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## Accepted Article

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.201802830
*Angew. Chem.* 10.1002/ange.201802830

**Link to VoR:** http://dx.doi.org/10.1002/anie.201802830
http://dx.doi.org/10.1002/ange.201802830

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# Rhodium(III)-Catalyzed Annulation of 2-Alkenylanilides with Alkynes via C–H Activation: a Direct Access to 2-substituted Indolines

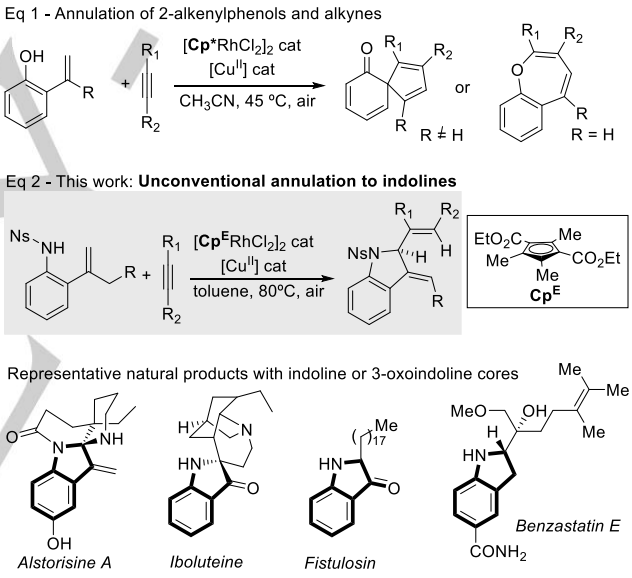
Marc Font, Borja Cendón, Andrés Seoane, José Luis Mascareñas,* Moisés Gulías*

**Abstract:** A Rh(III) complex featuring an electron-deficient $\eta^5$-cyclopentadienyl ligand catalyzes an unusual annulation between alkynes and 2-alkenylanilides, to form synthetically appealing 2-substituted indolines. Formally, the process can be viewed as an allylic amination with concomitant hydrocarbonation of the alkyne. Mechanistic experiments indicate that this transformation involves a peculiar Rhodium migration with a concomitant 1,5-H shift.

The functionalization of hitherto considered inert C–H bonds is becoming an extremely valuable synthetic tool.[1] Especially appealing are those reactions that involve transition metal-catalyzed oxidative annulations of non-activated precursors. This approach has demonstrated a great potential to build heterocyclic skeletons in a simple and an atom-economical fashion, and using readily available precursors.[2,3] In this regard, we have recently demonstrated that 2-alkenylphenols react with alkynes under Cp*Rh(III) catalysis to give interesting oxacyclic or spirocyclic products (scheme 1, eq 1).[4]

A major challenge in the area consists of the development of alternative annulations involving nitrogenated precursors, as this would allow the assembly of valuable aza-heterocycles. There are not specific studies on the annulation reactivity of 2-alkenylanilides under Rh(III) catalysis; however, isolated examples with 2-vinyltosylanilides and 2-phenylanilines suggest that these substrates fail to react with alkynes.[5] Despite these results, we considered that playing with the anilide substituents it might be possible to control the reactivity of the systems. In this context, we found that while the reaction of nosylanilide **1a** with diphenylacetylene using $[Cp^*RhCl_2]_2$ as precatalyst, leads to poor conversions and complex mixtures, we could isolate a small amount of the indoline **3aa** (Table 1, entry 1). This is an interesting product that can be formally viewed as the result of an anomalous tandem amination/hydrocarbonation process. Envisioning that the assembly of this product might involve π-allylrhodium intermediates,[6] we hypothesized that Rh complexes with less electron donor Cp ligands might further favor its formation.[7]

Herein we demonstrate that Rh(III) complexes featuring an electron deficient $Cp^E$ ligand promote the annulation of 2-alkenyl-nosylanilides and alkynes to give 2-substituted indoline products, in good yields and with excellent regioselectivities (Scheme 1, eq. 2). The transformation is robust and versatile, and provides a simple way of building highly functionalized indoline products from very simple precursors. The indoline skeleton is present in many natural products (see scheme 1 for some examples), and therefore practical methods for their assembly are of high interest.[8] Importantly, mechanistic investigations suggest that the reaction involves an interesting rhodium-promoted [1,5]-hydrogen shift. While [1,4]-H migrations mediated by rhodium are well known, and have been exploited in a large variety of transformations including enantioselective processes,[9] reports on related [1,5]-H shifts are very rare, and the existing examples involve Rh(I) catalysts.[10]




**Scheme 1.** Rh(III)-catalyzed annulation of 2-alkenylphenols (Eq. 1) and 2-alkenylanilides (eq. 2), and examples of natural products with indoline cores.

