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Transition-Metal Catalysis

Ruthenium-Catalyzed Oxidative Coupling of Primary Amines with Internal Alkynes through C–H Bond Activation: Scope and Mechanistic Studies

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Abstract: The oxidative coupling of primary amines with internal alkynes catalyzed by Ru complexes is presented as a general atom-economy methodology with a broad scope of applications in the synthesis of N-heterocycles. Reactions proceed through regioselective C–H bond activation in 15 minutes under microwave irradiation or in 24 hours with conventional heating. The synthesis of 2,3,5-substituted pyridines, benzo[*h*]isoquinolines, benzo[*g*]isoquinolines, 8,9-dihydro-benzo[*de*]quinoline, 5,6,7,8-tetrahydroisoquinolines, pyrido[3,4*g*]isoquinolines, and pyrido[4,3*g*]isoquinolines is achievable depending on the starting primary amine used. DFT calculations on a benzylamine substrate support a reaction mechanism that consists of acetate-assisted C–H bond activation, migratory-insertion, and C–N bond formation steps that involve 28–30 kcal mol^{-1}. The computational study is extended to additional substrates, namely, 1-naphthylmethyl-, 2-methylallyl-, and 2-thiophenemethylamines.

Introduction

The synthesis of nitrogen-containing heterocycles, such as pyridines, quinolines, isoquinolines, and benzoisoquinolines, has attracted the interest of the chemists since the early years of organic synthesis.[1] This attention is mainly due to their ubiquitous presence in natural products or drugs with a strong biological and pharmacological activity.[2] Some examples of such molecules are presented in Figure 1. For instance, dinapsoline is a drug that was developed for the treatment of the Parkinson's disease because it is an agonist of dopamine,[3] whereas cherylline, nomifensine, and dichlofensine show central-nervous-system activity as selective serotonin-reuptake inhibitors.[4]

Conventional methods employed for the synthesis of the aforementioned N-heterocycles comprise the reactions reported by Pomeranz and Fritsch,[5] Pictet and Spengler,[6] and Bischler and Napieralski[7] in the case of isoquinolines or the processes developed by Hantzsch,[8] Gattermann and Skita,[9] and Zecher and Kröhnke[10] in the case of pyridines. However, the major problems found when using conventional methods for the large-scale synthesis of these derivatives include tedious reaction procedures, low yields, and harsh reaction conditions for some products and a sometimes narrow scope of substituents in the formed cycle.

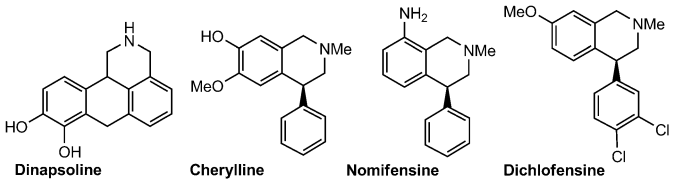

Figure 1. N-heterocycles from benzoisoquinoline or isoquinoline with biological and pharmacological activities.

Alternatively, the synthetic scope of the preparation of virtually any type of N-heterocycle has been enlarged by the development of methodologies that involve directed activation of Csp^2–H bonds by using catalytic amounts of a transition-metal species.[11] In this respect, simple Pd^{II}, Rh^{III}, or Ru^{II} complexes have been widely used for the promotion of oxidative coupling between internal alkynes and imines, amides, oximes, and acetamides (among other nitrogen-containing materials) to yield the corresponding isoquinolines, isoquinolones, isoquinolinium salts, pyridines, pyridones, and indoles.[12]

In spite of this great development, the use of primary amines as nitrogen sources for the building of a heterocycle is seldom used. Miura and co-workers reported one of the few reported examples of this approach, in which the synthesis of benzo[*h*]quinolines by coupling 1-naphthylmethylamine with

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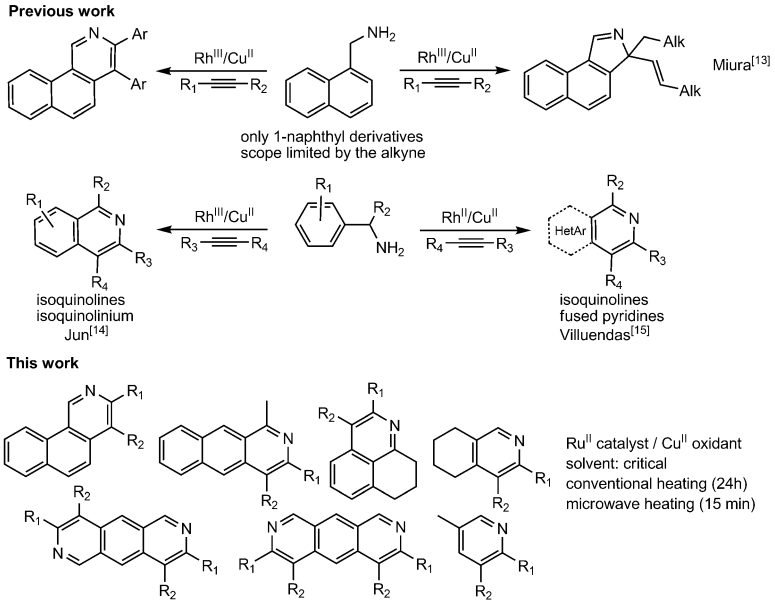


Figure 2. Most relevant previous reports and the work presented herein.

aryl-substituted alkynes catalyzed by expensive Rh^{III} complexes is covered.[13] The scope of this reaction may be limited because only the reaction with 1-naphthylmethylamine was reported. Also, when aliphatic alkynes were allowed to react, they gave benzo[*e*]isoindoles instead (Figure 2). More recently, almost simultaneous studies from Jun and co-workers[14] and our group[15] reported the synthesis of isoquinolines from benzylamines, but with substantial differences between the two contributions. The study of Jun and co-workers was devoted to the exclusive use of benzylamines (primary, secondary, and tertiary) to afford the corresponding isoquinolines or isoquinolinium salts,[14a] whereas our study was focused on the use of primary amines from both aryl and heteroaryl fragments and selected naphthyl and allyl groups, thus broadening the scope of the substrates as much as possible and defining a more general process. Further investigations by Jun and co-workers also dealt with allylamines and will be discussed later.[14b] Remarkably, all the processes reported by Jun and Miura were Rh-catalyzed, whereas our approaches were Ru-catalyzed, which is an important economical factor.

The proof of concept that the Ru-catalyzed functionalization of primary amines can be as efficient as those processes promoted by Rh species, or more so, prompted us to develop a general strategy to provide access to new heterocycles from modified primary amines. We have further expanded the scope of the substrates used, including different naphthylmethylamines, tetrahydronaphthylamines, cyclohexylamines, phenylenebis(methylamines), and even allylamines, to afford new and unexpected molecules that are difficult to synthesize by other methods. This protocol is highly efficient in terms of atom economy because unmodified amines are used (thus avoiding the specific preparation of the substrates) and the whole skeleton of the amine forms the basic scaffold of an N-heterocycle. As additional advantages, the experimental protocol is simple and cheap, avoids inert conditions and tedious workup procedures, and takes place in few minutes by using microwave radiation.

