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Published in:
Journal of the American Chemical Society

DOI:
10.1021/jacs.5b04858

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Heriot-Watt University Research Portal

Citation for published version (APA):
Experimental and DFT Studies Explain Solvent Control of C–H Activation and Product Selectivity in the Rh(III)-Catalyzed Formation of Neutral and Cationic Heterocycles

David L. Davies, Charles E. Ellul, Stuart A. Macgregor, Claire L. McMullin, and Kuldeep Singh

1 Department of Chemistry, University of Leicester, Leicester, LE1 7RH, United Kingdom
2 Institute of Chemical Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, United Kingdom

ABSTRACT: A range of novel heterocyclic cations have been synthesized by the Rh(III)-catalyzed oxidative C–N and C–C coupling of 1-phenylpyrazole, 2-phenylpyridine, and 2-vinylpyridine with alkyynes (4-octyne and diphenylacetylene). The reactions proceed via initial C–H activation, alkyne insertion, and reductive coupling, and all three of these steps are sensitive to the substrates involved and the reaction conditions. Density functional theory (DFT) calculations show that C–H activation can proceed via a heteroatom-directed process that involves displacement of acetate by the neutral substrate to form charged intermediates. This step (which leads to cationic C–N coupled products) is therefore favored by more polar solvents. An alternative non-directed C–H activation is also possible that does not involve acetate displacement and so becomes favored in low polarity solvents, leading to C–C coupled products. Alkyne insertion is generally more favorable for diphenylacetylene over 4-octyne, but the reverse is true of the reductive coupling step. The diphenylacetylene moiety can also stabilize unsaturated seven-membered rhodacycle intermediates through extra interaction with one of the Ph substituents. With 1-phenylpyrazole this effect is sufficient to suppress the final C–N reductive coupling. A comparison of a series of seven-membered rhodacycles indicates the barrier to coupling is highly sensitive to the two groups involved and follows the trend C–N > C–N > C–C (i.e., involving the formation of cationic C–N, neutral C–N, and neutral C–C coupled products, respectively).

1. INTRODUCTION

Methods to form polycyclic heterocycles through the construction of C–Y bonds (Y = C, N and O) are of vital importance for the synthesis of molecules targeting applications in pharmaceuticals and materials science. Moreover, new processes that realize this goal via the direct functionalization of C–H bonds are particularly desirable, as they avoid the prefunctionalization of the coupling partners and so benefit from an inherently improved atom economy. Among the range of late transition metals used for such catalytic C–H functionalization, dramatic progress has been made recently in Rh-catalyzed oxidative coupling, with high selectivity and functional group tolerance affording a variety of C–Y coupled products.1 In this regard the behavior of phenylpyrazoles presents some interesting contrasts. We and others recently demonstrated that the Rh- and Ru-catalyzed reactions of 3-phenylpyrazoles with internal alkynes lead to C–N coupled heterocycles (Scheme 1a).2 However, with 1-phenylpyrazole (1, Scheme 1b) only C–C coupled heterocycles have been reported to date; moreover the precise outcome depends on both the nature of the alkylene and the solvent.3 Previous studies from our groups have provided some mechanistic insight into the behavior of 1-phenylpyrazole. This species undergoes acetate-assisted C–H activation with both [MCl₂Cp*]₂ (M = Rh, Ir) and [RuCl₂(p-cymene)]₂ to form cyclometalated products (see Scheme 1c for the Rh complex, 2). These can then readily (room temperature) undergo insertion of either dimethylacetylene dicarboxylate or diphenylacetylene into the M–C bond to give seven-membered rhodacycles.4 No evidence for any subsequent C–N bond coupling to form a cationic heterocycle was seen. Indeed, it has been suggested that C–N coupling might only occur with anionic directing groups that result in neutral heterocycles.1d However, recently a number of groups have shown that cationic C–N coupled products can be formed with the involvement of a neutral directing group.5 The balance between C–C bond formation (to neutral products) and C–N bond formation (to cationic products) can be subtle, with Li and co-workers highlighting the role of the nature of the carboxylate and silver salts employed.5j In earlier work Pfeffer et al. showed that alkyne insertion into cycloruthenated N,N-dimethylbenzylamine gave seven-membered heterocycles with electron-withdrawing substituents on the alkyne but gave C–N coupling with electron-rich alkynes.6 Hence, the effect of a
formation of cyclometalated activation assisted by a heteroatom directing group suggest the product selectivity.