Whereas most Rh(III)-promoted C-H activation reactions so far described involve the use of complexes with Cp* ligands,[11] accumulative evidences suggest that the electronic properties of the Cp ligand could have a profound influence in the reactivity.[12] Of particular interest was the discovery by Shibata, Tanaka and coworkers of the increased activity of the complex $[Cp^ERhCl_2]_2$ in allylic activation and annulation reactions.[7,13] Therefore, after detecting the formation of product **3aa** (Table 1, entry 1), we investigated the reactivity of the nosylanilide **1a** in presence of this rhodium catalyst featuring the electron deficient Cp ligand. Using $Cu(OAc)_2$ as oxidant and 1.5 equiv of alkyne **2a**, we observed the formation of the indoline **3aa** in 65% yield (after heating in dioxane at 80ºC for 16h). Changing from dioxane to dry toluene, the reaction failed (only decomposition of the anilide was observed), however in presence of 5 equiv of water we could isolate an

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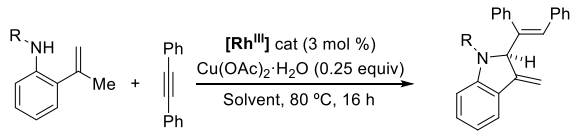
excellent 84% yield of product, after 16 h at 80 ºC (Table 1, entry 4). Likely the presence of water increases the solubility of the Cu(II) salt and favors the re-oxidation step required for turnover. The substituent at the nitrogen also plays a very relevant role. Therefore, while the free aniline decomposed, and the N-acetylated derivative gave almost no conversion; N-triflyl and N-tosyl anilides afforded a 40 and 25% of the corresponding products (entries 7 and 8).

***Table 1:*** Optimization of the reaction conditions.[a]



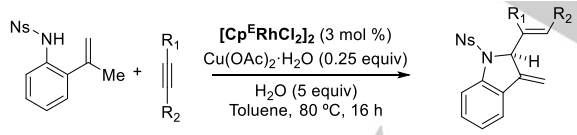

1 2a 3

| Entry | R | Solvent | Catalyst | Yield **3** (%) |
|---|---|---|---|---|
| 1 | Ns | Dioxane | $[Cp^*RhCl_2]_2$ | 13 |
| 2 | Ns | Dioxane | $[Cp^ERhCl_2]_2$ | 65 |
| 3 | Ns | Toluene | $[Cp^ERhCl_2]_2$ | 0 |
| **4** | **Ns** | **Toluene**[b] | **$[Cp^ERhCl_2]_2$** | **84** |
| 5 | H | Toluene[b] | $[Cp^ERhCl_2]_2$ | 0 |
| 6 | Ac | Toluene[b] | $[Cp^ERhCl_2]_2$ | 0[c] |
| 7 | Tf | Toluene[b] | $[Cp^ERhCl_2]_2$ | 40 |
| 8 | Ts | Toluene[b] | $[Cp^ERhCl_2]_2$ | 25[c] |
| 9 | Ns | Toluene[b][d] | $[Cp^ERhCl_2]_2$ | 0[c] |
| 10 | Ns | Toluene[b] | - | 0[c] |

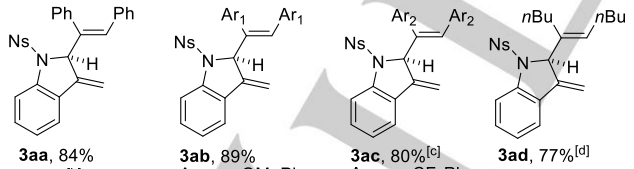
[a] Conditions: 0.1 mmol of **2a**, 0.15 mmol of **1a**, 1 mL Toluene. [b] 5 equiv of $H_2O$. [c] Starting material mostly recovered. [d] Without $Cu(OAc)\cdot H_2O$.

As expected, when copper diacetate or the rhodium catalyst is not added, starting material was mostly recovered (entry 9 and 10). Importantly, the reaction can be replicated in a gram scale without significant erosion in the yield (72%, Table 2).

