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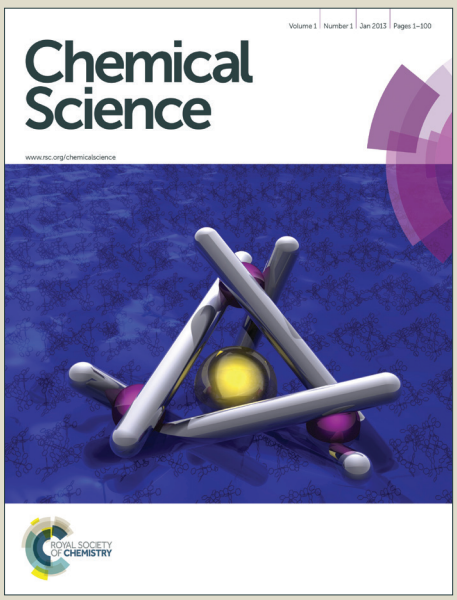

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Rh^{I}/Rh^{III} Catalyst-Controlled Divergent Aryl/Heteroaryl C–H Bond Functionalization of Picolinamides with Alkynes

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The ability to establish switchable site-selectivity through catalyst control in the direct functionalization of molecules that contain distinct C–H bonds remains a demanding challenge as it would enable the construction of diverse scaffolds from the same starting materials. Herein we describe the realization of this goal, namely a divergent heteroaryl/aryl C–H functionalization of aromatic picolinamide derivatives, targeting two distinct C–H sites, either at the pyridine ring or at the arene unit, to afford isoquinoline or *ortho*-olefinated benzylamine (or phenethylamine) derivatives. This complementary reactivity has been achieved on the basis of a Rh^{III}/Rh^{I} switch of the catalyst, resulting in different mechanistic outcomes. Notably, a series of experimental and DFT mechanistic studies reveal important insights about the mechanism of the reaction and reasons behind the divergent regiochemical outcome.

Introduction

The great potential of metal-catalyzed C–H bond functionalization to streamline synthetic schemes has been illustrated with many elegant methods featuring exquisite and predictable site-selectivity in the presence of multiple reactive C–H bonds.[1] However, despite the fast-paced development of this field, the discovery of procedures capable of divergent functionalization at distinct C–H sites through catalyst control is relatively uncommon,[2] yet highly appealing. In particular, achieving distinctive positional reactivities by simply varying the ligand environment and oxidation state of the catalytically active metal species could provide a unique opportunity for construction of diverse scaffolds from the same starting materials.

Rh-catalyzed coupling reactions of alkynes that involve C–H cyclometalation/annulation of (hetero)arenes provides an atom- and step-economical route to heterocycles, ubiquitous structural elements in nature, medicinal chemistry and material science.[3-7] Also, the use of alkynes as coupling partners allows access to aromatic compounds with a pendant *ortho*-vinyl group,[6] that could serve as versatile synthetic handle. In both contexts, rhodium(III)-catalysts, most often introduced as $Cp^*Rh^{III}L_n$ precursors in combination with the classical Cu^{I}/Cu^{II} redox couple, have proven to be particularly useful.[3-5] However, in contrast to the tremendous strides made with functionalized arenes,[3-6] there are few methods for Rh^{III}-catalyzed C–H activation of electron-deficient aza-heterocycles containing a basic nitrogen such as pyridine.[7] This deficiency is somewhat surprising given that nitrogen-containing heterocyclic compounds are privileged structures of medicinal chemistry.

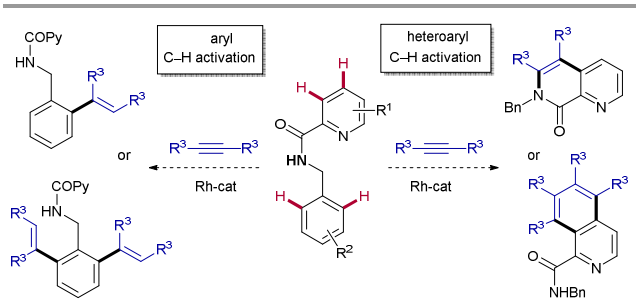

Figure 1. Proposed catalyst-controlled divergent aryl/heteroaryl C–H functionalization.

We envisaged that *N*-benzyl-2-picolinamides would provide an opportunity for developing a divergent C–H functionalization procedure targeting selectively either the pyridyl unit or the benzyl moiety. Our plan is outlined in Figure 1. There are several challenges behind the choice of this substrate. Firstly, the aminocarbonyl group at C2 might strengthen the interaction between the pyridinic nitrogen and the metal through a bidentate coordination, thereby preventing the catalyst from interacting with the target pyridinic C–H bond.[8] In fact, the picolinamide (COPy) has been extensively used as directing group in a variety of $C(sp^2)$– and $C(sp^3)$–H functionalization reactions.[9] In contrast, there have been only isolated examples of successful derivatization at the pyridine ring,[10] thus highlighting the challenging nature of this task. Recently, the groups of Shi[11] and our own[8] managed to overcome this difficulty and reported the Rh^{III}-catalyzed *ortho*-olefination/annulation of picolinamides with electron-deficient olefins. Secondly, the benzylamine unit embedded in the substrate is prone to dehydrogenation at the benzylic position under the oxidative Rh/Cu^{II} system, potentially leading to imine-type intermediates.[12a,b] The scarcity of precedents on functionalization of benzylamine derivatives[12] compared to the variety of methods available for benzoic acid derivatives[3] points toward a challenging transformation.

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: Experimental and computational details as well as spectroscopic and analytical data for new compounds. See DOI: 10.1039/x0xx00000x

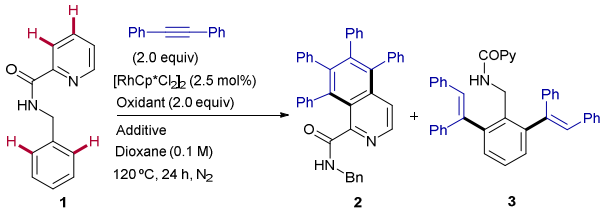
We herein describe a catalyst-controlled divergent heteroaryl/aryl functionalization of picolinamide derivatives that provides selective straightforward access to either isoquinoline-1-carboxamide or *ortho*-olefinated benzylamine (or phenethylamine) derivatives. This complementary reactivity has been achieved by simply choosing between either a Rh^{III} or a Rh^{I} catalysts.[2] To our knowledge, a Rh^{I}/Rh^{III} divergent control in C–H activation on the same substrate remains undocumented.

Results and Discussion

Optimization studies. The model reaction between the *N*-benzylpicolinamide (**1**) and diphenylacetylene was chosen for optimization studies (Table 1). A low but promising outcome was obtained with $[RhCp^*Cl_2]_2$ (2.5 mol %) in conjunction with $Cu(OAc)_2$ (2 equiv), providing a 1:3.7 mixture of the isoquinoline-1-carboxamide derivative **2**[13] and the di-olefinated benzylamine derivative **3**,[13] both resulting from two C–H activations and two alkyne insertions at the pyridyl or the benzene units (entry 1). Replacement of $Cu(OAc)_2$ with $Cu(TFA)_2$ led to suppression of the catalytic activity, likely due to the lower basicity of trifluoroacetate compared to acetate (entry 2). In fact, the addition of 4 equiv of NaOAc to the Rh/$Cu(TFA)_2$ system restored the catalytic activity (entry 3), suggesting the oxidant is a source of acetate necessary for the reaction to proceed. Further investigation (see SI), led us to find that the addition of $AgSbF_6$ (10 mol %) to sequester the chloride ligands remarkably improved both reactivity and site selectivity, allowing a clean and complete conversion of **1** into isoquinoline **2** as single coupling product (entry 4). Control experiments determined that product formation is completely inhibited in the absence of Rh catalyst (entry 5) or with the omission of copper salt, even when using O_2 as external co-oxidant (entry 6). Interestingly, however, the reactivity was partially restored leading selectively to the di-olefinated product **3**, albeit with moderate yield, without the Cu^{II} salt but in the presence of NaOAc (entry 7). These optimization studies evidenced the critical role played by both $Cu(OAc)_2$, as both oxidant and carboxylate source, and $AgSbF_6$, responsible for promoting ligand exchange at Rh, in determining the catalyst activity and selectivity towards formation of isoquinoline **2**.

