Scope and Mechanistic Study of the Ruthenium-Catalyzed *Ortho*-C-H Bond Activation and Cyclization Reactions of Arylamines with Terminal Alkynes

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Abstract

The cationic ruthenium-hydride complexes, $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ and formed *in situ* from $Ru_3(CO)_{12}/HBF_4 \cdot OEt_2$, were found to be highly effective catalysts for the C-H bond activation reaction of arylamines and terminal alkynes. The regioselective catalytic synthesis of substituted quinoline and quinoxaline derivatives was achieved from the *ortho*-C–H bond activation reaction of arylamines and terminal alkynes by using the catalyst $Ru_3(CO)_{12}/HBF_4 \cdot OEt_2$. The normal isotope effect ($k_{CH}/k_{CD} = 2.5$) was observed for the reaction of $C_6H_5NH_2$ and $C_6D_5NH_2$ with propyne. A highly negative Hammett value ($\rho = -4.4$) was obtained from the correlation of the relative rates from a series of *meta*-substituted anilines m-X-$C_6H_4NH_2$ with σ_p in the presence of $Ru_3(CO)_{12}/HBF_4 \cdot OEt_2$ (3 mol% Ru; 1:3 molar ratio). The deuterium labeling studies from the reactions of both indoline and acyclic arylamines with DC≡CPh showed that the alkyne C-H bond activation step is reversible. The crossover experiment from the reaction of 1-(2-amino-1-phenyl) pyrrol with DC≡CPh and HC≡CC$_6$H$_4$-p-OMe led to the preferential deuterium incorporation to the phenyl-substituted quinoline product. A mechanism involving rate-determining *ortho*-C–H bond activation and an intramolecular C-N bond formation steps via an unsaturated cationic ruthenium-acetylide complex has been proposed.

Introduction

Considerable research has been directed to the development of catalytic C-H bond activation methods which are applicable to the synthesis of biologically important quinolines, indoles and related nitrogen heterocyclic compounds.[1] In part due to their innate ability for functional group tolerance, late transition metal catalysts have been found to be suitable for directing regio- and chemoselective C–H bond activation reactions of nitrogen compounds. For example, Rh and Ir catalysts have been successfully utilized for highly regioselective sp[2] C–H bond activation reactions of benzoimidazole and related nitrogen heterocyclic compounds,[2] and sp[3] C–H bond insertion reactions of amine compounds.[3] Chelation control methodology has been shown to be particularly effective for mediating regioselective C–H bond activation reactions of nitrogen compounds,[4] and has recently been utilized for the synthesis of pharmaceutically important polycyclic alkaloids.[5] Both inter-[6] and intramolecular[7] oxidative C–H bond activation reactions of indole and pyridine derivatives have recently been achieved by using Pd, Pt and Cu catalysts. A remarkably selective catalytic sp[3] C-H bond oxidative amination method has been successfully applied to the synthesis of amino acid derivatives.[8]

Inspired by recent reports on the unusual reactivity of late-metal amido complexes,[9] we have begun to explore the catalytic activity of well-defined ruthenium-amido complexes for N-H

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and other unreactive bond activation reactions.[10] We recently discovered that the cationic ruthenium-hydride complexes are highly effective catalysts for the regioselective intermolecular C-H bond activation reaction of benzocyclic amines with terminal alkynes.[11] The catalytic method efficiently produces tricyclic quinoline derivatives from the direct coupling of unprotected amines and terminal alkynes without chelate-directing groups. This report delineates the scope and mechanistic study of the ruthenium-catalyzed C-H bond activation and cyclization reactions of arylamines and terminal alkynes.

Results and Discussion

Reaction Scope

While studying the ruthenium-catalyzed hydroamination and other C-C bond forming reactions, we initially discovered that the cationic ruthenium-hydride complex $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ (**1**) is an effective catalyst for the coupling reaction of benzocyclic amines and terminal alkynes (eq 1).[11] For example, the treatment of indoline (30 mg, 0.25 mmol) with excess propyne (20 equiv) in the presence of **1** (5 mol %) in benzene at 95 °C for 24 h cleanly produced the tricyclic products **2a** and **3a** (15:1) in 81% combined yield (eq 1).

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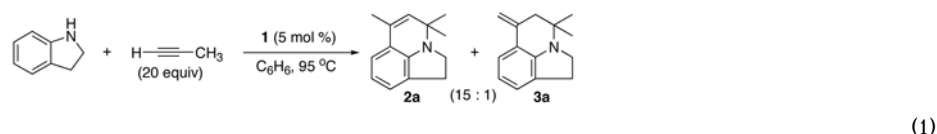
Since the complex **1** was found to be less effective for electron-deficient terminal alkynes, the activity of commonly available ruthenium catalysts and additives was surveyed to find a suitable catalytic system. The complex $Ru_3(CO)_{12}$ (**4**) with an additive NH_4PF_6 or $HBF_4 \cdot OEt_2$ was found to be the most effective catalyst for the coupling reaction of amines and alkynes.[12] For example, 1 mol % of **4**/NH_4PF_6 (1:3 molar ratio) gave a nearly quantitative yield of **2a** and **3a** (20:1, 99% combined yield) in less than 12 h for the reaction of indoline with propyne. Previously, the catalytic system $Ru_3(CO)_{12}$/NH_4PF_6 has been utilized for the hydroamination and C-C bond activation reactions.[13]