***Table 2:*** Scope of the reaction with different alkynes.[a]




1a 2 3



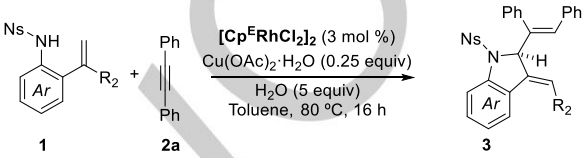

**3aa**, 84% (72%)[b] **3ab**, 89% $Ar_1$ = *p*-OMePh **3ac**, 80%[c] $Ar_2$ = *p*-$CF_3$Ph **3ad**, 77%[d]

**3ae**, 87% **3af**, 81%, 10:1 *r.r* **3ag**, 67% **3ah**, 64%

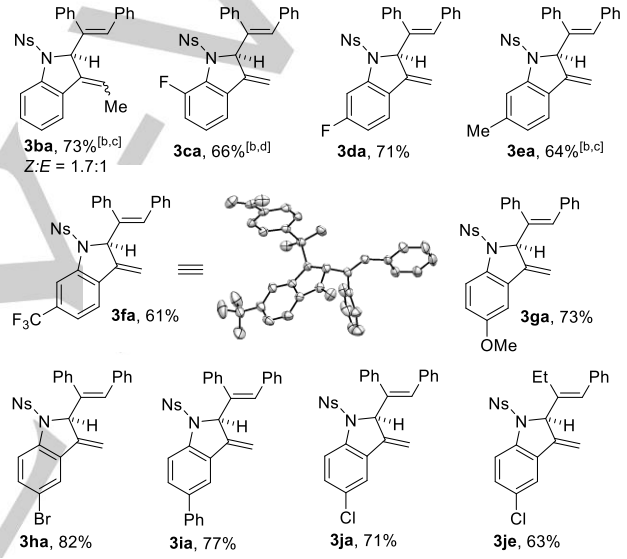
[a] Isolated yields. Regioisomeric ratios are > 20:1, unless otherwise noted. [b] Gram-scale experiment. [c] 90 ºC. [d] 24 h.

Encouraged by these results we then tested the scope with regard to the alkyne counterpart (Table 2). Thus, other symmetric alkynes with electron rich or electron poor aromatic substituents are efficient reaction partners, and the corresponding indoline products are obtained in very good yields (89% and 80% for **3ab** and **3ac**, respectively). Alkynes bearing aliphatic substituents also participate in the process. Therefore with 5-decyne we obtained the expected product **3ad** in 77% yield. In the case of non-symmetrical alkynes, the regioselectivities were very high, in favor of products with the aryl substituent at the terminal position of the alkene. Thus, products **3ae**, **3af** and **3ag** were obtained in very good yields (67-87%) and excellent regioselectivities. Pleasingly, the reaction also works nicely with enynes, as demonstrated for the formation of **3ah**.

***Table 3:*** Scope of the reaction with different 2-alkenylanilines.[a]




1 2a 3




**3ba**, 73%[b,c] *Z:E* = 1.7:1 **3ca**, 66%[b,d] **3da**, 71% **3ea**, 64%[b,c]

**3fa**, 61% **3ga**, 73%

**3ha**, 82% **3ia**, 77% **3ja**, 71% **3je**, 63%

[a] Isolated yields. [b] 5 mol% Rh catalyst. [c] 35 h. [d] 0.033 M

The reaction is not limited to *ortho*-propenylanilides. Therefore, the internal methyl group can be replaced by an ethyl, without compromising the annulation yield. The corresponding indoline products were obtained as a mixture of Z and E isomers (**3ba**, 73%, 1.7:1, *Z:E*, table 3). The reaction also tolerates different substitutions in the aryl ring of the anilide. It works well with substrates containing fluorine substituents *ortho* to the amide (**3ca**, 66% yield). With regard to the *meta* substitution, we found that the annulation proceeds with substrates bearing either fluorine, $CF_3$ or $CH_3$ substituents (**3da**, **3fa**, **3ea**), albeit in this latter case we had to increase the catalyst loading and the reaction time. In the case of substrates with substituents in *para* to the nosylamide, we found good yields of the products independently of the electronic characteristics of the substituents (**3ga-3ja**, 73-82% yield). Substituted anilides do also react with alkynes other than diphenylacetylene, with similar results (see for instance **3je**, 63% yield).