In addition, we observed during this study different reactivity trends as a function of the structure of the precursor and the reaction solvent. Clearly, fine-tuning of the reaction conditions is mandatory in each case to achieve a successful process, and the knowledge of the intimate mechanism of the reaction would help understand the role of each parameter. The extrapolation of previous mechanistic data is not always possible; for instance, we have recently shown that two stoichiometric Ru-mediated processes, apparently closely related, can involve completely unrelated intermediate species in different oxidation states.[16] Due to this fact and the shortage of computational data for the Ru-catalyzed oxidative coupling of nitrogen-containing species with internal alkynes,[17,18] we have determined the reaction mechanism for benzyl-, 1-naphthylmethyl-, 2-methylallyl-, and 2-thiophenemethylamines by using DFT calculations. Herein, we report the obtained results.

Results and Discussion

Oxidative coupling reactions between primary amines **1a**–**1f** and alkynes **2a**–**2f** were performed (Figure 3). These substrates were selected to cover a wide scope of structural situations. The initial reaction conditions were as described in our previous report.[15]

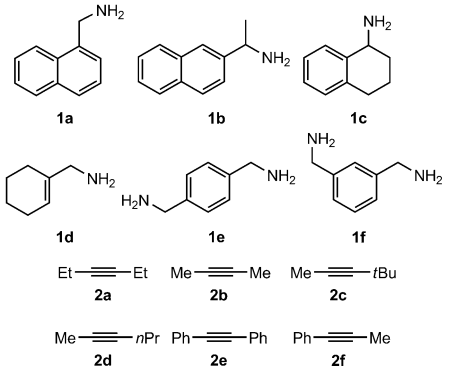
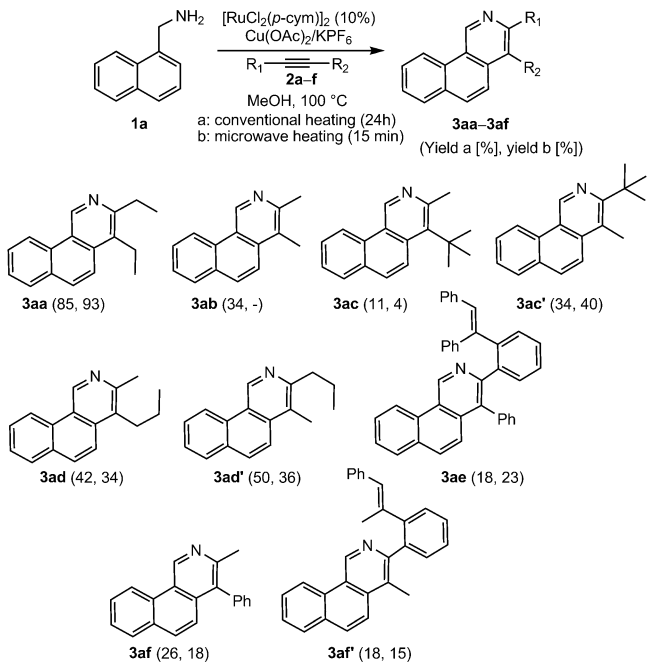


Figure 3. Primary amines **1** and internal alkynes **2** used herein.

Catalytic synthesis of benzoisoquinolines and related derivatives

We have previously shown that the coupling of **1a** (1 mmol) with **2a** (2 mmol) catalyzed by [{Ru(η^6-cymene)(μ-Cl)Cl}$_2$] (0.1 mmol) in the presence of Cu(OAc)$_2$ (1 mmol) and K[PF$_6$] (0.1 mmol) in methanol at 100 °C for 24 hours affords benzo[*h*]isoquinoline **3aa** in 85% yield.[15] A short screening of the reaction conditions showed that both the solvent MeOH and the oxidant Cu(OAc)$_2$ were the optimal choices. However, a notable improvement was achieved by using microwaves as the radiation source[19] because the reaction time can be drastically decreased to only 15 minutes, thus increasing the yield of the isolated product **3aa** by up to 93% (Scheme 1).

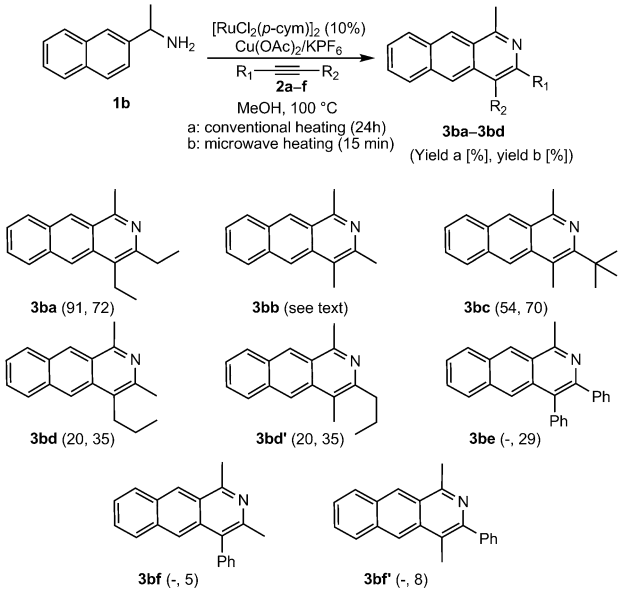


Scheme 1. Coupling of 1-naphthylmethylamine (**1a**) and alkynes **2** to give benzo[*h*]isoquinolines **3aa**–**3af**′.

To improve the catalytic results further, we decided to test different Ru catalysts with variable Ru/OAc/Cl ratios in their composition because it has been reported that the Ru/OAc/Cl ratio is critical for the promotion of the C–H bond activation.[20] In this respect, previous studies showed that although [Ru(η^6-cymene)Cl(OAc)] could promote the C–H bond activation in *N*-aryl substrates, [Ru(η^6-cymene)(OAc)$_2$] was totally inert toward the same substrates.[20] Notably, we obtained similar yields of the isolated product **3aa** by using the two complexes as catalysts under the same reaction conditions, thus obtaining 54 and 62% yields of the isolated product by using [Ru(η^6-cymene)Cl(OAc)] and [Ru(η^6-cymene)(OAc)$_2$], respectively. However, both of these yields are lower than the yield obtained by using [{Ru(η^6-cymene)(μ-Cl)Cl}$_2$] (93%). This tolerance toward different catalysts appears to be an important advantage with respect to other systems. Other Ru complexes, such as [RuCl$_2$(PPh$_3$)$_4$] or [RuH$_2$(CO)(PPh$_3$)$_3$], did not promote the formation of **3aa** at all. For that reason, we used the dimer [{Ru(η^6-cymene)(μ-Cl)Cl}$_2$] as a catalyst in subsequent reactions.

