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Intramolecular C–H insertion using NHC–di-rhodium(II) complexes: the influence of axial coordination

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ABSTRACT

In this work we show that the intramolecular C–H insertion of diazo-acetamides catalysed by di-rhodium(II) complexes can be highly influenced by the axial ligand on the di-rhodium(II) complex. Axially monocoordinated NHC–$Rh_2(OAc)_4$ complexes have a distinct reactivity from the parent $Rh_2(OAc)_4$ complex affording the cyclisation products in different rates and selectivities. Surprisingly, a new reaction mode emerged when using these complexes which led to a decarbonylation pathway.

Di-rhodium(II) complexes are a well-known class of catalysts among the organic chemistry community due to a broad catalytic activity.[1] They have been used in a variety of synthetically useful transformations involving the arylation of aldehydes, intramolecular and intermolecular C–H bond activation,[2] C–H bond amination, oxidations, cycloadditions and a variety of ylide-based transformations. Among these, they are mostly recognised for their ability to react with diazo substrates generating metallo-carbenes which are pivotal intermediates in the activation of unfunctionalised C–H bonds.[3]

The recognized catalytic activity of this class of complexes relies on their Rh(II) bi-metallic structure. They have a Rh–Rh bond and four bridging ligands, responsible for controlling the catalyst electrophilicity and asymmetry.[1,2] The two axial ligands (normally solvent molecules) are generally considered to have a less important role in catalysis as they form a much weaker bond with the electrophilic centre and, for that reason, are easily displaced from the rhodium active centers.[1,2] Recently, we reported that the axial ligands can have a more profound impact on the complex overall reactivity. In particular, we showed that the axial coordination of N-heterocyclic carbenes (NHCs) allowed the arylation of aldehydes using boronic acids to take place in considerably high yields and selectivities, later Jang et al. also reported the allylic oxidation using this family of complexes.[4,5] In line with these results, we became interested in understanding the influence of the NHC axial coordination when these complexes are used to generate metallo-carbenes from diazo substrates, and when these reactive intermediates are involved in intramolecular C–H bond insertions.

In 2001, Arduengo, Snyder et al., reported the first NHC–di-Rh(II) complex which was evaluated in a series of reactions with diazo substrates.[6] The observed results were identical to those obtained when the parent di-rhodium(II) complex was used, which

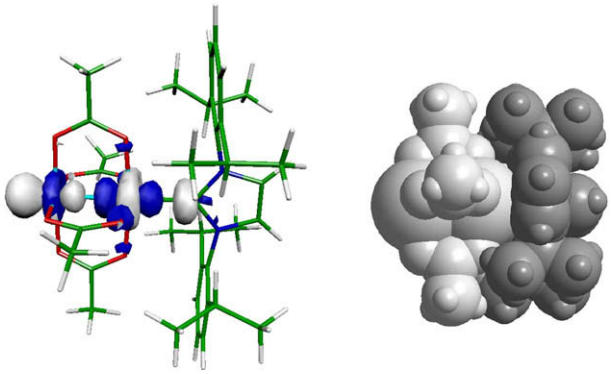

Figure 1. The *i*Pr-NHC ligand confers a high stereoprotection to the Rh centre due to a almost perfect structural match between the NHC and $Rh_2(OAc)_4$ as shown in the optimised geometry (B3PW91) for the $Rh_2(OAc)_4$(NHC) complex **8** (left, NHC is darkened) and its LUMO (right).[4]