Our study to the reactions of 2-phenylpyridine, tricyclic and tetracyclic heterocyclic products. We also extend the subtleties of modeling the energetics associated with the full C−H activation and functionalization catalytic cycle. Herein, we report new C−H activation and functionalization catalytic cycle.2a,9 We have also highlighted the diﬀerent outcomes seen in the reactions of alkynes with 1-phenylpyrazole, 1, and 4-octyne (a).

2. EXPERIMENTAL STUDIES

The different outcomes seen in the reactions of alkynes with 1-phenylpyrazole (Scheme 1b) prompted us to examine the reaction of the key C−H activated intermediate 2 with 4-octyne (a, Scheme 2). Remarkably, in MeOH a further new product, 1,3,5-trinonylpyridine, 8, and 2-vinylpyridine, 9, for which only C−N coupling is observed. DFT studies provide further mechanistic insight and in combination with experiment offer a rationale for the observed product selectivities. These reaction outcomes are sensitive to the combination of the heterocyclic and alkyne substrates involved as well as the choice of solvent and counterion. Understanding the interplay of these reaction variables is vital in the design of new catalytic processes for C−H functionalization that, as well as being efficient, must also allow control in product selectivity.

Table 1. Rh-Catalyzed Heterocycle Formation with 1-Phenylpyrazole, 1, and 4-octyne (a)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>equiv alkyn</th>
<th>time (hrs)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>EtOH</td>
<td>1.2</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>EtOH</td>
<td>1.2</td>
<td>1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>EtOH</td>
<td>1.2</td>
<td>16</td>
<td>trace</td>
</tr>
<tr>
<td>4b</td>
<td>B</td>
<td>EtOH</td>
<td>1.2</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>5c</td>
<td>B</td>
<td>EtOH</td>
<td>1.2</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>DCE</td>
<td>1.2</td>
<td>16</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>DCE</td>
<td>2.2</td>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>DCE</td>
<td>2.2</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>EtOH</td>
<td>2.2</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>B</td>
<td>EtOH</td>
<td>2.2</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

*Conditions: pyrazole (0.5 mmol), 4-octyne (see Table); catalysts A = [RhCl2Cp*]2 (2.5 mol %) and B = [Rh(NCMe)3Cp*]2 (5 mol %, cf. pyrazole); Cu(OAc)2-H2O (1.25 mmol); KPF6 (0.6 mmol); solvent (10 mL); 83 °C; yield determined by 1H NMR vs 1,3,5-trimethoxybenzene (0.25 mmol). **Na2CO3 (1 mmol) **DABCO (0.5 mmol) **Yield based on octyne

elimination and formation of 4a. This probably reﬂects a greater ease of chloride dissociation in MeOH, forming a vacant site and so facilitating the reductive elimination from a 16e intermediate. Despite this, the diphenylacetylene complex 3b showed no evidence for reductive elimination even after heating in MeOH at 60 °C for 24 h.

Based on these results we investigated the catalytic formation of 4a, initially in EtOH (see Table 1). Treatment of 1 with 1 equiv of 4-octyne and KPF6 with [RhCl2Cp*]2 (5 mol % Rh) as catalyst and Cu(OAc)2-H2O as oxidant, provided 4a in 78% yield in only 1 h (entry 1). Use of the cationic Rh precursor [Rh(MeCN)3Cp*][PF6]2 gave a slightly higher yield (entry 2), while entry 3 shows that Rh is essential. The addition of base
(Na₂CO₃ or DABCO) has no significant effect (entries 4 and 5).

As with the stoichiometric experiments, solvent was again found to play a significant role in the product selectivity under catalytic conditions. Thus, in DCE the major species formed was not 4a, but the new doubly inserted cationic product 5aa, even though the alkyl is present only in slight excess (entry 6). The identity of 5aa was confirmed by single-crystal X-ray diffraction (see Supporting Information). If the reaction was performed with 2.2 equiv of 4-octyne (entry 7), only traces of 4a were observed even at short reaction times, the major product being 5aa. After 24 h only 5aa was observed (entry 8). Repeating this reaction with 2.2 equiv of 4-octyne in EtOH (entry 9) gave mainly 4a (82%) after 3 h, but after 24 h 5aa was the major product (57%) along with some 4a (29%, entry 10). In contrast the corresponding reaction of 1-phenylpyrazole with PhCC₃ in EtOH gave no evidence for any cationic product of type 4 and after 24 h at 120 °C only showed low conversion (14%) to a naphthylpyrazole.

