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Experimental and DFT Studies Explain Solvent Control of C-H Activation and Product Selectivity in the Rh(III)-Catalysed Formation of Neutral and Cationic Heterocycles.

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C-H functionalization; oxidative coupling; Rh(III); DFT; neutral and cationic heterocycles; C-N and C-C bond formation.

ABSTRACT: A range of novel heterocyclic cations have been synthesised by the Rh(III)-catalysed oxidative C–N and C–C coupling of 1-phenylpyrazole, 2-phenylpyridine and 2-vinylpyridine with alkynes (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 which 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 stabilise unsaturated 7-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 7-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 which realize this goal via the direct functionalization of C–H bonds are particularly desirable, as they avoid the pre-functionalisation 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-catalysed 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-catalysed 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 alkyne and the solvent.1 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 [MCl2(Cp*)]2 (M = Rh, Ir) and [RuCl2(p-cymene)]2 to form cyclometalated products (see Scheme 1(c) for the Rh complex, 2). These can then readily (room temperature) undergo insertion of either dimethyldiacetylene dicarboxylate or diphenylacetylene into the M–C bond to give 7-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 coworkers highlighting the role of the nature of the carboxylate and silver salts employed.9 In earlier work Pfeffer et al. showed that alkyne insertion into cloruthenated N,N-dimethylbenzylamine gave 7-membered heterocycles with electron withdrawing substituents on the alkyne but gave C–N coupling with electron rich alkynes.6 Hence, the effect of a range of factors
including alkyne substituents, solvent, additives and directing group on the selectivity between C–N and C–C coupling are poorly understood.

**Scheme 1.** Different outcomes from the reactions of phenylpyrazoles with alkenes at Rh(III).

Density functional theory (DFT) calculations on C–H activation assisted by a heteroatom directing group suggest the formation of cyclometallated 2 will involve a carboxylate-assisted (AMLA/CMD) process.\(^7\)\(^8\) We have also highlighted the subtleties of modelling the energetics associated with the full C–H activation and functionalisation catalytic cycle.\(^3\)\(^4\)\(^9\) Herein, we report new C–N and C–C coupling reactions of 1-phenylpyrazole, 1, that result in the formation of cationic tricyclic and tetracyclic heterocyclic products. We also extend our study to the reactions of 2-phenylpyridine, 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.

### 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, the cationic heterocycle 4a, was obtained as a result of C–N coupling, in contrast to the C–C coupling processes previously reported in DMF and xylene. 4a was obtained in quantitative yield at room temperature within 3 h, with no observable intermediates, and was fully characterised by NMR spectroscopy and by single crystal X-ray diffraction (see Supporting Information). Repeating the same reaction in chloroform gave only slow insertion of 4-octyne to form the 7-membered rhodacycle (3a), as observed previously with diphenylacetylene (3b).\(^4\) However, redissolving 3a in methanol led to reductive 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.

**Scheme 2.** Stoichiometric reactions of C–H activated intermediate 2 with alkynes

Based on these results we investigated the catalytic formation of 4a, initially in EtOH (see Table 1). Treatment of 1 with one equivalent of 4-octyne and KPF\(_6\), with [RhCl\(_2\)Cp\(^*\)]\(_2\) (5 mol% Rh) as catalyst and Cu(OAc)\(_2\) as oxidant, provided 4a in 78% yield in only 1 hour (entry 1). Use of the cationic Rh precursor [Rh(MeCN)\(_3\)Cp\(^*\)][PF\(_6\)]\(_2\) gave a slightly higher yield (entry 2), whilst entry 3 shows that Rh is essential. The addition of base (Na\(_2\)CO\(_3\) or DABCO) has no significant effect (entries 4 and 5).

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

| Entry | Catalyst | Solvent | Equiv Alkyne | Time (hrs) | Yield (%) |
|-------|----------|---------|--------------|-----------|-----------|
| 1     | A        | EtOH    | 1.2          | 1         | 78        |
| 2     | B        | EtOH    | 1.2          | 1         | 88        |
| 3     | None     | EtOH    | 1.2          | 16        | Trace     |
| 4     | B        | EtOH    | 1.2          | 1         | 69        |
| 5     | B        | EtOH    | 1.2          | 1         | 75        |
| 6     | A        | DCE     | 1.2          | 16        | 72        |
determined by 1H NMR mmol). aNa2CO3 (1 mmol) bDABCO (0.5 mmol) c yield based on octyne

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 product cationic 5aa, even though the alkyne 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 equivalents 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 PhCCPh in EtOH gave no evidence for any cationic product of type 4 and after 24 h at 120 °C only showed low conversion (4%) 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 protons,5i,10 and recently for pyridinium and imidazolium salts.11

To investigate whether direct C–H activation of 4a is feasible, stoichiometric cyclometallation 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*], 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 cyclometallated 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 equivalent 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.

