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Combined Experimental and Computational Investigations of Rhodium-Catalysed C–H Functionalisation of Pyrazoles with Alkenes

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Abstract: Detailed experimental and computational studies have been carried out on the oxidative coupling of the alkenes \( \text{C}_2\text{H}_3\text{Y} \) (\( Y = \text{CO}_2\text{Me} \), Ph, \( \text{C(O)}\text{Me} \)) with 3-aryl-5-R-pyrazoles (\( R = \text{Me} \), Ph) using a \([\text{Rh(MeCN)}_3\text{Cp*}]\text{PF}_6\)\text{Cu(OAc)}_2\text{H}_2\text{O} catalyst system. In the reaction of methyl acrylate with \( 1\), up to five products (2aa–6aa) were formed, including the trans monovinyl product, either complexed within a novel Cu I dimer (2aa) or as the free species (3aa), and a divinyl species (6aa); both 3aa and 6aa underwent cyclisation by anaza-Michael reaction to give fused heterocycles 4aa and 5aa, respectively.

With styrene, only trans mono- and divinylisation products were observed, whereas with methyl vinyl ketone, a stronger Michael acceptor, only cyclised oxidative coupling products were formed. Density functional theory calculations were performed to characterise the different migratory insertion and \( \beta\)-H transfer steps implicated in the reactions of \( 1\) with methyl acrylate and styrene. The calculations showed a clear kinetic preference for 2,1-insertion and the formation of trans vinyl products, consistent with the experimental results.

Introduction

Metal-catalysed C–H functionalisations are now widely studied as atom-efficient methods for the construction of C–C and C–E (E = O, N) bonds.\(^1\) These circumvent the requirement to pre-functionalise the C–H bond and hence avoid the formation of salt waste in the subsequent C–C or C–E bond-formation reaction. Substrates with nitrogen- or oxygen-based directing groups are particularly efficient in this regard and the recognition of the role of carboxylates in providing facile C–H activation\(^2\) has led to a huge growth in the application of these methods in organic synthesis. The C–H activation occurs through a synergic process involving the Lewis acidic metal centre and an intramolecular carboxylate base, emphasised in the term “ambiphilic metal–ligand assistance” (AMLA) put for-ward by us,\(^2d, e\) whereas Fagnou and co-workers\(^2f\) have termed this “concerted metallation–deprotonation” (CMD).

Over the last few years, Rh\(^{III}\) catalysts for C–H activation and functionalisation based on \([\text{RhCl}_2\text{Cp*}]\) and related derivatives have been intensively studied and the field has recently been reviewed.\(^1g, h\) Reactions with alkenes often proceed by insertion into a cyclometallated intermediate followed by C,E reductive elimination to generate heterocycles. In contrast, with alkenes, insertion into a cyclometallated intermediate is usually followed by \( \beta\)-H elimination to form a vinyl species that dissociates from the metal. Exceptions to this can occur through the use of internal oxidants, as shown independently by Fagnou\(^3\) and Glorius\(^4\) and their co-workers for the reactions of alkenes and benzamides (Scheme 1). Thus, with \( R = \text{C(O)}\text{Bu} \), \( \text{O–C(sp)}^2\) bond formation leads to a saturated heterocycle in preference to the alternative \( \beta\)-H elimination product observed when \( R = \text{Me} \).

There are now numerous stoichiometric precedents for the C–H activation step at complexes based on the \([\text{RhCp*}]\) fragment\(^5\) and in some cases for the subsequent alkene inser-

Scheme 1. Alternative outcomes of the rhodium-catalysed coupling reactions of ethene and benzamides.
tions. However, in catalytic reactions intermediates are often not detected and so information on the accessibility of the various steps involved is difficult to establish. One means to gain mechanistic insight is to use density functional theory (DFT) calculations to complement experimental observations. We and others have investigated reactions with alkenes and DFT studies on related coupling reactions with alkenes have also appeared. Xia and co-workers studied dihydroquinolone formation through the coupling of PhC(O)NH(OR) (R = Me, C(O)tBu) and ethene at Rh(OAc)2Cp* and invoked a Rh(V)-nitrene intermediate to account for the role of the internal oxidant. Fu and co-workers also considered the oxidative Heck coupling of phenol carbamates with ethyl acrylate.

Herein we report the catalytic C–H functionalisation of 3-phenylpyrazoles with alkenes at a {RhCp*} centre. In particular, we have extended the range of alkenes as coupling partners and shown that [Rh(MeCN)3Cp*][PF6]2 is a more efficient catalyst precursor than [RhCl2Cp*]2. In addition, we have isolated a range of mono- and divinylation products, which lend greater insight into the underpinning mechanism of these reactions. DFT calculations have also been employed to probe the mechanism further and to understand the factors controlling product selectivity. Related studies involving the coupling of alkenes with N-heterocycles with a {RhCp*} catalyst include the vinylation of N-phenylpyrazole with styrenes and acrylates, the oxidative vinylation and subsequent aza-Michael cyclisation of pyridineamides with alkenes featuring electron-withdrawing substituents as well as similar reactions of 3-phenylpyrazoles with ethyl or butyl acrylate.

