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This is an **author produced version** of a paper published in:

Chemistry - A European Journal 25.22 (2019): 5733-5742

DOI: <http://dx.doi.org/10.1002/chem.201900162>

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Rhodium-Catalyzed Copper-Assisted Intermolecular Domino C–H Annulation of 1,3-Diynes with Picolinamides: Access to Pentacyclic π -Extended Systems

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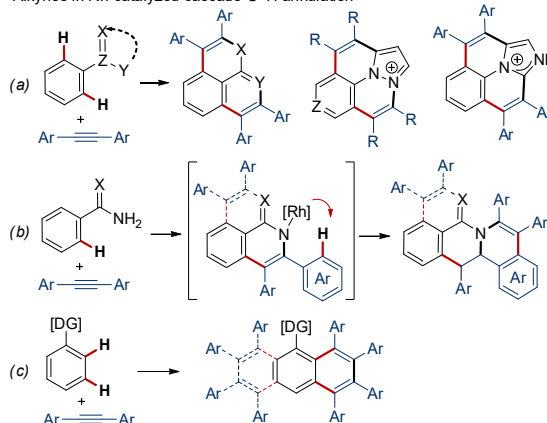
Abstract: A new reactivity mode of 1,3-diynes in Rh-catalyzed oxidative annulation enables the rapid assembly of extended π -systems from readily available picolinamide derivatives. The process involves a double C–H bond activation and iterative annulation of two units of 1,3-diyne, each alkyne moiety of which is engaged in an orchestrated insertion sequence with high regiocontrol, leading to the formation of five new C–C bonds and construction of four fused rings in a single operation. Either isoquinoline 1-carboxamides or fused-polycyclic systems can be accessed by a switch in regioselectivity for the second diyne insertion depending on the reaction conditions. DFT theoretical calculations have elucidated that the cooperative participation of both Rh and Cu in substrate activation, favored under excess of copper(II) salt, is key for such a reversal of the regioselectivity and subsequent multiple cyclization leading to fused polycyclic products. The role of Cu was found to be essential in assisting both multiple insertion and Rh walking sequences, with the implication of intermediates showing a Rh–Cu bond (2.60 Å).

Introduction

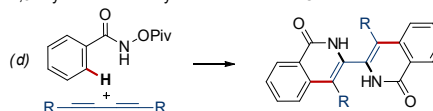
The high level of precision and predictability achieved in C–H activation^[1] has enabled recent research to target more difficult challenges such as iterative C–H functionalizations for a rapid buildup of molecular complexity.^[2,3] However, the application of such strategy for the synthesis of polycyclic (hetero)aromatic systems with extended π -conjugation remains underdeveloped^[4]

even though this class of compounds is of prime importance as functional materials.^[5] For example, although the $[\text{Cp}^*\text{Rh}^{\text{III}}]$ -catalyzed oxidative alkyne annulation of arenes is one of the most versatile methods to access heterocyclic compounds,^[6,7] only a handful of approaches have been reported on multiple C–H annulation involving two or more alkyne units to afford fused polyaromatic systems (Scheme 1). Most of these methods rely on: (i) di-*ortho*-alkenylation/annulation at both sides of a bidentate directing group (Scheme 1a),^[8] (ii) the use of a directing group that leaves a *N*-functionality proximal to the aryl substituent of the newly incorporated alkyne, whose coordination to Rh^{III} promotes a new C–H annulation with another molecule of alkyne (Scheme 1b),^[9] and (iii) a directed $[2+2+2]$ -type benzannulation via two-fold cyclorhodation-alkyne insertion, pioneered by Satoh and Miura (Scheme 1c).^[10] Despite this success, the development of conceptually different tactics in domino C–H annulation toward expanding the scope of conjugated π -scaffolds is an important goal.

Alkynes in Rh-catalyzed cascade C–H annulation



1,3-Diynes in Rh-catalyzed intermolecular C–H annulation



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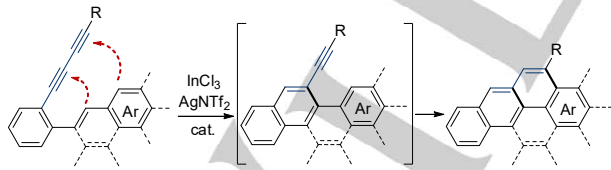
Scheme 1. Cascade Rh-catalyzed multiple C–H annulation of arenes with alkynes leading to π -extended systems.

1,3-Diynes have the potential to provide further complexity; however, the limited number of methods exploiting 1,3-diynes in C–H annulation highlights the challenges of regiocontrol in the insertion and mono-/diannulation selectivity.^[11–13] In a pioneering example, Glorius demonstrated the Rh^{III}-catalyzed diannulation of benzamides with 1,3-diynes, thus leading to bisheterocycles (Scheme 1d).^[11] This approach has later been extended to cobalt-catalysis.^[12]

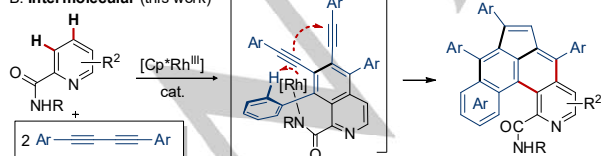
While in these transformations each π -system of the diyne undergoes migratory insertion independently of the other, we questioned whether an alternative mechanism would be possible in which the 1,3-diyne could engage both alkyne motifs in an orchestrated sequence of insertion events, thereby enabling the access to new polycyclic aromatic architectures. During the final stages of our investigations, Chalifoux and co-workers reported the first realization of this goal, namely the domino benzannulation reaction of 1,3-diynes.^[14] In their elegant protocol, π -expansion is achieved by an intramolecular double 6-*endo-dig* cyclization of properly designed diaryl-1,3-butadiynes in the presence of InCl₃-AgNTf₂ as catalyst (Scheme 2A). We envisaged that an intermolecular cascade C–H benzannulation of 1,3-diynes would be feasible under [Cp*Rh^{III}]-catalysis if, upon initial alkyne benzannulation, the other alkyne motif of the diyne is primed for a subsequent benzannulation with the aryl substituent of the 1,3-diyne component (Scheme 2B). Such a sequence of bond-forming events has, to our knowledge, never been described, yet it could greatly expand the repertoire of cascade annulation. Although we were aware that controlling regioselectivity in each of the four alkyne migratory insertions would present an immediate significant challenge, previous success on regioselectivity control in 1,3-diyne diannulation by Glorius and others offered hope that these obstacles would not be insurmountable.^[11,12]

New reactivity mode of 1,3-diynes: both alkynes are engaged in an orchestrated manner

A. Intramolecular (Chalifoux)



B. Intermolecular (this work)



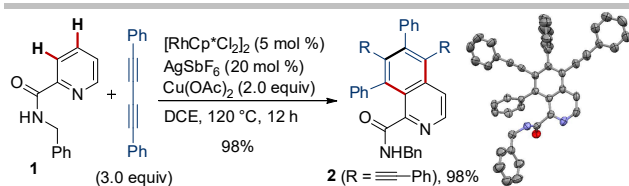
Scheme 2. Catalytic domino benzannulation of 1,3-diynes toward polycyclic aromatic π -extended systems.

