Palladium-catalyzed formal (5+2) annulation between ortho-alkenylanilides and allenes

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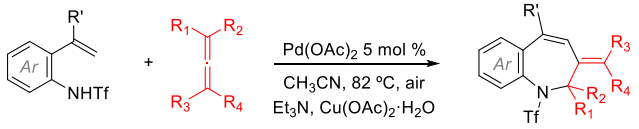
Supporting Information Placeholder



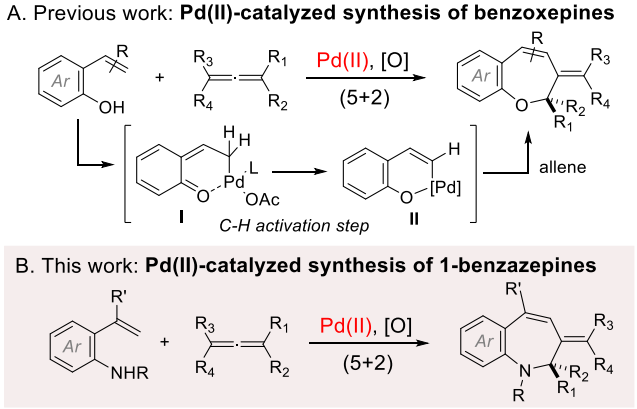
A catalytic (5+2) aza-annulation under operationally simple conditions

ABSTRACT: 2-Alkenyltrifylanilides react with allenes upon treatment with catalytic amounts of $Pd(OAc)_2$ and Cu(II) to give highly valuable 1*H*-benzo[*b*]azepines, in good yields, and with very high regio- and diastereoselectivities. Density functional theory (DFT) calculations suggest that the C-H activation of the alkenylanilide involves a classical concerted metallation-deprotonation (CMD) mechanism.

The assembly of heterocycles from simple precursors is a topic of major interest. In this context, the use of metal-catalyzed annulations is especially attractive owing to their intrinsic complexity-increasing potential. However, many of these reactions require the preparation of precursors containing specific functional groups. In recent years, there has been a growing number of reports on metal-promoted annulations that involve the formal activation of C-H bonds and therefore do not require elaborated substrates.[1,2]

Along these lines, our group has developed metal-promoted cycloadditions of 2-alkenylphenols with alkynes[3] or allenes[4] to give a variety of oxacyclic products. Remarkably, while allenes react with 2-alkenylphenols in presence of Rh(III) catalysts to give chromene type of products, under Pd(II) catalysis the reaction provides interesting benzoxepine skeletons (Scheme 1A).

Scheme 1. Palladium-promoted annulations with allenes



The reaction was hypothesized to involve the initial formation of an oxapalladacycle like **II** by formal activation of the terminal C-H bond of the alkene, followed by migratory insertion of the allene and reductive elimination. Experimental studies suggested that the C-H activation does not proceed through a classical concerted metallation-deprotonation (CMD), but rather it might involve an intramolecular attack of the conjugated alkene to the palladium center to give an intermediate like **I**, followed by a base-induced re-aromatization to form the six-membered palladacycle **II** (Scheme 1A).

As a natural extension of these studies, we wondered whether *ortho*-alkenylanilides might also engage in similar annulations, which would provide a straightforward and atom economical access to highly relevant benzazepine skeletons (Figure 1).[5,6] At the outset, the success was not guaranteed since *ortho*-alkenylanilines could provide indole products when treated with a Pd(II) catalyst, [7] and also because there were no precedents on the reactivity of allenes with related anilides.[8,9]

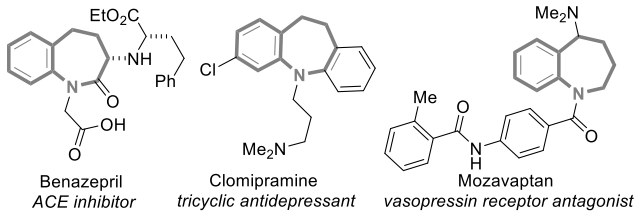
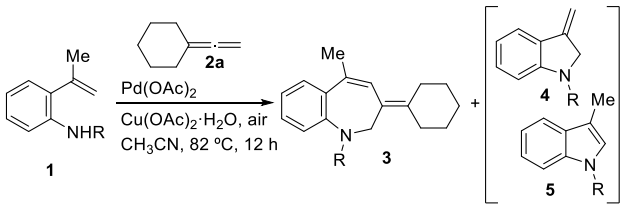


Figure 1. Drugs with the benzoazepine skeletons.