The reaction scope of benzocylic amines and alkynes was explored by using the catalytic system **4**/NH_4PF_6. Both 5- and 6-membered benzocyclic amines were found to readily undergo the regioselective coupling reaction with terminal alkynes to give the tricyclic products **2** and **3**. In most cases, only trace amounts of the isomerization products **3** were formed. Both aliphatic and aryl-substituted terminal alkynes were found to be suitable substrates, but no coupling product was formed with sterically demanding terminal alkynes such as 3-methyl-1-butyne and internal alkynes. A detailed description of the catalytic reaction has recently been reported.[11]

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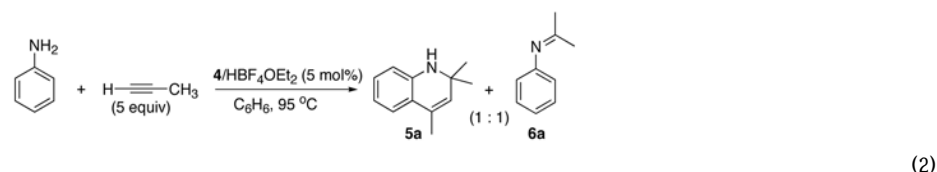
In an effort to extend the scope, we next surveyed the catalytic coupling reactions of acyclic arylamines and terminal alkynes. Initially, the reaction of aniline (50 mg, 0.54 mmol) and excess propyne (2.5 mmol) in the presence of **4**/$HBF_4 \cdot OEt_2$ (5 mol% **2**, 1:3 molar ratio) in benzene at 95 °C produced a ~1:1 mixture of the *ortho*-C–H bond activation product **5a** and the hydroamination product **6a** in ca. 80% combined yield (eq 2). A few optimization efforts

such as increasing alkyne concentration or altering the ratio of catalyst/co-catalyst did not significantly improve the product yield of **5a**. The organic products were readily separated by column chromatography and the structure was completely established by spectroscopic methods.

We reasoned that the *ortho*-C–H bond activation would be strongly influenced by the *meta*-substituent of arylamines. Indeed, *meta*-electron–donating group was found to promote the *ortho*-C–H bond activation of aniline to give the products **5** preferentially over the hydroamination products **6**, in which cases, less than 5% of **6** was formed in the crude reaction mixture (Table 1, entries 2–6). Both alkyl– and aryl–substituted terminal alkynes were found to be suitable substrates for the secondary arylamine (entries 8–11). For 3,4-disubstituted anilines, the coupling products **5l** and **5m** were formed from the *ortho*-C–H bond activation para to the electron–donating group R″ (entry 12, 13). Similar regioselective *ortho*-C–H bond activation was also observed for the functionalized bicyclic arylamines to give the tricyclic quinoline products **5n**–**5q** (entries 14–17). In contrast, arylamines with an electron–withdrawing group (e.g., *m*-chloroaniline) formed <5% of the C-H bond activation product **5** under the similar reaction conditions, giving mostly the hydroamination product (~90%). Substituted hydroquinoline core structure is commonly present in a variety of natural products and pharmaceutical agents.[14]

The catalytic method was successfully extended to the synthesis of quinoxaline derivatives (Table 2). Thus, the treatment of 1-(2-amino-1-phenyl)pyrrol with terminal alkynes gave the quinoxaline products **7**, in which α-pyrrole sp^2 C–H bond has been selectively activated (entries 1–4). Similarly, the coupling products **8** and **9** were resulted from the regioselective C–H bond activation/cyclization of N-(2-aminophenyl)- and 2-(2-aminophenyl)indoles, respectively (entries 5–10). Only one equivalent of terminal alkyne has been regioselectively inserted to sp^2 C–H bond to give the cyclic products for these cases. The quinoxaline derivatives have been shown to display a variety of biologically important functions including as agents for the treatment of tuberculosis.[15]

Mechanistic Study: Isotope Effect

The mechanism of the catalytic reaction was examined by employing both indoline and acyclic arylamines. First, a normal deuterium isotope effect was observed from the reaction of $C_6H_5NH_2$ and $C_6D_5NH_2$ with propyne. The pseudo–first order plots of the catalytic reaction of both $C_6H_5NH_2$ and $C_6D_5NH_2$ with propyne at 95 °C gave $k_{obs} = 9.6 \times 10^{-2}$ h^{-1} and $k_{obs} = 3.9 \times 10^{-2}$ h^{-1}, respectively, from which $k_{CH}/k_{CD} = 2.5\pm0.1$ was calculated (Figure S1, Supporting Information). In contrast, analogous reactions of m-OMe-C_6H_5NHCH$_3$ and m-OMe-C_6H_5NDCH$_3$ with propyne, and aniline with HC≡CPh and DC≡CPh at 95 °C gave negligible isotope effects of $k_{NH}/k_{ND} = 1.1\pm0.1$ and $k_{CH}/k_{CD} = 1.05\pm0.1$, respectively. These results indicate that the arene C-H bond activation is the rate-limiting step for the catalytic reaction.

