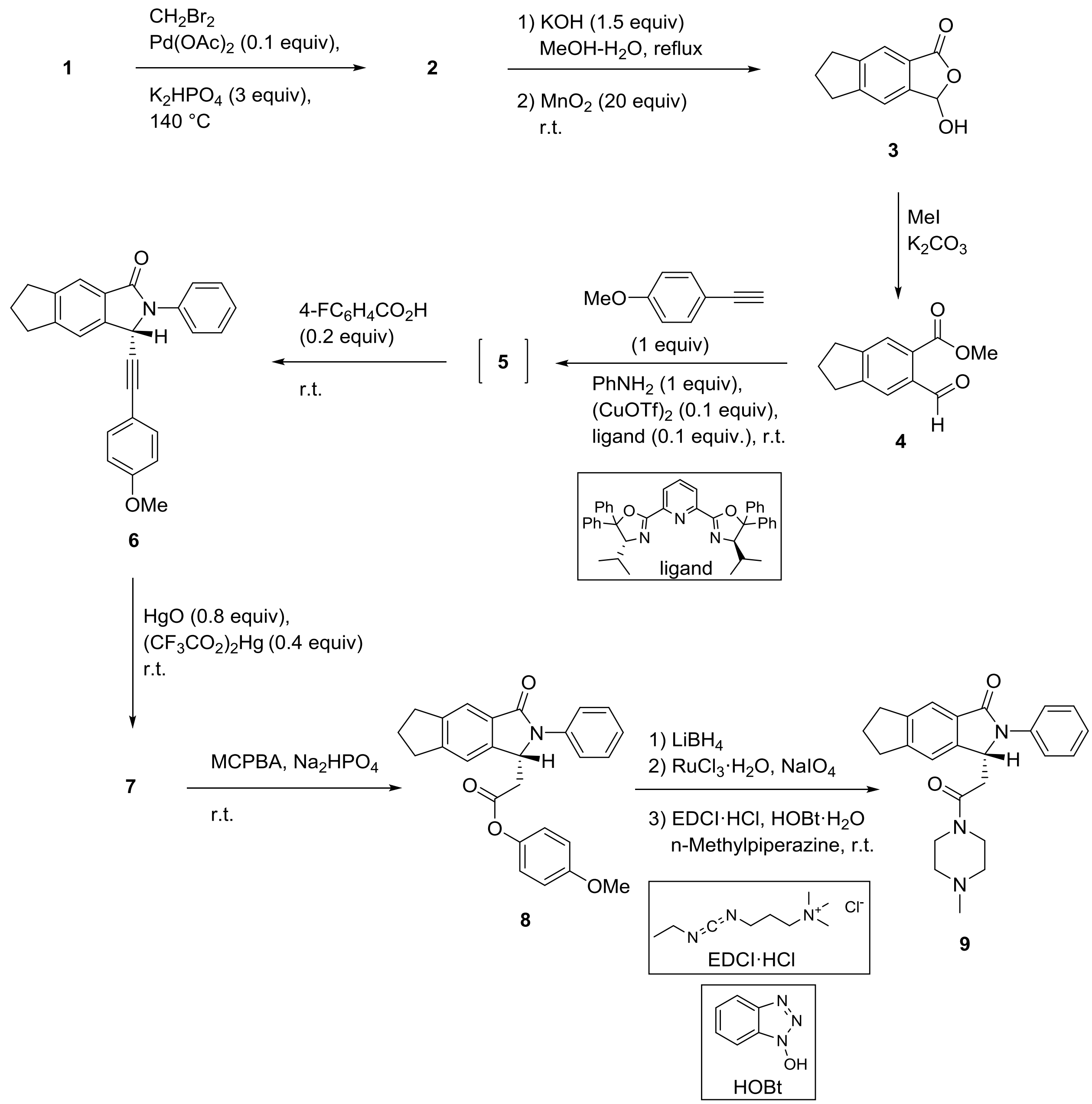
Total Synthesis of Isoindolinone (*R*)-JM 1232



1) Give the missing compounds **1** and **2**. What are the corresponding mechanisms to form **3** from **1**?
2) Give the intermediate **5** and the corresponding mechanism to form **6** from **4**.
3) What is the structure of **7**? Give the mechanism for the two transformations to form **8** from **6**.
What is the name of the second reaction and which other product could be formed?
4) Give the mechanism of the last step for the formation of the final product **9**.

