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Intermediacy of an N-Heterocyclic Carbene Complex in the Catalytic C−H Activation of a Substituted Benzimidazole

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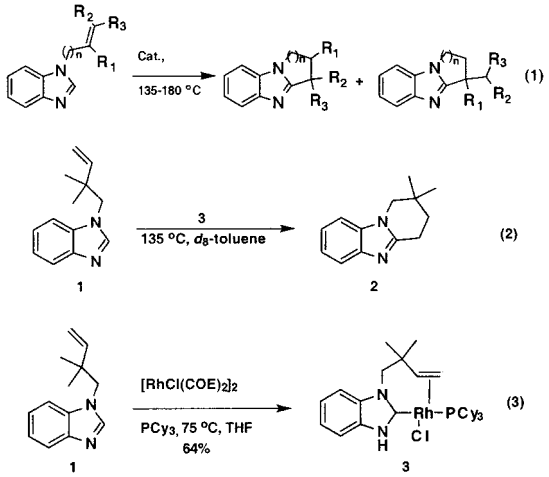
Metal-mediated C−H bond activation reactions have become important methods for the formation of carbon−carbon bonds.[1] Recently, our group has synthesized cyclic organic structures through Rh(I)-catalyzed C−H activation of aromatic and heterocyclic compounds with subsequent intramolecular coupling to an alkene (eq 1).[2] The conventional mechanism for this reaction postulates initiation by oxidative addition of an aromatic C−H bond to a coordinately unsaturated Rh center, leading to a vinylrhodium hydride intermediate. This species would then undergo insertion of a double bond into the Rh−H linkage, followed by reductive elimination to give the final product. We report a mechanistic study of the cyclization of **1** to **2** (eq 2) that reveals a substantially different mechanism involving an N-heterocyclic carbene (NHC)[3] complex **3** (eq 3) as a critical intermediate. Besides being a novel mechanism for this increasingly important type of carbon−carbon bond-forming reaction, this is one of the first examples in which a NHC plays a nonancillary role[4] in a catalytic transformation.[5]



At the outset of our mechanistic study, the first goal was to identify the catalyst resting state. Accordingly, heterocyclic alkene **1** was treated with stoichiometric quantities of $[RhCl(coe)_2]_2$ and PCy_3 at 75 °C (eq 3). Since the catalytic conversion of **1** to **2** is usually carried out at 135−160 °C, no cyclization was observed at this temperature. Rather, a single compound was formed which had an unusual singlet resonance in the ^{1}H NMR spectrum at δ 12.0. X-ray crystallographic analysis established that the complex was a square planar Rh(I) NHC/alkene complex[6] (**3**) (Figure 1), prompting us to conclude that the downfield ^{1}H NMR signal was due to the N−H resonance. The length of the Rh−$C_{carbene}$ bond of **3** was found to be 2.008(3) Å, which is consistent with other NHC Rh(I) complexes; this parameter reaffirms the single-bond nature of N-heterocyclic carbene−metal bonds.[7] The alkene C−C bond has

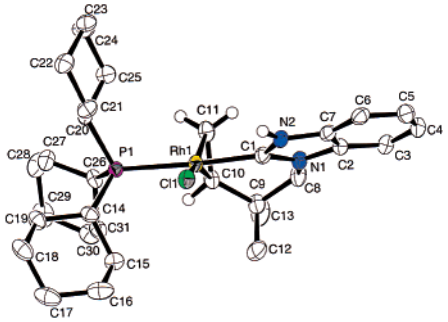


Figure 1. ORTEP of **3**. A molecule of THF was omitted for clarity.

a length of 1.409(5) Å. At the reaction temperature of 135 °C, complex **3** was found to catalyze the cyclization of benzimidazole derivative **1** at the same rate as the $[RhCl(coe)_2]_2/PCy_3$ system, implicating **3** as the resting state of the catalyst.

Next, kinetic investigation of the cyclization of **1** catalyzed by complex **3** was undertaken. The rate of reaction was measured using ^{1}H NMR spectroscopy to follow the disappearance of **1** at 135 °C in d_8-toluene (eq 2). Compound **1** is cleanly converted to product **2** under these conditions, and **3** is the major phosphine-containing species present in solution up to 75% conversion.[8] At higher conversions other unidentified phosphine-containing species begin to form, leading to increased experimental error in the kinetic plots. By monitoring the disappearance of starting material, the reaction was found to be zero-order in [**1**] with a rate constant ($k = k_{obs}$/[**3**]) of $4.2 \pm 0.6 \times 10^{-4}$ sec^{-1}. A plot of the log k_{obs} versus log [**3**] gave a straight line with some scatter and a slope of 1.2. We believe this provides evidence that the reaction is first order in [**3**]. These results suggest that the regeneration of the catalyst is not rate-determining, consistent with the experimental evidence that the carbene forms at a temperature below that required for cyclization.