Herein we present a method for the Rh-catalyzed oxidative intermolecular annulation of picolinamides with two molecules of diaryl-1,3-diyne in which the four alkyne units do participate in annulation, thereby enabling the assembly of up to four fused rings with extended π -conjugation in a single step through a double C–H bond activation and construction of five C–C bonds. Interestingly, by appropriate choice of the reaction conditions, either isoquinoline 1-carboxamides or fused-polycyclic systems can be obtained selectively through a switch in regioselectivity for the second diyne insertion. Computational studies have unveiled that the cooperative action of copper in substrate activation, favored under an excess amount of copper(II) salt, is key for a reversal of the regioselectivity in the insertion of the second 1,3-diyne unit. Furthermore, the role of the copper ion seems to be essential in assisting orchestrated alkyne insertion processes and metal walking sequences enabling distant activation and multiple cyclization towards construction of fused polycyclic products.

Results and Discussion

1. Optimization studies: single benzannulation to afford isoquinoline-1-carboxamides bearing alkyne handles (isoquinoline products, IQ)

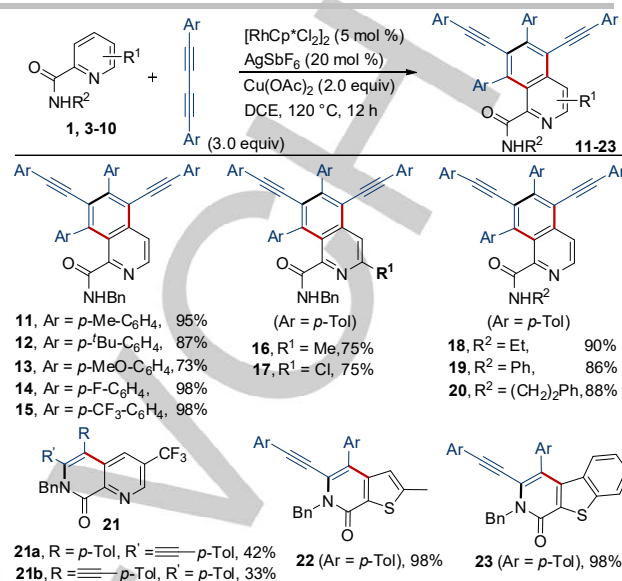
With these considerations in mind, we chose to explore the annulation reaction of diphenylbuta-1,3-diyne with *N*-benzyl-2-picolinamide (**1**).^[15–17] Interestingly, under similar conditions to those optimized in our previous Rh-catalyzed benzannulation with alkynes^[10e,15b] the model reaction of diphenylbuta-1,3-diyne with **1**^[16] led to clean conversion to the isoquinoline 1-carboxamide **2** in nearly quantitative yield (98%) with complete regiocontrol (Scheme 3). The alternate arrangement of the aryl and alkynyl substituents in the newly formed aryl ring was found to be opposite to that previously found in Rh^{III}-catalyzed benzannulation of arenes with unsymmetrically substituted alkyl aryl alkynes, which favors an orientation of the aromatic substituents at vicinal 2,3-position.^[10a,b,18] The regioselectivity for the first 1,3-diyne insertion is in complete agreement with the previous observations by Glorius, suggesting that the regioselectivity of the migratory insertion is highly affected by the hybridization of the carbon atom, with the order of preference being alkynyl > aryl for the group that remains distal to the target aryl C–H bond.^[11] However, in this case, the migratory insertion of the second 1,3-diyne component takes place with opposite regioselectivity to afford products featuring an alternate arrangement of the aryl and alkynyl substituents. The X-ray structure of **2** unambiguously establishes the regioselectivity of this reaction.^[19]



Scheme 3. Rh^{III}-catalyzed C–H annulation of **1** with diphenylbuta-1,3-diyne and ORTEP view of compound **2**.

The prevalence of isoquinoline skeleton in pharmaceuticals motivated us to explore the scope of this process (Scheme 4). Both electron-donating and electron-withdrawing groups at either the diaryl 1,3-diyne (**11–15**, 73–98%)^[20] or the pyridine unit (**16–17**, 75%) were tolerated. It is also remarkable the good tolerance towards a sensitive Ar–Cl substituent (**17**). Aryl or alkyl substituents (other than a benzyl group) on the amide nitrogen were found to be compatible (**18–20**, 86–90%); however, a primary amide group failed ($\text{R}^2 = \text{H}$, not shown).

Interestingly, the presence of a CF_3 group at the C5 position of the pyridine ring interrupted the aromatic homologation and led exclusively to the 1,7-naphthyridin-8(7*H*)-one skeleton with no regiocontrol (**21a** and **21b**, 42% and 33%, respectively). The lack of regiocontrol in this case could be related to the ability of this group to get involved in hydrogen bond formation (*vide infra*). Similar interrupted pathway featuring only one alkyne insertion was observed with thiophene- or benzo[*b*]thiophene-2-carboxamide substrates (**22** and **23**, 98%), which suggests that the second alkyne C–H insertion is sensitive to steric effects. Therefore, the presence of a substituent in the pyridyl-*ortho*-position to the reactive C–H site may impose a significant steric demand, thereby bypassing the normal reactivity outcome (the second alkyne C–H insertion) and favoring instead the competitive trapping of the plausible alkenyl rhodium intermediate by the amidic N–H.



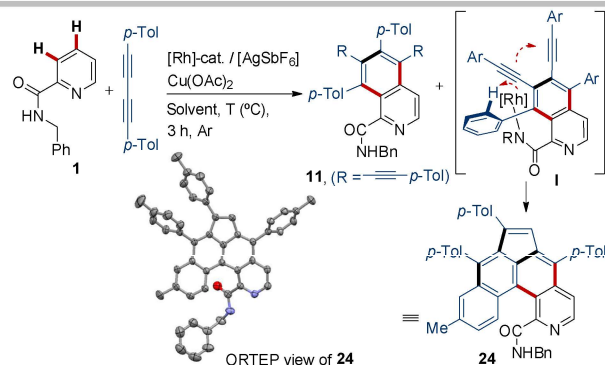
Scheme 4. Benzannulation of picolinamides and interrupted C–H/N–H annulation. Isolated yields after chromatography.

