

Direct Competition of Intramolecular C–H Insertions into Benzylic C–H and 4-Substituted Benzylic C–H by Rhodium(II)-mediated Carbenoids

Bei Chen, Fengting Liang, Haipeng Chen† and Jianbo Wang*

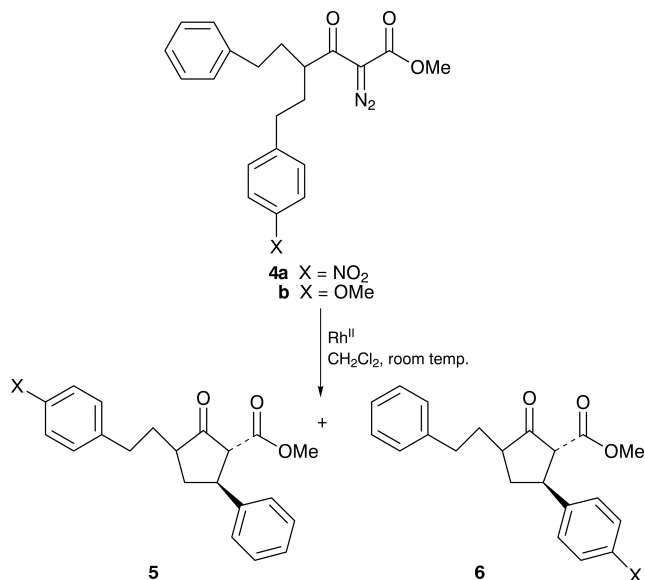
Department of Chemistry, Peking University, Beijing 100871, P.R. China

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Direct competitions of intramolecular C–H insertions into benzylic C–H and 4-nitro and 4-methoxy substituted benzylic C–H by rhodium(II)-mediated carbenoids were investigated, and the relative reactivities obtained by direct competition were comparable to those obtained by a previously reported indirect method.

Intramolecular C–H insertion by Rh^(II)-mediated carbenoids has attracted considerable interest in recent years.¹ In addition to its synthetic applications, there have been extensive investigations into the mechanism of this reaction.^{7,8} We have recently studied the electronic effects of this reaction through the measurement of the relative reactivities of Rh^{II}-mediated carbenoid insertion into a series of substituted benzylic C–H versus benzylic C–H by an indirect method, in which the insertion into an intramolecular secondary aliphatic C–H served as an internal standard. The relative reactivities thus obtained were found to give a good Hammett linear correlation with substituent constants.¹⁰ Since steric and conformational factors can also influence the C–H insertion selectivity,¹³ it is of interest to see if direct intramolecular competition gives the same results. We report in this paper the direct intramolecular competition between 4-nitro and 4-methoxy substituted benzylic C–H and its non-substituted counterpart (Scheme 2).



The diazo compounds **4a** and **4b** were synthesized by a similar method to that previously reported.¹⁰ The overall yields from diethyl (2-phenylethyl)malonate were 14% for **4a** and 20% for **4b**. The Rh^{II}-mediated C–H insertion was conducted under standard conditions as previously described.¹⁰ The product ratio **5**:**6** was carefully determined from the ¹H NMR (400 MHz) spectrum of the crude product mixture. Since it is known that the nitro group in the phenyl ring will deactivate the benzylic C–H, the structure

Table 1 Ratio of the products of competitive C–H insertions

| Catalyst | 6a : 5a | $k_{\text{NO}_2}/k_{\text{H}}^a$ | 6b : 5b | $k_{\text{OMe}}/k_{\text{H}}^a$ |
|---|-----------------------|----------------------------------|-----------------------|---------------------------------|
| Rh ₂ (OAc) ₄ | 0.090 | 0.093 | 2.28 | 2.61 |
| Rh ₂ (O ₂ CCF ₃) ₄ | 0.26 | 0.28 | 1.30 | 1.40 |
| Rh ₂ (acam) ₄ | 0.064 | 0.057 | 2.26 | 1.80 |

^aFrom an indirect method.¹⁰

of the major product in the insertion reaction of **4a** was reasonably assigned to be **5a**, while the minor product was assigned to be **6a**. These structure assignments were supported by the analysis of the mass spectra of **5a** and **6a**. The characteristic McLafferty rearrangements gave peaks at m/z 263 (base peak) for **6a** and m/z 218 (relative intensity, 44%) for **5a**. The structure of **6a** was further confirmed by a combination of COSY and NOESY experiments. For the insertion products of the reaction of **4b**, we assigned the major product to be **6b** since the 4-methoxy group in the phenyl ring is known to activate the benzylic C–H.¹⁰

Three different rhodium(II) catalysts, rhodium(II) acetate, rhodium(II) trifluoroacetate and rhodium(II) acetamide, were investigated. The ratios of **5** to **6** are collected in Table 1. For comparison, the ratios obtained in the previous indirect method are also shown in Table 1. It is obvious from the data that both the indirect and the direct method give comparable results in all cases. This supports the validity of the indirect method employed in the previous study for measuring the relative reactivities of substituted benzylic C–H.

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Techniques used: ¹H NMR, ¹³C NMR, IR, mass spectrometry

References: 20

Schemes: 5

Fig. 1: NOESY spectrum of **6a**

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*To receive any correspondence (e-mail: wangjb@pku.edu.cn).

†Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15020, USA.