Under the optimized conditions, a variety of internal alkynes **2a**–**2f** were successfully coupled with 1-naphthylmethylamine (**1a**). The C–H bond activation of **1a** is totally regioselective by taking place at the 2 position of the naphthyl unit to afford the corresponding 3,4-disubstituted-benzo[*h*]isoquinolines **3aa**–**3af** (Scheme 1). Electron-rich alkynes **2a**–**2d** give monoinserted products **3aa**–**3ad** in moderate-to-good yields, with small differences between conventional and microwave heating (Scheme 1), except for **2b**, which was too volatile for the microwave experiments. Obviously, the most important difference between the two methodologies is the reaction time. The coupling takes place with a high degree of regioselectivity when the alkyne has two substituents with large differences in steric requirements, such as 4,4-dimethylpent-2-yne (**2c**; a molar ratio of **3ac**/**3ac**′ of up to 10:1 under microwave conditions), whereas equimolar mixtures of regioisomers **3ad** and **3ad**′ were obtained in the absence of such differences (i.e., by using 2-hexyne (**2d**)). As previously observed, the largest *t*Bu substituent in regioisomer **3ac**′ is located adjacent to the nitrogen atom.[15,21] In both cases, the two isomers, that is, **3ac**/**3ac**′ and **3ad**/**3ad**′, were successfully separated by column chromatography and characterized separately (see the Supporting Information). Moreover, each isomer was assigned with its correct regiochemistry through selective 1D NOESY experiments. When the starting alkyne contains aryl substituents (i.e., **2e** and **2f**), the 3,4-disubstituted isoquinoline first generated after the insertion and coupling reactions undergoes a second alkyne insertion at the 3-aryl position to afford the corresponding *ortho*-alkenylated derivatives **3ae** and **3af**′, respectively.

We also studied the Ru-catalyzed coupling of 1-(2-naphthyl)-ethylamine (**1b**) with alkynes **2a**–**2f**, which affords 3,4-disubstituted-benzo[*g*]isoquinolines **3ba**–**3bf**′ (Scheme 2). Once

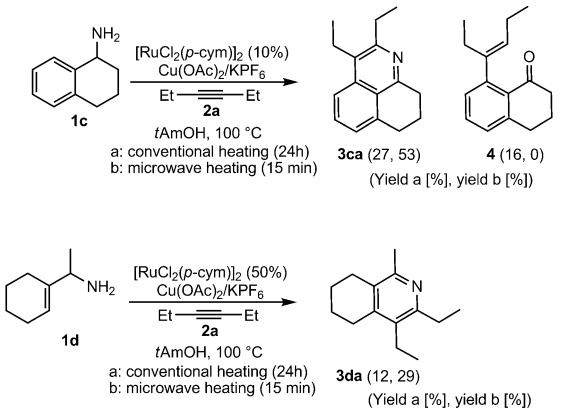


Scheme 2. Coupling of 1-(2-naphthyl)ethylamine (**1b**) with alkynes **2a**–**2f** to give benzo[*g*]isoquinolines **3ba**–**3bf**′. cym = cymene.

again the process is regioselective because only the 3-position of the starting substrate **1b** is activated by the Ru center. The reaction takes place with alkyl- and aryl-substituted alkynes, although better yields were obtained in the case of the electron-rich alkynes 3-hexyne (**2a**), 4,4-dimethylpent-2-yne (**2c**), and 2-hexyne (**2d**). Unfortunately, the reaction with 2-butyne (**2b**) could not be performed under microwave irradiation due to the volatility of the alkyne moiety, whereas the reaction with conventional heating afforded a very low yield of a product resistant to purification. More interestingly, the coupling of **1b** with unsymmetrical **2c** is regioselective, and **3bc** is obtained as a single regioisomer (Scheme 2), the structure of which was confirmed by selective 1D NOESY experiments. As expected, the more voluminous *t*Bu group is located near the N atom, as in **3ac** and previous benzylamines.[15] In the case of substituents with the same steric hindrance (i.e., **2d**), an equimolar mixture of the two possible regioisomers (**3bd** and **3bd′**) is obtained. In this case we could separate this mixture by means of column chromatography and characterize the corresponding benzo[*g*]isoquinolines separately, including the correct assignation of the structure by selective 1D NOESY experiments (see the Supporting Information).

We also attempted the coupling of **1b** with aryl-containing alkynes **2e** and **2f**. Complete conversions were observed with conventional heating and under microwave radiation, although poor yields were obtained for the final isolated products and only for the microwave-promoted reactions. Surprisingly, the selective insertion of only one alkyne unit was observed in both cases, therefore giving 1-methyl-3,4-diphenylbenzo[*g*]isoquinoline (**3be**) in 29% yield and the two isomers 1,3-dimethyl-4-phenylbenzo[*g*]isoquinoline (**3bf**) and 1,4-dimethyl-3-phenylbenzo[*g*]isoquinoline (**3bf′**) in 5 and 8% yield, respectively, which were separated by means of column chromatography (Scheme 2). Attempts to increase the yield by changing the reaction temperature and/or the reaction time did not provide any improvement. In spite of the low yields, what is really relevant for these three compounds is that they represent the only examples of the Ru-catalyzed coupling of amines in which a selective single insertion is observed with aryl-containing internal alkynes. In fact, in our preceding report[15] and as reported above (i.e., **3ae**, **3af′**), the double insertion of alkynes has always been achieved. Therefore, the diversity of the products achievable with this methodology increases notably. In this respect, the reactivity described herein for 1-(2-naphthyl)ethylamine (**1b**) as source of benzo[*g*]isoquinolines improved by a considerable extent relative to previous observations of Gül and Nelson, who reported the complete lack of reactivity of *ortho*-ruthenated *N*,*N*-dimethyl-α-(2-naphthyl)ethylamine with internal alkynes.[22]

Once we had shown that primary amines are adequate precursors for the synthesis of tricyclic aromatic skeletons such as benzo[*h*]isoquinolines and benzo[*g*]isoquinolines, we aimed to expand the scope of reachable molecules further into two different directions: 1) di- and tricyclic cores that contain saturated rings and 2) tricyclic aromatic cores with two nitrogen-containing rings. To achieve the first goal, the partially hydrogenated amines 1,2,3,4-tetrahydronaphthyl-1-amine (**1c**) and 1-(cyclohex-1-en-1-yl)ethan-1-amine (**1d**) were subjected to Ru-mediated coupling with 3-hexyne (**2a**; see Scheme 3).

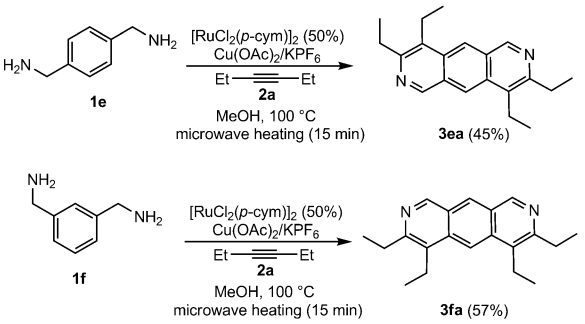


Scheme 3. Ru-catalyzed synthesis of dihydrobenzo[*de*]quinoline (**3ca**) and 5,6,7,8-tetrahydroisoquinoline (**3da**).

First attempts carried out in MeOH with conventional heating showed the formation of the expected products 2,3-diethyl-8,9-dihydro-7*H*-benzo[*de*]quinoline (**3ca**) and 3,4-diethyl-1-methyl-5,6,7,8-tetrahydroisoquinoline (**3da**), but in low yields. In the case of **1d**, stoichiometric amounts of the Ru catalyst were used. Moreover, the byproduct (*E*)-8-(hex-3-en-3-yl)-3,4-dihydronaphthalen-1(2*H*)-one (**4**) was also formed in the case of amine **1c**, although it was cleanly separated from the benzoquinoline **3ca** by means of column chromatography. Formally, the formation of **4** from **1c** implies that the carbon atom that supports the amino group was oxidized to a keto function,[23] thus giving a 8-vinyl-1-tetralone derivative. This oxidation likely takes place after the insertion of the alkyne unit, but before the C–N bond formation. This scenario is suggested by the fact that no reaction at all was observed between the pure 1-tetralone and 3-hexyne under the Ru-catalyst conditions. The change of the solvent from MeOH to *tert*-amyl alcohol (*t*AmOH) promoted a remarkable increase of the yield in all cases, although the formation of ketone **4** from amine **1c** after 24 hours of reaction is still evident. When the reaction is carried out with microwave radiation for 15 minutes, a double benefit is achieved because the yield is further increased up to 53% and the formation of **4** is totally suppressed.