Rh^{III}-catalyzed pyridyl C–H functionalization: synthesis of isoquinoline derivatives. The scope of this aromatic homologation method allows for the construction of variously substituted polyarylated isoquinoline derivatives (Scheme 1). It is important to note that the isoquinoline moiety forms the core of many biologically active molecules.[14] In this study microwave heating was generally applied since it dramatically reduced reaction times (from 24 h to just 1 h) while preserving high site-selectivity, as exemplified in the isolation of **2** in 90% yield. Both electron-donating and electron-withdrawing substituents at either the pyridine (**14-15**, 54-62%) or the diarylacetylene[15] (**11-12**, 61% and 63%) coupling partners were well tolerated. It is also remarkable that the Cl substituent survived the reaction conditions (**15**, 62%). The use of substituents on the amide nitrogen different than a benzyl group was also tolerated, as demonstrated by the good reactivity displayed by the substrate bearing an ethyl substituent (R = Et), which provided the corresponding isoquinoline derivative **13** in 85% yield.

Table 1. Optimization studies in the reaction of **1** with diphenylacetylene.[a]



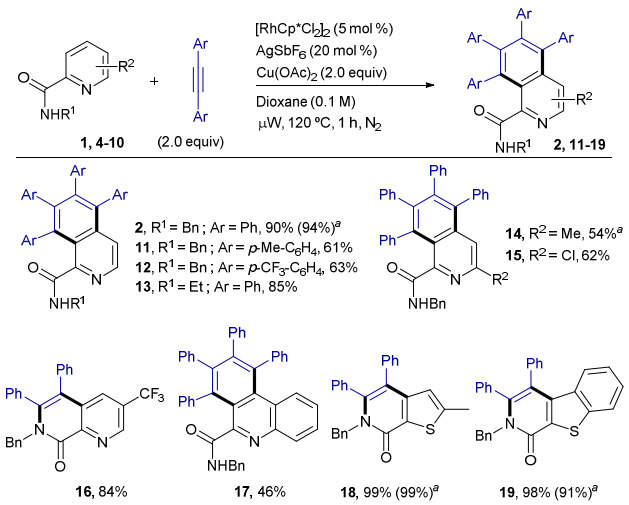
Entry	Oxidant	Additive	Conversion (%)[b]	**2**/**3** (%)[c]
1	$Cu(OAc)_2$	–	47	21/79
2	$Cu(TFA)_2$	–	–	– / –
3	$Cu(TFA)_2$	NaOAc[d]	66	44/56
4	$Cu(OAc)_2$	$AgSbF_6$[e]	>98	>98/<2
5[f]	$Cu(OAc)_2$	$AgSbF_6$[e]	–	– / –
6[g]	–	$AgSbF_6$[e]	–	– / –
7	–	NaOAc[d]/ $AgSbF_6$[e]	46	<2/>98

[a] **1** (0.15 mmol), alkyne (0.30 mmol), [Rh^{III}]-cat. (5 mol%), oxidant (2.0 equiv), dioxane (0.1 M), 120 °C, 24 h. [b] Determined by ^1H NMR from the crude mixture. [c] [Rh^{III}]-cat. (10 mol%) [d] 4.0 equiv. [e] 10 mol%. [f] Without Rh-catalyst. [g] Under O_2.

Interestingly, the presence of a CF_3 group at the C5 of the pyridine ring, residing in close proximity to one of the reactive C–H bonds, interrupted the aromatic homologation and led exclusively to the 1,7-naphthyridin-8(7H)-one derivative **16**[13] (84% yield), resulting from a double C–H/N–H activation[2c] and only one alkyne insertion. Although factors affecting these reactivity differences remain to be elucidated, this result suggests that the second alkyne insertion/C–H activation is sensitive to steric effects, so that the presence of a substituent in the aryl *ortho*-position to the reactive C–H site may impart a significant steric demand, thereby bypassing the normal reaction outcome and favouring the competitive trapping of the plausible alkenyl rhodium intermediate by the amidic N–H. Extension of this reaction to heteroaryl 2-carboxamides with quinoline, thiophene or benzo[*b*]thiophene skeletons proved successful, but whereas the first substrate evolved to give the expected aromatic homologation product in moderate yield (**17**, 46%), in the other two cases the reaction proceeded through the "interrupted" pathway, leading to the C–H/N–H cyclization products **18**[13] and **19** in excellent yields (98-99%).

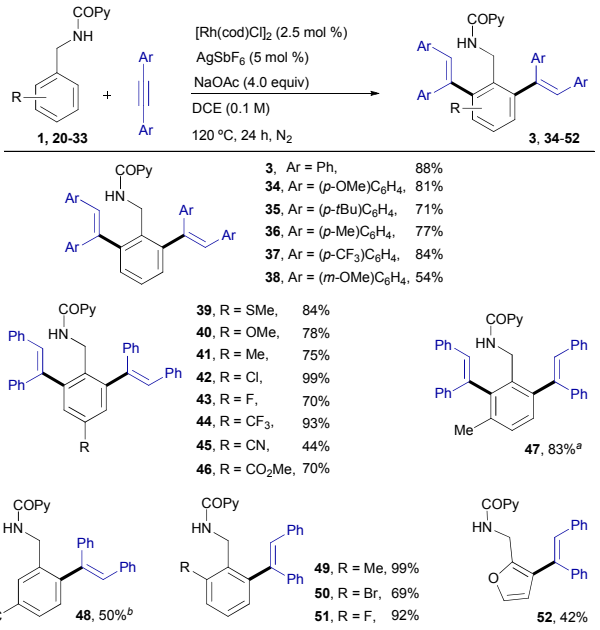
Rh^{I}-catalyzed C–H *ortho*-olefination at the benzylamine unit. Our desired goal of developing a divergent C–H functionalization protocol guided us to revisit the low-yielding but encouraging selective formation of the di-olefinated benzylamine **3** observed in the reaction of **1** with diphenylacetylene in the absence of $Cu(OAc)_2$ but using

NaOAc as acetate ion source (see Table 1, entry 7, 46% NMR conversion). We reasoned that in the absence of the Cu^{II}-terminal oxidant Rh^{I} species,[16] rather than Rh^{III}, could be a competent catalyst leading to the di-*ortho*-olefination product through a distinct mechanistic pathway. To our delight, this was indeed the case and the desired product **3** was obtained in 88% yield when using $[Rh(cod)Cl]_2$[17] (2.5 mol %) under conditions very similar to those in entry 7 of Table 1 (Scheme 2).



Scheme 1. Rh^{III}-catalyzed pyridyl C–H functionalization leading to isoquinoline derivatives. Conditions: benzylamine derivative (0.15 mmol), alkyne (0.30 mmol), $[Rh^{III}]$-cat. (5 mol%), $Cu(OAc)_2$ (2.0 equiv), dioxane (0.1 M), μW, 120 °C, 1 h. [a] Under conventional heating at 120 °C for 24 h.

As shown in Scheme 2, *N*-benzylpicolinamide **1** smoothly reacted with a variety of diarylacetylenes[15] equipped with both electron-rich and electron-poor *para*-substituted aryl groups, to give the corresponding di-olefinated benzylamine derivatives in good yield (**34-37**, 71-84%). *meta*-Substitution at the diaryl acetylene is also possible, albeit with lower efficiency (**38**, 54%), while no reaction was observed with the sterically more hindered *ortho*-substituted diaryl acetylenes (not shown).[18] A broad range of *para*-, *ortho*- and *meta*-substituents at the benzylamine unit with very different electronic properties proved to be suitable substrates (**39-51**, 44-99% yield). The functional-group compatibility is remarkable, including coordinating functionalities (CN or SMe), and halogens (Cl and, especially, the challenging Br). A *meta*-Me substituent led to the di-olefinated product in good yield (**47**, 83% yield), while a *meta*-CF_3 resulted mainly in mono-olefination at the sterically less hindered *ortho*-position (**48**, 50% yield). *ortho*-Substitution, which often result in reduced reactivity due to steric reasons, was well tolerated (**49-51**, 69-99%). Likewise, the successful use of a heteroaromatic substrate turned out to be viable, yet in lower yield (furanyl derivative **52**, 42%).