Submitted by Daniel

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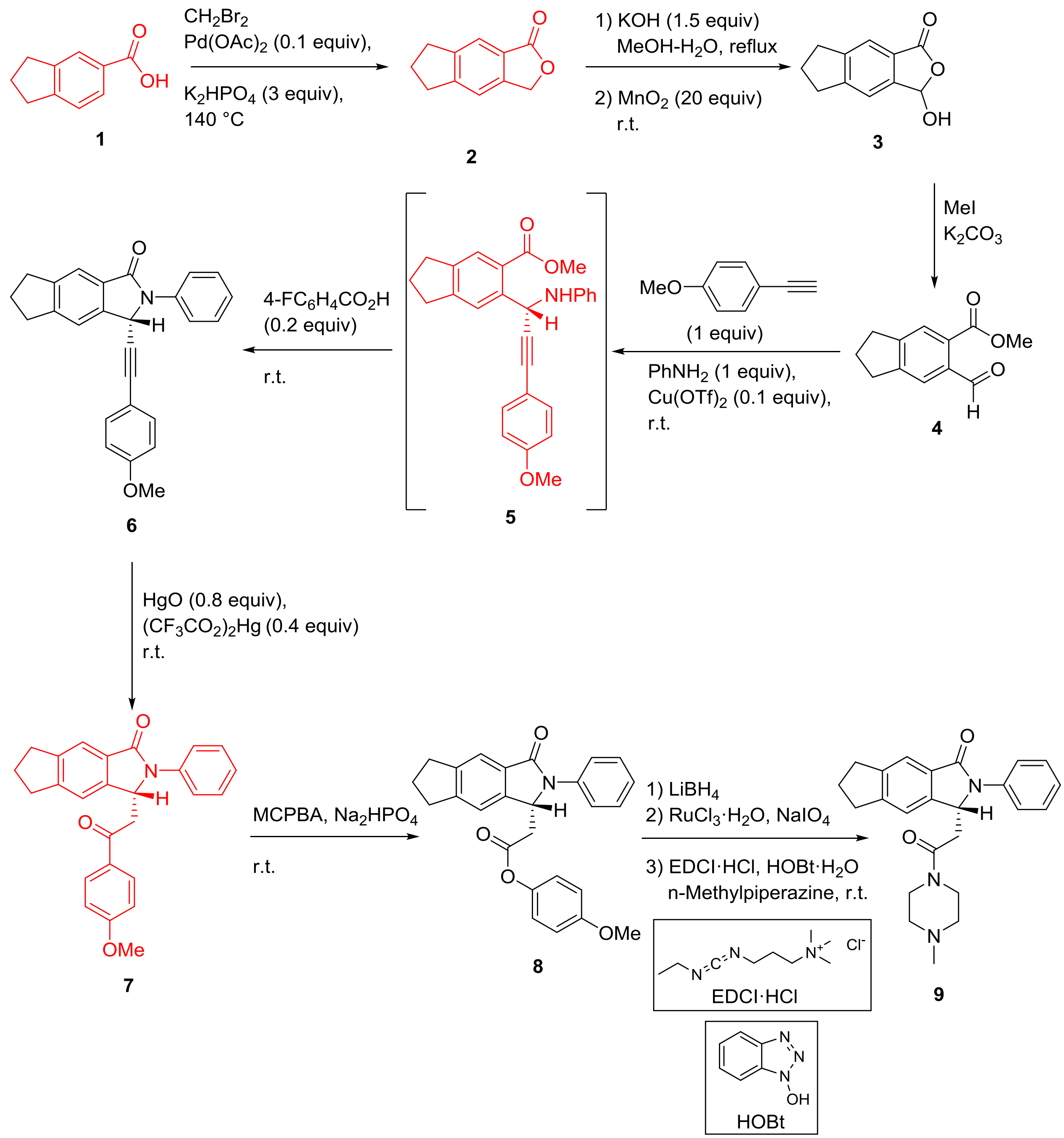

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J. Org. Chem. **2016**, *81*, 4779.

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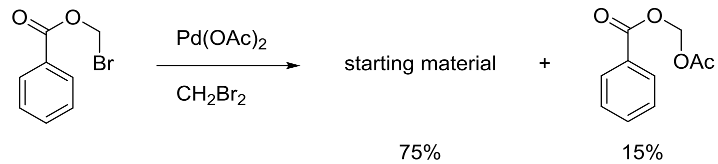
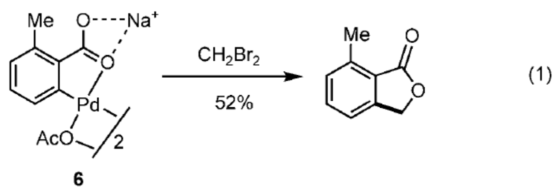
Mechanisms

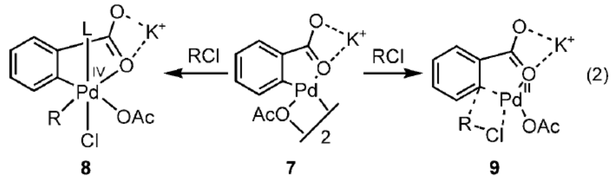
1 to 3

The following result speaks against a mechanism in which nucleophilic substitutions occurs first:

