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Synthesis of spiro-oxoindoles through Pd-catalyzed remote C–H alkylation using α-diazocarbonyl compounds

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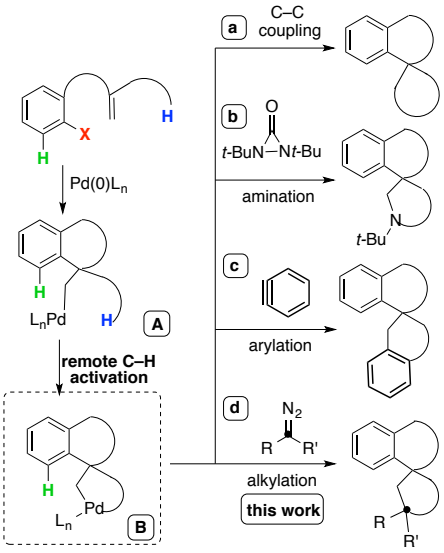
In this communication we describe a new route to spiro-oxoindoles derivatives through a novel Pd-catalyzed cascade process. This reaction is based on the remote C–H activation performed by σ-alkyl Pd(II) species generated *in situ* via intramolecular carbopalladation of alkenes, followed by insertion of a carbenoid coupling partner.

The transition metal (TM) catalyzed C–H activation field has grown into a major strand of synthetic organic chemistry.[1,2] In particular, the regioselective functionalization of remote C–H moieties within the molecular skeleton of organic substrates is addressing an enormous interest nowadays.[3] Generally the remote C–H activation processes are enabled by the presence of suitable directing groups in the core of the substrates which can regioselectively direct the TM toward an specific C–H moiety. Therefore, this approach has allowed the selective functionalization of *meta*- and *para*-C(sp^2)–H moieties of aromatic rings as well as δ- and γ-C(sp^3)–H moieties of aliphatic chains.

The Pd-catalyzed intramolecular carbopalladation of tethered alkenes has recently emerged as a complementary approach to remote C–H functionalization.[4] This strategy is based on the generation of σ-alkyl Pd(II) intermediates of type **A**,[5] (Scheme 1) where the impossibility to evolve through β-hydride elimination favors further cascade reactions such as the trapping with nucleophiles[6] or the insertion of unsaturated species.[7] The σ-alkyl Pd(II) intermediates of type **A** can



Scheme 1. Remote C–H functionalization through σ-alkyl Pd(II) intermediates.

effectively promote the regioselective C–H activation on the initially distal C–H moiety (in blue, Scheme 1) rather than the C–H in *ortho* position to the reactive C–halogen bond (in green, Scheme 1), leading to the formation of a C,C-palladacycle intermediate **B**, which can evolve through the reductive elimination of Pd(0) with concomitant C–C bond formation (path a, Scheme 1). These cascade reactions lead to interesting poly- and spirocyclic structures which include heterocyclic scaffolds such as indolin, oxoindol, and furan derivatives.[8] Alternatively to the direct C–C bond formation, a second coupling partner can be introduced in the reaction system to functionalize the reactive Pd–C bonds present in the intermediate **A** (path b, Scheme 1).[4a,9] For instance, our group has recently reported the synthesis of spiro-biaryls through a Pd-catalyzed cascade reaction based on the trapping of arynes with σ-alkyl Pd(II) species of type **A** (path c, Scheme 1).[10]