It seemed likely that the rate-limiting transition state for the catalytic cyclization is either that associated with a [2 + 2] cycloaddition of the metal−carbene and −alkene linkages or with insertion of the alkenyl group into the Rh-carbene bond. We investigated these possibilities with the aid of DFT calculations. Energy minima and transition-state structures were explored with a model system containing imidazole and PH_3 ligands. Furthermore, the geminal methyl groups were removed to expedite calculation times.[9] A search of the potential energy surface[10] revealed a pathway with four energy minima, including carbene complex **4** (Figure 2). These intermediates correspond to the formal zwitterion **6**, hydride **8**, and product-bound complex **10**, and were found to be 24.3, 12.0, and 9.1 kcal/mol higher in free energy (298 K, 1 atm) than the carbene **4**, respectively. The three transition states connecting these intermediates were also found, thus completing the calculated reaction coordinate diagram. Each transition-state structure exhibited

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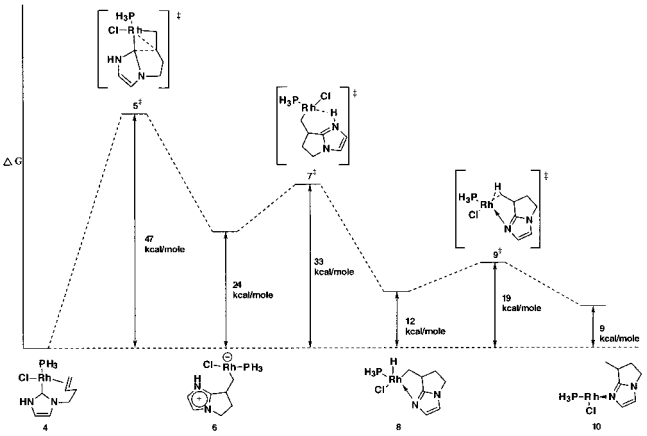

Figure 2. Calculated reaction coordinate diagram for cyclization.

a single imaginary vibrational frequency. The first transition state (**5**‡**)** is rate limiting with an energy 47 kcal/mol higher than resting state **4**. Although **5**‡ resembles a metallocyclobutane, resulting from a [2 + 2] cycloaddition between an alkene and carbene, visualization of the transition-state imaginary frequency[11] reveals that **5**‡ is more aptly described as a transition state leading to insertion of the alkenyl group into the Rh-C bond. Going from **4** to **5**‡ the Rh−$C_{carbene}$ bond is lengthened from 2.01 to 2.13 Å, whereas the distance from the carbene carbon to the internal alkene carbon decreases dramatically from 2.93 to 1.69 Å. The alkene insertion leads to the formation of zwitterion **6**, which lies only 24 kcal/mol above carbene **4** in part due to the aromatic character of the imidazolium ring. Intramolecular proton transfer generates neutral hydride **8**. The free energy required to reach **7**‡ from **6** was calculated to be 9 kcal/mol. C−H reductive elimination occurs at the Rh(III) center in complex **8** through **9**‡, with a decrease in the H−Rh−C angle from 75.3° to 44.1°. Presumably, the catalytic cycle is then renewed by the displacement of the product by another molecule of alkene with subsequent C−H activation to form the NHC complex **4**.

In summary, the cooperative use of experiment and theory has led to the discovery of a novel carbene insertion mechanism in the intramolecular coupling of an alkene to a benzimidazole. Furthermore, an N-heterocyclic carbene complex was found to be the resting state of the catalyst, and the carbene insertion was calculated to be the rate-limiting step of the reaction. Surprisingly, the NHC complex is formed in situ under mild thermal conditions via C−H activation of the heterocycle without necessitating pre-formation of the imidazolium salt. Currently, we are investigating the application of this annulation methodology to other heterocycles that are known to form N-heterocyclic carbenes, as well as investigating the mechanism of the formation of the carbene.

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Supporting Information Available: Experimental details, including ananlytical data for all compounds described in the article, X-ray diffraction data for **3**, kinetic data for the cyclization of **1** to **2**, and details for the calculated structures **4**, **5**‡, **6**, **7**‡, **8**, **9**‡, **and 10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Although the reaction was performed at 135 °C, the ^{31}P NMR spectrum was monitored at room temperature.

(9) Although compound **1** undergoes a formal 6-endo-trig cyclization, it has been previously reported that removal of the geminal methyl groups favors a formal 5-exo-trig cyclization (see ref 2). Therefore, in this paper the 5-exo-trig cyclization was studied. A more complete DFT study is currently underway.

(10) The structures were characterized at B3LYP/LACVP**++// B3LYP/LACVP** level of theory. Zero point and Gibbs free energy (1 atm, 298 K) corrections were applied based on unscaled frequency calculations. For further details see references below as well as the Supporting Information. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211. (c) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (d) Frisch, M. J.; Pople, J. A.; Binkeley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265. (e) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

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