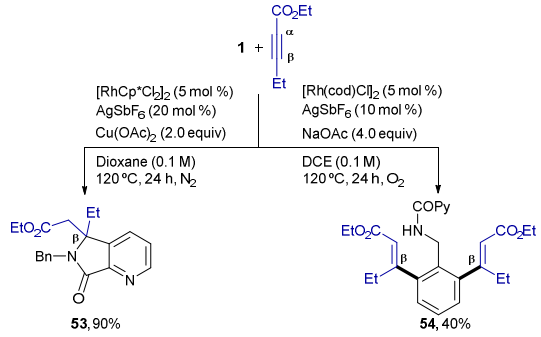
Scheme 2. Rh^{I}-catalyzed *ortho*-olefination of benzylamine derivatives. [a] The mono-*ortho*-olefinated product was also isolated in 8% yield. [b] The di-olefinated product was also isolated in 6% yield.

Exploration of unsymmetrical alkyl-substituted internal alkynes. We next explored unsymmetrical alkynes, for which regiocontrol in the insertion step becomes an issue of concern. Unsymmetrical aliphatic-substituted internal alkynes are a more challenging type of substrates due to their diminished reactivity and poor regioselectivity in the 1,2-migratory insertion often observed in the context of rhodium-catalyzed C–H functionalization.[4f] Interestingly, it was found that β-alkyl acetylenic esters did participate in the pyridyl/phenyl divergent C–H functionalization with excellent selectivity, albeit with a different reaction outcome than diarylalkynes (Scheme 3). For instance, the reaction of **1** with ethyl pent-2-ynoate under the Rh^{III}-catalyzed conditions (i.e., the isoquinoline formation conditions) led to *ortho*-functionalization at the pyridine ring but it did not yield the corresponding isoquinoline. Instead, the 5,5-fused bicyclic ester **53**, with a valuable 6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridine architecture holding a quaternary carbon center, was obtained as the sole reaction product in good yield (90%). This compound seems to arise from a competitive evolution of the alkyne insertion complex that prevents second alkyne insertion/C–H activation. On the other hand, this result demonstrates that the reaction outcome can be significantly influenced by changes in the alkyne substitution. However, when the same two reacting partners (**1** + ethyl 2-pentynoate) were submitted to the Rh^{I}-catalyzed conditions, a clean formation of the di-olefinated benzylamine derivative **54** was observed, yet in modest yield (40%). In the latter case, the reaction was found to be accelerated under aerobic conditions (air or balloon of O_2). Remarkably, both Rh^{III} and Rh^{I} C–H functionalization processes led to products with complete

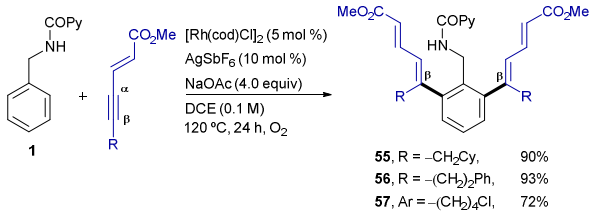
regioselectivity regarding the alkyne insertion (in both cases at the β-position of the ethyl 2-pentynoate).

The use of enynes as another type of non-aromatic alkyne coupling partners with an electronic bias for highly regioselective insertion, elegantly introduced by Huestis and co-workers in the context of C–H functionalization,[4q] led us to easily prepare di-*ortho*-dienyl benzylamine derivatives in good yields (products **55-57**, 72-93% yield, Scheme 4). This reaction revealed the tolerance of this catalyst system towards a sensitive alkyl chloride substituent (**57**, 73% yield). As occurred in the case of acetylenic esters, higher reaction rates were observed under aerobic conditions and in all cases studied the conjugated moiety attached to the alkyne ends up at the vinylic position away from the phenyl ring with complete regiocontrol.

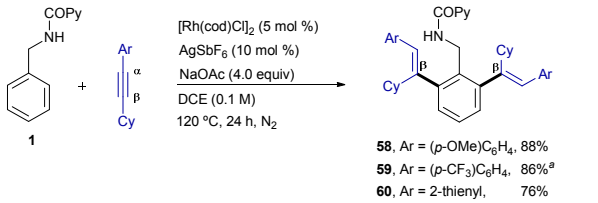
Finally, as shown in Scheme 5, some unsymmetrical alkyl-aryl-alkynes such as cyclohexyl-aryl-acetylenes did also participate in the Rh^{I}-catalyzed cross-coupling reaction, affording the desired di-olefinated products as single regioisomers and stereoisomers (products **58-60**, 76-88%) showing that, as in the previous examples, there is a complete regiocontrol in favour of the functionalization at the β-position of the starting conjugated alkyne. In contrast, very poor conversion was observed with oct-1-yn-1-ylbenzene while internal dialkyl-alkynes such as 2-butyne resulted in total lack of reactivity (not shown).



Scheme 3. Rhodium-controlled divergent aryl/heteroaryl C–H functionalization in the reaction of **1** with ethyl pent-2-ynoate.

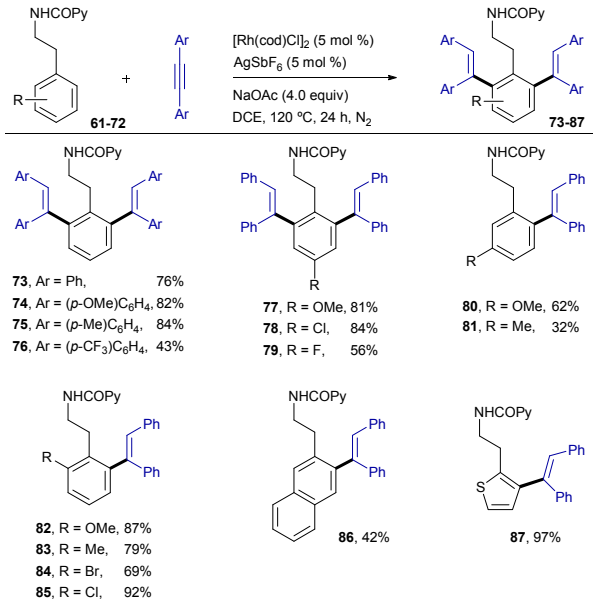


Scheme 4. Rh^{I}-catalyzed *ortho*-olefination of **1** with 1,3-enynes.



Scheme 5. Rh^{I}-catalyzed *ortho*-olefination of **1** with aryl-cyclohexyl-acetylenes. [a] Using 10 mol% $[Rh(cod)Cl]_2$ and 20 mol% of $AgSbF_6$.

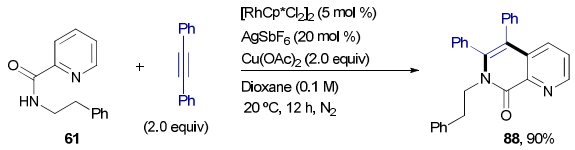
Extension of the reactions to phenethylamine derivatives. Pleasingly, this method could be extended to phenethylamine derivatives, which have a tether that is one carbon longer with regard to the directing group. The *N*(COPy)-phenethylamine (**61**)[19] reacted smoothly with diphenylacetylene under the optimized conditions to give the di-olefinated product **73**[13] in 76% yield (Scheme 6). In terms of scope, the results parallel those found with benzylamine derivatives, with the applicability to naphthalene (**86**, 42%) and heteroaromatic (**87**, 97%) compounds being of particular relevance. This structural flexibility is noteworthy, since very often the precise tether length of the directing group is found to be crucial for reactivity in C–H functionalizations.[20]



Scheme 6. Rh^{I}-catalyzed *ortho*-olefination of phenylethylamine derivatives.

