Rhodium-catalyzed annulation of *ortho*-alkenylanilides with alkynes: Formation of unexpected naphthalene adducts

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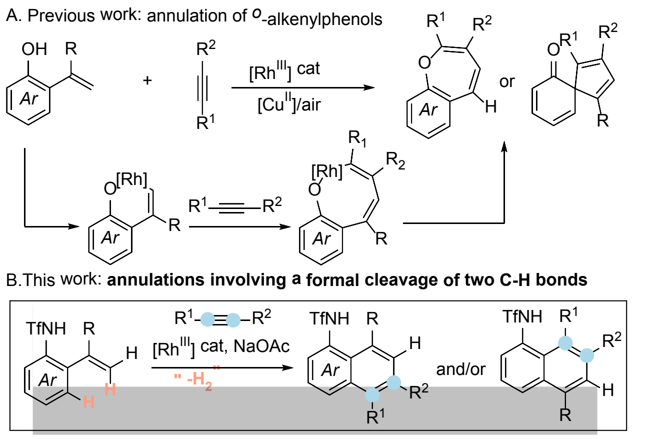
Abstract: *o*-Alkenyl-*N*-triflylanilides undergo Rh(III)-catalyzed oxidative annulations with alkynes to produce different types of naphthylamides, in a process which involves the cleavage of two C-H bonds. Remarkably, in addition to formal dehydrogenative (4C+2C) cycloadducts, the reaction also produces variable amounts of isomeric naphthylamides whose formation requires a formal migration of the alkenyl moiety from the *ortho* to the *meta* position of the anilide. Also interestingly, the annulation reaction can be efficiently carried out in the absence of external oxidants, such as $Cu(OAc)_2$.

The activation of C-H bonds by transition metal complexes has become a versatile and widely used tool for the construction of C-C and C-heteroatom bonds from non-functionalized precursors.[1] In addition to simple functionalizations, it is also possible to achieve oxidative annulations, which provide a practical way for assembling different types of cycles, specially heterocycles, through a concomitant C-H and X-H activation (X= heteroatom).[2] These transformations usually require the presence an external oxidant, normally a copper or silver salt,[3] or a built-in N-O or N-N bond.[4]

Recently we have reported that 2-alkenylphenols can react with alkynes upon treatment with Cp*Rh(III) catalysts to give either oxepines or spirocyclic products.[5] These reactions have been proposed to involve an initial activation of the terminal C-H bond of the alkene, followed by migratory insertion and C-O or C-C reductive elimination (A, Scheme 1). An appealing extension of this chemistry consists of the use of anilides instead of phenols, as this could allow to build azacyclic products. In this context, we recently found that o-alkenyl-*N*-nosylanilides can react with alkynes to give interesting indolines, albeit obtaining an efficient reaction required the use of a Rh(III) catalyst equipped with an electron deficient cyclopentadienyl ligand.[6]

Herein we demonstrate that *o*-alkenyl-*N*-triflylanilides can productively react with alkynes in the presence of Cp*Rh(III) catalysts, but instead of indolines or benzazepine products, the reactions provide naphthalene adducts, formally arising from a dehydrogenative carbo-annulation process.[7] This type of [4C+2C] annulations involving a double C-H cleavage of unactivated substrates, are essentially unknown.[8] Curiously, in addition to cycloadducts resulting from direct annulations, we also observe variable amounts of rearranged isomeric adducts whose formation requires a formal 1,2-migration of the alkenyl group. Indeed, depending on the structure of the alkyne partner, these rearranged isomers can even become the major product. Also, interestingly, while most related oxidative couplings or annulations involving C-H activations require external chemical oxidants, our process can be efficiently achieved in a catalytic manner, under air, without such additives, therefore simplifying the experimental protocol and improving the atom economy of the process.[9]



Scheme 1 Annulations of *o*-alkenyphenols and *o*-alkenylanilides with alkynes.

Our work started by checking the reactivity of 2-propenylanilides equipped with different substituents at the nitrogen. The assays were carried out using catalytic amounts of $[Cp^*RhCl_2]_2$ (Cp* = pentamethylcyclopentadienyl) and 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$, in acetonitrile, under an air atmosphere, in presence of 1 equiv of diphenylacetylene. Anilides with acetyl, trifluoroacetyl, and Boc groups, as well as the parent aniline, failed to give meaningful amounts of any relevant product, with most of the starting amine being recovered after heating at 82 ºC for 16 h. While the N-tosyl and nosyl derivatives gave traces of reaction adducts (GC-MS), the introduction of a trifluoromethanesulfonyl (Tf) group in the nitrogen (**1a**) allowed to isolate cycloadducts that were identified as the naphthylamides **3aa** and **4aa** (entry 1), albeit the overall yield of the reaction was low.

