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Cera, G.; Lanzi, M.; Balestri, D.; Della Cà, N.; Maggi, R.; Bigi, F.; Malacria, M.; Maestri, G. Synthesis of Carbolines via Palladium/Carboxylic Acid Joint Catalysis. *Org. Lett.* **2018**, *20*(11), 3220-3224.

DOI: 10.1021/acs.orglett.8b01072

Expedient Synthesis of Carbolines via Palladium/Carboxylic Acid Joint Catalysis

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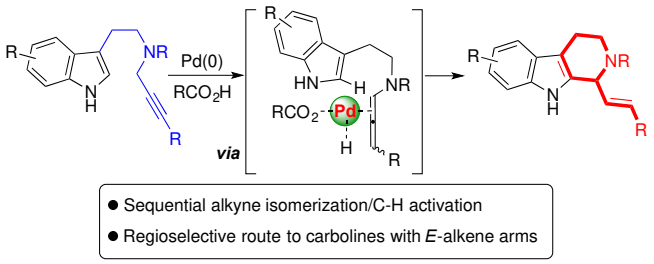


ABSTRACT:

Combination of a Pd(0) complex with benzoic acid converts propargylic tryptamines to the corresponding tetraidro-β-carbolines. The method uses unprotected indoles and affords desired products with ample functional group tolerance. Detailed modeling studies reveal a close synergy between the organic and metal catalysts, which enables sequential alkyne isomerization, indole C-H activation and eventual C-C reductive elimination to afford target heterocycles.

Tetrahydro-1H-β-carbolines (THCs) are important cores in organic chemistry due to their presence in many bioactive alkaloids and pharmaceuticals.1 Straightforward synthetic approaches are therefore on high demand.

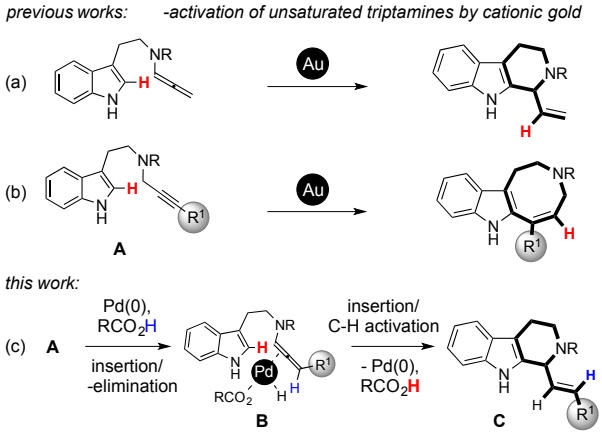
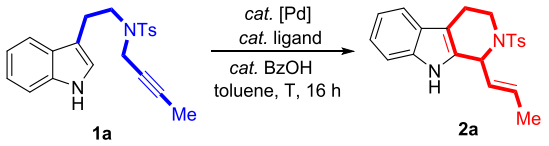


Figure 1. Alternative routes to THCs.

The synthesis of THC analogues traditionally relies on Pictet-Spengler reactions,[2] oxidative C-H functionalizations[3] and intramolecular hydroarylation of unsaturated substrates such as alkenes, allylic alcohols and their derivatives. These are mostly accomplished using 4d- and 5d-transition metal catalysts.[4] An important alternative has been recently realized by developing gold-catalyzed allenamide cyclizations (Figure 1, a).[5] However, this approach suffers from the inherent challenges of modular allenamide synthesis.[6] As part of our interest in catalytic cyclizations of polyunsaturated substrates,[7] we turned our attention to readily available propargylic tryptamines **A**. Their reactivity with soft π-acidic transition metals is well-established (Figure 1, b),[8] while yet unexplored with palladium (Figure 1, c).

Table 1. Ligand optimization.