The synthesis of tetrahydroisoquinoline **3da** means that this method is valid not only for the activation of Csp^2–H bonds in aromatic (het)aryl rings, but also Csp^2–H bonds in alkene-type units. This fact prompted us to explore other related substrates, such as allyl amines, which will be discussed later. The selective synthesis of **3da** also suggests that the activation of the Csp^2–H bonds is preferred to the activation of Csp^3–H bonds, which is usual for this type of substrate. In this respect, we also performed the Ru-mediated reaction of cyclohexylmethylamine with 3-hexyne (**2a**) mediated by Ru catalysis; however, no detectable coupling product was observed under the attempted reaction conditions.

In a further step, 1,4-phenylenebis(methylamine) (**1e**) and 1,3-phenylenebis(methylamine) (**1f**) were treated with an excess of **2a** under Ru-mediated conditions (Scheme 4), thus



Scheme 4. Ru-mediated synthesis of pyridoisoquinolines **3 ea** and **3 fa**.

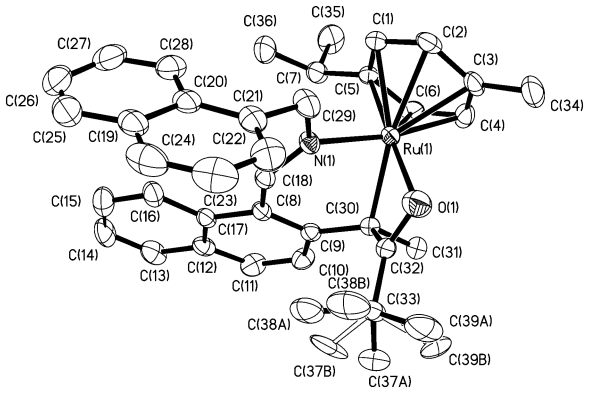


Figure 4. Drawing of the cationic part of complex **3 a·OM**. Selected bond distances [Å] and angles [°]: Ru(1)–N(1): 2.094(3), N(1)–C(29): 1.503(4), C(29)–C(21): 1.513(5), N(1)–C(18): 1.282(4), C(18)–C(8): 1.459(4), C(8)–C(9): 1.390(4), C(9)–C(30): 1.484(4), C(30)–Ru(1): 2.176(3), C(30)–C(32): 1.520(4), C(30)–C(31): 1.541(4), C(32)–O(1): 1.287(4), Ru(1)–O(1): 2.089(3); O(1)-Ru(1)-N(1): 80.35(11), O(1)-Ru(1)-C(30): 63.31(11), N(1)-Ru(1)-C(30): 83.19(11).

giving the corresponding 3,4,8,9-tetraethylpyrido[3,4*g*]isoquinoline (**3 ea**) and 3,4,6,7-tetraethylpyrido[4,3*g*]isoquinoline (**3 fa**) as single isomers.

The activity of the Ru center that promotes this coupling is remarkable because two coupling reactions on the same aromatic ring have to take place, regardless of whether they occur consecutively or simultaneously. The synthesis of bis-cycloruthenated compounds has experienced increasing interest very recently due to their interesting electronic and optical properties.[24] However, bis-cyclometalated species are seldom used in metal-mediated synthesis to promote this type of double functionalization.[25] In addition, the selectivity of this reaction is notable because several isomers are envisageable in both cases, but a single compound is isolated in each case. The structure of **3 fa** was assigned on the basis of the high symmetry of the NMR signals, whereas the structure of **3 ea** is based on the presence of strong NOE interactions between the protons at positions 5 and 10 and the methylene protons of the ethyl groups at positions 4 and 9 (see the Supporting Information), thus meaning that the activation of C–H bonds has occurred at the 2,5 positions in **1 e**.

Characterization of the crude reaction products

From the above discussion, it seems clear that primary amines can be used as versatile building blocks for the synthesis of diverse heterocycles through Ru-catalyzed oxidative coupling with internal alkynes. The easy and selective C–H bond activation step is remarkable, in spite of the very few examples reported of the cycloruthenation of primary amines.[26] However, the yields of the target compounds are not always high, even if all the processes are carried out under optimized conditions, thus suggesting that competitive processes take place at the same time. Therefore, we investigated the composition of the crude products just after removal of the copper salt. This analysis shows the presence of expected organic derivatives and, in many cases, small but detectable amounts of η^6-cymene organometallic complexes of the Ru^{II} species.

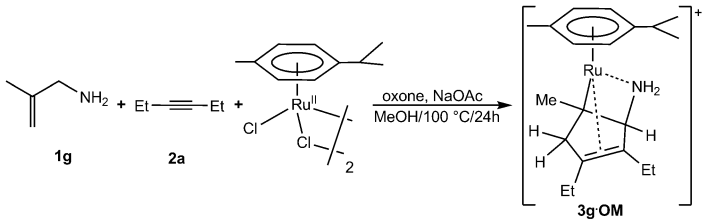
We achieved the isolation of a very stable representative of such species as **3 a·OM** in the reaction of **1 a** with alkyne **2 c**. Single crystals of **3 a·OM** adequate for X-ray determination studies were grown from CH_2Cl_2/*n*-hexane at 8 °C. A drawing of the cationic organometallic complex is shown in Figure 4, with selected bond distances and angles. Details of the isolation and full characterization of **3 a·OM** are given in the Supporting Information. This structure shows a really remarkable C,N,O-tridentate ligand, presumably formed by a mechanism that involves the self-condensation of two naphthylmethylamine compounds to give an amine–imine unit, orthoruthenation, alkyne coupling, and final hydration.

The formation of **3 a·OM** (and other related species) could explain the low yield observed because reagents such as naphthylmethylamine are consumed and, more importantly, because the Ru catalyst is sequestered in the stoichiometric synthesis of very stable complexes.

Catalytic synthesis of pyridines and related derivatives

We also achieved the synthesis of pyridines by using the same methodology, but starting from allylamines. Most of the work performed up to now for the metal-catalyzed synthesis of densely substituted pyridines is based on vinyl–imines and Rh^{III} or Rh^{I} catalysts.[12o,p,27] Only one contribution, as far as we know, reports the use of allylamines as a starting material, and even in this case the authors propose that the catalytically relevant species is the imine.[14b] Herein, we show not only that allylamines are good precursors for the synthesis of pyridines, thus showing a reactivity pattern different to what is expected for a classical allyl group, but also that different products can be obtained as a function of the reaction conditions. Of course, this example is also the first time that such a process has been catalyzed by Ru^{II} derivatives.