While the presence of **3aa** might be explained in terms of a dehydrogenative (4+2) annulation, the observation of **4aa** was surprising, as its formation necessarily involves the cleavage and formation of carbon-carbon bonds. After screening several solvents, we found that in THF at 66 ºC the overall yield is very good (84%, entry 3). As might be expected, in the absence of $Cu(OAc)_2$, the reaction does not take place (entry 4); however, if NaOAc is added, the transformation is again operative, and takes place with a very good overall yield (entry 5). This result

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) suggests that the copper(II) salt works more as an acetate source than as an oxidant, and the air atmosphere is enough for ensuring the redox balance of the process.

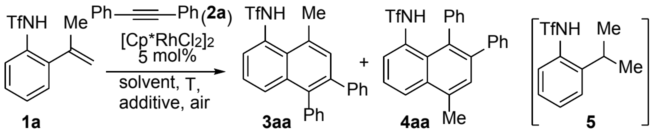


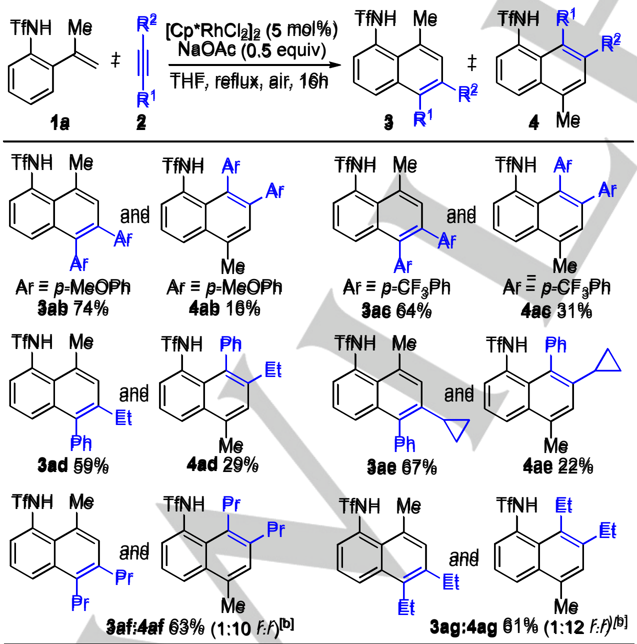
Table 1. Optimization of the reaction conditions[a]

entry	additive	solvent	T (ºC)	**3aa** (%)	**4aa** (%)	**5** (%)
1	$Cu(OAc)_2$	CH_3CN	82	28	17	-
2	$Cu(OAc)_2$	dioxane	101	60	19	-
3	$Cu(OAc)_2$	THF	66	63	21	-
4[b]	-	THF	66	-	-	-
5	NaOAc	THF	66	68	23	-
6[c]	NaOAc	THF	66	50	13	15
***7*[d]**	***NaOAc***	***THF***	***66***	***67***	***18***	**-**
8[e]	NaOAc	THF	66	15	3	-

[a] Conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), 1 equiv of additive/oxidant, under air, 16h. Isolated yields. [b] No conversion. [c] Under argon. [d] NaOAc (0.5 equiv). [e] Using 10 mol% of [Cp*Rh(COD)] as catalyst.

Curiously, the catalytic reaction is also possible under argon, albeit less efficient (entry 6). In this case we were able to identify the isopropylanilide **5** as secondary product (over 15% yield), a result which suggests the generation of hydrogen, and/or metal hydride species in the reaction medium.[10] The amount of NaOAc can be decreased to 0.5 equivalents without affecting the yield (entry 7, 88% yield). When [Cp*Rh(COD)] was used as catalyst, the products were formed, but in low yields (entry 8, 18% yield).