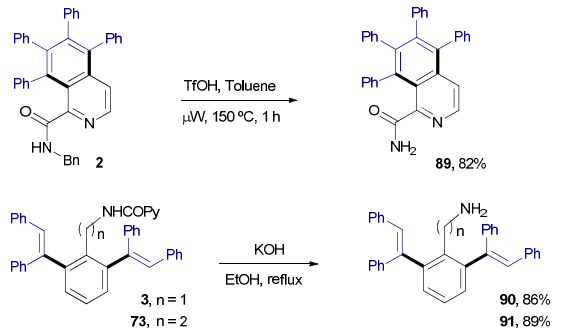
The complementary reactivity of the Rh^{III}-catalyzed oxidative alkenylation/annulation was also briefly explored with *N*-(2-picolinamide)-protected phenethylamine substrates (Scheme 7). As model reaction, when the parent substrate **61** was submitted to the standard optimized reaction conditions, the 1,7-naphthyridin-8(7H)-one **88** was produced as a single product in 90% yield. This product results from a double C–H/N–H activation and only one alkyne insertion (referred to as "interrupted" pathway) rather than the aromatic homologation *via* two-fold C–H activation previously observed for the reaction of the

analogous benzylamine derivative under identical reaction conditions (product **2**, 94% yield). This result adds additional weigh to the noticed sensitivity of this catalyst system to steric hindrance, which appears to strongly influence the reaction outcome.



Scheme 7. Rh^{III}-catalyzed pyridyl C–H functionalization leading to isoquinoline derivatives.

Chemoselective deprotection and removal of the auxilliary COPy group. Scheme 8 illustrates the chemoselective *N*-deprotection of **2** to give the isoquinoline-2-carboxamide derivative **89** (82%), as well as the facile removal of the auxilliary picolinamide directing group in both benzyl- and phenethylamine di-olefinated products (**90** and **91**, 86% and 89%, respectively).

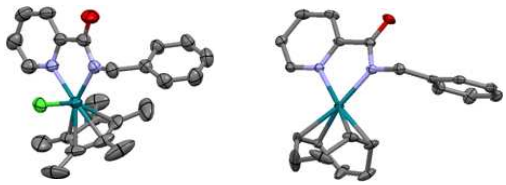


Scheme 8. Deprotection of the *N*-benzyl group and removal of the COPy directing group.

Mechanistic insights. *Stoichiometric reactions of isolated Rh-complexes.* To shed light on the basis of this divergent functionalization, we tried to identify a Rh-complex that could be involved in each catalytic cycle. The stoichiometric reaction of the *N*-benzylpicolinamide (**1**) with $[RhCp^*Cl_2]_2$, in the presence of NaOAc in CH_2Cl_2 at room temperature led to the Rh^{III}-complex **A**, showing *N,N*-coordination of picolinamide to Rh (see X-ray structure in Figure 2).[21] However, this bidentate coordination does not prevent the metal center from interacting with the target pyridinic C–H bond. In fact, **A** reacted with diphenylacetylene to afford in quantitative yield a 70:30 mixture of the isoquinoline derivative **2** and the di-olefinated product **3**, in the presence of NaOAc at 120 °C in only 4 h (Scheme 9). It is worth to remark that no reactivity is observed in the absence of NaOAc.

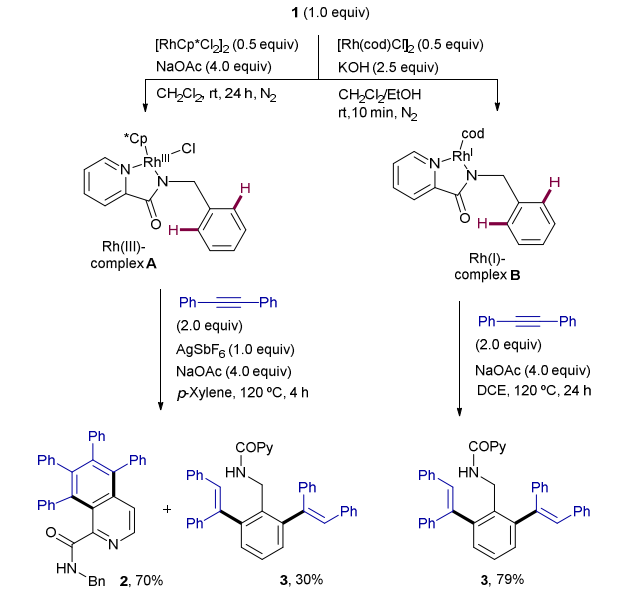
On the other hand, the stoichiometric reaction of **1** with $[Rh(cod)Cl]_2$, under similar conditions to those employed in the formation of complex **A**, provided the Rh^{I}-complex **B**, whose X-ray structure showed a similar *N,N*-bidentate metal coordination (Figure 1, see SI for details).[13] Remarkably, the reaction of complex **B** with diphenylacetylene afforded the di-olefinatinated product **3** as the only product (Scheme 9). Control experiments confirmed again that NaOAc is crucial for the reaction to proceed.

Deuterium labeling studies. To gain insight into both reaction mechanisms, a series of H/D exchange experiments were next carried out. The results obtained in the Rh^{III}-catalyzed C–H functionalization of picolinamides are depicted in Scheme 8. The reaction of **1** with diphenylacetylene in the presence of $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2$ in a dioxane/D_2O mixture at 120 °C at incomplete conversion (4 h) gave isoquinoline derivative **2-D** in 39% yield with partial deuterium scrambling at the *ortho*-positions of the benzyl substituent. Meanwhile, the recovered starting material **1-D**[1] (55% yield) showed similar levels of deuterium incorporation at the C3-Py position (50%D) and the benzyl ring (46%D). These data suggest that a reversible metalation/deutero (proto)demetalation takes place prior to the coupling with the alkyne. The fact that the C–H activation is reversible at both the pyridine moiety and the phenyl moiety under the catalytic conditions means that neither of them is rate-limiting. It also suggests that the selectivity is controlled not by the site of C–H cyclometalation but by the ease with which the two potential isomeric Rh-complexes undergo subsequent alkyne insertion.

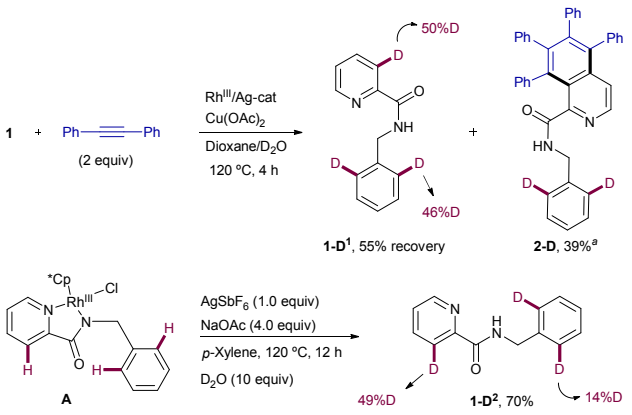


Rh^{III}-complex **A** Rh^{I}-complex **B**

Figure 2. ORTEP view of Rh^{III}-complex **A** and Rh^{I}-complex **B**. Hydrogen atoms have been removed for simplicity



Scheme 9. Stoichiometric studies with isolated Rh^{III}- and Rh^{I}-picolinamide complexes.



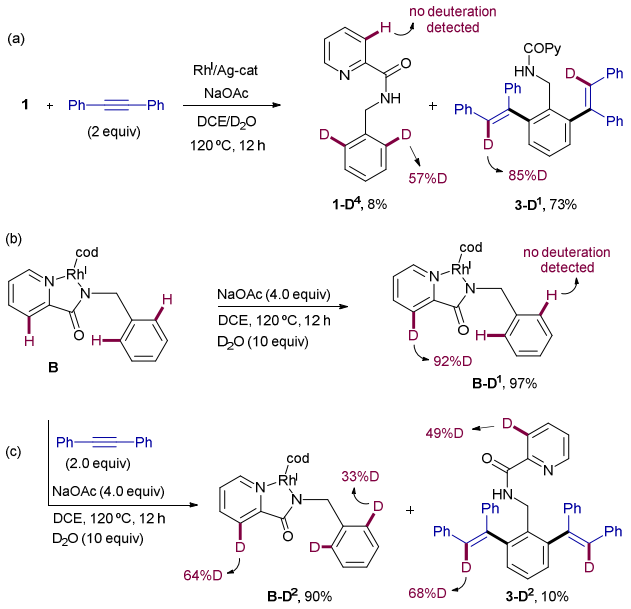
Scheme 10. H/D exchange experiments in the Rh^{III}-promoted C–H functionalization process. [a] H/D exchange detected with mass spectrometry in this case (the exact deuterium content could not be determined by NMR).