Hammett Study

The electronic effect of the *ortho*-C-H bond activation was examined for a number of different *meta*-substituted anilines. The Hammett ρ = −4.4 was obtained from the correlation of the relative rates with σ$_p$ for a series of *meta*-substituted anilines m-X-C_6H_4NH$_2$ (X = OMe, CH$_3$, H, F) with propyne in the presence **4**/HBF$_4$·OEt$_2$ (3 mol% **4**, 1:3 molar ratio) at 95 °C (Figure 1). Such highly negative ρ value has been commonly observed in organic substitution reactions involving a carbocation intermediate.[16] In our case, a highly negative ρ value suggests considerable cationic character on the transition state of arene C-H bond activation step via the formation of ruthenium-aryl species. The hydroamination product **6** was formed predominantly for the anilines with an electron-withdrawing group (for example, 85% of **6** and

~10% of **5** for *m*-F-C$_6$H$_4$NH$_2$), and this may be due to a relatively unfavorable *ortho*-C-H bond activation compared to the hydroamination reaction path. The fact that no correlation was observed between the relative rates of aniline with aryl-substituted alkynes *p*-X-C$_6$H$_4$C≡CH (X = OMe, CH$_3$, Cl, F) and the Hammett σ$_p$, indicates that the alkyne C-H bond activation step is not rate-limiting.

The coupling reaction catalyzed by **1** was found to be strongly inhibited by added phosphines. For example, the addition of 5 mol% of PCy$_3$ under the reaction conditions shown in eq 1 led to <30% of the product **2a** after 24 h. The pseudo-first order plots showed that the observed rate constant from the reaction with 5 mol% of added PCy$_3$ ($k_{obs} = 4.9 \times 10^{-2}$ h^{-1}) was found to be nearly three times smaller than the rate under normal conditions ($k_{obs} = 1.7 \times 10^{-1}$ h^{-1}) (Figure S2, Supporting Information). This result suggests that the reactive species is generated from the reversible dissociation of phosphines for the reactions catalyzed by **1**.

Deuterium Labeling Study

The reaction of indoline with excess DC≡CPh (10 equiv) and **4**/NH$_4$PF$_6$ (3 mol%) yielded the product **2b** with extensive deuterium incorporation on both vinyl (85%) and methyl (81%) positions as well as on the arene hydrogen para to the amine group (~50%) as measured by both ^{1}H and ^{2}H NMR (eq 3). Conversely, ca. 25% of the methyl group and 30% of the vinyl hydrogen of **2b** were found to contain the deuterium when *N*-deuterated indoline was reacted with 10 equiv of HC≡CPh.

(3)

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(5)
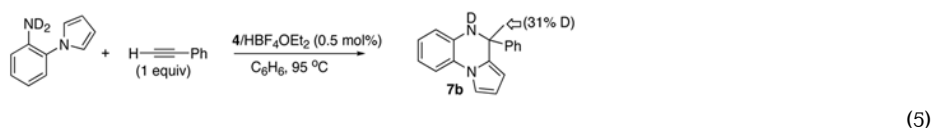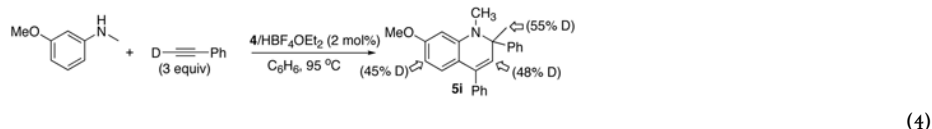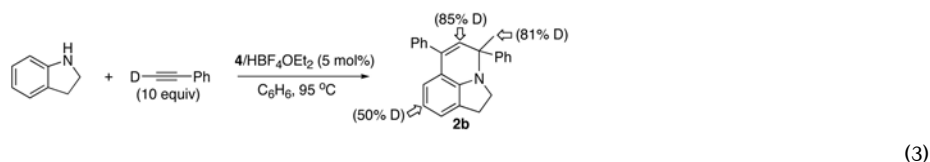
Similar results were obtained from the reactions of acyclic arylamines. For example, the treatment of *m*-OMe-C$_6$H$_4$NHCH$_3$ with DC≡CPh (3 equiv) gave the product **5i** with extensive deuterium incorporation on both α-methyl (55%) and vinyl (48%) as well as on the arene positions (45% combined at C$_6$ and C$_8$) (eq 4). Lower deuterium incorporation was observed to **5i** compared to **2b**, and this may be in part due to the smaller amount of DC≡CPh than in eq 3 and slower reaction rate for an acylic secondary amine, which might have led to H/D exchange to other arene positions. Conversely, the reaction of *m*-OMe-C$_6$H$_4$NDCH$_3$ with HC≡CPh (3 equiv) resulted in **5i** with significant amounts of deuterium on α-methyl (18%), vinyl (10%) and arene (11%) positions. The similar deuterium incorporation pattern was also observed for one-to-one coupling reaction of N-deuterated 1-(2-amino-1-phenyl)pyrrol with HC≡CPh (1 equiv) (eq 5). In this case, the deuterium was selectively incorporated to the α-methyl group (31%) of **7b** without significant exchange to other arene positions. In a control experiment, the treatment of *m*-OMe-C$_6$H$_4$NHCH$_3$ with DC≡CPh (3 equiv) in the presence of HBF$_4$·OEt$_2$ (6 mol%) under otherwise similar conditions led to <5% of deuterium exchange

to the *ortho*- and *para*-arene positions of *m*-OMe-C$_6$H$_4$NHCH$_3$ after 24 h of reaction time at 95 °C, without forming any measurable amount of the product **5i**. These results indicate that both the N–H and the acetylenic C–H bond activation steps are reversible.

