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Probing the mechanism of the anomalous intramolecular C–H insertion reaction of rhodium carbenoids by analysis of kinetic isotope effects

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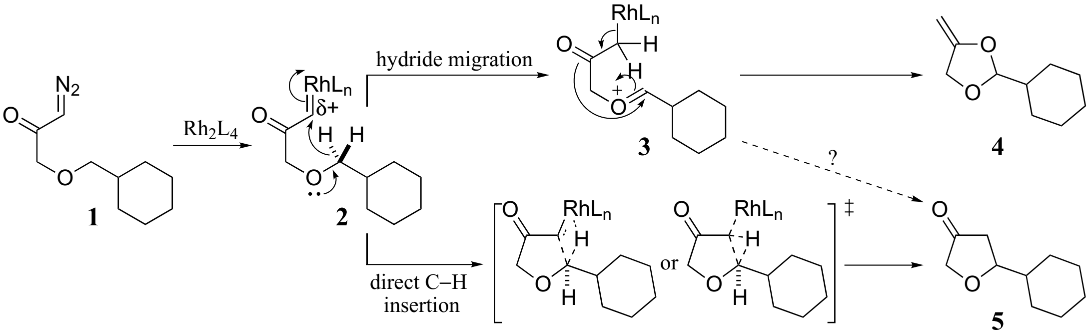
Abstract—The mechanism of the anomalous intramolecular insertion reaction of a rhodium carbenoid into an ethereal C–H bond has been explored using deuterium labelled substrates. Comparison of primary kinetic isotope effects and analysis of ratios of diastereoisomeric deuterated products suggests the reactions leading to the anomalous and conventional C–H insertion products are mechanistically distinct and do not share a common rate-determining step. © 2001 Elsevier Science Ltd. All rights reserved.

We recently reported that anomalous products are obtained during the preparation of 3(2*H*)-furanones by intramolecular C–H insertion of rhodium carbenoids into the α-C–H bonds of ethers.[1] For example, the unusual acetal **4** and the conventional C–H insertion product **5** were both obtained when the diazoketone **1** was exposed to a variety of rhodium(II) catalysts (Scheme 1). The formation of the anomalous product **4** suggests that a zwitterionic intermediate (**3**) is generated by hydride migration to the carbenoid. In principle, the ionic intermediate **3** could also serve as a precursor of the conventional C–H insertion product **5** allowing the reaction to circumvent the generally postulated transition states, which involve H-migration to rhodium with concomitant C–C bond formation.[2]

At the time we first reported the isolation of anomalous products from intramolecular insertion reactions of rhodium carbenoids into the α-C–H bonds of ethers, we believed that compounds of this type had not been isolated from carbenoid C–H reactions.[1] However, we subsequently discovered that Mander and Owen had isolated an analogous product from a copper carbenoid C–H insertion reaction.[3,4] Following our report, White and Hrnciar isolated several anomalous products from intramolecular rhodium carbenoid C–H insertion reactions which appear to be mechanistically related to those described by Mander and by us.[5] It is clear from these results that more than one reaction pathway is operative during the insertion of a metal carbenoid into an ethereal C–H bond. In order to gain a better mech-



Scheme 1.

Keywords: rhodium carbenoid; C–H insertion; deuterium; kinetic isotope effects.

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anistic understanding of the anomalous C–H insertion reaction and identify factors which might influence the reaction, we prepared deuterium labelled derivatives of the diazoketone **1** and investigated the product distribution obtained upon rhodium carbenoid generation.

The simple diazoketone **1** was selected as the precursor because we had found that a significant amount of the anomalous C–H insertion product **4** could be obtained by treating it with an appropriate rhodium catalyst. In addition, there were no overlapping signals in the ^{1}H NMR spectrum of the anomalous C–H insertion product **4** or in that of the conventional C–H insertion product **5** (Fig. 1). This greatly simplified peak assignment and meant that accurate integration of signals for individual protons could be performed.