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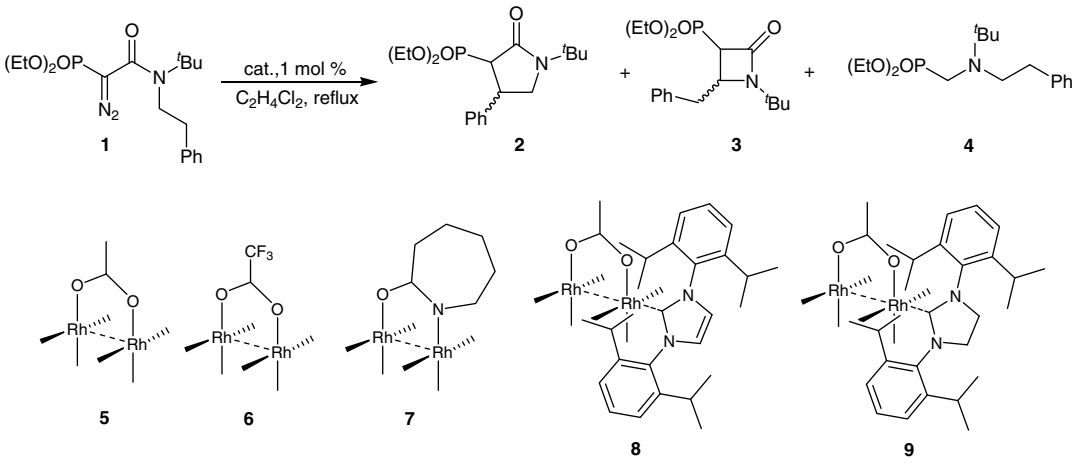


Scheme 1. Cyclisation of diazo-acetamide **1** using complexes **5**–**9**.

and accordingly with the authors, was a clear indication of complex NHC–Rh(II) fragmentation in the reaction conditions. Following this precedent, we anticipated that our complex, in which the isopropyl groups fit in between the AcO bridges and the carbene ring remains in an eclipsed conformation confering a high stereoprotection to the Rh centre (Fig. 1),[4] would endure the reaction conditions, enabling a more clear view over the NHC influence on the metallo-carbene formation and subsequent intramolecular C–H insertion.

We initiated our study with the cyclisation of substrate **1** in the presence of complexes **5**–**9** (Scheme 1, Table 1). Not surprisingly the reaction proceeded at a much slower rate when **8** and **9** were used and comparing with catalysts **5**–**7**. This fact is understandable considering that the first step of the metallo-carbene formation is a nucleophilic attack by the diazo compound onto the di-rhodium(II) complex which, in the case of complexes **8** and **9**, is less favourable due to an electron-richer terminal Rh resulting from the NHC coordination. The atomic charge of the Rh centres in complex **8** is 0.74 in terminal Rh centre and 0.89 in the Rh_{NHC} centre, while in the parent complex **5**, the Rh charge is 0.92.[4a]

More surprising was the effect over the intramolecular C–H insertion selectivity when using the NHC–Rh(II) complex. Typically, these reactions are known to proceed with high preference for the γ-lactam formation.[7–10] In line with this general consideration, the cyclisation of substrate **1** with complex **5** afforded the lactam **2** in high yield. Likewise, catalysts **6** and **7** bearing electron-withdrawing and electron-donating bridging ligands afforded the γ-lactam in 82% and 80% yield, respectively. Differently, complexes **8** and **9** derived from the parent complex **5**, not only afforded the γ-lactam (in considerably lower yields) and the β-lactam isomer but also, and more importantly, a new product formed with CO extrusion (Table 1, entries 4 and 5). Traces (less than 2%) of this product could also be found in the crude reaction mixture when using complex **7** but no decarbonylation product was formed with any of the other catalysts, nor was it observed in our recent studies regarding the UV-promoted cyclisation of diazo-acetamides (Table 1, entry 6).[11] Product **4** corresponds to a new reactivity mode, and as far as our knowledge goes, previously unreported for Rh(II) intramolecular C–H insertions.

Table 1
Cyclisation of diazo-acetamide **1** using complexes **5**–**9**

Entry	Catalyst	Conditions	**2**[c]	cis/trans[d]	**3**[c]	cis/trans[d]	**4**[c]
1[a]	**5**	4 h	91 (81)	0.06/1	5	2.1/1	—
2[e]	**6**	12 h	82 (66)	0.02/1	11 (10)	3.9/1	—
3[e]	**7**	7 h	80 (76)	0.09/1	3 (3)	2.3/1	<2 (0)
4[a]	**8**	46 h	60 (56)	0.07/1	9 (7)	2.7/1	25 (23)
5[a]	**9**	24 h	79 (66)	0.06/1	8 (7)	2.6/1	9 (9)
6[b]	*hν*	8 h 30 min (Hexanes)	66 (64)	1/1	—	—	—

[a] Substrate **1** (0.3 mmol), 1,2-dichloroethane (0.1 M) and catalyst (1 mol %).
[b] Substrate **1** (0.103 mmol), *n*-hexane (1 mL), UV lamp (mercury lamp Model Hanau TQ150).
[c] Observed conversion by ^{31}P NMR, in parenthesis are given the isolated yields.
[d] The cis/trans ratios were determined on the basis of the reaction crude mixture ^{31}P NMR.
[e] Substrate **1** (0.157 mmol), 1,2-dichoroethane (0.1 M) and catalyst (1 mol %).