Likewise, when Rh^{III}-complex **A** was dissolved in a *p*-xylene/D_2O mixture and heated at 120 °C in the presence of NaOAc and $AgSbF_6$ for 12 h but in the absence of alkyne, **1-D²** was recovered in 70% yield showing 49% of deuterium incorporation at the C3-Py and 14% of H/D scrambling at the *ortho*-positions of the benzyl moiety (Scheme 10). This result seems to indicate that under stoichiometric amount of Rh, C–H insertion at both aryl and heteroaryl sites become reversible also in the absence of the alkyne.

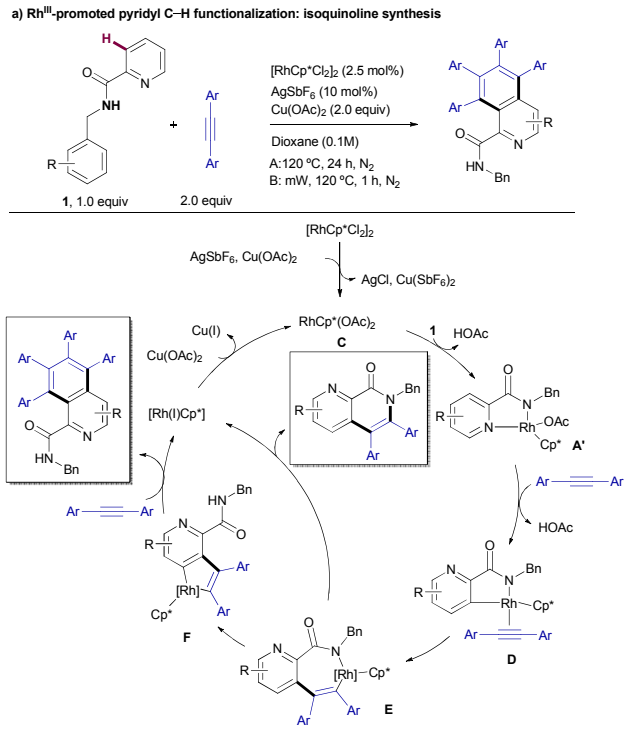
Similar deuterium labeling studies were performed in the Rh^{I}-promoted C–H functionalization process (Scheme 11). When substrate **1** was allowed to react with diphenylacetylene in a DCE/D_2O mixture at 120 °C for 12 h under otherwise standard Rh^{I}-catalyzed conditions {[Rh(cod)Cl]$_2$ (2.5 mol%)/$AgSbF_6$ (5 mol%) and NaOAc (4 equiv)}, unreacted **1** was recovered (in 8%) with significant deuterium incorporation at the *ortho*-position of the benzylamine moiety (57%D) but no H/D exchange detected at the pyridine ring. The main component of the reaction mixture was the di-olefinated product **3-D¹** (73% isolated yield), which showed high levels of deuterium incorporation at the vinylic position (85%D, Scheme 11a). This result suggests a reversible metalation/deutero(proto) demetalation at the reactive C–H sites, whereas activation at the pyridine ring appears to be less favorable. The high degree of deuteration at the vinylic positions of product **3-D¹** is compatible with a mechanism of arene activation by oxidative insertion (which should retain H/D incorporation from the starting material) if a hydride/deuterium ligand exchange by D_2O in the Rh^{III}-complex resulting upon oxidative addition of Rh^{I} into the *ortho*-C–H of **1** readily occurs prior to reductive elimination.[22]

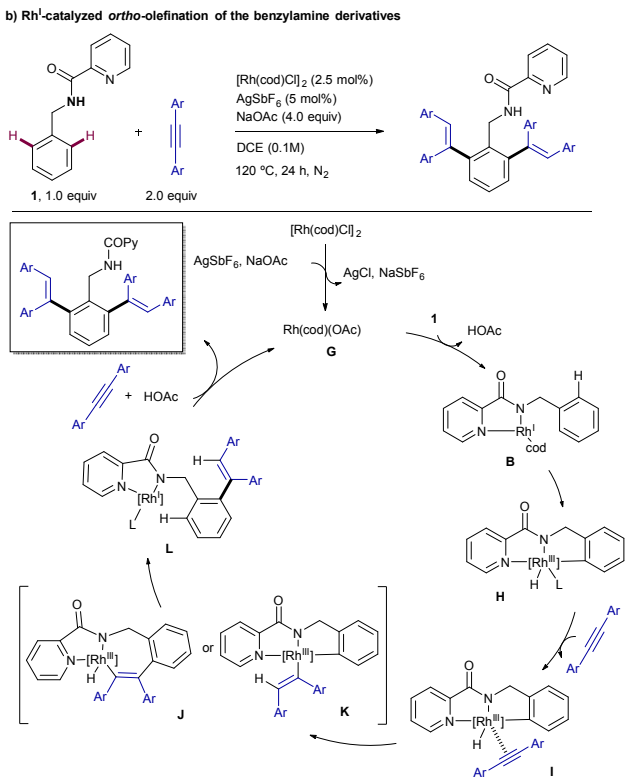
The evaluation of the potential of the Rh^{I}-complex **B** for metalation/deutero(proto)demetalation in the absence of alkyne using a hydrogen/deuterium exchange process led to almost complete deuteration of the C3-Py position in the Rh^{I}-complex **B** (**B-D¹**, 92%D), with no deuteration being observed at the benzylamine part (Scheme 11b). This result was in contrast to the high selectivity towards the benzylamine moiety observed under catalytic Rh^{I} in the presence of alkyne, where no deuteration was observed at the pyridine ring. Product **B-D¹** may arise from dissociation of the pyridinic nitrogen ligand from Rh (e.g., displaced by acetate ion), followed by metalation/deutero-demetalation at the *ortho* 2-pycolinamide moiety. Finally, when Rh^{I}-complex **B** was mixed with the diphenylacetylene in a DCE/D_2O mixture at 120 °C (Scheme 11c), very low conversion to the dialkenylation product **3-D²** was observed (10% isolated yield after 12 h), which showed significant deuterium incorporation at both 3-pyridyl (49%D) and vinylic (68%D) positions. The unreacted complex was recovered in 90% isolated yield with 64% H/D scrambling at the C3-Py position and 33% deuterium incorporation in the benzylic moiety. This result suggests that, as previously observed in the Rh^{III}-promoted outcome, the regioselectivity of the reaction is controlled not by the site of C–H cyclometalation but by the rate with which the two potential isomeric Rh-complexes undergo subsequent alkyne insertion, which turns out to be the opposite in the Rh^{I} or Rh^{III} pathways. The reasons behind the lower reactivity of complex **B** in the mixture DCE/D_2O are not fully understood at the present time.

Plausible mechanistic hypothesis. Simplified general catalytic cycles for the aromatic homologation towards isoquinoline formation and the di-*ortho*-olefination are shown in Scheme 12 based on the proposals described in the literature for related annulative processes with internal alkynes.[4,16] The former reaction might proceed through a Rh^{III}-catalyzed C–H activation of substrate **1** *via* a concerted metalation-deprotonation (CMD) mechanism assisted by the acetate ion (Scheme 12a), while the *ortho*-olefination of the benzylamine derivatives might occur *via* an oxidative addition of Rh^{I} to the C–H bond (Scheme 12b).



Scheme 11. H/D exchange experiments in the Rh^{I}-promoted C–H functionalization process.





Scheme 12. Simplified plausible mechanistic pathways.

