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Palladium-Catalyzed Synthesis of Dihydrobenzoindolones via C−H Bond Activation and Alkyne Insertion

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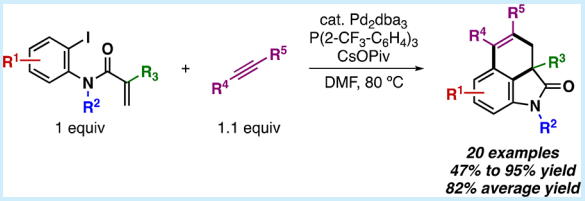
Supporting Information

ABSTRACT: A palladium-catalyzed intramolecular carbopalladation, intramolecular C−H bond activation, and alkyne insertion sequence for the generation of dihydrobenzoindolones is described. Products are obtained in moderate to excellent yields as single regioisomers. Various functional groups on both reaction partners were tolerated, and the scalability of this method was determined.

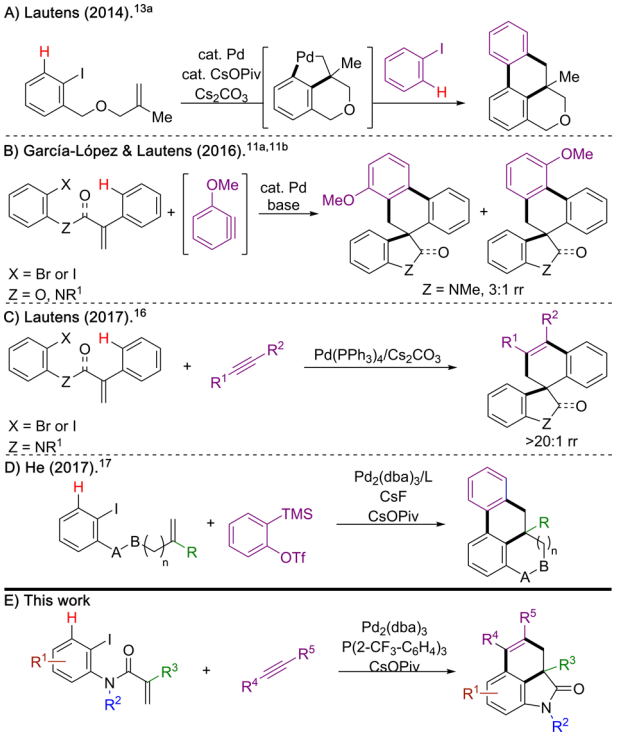


Transition-metal-catalyzed C−H bond activation has emerged as an important tool for the construction of carbon−carbon and carbon−heteroatom bonds due to its high atom and step economy.[1,2] This method has been employed in the synthesis of various scaffolds and opens up alternative synthetic disconnections while reducing waste generation.[1,3] A common requirement for this strategy is the presence of appropriate preinstalled or transient directing groups, which direct the metal center toward the desired C−H bond for subsequent functionalization.[3−6] This approach has been applied in challenging regioselective activation of *meta* and *para* C(sp^2)−H bonds of aromatic rings,[7] as well as aliphatic chains of carbonyl compounds.[8] Alternatively, palladium-catalyzed domino processes allow unique activation of remote C−H bonds.[1c,3a,c,9] These processes are initiated by the formation of an organopalladium species which undergoes an intramolecular migratory insertion on a tethered π-system, generating a σ-alkyl-Pd(II) intermediate that places the metal in close proximity to a formerly remote C−H bond. Following C−H activation, the corresponding palladacycle can either reductively eliminate[10b] or react with a range of coupling partners prior to reductive elimination.[11d] Such coupling partners include the following: diaziridinones,[10a] benzynes,[11] α-diazocarbonyl compounds,[12] alkyl and aryl halides,[5c,13] carbon monoxide,[14] disilanes,[15] and activated alkynes.[11e,16] Based on this method, we present herein a Pd-catalyzed C(sp^2)−H activation/alkyne insertion cascade for the synthesis of dihydrobenzoindolones.