Table 2
Cyclisation of diazo-acetamides **10** and **11** using complexes **8** and **9**

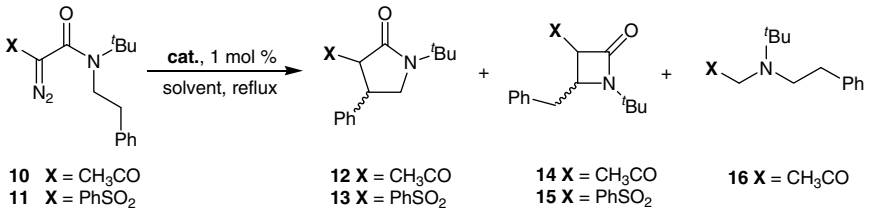
Entry	Catalyst	Substrate	Conditions[a]	**12**[b]	**14**[b]	**16**[b]
1	**5**	**10**	6 h, Reflux $C_2H_4Cl_2$	65 (47)	34 (25)	—
2	**8**	**10**	6 h, Reflux $C_2H_4Cl_2$	18 (17)	46 (35)	36
3	**9**	**10**	6 h, Reflux $C_2H_4Cl_2$	32 (18) **13**[b]	39 (14) **15**[b]	29
4	**5**	**11**	12 h, Reflux CH_2Cl_2	(95)[10]	—	—
5	**9**	**11**	53 h, Reflux CH_2Cl_2	89 (67)	8 (5)	—
6	**9**	**11**	4 h, Reflux $C_2H_4Cl_2$	64 (54)	30 (21)	—

[a] Substrate **1** (0.3 mmol), solvent (0.03 M for **10** and 0.1 M for **11**) and catalyst (1 mol % for **10** and 2.5 mol % for **11**).
[b] The conversions were determined on the basis of the reaction crude mixture ^{1}H NMR, in parenthesis are given the isolated yields.

Intrigued by this result, we extended this cyclisation to other families of diazo-acetamides with different α-substituents to determine if the formation of product **4** was an isolated event or if truly corresponds to a new reaction mode for these transformations. We were quite pleased to discover that the same event occurs with different substrates as shown in Table 2. The CO liberation is even more pronounced in substrate **10** possessing a more electron-withdrawing α-substituent. In this case, the decarbonylation product **16** was obtained in 36% using catalyst **8** (Scheme 2).

Apart from a distinct selectivity profile, no decarbonylation product was detected in the cyclisation of substrate **11** with complex **9** not even when the reaction was performed at higher temperatures (Table 2, entries 4–6) (Scheme 2).

The acetamide N-substituents normally play a crucial role in determining the metallo-carbene intermediate conformation.[2c] Therefore, to probe the influence of the diazo-acetamide structure in the decarbonylation process, we performed the reaction with the symmetrical diazo-acetamide **17** (Scheme 3). Differently from what happens with substrate **1** bearing a bulky N-substituent, no

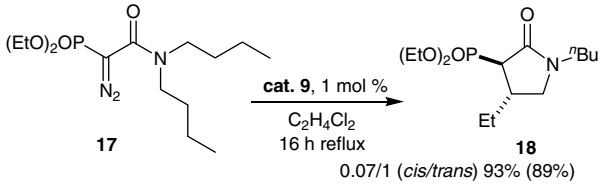


Scheme 2. Cyclisation of diazo-acetamides **10** and **11** using complexes **8** and **9**.