Results and Discussion

Catalysis studies

We have examined the reactions of 3-phenyl-5-R-pyrazoles (R = Me (1a), Ph (1b), CF3 (1c)) with methyl acrylate (a), styrene (b) and methyl vinyl ketone (c) catalysed by [Rh(MeCN)2Cp*] [PF6]2. The reaction of 1a with methyl acrylate (a) led to a mixture of products, as summarised in Scheme 2. It became apparent that the work-up procedure affected the product distribution. If the reaction mixture was simply passed through Celite three times to remove insoluble inorganic materials, one major product was formed (2aa, entry 1) with minor amounts of three others (3aa, 5aa and 6aa). The 1H NMR spectrum for the major component is consistent with a monovinyl product and shows two mutually coupled 1H doublets at δ = 5.06 and 6.47 ppm (J = 13.7 Hz). This large coupling constant is on the boundary between those of cis and trans vinyl groups and so the precise identification of this compound from the NMR data alone was not possible. If the reaction mixture was extracted with aqueous ammonia (2m) to remove any soluble copper species, then 3aa, 5aa and 6aa were again observed along with a new product denoted 4aa (entry 2). Further investigation showed that if the major product from entry 1 was isolated and then treated with aqueous ammonia it converted into a mixture of 3aa and 4aa.

Crystallisation of the initial major product 2aa allowed its molecular structure to be determined by X-ray crystallography. Surprisingly, the compound turned out to be a copper(I) dimer with bridging pyrazoles and one alkene bound to each copper (Figure 1). Compared with the free alkene 3aa (see below), the protons and carbons in 2aa are shifted upfield (1.3–1.6 ppm 1H, and 24–50 ppm 13C), consistent with some back-bonding component. In accord with this, the C=C distances are relatively long (1.377(12) and 1.410(13) Å in two independent molecules) compared with other copper(I)/C0 alkene complexes.

The other products formed after aqueous extraction were much easier to identify. Compound 3aa is formed by simple displacement of the vinyl-pyrazole ligands from copper in 2aa by ammonia. The 1H NMR spectrum for 3aa is very similar to 2aa except the vinyl protons are observed considerably downfield at δ = 6.39 and 8.13 ppm with a coupling of 16.0 Hz.

Scheme 2. Products from the reactions of 3-phenylpyrazoles with methyl acrylate (yields of isolated product are given in parentheses).
doublets at one proton. Analysis of the $^{13}$C NMR and HMQC spectra of compound 4a shows the same mass as 3aa and the $^1$H NMR spectrum shows three mutually coupled doublets of doublets at $\delta = 5.49$, 3.30 and 2.77 ppm, each integrating to one proton. Analysis of the $^{13}$C NMR and HMQC spectra showed that these signals correspond to a CHCH$_2$ group. The HMBC spectrum shows a correlation between the CH$_2$ and the CO$_2$Me, consistent with the CH$_2$ being next to the CO$_2$Me. This rules out a six-membered saturated N-heterocyclic product formed by C(sp$^3$)-N coupling (see also the Computational Studies section below). Based on these data and the crystal structure of the related compound 4ba (see Figure S1 in the Supporting Information), the structure was deduced to be the five-membered heterocyclic compound 4aa, formed from 3aa by an intramolecular Michael reaction (see below).

The fourth product, 5aa, arises from the reaction of 1a with 2 equivalents of methyl acrylate and exhibits a coupling constant of $J = 16.0$ Hz, which again suggests a trans vinyl. If 2.2 equivalents of methyl acrylate were used, 5aa was the only product formed, in a yield of 86%. On some occasions a fifth product, divinyl 6aa, was also observed. The $^1$H NMR spectrum of 6aa shows two mutually coupled doublets at $\delta = 6.26$ and 7.59 ppm ($J = 15.7$ Hz) corresponding to four vinyl protons; the low-field shift and large coupling constant both suggest trans vinyl groups. This compound was unstable in solution and readily isomerised to 5aa within 2 days through a non-catalysed Michael addition. Compound 5aa is analogous to the aza-Michael cyclisation products reported by Li and Zhao,[11] but we have now been able to demonstrate that these are formed directly from a divinyl precursor. The cyclisation of 6aa to 5aa is evidently easier than the cyclisation of 3aa to 4aa, as these monovinyl compounds are stable for more than a week in solution (see below). All of the compounds observed from the reaction of 1a with methyl acrylate result from the regioselective insertion of the alkene with the CO$_2$Me substituent placed adjacent to the metal and selective $\beta$-H elimination to provide trans vinyl compounds (see the Computational Studies section below).

