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Pd-Catalyzed Spirocyclization via C–H Activation and Regioselective Alkyne Insertion

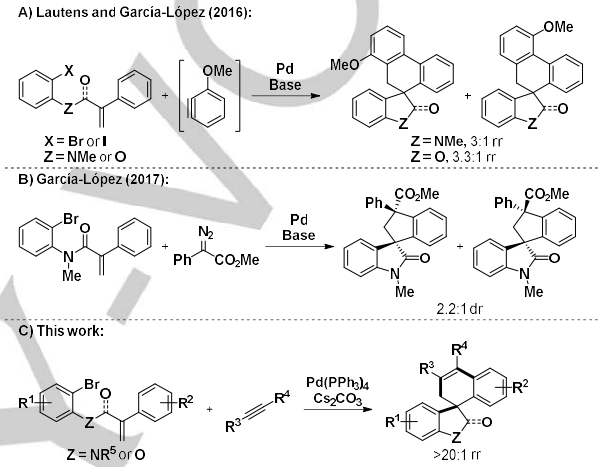
Hyung Yoon, Martin Rölz, Felicitas Landau, and Mark Lautens*[a]

Dedication ((optional))

Abstract: A Pd-catalyzed spirocyclization involving a sequential carbopalladation, intramolecular C–H activation and a highly regioselective alkyne insertion to afford spirooxindoles and spirodihydrobenzofurans has been achieved. The spirocyclic products were generated in good to excellent yields with complete regiocontrol in a readily scalable procedure.

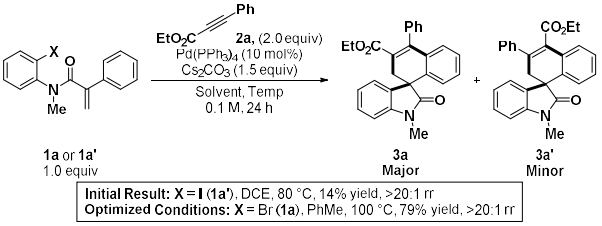
The use of C–H functionalization to enable the synthesis of novel scaffolds has become commonplace in modern organic chemistry and results in the improvement of both step- and atom-economy.[1] The vast majority of progress made in this field has relied on the use of a preinstalled directing group which greatly improve selectivity and reactivity.[2-4] The functionalization of C–H bonds in an intramolecular fashion, wherein oxidative addition to a carbon–halogen bond situates the metal centre in a favourable position to interact with a chosen C–H bond.[5] Despite the remarkable progress made in this field, selective functionalization remains a challenge. In this regard, the application of C–H functionalization in a domino process has extended the versatility and applicability of the reaction as it enables the metal centre to interact with remote bonds that may otherwise be unreactive.[6-10] Employing this approach, we present a novel Pd-catalyzed spirocyclization reaction.

Recently, our group and the García-López group have employed C–H functionalization in a domino process to generate spirocycles via carbopalladation, C–H activation, and migratory insertion or direct reductive elimination sequence.[11-14] Unfortunately, diastereo- and regioselective migratory insertion into the palladacycle involving highly reactive intermediates have proven to be challenging. In 2014, Garg and co-workers[15] have experimentally and computationally reported that unsymmetrical and electronically biased arynes show excellent regioselective addition reactions whereas in our study,[12,13] these arynes undergo the migratory insertion in poor regiocontrol (Scheme 1, A). Following this work, the García-López group reported the spirocyclization involving α-diazocarbonyl compounds albeit in modest diastereoselectivity (Scheme 1, B).[14] As a solution to circumvent the lack of selectivity observed in the described reactions, we sought to investigate less reactive π-systems (Scheme 1, C). Herein, we showcase the Pd-catalyzed spirocyclization via the insertion of unsymmetrical alkynes generating spirooxindoles and spirodihydrobenzofurans in good to excellent yields under high regiocontrol.



Scheme 1. Pd-catalyzed spirocyclization via C–H activation and insertion of π-system.

We began our study by synthesizing the proposed spirooxindole based on the reaction conditions outlined by Malinkova (Scheme 2).[16] Subjecting **1a'** to these reaction conditions gave **3a** in 14% yield and trace amounts of **3a'**. The spirocyclic structure of **3a** was confirmed by spectroscopic analysis and single crystal X-ray crystallography.[17] Encouraged by this initial result, the reaction conditions were optimized to yield **3a** in 79% yield and >20:1 ratio of regioisomers (rr) while minimizing the formation of side products.[18]



Scheme 2. Initial result and optimized conditions.

