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Kinetic isotope effects in the intramolecular insertion of a metal carbene into a C–H bond adjacent to nitrogen

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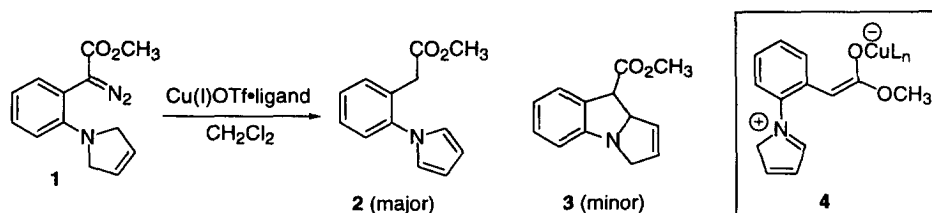
Abstract

An internal competition was used to estimate the kinetic isotope effect of an intramolecular metal carbene C–H insertion reaction alpha to a nitrogen atom. A stereoelectronic effect is proposed to explain the difference in magnitude of the observed KIEs for *cis* and *trans* diastereomers. © 1999 Elsevier Science Ltd. All rights reserved.

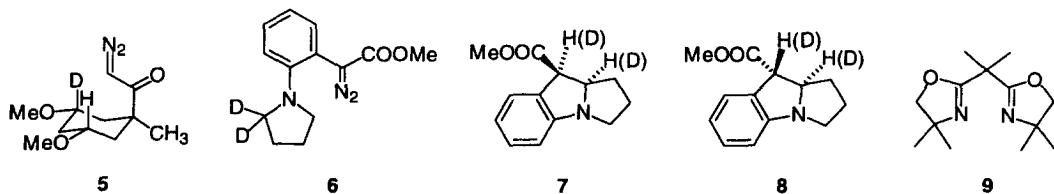
Keywords: carbene C–H insertion; deuterium kinetic isotope effect; stereoelectronic effect.

The intramolecular insertion of a metal carbene into a carbon–hydrogen bond has developed into an important method for ring formation.¹ The most significant features of this process include regioselectivity, stereospecificity and enantioselectivity. We have applied this reaction to the assembly of the mitomycin ring system by insertion of a metal carbene into a C–H bond alpha to a nitrogen atom.² One substrate we briefly examined was diazoester **1**, which on addition to a copper(I) complex provided pyrrole **2** as the major product and the expected C–H insertion product **3** as a minor component. One mechanistic explanation for the production of **2** is an initial hydride transfer to the electron deficient metal carbene to produce a metal enolate–immonium ion intermediate (**4**),^{3,4} proton transfer would then complete the generation of **2** and regenerate the copper(I) catalyst. Since one of our goals was to develop an enantioselective process using chiral catalyst the details of the reaction leading to carbon–carbon bond formation (e.g. **3**) were of interest. Issues to be addressed included whether the reaction proceeded by way of metal enolate–immonium ion intermediate **4** and the extent of a stereoelectronic effect imposed by the neighboring nitrogen atom. We therefore decided to carry out a kinetic isotope effect study, the subject of this letter.

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Deuterium kinetic isotope effects have been used to probe the insertion reaction of metal carbenes⁵ as well as metal-free carbenes⁶ into carbon–hydrogen bonds and silicon–hydrogen bonds.⁷ These studies demonstrate a dependency of the observed deuterium KIE on the electronic nature of the metal carbene. For instance, Wang and Adams observed deuterium KIEs of 1.2 and 2.0, respectively when using dirhodium(II) acetate and dirhodium(II) caprolactamate as catalysts and diazoketone **5** as the substrate.^{5b} Diazoketone **5** sets up an internal competition where the intermediate metal carbene can insert into either a C–H or C–D bond alpha to an oxygen atom. Our studies utilized a similar symmetrical substrate, diazoester **6** prepared from gamma-butyrolactone in four steps. Cyclization of diazoester **6** can lead to two stereoisomers, *cis*-**7** and *trans*-**8**. After separation, the deuterium kinetic isotope effect was determined for **7** and **8** by integration of the ¹H NMR spectrum.