Herein, we report a palladium(II)-catalyzed (5+2) formal oxidative cycloaddition between 2-alkenyltriflylanilides and allenes (Scheme 1B). The reaction provides a straightforward and regioselective access to a variety of interesting benzazepine skeletons in good yields. Importantly, DFT calculations suggest that while the C-H activation step in the annulations of alkenylphenols is better explained in terms of a non-concerted electrophilic addition to Pd(II) followed by rearomatization, in

the case of the anilides the C-H activation is more consistent with a concerted metalation deprotonation mechanism (CMD).

Table 1. Screening of amine R groups[a]



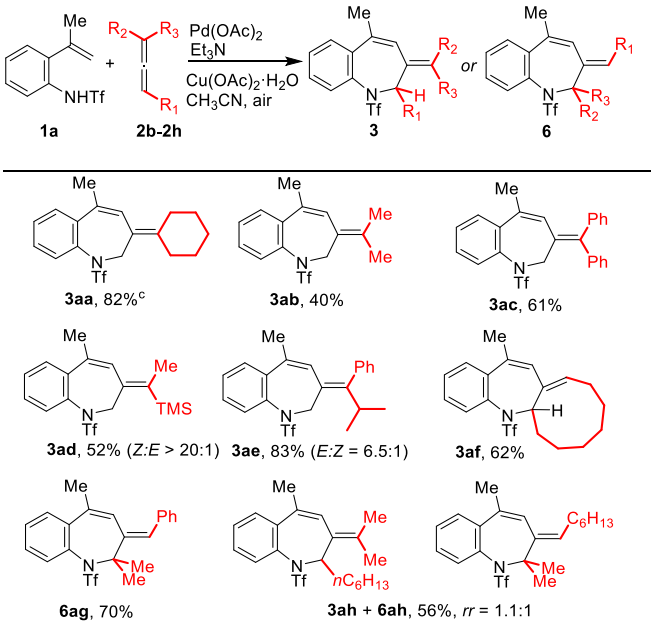
entry	R group	base	**3** (%)	**4/5** (%)
1	H	-	< 10	-
2	*i*Pr	-	58	-
3	Ac	-	-	-
4	Ts	-	43	8 [b]
5	Ns	-	51	~ 10 [b]
6	Tf (**1a**)	-	55 (**3aa**)	8 (**4a**)
7	Tf (**1a**)	Cs_2CO_3 [c]	27 (**3aa**)	8
8	Tf (**1a**)	Et_3N [d]	82 (**3aa**)	10 (**4a**)

[a] Conditions: 0.19 mmol of **1a**, 0.19 mmol **2a**, 10 mol % $Pd(OAc)_2$, 0.5 equiv $Cu(OAc)_2·H_2O$, CH_3CN (2 mL), 82 ºC, under air, 12 h. [b] Mixtures of indolidene **4** and indole **5**. [c] 1 equiv of Cs_2CO_3 [d] 5 mol % of $Pd(OAc)_2$, Et_3N (2 equiv), 3 h.

Our work started by identifying appropriate substituents at the N atom of the alkenylanilide that could favor the formation of the desired products. The reaction was tested with catalytic amounts of $Pd(OAc)_2$ and 0.5 equiv. of $Cu(OAc)_2·H_2O$ in acetonitrile, under air, using 2-vinylidenecyclohexane (**2a**) as partner. The parent aniline (2-(prop-1-en-2-yl)aniline) gave a very low yield of the desired product, however, the isopropylanilide participated in the process leading to the expected benzazepine in moderate yield (table 1, entry 2). Curiously, while the acetyl derivative failed to react (the starting material was mostly recovered), the presence of tosyl, nosyl or trifluoromethylsulfonyl substituents at the N atom allowed the formation of the corresponding adducts in moderate yields (43-55% yields), together with variable amounts of the indoline (**4**) and indole (**5**) products.[7,10] Importantly, the addition of triethylamine allowed to increase the yield of the reaction, so that the desired product **3aa** was obtained in 82% yield using just 5 mol% of $Pd(OAc)_2$ (table 1, entry 8).