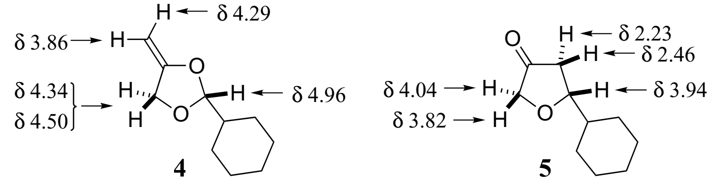
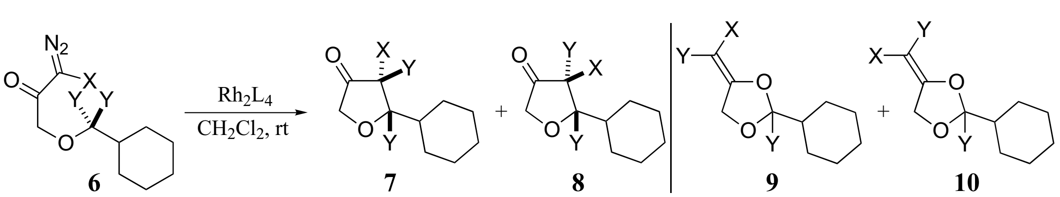


Figure 1. The ^{1}H NMR assignments for the anomalous and conventional C–H insertion products.

In preliminary studies, the deuterium labelled substrates **6a** and **6b** were prepared and treated with a sub-stoichiometric amount of either rhodium(II) acetate or rhodium(II) trifluoroacetate in dichloromethane at room temperature (Scheme 2). The resulting intramolecular insertion reactions delivered mixtures of the ketones **7** and **8** and the acetals **9** and **10**. The ketone and acetal products were separated by chromatography and the ratio of products within each reaction manifold was determined using ^{1}H NMR spectroscopy. Analysis of the spectra of the mixtures of conventional C–H insertion products **7** and **8** revealed that the ketone **7** predominated in all cases and that there was a modest but significant dependence of product ratio on the catalyst used. In the case of the anomalous products, the ratio of isomeric acetals **9a** and **10a** obtained from the rhodium(II) trifluoroacetate mediated reaction of the diazoketone **6a** was similar but not identical to the ratio of conventional C–H insertion products (**7a** and **8a**) obtained from the same reaction. In contrast, the ratio of isomeric acetals **9b** and **10b** obtained from the rhodium(II) trifluoroacetate mediated reaction of the diazoketone **6b** was much higher than the ratio of the ketones **7b** and **8b** obtained from the same reaction.

In subsequent studies, cyclisation reactions of the deuterated diazoketone **6c** were analysed and the deuterium isotope effect in both the conventional and anomalous C–H insertion reactions were calculated (Scheme 3). Previous work by Wang and Adams had shown that a kinetic isotope effect (k_H/k_D) of 1.2–2 was likely for the conventional intramolecular insertion reaction of a rhodium carbenoid into a deuterated ether,[6] and Sulikowski and Lee had obtained kinetic isotope effects of a similar magnitude during intramolecular insertion of rhodium and copper carbenoids into deuterated tertiary amines.[7] The diazoketone **6c** was treated with rhodium(II) acetate or rhodium(II) trifluoroacetate in CH_2Cl_2 at room temperature. ^{1}H NMR analysis of the conventional C–H insertion products obtained from the rhodium(II) acetate mediated reaction indicated a 65:35 ratio of the diastereoisomers **7b** and **8b** and a kinetic isotope effect (**11**/[**7b**+**8b**]) of 1.2. Unfortunately, it was not possible to isolate sufficient quantities of the products (**9b**, **10b** and **12**) arising from the anomalous C–H insertion to compare the kinetic isotope effect with that of the conventional rhodium(II) acetate mediated reaction.