2. Access to complex pentacyclic systems with extended π -conjugation (products PCS)

During the evaluation of the scope, we observed in some crude mixtures trace amounts of a side product showing intense fluorescence under UV irradiation on the TLC plate. This observation led to the postulation of a polyaromatic nature for this byproduct, which sparked our interest to find a way for its selective formation. We decided to re-optimize the catalyst system in the model annulation of **1** with 1,4-di-*p*-tolylbuta-1,3-diyne (Table 1, see SI for details). Gratifyingly, the selectivity towards **24** improved dramatically by increasing the loading of Rh-catalyst to 20 mol% in the presence of 2.2 equiv of diyne (at 130 °C in DCE for 3 h), providing product **24** in 45% isolated yield (entry 1). Higher loadings of $\text{Cu}(\text{OAc})_2$ (4.0 equiv) improved the reactivity to complete conversion, although with a slight decrease in selectivity (52% yield for **24**, entry 2). Pleasingly, switching the solvent to 1,4-dioxane, improved the yield in favor of **24** (60%, entry 3). This effect of the solvent on selectivity can be ascribed to the higher solubility of the Cu salt in 1,4-dioxane compared to DCE. Finally, the amount of silver salt can be reduced to 40 mol% without altering the outcome (entry 4).

Table 1. Optimization studies toward fused pentacyclic structures (PCS).

FULL PAPER

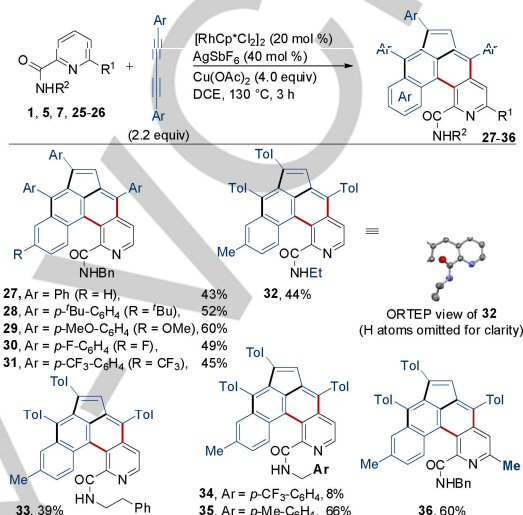


Entry ^[a]	Rh-cat (mol %)	Cu(OAc) ₂ (equiv)	Solvent	11 (%) ^[b]	24 (%) ^[b]
1	20	2.0	DCE	30	45
2	20	4.0	DCE	46	52
3	20	4.0	dioxane	39	60
4 ^[c]	20	4.0	dioxane	38	62

[a] Reaction conditions: **1** (0.15 mmol), 1,3-diyne (0.33 mmol, 2.20 equiv), [Cp*RhCl₂]₂ (x mol %), AgSbF₆ (4x mol %), Cu(OAc)₂, solvent (0.1 M), 130 °C, under Ar atmosphere. [b] Isolated yields. [c] AgSbF₆ (40 mol %).

The examination of the diyne scope showed tolerance to both electron-rich and electron-deficient *p*-substituted aromatic groups (Scheme 5, **27–31** 43–60%). Interestingly, the nature of the *N*-substituent showed a remarkable influence on the selectivity towards the fused polycyclic product, a *N*-benzyl group providing better results than *N*-ethyl (**32**, 44%) or *N*-phenethyl (**33**, 39%). This observation suggested that a potential interaction of the metal with the aromatic ring of the benzyl unit could play an essential role in enhancing selectivity. In line with this proposal, the substrate with an electron-poor *p*-(CF₃)benzyl substituent provided a very poor yield of **34** (8%), whereas the more electron-donating 4-methylbenzyl group restored the selectivity (**35**, 66%). The fused-pentacyclic ring structure of **32**

was again confirmed by X-ray diffraction analysis.¹⁹ Incorporation of a methyl substituent at C6 of the picolinamide is also compatible (**36**, 60%), whereas a Cl atom at C6 did not survive, leading only to the protodechlorination product **24** in 52% yield (not shown). This side-reaction is likely due to the excess of Cu present in the reaction medium.



Scheme 5. Scope of Rh-catalyzed annulation with 1,3-diynes. The corresponding isoquinoline 1-carboxamides were also isolated (typically 22–42% yield, see SI).

Although the selectivity is not complete towards formation of products **PCS**, a single fused polycyclic structure was observed in all cases despite multiple competing cyclization pathways are possible. This distinct feature suggests that the core pentacyclic framework is constructed sequentially through a highly orchestrated process involving multiple domino-type alkyne insertion and metal walking sequences.

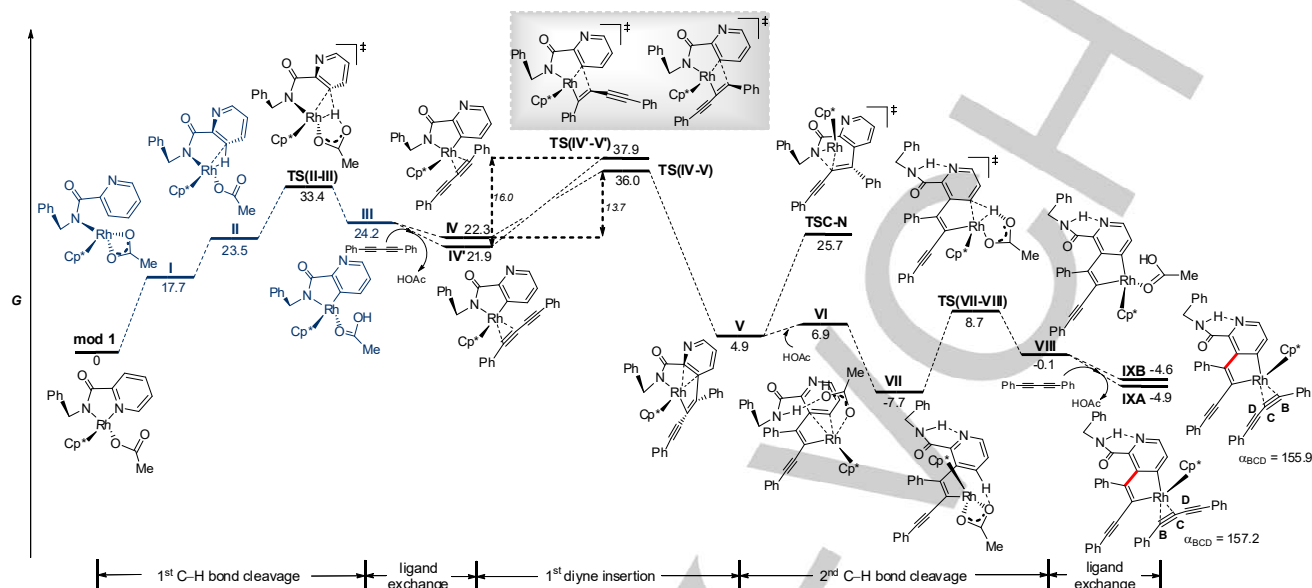


Figure 1. Energy profile for the C–H annulation of **1** with diphenylbuta-1,3-diyne from Rh^{III} complexes in the gas phase (M06/6-311++G(d,p)(C,H,N,O),LANL2TZ(f)(Rh)/B3LYP/6-31G(d)(C,H,N,O), LANL2DZ(Rh). Relative G values in kcal·mol⁻¹ at 298 K). Intermediates I–III, indicated in blue, had been previously studied^[10a] [M06/6-311+G(d,p)(C,H,N,O),SDD(Rh)/6-31G(d)(C,H,N,O), LANL2DZ(Rh), being 35.2 the free energy value for TS(II–III)].