The Rh^{III} catalytic pathway depicted in Scheme 12a is proposed to start by formation of the highly soluble presumed active catalyst $RhCp^*(OAc)_2$ (**C**) by ligand exchange from $[RhCp^*Cl_2]_2$ in the presence of excess of acetate ion. Then, displacement of acetate from **C** by the substrate (**1**) would lead to the intermediate **A'**, analogous to the X-ray characterized complex **A**. Subsequent "rollover" cyclometalation[23] *via* pyridine decomplexation and rotation around carbonyl-Py bond and then C–H bond activation, presumably by an acetate-assisted concerted metalation–deprotonation (CMD) pathway with concomitant loss of a second molecule of acetic acid, followed by alkyne coordination affords **D**. 1,2-Migration of the rhodium-carbon bond across the alkyne results in the formation of the seven-membered rhodacycle **E**, which presumably triggers a second intramolecular C–H activation leading to a more stable five-membered Rh complex **F**. After coordination and migratory insertion of the second molecule of alkyne, a reductive elimination step releases the isoquinoline product while the concomitantly formed Rh^{I} species is oxidized by Cu^{II} acetate to regenerate the $Rh^{III}Cp^*$catalyst. Alternatively, if formation of complex **F** from **E** is hampered (for instance by steric crowding next to the reactive C–H site), direct formation of the carbon-nitrogen bond from **E** *via* reductive elimination becomes more favorable to afford the mono-insertion product (previously referred to as "interrupted" pathway), at which time the metal catalyst is reduced to Rh^{I} and further oxidized to Rh^{III} by Cu^{II} acetate. In the case of using β-alkyl

acetylenic esters (such as ethyl 2-pentynoate) as coupling partner, the formation of the 6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridine skeleton (product **53**) may arise from a fast proto-demetalation of the complex type **E** followed by either intramolecular hydroamination and subsequent oxidation or oxidative cyclization through electrophilic activation of the olefin, C–N bond formation and subsequent β-hydride elimination.

The first step in the catalytic cycle proposed for the Rh^{I}-catalyzed *ortho*-olefination (Scheme 12b) likely would involve the formation of a catalytically active Rh-acetate complex **G** by chloride displacement with an acetate ion from the Rh^{I}-chloride precatalyst $[Rh(cod)Cl]_2$. Coordination to the substrate **1** in a bidentate fashion would lead to complex **B**,[13] which has been isolated and structurally characterized by X-Ray diffraction analysis. Complex **B** might undergo reversible oxidative addition of an *ortho* aromatic C–H bond to the Rh^{I} to form hydrometallacycle **H**. Upon metal-coordination of the alkyne to afford complex **I**, the further *syn*-insertion to the rhodium-hydride or rhodium-carbon bond would afford **J** or **K**, respectively. Subsequent reductive elimination from **J** or **K** delivers the mono-alkenylation Rh^{I} complex **L**, primed for subsequent oxidative insertion of the other *ortho* C–H bond followed by alkyne insertion and reductive elimination to afford the di-alkenylated benzylamine product while regenerating the Rh^{I} catalyst.

Theoretical DFT calculations. On the basis of the structure of isolated Rh-complexes, Rh^{III}-complex **A** and Rh^{I}-complex **B**, and these two plausible proposed mechanisms, DFT calculations provided further insights to explain the observed catalyst-controlled divergent C–H activation of picolinamide derivatives (Figures 3 and 4, see SI for details). Taking into account that acetate ion is always present and crucial for the reactions to proceed with both catalysts, neutral model complex **modA** and anionic model **modB**, obtained from complexes **A** and **B** changing "Cl" and "cod" ligands respectively for "OAc", were selected as the catalytically active species.[24] From these species the possible intermediates arising from the C–H activation of benzyl and pyridyl rings (species "b" and "a", respectively) and the diphenylacetylene insertion in each case have been studied.

Figure 3 depicts the calculated lowest energy profile for the postulated CMD mechanism assisted by the acetate ion when using the Rh^{III} catalyst. All species show an almost tetrahedral coordination around the Rh atom similar to that found in solid state for complex **A**. The C–H activation of either the pyridine ring or the arene unit (intermediates **IIA** and **TS(II-III)A**) requires the lack of the stabilizing interaction between the Rh atom and the pyridinic nitrogen and implies an important and quite similar activation barrier (36.1 and 35.2 $kcal \cdot mol^{-1}$ for benzyl and pyridyl rings respectively). However, the key step that really determines the selective functionalization of pyridine ring with the Rh^{III} catalyst is the insertion step on the diphenylacetylene unit. The activation barrier to reach that point after benzyl C–H activation (**TS(IV-V)Ab**), is almost 10 $kcal \cdot mol^{-1}$ higher than the required after pyridyl C–H activation (**TS(IV-V)Aa**). Once species **VAa** is formed, it will be involved in a second C–H activation-insertion sequence to afford the final product.

The energy profile for the reaction catalyzed by Rh^{I} *via* oxidative addition to the C–H bond is depicted in Figure 4. The different species show planar square coordination, similar to that observed in solid state for complex **B** (**modB** and **VIIBb**), pyramidal square (**IIBb**, **VBb** and **VIBb**) or octahedral coordination (**IIIBb** and **IVBb**) depending on the number of ligands around the Rh atom in each case. The C–H activation step of the benzyl ring through **TS(I-II)Bb**, that keeps the strong stabilizing interaction between Rh atom and pyridine nitrogen, is clearly favored over that of the pyridine ring (**TS(I-II)Ba**) with a low activation barrier (9.0 compared to 25.4 $kcal \cdot mol^{-1}$)[25] However, analyzing the energy profile, the alkyne insertion step is again the determining one through **TS(IV-V)Bb** in which the new C–H bond is being formed.[26] Structural reorganization gives species **VIBb** with a geometry being suitable for the reductive elimination process (**TS(VI-VII)Bb**). Species **VIIBb** would continue the same reaction sequence: decomplexation and conformational changes to achieve the cyclometalation, alkyne insertion and reductive elimination to afford the final product.

According to the energy profiles depicted in figures 3 and 4, the reaction catalyzed by Rh^{III} should follow selectively route "a" to afford products coming from pyridyl C–H activation whereas the reaction catalyzed by Rh^{I} should follow route "b" to afford the *ortho*-olefination of the benzyl ring. Thus, these models would explain the experimental results found in both catalytic processes: Rh^{III} catalyst affords products type **2** whereas Rh^{I} catalyst leads to products type **3**. The decrease of selectivity found in the stoichiometric reaction of complex **A** (Scheme 9). may be a consequence of the easy reduction of Rh^{III} by the base[27] in the absence of the usual Cu oxidant.

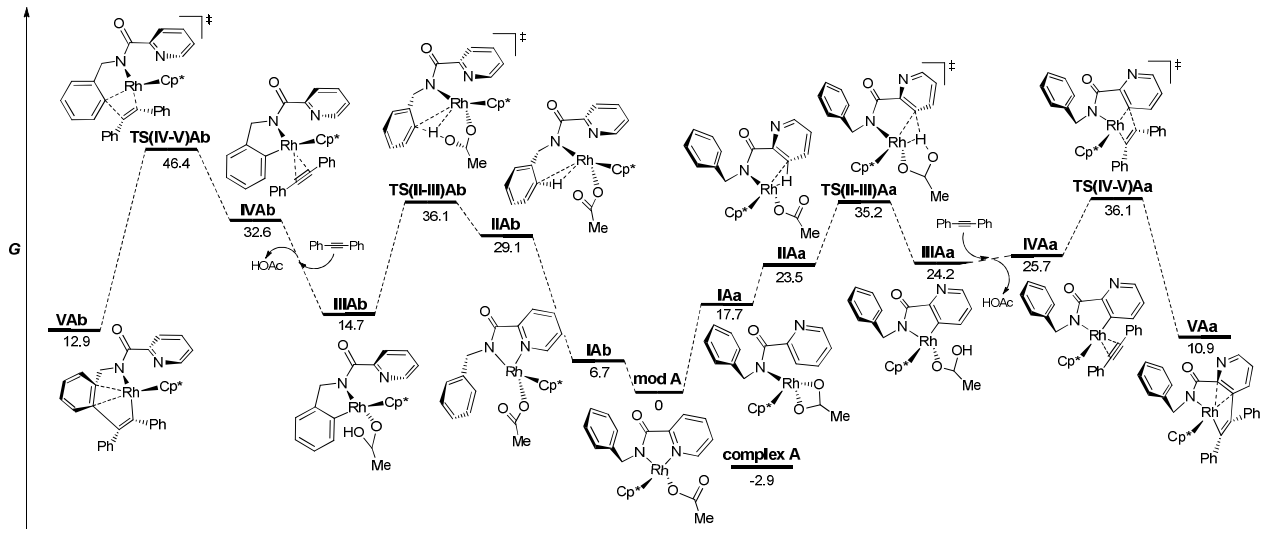


Figure 3. Energy profile for the C–H functionalization pathways of **1** with diphenylacetylene from neutral model Rh^{III} complexes in the gas phase (M06/6-311+G(d,p)(C,H,N,O),SDD (Rh)//6-31G(d)(C,H,N,O), LANL2DZ(Rh). Relative G values in kcal·mol^{-1} at 298 K).

