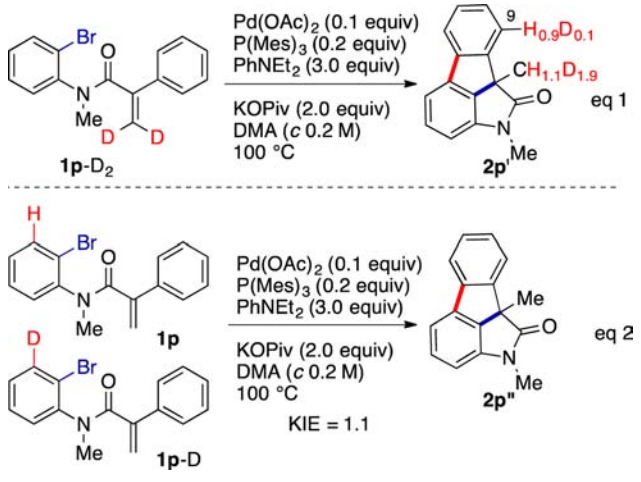
Scheme 3. Possible Reaction Pathway



via a 7-membered spiropalladacycle **E** was not observed regardless of the electronic properties of the aryl substituent.

To gain some insight into the reaction mechanism, a labeling experiment was carried out. Submitting deuterated substrate **1p**-D_2 to the standard reaction conditions afforded **2p′** in which a deuterium was partially incoporated at C9 of the oxindoles (eq 1, Scheme 4). The result of this control experiment

Scheme 4. Deuterium-Labeling Experiments



indicated that 1,4-palladium migration might be reversible. A one-pot intermolecular KIE experiment (KIE = 1.1) suggested that C(sp^2)−H activation was not the catalyst turnover limiting step (eq 2, Scheme 4).[20]

In conclusion, we have developed a new Pd-catalyzed domino reaction allowing an efficient synthesis of tetracyclic [3,4]-fused oxindoles in high yields from simple *o*-bromoanilides. In this transformation, one C(sp^2)−C(sp^3) and one C(sp^2)−C(sp^2) bond were formed with concurrent creation of a quaternary carbon center. A transient σ-C(sp^3)−Pd species generated in situ by an intramolcular carbopalladation served as a lynchpin to activate successively the two C(sp^2)−H bond leading to the formation of an aryl−aryl bond.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ^{1}H and ^{13}C NMR spectra for new compounds, and X-ray crystallographic data (CIF) of compounds **2a** and **2s**. 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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