Turning to the mechanism of these processes, in EtOH it seems reasonable to postulate that 4a is an intermediate in the formation of 5aa. In addition, the formation of 4a is much faster than its subsequent conversion to 5aa. In contrast, in DCE 4a is only observed at short reaction times and then only in small amounts, suggesting that the onward conversion of 4a to 5aa is faster than the initial formation of 4a itself. Conversion of 4a to 5aa requires a double C–H activation without any heteroatom assistance, and such processes have been reported to occur in a number of heterocycles containing acidic protons⁵⁵ and recently for pyridinium and imidazolium salts.¹¹

To investigate whether direct C–H activation of 4a is feasible, stoichiometric cyclometalation of 4a[PF₆] with [RhCl₂Cp*]₂ and NaOAc was attempted in MeOH. Monitoring by ¹H NMR spectroscopy showed the signals for 4a are unchanged even after 24 h at 83 °C. Repeating the reaction in methanol-d₄ with catalytic [RhCl₂Cp*]₂ led, after heating in a sealed tube at 83 °C for 48 h, to 29% deuteration at the ortho-H position on the phenyl ring alongside substantial deuteration at all the pyrazole ring positions. Heating 4a[PF₆] in methanol-d₄ under the same conditions but with no Rh present also exchanged the pyrazole protons, but in this case no exchange was observed at the phenyl ring. Thus, the Rh catalyst can effect the non-heteroatom directed C–H activation of 4a, but the non-observation of any cyclometalated intermediates indicates this step is thermodynamically unfavorable and so reversible.

To confirm that 4a is an intermediate to 5aa, isolated 4a[PF₆] was used as a substrate for the catalysis with 4-octyne (see Scheme 3). Surprisingly, only very low conversions to 5aa were observed in either EtOH (3%) or DCE (8%) after 16 h. Repeating the reactions in the presence of 1 equiv of KOAc increased the conversion of 4a to 5aa in both EtOH (54%) and DCE (99%). Similar results are observed in the reaction of 4a[OAc] with 4-octyne in either DCE or EtOH, hence the presence of a significant concentration of OAc⁻ appears to be a key requirement to form 5aa from 4a. Interestingly, in contrast to 1-phenylpyrazole, 4a will also undergo C–C coupling with diphenylacetylene in the presence of KOAc to form 5ab.

Having shown that C–N coupling to form 4a can be followed by C–C coupling to form 5aa and 5ab, we considered whether the reactions could be performed in the opposite order. Thus, the alternative C–C coupled substrates, 6a and 6b were prepared using Miura’s method⁶⁸ and shown to undergo acetate-assisted cyclometalation in high yield upon treatment with [RhCl₂Cp*]₂ and NaOAc (Scheme 4). Both cyclometalated complexes 7a/b were fully characterized by NMR spectroscopy and single-crystal X-ray diffraction (see Supporting Information).

Scheme 4. Cyclometallation of 6a and 6b

![Scheme 4. Cyclometallation of 6a and 6b](image)

Reaction of complexes 7a/b with 4-octyne in methanol then proceeded as for the phenylpyrazole analogue, 2 (Scheme 2), to afford cationic heterocycles 5aa and 5ab, respectively, in quantitative yield. However, in contrast to 2, complexes 7a/b also reacted, though more slowly, with diphenylacetylene in methanol to give cationic species 5ba and 5bb, respectively. Hence by making the substrate more rigid, the C–N coupling with diphenylacetylene will proceed. In none of these reactions was there any evidence of a seven-membered ring insertion intermediate similar to 3.

The catalytic conversion of substrates 6 to tetracyclic cations 5 was also tested, and the results are shown in Table 2. As found in the stoichiometric reactions described above, 6a and 6b could be catalytically converted in good yields to 5aa and 5ab, respectively, by reaction with 4-octyne. The reactions with diphenylacetylene also proceeded to give 5ba and 5bb, respectively, in slightly reduced yields. Formation of 5bb is least favored, giving only a 39% yield and formation of some byproducts. The identity of salts 5ba and 5bb has been confirmed by X-ray crystallography (see Supporting Information).