Table 2. Scope with respect to the alkynes[a]

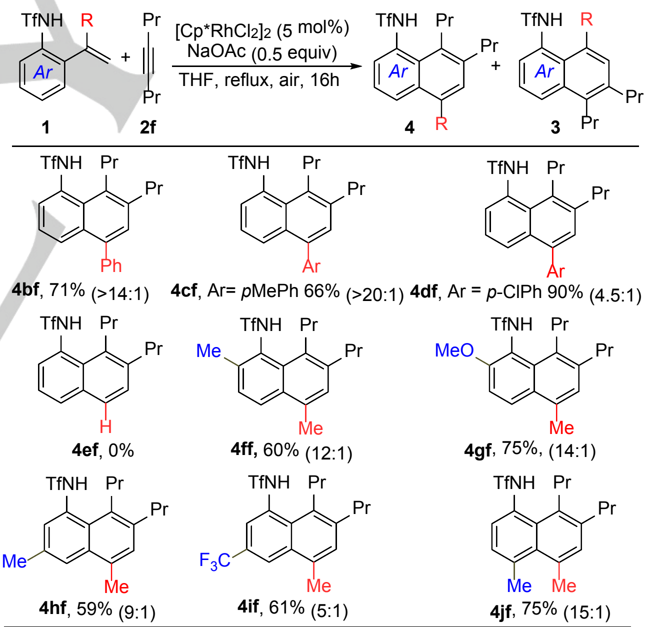


[a] Isolated yields. [b] Minor isomer could not be separated.

As it is shown in the scheme 2, symmetrical diarylacetylenes, either electron-rich (**2b**) or electron-poor (**2c**), provided the expected naphthylamides in good overall yields (90-95%) and isomeric ratios of up to 4.6:1. On the other hand, unsymmetrical alkyl-aryl alkynes such prop-1-yn-1-ylbenzene (**2d**) or (cyclopropylethynyl)benzene (**2e**) led to only one of the possible regioisomers, for each of the adducts. With aliphatic alkynes, the reaction also takes place, but remarkably, we observed a total change in selectivity so that *the rearranged products **4** become majoritary*. Thus, using 4-octyne (**2f**) as coupling partner the naphthylamides **3af**:**4af** were isolated in a 1:10 ratio with a total yield of 63%; while in the reaction with hexyne (**2g**) the selectivity was even better (Table 2).

We also explored the scope with other alkenyl triflylanilides bearing different substituents at the internal position of the olefin, using 4-octyne as reaction partner. As shown in the table 3, naphthylamides **4bf**, **4cf** and **4df** were obtained in good yields (66-90%) and up to >20:1 selectivity (Scheme 3). Curiously, the unsubstituted vinylanilide **1e** failed to provide the products, being mostly recovered after 16h.[11] Importantly, the reaction can be reproduced at a larger scale (1 mmol), as demonstrated for the case of **4bf,** which was obtained in an excellent 74% yield after 16 h.

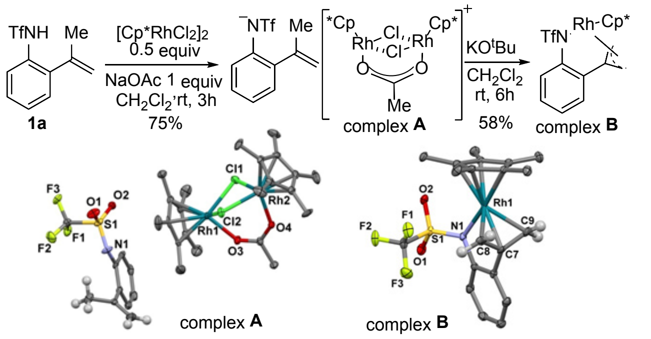
Table 3. Scope with respect to the anilide[a,b]



[a] Isolated yields. [b] Main isomeric product is depicted.

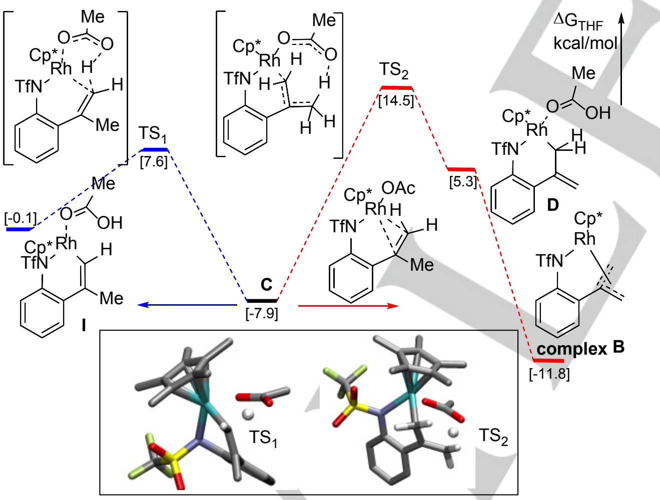
The reaction is compatible with other aromatic rings equipped with either electron rich or electron poor substituents. Thus, methyl and methoxy substituted substrates in ortho to the nitrogen led to the corresponding naphthylamides (**4ff**, **4gf**) in 60 and 75% yield respectively with a selectivity of up to 15:1. Substituents in *para* to the alkene (**4hf**, **4if**, 59-61% yield) and to the amide (**4jf**, 75% yield, 15:1 ratio) are also tolerated.