A similar reaction between 1b and methyl acrylate (a) gave the corresponding monovinyl (3ba), cyclised (4ba) and divinyl (6ba) products in a combined yield of 54% after chromatography. The low-field shifts ($\delta = 6.43$ and 8.11 ppm) and large coupling constant (ca. 16 Hz) of the vinyl protons in 3ba suggest a trans geometry, and in this case no copper complex (2ba) was observed. Similarly, the divinyl product 6ba shows a trans geometry. Crystals of 4ba were obtained and its molecular structure determined by X-ray diffraction (see Figure S1 in the Supporting Information). The structure clearly shows that 1 equivalent of methyl acrylate reacted with 1b and that an intramolecular Michael reaction has occurred to form a new five-membered ring. The reaction of 1c with methyl acrylate (a) gave monovinyl product 3ca in a yield of 73% along with a small amount (9%) of the copper complex 2ca. In this case no cyclised product 4ca was observed.

The cyclisations of 3aa and 3ba were attempted by adding base (Scheme 3). For 3aa no reaction occurred in the presence of the weak base K$_2$CO$_3$, but addition of tBuOK led almost immediately to the formation of 4aa (as shown by $^1$H NMR spectroscopy); the equivalent cyclisation also occurred with 3ba to give 4ba. It is therefore likely that the aqueous ammonia used to remove the copper acts as a base catalyst for the formation of the cyclisation products observed in the original catalytic reactions. Although the Michael addition cyclisations of the initially formed vinyl products have been observed before, the role of the work-up procedure in forming such products has not been recognised previously.

We have previously shown that the cationic catalyst [Rh(MeCN)$_2$Cp$^+$][PF$_6^-$]$_2$ is more reactive than [RhCl(Cp$^+$)$_2$] in the reactions of pyrazoles with alkynes,[10] and so the reactions of substrates 1 with styrene (b), an alkene that has not previously undergone coupling with 3-phenylpyrazoles,[11] were attempted (Scheme 4).

The reaction between 1a and styrene worked well and gave mainly the monovinyl product 3ab in an overall yield of 60%.
The geometry of the vinyl group was assigned as trans based on the chemical shifts and coupling constant. As for methyl acrylate, insertion of styrene is regioselective and occurs such that the phenyl substituent is adjacent to the metal. A minor amount of a product believed to be the divinyl 6ab was also isolated. As found in the reaction of 1a and methyl acrylate, the products formed with styrene are exclusively trans. The reaction of diphenylpyrazole (1b) with styrene gave only the monovinyl product 3bb in a yield of 89%, again as the trans isomer. Unlike methyl acrylate, no cyclised products were formed with styrene, consistent with the fact that styrene is a poorer Michael acceptor.

Reactions with the better Michael acceptor methyl vinyl ketone (c) were then attempted (Scheme 5). With 1a, the tricyclic compound 4ac was formed as the major product (70%). There is no directing group available for the second C–H activation and subsequent addition of the second alkene group. At this stage we cannot say whether hydrogenation occurs before the addition of the second alkene and cyclisation or whether it occurs after the formation of a product of type 5. In contrast to the reaction with 1.2 equivalents of alkene, excess alkene leads to less competition with the direct aza-Michael addition and so no 7ac was formed.

To assess the role of rhodium and copper in the formation of 7ac, the reaction of 1a with 1.2 equivalents of methyl vinyl ketone was repeated in the absence of [Rh(MeCN)3Cp*][PF6]2 and Cu(OAc)2·H2O. This gave 7ac as the sole product in a yield of 94% isolated product in the same period of time, which confirms that 7ac is formed by Michael addition without the need for rhodium or copper.

![Scheme 5. Products from the reactions of 3-phenylpyrazoles with methyl vinyl ketone (yields of isolated product are given in parentheses).](image)

and the simple Michael addition compound 7ac as a minor product (8%). The 1H NMR spectrum of 7ac shows two 2H triplets at δ = 3.06 and 4.24 ppm, the latter shows an NOE to the methyl signal of the pyrazole, but does not show an NOE to any of the phenyl protons, hence the alkyl chain is proposed to be on the nitrogen further away from the phenyl ring. The reaction of 1b with methyl vinyl ketone gave solely 4bc in high yield (92%). Products 4ac and 4bc presumably arise from the initial formation of a monovinyl species that cyclises by an aza-Michael reaction before the second C–H activation and insertion 5 may occur. The failure to observe any monovinyl product is also consistent with the aza-Michael reaction being more favoured with methyl vinyl ketone than with methyl acrylate, as is the formation of a minor amount of the direct Michael addition product 7ac.