Having investigated the reactions of 1-phenylpyrazole, we considered the effect of the heterocycle substrate on the outcome by investigating the analogous reactions with 2-phenylpyridine, 8, and 2-vinylpyridine, 9 (Table 3). As with 1, the reactions of 8 and 9 with 4-octyne work well (Table 3, entries 1 and 3); moreover for these pyridine substrates, reaction with diphenylacetylene is also successful, giving C–N coupled products in reasonable to good yield (entries 2 and 4). The same products have been recently reported using Ru or Rh catalysis.⁵⁵,⁵⁶ In contrast, all attempts to get the salts 10 to react further with alkynes to generate tetracyclic products (similar to the conversion of 4a to 5aa/5ab) were unsuccessful, even in
5b, R, R' = Pr, R'' = Ph
5a, R = 'Pr, R, R' = 'Pr
5a, R, R' = Ph, R'' = Ph
5b, R, R = 'Pr, R' = Ph
5b, R, R' = Ph, R = Ph

Tetracycle formation also depends on the system involved: the alkyne to form heterocycles 10a/b contrast, the phenyl- and vinylpyridines C only occurs with 4-octyne (\(\text{EtOH} = +1.3 \text{ kcal/mol}\)), where the preceding superscript indicates the substrate involved), from which C–H activation proceeds in a formally two-step process via the agostic/H-bonded intermediate \(1\text{C}1\text{B} \rightarrow \text{C} (\text{G}\text{D} = +1.7 \text{ kcal/mol})\). C–H activation therefore has an overall barrier of 13.0 kcal/mol and gives the cyclometalated AcOH adduct, \(\text{C} = +6.2 \text{ kcal/mol}\). The onward reaction with 4-octyne then involves AcOH substitution to give intermediate \(1\text{Da} \rightarrow \text{D} (\text{G}\text{D} = -5.1 \text{ kcal/mol})\) followed by sequential alkynyl insertion and C–N reductive coupling to give \(1\text{Fa}\) in which the heterocyclic product \(4a\) is bound to Rh in an \(\eta^1\)-fashion. Both these steps are exergonic and have reasonable barriers of 15.1 and 22.2 kcal/mol, respectively.

With diphenylacetylene an analogous mechanism is computed but with some important changes in energetics. Thus, intermediate \(1\text{DB}\) is less stable than \(1\text{Da}\), and the subsequent migratory insertion has a similar barrier (12.7 kcal/mol), this step becomes significantly more favorable (\(\Delta\text{G}\text{D} = -8.8 \text{ kcal/mol}\)) than with 4-octyne. This result can be traced to an additional interaction between the formally unsaturated Rh center in \(1\text{Eb}\) and one of the Ph substituents (Rh–C\(^9\) = 2.31; Rh–C\(^10\) = 2.49 Å, see Figure 2 which also defines the atom labeling scheme employed). This greater stabilization of \(1\text{Eb}\) disfavors the C–N reductive coupling which has an increased barrier of 27.3 kcal/mol and becomes endergonic by 4.3 kcal/mol. These less favorable energetics are consistent with the non-observation of any heterocyclic products experimentally with diphenylacetylene, while the facile migratory insertion is in accord with the formation of the seven-membered rhodacycle, \(3\text{B}\), in the stoichiometric reactions (see Scheme 2). As no stabilization occurs with the 'Pr substituents in \(1\text{Ea}\), C–N reductive coupling from that species is both more kinetically accessible and exergonic and can proceed to ultimately the heterocycle \(4a\). The Rh(I) species formed in this reductive coupling step can then be reoxidized by Cu(OAc)\(_2\) to regenerate catalytically active Rh(OAc)\(_2\)Cp\(^*\), \(A\).

The onward reaction of \(4a\) with 4-octyne or diphenylacetylene to form tetracycles \(5aa\) or \(5ab\), respectively, requires the double C–H bond activation of \(4a\) prior to the alkyn insertion.
and C–C reductive coupling steps. The first C–H bond activation is necessarily a non-directed process, at either the pyrazole C3–H3 bond or the aren C5–H5 bond. The former possibility was found to be more accessible and proceeds via 4aTS(A-B) +1.91 Å between the protic H3 and O1, the pendant acetate-assisted C–O3 bond formation (2.26 Å), a process that would therefore be readily formed, as is observed experimentally. The similar behavior of 4-octyne and diphenylacetylene with 4a is in marked contrast to their reactions with 1. This may in part reflect the intrinsically more facile C–C coupling (involving two formally anionic C-centers) that is involved in tetracyclic formation compared to the C–N coupling necessary to form 4a (combining an anionic C with a neutral N center, see Discussion section). In addition, whereas intermediate 4EB was stabilized by an interaction with the alkyne phenyl substituent, no such interaction is seen in 4a where the increased rigidity imposed by the C2Pr2 group and leads to the cyclometalated AcOH adduct 4aC (ΔG(EOH) = +3.3 kcal/mol) in which the tetracyclic product Saa is bound in an η1-fashion to Rh.