Mechanistically, the above annulations present several intriguing features which range from the C-H activation step to the formation of the rearranged adducts of type **4**. Treatment of substrate **1a** with $[Cp^*RhCl_2]_2$ in dichloromethane with slight excess of NaOAc for 3h, at room temperature, allowed to isolate a solid product that was crystalized and identified as the rhodium complex **A**. This compound consists of a cationic dimeric Rh(III) species in which two chloride ligands are replaced by a κ^2-acetate with the deprotonated anilide acting as counterion. When this complex was treated with 1 equivalent of KO^{t}Bu, a π-allyl derivative **B** was formed after 6 h. This complex can be also formed directly by treatment of **1a** with stoichiometric amounts of $[Cp^*RhCl_2]_2$ and sodium acetate in THF, although in lower yield.



Scheme 3. Isolation of complexes **A** and **B**, and X-Ray structures. Most hydrogen atoms were omitted for clarity.

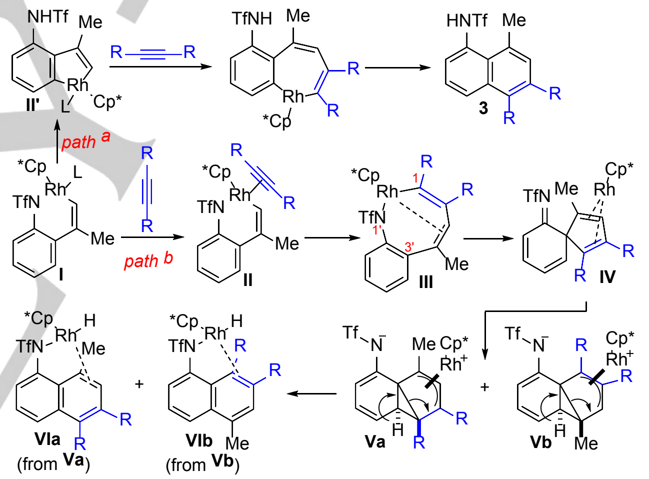
The isolation of complex **B** suggests that it might be an intermediate in the catalytic cycle, however heating **B** with the alkyne **2a** in THF at reflux did not give the cycloadduct. Conversely, π-allyl complex **B** presents catalytic activity, which suggests that it can revert to an active catalytic species.



Scheme 3. DFT calculations of the C-H activation step. Energetic values are with respect to **1a**.

On these bases, we hypothesized that the cycloaddition requires the activation of the alkenyl C-H bond, which according to DFT calculations takes place through a classical CMD mechanism (activation barrier: 15.5 kcal/mol from intermediate **C**). This process contrasts with the non-concerted metalation/deprotonation proposed for the Rh(III)-promoted activation of 2-alkenylphenols (see supporting information for more details).[5] Likely, the presence of a triflyl group in the nitrogen decreases its electron donating character in comparison to that of the hydroxyl group of alkenylphenols, and this favors a CMD process. The calculations confirmed the viability of an allylic activation to give complex **B**, albeit the activation barrier is higher [ΔΔG‡ (TS_2-TS_1) = +6.9 kcal/mol]. However, the resulting π-allyl product is more stable, which could explain why we isolated it.

This information suggests that the catalytic process might start with the activation of the alkenyl C-H bond to give rhodacycle **I**. Rhodium-rollover with a second C-H activation, would give intermediate **II'**, which by alkyne migratory insertion and reductive elimination yields products **3** (*Path a*, Scheme 4). However, how do we explain the formation of naphthalenes **4**?. Intermediate **I** might alternatively evolve by migratory insertion of the alkyne to give intermediate **III**, which upon a formal [1,3′]-reductive elimination provides spirocycles of type **IV** (*path b*).[5,12] Indeed, DFT calculations confirmed the energetic feasibility of these steps, with present barriers lower than that of the C-H activation step to give **II'** (*path a*, see the supporting information for details).[13]



Scheme 4. Hypothesis for the formation of both naphthalene isomers.