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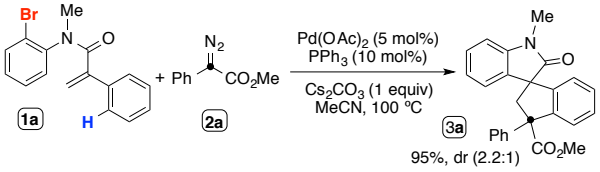
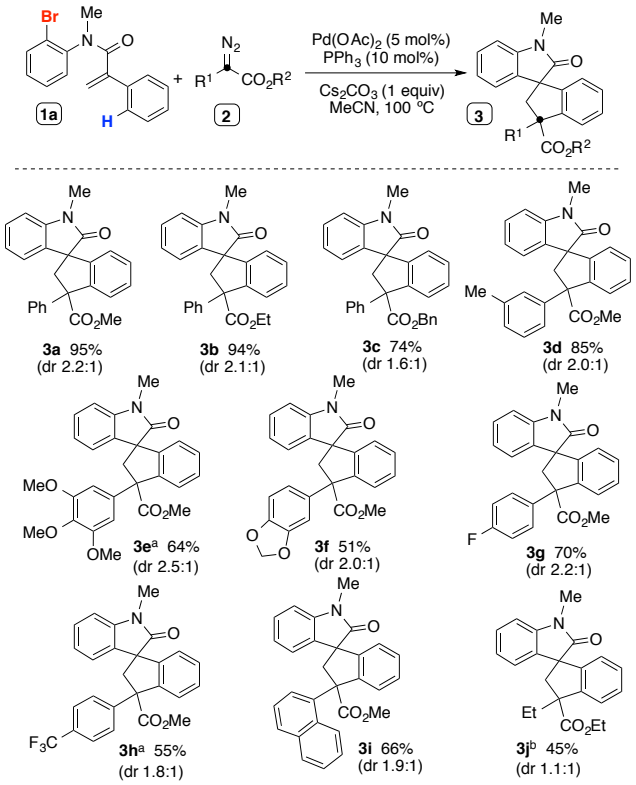
α-Diazocarbonyl compounds have been successfully used in a plethora of synthetic transformations.[11,12] Usually, the N_2 moiety of these compounds can be replaced by two new functional groups, hence making a double functionalization on the same carbon atom. Building on this concept and in connection with our interest in palladium chemistry,[9,13] we envisioned that a carbenoid precursor such as an α-diazocarbonyl compound could be used to trap the two reactive positions present in intermediates of type **B**, therefore, expanding the utility of this new mode of remote C–H functionalization.

We started our study by screening the conditions to get the spiro-oxoindole derivative **3a** from the acrylamide substrate **1a** and the α-diazocarbonyl compound **2a** (Scheme 2). Following the conditions established in our previous work for the remote C–H activation of this type of substrates,[10] we performed a set of experiments using $Pd(OAc)_2$ (10 mol%)/PPh_3 (20 mol%) as the catalyst source, in the presence of Cs_2CO_3 (1 equiv) at 100 °C. We observed that while in 1,4-dioxane some product **3a** was formed, the use of dry MeCN as the solvent led to a full conversion of the starting material **1a**, obtaining a 96% NMR yield of **3a** as a 2.2:1 mixture of diastereomers. The use of other ligands such as dppe, dppf or BINAP did not improve the diastereoselectivity (see the S.I. file). The $Pd(OAc)_2$ loading was decreased from 10 to 5 mol% without a significant impact on the yield of the product; however, lower catalyst loading dropped the yield of **3a**. No product **3a** was observed in the absence of the Pd catalyst.

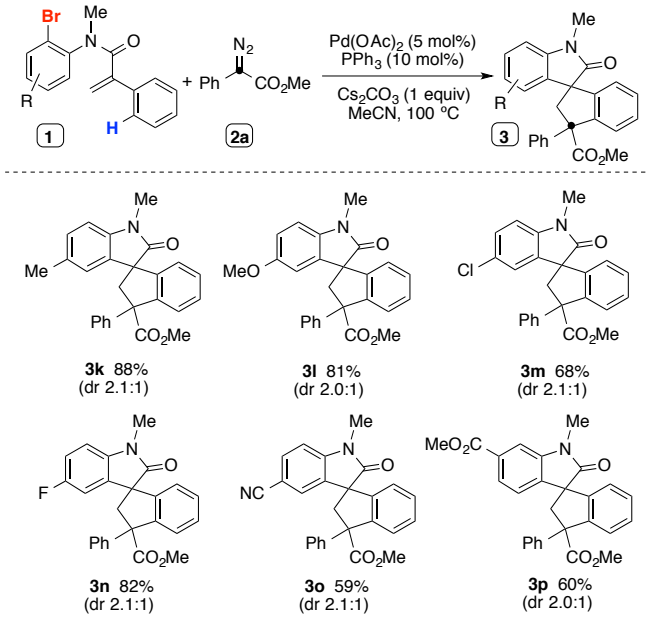


Scheme 2. Optimized conditions for the remote C–H alkylation.