The onward reaction of 4C with diphenylacetylene shows very similar energetics to those computed with 4-octyne, and in particular, the final C–C bond coupling event again has a minimal barrier (1.9 kcal/mol) and is strongly exergonic. Saa should therefore be readily formed, as is observed experimentally. The activation of the C3–H3 bond (combining an anionic C with a neutral N center, see Discussion section). In addition, whereas intermediate 4EB was stabilized by an interaction with the alkyne phenyl substituent, no such interaction is seen in 4a, as the increased rigidity of the “strapped” rhodacycle does not allow the substituent to approach the Rh center (the shortest Rh–Cphenyl contact is to the ipso carbon, at 3.04 Å).

The marked solvent dependency of the reaction of 1 with 4-octyne prompted us to recompute the reaction profiles in Figures 1 and 3 with a correction for DCE solvent (see Supporting Information for full details). The major change is centered on the first step in the reaction of 1 that involves the displacement of an acetate anion in A by the neutral substrate to form cationic B and free acetate. This process is more accessible in EtOH (ΔG(EOH) = +1.3 kcal/mol) than in DCE.

From 4aC the formation of Saa readily proceeds via substitution of AcOH by 4-octyne to give 4aDa (ΔG(EOH) = −12.5 kcal/mol) followed by insertion into the Rh–aryl bond (ΔG(EOH) = +16.6 kcal/mol). This step is markedly endergonic (ΔG(EOH) = +5.8 kcal/mol), in contrast to the equivalent step in the formation of 1Ea (ΔG(EOH) = −2.4 kcal/mol), and reflects the increased rigidity imposed by the {C2Pr2} “strap” in the seven-membered rhodacycle 4aEa. The final C–C coupling step in 4aEa is also far more accessible than C–N bond coupling in 1Ea and proceeds with a barrier of only 2.2 kcal/mol to give 4aFa (ΔG(EOH) = −33.0 kcal/mol) in which the tetracyclic product Saa is bound in an η1-fashion to Rh.

Supporting Information. The onward reaction of 4C with diphenylacetylene shows very similar energetics to those computed with 4-octyne, and in particular, the final C–C bond coupling event again has a minimal barrier (1.9 kcal/mol) and is strongly exergonic. Saa should therefore be readily formed, as is observed experimentally. The similar behavior of 4-octyne and diphenylacetylene with 4a is in marked contrast to their reactions with 1. This may in part reflect the intrinsically more facile C–C coupling (involving two formally anionic C-centers) that is involved in tetracyclic formation compared to the C–N coupling necessary to form 4a (combining an anionic C with a neutral N center, see Discussion section). In addition, whereas intermediate 4EB was stabilized by an interaction with the alkyne phenyl substituent, no such interaction is seen in 4a, as the increased rigidity of the “strapped” rhodacycle does not allow the substituent to approach the Rh center (the shortest Rh–Cphenyl contact is to the ipso carbon, at 3.04 Å).

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Figure 1. Computed reaction profiles (kcal/mol) for the coupling of 1-phenylpyrazole, I, with 4-octyne (a) and diphenylacetylene (b) at Rh(OAc)2Cp*. A, in EtOH. In each case free energies are quoted relative to A and the free substrates.

Figure 2. Computed structures of 1Ea and 1Eb with selected distances in Å. Structures are viewed approximately along the Rh–Cp* centroid axis, with the Cp* ligand and all H atoms omitted for clarity.
In EtOH acetate loss and C-observed buildup of mol). Substrate therefore not signifi-
cantly a non-directed C-H activation in DCE to +17.8 kcal/mol, and has the e-
ding propensity of acetate to dissociate in a more polar solvent and also explains the need for an additional acetate to facilitate the formation of 5aa from isolated 4a.

Reactivity of 6a and 6b with Alkynes. Experimentally the neutral C-C strapped substrates 6a and 6b are able to react with both 4-octyne and diphenylacetylene to form (with 6a) tetracycles 5aa and 5ba and (with 6b) 5ab and 5bb. Thus, C-N coupling is now feasible with both alkynes, in contrast to what is observed with substrate 1. The computed reaction profiles for the reactions of 6a with 4-octyne and diphenylacetylene in EtOH are shown in Figure 5 (those for the reactions of 6b are provided in the Supporting Information). The energetics of C-H activation are similar to those computed with 1, although the more rigid structure of 6a results in a one-step process via 4aTS(B-C) at +14.6 kcal/mol with no agostic intermediate being located. The energetics of HOAc/alkyne substitution and migratory insertion are again similar to those computed with the neutral C-C strapped substrates of 1, although with 6a migratory insertion is significantly endergonic for both alkynes (by ca. 5.5 kcal/mol), and the subsequent C-N coupling steps have barriers of ca. 11 kcal/mol, significantly lower than from 1Ea/b. This pattern of a thermodynamically uphill insertion followed...
by facile reductive coupling is similar to the behavior of the C–N strapped substrate 4a, suggesting that the rigid strap plays an important role in promoting the reaction in both cases.