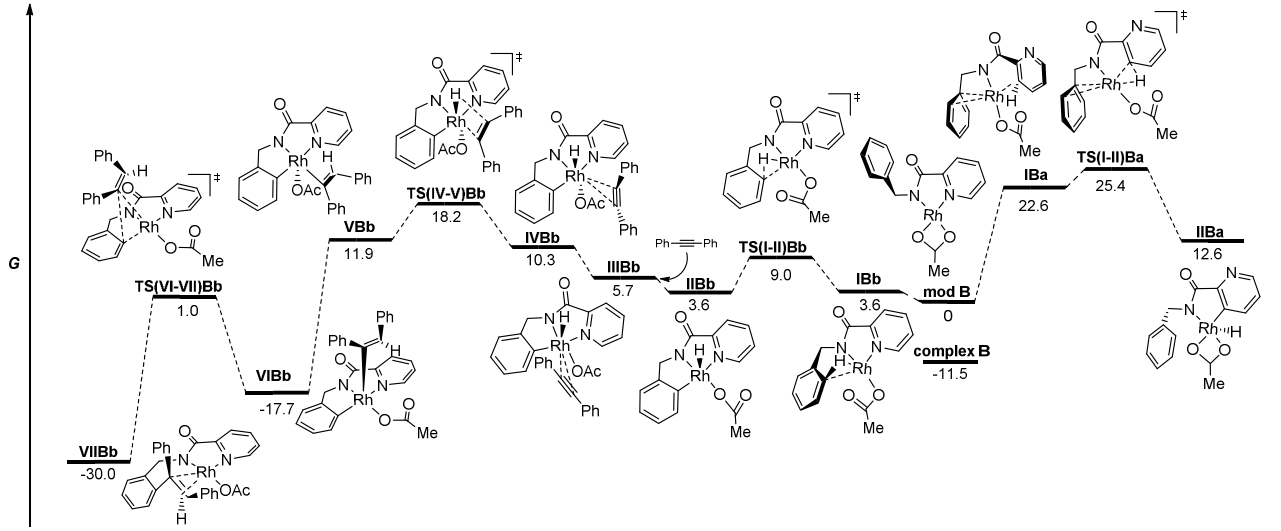


Figure 4. Energy profile for the C–H functionalization pathways of **1** with diphenylacetylene from anionic model Rh^{I} complexes in the gas phase (M06/6-311+G(d,p)(C,H,N,O),SDD (Rh)//6-31G(d)(C,H,N,O), LANL2DZ(Rh). Relative G values in kcal·mol^{-1} at 298 K). For simplicity, the negative charge has been omitted.

The results found in H/D exchange experiments can also be rationalized on the basis of the species depicted in Figure 3 for the reaction catalyzed by Rh^{III}. The C–H functionalization is favored at the C3-Py position and is a reversible process. However, when Rh^{I} is used as catalyst (Scheme 9), the results found in the stoichiometric reaction pointed out the possible role of other ligands such as "cod" and the alkyne partner to reach the catalytically active species or affect the C–H activation process. To shed some light to this point, complexes including these ligands and the corresponding C–H activation processes where studied taking complex **B** as starting model (Figure 5).

From this species, the coordination of an acetate ligand could shift one of the olefin units of "cod" to afford a more stable complex **B(cod)**. Additionally, the resulting monocoordinated cod ligand could be effectively shifted by the alkyne partner to afford complex **B(diphenylacetylene)**, that is even more stable.[28] This fact could explain the crucial role of the alkyne for the *ortho* C–H metalation reaction to take place because otherwise "cod" ligand would stay bonded to Rh atom.

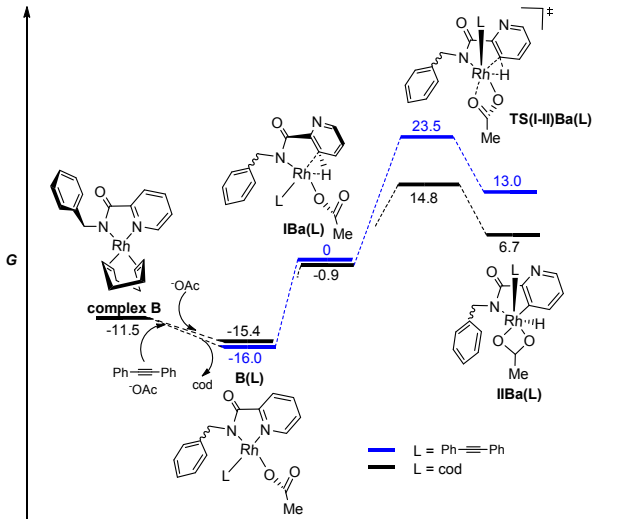


Figure 5. Energy profile for the C–H activation pathways of picolinamides from anionic model Rh complexes, with monocoordinated "cod" or alkyne ligands in the gas phase (M06/6-311+G(d,p)(C,H,N,O),SDD (Rh)//6-31G(d)(C,H,N,O), LANL2DZ(Rh). Relative G values in kcal·mol^{-1} at 298 K).

Complexes **IBa(L)** previous to the C–H activation resulted quite similar in energy with both ligands. However, the C–H activation of pyridyl ring through **TS(I-II)Ba(L)** resulted to be much more favored in the case of the "cod" ligand than in the case of the alkyne one ($\Delta\Delta G^{\ddagger}$= 7.8 kcalmol^{-1}). Thus, a reversible C–H activation of the pyridine ring could be expected in the absence of the alkyne, in agreement with experimental results (Scheme 11b), whereas if the alkyne is present the evolution through **modB** should be favored instead of the pyridyl C–H activation. All attempts to find any intermediate, that keeping either "cod" or alkyne ligand bonded to Rh atom would be involved on the *ortho* C–H activation of the benzyl ring, were unsuccessful, thus reinforcing the hypothesis of **modB** as catalytically active species for the benzyl ring functionalization.