Entry[a]	[Pd]	Ligand	T [°C]	**2a** [%]
1	$Pd(PPh_3)_4$	PCy_3	100	38
2	$Pd(PPh_3)_4$	dppe	100	59[b]
3	$Pd(PPh_3)_4$	dppf	70	45[b]
4	$Pd(PPh_3)_4$	PPh_3	100	71
5	$Pd(PPh_3)_4$	PPh_3	70	70
6	$Pd(dba)_2$	DavePhos	100	40
7	$Pd(OAc)_2$	PPh_3	100	--
8	$Pd(PPh_3)_4$	*t*-BuXPhos	70	48
9	$Pd(PPh_3)_4$	PPh_3	100	78[c]
10	$Pd(PPh_3)_4$	PPh_3	100	--(13)[d]

[a] Reaction conditions: **1a** (0.20 mmol), [Pd] (5 mol %), ligand (10 mol %), BzOH (30 mol %), toluene (0.1 M), yields of isolated product. [b] Ligand (5 mol %). [c] [Pd] (10 mol %), PPh_3 (20 mol %). [d] without BzOH, conversion of **1a** in brackets.

Gratifyingly, THC **2a** was isolated as a single *E*-isomer in 38% yield (Table 1, Entry 1) using PCy_3. Bidentate phosphines yield **2a** with slightly better performances (Entries 2, 3). The use of cheaper PPh_3 promoted the catalytic transformation with moderate yields and high chemoselectivity even at lower temperature (Entries 4, 5). $Pd(dba)_2$ could be applicable, although in lower extent (Entry 6).[11] On the contrary, a Pd(II) precursor, such as popular $Pd(OAc)_2$, was not a suitable catalyst for this transformation (Entry 7). Buchwald's ligands and substituted triarylphosphine analogues were unable to improve the

catalytic system (Entry 8, details in SI). Hence, **2a** was isolated in 78% yield by increasing the catalyst loading (Entry 9).[12]The reaction without benzoic acid provided traces of **2a** (Entry 10), highlighting the crucial role of the former.

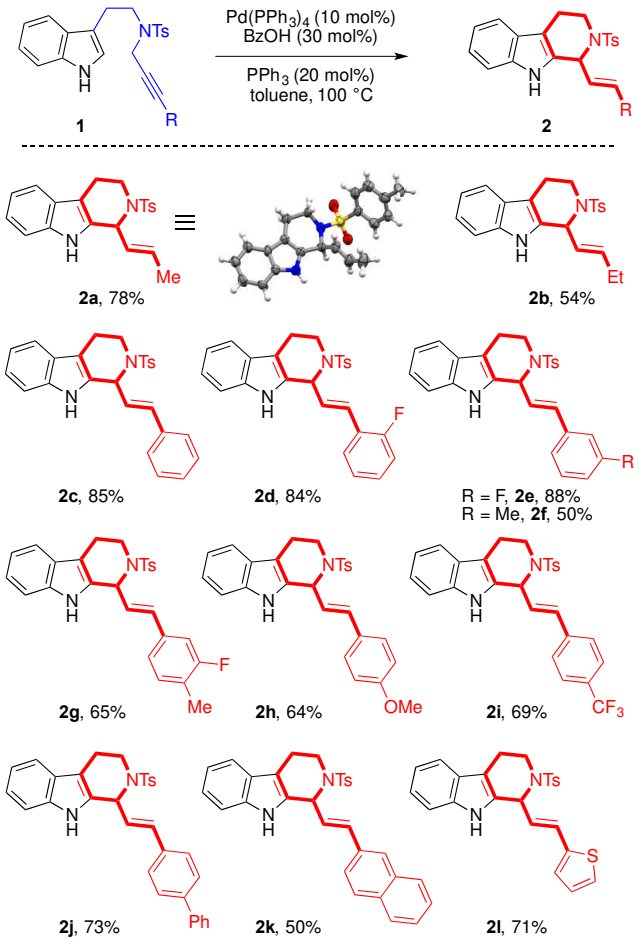


Figure 2. Synthesis of THCs **2**.

In all cases, we observed complete control of the alkene configuration, retrieving **2a** as a single *E*- isomer. A family of diversely functionalized propargylic tryptamines **1** was then submitted to the optimized catalytic system (Figure 2).

