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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-diyn, 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 [Cp*RhIII]-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 RhIII 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.

[Scheme 1](a) 1,3-Diynes in Rh-catalyzed cascade C–H annulation

[Scheme 1](b) Alkyynes in Rh-catalyzed cascade C–H annulation

[Scheme 1](c) 1,3-Diynes in Rh-catalyzed intermolecular C–H annulation

[Scheme 1](d) Asymmetric 1,3-Diynes in Rh-catalyzed intermolecular C–H annulation

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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, Gloria demonstrated the Rh\[^{III}\]-catalyzed diannulation of benzamides with 1,3-diynes, thus leading to bis(heterocycles) (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 \(6\text{-endo-dig}\) cyclization of properly designed diaryl-1,3-buta-1,3-diyne in the presence of InCl\(_3\)-AgNTf\(_2\) as catalyst (Scheme 2A). We envisaged that an intermolecular cascade C–H benzannulation of 1,3-diynes would be feasible under [Cp*Rh\(^{III}\)]\(^{\cdot}\)-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, 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 diphenyl-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\[16a,16b\] the model reaction of diphenyl-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 alkyaryl alkyynes, which favors an orientation of the aromatic substituents at vicinal 2,3-position.\[16a,b,16\] 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.\[19\]
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%) 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 (R² = H, not shown).

Interestingly, the presence of a CF₃ group at the C5 position of the pyridine ring interrupted the aromatic homologation and led exclusively to the 1,7-naphthyridine-8(7H)-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 amideic N–H.

Table 1. Optimization studies toward fused pentacyclic structures (PCS).
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 \( p \)-(CF\(_3\))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.

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 being 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.
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, a RhIII-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). 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). 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.

From this point, instead of evolving through reductive elimination leading to a naphthylidine 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 VII through a second CMD (TS(VII-VIII)). After displacement of AcOH by the second unit of diyne, two similarly stable regioisomeric complexes might form: IXA.
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 dyne 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. 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 dyne. 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 Cu²⁺ salts in the gas phase (M06/6-311+G(d,p)/(C,H,N,O,Cl), LANL2TZ(Cu,Rh)/BSLYP/6-31G(d)) and 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 dyne. The experimental observation that polycyclic products (PCS) are favored when the amount of Cu²⁺ 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), the resulting complex IXBCu was
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 aren–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 alkynyl 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 alkynyl moiety. A change in the coordination mode of both metals to the alkynyl ligand would afford XVIII, in which chloride ligand has been transferred 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.

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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*Cl]₂, promoted by silver salt in the presence of an excess of acetic acid. Intermediate acetate-assisted CMD pathway with loss of a second molecule decomplexation and rotation around the carbonyl–Py bond cyclometalation lead to intermediate acetate or chloride from acetate ions would form the presumed active catalyst [RhCp*Cl₂]₂. Clearly, this process requires 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 alkene (with the alkynyl 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 Rh³ species H by Cu⁴⁺ to regenerate the Cp²Rh catalyst.

In the presence of increased amounts of CuCl 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 alkynyl moiety of F introduces steric interactions with the incoming diyne unit that makes more favorable an approach in which the two-alkynyl moieties are
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 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) species and CuX(OAc). CuII 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.
Conclusions

In conclusion, the Rh-catalyzed oxidative annulation of picolinamide derivatives with diaryl 1,3-dienes 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-diene, 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-dienes 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 Teflon-coated stirrer bar and dry septum. All reactions were performed using oven-dried glassware under an argon atmosphere containing 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 Teflon-coated stirrer bar and dry septum. All reactions were performed using oven-dried glassware under an argon atmosphere containing 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 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

Synthesis of N-benzyl-6,8-diphenyl-7,7-bis(phenylethylnyl)isoquinoline-1-carboxamide (2). An oven-dried, argon-flushed 20.0 mL vessel was charged with N-benzylpicolinamide (1) (51.8 mg, 0.15 mmol, 1.00 equiv), [RhCl\(\text{Cp}^*\)]_2 (8.44 mg, 0.03 mmol, 20 mol %), Cu(OAc)_2 (109 mg, 0.60 mmol, 4.00 equiv) and AgSBF_6 (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-diene (II) (75.9 mg, 0.33 mmol, 2.20 equiv) were added via syringe and the resulting mixture was stirred at 130 °C for 3 h. After the reacion 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 yellow solid; yield: 62.3 mg (62%).

1H NMR (Chloroform-d, 300 MHz, 6): 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 (d, J = 8.5 Hz, 1H), 6.83 – 6.71 (m, 4H), 6.41 (d, J = 4.3 Hz, 2H), 2.49 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H), 1.20 (s, 6H).

13C NMR (Chloroform-d, 75 MHz, 6): 176.3, 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, 128.6, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.5, 127.2, 120.0, 121.4, 4.41, 21.8, 21.4, 21.2, 21.2. HRMS – ESI (m/z): [M + H]^+ calcd for C_{37}H_{33}N_{2}O: 671.2305; Found: 671.2300.

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


CCDC 1857910 (for 2); 1857911 (for 3); 1857912 (for 4) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Attempts to utilize dialkyl 1,3-dienes failed (see SI). 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(V–IV')(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 due to the origin of the lack of selectivity observed in the preparation of products 21 (see SI). No significant steric interactions are observed in the structure of TS(VI–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 annihilation’ in Scheme 4).

For a complete energy profile of this step see SI.

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
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.

A Rh-catalyzed Cu-assisted method for the intermolecular annulation of picolinamides with two molecules of diaryl-1,3-diynes is described. The four alkyne units participate in an orchestrated sequence of insertions/annulations, thereby enabling the assembly of up to four fused rings in a single step through double C–H bond activation and construction of five C–C bonds.