3. Mechanistic insights

For a deeper insight into the reaction pathway and the origin of the selectivity for these complex cyclization processes, we performed a study of each reaction step by DFT calculations (see SI for details).

Single benzannulation to afford the isoquinoline-1-carboxamide (products **IQ**). On the basis of our previous studies,^{10e} a Rh^{III}-complex derived from **1** (**mod1**) would evolve through an acetate-assisted CMD process to afford intermediate **III** that could exchange the AcOH ligand for a diyne unit (Figure 1). As a result, the two regioisomeric intermediates **IV** and **IV'** could form, being both similar in energy. However, from this point onwards, the formation of **V** is favored due to the lower-energy barrier via **TS(IV–V)** than through **TS(IV'–V')** (13.7 and 16.0 kcal·mol⁻¹, respectively).^[21] The higher stability of **TS(IV–V)** compared to **TS(IV'–V')** could be related to the degree in which the diyne moiety loses its linear conjugation (Figure 2).^[18] The diyne moiety remains with a smaller deformation of the bond and dihedral angles in **TS(IV–V)** in comparison to **TS(IV'–V')**. Thus, the delocalization of charge is stronger in **TS(IV–V)** than in **TS(IV'–V')**, resulting into an increase of the negative charge values located on the Ph ending groups.

It is interesting to note that according to the energy profile, the 1,2-migratory insertion of the first diyne unit should selectively occur leading the alkynyl group distal to the functionalized C–H bond. This is in complete agreement with the observation that no

products arising from the opposite regioselectivity have been experimentally observed in this step.

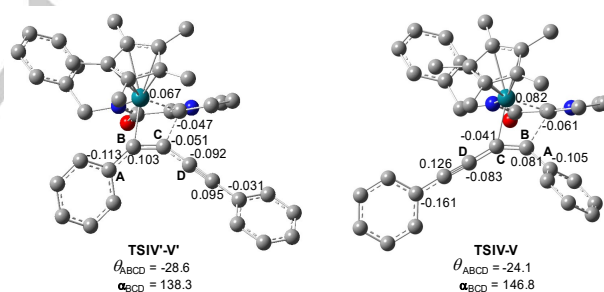


Figure 2. Structure of **TS(IV'–V')** and **TS(IV–V)**. Natural charges (q_i , in a.u.) of Rh and C atoms involved in the C–C and C–Rh bond formation, charge delocalization and relevant bond and dihedral angles ($^\circ$) of the diyne moiety are indicated.

From this point, instead of evolving through reductive elimination leading to a naphthyridinone skeleton (**TSC–N**), intermediate **V** would rather follow an alternative pathway. Protonation of the amide N with AcOH (**VI**) would allow the Rh-atom to coordinate the C4–H bond of the pyridine (**VII**) leading to intermediate **VIII** through a second CMD (**TS(VII–VIII)**).^[22] After displacement of AcOH by the second unit of diyne, two similarly stable regioisomeric complexes might form: **IXA**

FULL PAPER

and **IXB**. On one side, intermediate **IXA** would afford the isoquinoline derivatives featuring an alternate arrangement of aryl and alkynyl substituents (products **IQ**). On the other side, **IXB** could progress to the isoquinoline derivatives with the alkynyl substituents at vicinal positions that would further evolve to the fused polycyclic skeleton (**PCS**) products. Therefore, from here, the regioselectivity achieved in the insertion of the second unit of diyne would be the key to define the selectivity of the process.

For the second insertion step, there could be two distinct reaction pathways to consider for each regioisomeric complex (Figure 3). The route named as “a” implies that the second insertion step takes place into the alkene–Rh bond. The pathway “b” considers the insertion to occur into the C4(Py)–Rh bond. In the case of model **A**, the “path a” through **TS(IX-X)Aa** would be favored with an energy barrier of 12 kcal·mol⁻¹ approximately, either in the gas phase or considering solvation effects of DCE or 1,4-dioxane.^[23] In contrast, “path b” seems to be preferred for model **B**, proceeding via **TS(IX-X)Bb** with an energy barrier about 13 kcal·mol⁻¹. However, in any case, the energy barrier found for model **A** would be lower than for model **B**,

supporting the selectivity initially observed for the synthesis of isoquinoline 1-carboxamide products (**IQ**).

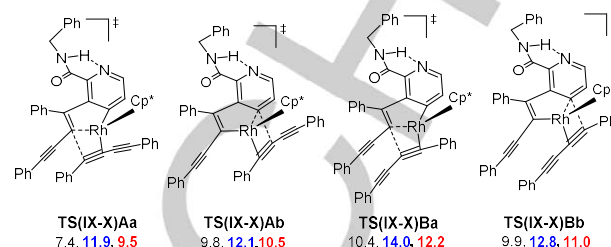


Figure 3. Possible transition states for the insertion step of the second unit of the diyne. The relative *G* values in kcal·mol⁻¹ at 298 K are indicated respect to **mod 1** (Figure 1) in the gas phase (in black). Single point solvation energy corrections (SMD model) in DCE (blue) and 1,4-dioxane (red) are also provided.