The overall barriers for C–N coupling from intermediates 6aDa and 6aDb are 17.4 and 16.1 kcal/mol respectively, consistent with both processes readily occurring experimentally. For 6aDa the formation of the initial product 6aFa featuring the Rh-bound tetracycle 5aa is exergonic by 3.3 kcal/mol, while the equivalent process with diphenylacetylene (6aDb → 6aFb) is marginally uphill, and this difference may be related to the lower yield seen experimentally for 5ba (52%) compared to 5aa (85%, see Table 2). The barriers for the C–N coupling step from 6aEa/6aEb are ca. 10 kcal/mol higher than the equivalent C–C coupling in 4aEa/4aEb, reiterating the intrinsically greater accessibility of C–C coupling when other factors are equal. We also computed the C–H activation and coupling of substrate 6b with 4-octyne and diphenylacetylene, to give 5ba and 5bb. Very similar patterns to those seen in Figure 5 were found, and full details are given in the Supporting Information.

Reactions of 8 with Alkynes. In contrast to the behavior seen in the reactions of 1, 4a, and 6a/6b with alkynes, 2-phenylpyridine, 8, shows a further distinct reactivity pattern in
that it undergoes C–N coupling with both 4-octyne and diphenylacetylene, but then neither of the resultant cationic heterocycles, 10a or 10b, reacts further to form tetracyclic products. Similar results are seen experimentally with vinylpyridine, 9. We focus here on the computed profiles for the reactions of 2-phenylpyridine with 4-octyne and diphenylacetylene (see Figure 6, where the data are corrected for EtOH solvent). In this case substitution of OAc by substrate 8 followed by C–H activation proceeds a small overall barrier of only 8.8 kcal/mol to give, after HOAc/alkyne substitution, complexes 8Da and 8Db at −7.6 and −6.6 kcal/mol, respectively. As with the 1-phenylpyrazole-based substrates, the insertion barrier is slightly lower with diphenylacetylene (12.6 kcal/mol) than with 4-octyne (15.2 kcal/mol), and this step is exergonic, as was seen with the other unstrapped substrate 1. Importantly, the C–N reductive coupling step is also exergonic (8Da → 8Fa, $\Delta G_{\text{EtOH}} = −7.8$ kcal/mol; 8Eb → 8Fb, $\Delta G_{\text{EtOH}} = −2.5$ kcal/mol), and similar barriers are now computed with both alkynes (22.8 kcal/mol from 8Da and 23.8 kcal/mol from 8Eb). The computed energetics for C–N bond coupling en route to the formation of 10a are therefore very similar to those computed for the reaction of 1 and 4-octyne (1 → 1Fa: $\Delta G_{\text{EtOH}} = −3.2$ kcal/mol; $\Delta G_{\text{EtOH}}^2 = 22.2$ kcal/mol), while the C–N coupling to form 10b appears to be more accessible than for 4b (1 → 1Fb: $\Delta G_{\text{EtOH}} = +4.3$ kcal/mol; $\Delta G_{\text{EtOH}}^2 = 27.3$ kcal/mol). The computed trends are therefore consistent with the observation of both 10a and 10b experimentally.

As with substrate 4a, the potential onward reaction of 10a or 10b to form tetracyclics requires an initial non-directed C–H activation at A. This step was investigated for 10a in EtOH, and the most accessible process was found to have a barrier of 28.8 kcal/mol,16 much higher than the barrier of 18.9 kcal/mol computed for the equivalent reaction with 4a. C–H activation is therefore significantly harder for 10a, so much so that onward reaction to form tetracyclic products is not observed.

4. DISCUSSION

The current experimental and computational mechanistic studies detail the various outcomes of Rh-catalyzed oxidative coupling when combining different directing group substrates (1-phenylpyrazole, 2-phenylpyridine, and 2-vinylpyridine) with alkynes (4-octyne and diphenylacetylene) under varying reaction conditions (solvent and anion concentration). DFT calculations have accounted for the specific observations but also highlight some more general trends of wider relevance beyond this specific study.