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(7)
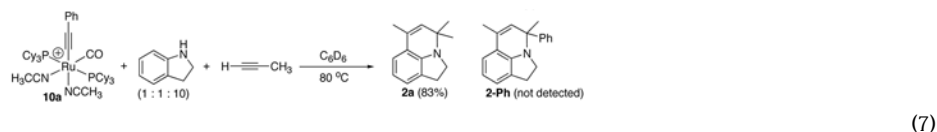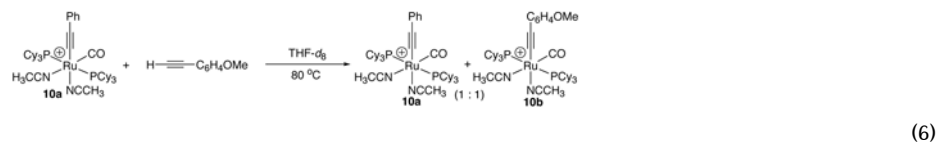
Reactions of the Cationic Ruthenium-Acetylide Complex

We previously detected the formation of cationic ruthenium-acetylide complexes during the catalytic reactions mediated by **1**. The cationic ruthenium-acetylide complex [(PCy$_3$)$_2$(CO) (CH$_3$CN)$_2$RuC≡CPh]$^+$BF$_4^-$ (**10a**) was subsequently isolated in 81% yield from the reaction of **1** with HC≡CPh in THF, and its structure was established by X-ray crystallography.[11] The activity of isolated complex **10a** was found to be very similar to that of **1** for the catalytic coupling reactions of both indoline and aniline with terminal alkynes. The isolation of the catalytically active complex **10a** enabled us to further examine the reactions that are relevant to the catalysis. For example, the treatment of **10a** with HC≡CC$_6$H$_4$-*p*-OMe (5 equiv) in THF for 3 h at 80 °C produced a ~1:1 mixture of **10a** and the alkyne-exchanged complex [(PCy$_3$)$_2$(CO)(CH$_3$CN)$_2$RuC≡CC$_6$H$_4$-*p*-OMe]$^+$BF$_4^-$ (**10b**) (eq 6). Similarly, the reaction of **10a** with indoline (1 equiv) and propyne (10 equiv) was monitored by NMR (eq 7). In this case, only the propyne coupling product **2a** was formed without any observable amount of the phenyl-substituted product **2-Ph**. Both of these results indicate that the alkyne exchange process is relatively facile under the catalytic reaction conditions.

Mechanism of the Catalytic Reaction

We initially considered a few different mechanistic pathways to explain the formation of C-H bond activation products. One of the possible mechanisms involves a sequential *ortho*-C-H bond activation and hydroamination reactions as depicted in Scheme 1. The key features of this mechanism are that the ruthenium-mediated *ortho*-C-H bond insertion of an alkyne to form the *ortho*-vinylated amine, the hydroamination of the second alkyne and the subsequent electrocyclization to give the product **5**. Both hydroamination of alkynes and *ortho*-C-H bond insertion of arylamines have been well-documented in the literature.[1,17]

We reasoned that the reaction of independently prepared 2-vinylaniline with terminal alkynes would result the product **5** under the similar catalytic conditions if 2-vinylaniline is an intermediate for the catalytic reaction. We tested this hypothesis by examining the reaction of 2-isopropenylaniline with terminal alkynes (Scheme 2). The hydroamination product **6-Ph** was *exclusively* produced from the reaction of 2-vinylaniline with phenylacetylene under the catalytic conditions, and moreover, **6-Ph** was not converted to the cyclized product **5-Ph** even after prolonged heating at 95 °C for 48 h. In a separate experiment, the treatment of the independently formed hydroamination product **6b** with excess propyne did not give the cyclized product **5-Ph**. Though the reaction of independently generated 2-isopropenylaniline with excess propyne resulted in a mixture of products **5a** and **6-Me** (40 : 60), the hydroamination product **6-Me** was not converted to the cyclized product **5a** under the reaction conditions. The treatment of **6a** with excess propyne did not give the product **5-Ph**, either. The similar [3,3]-electrocyclic reactions are often conducted under strongly acidic conditions at

elevated temperature,[18] and we believe that HBF_4 might have acted as an acid catalyst in forming the cyclization product **5a** in the case of propyne. Since the formation of hydroamination product **6** is generally much favored over the *ortho*-C-H bond insertion product **5** for the reaction of arylamines with alkynes and that **6** does not convert to the cyclized product **5**, 2-isopropenylaniline cannot be a viable intermediate for the catalytic reaction. Uchimaru also reported that the reaction of arylamines with alkynes predominantly formed the hydroamination product over the *ortho*-C-H bond activation product.[13b] Taken these results together, we ruled out the sequential mechanism of *ortho*-vinylation and hydroamination of alkynes for the catalytic reaction.

The observed data are consistent with a mechanism involving an unsaturated cationic ruthenium–acetylide complex **10** as the key species (Scheme 3). We previously showed that the catalytically active acetylide species **10a** is generated during the reactions catalyzed by the cationic hydride complex **1**. Two possible mechanistic pathways can be considered for the C-N bond forming step from **10**, an intermolecular nucleophilic addition vs an intramolecular migratory insertion mechanism (Scheme 4), both of which would lead to the cationic enaminyl species **11**. The subsequent *ortho*-arene C-H bond activation and the reductive elimination of vinyl group would form the *ortho*-metallated species **12**. The fact that extensive deuterium incorporation to aryl positions on the product **5** can be rationalized by the formation of *meta*- and *para*-metallated species from reversible arene-C-H bond activation steps, of which the enamine-coordinated *ortho*-metallated species would lead to the product formation. Furthermore, the results from the deuterium labeling studies indicate that the arene C-H bond activation step is reversible as shown in Scheme 3. Both the normal isotope effect of k_{CH}/k_{CD} and a highly negative Hammett ρ value are consistent with the arene C–H bond activation rate–limiting step. The negative ρ value also suggests the formation of cationic ruthenium-aryl species during the arene *ortho*-C–H bond activation step. The second alkyne insertion and the regioselective migratory insertion/cyclization steps would yield the cationic alkyl species **13**. Since **13** does not have any β-hydrogens, either the oxidative addition/reductive elimination or the σ-bond metathesis of the terminal alkyne must be invoked for the formation of **5** and the regeneration of the acetylide complex **10**. For arylamines with a *meta*-electron-withdrawing group, the predominant formation of hydroamination product **6** can be readily rationalized by the preferential oxidative addition/reductive elimination of another terminal alkyne from **11**. Site–selective C–H activation and functionalization reactions by trimetallic $Ru_3(CO)_{12}$ have been observed for a number of different catalytic reactions.[19]