With the optimized conditions at hand, we investigated the scope of the reaction with regard to the allene component (Scheme 2). Other 1,1-disubstituted symmetrical allenes such as dimethyl and diphenyl allenes led to the corresponding products **3ab** and **3ac** (40 and 61% yield). The lower yield obtained in the case of **3ab** is probably associated to the high volatility of the allene. Non symmetrical allenes, such as **2d** and **2e** led to the corresponding products (**3ad** and **3ae**) in good yields and good to excellent *E:Z* ratios. Cyclonona-1,2-diene is also a good annulation partner, leading to the formation of a tricyclic product **3af** in 62% yield. Tri-substituted allenes also engage in the process. The heavily substituted product **6ag** could be obtained in a 70% yield, while with the allene **2h** we observed the formation of a 1.1:1 mixture of isomeric products **3ah** and **6ah** (56% overall yield).[11]

Scheme 2. Scope with different allenes.[a,b]

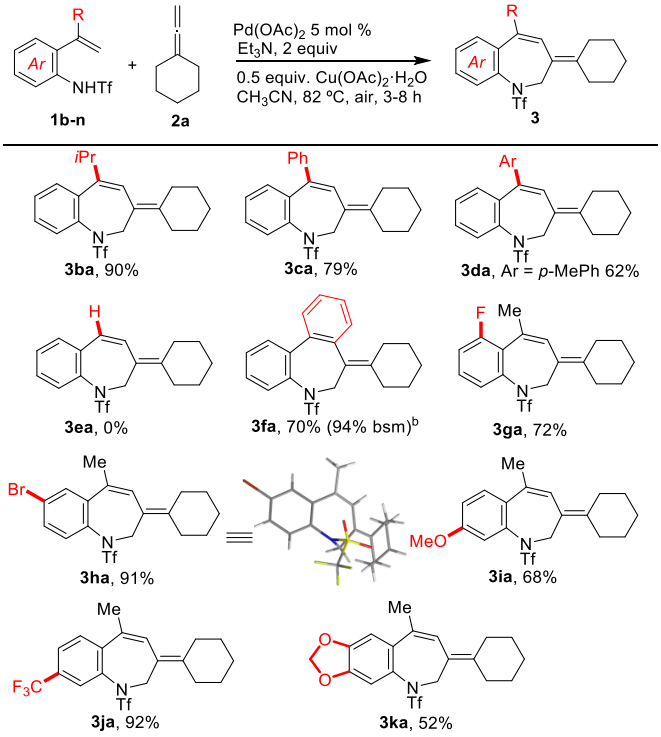


[a] Conditions: **1a** (1 equiv), **2a** (1 equiv), 7.5 mol % $Pd(OAc)_2$, Et_3N (2 equiv), 0.5 equiv $Cu(OAc)_2·H_2O$, CH_3CN (0.095 M), 82 ºC, under air, 3-8 h. [b] *E:Z* are > 20:1, unless otherwise noted. [c] 5 mol % of $Pd(OAc)_2$.

As shown in Scheme 3, the reaction is not restricted to the 2-alkenylanilide **1a**, but also works with related substrates bearing other substituents at the internal position of the alkene, such as *i*-propyl (**1b**) or aryl (**1c**, **1d**). In all the cases the expected benzazepine adducts were obtained in good to excellent yields (**3ba-3da**, 62-90% yields). Curiously the reaction does not work with the substrate that bears a simple vinyl group (**3ea**), apparently because it is not stable enough under the reaction conditions. Importantly, the reaction is also operative with 2-phenylanilides, to give the expected dibenzoazepines like (**3fa** in good yields, albeit achieving good conversions required longer times).[12] In order to analyze functional group compatibilities, we also tested the reactivity of precursors with different substituents in the aryl group of the anilide precursors. Sensible functionalities such as fluoride (**3ga**, 72%) or bromide (**3ha**, 91%) are well tolerated in *ortho* or *meta* positions to the alkenyl group. Substituents in *para* to the alkenyl group are also tolerated, irrespective of whether they are electron donors (**3ia**, 68% yield) or electron withdrawing (**3ja**, 92% yield). Disubstituted starting materials also work efficiently (**3ka**, 52% yield).