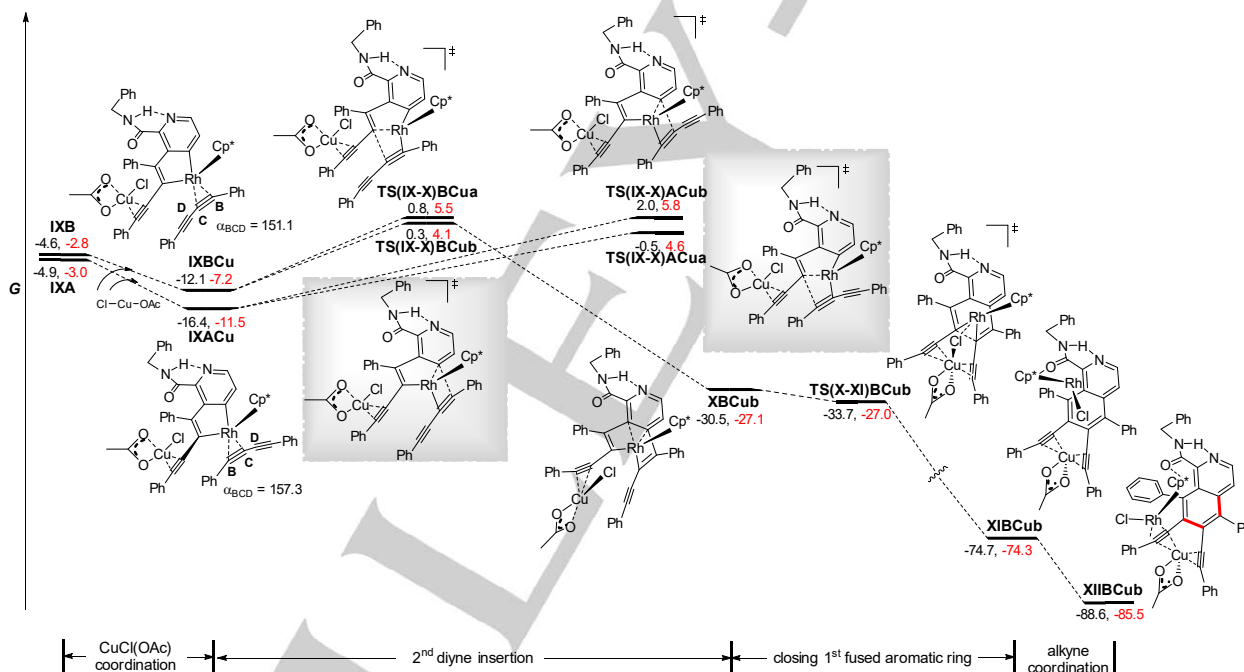


Figure 4. Energy profile for the insertion-reductive elimination steps of complexes **IXA** and **IXB** with Cu^{II} salts in the gas phase (M06/6-311++G(d,p)(C,H,N,O,Cl), LANL2TZ(f)(Cu,Rh)/B3LYP/6-31G(d)(C,H,N,O,Cl), LANL2DZ(Cu,Rh). Single point solvation energy corrections (SMD model) in 1,4-dioxane are indicated in red. Relative *G* values in kcal·mol⁻¹ at 298 K). Hydrogen bonds between Cp* ligand and carbonyl group are indicated.

*Complex polycyclic systems with extended π -conjugation (products **PCS**).* To explain the formation of products **PCS**, we next investigated the reasons behind the regioselectivity switch in the 1,2-migratory insertion of the second unit of diyne. The experimental observation that polycyclic products (**PCS**) are

favored when the amount of Cu^{II} is increased seemed to indicate that this metal could play a relevant role in the reaction outcome beyond regenerating the Rh-catalyst. In fact, when the structures of the regioisomers **IXA** and **IXB** were optimized incorporating CuCl(OAc) (Figure 4),^[24] the resulting complex **IXBCu** was

FULL PAPER

significantly less stable than **IXACu**. In principle, both complexes show a similar coordination mode of the copper atom with only one of the alkyne moieties. However, the orientation of the diyne unit does not allow an additional coordination with Cu in **IXBCu**, and the steric hindrance with the alkyne-Cu moiety provokes a stronger deformation of the diyne unit in the case of **IXBCu** than in the case of **IXACu**. The angle BCD decreases from **IXB** to **IXBCu** ($\Delta\alpha_{BCD} = 4.8^\circ$) whereas remains almost constant from **IXA** to **IXACu** ($\Delta\alpha_{BCD} = 0.1^\circ$).

From complexes **IXCu**, the insertion step would take place with a lower barrier for model **B** through **TS(IX-X)BCub** (12.4 and 11.3 kcal·mol⁻¹ in gas phase or 1,4-dioxane respectively) than for model **A** through **TS(IX-X)ACua** (15.9 and 16.1 kcal·mol⁻¹ in gas phase or 1,4-dioxane, respectively). Therefore, we could explain the favored regioselectivity towards the formation of the isoquinoline 1-carboxamide intermediate with the alkynyl substituents at vicinal. Following this pathway, the resulting complex **XBCub** would easily evolve through **TS(X-XI)BCub** to give **XIBCub**, featuring a 3-fold-coordinated copper ion set up by two π -bonded alkyne ligands and one acetate ion. The structure of this intermediate brings to light that, along with the reductive elimination process leading to the formation of the new C–C bond, an electron transfer between both metals through the chloride bridge ligand, might have taken place. The arrangement of Rh–Cl–Cu atoms in **TS(X-XI)BCub** (Rh–Cl: 2.60 Å, Cu–Cl: 2.31 Å, Rh–Cl–Cu: 99.4°) resembles that found by Funes-Ardoiz and Maseras in their recently reported DFT-based mechanistic studies on the cooperative role of Cu(OAc)₂ in the reductive elimination process of the rhodium-catalyzed oxidative coupling of benzoic acid and alkynes.^[24] Moreover, in the resulting **XIBCub**, the chloride ligand is almost completely transferred to the Rh-atom, that is eventually displaced towards the carbonyl group. Subsequent to this, complex **XIBCub** would easily evolve to **XIIBCub**. In this intermediate, both metals are coordinated to

the alkyne moiety, making the closest phenyl group more prone to further functionalization, presumably through an electrophilic aromatic substitution process.^[25] According to this, we could explain we had never detected the corresponding regioisomeric isoquinoline 1-carboxamide intermediate.^[26]

From this point on, the arene-alkyne cyclization would be initiated through **TS(XII-XIII)** (Figure 5, only roman numbers are kept for simplicity),^[27] leading to the Wheland-type intermediate **XIII**. This intermediate shows a bond between both metals (Rh–Cu: 2.60 Å) – a feature that seems to be the key for the subsequent cyclization. Then, coordination of an acetate ion to Rh promotes the displacement of the chloride ligand to Cu (**XIV**). Subsequent intramolecular deprotonation of the Wheland-type intermediate by Rh-coordinated acetate [**TS(XIV-XV)**] followed by release of HOAc would result into intermediate **XVI**, having the rhodium coordinated to the other alkyne unit. This intermediate would evolve through alkyne insertion into the Rh–Cu bond involving oxidation of both metals (see natural charges) and cleavage of the Rh–Cu bond (Rh–Cu: 2.89 Å) to afford intermediate **XVII**. In this intermediate, the Cu-atom has been displaced from the arene carbon by rhodium that is also coordinated to the alkyne moiety. A change in the coordination mode of both metals to the alkyne would afford **XVIII**, in which chloride ligand has been removed from the coordination sphere of metals but keeps small interactions with the Cp* ligand. Because of the departure of this ligand, the positive charges of both metals increase. Finally, a reductive elimination step through **TS(XVIII-XIX)**, that implies a decrease in the positive charge of both metals, would afford intermediate **XIX** with the polycyclic system and all the C–C bonds completed. Further studies are ongoing in our group to understand these redox processes as well as the following steps to reach the final product.