Alkyl- and aryl-alkyne derivatives were tolerated, leading to the corresponding products **2b-c** in 54 and 85% yields respectively. A broad family of 3-arylprop-2-yn-1-yl-indole derivatives **1** was efficiently converted to THCs **2** (**2d-I**, 50-88%). The method is thus suitable for the synthesis of various fluorinated THCs. Substrates bearing EWG performed better with respect to the corresponding electron-rich ones. However, substitution at the *para*-position of the aryl ring with different halogen atoms, namely chlorides and bromides, did not afford **2**.[13] Tryptamine derivatives bearing biphenyls, naphthalenes and heteroarenes, such as thiophene, delivered the corresponding THCs in good yields (**2j-l**, 50-73%). Reactions involving arylalkynes (**2c-l**) deliver desired products only and unreacted starting materials can be recovered by chromatography. We then studied substituted tryptamines (Figure 3).

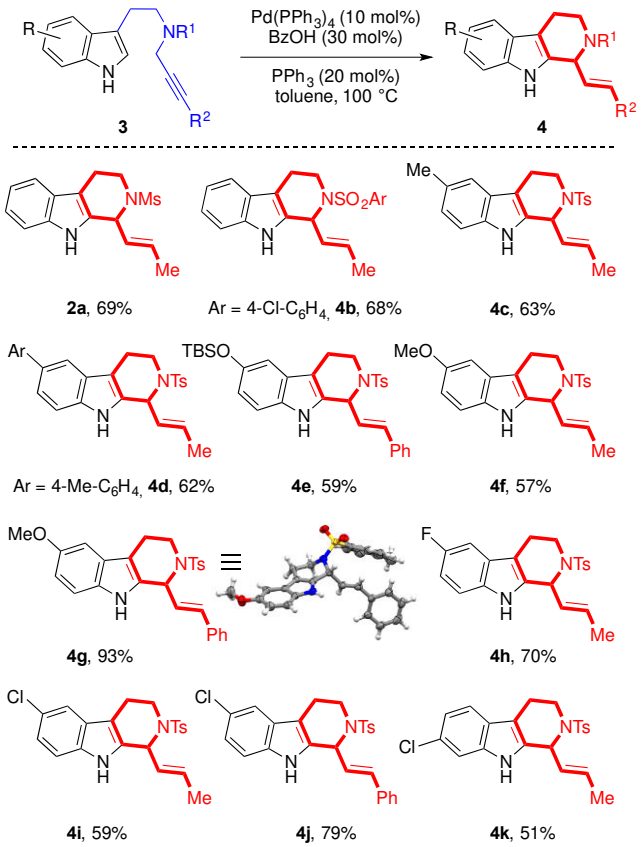


Figure 3. Synthesis of THCs 4.

Protection of tryptamine with either methanesulfonyl (Ms) or *p*-Cl-benzensulfonyl did not affect the outcome of the catalytic reaction (Figure 3, **4a-b**). Electron-donating functional groups such as alkyl, aryl, silylethers and ethers at the C(5)-position of the indole were well tolerated delivering THCs **4c**-**g** with good to excellent yields (57-93%). The method allowed the synthesis of THCs **4h**-**k** with electron-withdrawing groups located at the C(5)- and C(6)-position with moderate to good yields (51-79%). The robustness of the sequence was further mirrored by the synthesis of a symmetrical THCs dimer (Figure 4). Noteworthy, the synthesis of **4l** proceeds smoothly with high chemoselectivity and a synthetically useful yield (56%).

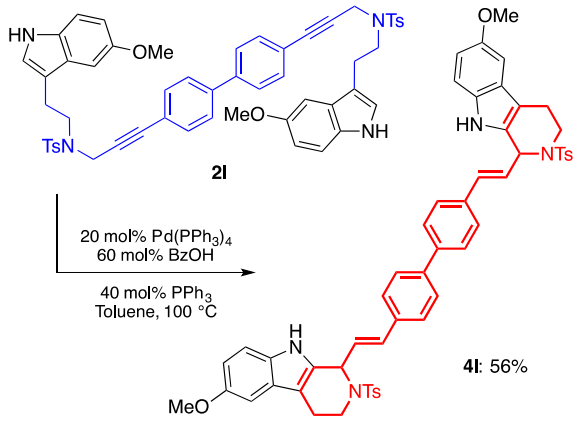


Figure 4. Synthesis of dimeric THCs **4l**.