While the above data confirm the synthetic potential of the annulations, the transformation entails interesting mechanistic issues, particularly in relation with the C-H activation process. Control experiments with substrate **1a** in the absence of the allene, using the standard reaction conditions, revealed the formation of a mixture of products from which we could isolate the indoline **4a** and indole **5a** in an overall 18% yield. These products, particularly **4a**, might arise from aza-Wacker-type mechanism involving the addition of the amine to the alkene followed by β-hydride elimination of the resulting Pd-complex.[13] The formation of the indole could also be explained in terms of a reductive elimination from **II'** (Figure 2).[7, 14]

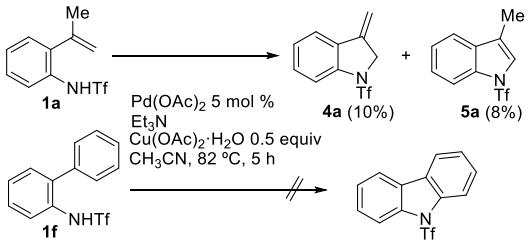
Scheme 3. Scope with respect to the alkenylanilide component.



[a] Conditions: **1a** (1 equiv), **2a** (1 equiv), 5 mol % $Pd(OAc)_2$, Et_3N (2 equiv), 0.5 equiv $Cu(OAc)_2·H_2O$, CH_3CN (2 mL), 82 ºC, under air, 3-8 h. [b] 10 mol % of $Pd(OAc)_2$, 1 equiv of $Cu(OAc)_2$

In consonance with its lower reactivity and the absence of competitive aza-Wacker processes, the arylanilide **1f** remained intact after heating for several hours under the standard reaction conditions. These results suggest that the presence of the allene partner opens accessible pathways that avoid the decomposition of the alkenylanilides or promote the reactivity of the arylanilides.

Scheme 4. Control experiments in the absence of allene



In order to gain more information about the C-H activation step, and compare the reactivity of 2-alkenylphenols and 2-alkenylanilides, we carried out DFT calculations with 2-(prop-1-en-2-yl)phenol and the triflylanilide **1a**.[15] In consonance with our previous hypothesis based on experimental data,[4a] in the case of the phenol derivative the initially formed palladium alkoxide evolves rapidly to a species that is better accommodated with an structure like **I** (Figure 2), exhibiting a partial dearomatization of the phenyl ring. Analysis of the C-C distances confirm that the C1-C2 bond order is less than 2, while the C2-C3 distance has gained a considerable double bond character. Moreover, the C1-Pd distance is 2.06 Å, which is characteristic for a C-Pd sigma bonding. This compound evolves by rearomatization to form a six-membered palladacycle **II**, by intramolecular abstraction of one of the hydrogens by the acetate (**TS1**, 15.6 Kcal/mol). Interestingly, the palladium complex obtained with the nitrogenated substrate **1a** presents a structure with a standard η^2 coordination of the alkene to the Pd center, while the C2-C3 distance (1.50 Å) is typical for a single C-C bond (structure **I'**). Therefore, in this case the coordination to the metal center doesn't drive the dearomatization of the molecule. Importantly, the TS for the C-H activation process (**TS1'**) is fully consistent with a CMD-type mechanism (see the Supporting Information for details).[16]