FULL PAPER

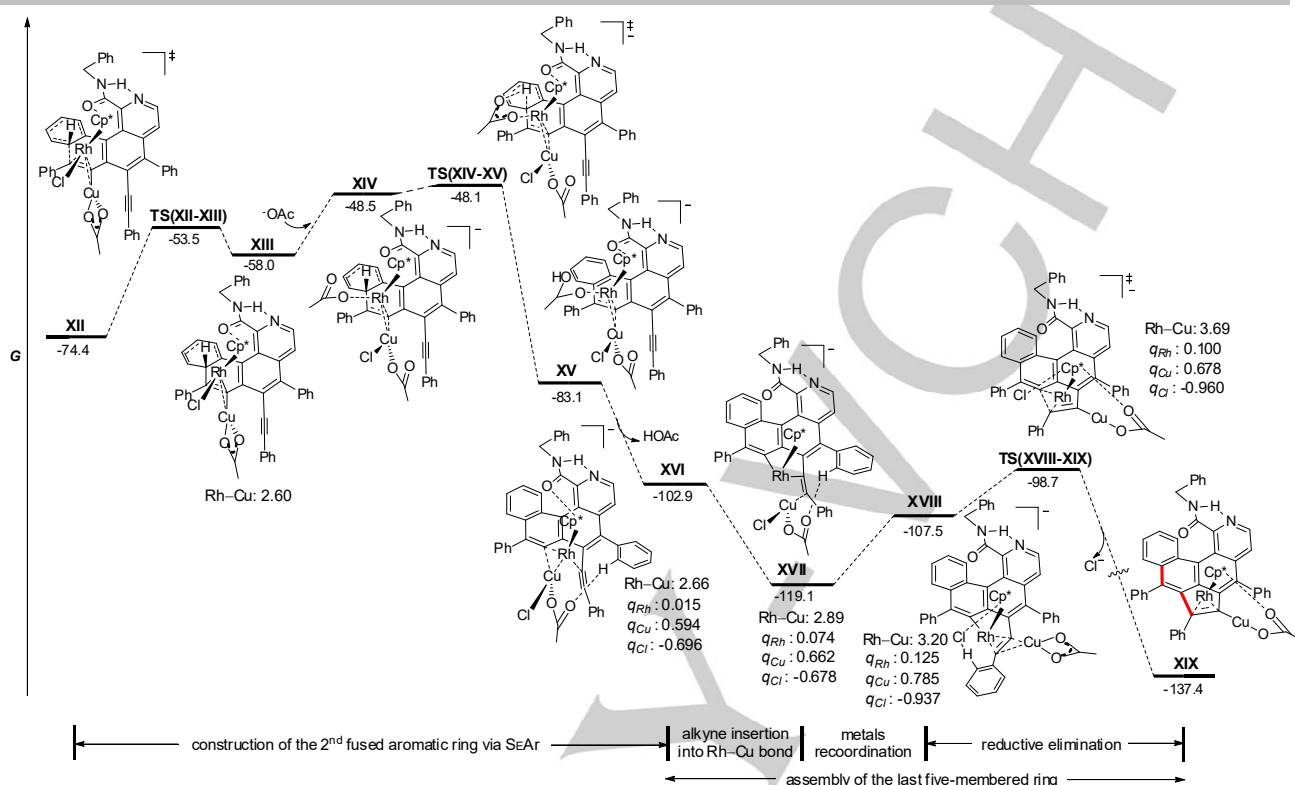


Figure 5. Energy profile for the final cyclization of intermediate **XII** in 1,4-dioxane (B97D/6-311++G(d,p)(C,H,N,O,Cl),LANL2TZ(f)(Rh,Cu)//6-31G(d)(C,H,N,O,Cl), LANL2DZ(Rh,Cu), SMD model). Relative G values in kcal·mol⁻¹ at 298 K. Hydrogen bonds between Cp* ligand and carbonyl group or chloride ligand are indicated with dashed bonds. Natural charges (q , in a.u.) and relevant distances Rh-Cu (Å) are also indicated.

Simplify plausible mechanistic pathways. A simplified general catalytic cycle for the formation of products **IQ** and **PCS** is shown in Scheme 6 based on our preliminary mechanistic investigation and the proposals put forth in the literature for annulative processes of (hetero)arenes with alkynes. Ligand exchange from [RhCp*Cl₂]₂ promoted by silver salt in the presence of an excess of acetate ions would form the presumed active catalyst [RhCp*X(OAc)] (**A**) (X = Cl or OAc). Then, displacement of an acetate or chloride from **A** by the picolinamide substrate would lead to intermediate **B**, which would undergo "rollover" cyclometalation^[28] to afford **C**. This process requires *N*-decomplexation and rotation around the carbonyl-Py bond followed by *ortho*-C-H bond activation, presumably by an acetate-assisted CMD pathway with loss of a second molecule of acetic acid. Intermediate **C** would evolve through alkyne coordination (**D**) and subsequent 1,2-migration of the rhodium-carbon bond across the alkyne, resulting in the formation of the seven-membered rhodacycle **E**, with the alkyne substituent regioselectively placed at the position closer to the rhodium atom. Protonation of the amide nitrogen of **E** by AcOH could trigger a second cyclometalation at C4 of the pyridine ring (via