Different experiments were then carried out to rationalize the reaction mechanism and gain insights on its complete chemo- and site selectivities. THC **4m** was isolated in 70% yield using allenamide **3m** under typical reaction conditions (Figure 5, a). This result is consistent with the intermediate formation of allenamides in the sequence. The influence of indole *N*-substitution was then investigated. We observed the formation of acyclic diene **4n'** and no traces of THC **4n** by testing precursor **3n** (Figure 5, b). This result shows that the free N-H of the indole is crucial for the annulation step and shows once more the virtues of protecting-group free synthesis.[14] Finally, the attempted intramolecular desymmetrization of propargylic precursor **3o**,[15] in which the indole C(2) is substituted with a methyl group, failed to provide any product (Figure 5, c). This result was highly unexpected based on literature precedents[2,5,8] and lead us hypothesize that a C–H activation step could operate in our case. We are unaware of literature precedents on C-H activation/alkylation at C(2) of unprotected indoles.[16]

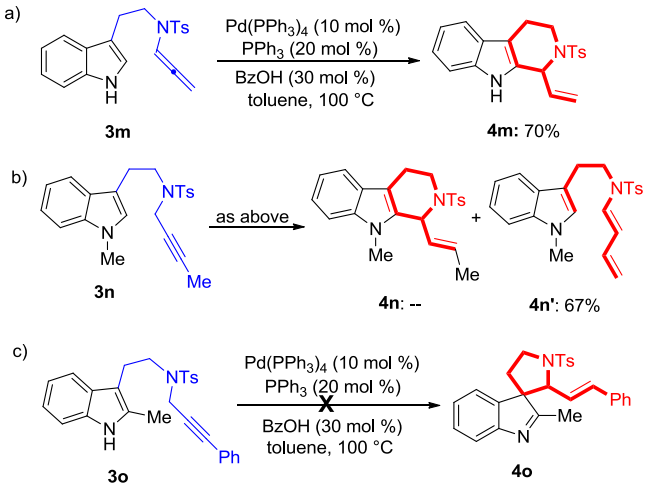


Figure 5. Experimental mechanistic evidences.

We thus resorted to DFT modeling in order to solve the riddle. Investigation begun using the M06 functional in combination with either lacvp(d) and Def2-svp(d) basis sets, which proved to be reliable methods to describe elaborate palladium catalyzed sequences.[17] Complete pathways were modeled with PMe_3 as ligand both in the gas phase and using toluene as implicit solvent to further reduce the odds of modeling artifacts.

Different functionals too were tested and key steps were reoptimized with PPh_3 (see SI for details, Figures S2-13). Overall, coherent results were obtained in all cases, which let us propose the mechanism of Figure 6 to account for the formation of THC 2 in these sequences.