Scheme 3. Reactions of 4a with alkynes (X = PF6 or OAc, see text).

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 method3b and shown to undergo acetate-assisted cyclometallation in high yield upon treatment with [RhCl2Cp*]2 and NaOAc (Scheme 4). Both cyclometallated complexes 7a/b were fully characterised by NMR spectroscopy and single crystal X-ray diffraction (see Supporting Information).

Scheme 4. Cyclometallation of 6a and 6b.

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 for a 7-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 but in slightly reduced yields. Formation of 5bb is least favored, giving only a 39% yield and formation of some by-products. The identity of salts 5ba and 5bb have both been confirmed by X-ray crystallography (see Supporting Information).

Table 2. Rh-Catalysed Coupling of 6a and 6b with Alkynes.

| Entry | Substrate | Alkyne    | Yield (%) |
|-------|-----------|-----------|-----------|
| 1     | 6a        | 4-octyne  | 85 (5aa)  |
| 2     | 6a        | PhCCPh    | 52 (5ba)  |
| 3     | 6b        | 4-octyne  | 67 (5ab)  |
| 4     | 6b        | PhCCPh    | 39 (5bb)  |

Conditions: Pyrazole (0.5 mmol), alkyne (0.6 mmol), [RhCl2Cp*]2 2.5 mol% Cu(OAc)2·H2O (1.25 mmol), KPF6 (0.6 mmol), 1,3,5 trimethoxybenzene (0.25 mmol), EtOH (10 mL), 83 °C, 6 h, yield determined by 1H NMR spectroscopy.

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-based heterocycles. 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. 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 DCE which was shown to promote this process for 4a. Thus double C-H activation and C-C coupling is also highly dependent on the precise substrate employed.

Table 3. Rh-Catalysed Coupling of 2-phenylpyrididine (8) and 2-vinylpyrididine (9) with Alkynes.

| Substrate | Alkyne | Product | Yield (%) |
|-----------|--------|---------|-----------|
| 10a       | R = nPr | 10a     | 72        |
| 10b       | R = Ph  | 10b     | 61        |
| 11a       | R = nPr | 11a     | 67        |
| 11b       | R = nPr | 11b     | 45        |

Conditions: Pyridine (0.5 mmol), alkyne (0.6 mmol), [RhCl2Cp*]2, 2.5 mol% Cu(OAc)2·H2O (1.25 mmol), KPF6 (0.6 mmol), EtOH (10 mL), 83 °C, 6 h, yield determined by 1H NMR spectroscopy.

3. Computational Studies

In order to understand the factors determining the different product selectivities observed experimentally, density functional theory (DFT) calculations have been undertaken to establish the mechanisms and energetics of these various C-N and C-C oxidative coupling reactions. Experimentally, the reaction outcomes depend on the combinations of the alkyne, substrate and solvent employed. Thus with 1 in EtOH C-N coupling only occurs with 4-octyne (a) to give 4a, while no equivalent C-N coupled product is seen with diphenylacetylene (b). In contrast, the phenyl- and vinyl-pyridines 8 and 9 react with both alkynes to form heterocycles 10a/b and 11a/b respectively. Tetracycle formation also depends on the system involved: the C–N strapped substrate 4a reacts with both alkynes to form heterocycles 10a/b and 11a/b and these can also be formed from the C-C strapped substrates 6a and 6b, from which the complementary 5ba and 5bb can also be accessed. In contrast, no further reaction of the C-N coupled pyridine-based heterocycles 10a/b and 11a/b is seen with either alkynyl. The choice of solvent also affects reactivity: in EtOH the reaction of 1 to form 4a is faster than the onward reaction of 4a to give 5aa. However in DCE the second C-C coupling to give tetracycle 5aa competes with the initial C-N coupling with the result that 4a does not build up significantly during catalysis.

In modelling these various processes with DFT calculations, all geometries have been optimised using the BP86 functional and a modest basis set (BS1). As in previous related work, we report computed free energies, with corrections for solvation (PCM approach), dispersion (Grimme’s D3 parameter set) and basis set effects (with a larger basis set, BS2, including diffuse functions). See the Computational Details section for full details.