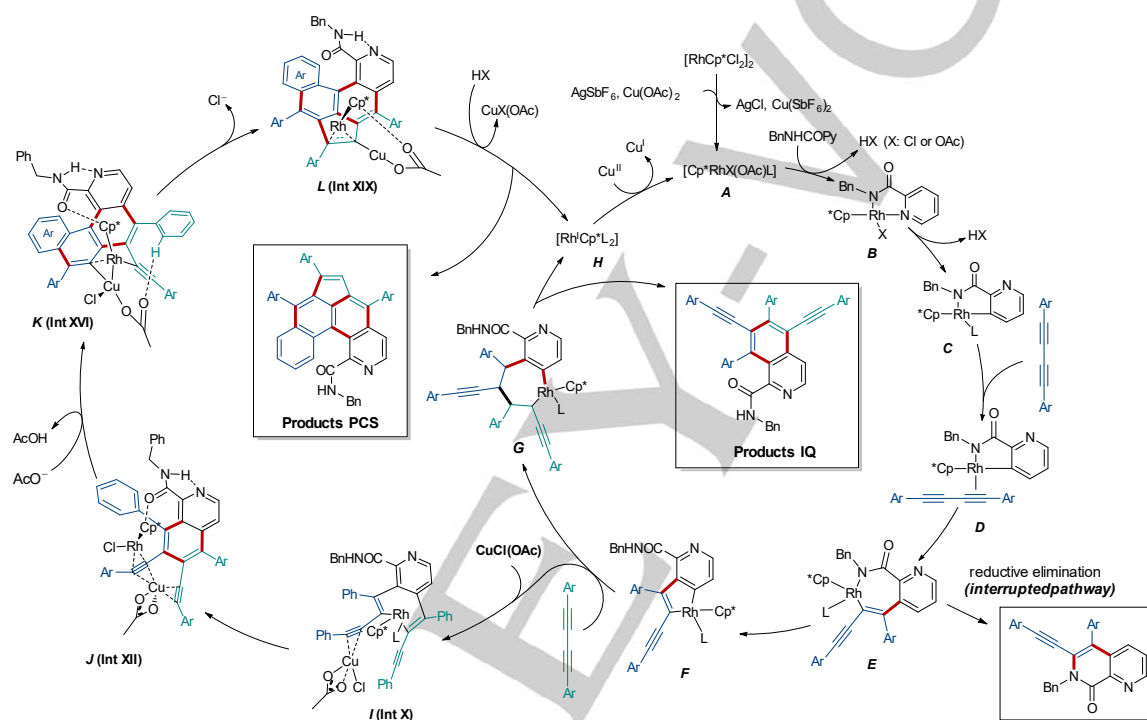
concerted CMD), leading to a more stable five-membered complex **F**. Alternatively, if cyclometalation from **E** is hampered (e.g., by steric crowding), reductive elimination becomes a more favorable pathway, leading to the mono-insertion product ("interrupted" pathway). From the key intermediate **F**, two alternative mechanisms can operate depending on the reaction conditions. Under standard conditions, the coordination of a second diyne molecule in an orientation favoring an alternate arrangement of aryl and alkynyl groups followed by regioselective migratory insertion of the alkene-Rh bond across the coordinated alkyne (with the alkyne substituent positioned closer to the rhodium atom) would lead to **G**. Finally, a reductive elimination step releases the alkynyl-substituted isoquinoline product (**IQ**) with concomitant oxidation of the formed Rh^I species (**H**) by Cu^{II} to regenerate the Cp*Rh^{III} catalyst.

In the presence of increased amounts of Cu^{II} salt, an alternative reaction pathway from complex **F** involving Rh-Cu bimetallic complexes tends to predominate. In this case, coordination of the Cu to the alkyne moiety of **F** introduces steric interactions with the incoming diyne unit that makes more favorable an approach in which the two-alkyne moieties are

FULL PAPER

projected facing each other. In this orientation, insertion of the C4(Py)-Rh bond across the triple bond is favored over insertion of the alkene-Rh bond (again the alkyne substituent ends up closer to the rhodium atom), thereby furnishing complex **I** (intermediate **X** in Figure 4). This vicinal arrangement of the alkynes favors a reductive elimination involving electron transfer between both metals, to afford complex **J** (intermediate **XII** in Figure 4) in which the copper ion is π -coordinated to the two alkynes and the rhodium ion is π -bonded to one of the alkyne groups. Next, the alkyne moiety that is coordinated to both

metals would promote cyclization with the proximal phenyl ring through electrophilic aromatic substitution, leading to complex **K** (intermediate **XVI** in Figure 5), which has the rhodium coordinated to the other alkyne unit. Intermediate **K** would evolve through alkyne insertion into the Rh-Cu bond to afford complex **L** (intermediate **XIX** in Figure 5). This complex would undergo protodemetalation promoted by HX (X = Cl or OAc) to afford the pentacyclic system (**PCS**), along with Rh^I (**H**) species and CuX(OAc). Cu^{II} would further oxidize the Rh^I species to Rh^{III}, thus closing the cycle.



Scheme 6. Simplified catalytic cycle for the rhodium-catalyzed intermolecular C-H annulation of 1,3-diynes with picolinamides.

FULL PAPER

Conclusions

In conclusion, the Rh-catalyzed oxidative annulation of picolinamide derivatives with diaryl 1,3-diynes can be directed to the formation of either isoquinoline 1-carboxamides incorporating alkyne handles or structurally complex polycyclic extended π -systems by modifying the catalyst system and reaction conditions. The latter pathway represents a new reactivity pattern involving a double C–H bond activation and iterative annulation of two units of 1,3-diyne, resulting in the formation of five new C–C bonds and construction of four fused rings in a single operation. DFT mechanistic studies have provided understanding of the factors that govern the regioselectivity in the 1,2-migratory insertion of the first unit diyne as well as the origin of the divergent regiochemical outcome in the second diyne insertion. Importantly, a cooperative participation of copper, favored under an excess amount of copper(II) salt, facilitates reversal of the regioselectivity in the second diyne insertion and plays an important role in assisting orchestrated alkyne insertion processes and rhodium displacement throughout the heterocyclic framework, thereby enabling distant activation and sequential construction of multiple ring systems. We believe that this work could inspire the development of other novel metal-catalyzed annulations of 1,3-diynes toward more complex systems, as well as contribute to the understanding of cooperative participation of copper in rhodium-catalyzed multiple annulation processes.

Experimental Section

General methods. The corresponding starting materials were synthesized using oven-dried glassware under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum. All reactions were performed under argon atmosphere in oven-dried 10 mL vessels equipped with a Teflon-coated stirrer bar and sealed with a cap designed to vent and re-seal in the case of overpressure during reaction. Solvents were purified by standard procedures prior to use. All other compounds are commercially available and were used without further purification. Flash column chromatography was performed using 230–400 mesh ultra-pure silica gel. Mass spectral data were acquired on a VG AutoSpec mass spectrometer.

Synthesis of *N*-benzyl-6,8-diphenyl-5,7-bis(phenylethynyl)-isoquinoline-1-carboxamide (2). An oven-dried, argon-flushed 20.0 mL vessel was charged with *N*-benzylpicolinamide (1) (31.8 mg, 0.15 mmol, 1.00 equiv), [RhCp*Cl₂]₂ (4.64 mg, 0.0075 mmol, 5 mol %), Cu(OAc)₂ (54.5 mg, 0.30 mmol, 2.00 equiv) and AgSbF₆ (10.3 mg, 0.03 mmol, 20 mol %). Under argon atmosphere the solvent DCE (1.00 mL) and the 1,4-diphenylbuta-1,3-diyne (I) (90.9 mg, 0.45 mmol, 3.00 equiv) were added *via* syringe and the resulting mixture was stirred at 120 °C for 12 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (Cy/DCM/EtOAc, 8:1:1), yielding **2** as a pale orange solid; yield: 90.3 mg (98%). ¹H NMR (Chloroform-d, 300 MHz, δ): 8.56 (d, *J* = 5.6 Hz, 1H), 8.42 (d, *J* = 5.6 Hz, 1H), 7.70–7.62 (m, 2H), 7.60–7.41 (m, 6H), 7.36–7.26 (m, 10H), 7.21–7.12 (m, 4H), 6.94 (d, *J* = 4.6 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 2H), 6.49 (t, *J* = 4.9 Hz, 1H), 4.01 (d, *J* = 5.0 Hz, 2H). ¹³C NMR (Chloroform-d, 75 MHz, δ): 167.3, 155.3, 148.5, 142.8, 142.1, 139.5, 139.3, 137.4, 131.7, 131.6, 131.4, 131.3, 130.3, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.7, 127.6, 127.3, 125.0, 124.0, 122.9, 122.9, 121.1, 119.6, 99.8, 99.4, 88.4, 85.7, 44.1. HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₄₅H₃₁N₂O: 615.2431; Found: 615.2435.