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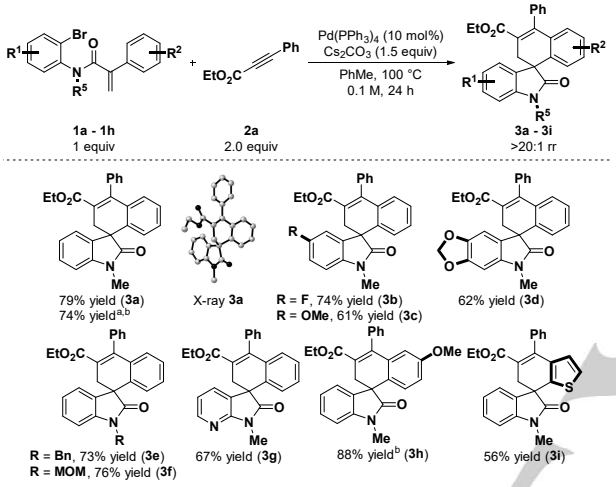
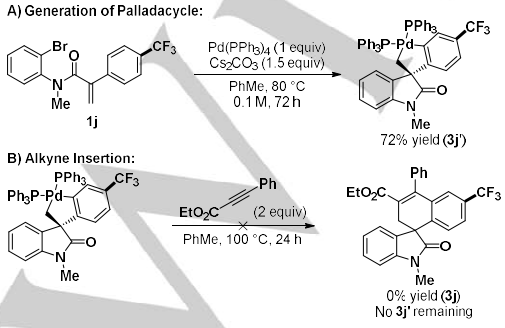
With the optimized conditions in hand, the generality of the methodology was explored (Scheme 3). Unless stated otherwise, all spirocycles were generated in >20:1 rr. On gram scale, **3a** was synthesized in 74% yield, however, a longer reaction time was necessary for the full consumption of **1a**. Fluorinated acrylamide **1b** provided **3b** in 74% yield. Electron-rich substituents were tolerated and gave **3c** and **3d** in moderate yields (61% and 62% yield respectively). Other nitrogen protecting groups such as –Bn and –MOM were tolerated in the cyclization (**3e** and **3f,** 73% and 76% yield respectively). Substitution by a pyridinylbromide did not impede the generation of **3g**. Electron-rich substituents on the pendant aromatic ring aided in the cyclization forming **3h** in 88% yield. A tethered thiophene group participated in the C–H activation forming **3i** in moderate yield.



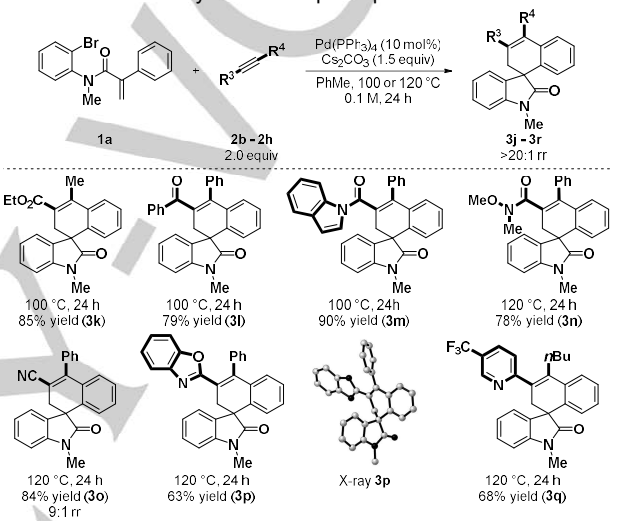
Scheme 3. Pd-catalyzed spirocyclization forming spirooxindoles. Reaction scope with varied acrylamides. 0.2 mmol scale. All yields refer to isolated proucts. rr values determined by ^{1}H NMR analysis of the crude reaction mixture. [a] Reaction run on 3.16 mmol scale. [b] Reaction run for 48 h.

Surprisingly, functionalization of the pendant aromatic ring with electron-poor substituents interfered in the generation of the desired spirooxindole (Scheme 4). Intrigued by this result, palladacycle **3j'** was independently synthesized (Scheme 4, A). The subsequent reaction with the model alkyne led to full consumption of **3j'** however, no desired spirooxindole **3j** was formed. This suggests that the insertion of the alkyne is kinetically disfavoured with respect to the decomposition of **3j'**.



Scheme 4. Stepwise Pd-catalyzed spirocyclization. All reactions run on 0.2 mmol scale. Yield refers to isolated proucts.