2-Methylallylamine (**1 g**) was allowed to react with 3-hexyne (**2 a**) under the conditions reported previously (i.e., $Cu(OAc)_2$, MeOH, 24 h, 100 °C), but less than 5% yield of the isolated product of pure pyridine **3 ga** was obtained, which proved difficult to obtain in its pure form.[15] When oxone was used as the oxidant and NaOAc as the base in MeOH at 100 °C, the full conversion of **1 g** was observed. However, the result of the reaction is a new organometallic compound **3 g·OM** (Scheme 5),

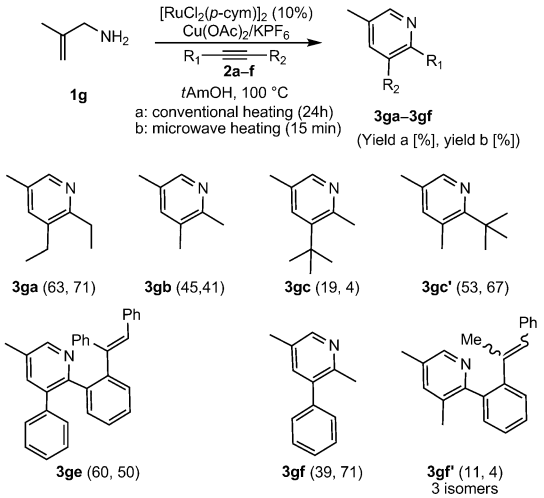


Scheme 5. Stoichiometric coupling of **1 g** with 3-hexyne (**2 a**) in MeOH to give **3 g·OM**.

which contains the Ru center bonded to a η^6-cymene ligand and to a η^1-η^2-aminocyclopentene moiety, assigned on the basis of analytic and spectroscopic data and comparison with those complexes found in similar structural arrangements (see the Supporting Information).[28] The synthesis of **3 g·OM** can be explained (see Figure S3 in the Supporting Information) through the formation of an η^3-allyl intermediate, migratory insertion, and Csp^2–Csp^2 coupling (similar to couplings reported by Davies et al.)[29] or through directed ruthenation at the $=CH_2$ position, migratory insertion, and a 1,3-sigmatropic shift.[30]

All our attempts to liberate the aminocyclopentene ligand from the Ru center were unsuccessful, which suggests that **3 g·OM** is not an adequate precursor in the design of a plausible catalytic cycle. Therefore, **3 g·OM** represented a dead-end pathway for the synthesis of pyridines, and a new optimization process was needed.

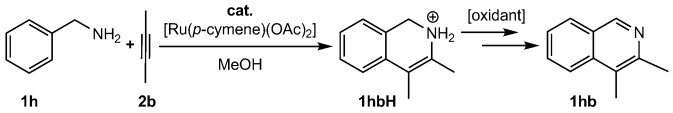
For the screening of new reaction conditions, we carried out the process in *t*AmOH at 100 °C due to the success obtained in the catalytic couplings that started from **1 c** and **1 d** with different oxidants and reaction times. Thankfully, we found that allylamine **1 g** couples with **2 a** to give pyridine **3 ga** with $Cu(OAc)_2$ as the oxidant in *t*AmOH at 100 °C. The optimum reaction time is 24 hours, which could be reduced to 15 minutes under microwave radiation. Under optimal conditions, **1 g** oxidatively couples with different internal alkynes **2 a**–**2 f** to give the corresponding pyridines **3 ga**–**3 gf** (Scheme 6). The obtained yields range from moderate (45%) to good (> 70%) of the analytically pure products and, as expected, the reaction works for alkynes with alkyl and aryl substituents. The observed regioselectivity is high in the case of asymmetric alkynes, but not as complete as it was in some of the preceding cases. Interestingly, this regioselectivity is notably improved (i.e., for **3 gc** and **3 gf**) when the reaction is carried out under microwave conditions (Scheme 6). Finally, as observed in the previous examples, a double insertion of the alkyne unit takes place when an aryl ring is at position 2 (i.e., **3 ge** and **3 gf'**) due to the formation of the 2-phenylpyridine moiety.



Scheme 6. Ru-catalyzed synthesis of pyridines **3 ga**–**3 gf'**.

DFT mechanistic studies

The experimental results proved the capability of Ru complexes to catalyze the oxidative coupling of primary amines with internal alkynes (Schemes 1–4 and 6). To investigate the reaction mechanism to a greater extent, DFT calculations were performed on the reaction shown in Scheme 7 (see the Computational Details for further information), that is, the Ru-catalyzed coupling of benzylamine (**1 h**) with 2-butyne (**2 b**) to form dihydroisoquinoline **1 hbH**. Further oxidation processes are assumed to yield the final isoquinoline derivative **1 hb**.[15] Regarding the catalyst, the monomer $[Ru(p\text{-cymene})(OAc)_2]$ (**cat.**) was used in the calculations. Although the related dimer precursor $[\{Ru(p\text{-cymene})(\mu\text{-Cl})Cl\}_2]$ can provide better yields, $[Ru(p\text{-cymene})(OAc)_2]$ (**cat.**) is quite feasible in the presence of $Cu(OAc)_2$.[17,18]



Scheme 7. Ru-catalyzed reaction between **1 h** and **2 b** under theoretical study.

Herein, the reaction mechanism is discussed for benzylamine (**1 h**), but it also works for 1-naphthylmethyl-, 2-methylallyl-, and 2-thiophenemethylamines (**1 a**, **g**, **i**, respectively; see the Supporting Information) and, presumably, for other related analogues. The DFT-proposed reaction mechanism entails three main steps: 1) C–H bond activation, 2) migratory insertion, and 3) C–N bond formation (Scheme 8).[18,31] The Gibbs energy reaction profile is depicted in Figure 5 and will be discussed as follows. All the reported energies correspond to Gibbs energies in methanol in kcal mol^{-1}.

The Ru catalyst **cat.**, amine **1 h**, and alkyne **2 b** were taken separately as zero of the Gibbs energies. The initial interaction between **1 h** and **cat.** through hydrogen bonding forms the adduct **cat.·1 h** (5.9 kcal mol^{-1}). Next, acetate-by-amine substitution leads to **5·OAc** (6.9 kcal mol^{-1}), which keeps the formally coordinated acetate species at the surroundings of the amine moiety.