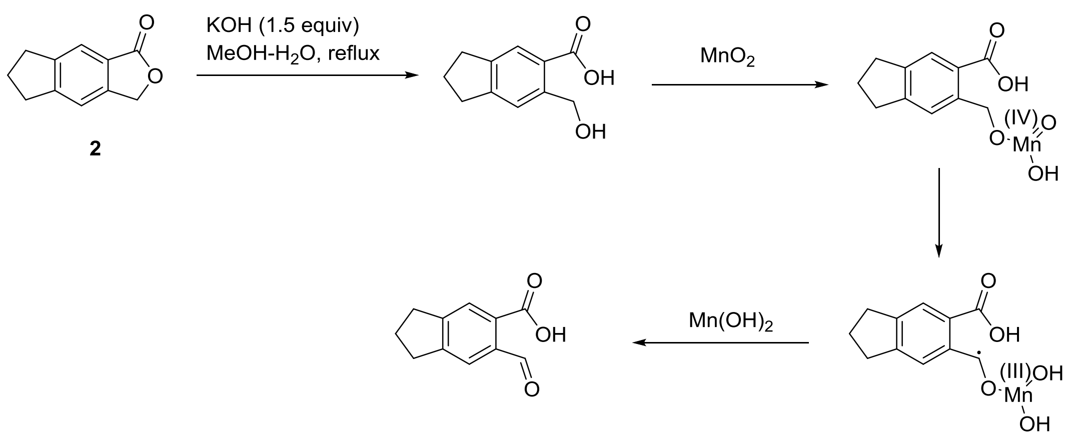


They propose a first *ortho* C-H insertion of the Pd(II). For the next step they proposed a pathway through a Pd(IV) species by oxidation of the arylpalladium(II) intermediate with R-X or by direct σ-bond metathesis between the aryl-Pd bond and the alkyl halide.

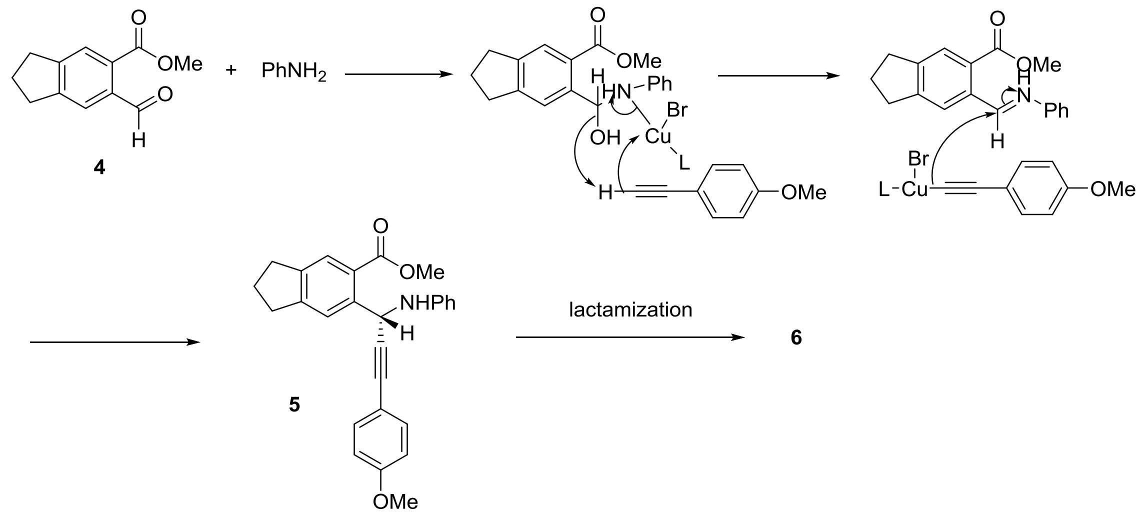




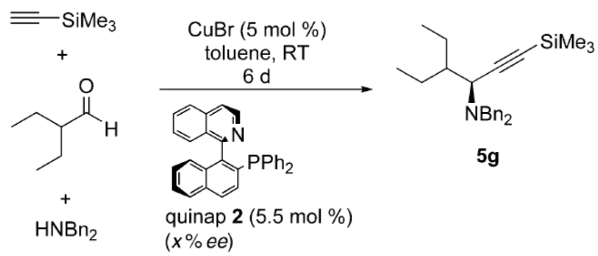
Angew. Chem. Int. Ed. **2009**, *48*, 6097.