With the optimized conditions in hand, we studied the scope of the reaction by varying the substitution pattern of both coupling partners. The increase of the steric bulk in the ester function from CO_2Me to CO_2Et or CO_2Bn of the diazo compound **2** did not have a considerable impact on the yield of the expected spirocycles **3**, however the diastereosiomeric ratio (dr) of the products **3a**, **3b**, and **3c** decreased from 2.2:1 to 2.1:1 and 1.6:1 respectively. The cascade reaction of the acrylamide **1a** with a range of diazocarbonyls **2** afforded moderate to good yields for substrates bearing aryl groups with both electron-donating and -withdrawing substituents. Nevertheless, some substrates **2**, such as those leading to the products **3e** and **3h**, required the use of a 10 mol% of $Pd(OAc)_2$ to reach full conversion of the starting materials, instead of the usual 5 mol%. Only low amounts of the expected cascade product could be detected when the substrate **2** contained a chlorine atom in *ortho* position of the aryl ring. No reaction was observed when the substituent R^1 of the diazocompound **2** (Scheme 3) was H or CO_2Et. The reaction tolerated well the presence of substituents on the aryl acrylamide coupling partner (Scheme 4), including cyano and ester groups (products **3o** and **3p**).



Scheme 3. Scope with different α-diazocarbonyl compounds. a) Obtained using 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3. b) NMR yield of **3j** was 45%, but only one diastereomer could be purified (23% isolated yield).

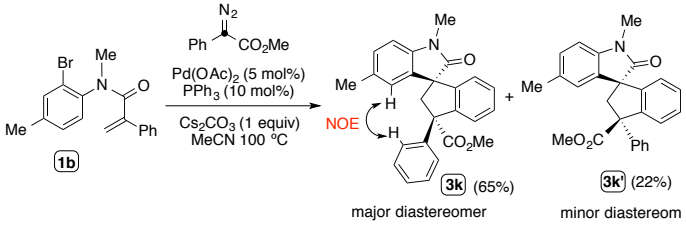


Scheme 4. Scope of the cascade reaction with different acrylamides.

We tried to expand the scope of the reaction to other substrates such as alkenes tethered to arylethers or *N*-

arylsulfamides instead of *N*-arylamides, but in these cases the reaction afforded more complex mixtures where we could not identify the desired products.

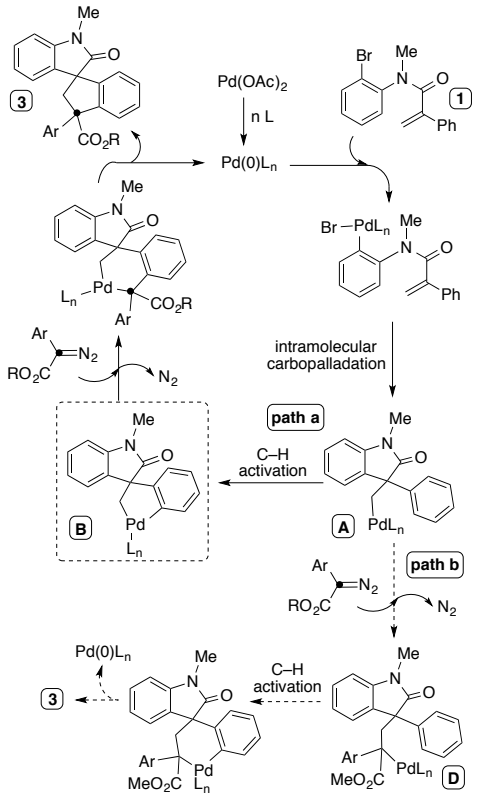
Noteworthy, the organic products arising from the cascade reaction bear two all-carbon quaternary chiral centers, hence, all the reactions rendered a mixture of diastereomers which could be separated by chromatography and characterized in most cases. Each proton present in the methylene group of the indene core of products **3** appeared as a doublet (*J* approx. 14 Hz), with characteristic and distinct chemical shift for the major and minor diastereomers. A NOESY experiment of both diastereomers **3k** (Scheme 5), revealed that the major one beared the amide and the carboxymethyl group in *syn* position within the indene nucleus. Furthermore, the crystal structure of the major diastereomer of **3b** could be determined by X-ray diffraction (Figure 1),[14] confirming the relative stereochemistry of the quaternary centers.