To determine whether divinylation was possible, the reaction of 1a was repeated with 2.2 equivalents of methyl vinyl ketone. This gave two products in a roughly 1:1 ratio and combined yield of 86%. The first product was 4ac (40%), as found in the reaction with just 1.2 equivalents of methyl vinyl ketone. However, the second product was not the expected monocyclised monovinyl (c.f. 5aa found with methyl acrylate), but the related product 8ac formed in a yield of 46%, in which the vinyl group of the expected 5ac has been hydrogenated, as confirmed by the mass spectrum. The mechanism of formation of 8ac is uncertain. It seems unlikely to arise from 4ac because approach was adopted in this work, with geometries initially optimised in the gas phase with the BP86 functional and a medium-sized basis set (BS1) and the resultant free energies then being corrected for solvation (dichloroethane (DCE), polarizable continuum model (PCM) approach), dispersion (Grimme’s D3 parameter set) and basis-set effects (with an extended basis set, BS2). The final energies computed by using this protocol are referred to as G_{DCE} (see the Supporting Information for full details).

The key steps in the overall catalytic cycle are summarised in Scheme 6. Under the catalytic conditions we expect Rh(OAc)2Cp* to be formed from [Rh(MeCN)3Cp*][PF6]2 and Cu(OAc)2·H2O and we have previously shown[10] that this readily forms an N-bound adduct with 1a. This species, Int(A-B), is the most stable precursor to the subsequent coupling reaction and so all energies are quoted relative to this (and the relevant free alkene) at 0.0 kcal mol⁻¹. Sequential N–H and C–H activation of 1a in Int(A-B) leads to cyclometallated C2 and the computed energetics of these steps from our earlier work are also shown in Scheme 6.[18] Substitution of acetic acid in C2 by an alkene gives intermediate D in which migratory insertion into the Rh–aryl bond leads to seven-membered metallacycle E. In principle, reductive coupling in E could give F in which a heterocyclic product is bound to rhodium. However, in this case such a C(sp²)–N bond formation is disfavoured and instead E undergoes β-H transfer to give G from which the final

Computational studies

DFT calculations have been used to probe the mechanism and selectivity of the coupling reactions between 3-phenyl-5-methylpyrazole (1a) and alkenes C₂H₄Y in which Y = CO₂Me (a) and Ph (b). Previous work on catalytic heterocycle formation between 1a and alkenes has shown the importance of including corrections for both solvent and dispersion effects in the computed energetics.[10] A similar
C–C coupled product can be displaced by additional 1a. This, along with the re-oxidation of the Rh metal centre by Cu(OAc)$_2$, regenerates the catalytically active Rh III species and so completes the cycle.

Within this mechanistic picture, the regio- and stereoselectivity of the reaction are dictated by the migratory insertion and β-H transfer steps, respectively. With the monosubstituted alkenes C$_2$H$_3$Y (Y = CO$_2$Me, Ph), four migratory insertion processes are possible that differ according to the orientation of the alkene in intermediate D. Two pathways follow the 2,1 insertion illustrated in Scheme 6 that places the substituent Y beside the metal in metallacycle E. β-H transfer then gives 1,2-disubstituted alkenes with potentially either a trans or cis stereochemistry.

The alternative 1,2-insertions place Y beside the aryl ring in E and would give a 1,1-disubstituted alkene, although only 1,2-disubstituted products have been observed experimentally. In the following we consider the details of these processes, first for methyl acrylate (a) and then styrene (b), both coupling with 3-phenyl-5-methylpyrazole (1a).

**Reaction with methyl acrylate:**

**Migratory insertion**

The computed energy profiles for the four possible migratory insertion steps involving methyl acrylate are shown in Figure 2, which also defines the atom-labelling scheme employed. Selected computed structures are shown in Figure 3. The profiles start with two pairs of alkene adducts, D$_{12,1}$/D$_{22,1}$ (2,1 insertion, see Figure 2i) and D$_{11,2}$/D$_{21,2}$ (1,2 insertion, Figure 2ii), which all lie within 0.5 kcal mol$^{-1}$ of one another. Starting with D$_{22,1}$ ($G_{DCE} = +4.1$ kcal mol$^{-1}$), migratory insertion proceeds by initial rotation of the alkene ligand to achieve a near-planar four-centred transition state, TS(D$_2$-E$_2$)$_{2,1}$ ($G_{DCE} = +19.7$ kcal mol$^{-1}$). As this occurs, the new C$_4$···C$_3$ bond begins to form (1.91 Å, cf. 2.19 Å in D$_{22,1}$) with elongation of both the Rh···C$_4$ (2.34 Å, cf. 2.19 Å in D$_{22,1}$) and C$_4$···C$_5$ distances (1.46 Å, cf. 1.38 Å in D$_{22,1}$).