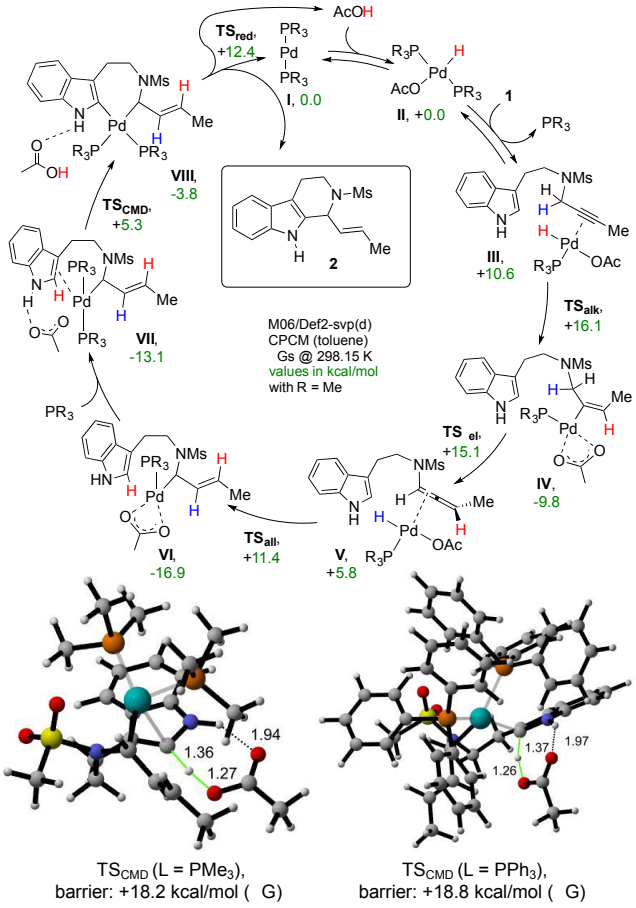


Figure 6. Most favorable modeled mechanism and key transition states.

Reaction of the carboxylic acid with Pd(0) complex **I** can deliver *trans*-Pd(II) hydride **II**. Its *cis*- peer is less stable and further steps provide higher barriers too (Figure S4 in SI). Endoergonic phosphine replacement by the substrate yields complex **III**, which evolves to vinyl species **IV** via migratory insertion. Barriers for this step were expectedly low (between +2.8 and +6.8 kcal/mol among the different models). The subsequent β-elimination affords allenamide complex **V**. It proved to be the most energy demanding barrier of the whole sequence because of the limited rotational flexibility of the allylic methylene (ΔG of +24.9 kcal/mol; up to +28.1 at the B3LYP level). Complex **V** is more stable than its alkyne peer **III** (by -4.8 kcal/mol). This suggests that allenamides bind Pd(II)-hydrides more strongly than internal alkynes. Second insertion into the Pd-H bond gives allyl complex **VI** through a low barrier (+5.2 kcal/mol in ΔG). Replacement of the acetate ligand by phosphine provides complex **VII**, in which the metal presents a slipped η^2-indole coordination and the carboxylate is engaged in hydrogen bonding with the indole N-H group. This is crucial to favor the sequential C-H activation, which occurs through an outer-sphere CMD pathway[18] (barriers of +18.2 and +18.8 kcal/mol in ΔG with PMe_3 and PPh_3 respectively). This is consistent with the positive role of additional ligands on yield (Table 1). It is worth noting that direct C-H activation of indole is on the contrary usually prevented by the presence of a free N-H group, which sunk the basicity of metal-bound carboxylates via hydrogen bonding.[16,18] Modeling an inner-sphere CMD provided indeed higher barriers (+29.2 kcal/mol in ΔG). Try as we might, we failed to obtain any stationary point for Pictet-Spengler-like pathways from

either complex **V** or **VI** (Figure S9). Scans of these pathways show linear increase of E only (up to above 40 kcal/mol). Heck-like insertion on indole from **VII** provided a sky-high barrier of +50.5 kcal/mol (Figure S10). Taken together within the framework of the energy span model,[19] these results strongly suggest that indole functionalization occurs via C-H activation in this sequence. They highlight as well the dual nature of the carboxylic acid in this cascade. It initially serves to generate the Pd hydride that triggers alkyne isomerization. The resulting carboxylate becomes then crucial too. It plays the role of a base assisting the metal in the C-H activation, acting therefore in a catalytic fashion. Desired product is eventually released by C-C reductive elimination from metallacycle **VIII**. This step has a barrier comparable to those of similar Pd(II) complexes (+16.2 kcal/mol in ΔG).[17]

We presented the first catalytic synthesis of tetrahydro carbolines from propargylic tryptamines by means of palladium and carboxylic acid joint catalysis. The method combines interesting synthetic features with unexpected mechanistic findings. We anticipate that the latter will pivot ample future developments of indole chemistry in C-H activation sequences.

ASSOCIATED CONTENT:

Supporting Information

Experimental details, complete modeling data, characterization of products, copies of NMR spectra, XYZ coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We warmly thank support from UniPr (Grant RADI-CAT), MIUR (Grant AROMA-TriP and Departments of Excellence framework),CNRS and UPMC. Use of modeling facilities was provided by ICSN-CNRS(UPR2301, Gif s/Yvette, France).

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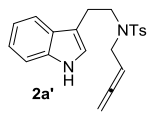

2a'

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