Internal alkynes other than ethyl phenylpropiolate were also investigated (Scheme 4). The insertion of ethyl 2-butynoate provided **3k** in 85% yield. Substitution of the ester to a non-enolizable ketone generated **3l** in 79% yield. Indole derived alkyne **2d** was incorporated to give **3m** in excellent yield (90% yield) while the Weinreb amide **2e** required higher temperature to generate **3n** (120 ºC, 78% yield). Phenylpropionitrile reacted in good yield albeit with slightly lower regioselectivity (**3o**, 84% yield, 9:1 rr). The diaryl alkyne **2g** underwent the regioselective insertion at elevated temperatures to give **3p** in 63% yield. The connectivity was confirmed by spectroscopic analysis and X-ray crystallography.[17] The 4-trifluoromethyl-2-pyridine bearing alkyne **2h** gave **3q** in 68% yield at elevated temperature.[19] Less activated internal alkynes did not participate in the reaction.[20]



Scheme 5. Pd-catalyzed spirocyclization forming spirooxindoles. Reaction scope with varied internal alkynes. 0.2 mmol scale. All yields refer to isolated products. rr values determined by ^{1}H NMR analysis of the crude reaction mixture.

Following the success making spirooxindoles, spirodihydrobenzofurans were also targeted (Scheme 5). Using the aryliodide **4a**, 5 mol% of $Pd(PPh_3)_4$, and slight excess of Cs_2CO_3 and alkyne **2a**, **5a** was generated in 88% yield and 20:1 rr.[17] On gram-scale, **5a** was isolated in 94% yield with identical regioselectivity. Sterically encumbered aryliodide **4b** reacted in good yield (83% yield). In the presence of a second halogen, the cyclization generated **5c** in 88% yield. The spirocyclic structure was confirmed by spectroscopic analysis and x-ray crystallography.[17] Electron-rich substituents on the aryliodide and pendant aromatic ring cyclized in good to excellent yields (**5d** and **5f**, 75% and 92% yield respectively). Electron-poor substituents on the aryliodide or tethered aromatic ring required longer reaction times and gave moderate yields (**5e** and **5g**, 66% and 55% yield respectively). *N*-tosyl spiroindoline was cyclized in good yield (**5h**, 83% yield).

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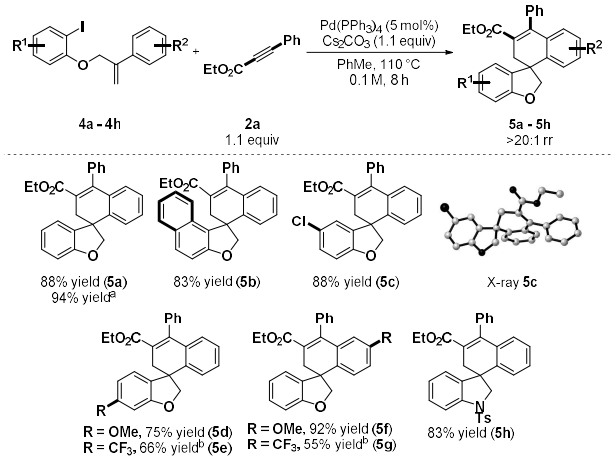
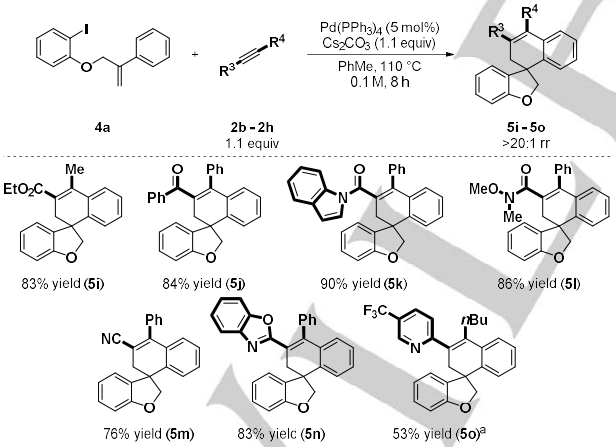


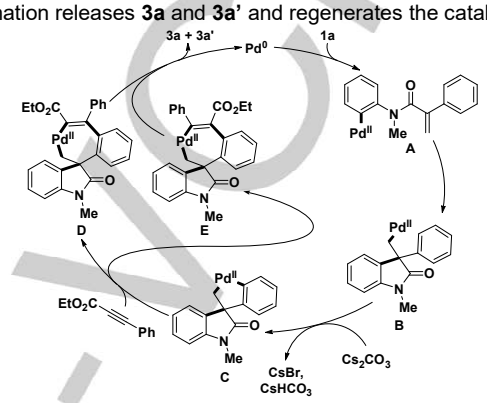
Scheme 6. Pd-catalyzed spirocyclization forming spirodihydrobenzofurans. Reaction scope with varied aryliodides. 0.2 mmol scale. All yields refer to isolated products. rr values determined by ^{1}H NMR analysis of the crude reaction mixture. [a] Reaction run on 2.97 mmol scale. [b] Reaction run for 24 h.