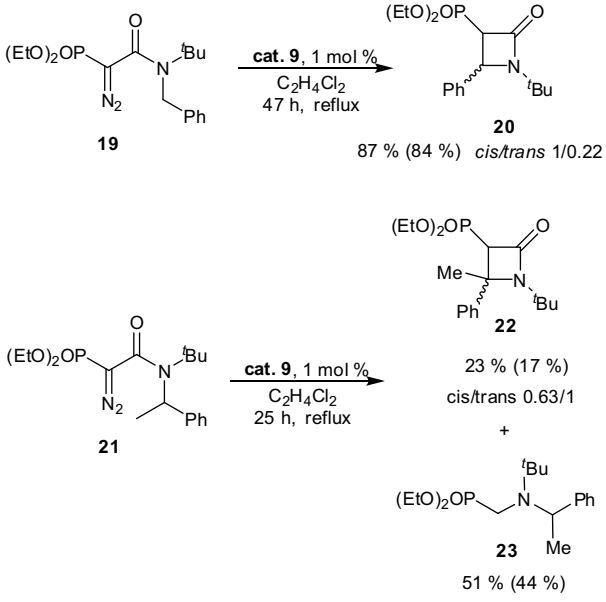
decarbonylation product was formed, and the γ-lactam **18** was obtained in a 93% yield, similarly to what occurs when using $Rh_2(OAc)_4$.[7]

In line with these results, the reaction was performed with asymmetrical diazo-acetamides which typically afford β-lactams. Substrate **19** afforded the lactam in 87% yield with high preference for the cis stereoisomer (Scheme 4). The selectivity was slightly improved when using complex **9** (comparing with the selectivity obtained with **5** (cis/trans 1/0.40)). The cyclisation of diazo-acetamide **21**, which differs from **19** due to an extra methyl group in the insertion centre, afforded the decarbonylation product in 51% yield. This surprising result clearly highlighted the influence of the diazo-acetamide structure in the formation of this product.

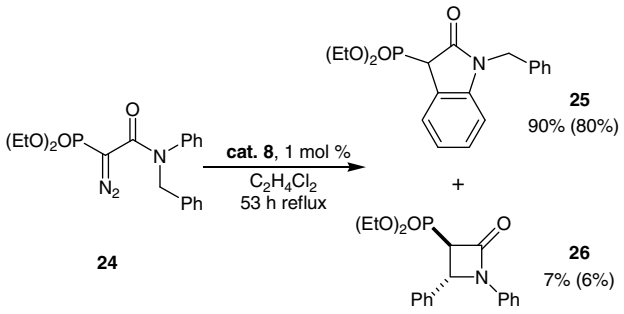
The insertion centre nature was also evaluated using substrate **24** (Scheme 5). This diazo-acetamide may afford two regioisomers via two different reaction mechanisms: the β-lactam via C–H insertion and the γ-lactam via aromatic substitution. Interestingly, a slight increase in the selectivity was obtained with complex **8** comparing with the same reaction performed in chlorinated solvents



Scheme 3. Cyclisation of substrates **17** using complex **9**.



Scheme 4. Cyclisation of substrates **19** and **21**.



Scheme 5. Cyclisation of diazo-acetamide **24** using complexes **8**.

using catalyst **5** (the reaction performed in refluxing $C_2H_4Cl_2$ afforded a 83:12 ratio of **25**:**26**).

Differently from the NHC–Rh(II) catalysts prepared by Arduengo, Snyder et al., complexes **8** and **9** appear to be stable under our reaction conditions, and they were isolated from the crude reaction mixtures of different reactions presented in this study. Despite this fact, it was impossible to determine the exact mass of recovered catalyst due to product contamination, a problem we were unable to overcome.

A likely explanation for the effect observed when using the NHC–Rh(II) complex stems from the possibility of this complexes to engage in an axial *push–pull* mechanism via the Rh–Rh bond, this may influence the cyclisation process reducing the tendency to suffer the diazo nucleophilic attack, though once established, the diazo liberation may be favoured due to the NHC effect. At this moment, the effect of the NHC over the metallo-carbene, is still unclear though it must be substantial because in our view the decarbonylation pathway must be a direct consequence of this axial coordination. DFT calculation is currently being carried out in order to understand this process.

In summary, this study shows for the first time that axial-coordination of NHC ligands onto dirhodium(II) complexes can have an impact on the intramolecular reaction rate and selectivity. Most importantly, a new reaction mode was discovered which leads to a decarbonylation pathway. The formation of this product strongly depends on the three most important aspects of the diazo-acetamide structure: the α-substituent nature, the N-substituent and the insertion centre.

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Supplementary data

Supplementary data (products full characterization and crude mixture analysis using ^{31}P NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.054.

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