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**Figure 2.** Computed energy profiles ($G_{DCE}$, kcal mol$^{-1}$) for the migratory insertion of methyl acrylate into adduct D by i) 2,1-insertion and ii) 1,2-insertion. Energies ($G_{DCE}$) are quoted relative to Int(A-B) and free methyl acrylate set to 0.0 kcal mol$^{-1}$.
Furthermore, reaction is therefore required to access bond (C5-D1)2,1. The geometry of E12,1 is included for comparison. The Cp* ligand (which lies above the plane of the page) and all hydrogen atoms except those on C4 and C5 have been omitted for clarity.

Figure 3. Computed structures for 2,1-insertion starting from D2,1 with relative energies in kcal mol\(^{-1}\) and selected distances in Å. The geometry of E12,1 is included for comparison. The Cp* ligand (which lies above the plane of the page) and all hydrogen atoms except those on C4 and C5 have been omitted for clarity.

1.42 Å in D2,1. TS(D2-E2)2,1 leads to E2,1 (G^+ = +5.2 kcal mol\(^{-1}\)) in which the seven-membered metallacycle adopts a twist-boat conformation, characterised by a N2–C1–C4–C5 torsion angle of 33°. Also noticeable is a short contact of 2.41 Å between the rhodium and the methoxy oxygen of the ester substituent. Overall the migratory insertion step proceeds with a barrier of 15.6 kcal mol\(^{-1}\) and is slightly endergonic (ΔG_DCE = +1.1 kcal mol\(^{-1}\)).

In D1,1, the CO2Me group is oriented towards the Cp* ring and this forces the alkene to lie near-parallel to the Rh–N2 bond (C5–C4–Rh–N2 = 19.7°). A greater degree of alkene rotation is therefore required to access TS(D1-E1)2,1, but despite this the insertion barrier is the same as that from D2,1 (15.6 kcal mol\(^{-1}\)). TS(D1-E1)2,1 and TS(D2-E2)2,1 therefore only differ in energy by 0.1 kcal mol\(^{-1}\).[19] In contrast, E1,1 is 3.6 kcal mol\(^{-1}\) higher in energy than E2,1. This may reflect the different conformation of E1,1, which exhibits a boat-type structure with (RhCp*) and the C2–C3 bond in the prow and stern positions, respectively, and an N2–C1–C4–C5 torsion angle of 5°. Furthermore, E1,1 does not feature a Rh···O short contact such as that seen in E2,1 (see Figure 3). Full details of all computed structures are supplied in the Supporting Information.

Computed profiles for the alternative 1,2-insertions of methyl acrylate from D1,1 and D2,1 are summarized in Figure 2ii. Both pathways proceed through the expected four-centred transition states, but these are now significantly higher in energy (TS(D1-E1)1,2: +26.5 kcal mol\(^{-1}\); TS(D2-E2)1,2: +26.7 kcal mol\(^{-1}\)). Thus, this insertion is clearly disfavoured kinetically over 2,1-insertion, consistent with the observation of only 1,2-disubstituted alkenes experimentally. Therefore only pathways derived from the 2,1-migratory insertion will be considered in the following.

Reaction with methyl acrylate: Rearrangement/β-H transfer

The stereoselectivity of the vinylation reactions will reflect the ease of β-H transfer in E1,1 and E2,1 and so pathways leading to both the trans and cis isomers of the product were characterised. Along both pathways β-H transfer requires an initial rearrangement to form an agostic intermediate, either E1,1 (G_DCE = +11.5 kcal mol\(^{-1}\)) or E2,1 (G_DCE = +6.3 kcal mol\(^{-1}\)). The seven-membered rhodacycles in E1,1 and E2,1 proved to be highly flexible and so allowed pathways linking each of these species to both E_\text{cis} and E_\text{trans} to be defined. The more accessible routes stem from E2,1 and both involve two steps (see Figures 4 and 5). To form E_\text{trans} initial rotation about the Rh–C5 bond disrupts the Rh–OMe interaction in E2,1, and leads to a new conformer E2,1 (G_DCE = +13.1 kcal mol\(^{-1}\)) in which the rhodacycle exhibits a flattened, twist-boat conformation. The C4–H1 bond can then approach the rhodium centre via TS(E2-E'\text{trans}) (G_DCE = +14.1 kcal mol\(^{-1}\)) to give E_\text{trans}. E_\text{trans} exhibits a near-planar arrangement of the Rh, N2 and C1 to C4 centres, whereas the C5 position sits well above this plane to accommodate the approach of the C4–H bond to form the β-agostic interaction.