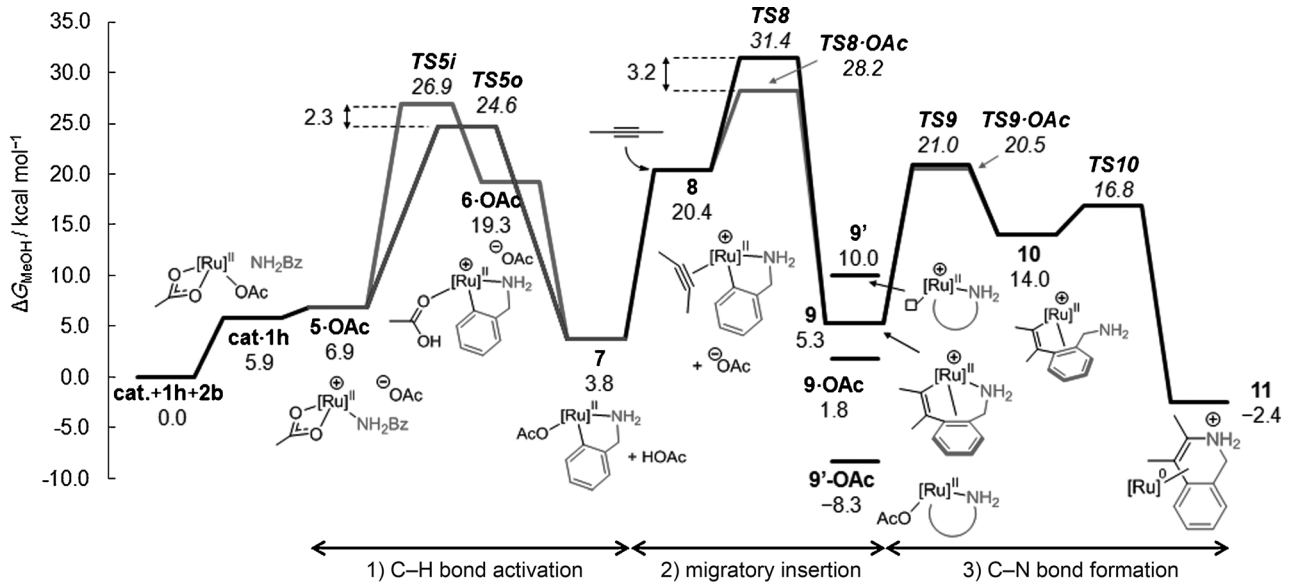
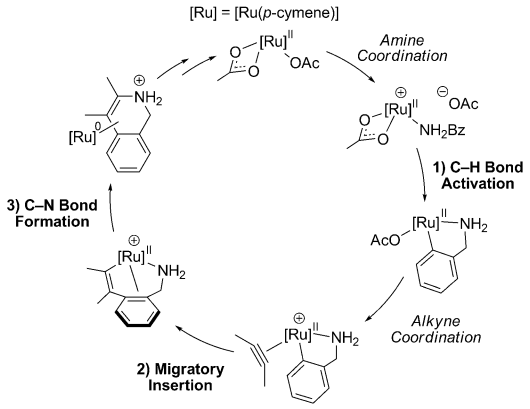


Figure 5. Gibbs-energy profile for the Ru-catalyzed coupling of amine **1h** with alkyne **2b**. ΔG_{MeOH} is given in kcal mol^{-1}.



Scheme 8. General mechanism for the Ru-catalyzed oxidative coupling of primary amines **1** with internal alkynes **2**.

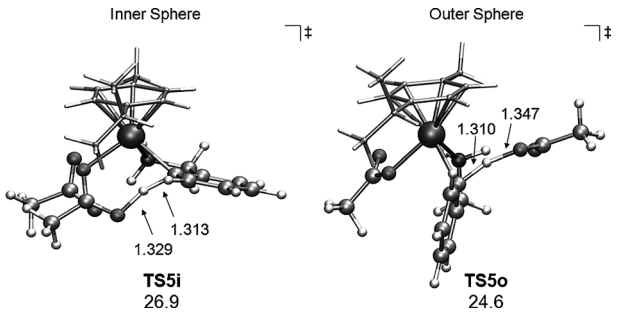


Figure 6. Acetate-assisted C–H bond activation transition states **TS5i** (IS, left) and **TS5o** (OS, right). ΔG_{MeOH} is given in kcal mol^{-1} and distances in Å.

1) C–H bond activation

Once **5·OAc** is formed, the C–H bond activation[32] takes place regioselectively at the *ortho* carbon atom of the phenyl ring of amine **1h**. It is well known that the acetate ion can assist C–H bond activation reactions,[33] in which both innersphere (IS)[34,35] and outersphere (OS)[36] mechanisms have been reported. Herein, both pathways were computationally considered by starting from **5·OAc**. For the IS mechanism, **TS5i** (Figure 6 left)[37] shows the migration of the hydrogen atom from the phenyl ring to one oxygen atom of the coordinated acetate. **TS5i** is located at 26.9 kcal mol^{-1} above the reactants and gives rise to **6·OAc**. Further exchange of the resulting acetic acid by the acetate species yields intermediate **7** at 3.8 kcal mol^{-1}.[38] For the OS mechanism, **TS5o** (Figure 6 right) displays the hydrogen abstraction by a non-coordinated acetate ion. **TS5o** involves 24.6 kcal mol^{-1} and finally ends as intermediate **7**. The OS mechanism is favored over the IS mechanism by only 2.3 kcal mol^{-1} (Figure 5); therefore, the dominant reaction mechanism cannot be discriminated unambiguously.

2) Migratory insertion

Alkyne **2b** can then coordinate to the Ru center through an acetate-ligand exchange in **7**, thus forming the Ru–alkyne intermediate **8** (20.4 kcal mol^{-1}). The alkyne ligand in **8** undergoes migratory insertion into the Ru–C bond via **TS8** at 31.4 kcal mol^{-1} (Figure 7, left). However, when coordinating the former acetate ion to the NH_2 fragment, the new transition state **TS8·OAc** is found (Figure 7, right). **TS8·OAc** is placed at 28.2 kcal mol^{-1}, which is 3.2 kcal mol^{-1} less than **TS8**. Noteworthy, the acetate species does not play an active role during the insertion step; the stabilization merely comes from additional [Ru]···OAc interactions in **TS8·OAc** (Figure 7, right) that are not present in **TS8**. The insertion process finally yields intermediate **9** (5.3 kcal mol^{-1}), which coordinates to the phenyl moiety to stabilize the freshly formed vacant site. The corresponding acetate adduct **9·OAc** is found at 1.8 kcal mol^{-1}. Whether the vacancy is or is not stabilized by intramolecular interactions,

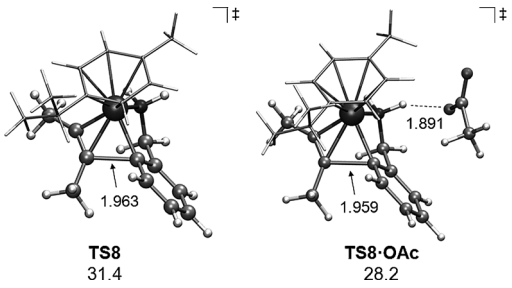


Figure 7. Migratory-insertion transition states **TS8** (left) and **TS8·OAc** (right). ΔG_{MeOH} is given in kcal mol^{-1} and distances in Å.

a less favorable conformer **9′** (10.0 kcal mol^{-1}) is found. Because this vacant coordination site is solvent exposed, **9′** can eventually be trapped by other species present in solution, for instance, a free acetate ion to form **9′·OAc** (−8.3 kcal mol^{-1}). Actually, resting states such as **9′·OAc** (and analogues with other substrates) may indeed facilitate detours that produce lower yields as experimentally observed (see Figure 4 and Scheme 5).