Two different pathways have been commonly proposed for the hydroamination reactions. For example, Hartwig provided strong evidence for an intermolecular nucleophilic addition mechanism for the Pd-catalyzed hydroamination of aryl-substituted alkenes.[20] Both concerted and stepwise intramolecular migratory insertion mechanisms via metal-amido complexes have been commonly proposed for early transition and lanthanide metal-mediated hydroamination reactions.[21] In our case, intermolecular nucleophilic addition of amine to the β-acetylide carbon and the subsequent proton transfer would form the enaminyl intermediate **11** (Scheme 4, Path A). Alternatively, the formation of an alkyne-coordinated amido complex (from initial N-H bond activation and the hydrogen transfer to the acetylide ligand) and the intramolecular migratory insertion of the amido group should lead to the same enaminyl intermediate **11** (Path B).

We envisioned a crossover experiment to probe between inter- vs intramolecular mechanistic pathways for the C-N bond-forming step (Scheme S1, Supporting Information). We reasoned that the amount of deuterium atoms at the α-methyl positions reaction of an arylamine with a 1:1 mixture of $DC{\equiv}CPh$ and $HC{\equiv}CC_6H_4$-*p*-OMe would be significantly different for the inter- vs intramolecular mechanisms. According to the *intermolecular* nucleophilic addition mechanism, an equal amount of deuterium (17%) is expected to be incorporated to both α-

CH$_3$ groups of the products from the statistical H/D distribution of the alkyne C-H bond to the products (Scheme S1, Path A). The sequential mechanism as described in Scheme 1 would also result in a similar deuterium incorporation pattern. In contrast, the *intramolecular* migratory insertion mechanism is expected to give the products with a substantially higher deuterium incorporation to the α-CH$_3$ of the phenyl-substituted product (50%) compared to that of *p*-OMe-C$_6$H$_4$-substituted product (17%), if one assumes a rapid and reversible alkyne substrate exchange and the subsequent statistical H/D distribution from alkyne C-H bond oxidation/reductive elimination steps (Scheme S1, Path B).
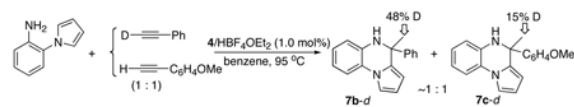
(8)

Initial reaction survey for both indoline and *meta*-substituted aniline with a mixture of two different alkynes produced a complex mixture of both homo- and cross-coupling products. To simplify the product analysis, pyrrol-substituted aniline was employed since it incorporates only one equivalent of terminal alkyne per molecule of amine. Thus, the treatment of 1-(2-aminophenyl)pyrrole (1.9 mmol) with a 1:1 mixture of DC≡CPh and HC≡CC$_6$H$_4$-*p*-OMe (1 equiv each) in the presence of the catalyst **4**/HBF$_4$·OEt$_2$ (1 mol%) at 95 °C in benzene solution produced ~1:1 mixture of **7b**–*d* and **7c**–*d* after 24 h (eq 8). The products were separated by a simple column chromatography on silica gel, and the deuterium content of the products was analyzed by both ^{1}H and ^{2}H NMR. The NMR analysis clearly showed substantially higher deuterium incorporation on the α-CH$_3$ group of **7b**–*d* (48%) compared to that of **7c**–*d* (15%). In a control experiment, the reaction in the absence of the ruthenium catalyst **4** neither resulted in any significant H/D exchange between DC≡CPh and HC≡CC$_6$H$_4$-*p*-OMe nor gave any measurable products **7**. Thus, the observed deuterium incorporation pattern must have occurred during the catalytic reaction, and provides a strong evidence for the *intramolecular* migratory insertion mechanism.

Conclusion

A new catalytic C-H bond activation/cyclization protocol has been developed for the synthesis for quinoline and quinoxaline derivatives. The mechanistic data are consistent with the mechanism involving an intramolecular migratory insertion of amine and the subsequent *ortho*-C-H bond activation and cyclization via an unsaturated cationic ruthenium-acetylide complex. The catalytic C-H bond activation/cyclization method should find a range of new applications for the synthesis of quinoline and other nitrogen heterocyclic compounds.

Experimental Section

General Information

All operations were carried out in a nitrogen-filled glove box or by using standard high vacuum and Schlenk techniques unless otherwise noted. Tetrahydrofuran, benzene, hexanes and Et$_2$O were distilled from purple solutions of sodium and benzophenone immediately prior to use. The NMR solvents were dried from activated molecular sieves (4 Å). All amine and alkyne substrates were received from commercial sources and used without further purification. RuCl$_3$·3H$_2$O and Ru$_3$(CO)$_{12}$ were obtained from commercial sources, and the complex **1** was prepared by following a reported procedure.[22] The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury 300 MHz FT-NMR spectrometer. Mass spectra were recorded from a Hewlett-Packard HP 5970 GC/MS spectrometer. High-resolution FAB mass spectra

were obtained at the Center of Mass Spectrometry, Washington University, St. Louis, MO. Elemental analyses were performed at the Midwest Microlab, Indianapolis, IN.