Two different C–H activation processes have been characterized at Rh(OA)C3Cp*: a standard ligand directed intramolecular C–H activation and an alternative non-directed intermolecular C–H activation. For the directed C–H activation the initial substitution of one acetate ligand by the directing group is required, resulting in the formation of charged intermediates that will be favored by more polar solvents. In contrast, the non-directed process necessitates both acetates to be bound to Rh, and the reaction therefore proceeds through neutral intermediates, the accessibility of which will be less solvent dependent. These distinctions are confirmed in Figure 7 that displays the overall barriers computed in different solvents for both the directed and non-directed C–H activation of some of the heterocyclic substrates in this study.17 For 1-phenylpyrazole, 1, directed C–H activation is favored in both EtOH and DCE, and alkyn insertion in these systems forms seven-membered rhodacycles that are set up for C–N bond coupling to form cationic heterocyclic products. Interestingly, the alternative non-directed C–H activation also has reasonable barriers of around 22 kcal/mol at the C–H3 bond but is actually kinetically more accessible at the backbone ortho-C–H bond of the phenyl group (ca. 19 kcal/mol). These values are also largely independent of the solvent, as anticipated. In the very low polarity xylene solvent, non-directed C–H activation is favored. A detailed computational study of the subsequent reaction with alkynes to give the neutral C–C coupled products reported by Miura and co-workers18 (viz. substrates 6a and 6b used in this study) and the observed competition for the formation of naphthalene products is currently underway.

C–H activation barriers for the "strapped" substrates 4a and 6a are also given in Figure 7. For cationic 4a, barriers for non-directed C–H activation of ca. 19 kcal/mol are computed in both EtOH and DCE, approximately 3 kcal/mol lower than the equivalent processes for 1. Oxidative coupling to 5aa and 5ab proved possible in both solvents, although this is sensitive to the concentration of acetate (and hence the form in which this anion is introduced into the reaction) due to the need for Rh(OA)C3Cp* to be present to effect the non-directed C–H activation. This was evident in the more efficient onward reaction of 4a as its OAc− rather than its PF6− salt. We would also predict that oxidative coupling should be possible in xylene. In contrast the directed C–H activation of 6a is very solvent dependent: this is accessible in both EtOH and DCE leading ultimately to the formation of 5aa and 5ba. In xylene, however, directed C–H activation is not possible, and so no further reaction to tetracyclic products is seen, as was reported by Miura. 2-phenylpyridine, 8, has the lowest barrier to directed C–H activation of those substrates considered here, but then in contrast, isoquinolinium 10a has the highest barriers to non-directed C–H activation, even when the slightly lower barriers at the ortho-C–H position are taken into account. This seems likely to relate to the lower acidity of the backbone C–H bonds
associated with the pyridinium ring (with one electronegative nitrogen) compared to pyrazole-based 4a with two nitrogens. NBO atomic charge calculations support this with a much reduced negative charge at the C$^5$ position in 4a ($q_{C^5} = -0.02$) compared to that in 10a ($q_{C^5} = -0.22$), although a similar charge of +0.28 is computed at H$^6$ in each case.

Comparing the two alkynes shows some subtle changes in the reaction energetics. With 1 and 8 (Figures 1 and 6) migratory insertion is always exergonic and exhibits lower barriers and is more favorable thermodynamically for diphenylacetylene compared to 4-octyne. The opposite trend then pertains for the reductive coupling, with this difference being most apparent in the reaction with 1, where the phenyl substituent stabilizes the Rh center in the seven-membered rhodacycle, $^1E_b$, to such an extent that reductive coupling does not occur at all. The slightly different geometry imposed on the system by the 2-phenylpyridine moiety in $^8E_b$ reduces this extra stabilization, and exergonic reductive coupling can still occur with an accessible barrier. With substrates 4a and 6a (Figures 3 and 5) the extra rigidity imposed by the backbone ($C_5^2Pr_2$) "strap" destabilizes the seven-membered rhodacycles. As a result the alkyne insertion becomes endergonic, but by the same token, the final reductive coupling is facilitated; this process is again more favorable for 4-octyne compared to diphenylacetylene.

The relative reactivities of the two alkynes with 1 and 8 can also be assessed by the isodesmic reactions shown in Figure 8.

![Figure 8](image)

**Figure 8.** Calculated free energy changes (kcal/mol, in EtOH) for exchange of the alkyne moieties in 4a/4b and 10a/10b and the 1-phenylpyrazole and 2-phenylpyridine moieties in 10a/4a and 10b/4b.