Reactivity of 1 and 4a with alkynes. The free energy profiles for the initial C-H activation of 1-phenylpyrazole and the subsequent coupling with 4-octyne and diphe
nlylacetylene in EtOH are shown in Figure 1. We consider Rh(OAc)₂Cp*, A, to be the catalytically active species formed under the reaction conditions and so all free energies are quoted relative to this species combined with those of the relevant substrates. Cyclometalation of 1 proceeds via initial substitution of an acetate ligand in A to give N-bound precursor ¹B (GEtOH = +1.3 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 ¹INT(B-C) (GEtOH = +11.7). C–H activation therefore has an overall barrier of 13.0 kcal/mol and gives the cyclometallated AcOH adduct, ¹C, at +6.2 kcal/mol.12 The onward reaction with 4-octyne then involves AcOH substitution to give intermediate ¹Da (GEtOH = -5.1 kcal/mol) followed by sequential alkyne insertion and C–N reductive coupling to give ¹Fa in which the heterocyclic product 4a is bound to Rh in an η⁴-fashion. Both these steps are exergonic and have reasonable barriers of 14.8 kcal/mol and 22.2 kcal/mol, respectively.13

With diphenylacetylene an analogous mechanism is computed but with some important changes in energetics. Thus intermediate ¹Db is less stable than ¹Da and, while the subsequent migratory insertion has a similar barrier (13.8 kcal/mol), this step becomes significantly more favorable (ΔGEtOH = -8.8 kcal/mol) than with 4-octyne. This result can be traced to an additional interaction between the formally unsaturated Rh centre in ¹Eb and one of the Ph substituents (Rh–C₉ = 2.31; Rh–C₁₀ = 2.49 Å, see Figure 2 which also defines the atom labelling scheme employed). This greater stabilisation of ¹Eb 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 7-membered rhodacycle, 3b, in the stoichiometric reactions1 (see Scheme 2). As no equivalent stabilisation occurs with the ⁵Pr substituents in ¹Ea, C–N reductive coupling from that species is both more kinetically accessible and exergonic, and can proceed to give ultimately the heterocycle 4a. The Rh(I) species formed in this reductive coupling step can then be re-oxidised by Cu(OAc)₂ to regenerate catalytically active Rh(OAc)₂Cp*, A.

Figure 1. Computed reaction profiles (kcal/mol) for the coupling of 1-phenylpyrazole, 1, 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.
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 alkyne 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 arene C5–H5 bond. The former possibility was found to be more accessible and proceeds via 4aTS(A-B) at +18.9 kcal/mol (see Figures 3 and 4), 5.0 kcal/mol below that for the alternative C5–H5 bond activation (see Supporting Information). The activation of the C3–H3 bond starts from an adduct of A and 4a, A•4a, which displays a short contact of 1.91 Å between the protic H3 and O1, the pendant oxygen of the κ1-OAc ligand. 4aTS(A-B) then incorporates H-transfer onto oxygen (C3–H3 = 1.22 Å; O1–H3 = 1.59 Å) with concomitant Rh–C3 bond formation (2.26 Å), a process that also requires the dissociation of one arm of the spectator acetate ligand to accommodate the new Rh–C bond (Rh–O3 = 3.44 Å cf. 2.20 Å in A•4a). After HOAc dissociation the subsequent C3–H3 bond activation in intermediate 4aB (GEtOH = -3.3 kcal/mol) exploits the new Rh–C3 bond as a directing group and leads to the cyclometalated AcOH adduct 4aC (GEtOH = +1.7) through a regular two-step intramolecular acetate-assisted C–H activation. The reaction of A with 4a to form 4aC is computed to be endergonic, and to have barriers of 18.9 kcal/mol and 24.3 kcal/mol for the forward and reverse directions, respectively. This is consistent with the slow H/D exchange seen experimentally in the absence of alkyne, where relatively forcing conditions are required, as well as the non-observation of any cyclometalated intermediates.

From 4aC the formation of 5aa readily proceeds via substitution of AcOH by 4-octyne to give 4aDa (GEtOH = -12.5 kcal/mol) followed by insertion into the Rh–aryl bond (∆G‡EtOH = +15.3 kcal/mol). This step is markedly endergonic (∆GEtOH = +6.3 kcal/mol), in contrast to the equivalent step in Figure 1 (1Da → 1Ea, ∆GEtOH = -2.4 kcal/mol) and reflects the increased rigidity imposed by the {C2Pr2} ’strap’ in the 7-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 1.4 kcal/mol to give 4aFa (GEtOH = -33.0 kcal/mol) in which the tetracyclic product 5aa is bound in an η4-fashion to Rh.