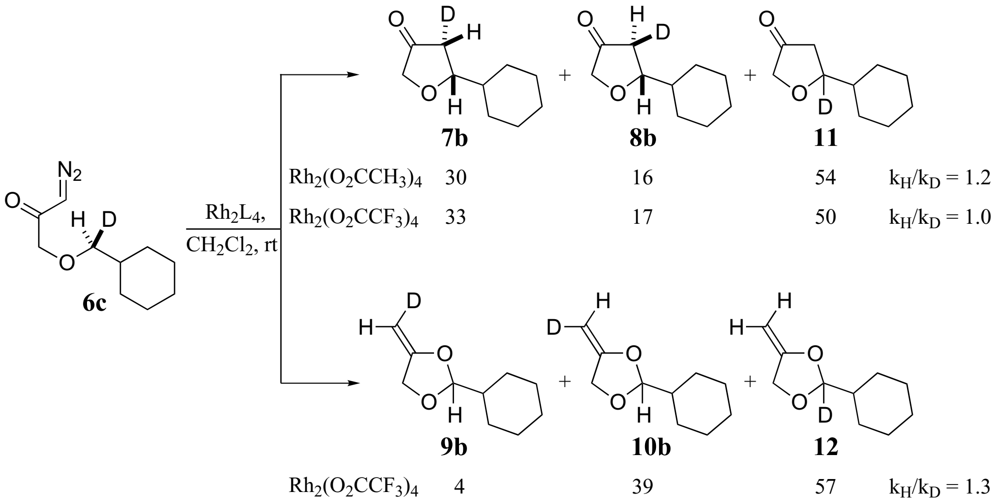


		7:8	7/8	9:10	9/10
a X = H, Y = D	$Rh_2(O_2CCH_3)_4$	77:23	3.3		
	$Rh_2(O_2CCF_3)_4$	71:29	2.4	75:25	3.0
b X = D, Y = H	$Rh_2(O_2CCH_3)_4$	75:25^a	3.0^a		
	$Rh_2(O_2CCF_3)_4$	68:32^b	2.1^b	88:12^b	7.1^b

a Diazoketone **6b** had 96% deuterium incorporation (ratio corrected)

b Diazoketone **6b** had 91% deuterium incorporation (ratio corrected)

Scheme 2.



Scheme 3.

However, both sets of products could be isolated from the rhodium(II) trifluoroacetate catalysed reaction. In this case, the diastereoisomers **7b** and **8b** were obtained in a 66:34 ratio and the kinetic isotope effect (**11**/[**7b**+**8b**]) was 1.0. In contrast, the isomeric anomalous products **9b** and **10b** were obtained as a 9:91 mixture and the kinetic isotope effect (**12**/[**9b**+**10b**]) was 1.3.

We also explored the temperature and solvent dependence of the reaction. The ratios of products obtained from the rhodium(II) trifluoroacetate mediated reaction in dichloromethane were identical at 0°C, room temperature or reflux.[8] When the same reaction was performed in 1,2-dichloroethane the ratio of products differed from those obtained in dichloromethane, but there was little variation in the relative ratios of products within each reaction manifold between 0 and 83°C.[9]

Several important findings emerge from our results. Firstly, there is a modest but significant difference between the kinetic isotope effects for the conventional and anomalous C–H insertion reactions of diazoketone **6c** mediated by rhodium(II) trifluoroacetate. This finding rules out a common rate determining C–H bond cleavage step for the conventional and anomalous C–H insertion reactions (Scheme 1). Secondly, the high level of diastereocontrol (**9b**:**10b**, 9:91) obtained from the anomalous C–H insertion reaction contrasts with the modest level of diastereocontrol (**7b**:**8b**, 66:34) obtained during the conventional C–H insertion reaction; a similar though less pronounced effect was observed during the cyclisation of the diazoketones **6a** and **6b**. This result demonstrates that the stereochemistry defining steps differ in the conventional and anomalous C–H insertion reactions. It also precludes the intermediacy of an equilibrating or freely rotating rhodium enolate **3** generated by hydride transfer prior to C–C bond formation since this would produce a 1:1 mixture of the labelled acetals **9** and **10** (Scheme 1). Finally, the kinetic isotope effects for both C–H insertion reactions are generally independent of the reaction temperature, a finding which is indicative of the non-linear transition state required for intramolecular H-transfer.[10]

In summary, our results demonstrate that the conventional and anomalous C–H insertion products **5** and **4** are not produced by a common rate-determining step and that the ionic intermediate **3** is unlikely to be an intermediate prior to formation of the acetal **4**. Further studies to elucidate the mechanism of the reaction leading to anomalous C–H insertion products are in progress.

Acknowledgements

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8. Product ratios in dichloromethane: 0°C **7b**:**8b**:**11** (33:16:51), **9b**:**10b**:**12** (5:39:56); reflux **7b**:**8b**:**11** (34:15:51); **9b**:**10b**:**12** (5:39:56).
9. Product ratios in 1,2-dichloroethane: 0°C **7b**:**8b**:**11** (31:13:56), **9b**:**10b**:**12** (3:42:55); room temperature **7b**:**8b**:**11** (30:12:58), **9b**:**10b**:**12** (2:42:56); reflux **7b**:**8b**:**11** (29:14:57), **9b**:**10b**:**12** (5:40:55).
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