Synthetic Methods

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Palladium-Catalyzed Tandem Heck Reaction/C–H Functionalization—Preparation of Spiro-Indane-Oxindoles

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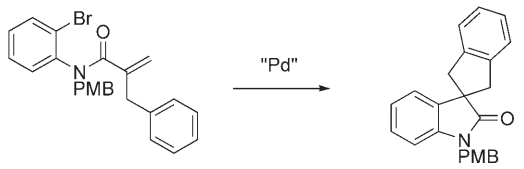
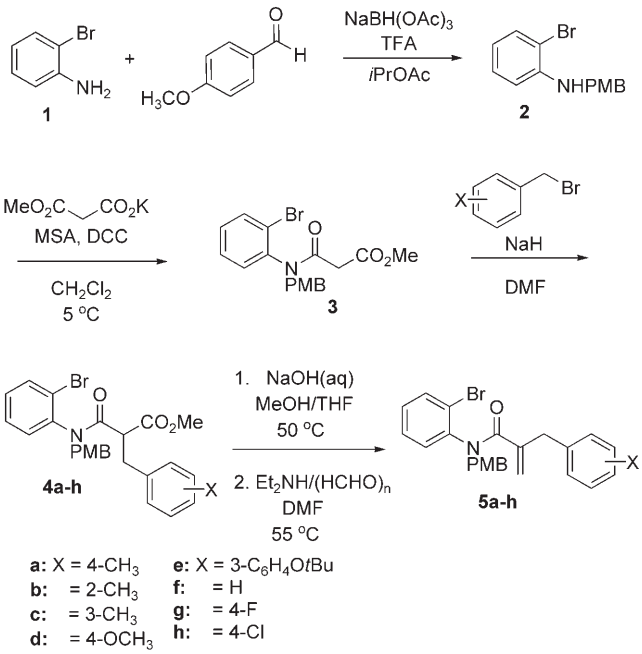
The oxindole framework is a motif common to natural products[1] and pharmaceutically active compounds.[2] In particular, 3,3-disubstituted oxindoles have shown promising biological activity.[1a,e] Considerable efforts have been dedicated to developing new methods for the preparation of these pharmacaphores, especially spiro-oxindoles: functionalization of heterocycles,[3] variations of the Stolle reaction,[4] epoxide rearrangement,[5] Lewis acid promoted cyclization,[6] Pummerer rearrangement,[7] and various palladium-catalyzed methodologies.[8] Within that last category, the intramolecular Heck reaction is of particular relevance here.[8e]

Although tremendous efforts have been invested in the discovery of new palladium-catalyzed processes, there remains limited overlap between two key transformations, namely the Heck reaction[9] and the direct arylation reaction,[10] which appear to be orthogonal methodologies. Most relevant examples of reaction commonality entail carbopalladation to form a vinylpalladium intermediate and subsequent C–H functionalization.[11] The two examples that proceed by olefin insertion to form an alkylpalladium intermediate undergo C–H insertion to form a cyclobutane product after reductive elimination.[12] Of particular relevance to this work is the report from Grigg et al. on a Heck reaction that forms an alkylpalladium complex and then undergoes a heteroatom-directed arylation reaction to make a five-membered ring.[13] Herein we report an efficient preparation of spiro-fused indane-oxindoles by carbopalladation to form an alkylpalladium intermediate and subsequent functionalization of an unactivated aryl C–H bond. (Scheme 1).



Scheme 1. Heck/C–H functionalization tandem reaction. PMB = *p*-methoxybenzyl.

To investigate the viability of a tandem Heck/arylation reaction sequence, we prepared *N*-(2-bromophenyl)acrylamides (**5a–h**) in a five-step sequence from 2-bromoaniline (**1**) (Scheme 2). Reductive amination between *p*-anisaldehyde and 2-bromoaniline afforded PMB-protected aniline **2** (PMB = *p*-methoxybenzyl).[14] Amide bond formation between compound **2** and potassium *mono*-methyl malonate provided malonamic acid methyl ester **3**, which was alkylated with the requisite substituted benzyl bromide to afford alkylation products **4a–h**. Hydrolysis of the methyl ester,



Scheme 2. *N*-(2-bromophenyl)acrylamide synthesis. TFA = trifluoroacetic acid; MSA = methanesulfonic acid.

and treatment of the liberated carboxylic acid with diethylamine and paraformaldehyde, furnished acrylamides **5a–h** in good yields.