Isotope Effect Study

In a glove box, an equal amount of $C_6H_5NH_2$ and $C_6D_5NH_2$ (0.4 mmol, 37 µL) was added via a syringe to two separate 25 mL Schlenk tubes. Predissolved $Ru_3(CO)_{12}$ (8 mg, 3 mol %) in benzene solution (3 mL) was added to each Schlenk tubes. The reaction tubes were brought out of the box and $HBF_4 \cdot OEt_2$ (8 µL, 9 mol % based on amine) was added to each tube under a nitrogen stream. The reaction tubes were cooled in a liquid nitrogen bath, and excess propyne (2 mmol) was condensed into each tube via a vacuum line transfer. The reaction tubes were warmed to room temperature, and stirred in an oil bath at 95 °C. A small portion of the aliquot under a nitrogen stream was drawn periodically from the reaction tube, and the product conversion was determined by GC.

Hammett Study

In a glove box, *meta*-substituted aniline m-X-$C_6H_4NH_2$ (X = OMe, CH_3, H, F) (0.54 mmol), $Ru_3(CO)_{12}$ (10 mg, 0.016 mmol) and benzene (3 mL) were added to each of four separate 25 mL Schlenk tubes equipped with a stirring bar. The reaction tubes were brought out of the box, and $HBF_4 \cdot OEt_2$ (10 µL, 9 mol % based on amine) was added to each tube under a nitrogen stream. The reaction tubes were cooled in a liquid nitrogen bath, and excess propyne (2 mmol) was condensed into each tube via a vacuum line transfer. The reaction tubes were warmed to room temperature, and stirred in an oil bath at 95 °C. A small portion of the aliquot under a nitrogen stream was drawn periodically from each reaction tube. The k_{obs} was determined from a first-order plot of ln[**5**] vs time as measured by the appearance of the product **5** by GC.

Representative Procedure of Deuterium Labeling Study: Reaction of m-OMe-$C_6H_4NHCH_3$ with DC≡CPh

In a glove box, m-OMe-$C_6H_4NHCH_3$ (300 mg, 2.2 mmol), DC≡CPh (676 mg, 6.6 mmol), $Ru_3(CO)_{12}$ (28 mg, 43 µmol) were dissolved in 5 mL benzene in a 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and $HBF_4 \cdot OEt_2$ (28 µL, 3 equiv based on Ru) was added via a microsyringe under a stream of nitrogen. The reaction tube was stirred in an oil bath at 95 °C for 24 h. The solvent was removed from a rotary evaporator, and the organic product was isolated by a column chromatography on silica gel (hexane/CH_2Cl_2 = 3:2). The deuterium content of the product **5i** was measured by both ^1H NMR ($CDCl_3$ and cyclohexane (10 mg, external standard)) and ^2H NMR (CH_2Cl_2 and $CDCl_3$ (0.05 mL)).

Crossover Experiment

In a glove box, 1-(2-aminophenyl)pyrrole (300 mg, 1.9 mmol), DC≡CPh (196 mg, 1.9 mmol), HC≡C-C_6H_4-p-OMe (250 mg, 1.9 mmol) and $Ru_3(CO)_{12}$ (0.012 mg, 0.019 mmol) were dissolved in 5 mL benzene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and $HBF_4 \cdot OEt_2$ (3 eq based on ruthenium) was added via a microsyringe under a stream of nitrogen. The reaction tube was stirred in an oil bath at 95 °C for 24 h. The solvent was removed from a rotary aspirator, and the organic products **7b** and **7c** were isolated by a column chromatography on silica gel (hexane/CH_2Cl_2 = 1:1). The deuterium content of each product was measured by both ^1H NMR ($CDCl_3$, cyclohexane as an external standard) and ^2H NMR (CH_2Cl_2 and 0.05 mL of $CDCl_3$).

Phosphine Inhibition Study

In a glove box, complex **1** (36 mg, 5 mol %), PCy$_3$ (12 mg, 5 mol %) and indoline (100 mg, 0.8 mmol) were dissolved in 5 mL of benzene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and cooled in a liquid nitrogen bath. Excess propyne (20 mmol) was condensed into the tube via a vacuum line transfer. The reaction tube was warmed to room temperature, and stirred in an oil bath at 95 °C. A small portion of the aliquot was drawn periodically from the reaction mixture under a nitrogen stream, and the product conversion was determined by GC.