While the mechanism of the reaction is intriguing, it likely starts by formation of reactive rhodium acetate complexes, and the exchange of one of the acetates by the amide of the anilide. The resulting complex **I** might then evolve to the π-allyl complex

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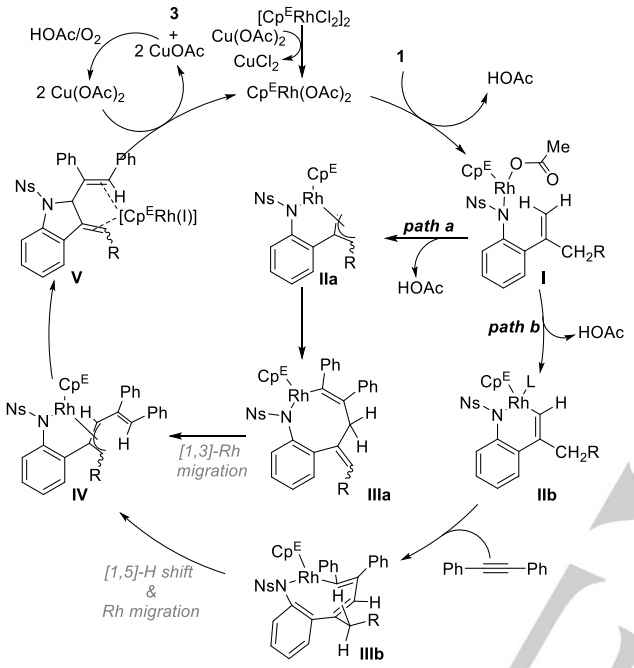
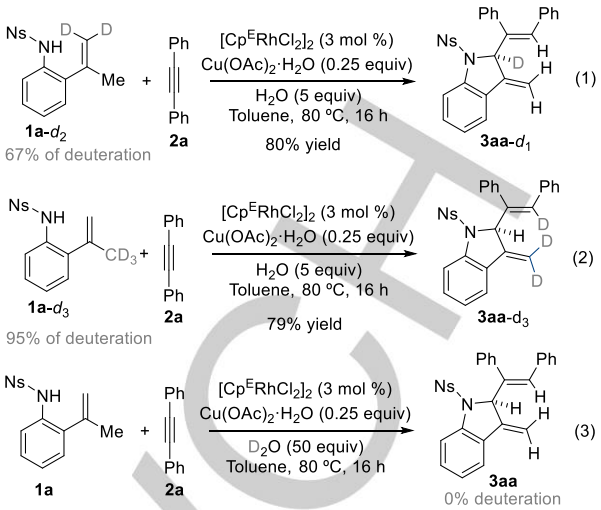
**IIa** by allylic C-H activation (Scheme 2, *path a*).[6,7] After alkyne carbometallation and 1,3-rhodium migration a new rhodacycle **IV** is formed, that evolves by reductive elimination to form the corresponding indoline product **3**. The resulting Rh(I) complex is then reoxidized to Rh(III) by the Cu(II) salt and air. A favorable coordination of the diarylalkene substituent to Rh may explain why the reductive elimination occurs at the most substituted carbon.
A mechanistic alternative would consist of the activation of olefinic C-H bond (Scheme 2, *path b*), followed by carbometallation to generate **IIIb**, and a 1,5- hydrogen shift to generate the key π-allyl intermediate **IV**.




**Scheme 2.** Mechanistic hypothesis

In order to shed light into the mechanism of the reaction, we carried out several deuterium labelling experiments, which provided relevant information. The reaction of deuterated substrate **1a**-*d*$_2$ under standard conditions led to the product **3aa**-*d*$_1$, in which only one deuterium remains in the molecule (Scheme 3, eq 1). This result seems to discard the 1,3-Rh migration step proposed in *path a*, as this should lead to a product with deuterium at the terminal position of the alkene. Additionally, the lack of deuterium scrambling suggests that the formation of a π-allyl intermediate of type **IIa** is unlikely.

Importantly, reaction of the deuterated substrate **1a**-*d*$_3$ led to product **3aa**-*d*$_3$, with deuterium in both positions of the exo-methylidene group, and in the alkene resulting from the alkyne insertion (Scheme 3, eq 2). This deuterium labelling pattern is fully compatible with *pathway b*, and with an internal 1,5-deuterium shift in intermediate **IIIb**. This migration might also take place in an acyclic Rh-acetate species resulting from the cleavage of this rhodacycle (see the supporting information). In consonance with the internal hydrogen/rhodium exchange, running a standard experiment in the presence of deuterated water led to the corresponding product without deuterium incorporation (Scheme 3, eq. 3).