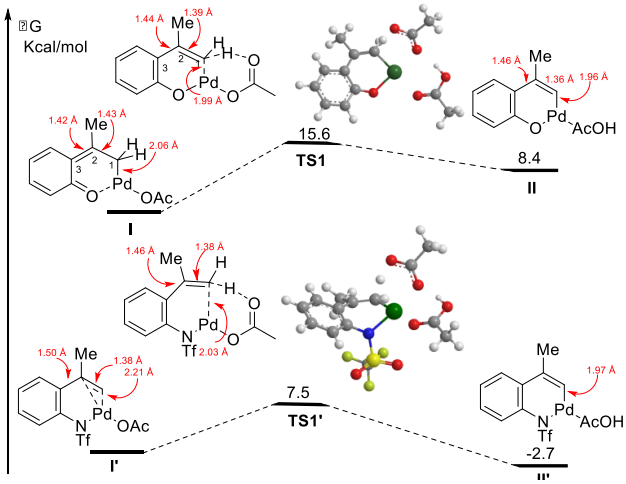


Figure 2. Energetic profiles of pathways for the C-H activation step in the phenolic and triflylanilide substrates. The Pd center in the intermediates contains an additional ligand (acetic acid) that contributes favorably to their stabilization Values are given in kcal/mol and correspond to ΔG in acetonitrile.

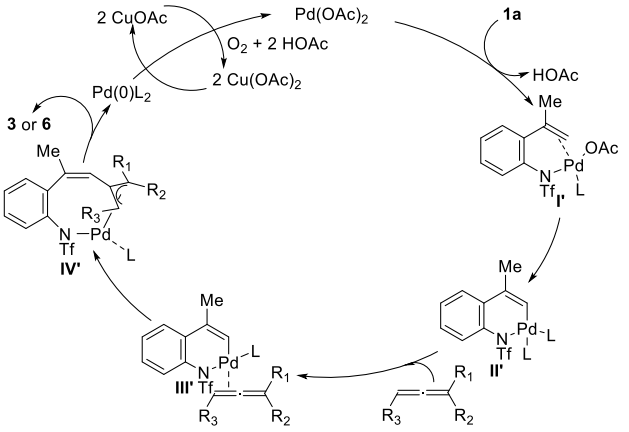
Therefore, the most probable catalytic cycle for the annulations process might involve an initial ligand exchange between the alkenylanilide derivative **1a** and the palladium acetate complex to give a species of type **I'**, which undergoes a C-H activation to form the six-membered palladacycle **II'** through a CMD mechanism. Coordination of the allene followed by regioselective migratory insertion gives a π-allylic palladacycle **IV'**,[17] which undergoes a reductive elimination to the benzo[*b*]azepine (Scheme 5).[18] The resulting Pd(0) species is reoxidized to Pd(II) by copper diacetate and air. The regioselectivity of the ring closing depends on the allene structure and electronic characteristics of the substituents.

The beneficial role of Et_3N as additive is not yet clear, but in addition to buffer acetic acid it might facilitate the initial formation of the N-Pd bond, and hence avoid secondary pathways involving an outer-sphere Pd(II) activation of the alkene.

In summary, we describe a new annulation reaction which provides a particularly rapid and practical method to obtain 1*H*-benzo[*b*]azepine skeletons. The transformation consists of palladium-catalyzed (5+2) formal cycloaddition and involves a formal C-H activation process. In contrast to that occurring with the alkenylphenol precursors, the C-H activation in the case of the anilides seems to involve a CMD process. Probably the electronic pair of the nitrogen atom is not available for conjugation with the aromatic ring and as consequence the alkene group is less prone to form a species of type **I**.

The reaction provides a novel way of obtaining benzazepines and represents one of the few examples of the synthesis of seven-membered rings through annulations involving the cleavage of olefinic C-H bonds.

Scheme 5. Mechanistic hypothesis



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, computational details, and other information

X-ray crystallographic analysis for **6ag**, **3fa**, **3ha**, and **4a**

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(10) The Ns and Ts-substituted indoline products slowly isomerize in $CDCl_3$ to the indole structures.

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(15) For full details see the Supporting Information.

(16) A dearomatized structure analogous to **I** was not found for **I**'.

(17) An experiment with a chiral allene led to almost racemic cycloadducts (see Supporting Information).

(18) A mechanism involving an *anti* attack of nitrogen on the π–allyl palladium complex cannot be fully discarded.