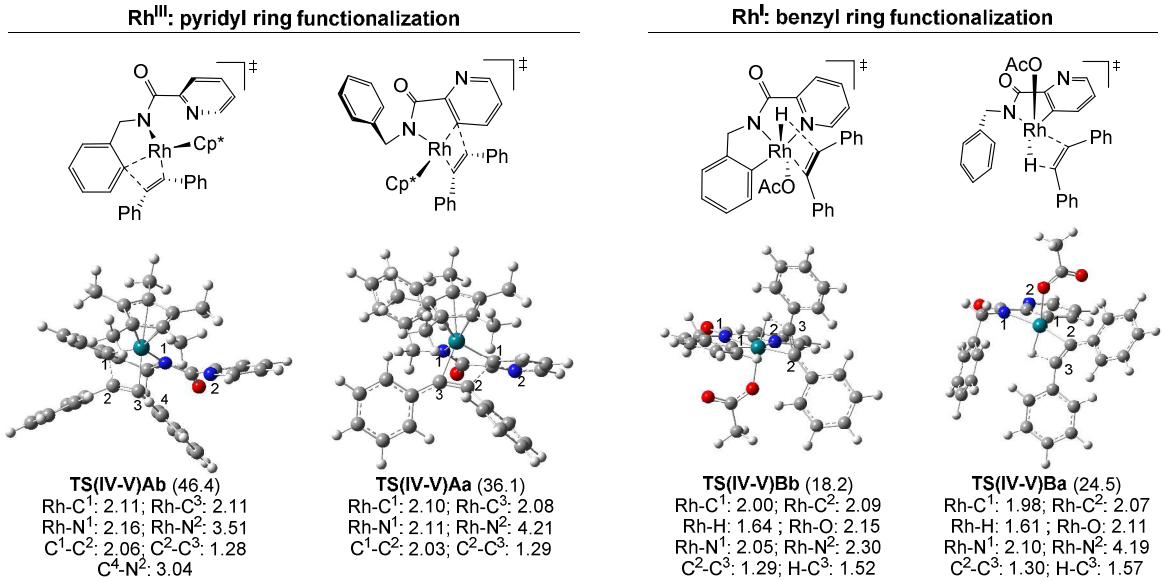


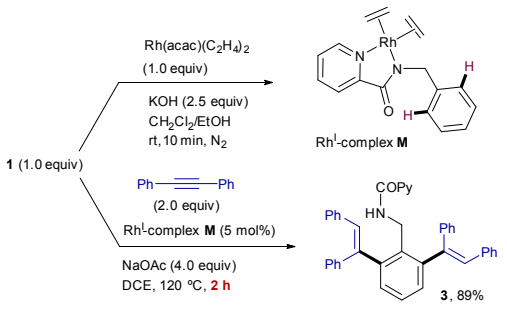
Figure 6. Molecular structure of the key transition states. Bond lengths are given in Å and relative free energies respect to **modA** and **modB** are indicated in parenthesis (kcal·mol^{-1}).

The energy difference between each couple of key transition states **TS(IV-V)Ab** / **TS(IV-V)Aa** and **TS(IV-V)Bb** / **TS(IV-V)Ba** can be attributed to different steric and /or electronic interactions (Figure 6). In the case of the reaction catalyzed by Rh^{III}, transition state **TS(IV-V)Ab** and **TS(IV-V)Aa** show important steric differences. Whereas **TS(IV-V)Aa** is a late transition state that shows a shorter distance C_1-C_2 and longer C_2-C_3 with phenyl groups spun around to avoid steric hindrance in the *Z*-alkene that is being formed, in **TS(IV-V)Ab** the pyridine ring does not allow the Ph group to reach an equivalent conformation giving rise to an early transition state with a very distorted alkyne partner. In the case of the reaction catalyzed by Rh^{I}, there are not relevant steric interactions. However, ligands around Rh atoms are quite different. Whereas **TS(IV-V)Bb** shows an octahedral coordination with one of the ligands being pyridine nitrogen, **TS(IV-V)Ba** lacks this stabilizing interaction and only five ligands (instead of six) coordinate the Rh atom.

Role of the base in the Rh^{I}-catalyzed ortho-*olefination of benzylamine derivatives.* Based on our experimental studies, the acetate ion has a crucial role in the Rh^{I}-catalyzed *ortho*-olefination of benzylamine derivatives (see SI for further experimental details). This observation is supported by the above theoretical studies which suggest that the acetate

ion leads to the anionic species active in the catalytic cycle. In order to gain better understanding of the role of the acetate ion, we embarked on synthetizing the new Rh^{I}-complex **M**, related to complex **B** with two monodentate ethylene molecules replacing the bidentate "cod" ligand. We envisaged that the greater lability of the bis(ethylene) complex should facilitate the formation of the postulated anionic Rh^{I}-acetate complex.

The stoichiometric reaction of the *N*-benzylpicolinamide (**1**) with $Rh(acac)(C_2H_4)_2$, in the presence of KOH in a mixture CH_2Cl_2/EtOH at room temperature allowed the isolation and full characterization of the Rh^{I}-complex **M** (Scheme 13). All attempts to crystalize $Rh^{I}(C_2H_4)_2$-complex **M** have failed so far due to its moderate stability. The activity of complex **M** was tested in the model reaction between the *N*-benzylpicolinamide (**1**) and diphenylacetylene in otherwise standard reaction conditions. In line with our proposal, product **3** was isolated in 89% yield after only 2 h of reaction. In contrast, the reaction with catalytic amounts of Rh^{I}-complex **B** was notably slower, observing a similar conversion only after 12 h (see SI for further details). Indeed, as evidenced the kinetic catalytic profile of both complexes shown in Figure 7 from parallel reactions, complex **B** requires an activation period (more than 1 h) prior to becoming active, whereas catalyst **M** promoted almost complete conversion within 1.5 h without noticeable induction period. This stark difference between the activity of complexes **B** and **M** was ascribed to the much easier displacement of ethylene ligands from Rh^{I} by acetate compared to the bidentate "cod" group, thereby accelerating the catalyst turnover, along with a loss of the "cod" ligand along the course of the reaction with generation of vacant coordination sites.



Scheme 13. Synthesis and activity of Rh^{I}-complex **M**.

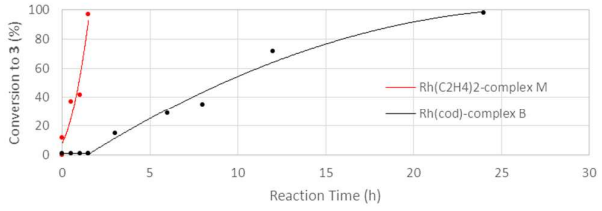


Figure 7. Kinetic profile of complexes **B** and **M** as catalysts in parallel dialkenylation reactions of **1** with diphenylacetylene.

Conclusions

In conclusion, a divergent high site-selective control in the direct functionalization of both aryl and heteroaryl C–H bonds of *N*-substituted picolinamide substrates has been cleanly achieved by simply using either a Rh^{I} or Rh^{III} catalyst precursor, either using $[RhCp^*Cl_2]_2$/$AgSbF_6$/$Cu(OAc)_2$ or $[Rh(cod)Cl]_2$/$AgSbF_6$/NaOAc. This method provides access to either isoquinoline derivatives or *ortho*-olefinated benzylamine and phenethylamine derivatives, respectively. Some experimental mechanistic studies based on the isolation of Rh^{I} and Rh^{III} picolinamide complexes, stoichiometric experiments and deuterium labeling studies, as well as DFT theoretical calculations, have been performed to explain this site-selectivity control for both Rh^{I} and Rh^{III} catalytic systems and the intimate involvement of the acetate ion in the mechanism of these reactions.

Acknowledgements

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25 With regard to the apparent very low energy barrier, it must be pointed out that the catalytically active intermediate **mod B** has to be formed from the catalytically competent complex **B** (11.5 $kcal \cdot mol^{-1}$ more stable) by ligand exchange between acetate ion and "cod". In this process, the alkyne partner may be involved according to the results of H/D exchange experiments (scheme 9 and *vide supra*).

26 The corresponding alkyne insertion transition state in the case of pyridine functionalization lies close to the previous C–H activation transition state **TS(I-II)Ba** (24.5 $kcal \cdot mol^{-1}$, see *vide supra* and SI). The model transition state in which a C–C bond instead of C–H one is formed (affording species **J** instead of **K**, scheme 10) showed a much higher activation barrier (37.4 $kcal \cdot mol^{-1}$, see SI). When 2-butyne was used as a dialkylalkyne model, the activation barrier for this insertion step was also higher (24.5 $kcal \cdot mol^{-1}$ instead of 18.2 $kcal \cdot mol^{-1}$ for the diphenylacetylene, see SI) which is in agreement with the lack of reactivity experimentally found for these substrates.

27 Rh^{I} is frequently invoked as catalyst species under basic conditions (see 16e and references therein).

28 The corresponding complex with 2-butyne resulted to be 4.6 $kcal \cdot mol^{-1}$ less stable than complex **B**, indicating that in this case the "cod" ligand likely stays bonded to Rh atom. This fact along with the higher activation barrier for the key transition state (see ref. 26) could justify the lack of reactivity observed with dialkylalkynes.