The onward reaction of 4aC 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 (2.2 kcal/mol) and is strongly
exergonic. 5ab 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-centres) that is involved in tetracycle formation compared to the C–N coupling necessary to form 4a (combining an anionic C with a neutral N centre, see Discussion below). In addition, whereas intermediate 4Eb was stabilised by an interaction with the alkyne phenyl substituent, no such interaction is seen in 4aTs, as the increased rigidity of the ‘strapped’ rhodacycle does not allow the substituent to approach the Rh centre (the shortest Rh…-C phenyl 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 re-compute the reaction profiles in Figures 1 and 3 with a correction for DCE solvent (see Supporting Information for full details). The major change is centred on the first step in the reaction of 1 which 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 (δGDCE = +1.3 kcal/mol) than in DCE (δGDCE = +5.9 kcal/mol) and has the effect of raising the overall barrier to C–H activation in DCE to +17.8 kcal/mol, compared to only 13.0 kcal/mol in EtOH. In contrast, the reaction of 4a is less solvent dependent, as in this case it is the neutral bis-OAc species A that effects a non-directed C–H activation without requiring any dissociation of acetate. The energy of the key transition state in this process, 4aTS(A–B), is therefore not significantly affected by the solvent employed (δG(OH) = +18.9 kcal/mol cf. δG(DCE) = +18.2 kcal/mol). Under catalytic conditions once 4a is formed it will be in competition with 1 for C–H activation at the catalytically active species A. In EtOH acetate loss and C–H activation of 1 (δG(OH) = +13.0 kcal/mol) is clearly kinetically favored over the non-directed C–H activation of 4a at A (δG(OH) = +18.9 kcal/mol). Substrate 1 therefore reacts preferentially, resulting in the observed build-up of 4a in EtOH. The onward reaction of 4a to give 5aa will then only occur later in the catalysis once the concentration of 1 in solution is reduced. In DCE, however, the C–H activations of both 1 and 4a are competitive (δG(OH) = 17.8 kcal/mol cf. δG(DCE) = 18.2 kcal/mol) and so as 4a is formed it can react on to give tetracycle 5aa. A further factor in the more efficient onward reaction of 4a in DCE is the greater stability of adduct A:4a (δG(DCE) = +0.2 kcal/mol) over intermediate B (δG(DCE) = +5.9 kcal/mol) which will favor the non-directed C–H activation.4 In contrast in EtOH these two species are much closer in energy (δG(OH) = 1.1 kcal/mol). This difference reflects the greater propensity of acetate to dissociate in a more polar solvent and also explains the need for 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 6aTs(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 1, although, with 6a migratory insertion is significantly endergonic for both alkynes (by ca. 5.5 kcal/mol) and the subsequent C–N coupling step has barriers of ca. 11 kcal/mol, significantly lower than from 6aEa/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 kcal/mol 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 (87 %, 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 4 were found and full details are given in the Supporting Information.
Figure 5. Computed reaction profiles (kcal/mol) for the coupling of 6a with 4-octyne and diphenylacetylene at Rh(OAc)2Cp*, A. Results are computed in EtOH and free energies are quoted relative to A and the free substrates.

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- in A 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 (8Ea → 8Fa, ΔG_{EtOH} = -7.8 kcal/mol; 8Eb → 8Fb, ΔG_{EtOH} = -2.5 kcal/mol) and similar barriers are now computed with both alkynes (22.8 kcal/mol from 8Ea 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 (8Ea → 8Fa: ΔG_{EtOH} = -3.2 kcal/mol; ΔG^‡_{EtOH} = 22.2 kcal/mol), while the C–N coupling to form 10b appears to be more accessible than for 4b (8Eb → 8Fb: ΔG_{EtOH} = +4.3 kcal/mol; ΔG^‡_{EtOH} = 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 tetracycles 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 28.6 kcal/mol, 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-catalysed 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 characterised at Rh(OAc)2Cp*: a standard ligand directed intramolecular C–H activation and an alternative non-directed intermolecular C–H activation. For the directed C–H acti
Figure 6. Computed reaction profiles (kcal/mol) for the coupling of 2-phenylpyridine, 8, with 4-octyne and diphenylacetylene at Rh(OAc)2Cp*, A, in EtOH. In each case free energies are quoted relative to A and the free substrates.