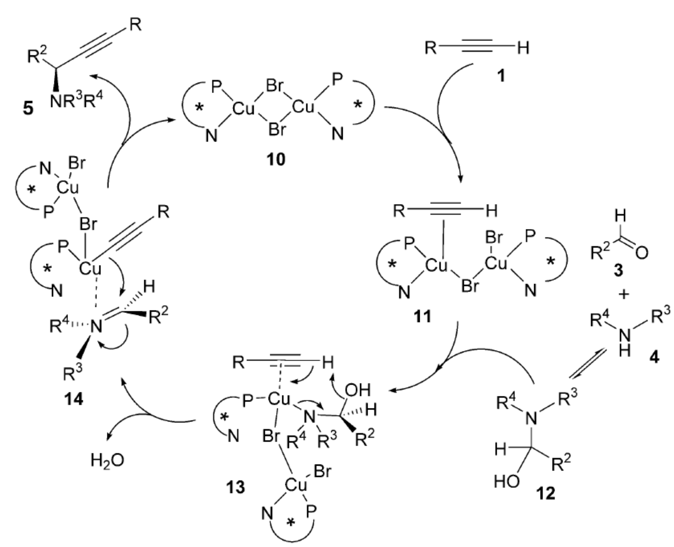


4 to 6



Mechanism according Knochel et al.

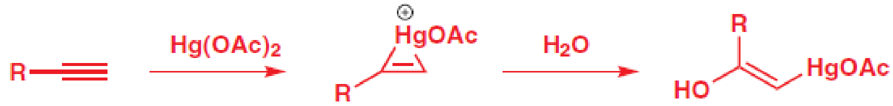




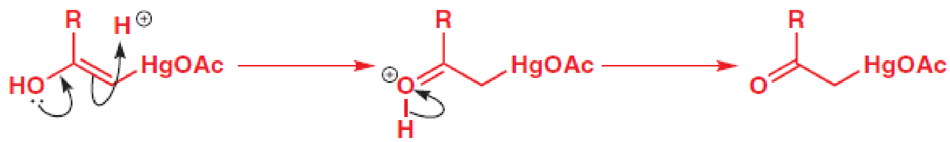
Angew. Chem. Int. Ed. **2003**, *42*, 5763.

6 to 7

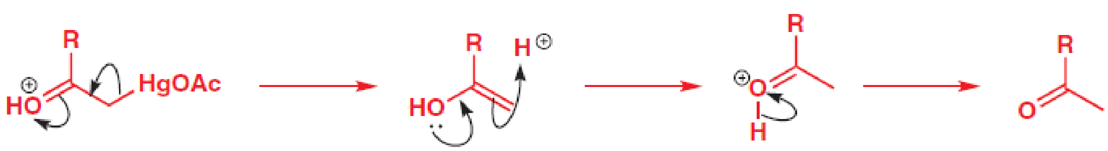
Oxymercuration of alkynes (Markovnikov)



But the product isolated from an alkyne oxymercuration is in fact a ketone. You can see why if you just allow a proton on this initial product to shift from oxygen to carbon—first protonate at C then deprotonate at O. C=O bonds are stronger than C=C bonds, and this simple reaction is very fast.

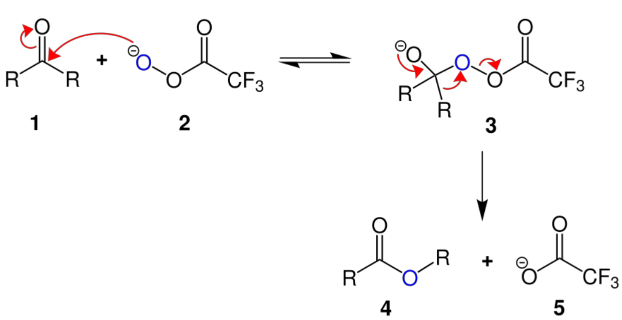


We now have a ketone, but we also still have the mercury. That is no problem when there is a carbonyl group adjacent because any weak nucleophile can remove mercury in the presence of acid, as shown below. Finally, another proton transfer (from O to C again) gives the real product of the reaction: a ketone.

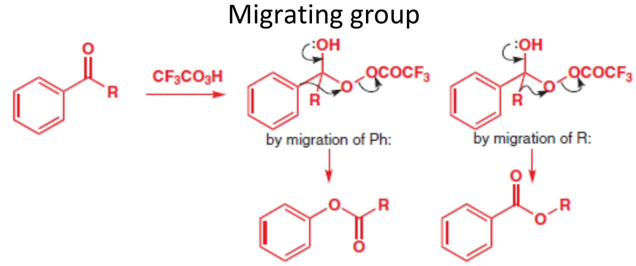


7 to 8

Bayer-Villiger Oxidation under basic conditions



Migrating group



R =	Yield for R (%)	Yield for R (%)
Me	90	0
Et	87	6
i-Pr	33	63
t-Bu	2	77

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8 to 9