In 2014, our group reported a Pd-catalyzed intermolecular domino reaction encompassing two C(sp^2)−H bond functionalizations, which was proposed to proceed via a five-membered palladacycle intermediate (Scheme 1A).[13a]

When an aryl group replaced the methyl substituent on the alkene, C(sp^2)−H insertion occurred preferentially on the tethered phenyl moiety so as to form spiro metalated intermediates (Scheme 1B). As reported independently by García-López and Lautens, benzynes react smoothly, but low regioselectivities were observed with unsymmetrical benzynes.[11a,b] As a strategy to circumvent this challenge, our group recently developed a Pd-catalyzed spirocyclization reaction involving a sequential C(sp^2)−H bond activation of a tethered phenyl moiety, using polarized, unsymmetrical alkynes as reactive coupling partners (Scheme 1C).[16] The spirooxindole and spirodihydrobenzofuran products were generated in high

Scheme 1. Pd-Catalyzed C(sp^2)−H Bond Activation Domino Processes



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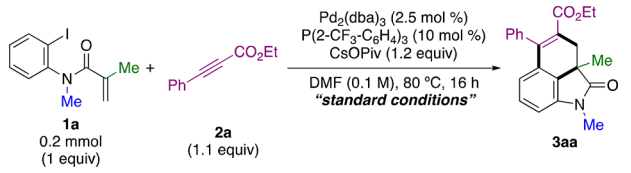
yields and regioselectivities (>20:1 rr). In 2017, He and co-workers reported a Pd-catalyzed synthesis of heterocycle-fused 9,10-dihydrophenanthrenes via a related C(sp^2)−H activation/benzyne insertion sequence (Scheme 1D).[17] Similarly to previous reports, however, low regioselectivities were obtained when unsymmetrical benzyne precursors were employed. We envisioned that unsymmetrical alkynes could be suitable coupling partners in a process involving the C(sp^2)−H bond activation at the *ortho* position of the aryl halide in the absence of a tethered phenyl group (Scheme 1E). Herein, we disclose the successful realization of this approach in the synthesis of dihydrobenzoindolones in good to high yields and excellent regioselectivities.

We began our investigation by reacting acrylamide **1a** and 3-ethyl phenylpropiolate (**2a**, 1.1 equiv) in the presence of a Pd(0) catalyst under various reaction parameters (see Supporting Information (SI)). The combination of $Pd_2(dba)_3$ (2.5 mol %), P(2-CF_3−C_6H_4)$_3$ (10 mol %), and CsOPiv (1.2 equiv) in DMF (0.1 M) at 80 °C for 16 h was found to be optimal, affording product **3aa** in 91% isolated yield (Table 1, entry 1). The structure of **3aa** was unambiguously determined by spectroscopic analysis and single crystal X-ray crystallography (CCDC 1848230; see SI). The effect of varying different reaction parameters on the efficiency of the reaction was evaluated (Table 1). Toluene and acetonitrile have typically been optimal solvents in various related Pd-catalyzed domino C−H activation methods.[11a,b,16,17] Replacing DMF with toluene in our case, however, severely decreased the product yield (entry 2), while acetonitrile provided the product in 81% yield (entry 3). The yield was marginally decreased upon varying the reaction concentration (entries 4 and 5). Interestingly, decreasing the reaction temperature to 60 °C afforded the desired product in 90% yield (entry 6), while running the reaction at 100 °C afforded **3aa** in 87% yield (entry 7). Cesium pivalate was found to be essential, as other bases, such as Cs_2CO_3, resulted in attenuated reactivity (entry 8). The reaction efficiency was significantly decreased when ligands other than P(2-CF_3−C_6H_4)$_3$ were employed. Utilizing 10 mol % PPh_3 was found to be ineffective (entry 9), while using 10 mol % P(*o*-tol)$_3$ furnished the product in low yield (entry 10). Similarly, low yields were obtained when 10 mol % X-Phos or 5 mol % dppf were used (entries 11 and 12).

With the optimized conditions in hand, we evaluated the generality of this process by subjecting various acrylamides to the optimal reaction conditions and employing 3-phenyl ethylpropiolate (**2a**) as the coupling partner (Scheme 2). We first sought to determine the effect of different substituents on the nitrogen atom. Substrates possessing *N*-Bn (**1b**) and *N*-PMB (**1c**) groups led to product formation in 86% and 87% yields, respectively. When substrate **1d** containing an *N*-MOM was subjected to the reaction conditions, product **3d** was generated in 83% yield. Products containing *N*-methylenecyclopropane (**1e**) and *N*-methallyl (**1f**) groups were accessed in 90% and 88% yields, respectively. To study the effect of the substitution on the α-position, acrylamides containing α-Bn (**1g**), α-^{i}Pr (**1h**), and α-^{n}Bu (**1i**) groups were reacted, affording products **3g**, **3h**, and **3i**, in 47%, 92%, and 95% yields, respectively. The lower yield of product **3g** is attributed to a competitive C−H activation at the benzylic substituent, generating a spirooxindole byproduct (detected by ^{1}H NMR analysis of the crude reaction mixture) upon reductive