The first step in forming E_\text{cis} from E2,1 involves the initial rotation of the CO2Me substituent to give the conformer E2,1 (G_DCE = +7.1 kcal mol\(^{-1}\)). This again interrupts the Rh–OMe interaction but does not cause any significant change in the conformation of the rhodacycle at this point. In the second step the C3–C4–C5 moiety flips via TS(E2-E\text{cis}) (G_DCE = +17.5 kcal mol\(^{-1}\)) with rotation of the central (CH2) group that permits the C4–H2 bond to approach the rhodium centre in E_\text{cis}. Both E_\text{cis} and E_\text{trans} feature strong agostic interactions with elongated C4–H distances of around 1.23 Å and short Rh–H contacts of around 1.8 Å. β-H transfer therefore readily occurs with minimal barriers to form G_\text{cis} (G_DCE = +7.4 kcal mol\(^{-1}\)) and G_\text{trans}.

(\(G_{\text{DCE}} = +4.9\) kcal mol\(^{-1}\)) in which the bound alkene has either a cis or trans stereochemistry, respectively. \(G_{\text{cis}}\) and \(G_{\text{trans}}\) (as well as their agostic precursors, \(E_{\text{cis}}\) and \(E_{\text{trans}}\)) are chiral at the rhodium atom and are distinguished by an inversion centre at the rhodium as well as a difference in the nature of the geometric isomer of the alkene (see Figure S3 in the Supporting Information).

Considering now the overall pathway from \(D_{12,1}\) and \(D_{22,1}\), both initial migratory insertion processes have very similar barriers (Figure 2), which suggests that a mixture of \(E_{12,1}\) and \(E_{22,1}\) would be generated. Both can then undergo rearrangement and \(\beta\)-H transfer to give \(G_{\text{trans}}\) and \(G_{\text{cis}}\) with these processes being more accessible from \(E_{22,1}\). The lower barrier to rearrangement/\(\beta\)-H transfer to form \(G_{\text{trans}}\) along with the greater stability of \(G_{\text{trans}}\) suggests a preference for the formation of this species and by extension the trans alkene product 3aa. This is consistent with the experimental results in which only 3aa is formed, either as a free species or bound in the dimeric Cu I complex 2aa. Interestingly, the high trans selectivity (also observed with the other pyra-
zoles) originates from the rearrangement of \( E_{22,1} \) to form \( E_{\text{trans}} \) rather than in the subsequent \( \beta \)-H transfer step.

**Reaction with styrene: Migratory insertion**

Migratory insertion was computed for all four forms of the styrene adduct \( D \) (2,1-insertion is shown in Figure 6 with those for 1,2 insertion presented in Figure S4 in the Supporting Information). As with methyl acrylate, a clear preference for 2,1-insertion was computed, with \( TS(D2-E2)_{2,1} \), \( G_{\text{DCE}} = +23.6 \text{ kcal mol}^{-1} \) and \( TS(D1-E1)_{2,1} \), \( G_{\text{DCE}} = +23.2 \text{ kcal mol}^{-1} \) lying 3–4 kcal mol\(^{-1} \) below the equivalent transition states for 1,2-insertion. The seven-membered rhodacycles are also more stable along the 2,1-insertion pathway, particularly \( E_{22,1} \), \( G_{\text{DCE}} = +1.6 \text{ kcal mol}^{-1} \) for which the insertion step from \( D_{22,1} \) is exergonic. The computed structure of \( E_{22,1} \) reveals a stabilizing allylic interaction in which the Rh–C5 bond (2.13 Å) is reinforced by interactions with the ipso (Rh–C6 = 2.25 Å) and ortho (Rh–C7 = 2.40 Å) positions of the phenyl substituent. This is similar to the Rh–O interaction noted in \( E_{22,1} \) with methyl acrylate, although the stabilisation is clearly more significant with the phenyl group. No such interaction is possible in \( E_{12,1} \), \( G_{\text{DCE}} = +13.7 \text{ kcal mol}^{-1} \) as the phenyl substituent is directed away from the metal centre.

**Reaction with styrene: Rearrangement/\( \beta \)-H transfer**

The lowest-energy pathways for the formation of \( G_{\text{trans}} \) and \( G_{\text{cis}} \) are shown in Figure 7. \( G_{\text{trans}} \) is accessed directly from \( E_{22,1} \) in an analogous fashion to that computed with the methyl acrylate system. In this case a significantly larger overall barrier of 19.2 kcal mol\(^{-1} \) is computed (cf. 8.9 kcal mol\(^{-1} \) with methyl acrylate). This again reflects the greater stability of \( E_{22,1} \) with the initial rearrangement step to give \( E'_{22,1} \) having a barrier of 17.8 kcal mol\(^{-1} \) before \( E_{\text{trans}} \) is accessed via \( TS(E2'_{2,1}-E_{\text{trans}}) \) (\( +20.8 \text{ kcal mol}^{-1} \)). The strong agostic interaction in \( E_{\text{trans}} \) (C4–H1 = 1.23 Å; Rh–H1 = 1.76 Å) then allows facile \( \beta \)-H transfer to give \( G_{\text{trans}} \) (\( +7.4 \text{ kcal mol}^{-1} \)). In contrast to the situation with methyl acrylate, the lowest-energy pathway to \( E_{\text{cis}} \) involves the initial rearrangement to \( E_{12,1} \) via \( TS(E2-E1)_{2,1} \), \( G_{\text{DCE}} = +22.7 \text{ kcal mol}^{-1} \), see Figure 7). \( E_{\text{cis}} \), \( G_{\text{DCE}} = +13.8 \text{ kcal mol}^{-1} \) is then accessed via \( TS(E1-E_{\text{cis}}) \) (\( +21.7 \text{ kcal mol}^{-1} \)) with facile \( \beta \)-H