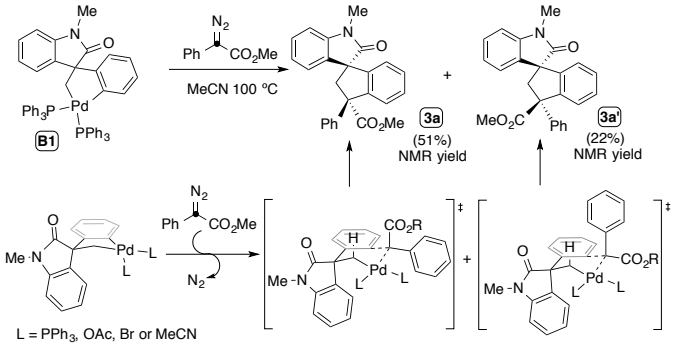
Scheme 5. Relative stereochemistry of the major and minor diastereomers **3k** and **3k'** arising from the cascade reaction.

The development of new methods to obtain scaffolds containing all-carbon chiral centers is a topic of growing interest since these motifs are present in many natural and biologically active compounds.[15]

Likely, the mechanistic pathway of the cascade spirocyclization reaction leading to the products **3** proceeds through the intramolecular 5-*exo-trig* carbopalladation of the alkenyl substrate **1**, giving rise to the σ-alkyl Pd(II) intermediate of type **A** (Scheme 6). Next, a C–H activation step would afford the five-membered C(sp²),C(sp³)-palladacycle of type **B** (path a, Scheme 6), which in turn, would undergo the carbene transfer from the diazo compound **2**, with subsequent N_2 release. A final C–C coupling step with reductive elimination of Pd(0) would afford the spiro-oxoindole **3**.[16] The reaction of the spiro-palladacyle **B1**, prepared following the procedure reported by Lautens, [9b] and the diazoester **2a** in MeCN at 100 °C afforded a 73% of **3a** with a similar dr to the catalytic procedure (Scheme 7). The diastereoselectivity of the reaction might be explained through a chair-like transition state where the bulky aryl group occupies the equatorial position. We could not detect a possible by-product resulting from a *β*-hydride elimination of intermediate **D** arising form the alternative reaction path b (Scheme 6). Remarkably, under the reaction conditions given above, the secondary competitive side reactions reported for Pd-catalyzed cascade transformations in similar substrates (such as C–C coupling of the C(sp²),C(sp³)-palladacycle of type **B** leading to spirocyclic scaffolds or cyclizations through 1,4-Pd migration processes), could be avoided or minimized.[4,17]



Scheme 6. Proposed reaction pathway for the remote alkylation.



Scheme 7. Stoichiometric reaction and possible stereochemical model.

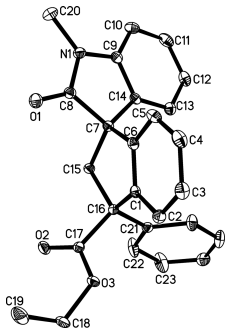


Figure 1. Thermal ellipsoid plot of the RR-diastereomer of **3b**.

In conclusion we have expanded the versatility of the intramolecular remote C–H activation by means of σ-alkyl

Pd(II) intermediates generated *in situ*. This new methodology allows the construction of complex molecular architectures such as poly-spirocyclic oxoindoles containing two all-carbon stereocenters from simple starting materials in a straightforward manner.

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