General Procedure of the Catalytic Reaction

In a glove box, an amine (1–2 mmol), a terminal alkyne (5–10 mmol) and Ru$_3$(CO)$_{12}$ (10–50 mg, 1–5 mol %) were dissolved in 5 mL benzene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and HBF$_4$·OEt$_2$ (10–50 μL, 3 equiv based on Ru) was added via a microsyringe under a stream of nitrogen. The vacuum-line technique was used to transfer volatile alkynes such as propyne and 1-butyne. The reaction tube was stirred in an oil bath at 95 °C for 16–24 h. The tube was opened to air at room temperature, and the crude product mixture was analyzed by GC. The solvent was removed from a rotary evaporator, and the organic product was isolated by a column chromatography on silica gel (hexane/CH$_2$Cl$_2$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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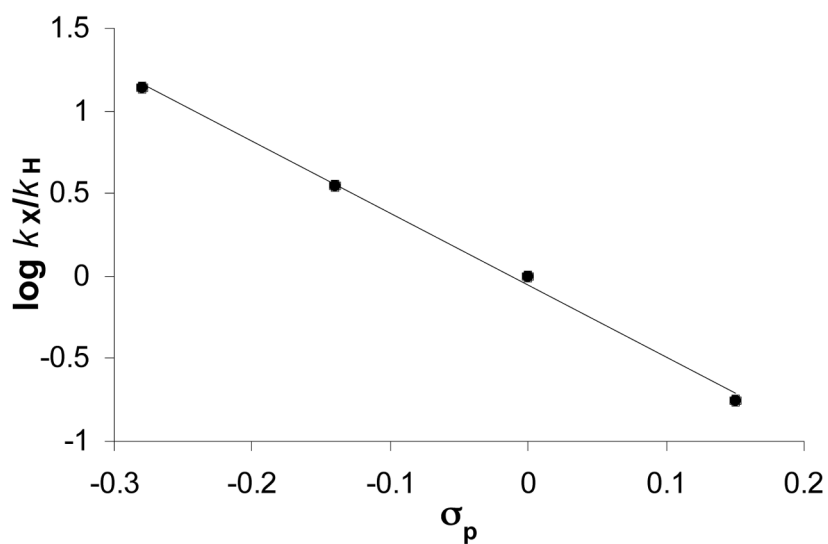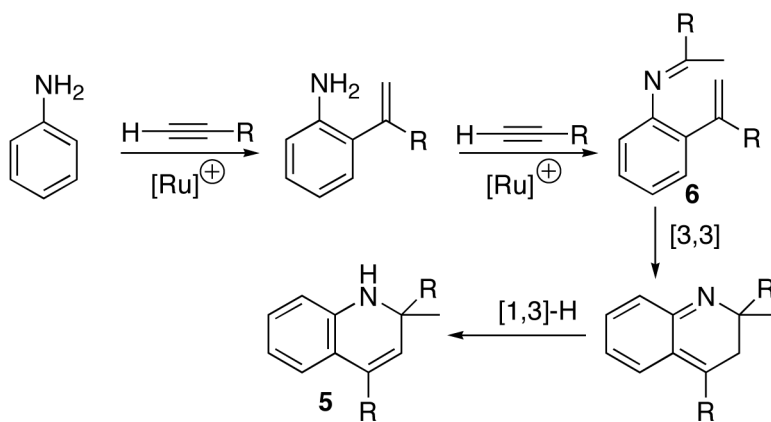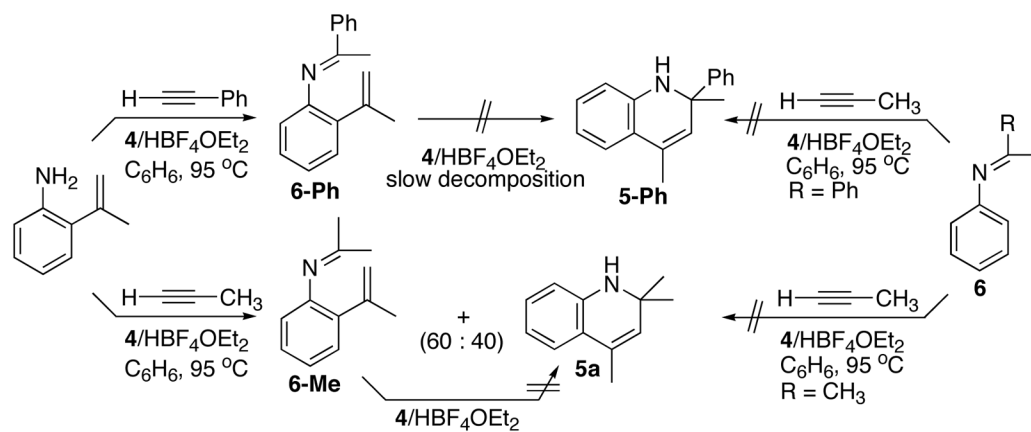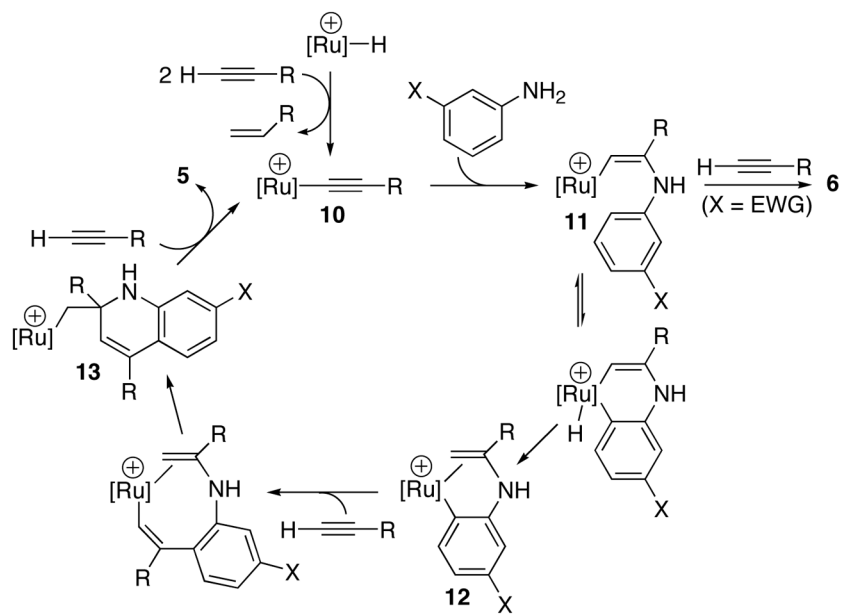
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Figure 1.
Hammett plot for the coupling reaction of m-X-$C_6H_4NH_2$ (X = OMe, CH_3, H, F) with $HC{\equiv}CCH_3$ using the catalyst **4**/$HBF_4{\cdot}OEt_2$ (3 mol%, 1:3 ratio).