**Scheme 3.** Deuterium-labelling experiments

Overall, these data suggest that the reaction can be better explained through a pathway of type b, involving an activation of the alkenyl C-H bond, migratory insertion of the alkyne, rhodium C-C migration with a simultaneous H-shift, and reductive elimination. While the exact role of the electron deficient Cp$^E$ ligand is not clear, likely, by making the rhodium more electrophilic, it might favor the 1,5-H shift with concomitant formation of the π-allyl intermediate **IV**.

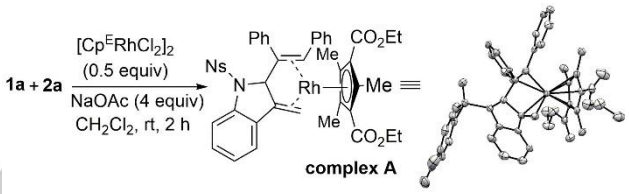
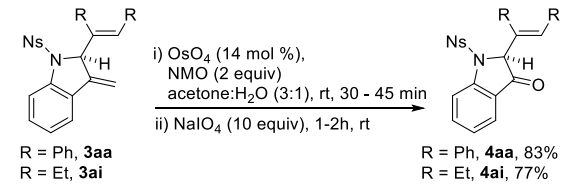



**Figure 1**. Formation of Rh(I)-complex A

Finally, a stoichiometric reaction of substrate **1a** with diphenylacetylene, in the absence of copper(II) acetate, afforded the rhodium(I) complex **A** (79% yield) that could be isolated and characterized by X-ray diffraction,[14] confirming an operative Rh$^I$/Rh$^{III}$ redox pair governing the reaction pathways (Figure 1).

As a preliminary demonstration of the manipulation potential of the indoline adducts, we found that products **3aa** and **3ai** can be readily converted into the corresponding 3-oxoindolines by selective oxidation of the exo-methylene group (Scheme 4).[15] Since there are many natural structures with 3-oxoindoline skeletons (see some examples in Scheme 1), our methodology promises to provide a rapid entry to this type of products.




**Scheme 4.** Synthesis of 3-oxoindolines.

In conclusion, we have discovered a new oxidative annulation involving 2-alkenyl nosylanilides and alkynes, that allows the synthesis of a wide range of 2-substituted indoline skeletons in a simple, mild and selective manner. The use of an electron deficient $Cp^E$ ligand for the Rh(III) catalyst is essential for the outcome of the reaction, and the choice of the group at the nitrogen is also important in terms the efficiency of the transformation. Mechanistic data suggest that the transformation starts with the activation of terminal olefinic C-H ($sp^2$) bond and involves an intramolecular rhodium migration with a formal 1,5-hydrogen shift. Our results come to further confirm that tuning the electronic characteristics of Cp ligands can have a profound effect in the reactivity outcome of Rh(III) promoted reactions.

## Acknowledgements

This work has received financial support from Spanish grants (SAF2016-76689-R and CTQ2016-77047-P), the Xunta de Galicia (ED431C 2017/19, 2015-CP082 and Centro Singular de Investigación de Galicia accreditation 2016-2019, ED431G/09) the European Regional Development Fund (ERDF), and the European Research Council (Advanced Grant No. 340055). The orfeo-cinqa network CTQ2016-81797-REDC is also kindly acknowledged.

**Keywords:** rhodium • C-H activation • indoline • annulation • rhodium shift

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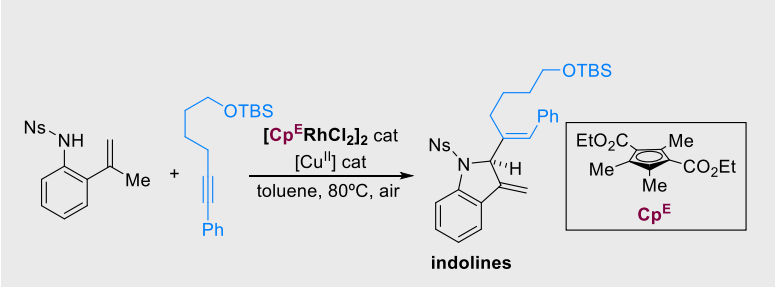


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