**Figure 6.** Computed energy profiles \( (G_{\text{DCE}}, \text{kcal mol}^{-1}) \) for the migratory insertion of styrene from adducts \( D \) by 2,1-insertion. Energies \( (G_{\text{DCE}}) \) are quoted relative to Int(A-B) and free styrene set to 0.0 kcal mol\(^{-1} \).

**Figure 7.** Computed energy profiles \( (G_{\text{DCE}}, \text{kcal mol}^{-1}) \) for \( \beta \)-H transfer from \( E_{22,1} \) formed with styrene. Energies \( (G_{\text{DCE}}) \) are quoted relative to Int(A-B) and free styrene set to 0.0 kcal mol\(^{-1} \) with the exception of the organic products for which trans 3ab provides the reference energy.
transfer then giving $G_{\text{trans}}$ (+7.3 kcal mol$^{-1}$). $G_{\text{trans}}$ is therefore formed from $E_{2,1}^b$ with an overall barrier of 21.1 kcal mol$^{-1}$.[22]

The extra stability of intermediate $E_{2,1}^b$ in the styrene system has a significant effect on the rearrangement/\(\beta\)-H transfer pathways. This species is the most stable intermediate along the entire pathway from $D$ and it makes the rearrangement/\(\beta\)-H transfer process significantly endothermic. The stereoselectivity will therefore be dictated by the barrier to forming $G_{\text{trans}}$ or $G_{\text{trans}}$ from $E_{2,1}^b$ and the calculations indicate this is again determined by the ease of rearrangement of the seven-membered rhodacycles. As for methyl acrylate, this rearrangement is found to be more accessible for the formation of $G_{\text{trans}}$ ($\Delta G_{\text{OCHE}}^{\text{trans}} = +19.2$ kcal mol$^{-1}$) than for $G_{\text{trans}}$ ($\Delta G_{\text{OCHE}}^{\text{trans}} = +21.1$ kcal mol$^{-1}$). Assuming facile product release, $3\text{ab}$ would then be formed, consistent with experimental results in which only organic products with a trans stereoselectivity were observed.

**Discussion**

The rhodium-catalysed vinylation of 3-phenylpyrazoles based on an oxidative C–H coupling strategy has been demonstrated for a range of alkenes, $C_3H_7Y$ ($Y=CO_{3}Me$, Ph, C(O)Me). Compared with $[\text{RhCl}_2\text{Cp}^*]_2$, $[\text{Rh(MeCN)}_3\text{Cp}^*][\text{PF}_6]$ acts as a particularly efficient catalyst, effecting previously unreported vinylation with both styrene and methyl vinyl ketone. For all three alkenes, insertion occurs regioselectively with the substituted atom being placed next to the metal and leading to linear 1,2-disubstituted vinylation products. The stereoselectivity of the process is very high with the trans alkene products being favoured in each case. The final product distribution depends on the ease ofaza-Michael cyclisation of the initial vinyl product, which itself reflects the alkene involved. Interestingly, for methyl acrylate the trans mono- and divinylation products ($3\text{aa}$ and $6\text{aa}$) can undergo an aza-Michael reaction to give fused heterocyclic products ($4\text{aa}$ and $5\text{aa}$). Such vinylation Michael cyclisations have been observed previously with pyrazoles[13] and amides,[14] however here, the vinyl species and the resultant cyclised product have both been isolated for the first time. Moreover, the divinyl product $6\text{aa}$ has been shown to cyclise more readily than the monovinyl $3\text{aa}$. Mechanistic experiments indicate that these cyclisations are not metal-catalysed. As the cyclisation of $3\text{aa}$ is base-catalysed it can occur when aqueous ammonia is used in the work-up procedure to sequester the copper used in the catalysis. Oxidative C–H coupling with the stronger Michael acceptor methyl vinyl ketone led only to fused heterocyclic products.