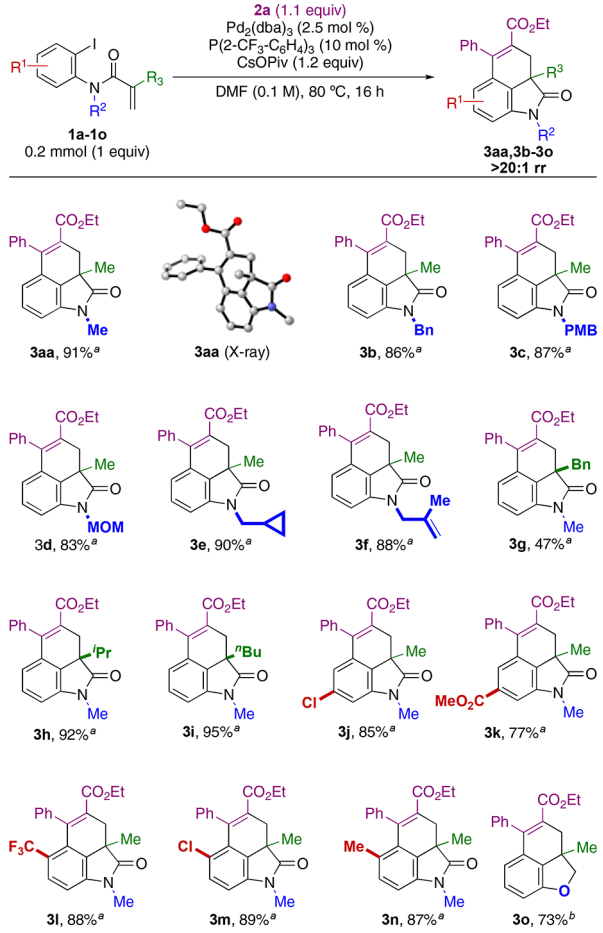
Table 1. Effect of Varying Reaction Parameters



entry	variation from "standard conditions"	**3aa** (%)[a]
1	none	94 (91[b])
2	PhMe instead of DMF	9
3	MeCN instead of DMF	81
4	0.05 M	88
5	0.2 M	88
6	60 °C	90
7	100 °C	87
8	Cs_2CO_3 instead of CsOPiv	32
9	PPh_3 (10 mol %)	N.R.
10	P(*o*-tol)$_3$ (10 mol %)	39
11	X-Phos (10 mol %)	28
12	dppf (5 mol %)	N.R.

[a]Yields were determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield in parentheses. N.R. = No reaction.

Scheme 2. Substrate Scope



[a]Isolated yields of products. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

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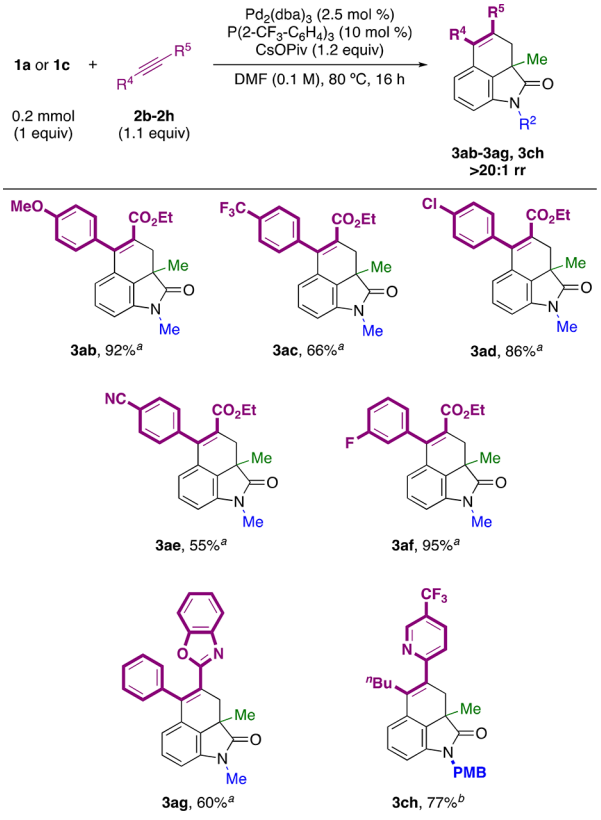
elimination, as reported by Ruck and co-workers.[18,19] Substrates containing 4-chloro and 4-ester functional groups were subjected to the reaction conditions, and products **3j** and **3k** were obtained in good yields. Various other substituents in the aryl moiety of the acrylamide substrates were tolerated, and substrates containing 5-CF_3 (**3l**), 5-Cl (**3m**), and 5-Me (**3n**) substituents rendered products in 88%, 89%, and 87% yields, respectively. Furthermore, benzofuran derivative **3o** was obtained in 73% ^{1}H NMR yield. Unfortunately, attempts to isolate this product were unsuccessful due to coelution of an unknown impurity using silica-gel chromatography. Of note, ^{1}H NMR analysis of crude reaction mixtures indicates all products were obtained as single regioisomers.