The computational data also revealed that these Rh(I)-spirocyclic complexes can readily progress into the cyclopropyl tricyclic intermediates **Va** or **Vb**, with a clear kinetic preference for the formation of **Vb** when R = Pr (Figure 1). Likely, the presence of the propyl substituents generates a more sterically congested transition state structure in the path to **Va**.

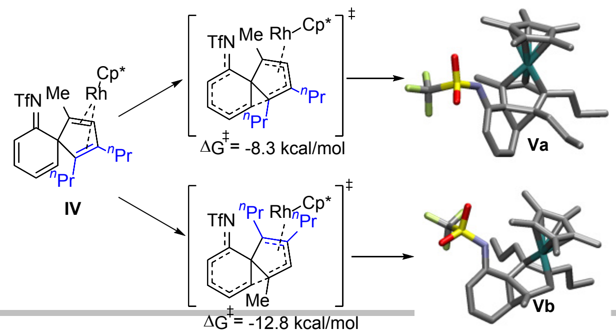
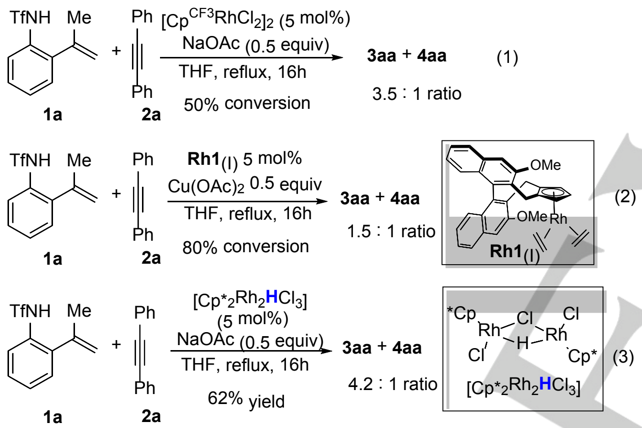


Figure 1. Calculated barriers to **Va** and **Vb**. Hydrogens are omitted for clarity. ΔG variation in THF with respect **1a**. $\Delta\Delta G^{\ddagger}$ = +4.5 kcal/mol

The lower activation barrier to **Vb** is consistent with the preferred experimental formation of the rearranged adducts **4**. Aromatization through ring expansion generates the naphthylamides **VI** featuring a rhodium hydride complex.

In consonance with these mechanisms and with the involvement of rhodium complexes in the different steps, we observed that the characteristics of the Cp ligand influence the ratio of products. Thus, reaction with electron deficient rhodium complex $[CpCF_3RhCl_2]_2$, led to the corresponding adducts in a 3.5:1 ratio (Scheme 6, eq 1), while with the bulky rhodium complex **Rh1** we observed a 1.5:1 mixture of isomers (eq 2). With regard to the reoxidation step, it might involve a redox reaction between the Rh hydride in the product and AcOH or the starting triflimide. In this context we have observed that a well-defined Rh hydride precatalyst replicates the catalytic activity observed with $[Cp^*RhCl_2]_2$ (Scheme 6, eq 3).[14]



Scheme 6. Selected mechanistic experiments.

In conclusion we have discovered new rhodium-catalyzed oxidative annulation processes involving formal double C-H activation processes. The transformations are operationally simple, atom economical, highly chemo- and regioselective, and present a remarkable synthetic scope. Importantly, we have unveiled intriguing mechanistic aspects, including an unprecedented rearrangement process requiring the cleavage and formation of C-C bonds which are of general significance.

Acknowledgements

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Keywords: C-H activation • rhodium • annulation • anilide • naphthylamine

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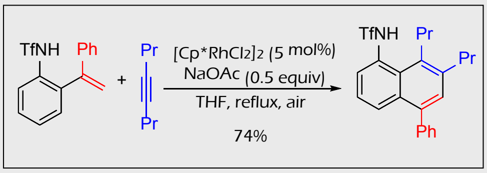

- Formal double C-H activation/annulation process
- Formal cleavage and formation of C-C bonds
- No external oxidizing additives required
- Easy set up
- Atom economy entry to naphthylamines

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