The exchange of the alkyne moieties in 4a/4b and 10a/10b pairs is shown to be thermodynamically uphill, indicating an intrinsic preference for the coupling reactions of 4-octyne over diphenylacetylene with both 1-phenylpyrazole and 2-phenylpyridine. It is noteworthy that this preference is slightly higher with 1-phenylpyrazole and that, experimentally, this system proved more sensitive to the alkyne identity compared to 2-phenylpyridine. Likewise exchange of the 1-phenylpyrazole and 2-phenylpyridine moieties in the 4a/10a and 4b/10b pairs indicates oxidative coupling is more favored with 2-phenylpyridine, probably due to the reduced ring strain in tricyclic products featuring three six-membered rings. The combination of 1-phenylpyrazole and diphenylacetylene is most disfavored, and this again fits with the difficulty in forming 4b experimentally. These additional thermodynamic factors combine with the extra stabilization of intermediate $^1E_b$ to make the formation of 4b inaccessible in the present system.

This and previous work allows us to monitor the ease of the final reductive coupling step as the nature of the participating groups changes. Data for five rhodacycles constructed via insertion of 4-octyne with different phenylpyrazoles are compared in Figure 9. The highest barrier ($\Delta G^\ddagger = 22.2$ kcal/mol) is for the 1-phenylpyrazole system, where a formally anionic alkenyl C couples with a neutral N to form a cationic heterocycle ("C–N+ coupling"). Incorporating the $\{C_5^2Pr_2\}$ strap reduces this barrier to 11.9 kcal/mol, for the reasons discussed above. Combining anionic C and N centers to form a neutral heterocycle (C–N coupling), as in our previous study based on 5-methyl-3-phenylpyrazole (12), is a much easier process, with a barrier of only 9.9 kcal/mol, less than half of that for the C–N+ coupling. We have also extended the current study to the coupling of two anionic C centers in $^1E_a^\prime$, a species derived from 1 via non-directed C–H activation and alkyne insertion and a putative intermediate for the formation of species 6a. Such C–C coupling is even more facile and is further facilitated (as was the case for C–N+ coupling) through the introduction of the $\{C_5^2Pr_2\}$ strap as in $^4E_a^\prime$.

In conclusion, we have shown through experimental and computational means how a number of steps in the Rh-catalyzed oxidative coupling of N-heterocycles with alkynes can be affected by the precise substrates involved and the reaction conditions. Directed C–H activation requires substitution of acetate by the N-heterocycle and so is favored by more polar solvents. Further reaction leads to cationic tricyclic or tetracyclic products, although the ability of diphenylacetylene to stabilize a key rhodacyclic intermediate can suppress the former. Non-directed C–H activation is an energetically feasible process that, as it does not involve acetate dissociation, does not display significant solvent dependence. Hence in low polarity solvents this process becomes favored and may lead to
neutral C–C coupled products. Barriers for a range of key C–Y coupling events have been assessed and shown to follow the trend C–N' > C–N > C–C.

5. EXPERIMENTAL SECTION

General Procedure for Catalytic C–N Coupling Reactions. Ethanol (10 mL), substrate (0.5 mmol), and alkyne (0.6 mmol) were placed into a Schlenk tube with a stirrer bar, followed by the addition of the rhodium catalyst (0.0125 mmol, 5 mol % [Rh]), KPF₆ (0.6 mmol), and Cu(OAc)₂·H₂O (1.25 mmol). The suspension was stirred at 83 °C in an oil bath. After cooling to room temperature the product was extracted into dichloromethane (2 × 10 mL) and washed with water (20 mL) containing ethylene diamine (1 mL). The organic fraction was collected and dried over MgSO₄. The filtrate was concentrated, and the product was isolated by column chromatography using alumina eluted with ethyl acetate/methanol (100:0 to 50:50 ethyl acetate/methanol).

Computational Details. DFT calculations were run with Gaussian 03 (Revision D01) and Gaussian 09 (Revision A02). Rh centers were described with the Stuttgart RECPs and associated basis sets,¹⁹ and 6-31G* basis sets were used for all other atoms.⁰ Initial BP86 optimizations were performed with Gaussian 03 using the ‘grid = ultrasoft’ option, with all stationary points being fully characterized via analytical frequency calculations as either minima (all positive frequencies) or transition states. All energies were recomputed with a larger basis set, BS2, featuring cc-pVTZ on Rh and 6-311++G on all other atoms. Corrections for the exchange and correlation energy were described with the Stuttgart RECPs and associated basis sets,¹⁹ and 6-31G* basis sets were used for all other atoms. 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