3) C–N bond formation

Finally, the C–N bond formation step should proceed to give rise to **11**. Intermediate **9** can undergo a concerted reductive-elimination process via **TS9c** at 32.3 kcal mol^{-1}.[39] This transition state is, however, placed at 40.6 kcal mol^{-1} above **9′·OAc**; therefore, this route is likely blocked. Deprotonation of the amine group in **9** by the acetate species prior to reductive elimination is also considered. The resulting neutral species **9NH** is found at 21.4 kcal mol^{-1}, whereas the transition state **TS9cNH** is placed at 41.4 kcal mol^{-1}. This process also entails a high barrier that is 49.7 kcal mol^{-1} above **9′·OAc** and can be ruled out. Consequently, an alternative pathway that starts from **9** is proposed instead. This pathway involves two steps, that is, de-coordination of the nitrogen atom and subsequent intramolecular nucleophilic attack (Figure 5). The amine arm first de-coordinates from the Ru center via **TS9** (Figure 8, left) at 21.0 kcal mol^{-1} (i.e., 29.3 kcal mol^{-1} above **9′·OAc**). The resulting intermediate **10** (14.0 kcal mol^{-1}) exhibits a η^4-coordination mode between the Ru center and the organic moiety. Then, the free amine group in **10** easily attacks the carbon atom intramolecularly through **TS10** (Figure 8, right) at

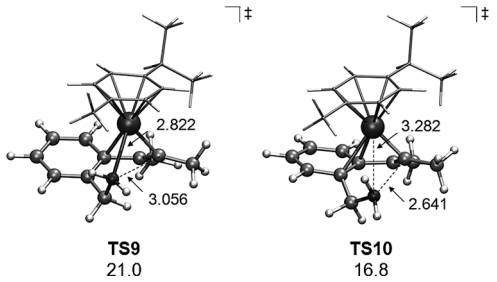


Figure 8. C–N bond formation transition states though the de-coordination of the nitrogen atom in **TS9** (left) and intramolecular nucleophilic attack **TS10** (right). ΔG_{MeOH} is given in kcal mol^{-1} and distances in Å.

16.8 kcal mol^{-1} (i.e., 25.1 kcal mol^{-1} above **9′·OAc**) to yield **11** (−2.4 kcal mol^{-1}). When considering one explicit acetate moiety in **TS9**, the resulting transition state **TS9·OAc** is found at 20.5 kcal mol^{-1} (i.e., 28.8 kcal mol^{-1} above **9′·OAc**).[40] Finally, the species **1hbH** can be released from intermediate **11**. Further steps shall produce the final product **1hb** and regenerate the catalyst.

Overall, a plausible reaction mechanism has been proposed by computational means. According to DFT calculations, no unique rate-determining transition state could be found for the Ru-catalyzed coupling of benzylamine (**1h**) with 2-butyne (**2b**). The Gibbs energy barriers for the C–H bond activation (**TS5l** and **TS5o**) are 25–27 kcal mol^{-1}, whereas the barriers for the migratory insertion (**TS8·OAc**) and de-coordination of the nitrogen atom (**TS9·OAc** above **9′·OAc**) are in the range of 28–30 kcal mol^{-1}, which is in agreement with the experimental conditions (i.e., $T = 100\,^{\circ}C$).

As concerns other nitrogen-containing substrates, the reaction profile for the 1-naphthylmethyl derivative **1a** also shows a Gibbs energy barrier of approximately 28 kcal mol^{-1} (see Figure S4 in the Supporting Information). In the case of 2-methylallylamine (**1g**), the C–H bond activation through the OS mechanism is favored with respect to the IS mechanism, and the most demanding step corresponds to the migratory insertion at approximately 28 kcal mol^{-1} (see Figure S5 in the Supporting Information). Lastly, the migratory insertion for the reaction profile for 2-thiophenemethylamine (**1i**) appears again to be the most demanding step at approximately 30 kcal mol^{-1} (see Figure S6 in the Supporting Information). These results agree with previous studies that suggest that the insertion process is the most demanding process.[15]

Conclusion

A large variety of N-heterocycles such as benzo[*h*]isoquinolines, 8,9-dihydro-benzo[*de*]quinoline, 5,6,7,8-tetrahydroisoquinolines, pyrido[3,4*g*]isoquinolines, pyrido[4,3*g*]isoquinolines, and 2,3,5-substituted pyridines can be synthesized by a Ru-catalyzed oxidative coupling of the corresponding unprotected primary amines with internal alkynes. These syntheses can be accomplished in moderate-to-good yields in reaction times as short as 15 minutes by using microwave irradiation. Stable organometallic complexes, formed in alternative reaction pathways, were characterized for cases in which low yields were obtained. These species behave as Ru-sequestering agents and show the complexity of this type of reaction. DFT calculations support a reaction mechanism through acetate-assisted C–H bond activation, migratory-insertion, and C–N bond formation steps, which involve energy of approximately 28–30 kcal mol^{-1}. This latter process occurs in a stepwise fashion rather than a concerted pathway. No unique rate-determining transition state was found for benzyl- and 2-naphthylmethylamines, although the migratory-insertion step appears to be the most demanding process for 2-methylallyl- and 2-thiophenemethylamines (28–30 kcal mol^{-1}).

Experimental Section

General methods

See the Supporting Information for full details.

General procedure for the catalytic synthesis of benzoisoquinoline derivatives

$\{[RuCl_2(p\text{-cymene})\}_2]$ (61.2 mg, 0.1 mmol), KPF_6 (17 mg, 0.1 mmol), and $[Cu(OAc)_2]$ (181 mg, 1 mmol) were added to a solution of the corresponding amine **1a–f** (1 mmol) and alkyne **2a–f** (1 mmol) in MeOH (5 mL; except for amines **1c** and **1d**, for which the reactions were carried out in *t*AmOH). The reaction mixture was heated in a microwave reactor at 100 °C for 15 min or in a Young's flask for 24 h with conventional heating. The solvent was removed and the residue was redissolved in CH_2Cl_2 and purified by flash column chromatography on neutral alumina with CH_2Cl_2 then CH_2Cl_2/MeOH (95:5) as the eluents. Analytically pure materials were obtained with further purification by column chromatography on SiO_2 with different mixtures of solvents. The characterization of **3ca** is shown below (the data for the other compounds are collected in the Supporting Information).

2,3-Diethyl-8,9-dihydro-7*H*-benzo[de]quinoline (3ca): Yellow oil. Yield on conventional heating: 60 mg (27%); yield on microwave heating: 120 mg (53%). ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): $\delta = 1.31$ (t, $^3J_{HH} = 7.6$ Hz, 3H; CH_2CH_3) 1.36 (t, $^3J_{HH} = 7.6$ Hz, 3H; CH_2CH_3), 2.18 (m, 2H; CH_2), 2.99 (q, $^3J_{HH} = 7.6$ Hz, 2H; CH_2CH_3), 3.05 (q, $^3J_{HH} = 7.6$ Hz, 2H; CH_2CH_3), 3.12 (t, $^3J_{HH} = 6.2$ Hz, 2H; CH_2), 3.24 (t, $^3J_{HH} = 6.4$ Hz, 2H; CH_2), 7.27 (m, 1H; C_6H_3), 7.58 (m, 1H; C_6H_3), 7.80 ppm (m, 1H; C_6H_3); $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$, 25 °C): $\delta = 15.0$, 15.2, 20.9, 23.4, 28.5, 34.4, 30.8, 120.7, 123.8, 129.6, 135.4, 139.1, 144.5, 152.4, 157.4 ppm; HRMS (ESI-TOF) *m/z*: calcd for $C_{16}H_{20}N$: 226.1590 $[M+H]^+$; found: 226.1570.