Initial efforts to effect the desired transformation from compound **5a** to **6a** employed the catalytic system reported by Fagnou and co-workers: $Pd(OAc)_2$ (10 mol%), $PtBu_3$-HBF_4 (20 mol%), and K_2CO_3 in DMA at 130 °C.[15,17] Gratifyingly, spiro-fused indane-oxindole **6a** was observed under these conditions. A second product (**7**; see Scheme 4), assigned as the product formed by a reductive Heck reaction, was also observed in the complex reaction mixture.[16] A series of palladium sources and ligands was screened in an effort to develop a cleaner reaction. Decreasing the catalyst loading in

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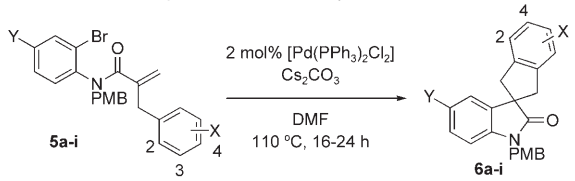
the original $Pd(OAc)_2/PtBu_3$ system led to incomplete reaction. $Pd(OAc)_2$ alone was sufficient to catalyze the transformation, but reaction progress again stalled at less than 100% conversion of the starting material. Catalysis by $PdCl_2(dppf)$ (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) increased the reaction rate, but led to the formation of more reductive Heck product **7**. $[Pd(PPh_3)_2Cl_2]$ emerged as the catalyst that offered the optimal balance of reaction rate and selectivity for C–H functionalization over a reductive Heck reaction. As a base, Cs_2CO_3 provided a cleaner reaction profile than K_2CO_3 or K_3PO_4. The reaction in DMF at 110 °C was equivalent to that in DMA, and superior to the reaction in less polar solvents. The optimal reaction conditions were determined to be $[Pd(PPh_3)_2Cl_2]$ (2 mol%) and Cs_2CO_3 (2.5 equiv) in DMF at 110 °C.

The tandem Heck/C–H functionalization reaction afforded spiro-fused indane-oxindoles **6a–i** in excellent yields, ranging from 64 to 91%. The transformation was effective over a range of electronic properties on the phenyl ring to be C–H functionalized, from electron-donating (Table 1, entries 4 and 5) to electron-deficient (Table 1, entries 7 and 8).[17] Substitution at the 2-, 3-, and 4-positions of the phenyl ring in the starting material was tolerated in this system, and afforded products that have been defined as 2- or 4-substituted in the product. The reaction rate was fastest in the case of *ortho* substitution (Table 1, entry 2), a surprising observation given that this substrate has the kinetic disadvantage of only one *ortho*-C–H bond that may be functionalized, whereas the 3- and 4-substituted substrates have two available *ortho*-C–H bonds. In the case of the 3-substituted starting material, functionalization can occur at either of the two *ortho*-C–H bonds to give two distinct products; these products correspond to the products obtained from the 4-substituted or the 2-substituted starting material. The ratio of these two products was governed by the size of the 3-substituent. In the case of the relatively small methyl group, functionalization of the less sterically hindered *para*-C–H bond (with respect to the methyl group) was preferred over the *ortho*-C–H bond by a ratio of 3:1 (Table 1, entry 3). When the steric bulk of the 3-substituent was increased by using a *tert*-butoxy group, C–H functionalization occurred almost exclusively at the *para* position (Table 1, entry 5).

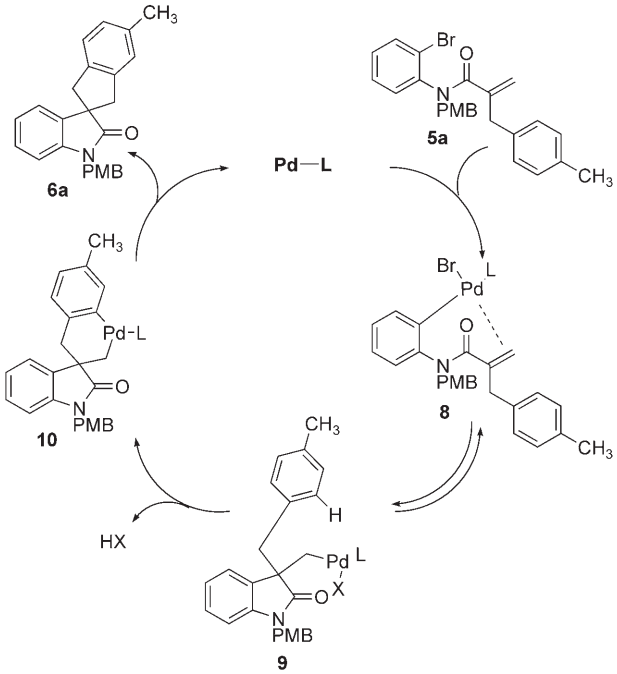
Table 1: Substrate scope of tandem Heck/C–H functionalization.