Alkynes **2b** - **2h** were also probed for the synthesis of spirodihydrobenzofurans (Scheme 6). Ethyl 2-butynoate generated **5i** in 83% yield. The phenyl ketone substituted alkyne **2c** inserted to form **5j** in good yield (84% yield). Spirocycles **5k** and **5l** were successfully synthesized in excellent yield via the insertion of alkynes **2d** and **2e** respectively. Unlike the selectivity observed with the spirooxindole, nitrile bearing spirocycle **5m** was generated in >20:1 rr. Diaryl alkyne **2e** participated in the reaction to give **5n** in 83% yield. The 5-trifluoromethyl-2-pyridine bearing alkyne also provided the desired spirocycle but required an extended reaction time.[21]



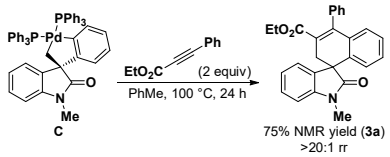
Scheme 7. Pd-catalyzed spirocyclization forming spirodihydrobenzofurans. Reaction scope with varied internal alkynes. 0.2 mmol scale. All yields refer to isolated products. rr values determined by ^{1}H NMR analysis of the crude reaction mixture. [a] Reaction run for 24 h.

In analogy to the benzyne insertion spirocyclization, the mechanism is thought to proceed via a similar sequence (Scheme 7). Acrylamide **1a** undergoes oxidative addition followed by a 5-*exo trig* carbopalladation forming the alkylpalladium(II) intermediate **B**. The generation of **B** places the Pd center in close proximity to the pendant aromatic ring to generate the spirocyclic palladacycle **C** via C–H activation. A regioselective migratory insertion of the activated alkyne predominantly generates palladacycle **D** and trace amounts of **E**.[22] Lastly, reductive elimination releases **3a** and **3a'** and regenerates the catalyst.



Scheme 8. Postulated mechanism for the spirocyclization.

Palladacycle **C**, which was synthesized previously in our group,[12] reacted with ethyl phenylpropiolate to afford **3a** in 75% yield and >20:1 rr (Scheme 8). This result suggests that this complex is a likely intermediate in the catalytic cycle and the consistent regioselectivity observed further supports to the proposed mechanism.



Scheme 9. Stoichiometric experiment forming the spirooxindole via the preformed palladacycle. 0.1 mmol scale. Yield was determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

In conclusion, we have developed a Pd-catalyzed spirocyclization via C–H activation and alkyne insertion forming spirooxindoles and spirodihydrobenzofurans. Various functional groups were tolerated and the products were synthesized in good to excellent yields and excellent rr (>20:1). Analagous to the previous work incorporating arynes, the transformation is thought to proceed through the generation of the spirocyclic palladacycle followed by a highly regioselective insertion of the alkyne. We are currently working on expanding the scope of the reaction and the application of this transformation. We are currently carrying out a comprehensive study on the mechanism of this class of reactions.

Acknowledgements ((optional))

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Keywords: Alkynes • C–H Activation • Palladium • Regioselectivity • Spiro compounds

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[17] CCDC 1557699 (**3a**), 1557701 (**3p**) and 1557700 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center.

[18] Refer to the SI for deoptimization table for spirooxindoles and spirodihydrobenzofurans.

[19] Increasing the reaction temperature to 120 ºC led to the 1,4-Pd shift and C–H activation sequence to generate the side product in higher quantities. Reference: A. Bunescu, T. Piou, Q. Wang, J. Zhu, *Org. Lett.* **2015**, *17*, 334.

[20] The internal unactivated alkynes probed were diphenylacetylene, hex-3-yne, and 1,4-dimethoxybut-2-yne. Unfortunately, dimethyl but-2-ynedioate also did not insert.

[21] The benzofused cyclobutane byproduct was observed when reacting the 5-trifluoromethyl-2-pyridine bearing alkyne. Reference: J. Ye, Z. Shi, T. Sperger, Y. Yasukawa, C. Kingston, F. Schoenebeck, M. Lautens, *Nat. Chem.* **2017**, *9*, 361.

[22] There are 4 possible regioisomers after the insertion of the alkyne however, the 2 most plausible isomers are shown. All 4 possible regioisomers are shown in the supporting information.

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Pd-Catalyzed Spirocyclization via C–H Activation and Regioselective Alkyne Insertion

C–H activate and insert: A Pd-catalyzed cascade reaction involving a sequential carbopalladation, intramolecular C–H activation and a highly regioselective alkyne insertion generates a variety of spirooxindoles and spirodihydrobenzofurans. The spirocycles are generated in good to excellent yield and >20:1 ratio of regioisomers.