General procedure for the catalytic synthesis of pyridine derivatives

$[\{RuCl_2(p\text{-cymene})\}_2]$ (61.2 mg, 0.1 mmol), KPF_6 (17 mg, 0.1 mmol), and $[Cu(OAc)_2]$ (181 mg, 1 mmol) were added to a solution of allylamine **1g** (1 mmol) and alkyne **2a–f** (1 mmol) in *t*AmOH (5 mL). The reaction mixture was heated in a microwave reactor at 100 °C for 15 min or in a Young's flask for 24 h with conventional heating. After the reaction time, the solvent was removed and the residue was redissolved in CH_2Cl_2 and purified by flash column chromatography on neutral alumina with CH_2Cl_2 then CH_2Cl_2/MeOH (95:5) as the eluents. The compounds were further purified by using different methods to yield analytically pure products. The method will be specified for each case: washing, column chromatography on SiO_2 with different mixtures of solvents, and so forth. The characterization of **3ga** is shown (data for the other pyridines are collected in the Supporting Information).

2,3-Diethyl-5-methylpyridine (3ga): After flash column chromatography, the resulting solution was evaporated to dryness, and the oily residue was extracted with Et_2O (10 mL). The insoluble red oil was discarded and the solution in diethyl ether was evaporated to dryness to afford **3ga** as a pale-yellow oil (yield on conventional heating: 94 mg (63%); yield on microwave heating: 106 mg (71%)). ^{1}H NMR (400.13 MHz, $CDCl_3$, 25 °C): $\delta = 1.14$ (t, $^3J_{HH} = 7.4$ Hz, 3H; CH_3), 1.19 (t, $^3J_{HH} = 7.5$ Hz, 3H; CH_3), 2.19 (s, 3H; CH_3), 2.55 (q, $^3J_{HH} = 7.4$ Hz, 4H; CH_2), 2.71 (q, $^3J_{HH} = 7.4$ Hz, 4H; CH_2), 7.17 (d, $^4J_{HH} = 1.4$ Hz, 1H; H_4), 8.13 ppm (d, $^4J_{HH} = 1.4$ Hz, 1H; H_6); $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$, 25 °C): $\delta = 12.7$, 13.8, 16.9, 23.9, 26.5, 129.3, 134.8, 135.6, 145.8, 157.0 ppm; HRMS (ESI-TOF) *m/z*: calcd for $C_{10}H_{17}N$: 150.1277 $[M+H]^+$; found: 150.1265.

NMR experiments in situ and the formation of complex 3g·OM

In a Wilmad low-pressure NMR tube $[\{RuCl_2(\eta^6\text{-cymene})\}_2]$ (0.05 mmol, 30.6 mg), $H_2NCH_2C(Me)=CH_2$ (**1g**; 0.1 mmol, 11 μL), 3-hexyne (**2a**; 0.3 mmol, 40 μL), NaOAc (0.1 mmol, 8.3 mg), oxone (0.1 mmol, 30.7 mg), and KPF_6 (0.1 mmol, 20 mg) were suspended in CD_3OD (0.6 mL). The reaction mixture was heated at 100 °C and a clear solution was obtained once this temperature was reached. The NMR spectra were recorded at regular intervals over 24 h. After heating for 24 h at 100 °C, the only species detected in solution was complex **3g·OM**. ^{1}H NMR (500.13 MHz, CD_3OD): $\delta = 0.95$ (s, 3H; RuCCH_3), 1.16 (t, $^3J_{HH} = 7.5$ Hz, 3H; CH_2CH_3), 1.32 (d, $^3J_{HH} = 7.2$ Hz, 3H; $CH(CH_3)_2$), 1.33 (d, $^3J_{HH} = 7.2$ Hz, 3H; $CH(CH_3)_2$), 1.34 (t, $^3J_{HH} = 6.9$ Hz, 3H; CH_2CH_3), 1.61 (q, $^2J_{HH} = 11.5$ Hz, 1H; CH_2CH_3), 1.65 (d, $^3J_{HH} = 7.6$ Hz, 1H; RuCCH_2), 2.10 (s, 3H; Me, cym), 2.32 (q, $^3J_{HH} = 7.6$ Hz, 1H; CH_2CH_3), 2.45 (q, $^3J_{HH} = 7.6$ Hz, 1H; CH_2CH_3), 2.77 (septet, $^3J_{HH} = 6.7$ Hz, 1H; $CH(CH_3)_2$), 2.83 (d, $^2J_{HH} = 11.5$ Hz, 1H; RuCCH_2), 2.95 (q, $^3J_{HH} = 7.5$ Hz, 1H; CH_2CH_3), 3.83 (s, 1H; RuCCH), 5.35 (d, $^3J_{HH} = 6.0$ Hz, 1H; CH cym), 5.70 (m, 2H; CH cym), 5.92 ppm (d, $^3J_{HH} = 6.0$ Hz, 1H; CH cym); $^{13}C\{^1H\}$ NMR (125.76 MHz, CD_3OD): $\delta = 13.1$ (CH_2CH_3), 14.9 (CH_2CH_3), 17.6 (CH_3 cym), 19.2 (RuCCH_3), 20.7 ($CH(CH_3)_2$), 22.6 ($CH(CH_3)_2$), 23.3 (CH_2CH_3), 24.3 (CH_2CH_3), 31.6 ($CH(CH_3)_2$), 38.7 (Ru-*C*), 50.7 (RuCCH_2), 68.3 (RuCCH), 82.3, 82.5, 83.3, 86.2 (CH; cym), 95.9, 96.1 (C=C), 97.7, 112.2 ppm (Cquat, cym); MS (ESI^+) *m/z* (%): 389 (100) $[M+H]^+$; HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{33}NRu$: 389.1656 $[M+H]^+$; found: 389.1649.

X-ray crystallography

Crystallographic data (excluding structure factors) for the structure of **3a·OM** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1033948. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational details

All the calculations were performed at the density-functional theory (DFT) level by using the M06 functional[41] (ultrafine grid[42]) as implemented in Gaussian 09.[43] This functional correctly reproduces dispersive interactions and performs well for transition-metal chemistry.[44] The Ru atom was described by means of an effective core-potential SDD for the inner electrons and its associated double-ζ basis set for the outer electrons,[45] complemented with a set of f-polarization functions.[46] The 6–31G** basis set was used for the H, C, N, and O atoms.[47] All the intermediates and transition states were fully optimized in solution (MeOH; $\varepsilon = 32.61$) by using the continuum method SMD.[48] The transition states were identified by having one imaginary frequency in the Hessian matrix. IRC calculations[49] were used to confirm that the transition state connected the expected reactant and product states. All the reported energies correspond to Gibbs energies in MeOH in kcal mol^{-1}.

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FULL PAPER

Transition-Metal Catalysis

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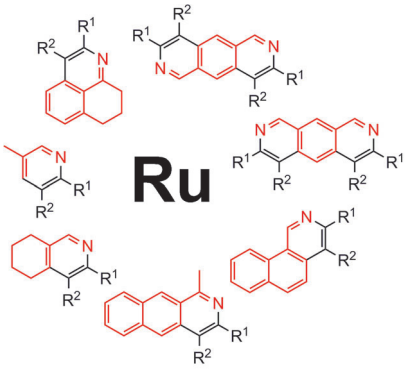
Ruthenium-Catalyzed Oxidative Coupling of Primary Amines with Internal Alkynes through C–H Bond Activation: Scope and Mechanistic Studies



Efficiency of ruthenium: The oxidative coupling of primary amines with internal alkynes catalyzed by Ru complexes is presented as a general atom-economical methodology with a broad scope of applications in the synthesis of N-heterocycles (see figure). DFT calculations support a reaction mechanism that consists of acetate-assisted C–H bond activation, migratory-insertion, and C–N bond formation steps.