The scope of this transformation with respect to the unsaturated alkyne component was also investigated (Scheme 3). An electron-rich aryl substituent on the alkyne was

Scheme 3. Alkyne Scope

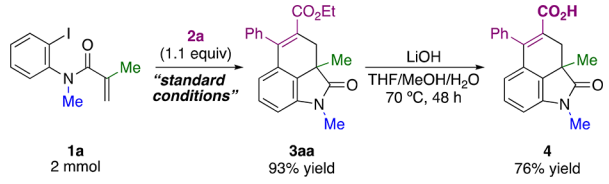


[a]Isolated yields of products. [b]Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

tolerated, and product **3ab** containing a *para*-OMe group was obtained in 92% yield. Products containing electron-withdrawing *para*-CF_3 (**3ac**), -Cl (**3ad**), and -CN (**3ae**) were generated in 66%, 86%, and 55% yields, respectively. Alkyne **2f** bearing a *meta*-F substituent generated product **3af** in 95% yield. The reaction was also expanded to alkynes encompassing heterocyclic motifs. Reaction of **1a** and alkyne **2g** afforded product **3ag** containing a benzoxazole motif in 60% yield, while the product **3ch** showcasing a pyridine moiety was obtained in 77% ^{1}H NMR yield.[20] As discussed previously, all products were obtained as single regioisomers (>20:1).

To highlight the scalability of this process, a 2.0 mmol scale reaction was performed using acrylamide **1a** and alkyne **2a** as the coupling partner, generating benzoindolone **3aa** in 93% yield (Scheme 4). The ester functional group of the product was hydrolyzed to form carboxylic acid **4** in 76% yield (Scheme 4).

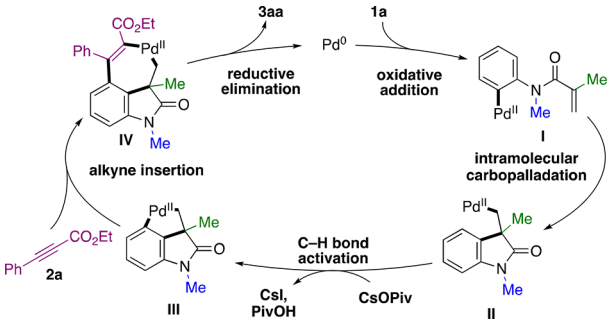
Scheme 4. Scale-Up Reaction and Derivatization[a]



[a]Isolated yields are shown.

Based on previous work reported by García-López,[11] our group,[11,16] and He,[17] a plausible mechanism for this transformation is presented in Scheme 5. Substrate **1a** undergoes

Scheme 5. Proposed Mechanism



oxidative addition to form aryl-Pd(II) intermediate **I**. Intramolecular 5-*exo*-trig carbopalladation furnishes σ-alkylpalladium(II) intermediate **II**. The palladium center is in close proximity to the C(sp^2)−H bond, generating palladacycle intermediate **III** upon C−H bond activation. Subsequent coordination and migratory insertion of **2a** generates intermediate **IV**. Final reductive elimination releases product **3aa** and regenerates the active Pd(0) catalyst.

In conclusion, we have developed a Pd-catalyzed C(sp^2)−H bond activation/alkyne insertion cascade that affords access to dihydrobenzoindolones in good to high yields and excellent regioselectivities. The use of P(2-CF_3−C_6H_4)$_3$ as a ligand was instrumental in obtaining high reaction efficiencies. The scope of various acrylamides was investigated, and substrates containing *N*-, α-, and aryl-substituents were participants in this domino process. Additionally, several unsymmetrical alkyne coupling partners were subjected to the reaction conditions, furnishing products as single regioisomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01856.

Experimental procedures, optimizations, characterizations, and X-ray data (PDF)

Accession Codes

CCDC 1848230 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

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via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) The spirooxindole byproduct was generated in 49% ^{1}H NMR yield, using 1,3,5-trimethoxybenzene as the internal standard.

(20) Purification of product **3ch** by chromatography was not possible due to rapid decomposition.

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