Scheme 1.

Scheme 2.

Scheme 3.

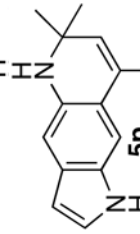Path A. Intermolecular nucleophilic addition of amine.
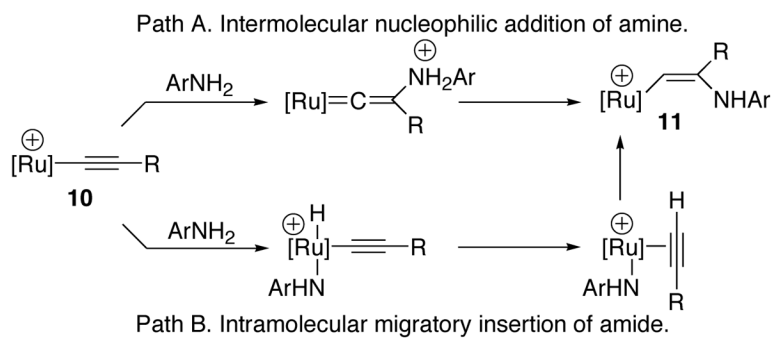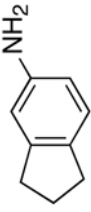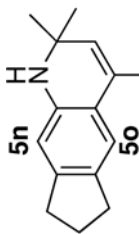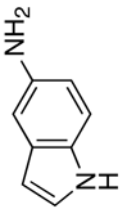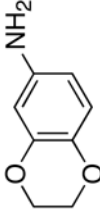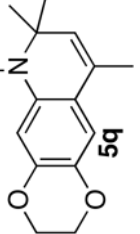
Scheme 4.

Table 1

The coupling reaction of arylamines and terminal alkynes.[a]

entry	amine	alkyne	product	4 (mol %)	t (h)	yd (%)[b]
1	X = H	R = Me	5a	5	24	43[c]
2	X = Me	R = Me	5b	2	24	83
3	X = i-Pr	R = Et	5c	2	24	51
4	X = OMe	R = Me	5d	1	20	90
5	X = OMe	R = n-Bu	5e	3	24	78
6	X = OPh	R = Me	5f	2	24	92
7	X = OH	R = Me	5g	5	24	38[c]
8		R = Me	5h	2	20	93
9		R = Ph	5i	3	24	88
10		R = C$_6$H$_4$-p-OMe	5j	3	24	69
11		R = 2-SC$_4$H$_3$	5k	2	24	94
12	R' = OMe	R'' = OMe	5l	1	16	90
13	R' = Cl	R'' = Me	5m	5	24	42[c]
14		5n		4	24	92

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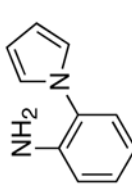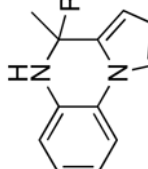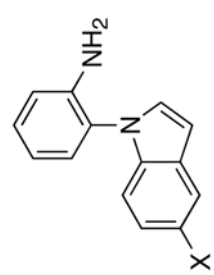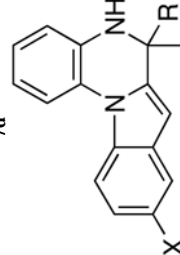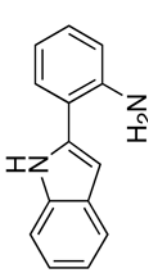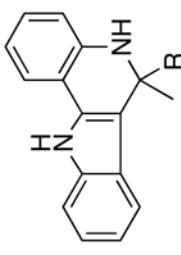
entry	amine	alkyne	product	4 (mol %)	t (h)	yd (%)[b]
15		5o	5n, 5o	4	24	85
16		5p	5p	4	24	41[c]
17		5q	5q	2	24	81

[a] Reaction conditions: amine (1.5 mmol), alkyne (5–10 mmol), Ru3(CO)12/HBF4·OEt2 (1:3), benzene (2–5 mL), 90–100 °C.

[b] Isolated yield based on amine.

[c] 40–50% of 6 was formed.

Table 2

The coupling reaction of pyrrol– and indol–substituted aniline and terminal alkynes.[a]

entry	amine	alkyne	product		4 (mol %)	t (h)	yd (%)[b]
1		R = Et		7a	1	24	96
2		R = Ph		7b	2	24	93
3		R = C₆H₄-p-OMe		7c	2	20	90
4		R = 2-SC₄H₃		7d	5	24	92
5		R = Me		8a	2	20	93
6		R = p-Tol		8b	3	24	75
7		R = C₆H₄-p-Cl		8c	3	24	70
8		R = Et		8d	3	24	82
9		R = n-Bu		9a	5	20	70
10		R = Ph		9b	5	24	91

[a] Reaction conditions: amine (1.5 mmol), alkyne (2–5 mmol), Ru₃(CO)₁₂/HBF₄·OEt₂ (1:3), benzene (2–5 mL), 90–95 °C.

[b] Isolated yield based on amine.