Entry	SM	X (SM)	Y	Product	X (Product)	Yield [%]
1	**5a**	4-CH_3	H	**6a**	4-CH_3	90
2	**5b**	2-CH_3	H	**6b**	2-CH_3	91
3	**5c**	3-CH_3	H	**6a** and **6b**	4-CH_3:2-CH_3	75 (3:1)[a]
4	**5d**	4-OCH_3	H	**6d**	4-OCH_3	87
5	**5e**	3-O*t*Bu	H	**6e** and **6e′**	4-O*t*Bu: 2-O*t*Bu	80 (>50:1)[b]
6	**5f**	H	H	**6f**	H	65
7	**5g**	4-F	H	**6g**	4-F	84
8	**5h**	4-Cl	H	**6h**	4-Cl	64
9	**5i**	4-CH_3	CH_3	**6i**	4-CH_3	82

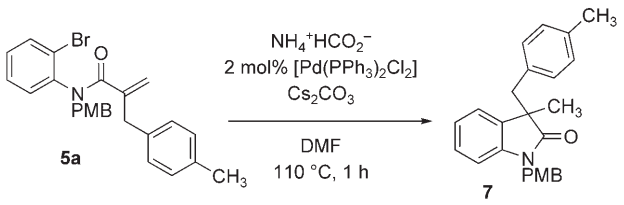
[a] Combined yield for **6a** and **6b**. Ratio in parentheses represents the ratio of **6a**:**6b**. [b] The yield is for the major regioisomer **6e**; **6e′** was assigned based on LC/MS analysis. SM = starting material.

A proposed catalytic cycle for the tandem Heck/C–H functionalization reaction is shown in Scheme 3. In this mechanism, the palladium–ligand complex undergoes oxidative addition to the carbon–bromine bond of acrylamide **5a** to form intermediate **8**. The intramolecular Heck insertion proceeds by a 5-*exo*-trig cyclization to form primary alkylpalladium species **9**. Reaction at the highlighted C–H bond affords six-membered palladacycle **10**,[18] and subsequent reductive elimination provides spiro-fused indane-oxindole **6a**.



Scheme 3. Proposed Heck/C–H functionalization catalytic cycle.

Overman and others have reported many examples of asymmetric Heck reactions to generate 3,3-disubstituted oxindoles in moderate to high enantioselectivities.[19] Unfortunately, considerable ligand screening has failed to identify an enantioselective variant of our tandem transformation, a reaction sequence with an analogous enantiodetermining step. These negative results may be explained by two proposals. First, there is a fast and reversible olefin insertion with a subsequent, slow C–H insertion.[20] In this way, facial selectivity may exist for the initial insertion to generate intermediate **9**, but, in a Curtin–Hammett situation, there is a minimal preference for C–H functionalization to occur from either of the two diastereomers of **9**.[21] Olefin insertion was shown to be fast by running the reaction under reductive Heck conditions,[22] with 100% conversion into compound **7** achieved in less than one hour (Scheme 4). If β-



Scheme 4. Reductive Heck reaction.

hydride elimination is fast and olefin insertion is rate-determining in a standard Heck reaction, this change in mechanism with reversible C–C bond formation would explain the lack of enantioselectivity.

The olefin substitution pattern for the tandem Heck/C-H functionalization may also explain the failed asymmetric variant. The 1,1-disubstituted olefin employed in this chemistry cannot participate in the standard enantioselective Heck reaction, which requires a 1,1,2-trisubstituted olefin. In this case, the absence of substitution at the β position of the olefin may prevent enantiofacial discrimination by the catalyst.[23] Indeed, the reductive Heck reaction above also provided compound **7** in 0% *ee*, when the catalyst was modified to [((*S*)-binap)$PdCl_2$] (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl),[24] a catalyst commonly employed in asymmetric intramolecular Heck reactions.[19]

In conclusion, we have developed a novel tandem Heck/C–H functionalization reaction to generate spiro-fused indane-oxindoles in high yields. The reaction employs only 2 mol% of a commercially available palladium catalyst to effect a 5-*exo*-trig Heck cyclization with subsequent functionalization of an unactivated C–H bond. Efforts are ongoing to discover a chiral ligand that may facilitate the development of an asymmetric variant of the tandem Heck/C–H functionalization reaction.

Experimental Section

Spiro-fused indane-oxindole **6a**: A 10 mL round-bottom flask was charged with 4-methylacrylamide **5a** (450 mg, 1.0 mmol), [Pd-(PPh_3)$_2$$Cl_2$] (14 mg, 0.020 mmol) and Cs_2CO_3 (815 mg, 2.5 mmol). The flask was purged with nitrogen. DMF (4 mL) was then added by syringe and the mixture was sparged with nitrogen. The reaction mixture was heated in an oil bath at 110 °C for 24 h and then cooled to room temperature. Ethyl acetate (20 mL) and water (12 mL) were added and the reaction mixture was filtered to remove palladium. The two layers were separated and the organic layer was washed two times with water. The ethyl acetate layer was dried over Na_2SO_4 and evaporated under reduced pressure. Silica gel chromatography (35% ethyl acetate/hexane) afforded spiro-fused indane-oxindole **6a** (341 mg, contaminated with 3% reductive Heck byproduct **7**,[14] 90% yield corrected for purity). The mixture was recrystallized from MTBE/heptane (MTBE = methyl *tert*-butyl ether) to isolate an analytically pure sample.

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