DFT calculations have allowed comparison of the possible pathways for the migratory insertion (computed intermediates $D$–$E$) and rearrangement/\(\beta\)-H transfer steps ($E$→$G$) implicated in the formation of monovinylation products from the reaction of 3-phenyl-5-methylpyrazole with both methyl acrylate and styrene. The calculations showed that migratory insertion has a higher barrier than the subsequent rearrangement/\(\beta\)-H transfer. Moreover, the 2,1-insertion mode is kinetically favoured, which reflects the preference for 1,2-disubstituted vinylation products observed experimentally. For methyl acrylate the difference between the alternative 2,1- and 1,2-insertion transition states is around 7 kcal mol$^{-1}$, whereas for styrene this is reduced to 3–4 kcal mol$^{-1}$. The greater discrimination with methyl acrylate is consistent with the results of work on the selectivity of the intermolecular Heck reaction, which also revealed that electronic effects determine the regioselectivity of the reaction.[23] This is supported here by the computed gas-phase enthalpies of the insertion transition states, which also show a preference for 2,1-insertion, that is, this intrinsic electronic preference is not affected by the inclusion of entropy, solvent, dispersion and basis-set effects (see Tables S2 and S3 in the Supporting Information). The calculations highlight a high degree of conformational flexibility in the seven-membered rhodacycles $E_{2,1}^b$ and $E_{2,1}^b$ formed upon the 2,1-insertion of methyl acrylate or styrene. The interconversion of $E_{1,2}^b$ and $E_{2,2}^b$ is therefore possible, whereas the stereoselectivity is ultimately determined by the ease of rhodacycle rearrangement that must occur prior to the \(\beta\)-H transfer step. The flexibility of these rhodacycles means that both the cis and trans alkene products can be accessed from either insertion intermediate $E_{1,2}^b$ or $E_{2,2}^b$; however, the calculations correctly indicate a preference for the formation of trans vinyl products, as seen experimentally.

The energies of the migratory insertion transition states (methyl acrylate ca. +19.6 kcal mol$^{-1}$; styrene ca. +23.4 kcal mol$^{-1}$) can also be compared with that of the C–H cleavage transition state $TS(B-C\text{)}^2$ ($G_{\text{OCHE}} = 19.5$ kcal mol$^{-1}$), which is the highest point of the preceding N–H/C–H activation pathway (see Scheme 6). Thus, for methyl acrylate, migratory insertion will be competitive with C–H activation, and so a similar situation arises to that seen in the reaction of 4-octyne with 3-methyl-5-phenylpyrazole.[15] In contrast, for styrene, the 2,1-insertion transition state is clearly higher in energy and so migratory insertion would correspond to the overall rate-determining step in the cycle.

**Conclusions**

We have shown that the Rh$^{III}$-catalysed oxidative coupling of monosubstituted alkenes with 3-phenylpyrazoles gives a range of 1,2-disubstituted vinylation products depending on the substituents on both the alkene and the 3-phenylpyrazole substrates. The use of aqueous ammonia to remove copper can affect the product distribution by causing base-catalysed cyclisation of the monovinyl product whereas the divinyl product can cyclise without base catalysis. Computational studies have defined the key migratory insertion and rearrangement/\(\beta\)-H transfer steps and correctly model both the regio- and stereoselectivity of the oxidative coupling reactions with methyl acrylate and styrene. The observed trans stereoselectivity is linked to the rearrangement of the rhodacycles formed upon migratory insertion.

**Experimental Section**

For details of instruments used and the general experimental and computational procedures, see the Supporting Information.
General procedure for catalysis reactions with rhodium: The appropriate pyrazole (1 equiv), alkene (1.2 equiv), [CP*Rh(MeCN)₃]
(PF₆)₂ (33 mg, 5 mol%), Cu(OAc)₂·H₂O (2.5 equiv) and DCE (10 mL) were added to a Schlenk flask, which was sealed with a screw cap and
then transferred to a preheated oil bath and stirred at 83 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with Et₂O (10 mL) and transferred to a separating funnel to
which ammonium hydroxide solution (10 mL, 2 m) was added. The aqueous layer was extracted with Et₂O (3 × 10 mL) and the organic
layers were combined and dried over MgSO₄.

X-ray crystal structure determinations of 2aa and 4ba: A de-
scription of the procedure for the collection of crystallographic data for 2aa and 4ba, including a diagram of the molecular structure
and the crystal data of 4ab, are given in the Supporting Informa-
tion.

Crystal data for 2aa: C₁₅₃H₂₁₈Cu₂N₄O₈, M = 609.64, triclinic, a = 12.007(3), b = 12.325(4), c = 20.235(6) Å, α = 96.748(6), β = 90.416(6), γ = 115.197(6)°, V = 2685.2(13) Å³, T = 150(2) K, space group P1, Z = 2, 21286 reflections measured, 10420 independent reflections. The final R1 values were 0.0875 (>2σ(I)), 0.1767 (all data). The final wR2 values were 0.1719 (>2σ(I)), 0.2095 (all data). GOF = 0.856.

CCDC 1025819 (2aa) and CCDC 1021466 (4ba) contain the supple-
mentary crystallographic data for this paper. These data can be ob-
tained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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