vation 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 necessi-
tates 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 which dis-
plays 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. For 1-
phenylpyrazole, 1, directed C–H activation is favored in
both EtOH and DCE and alkyne insertion in these sys-
tems forms 7-membered rhodacycles that are set up for
C–N bond coupling to form cationic heterocyclic pro-
ducts. Interestingly, the alternative non-directed C–H acti-
vation also has reasonable barriers of around 22 kcal/mol
at the C 5–H 5 bond, but is actually kinetically more acces-
sible at the backbone ortho-C–H bond of the phenyl
group (ca. 19 kcal/mol). These values are also largely in-
dependent 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 subse-
quent reaction with alkynes to give the neutral C–C cou-
pled products reported by Miura and co-workers3b (viz.
substrates 6a and 6b used in this study) and the observed
competition for the formation of naphthalene products is
currently underway.

Figure 7. Computed barriers for directed and non-directed
C–H activation of various heterocyclic substrates at
Rh(OAc)2Cp*. Barriers are quoted relative to the most stable
precursor set 0.0 kcal/mol; this is generally Rh(OAc)2Cp* and
the free substrate except in those cases marked with an aster-
isk where it is a H-bonded adduct (similar to A•4a in the
main text). Barriers are computed for EtOH (plain text), DCE (italics) and xylene (bold) solvents; values in parenthesis for substrates 1 and 8 are for non-directed C-H activation at the ortho-C-H position of the phenyl group.22

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(OAc)2Cp* 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 Pf\(_6\) 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 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\(^1\) position in 4a (\(q_C = -0.02\)) compared to that in 10a (\(q_C = -0.22\)) although a similar charge of +0.28 is computed at H\(^3\) 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 stabilises the Rh centre in the 7-membered rhodacycle, \(E^b\), 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 \(E^b\) reduces this extra stabilisation 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 \(\{C^aPr_3\}\) ‘strap’ destabilises the 7-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. The exchange of the alkyne moieties in the \(4a/4b\) 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 favoured with 2-phenylpyridine, probably due to the reduced ring strain in tricyclic products featuring three 6-membered rings. The combination of 1-phenylpyrazole and diphenylacetylene is most disadvantaged and this again fits with the difficulty in forming 4b experimentally. These additional thermodynamic factors combine with the extra stabilisation of intermediate \(E^b\) 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 \(\Delta G = 22.2 \text{ kcal/mol}\) is for the 1-phenylpyrazole system where a formally anionic alkyl C couples with a neutral N to form a cationic heterocycle (“C-N+ coupling”). Incorporating the \(\{C^aPr_3\}\) strap reduces this barrier to 15.3 kcal/mol, for the reasons discussed above. Combining anionic C and N centres 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,20 less than half of that for the C–N' coupling. We have also extended the current study to the coupling of two anionic C centres in 6aEa. 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(Pr)_3] strap as in 6aEa.

In conclusion, we have shown through experimental and computational means how a number of steps in the Rh-catalysed 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 stabilise a key rhodacyclic intermediate can suppress the former. Non-directed C–H activation is an energetically feasible process which, 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 Etanol (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]), KPF_6 (0.6 mmol), and Cu(OAc)_2.H_2O (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 x 10 mL) and washed with water (20 mL) containing ethylene diamine (1 mL). The organic fraction was collected and dried over MgSO_4. 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 D.01)17 and Gaussian 09 (Revision A.02).18 Rh centres were described with the Stuttgart RECPs and associated basis sets19, and 6-31G** basis sets were used for all other atoms.20 Initial BP8621 optimizations were performed with Gaussian 03 using the ‘grid-ultrafine’ option, with all stationary points being fully characterized via analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue). IRC calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. 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 effects of ethanol (ε = 24.852), dichloromethane (ε = 10.125) and xylene (ε = 2.3879) solvents were run with Gaussian 09 and used the polarizable continuum model.22 Single-point dispersion corrections to the BP86 results employed Grimme’s D3 parameter set as implemented in Gaussian 09.23

ASSOCIATED CONTENT

Crystallographic data (CIF), full experimental details, NMR spectra, details of kinetics and KIE measurements, and details of all computed structures and associated energies, as well as functional testing. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1062469-1062474 contain complete crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes
The authors declare no competing financial interest.

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Computed barriers 
BP86-D3(kcal/mol)

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