Synthesis of *N*-benzyl-10-methyl-5,7,8-tri-*p*-tolylbenzo[5,6]indeno[1,7-*gh*]isoquinoline-1-carboxamide (24). An oven-dried, argon-flushed 20.0 mL vessel was charged with *N*-benzylpicolinamide (1) (31.8 mg, 0.15 mmol, 1.00 equiv), [RhCp*Cl₂]₂ (18.6 mg, 0.03 mmol, 20 mol %), Cu(OAc)₂ (109 mg, 0.60 mmol, 4.00 equiv) and AgSbF₆ (20.6 mg, 0.06 mmol, 40 mol %). Under argon atmosphere 1,4-dioxane (1.00 mL) and 1,4-di-*p*-tolylbuta-1,3-diyne (II) (75.9 mg, 0.33 mmol, 2.200 equiv) were added *via* syringe and the resulting mixture was stirred at 130 °C for 3 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (Cy/DCM/EtOAc 8:1:1), yielding **24** as a yellow solid; yield: 62.3 mg (62%). ¹H NMR (Chloroform-d, 300 MHz, δ): 8.48 (d, *J* = 5.4 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 7.90 (d, *J* = 5.4 Hz, 1H), 7.67 (s, 1H), 7.46–7.32 (m, 10H), 7.17 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.83–6.71 (m, 4H), 4.61 (d, *J* = 4.3 Hz, 2H), 2.49 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H). ¹³C NMR (Chloroform-d, 75 MHz, δ): 167.3, 151.8, 150.9, 140.8, 140.3, 140.0, 139.4, 138.6, 137.9, 137.0, 136.0, 135.8, 134.4, 133.9, 133.8, 133.6, 131.9, 131.4, 131.1, 131.0, 129.3, 129.0, 128.8, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 122.3, 122.0, 121.4, 44.1, 21.8, 21.4, 21.2, 21.2. HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₄₉H₃₉N₂O: 671.3057; Found: 671.3050.

Acknowledgements

We thank the Spanish Ministerio de Economía, Industria y Competitividad (MINECO, Grants CTQ2012-35790 and CTQ2015-66954-P, MINECO/FEDER, UE) for financial support. N.R. thanks the MICINN for a Ramón y Cajal contract and the European Commission for a Marie Curie Career Integration Grant (CIG: CHAAS-304085). The Centro de Computación Científica (UAM) is acknowledged for generous allocation of computer time. We also thank Dr J. Lloret for helpful discussions.

Keywords: Cascade C–H annulation • 1,3-diynes • rhodium • isoquinoline • π -extended systems

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- [20] Attempts to utilize dialkyl 1,3-diynes failed (see SI).
- [21] The introduction of a CF₃ group at the C5 position of the pyridine ring gives rise to the formation of hydrogen bonds between a F atom and the closest C-H bond of the diyne Ph group in the case of **IV'**(CF₃) and **TS(IV'-V')**(CF₃) (F-H distances: 2.42 and 2.47 Å respectively). These interactions decrease the barrier differences from 2.3 (in Figure 1) to 1.1 kcalmol⁻¹, in the gas phase, and could be at the origin of the lack of selectivity observed in the preparation of products **21** (see SI).
- [22] No significant steric interactions are observed in the structure of **TS(VII-VIII)**, whereas a H-bond between both N atoms provides an important stabilization. These structural features agree with the fact that the second C-H functionalization always takes place unless certain groups close to the reaction center hamper it ("interrupted annulation" in Scheme 4).
- [23] For a complete energy profile of this step see SI.
- [24] Since a scarce effect of silver salts was observed, a chlorine atom was kept in the copper salt employed as a model to assess the possible interaction between Rh and Cu through a chlorine bridge in any of the

FULL PAPER

following steps. These types of interactions had been proposed in the bibliography: a) I. Funes-Ardoiz, F. Maseras, *Angew. Chem.* **2016**, *128*, 2814; *Angew. Chem. Int. Ed.* **2016**, *55*, 2764. In this precedent, the effect of copper salts was also evaluated in the C–H activation and insertion steps in which a decrease in the barrier was obtained. This effect cannot be ruled out in our case. The cooperation of rhodium and copper throughout the oxidative coupling mechanism between benzoic acid and alkynes has also been proposed recently by the same authors: b) I. Funes-Ardoiz, F. Maseras, *Chem. Eur. J.* **2018**, *24*, 12383. For rhodium(III)/copper(II)-mediated heteroaryl acyloxylation of alkynes that is proposed to occur via migratory insertion of alkyne and subsequent transmetalation to copper(II), see: c) M. V. Pham, N. Cramer, *Angew. Chem.* **2014**, *126*, 14803; *Angew. Chem. Int. Ed.* **2014**, *53*, 14575.

- [25] This electrophilic cyclization was also considered in previous steps (**TSIXBSEAr**, **TSIXASEAr**, **TSXBSEAr**) being less favorable than the formation of the isoquinoline skeleton. For a complete energy profile of this step, see SI.
- [26] Other possibilities for the cyclization with only Rh were also explored. However, they were more energy demanding and afforded a five-membered cycle, instead of a six one, what ruled out these proposals (see SI) reinforcing the hypothesis of the participation of both metals, Rh and Cu, during the cyclization process.
- [27] Taking into account the importance of dispersion forces in the system, we decided to change the functional (B97D instead of B3LYP) and to include the solvent in the optimization of all structures involved in the following steps. Although comparable in energy relative to **mod 1**, complex **XII** showed a slight shortening of distances C–M and a preferred conformation with the benzyl group in a parallel arrangement to the polycyclic aromatic moiety. This conformational stabilization could be at the origin of the better results obtained with the N-Bn group.
- [28] For a review on “rollover” cyclometalation, see: B. Butschke, H. Schwarz, *Chem. Sci.* **2012**, *3*, 308.

FULL PAPER

Entry for the Table of Contents

FULL PAPER

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Page No. – Page No.

**Rhodium-Catalyzed Copper-Assisted
Intermolecular Domino C–H
Annulation of 1,3-Diynes with
Picolinamides: Access to Pentacyclic
 π -Extended Systems**