The results of our investigation are summarized in Table 1. Three sets of reaction conditions were examined. The first two sets presumably proceeded by way of a metal carbene, either rhodium(II) or copper(I) metal carbenes. The third set of reaction conditions generated a carbene either thermally or photochemically. In the case of metal carbene mediated cyclizations, the *trans* isomer (**8**) correlated with a higher deuterium KIE relative to the *cis* isomer (**7**). An unexpected result was the ineffectiveness of electron rich or electron poor dirhodium(II) catalysts to alter the observed deuterium kinetic isotope effect (entries a–c).⁸ Specifically, based on Wang and Adams^{5b} results Rh₂(cap)₄ (entry b) should provide larger *k_H/k_D* relative to Rh₂(OAc)₄ (entry a). However, the only notable difference in these two cyclizations was a change in stereoselectivity in the case of Rh₂(cap)₄ relative to Rh₂(OAc)₄ and Rh₂(*n*-C₃F₇COO)₄ now favoring the *cis* isomer (**7**) over the *trans* isomer (**8**). Relatively large primary kinetic isotope effects were observed using a copper(I) complex derived from bis(oxazoline) ligand **8** and copper(I) triflate. Interestingly, a larger KIE was observed when using chloroform as a solvent rather than dichloromethane (entries d and e). Finally, the thermal and photochemical carbene insertion reactions (entries f and g) showed no deuterium kinetic isotope effect. The *cis* stereoselectivity of both photochemically and thermally mediated processes is notable.

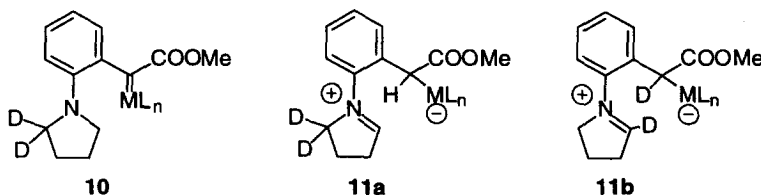
The most striking observation of our studies was the consistently higher kinetic isotope effect (1.5 to 3.1) in the reaction pathway leading to the *trans* isomer (**7**) relative to the KIE (1.1–1.8) in the *cis* manifold (**8**) (entries a–e). This observation supports a concerted insertion of a metal carbene into a C–H bond rather than stepwise process proceeding by way of enolate–immonium intermediate (cf. **11a** and **11b**) since identical KIEs for the *cis* and *trans* isomers (**7** and **8**) would be expected if the latter pathway was operative. In other words the deuterium kinetic isotope effect would be determined prior to the stereochemical determining step (i.e. cyclization of **11a** and **11b**).

Table 1
Deuterium kinetic isotope effect using diazoester **6**

entry	catalyst ^a	conditions	k_H/k_D^b		cis/trans	yield (%) ^c
			cis 7	trans 8		
a	Rh ₂ (OAc) ₄	CH ₂ Cl ₂ , 23 °C, 18 h	1.1	1.5	1:1.5	89%
b	Rh ₂ (cap) ₄	benzene, 70 °C, 19 h	1.2	1.6	3:1	97%
c	Rh ₂ (CF ₃ COO) ₄	CH ₂ Cl ₂ , 23 °C, 18 h	1.2	1.5	1:1.5	82%
d	CuOTf•BOX	CH ₂ Cl ₂ , 23 °C, 18 h	1.5	2.7	1:1	85%
e	CuOTf•BOX	CHCl ₃ , 23 °C, 18 h	1.8	3.1	1:1.5	91%
f	hv (pyrex) ^d	benzene, 23 °C, 3 h	1.0	1.0	7:1	84%
g	thermal	PhMe, reflux, 16 h	1.0	1.0	31:1	91%

^a3-5 mol% catalyst. ^bDetermined by integration of ¹H NMR spectrum. Average of three experiments. ^cIsolated yield.

^dIrradiation with a 450 W Hanovia lamp.



Based on a concerted C–H insertion pathway differences in KIEs for **7** and **8** can be explained by examining the transition state structures leading to their formation. Representations of the transition states for the (metal) carbene insertions leading to **7** and **8** are invoked in the figure below (cf. **12** and **13**). In general terms we assume a preferred approach of the metal carbene carbon to the C–H bond along a pathway perpendicular to the bond axis and midway between the carbon and hydrogen.^{9–11} Overall, this structure consists of a two-electron three center transition state where carbon–hydrogen and carbon–carbon bond formations are concerted.^{6,9} In the present case, we also assume the hydrogen *trans* to the nitrogen lone pair undergoes migration based on stereoelectronic considerations.^{5b} Interestingly, the structure (**12**) leading to the *trans* isomer (**7**) fully benefits from a stereoelectronic effect due to the anti-periplanar orientation of the nitrogen lone pair relative to the reacting C–H bond. In contrast, the lone pair in structure **13** bisects the neighboring methylene group and does not provide full stereoelectronic stabilization to the reacting C–H bond en route to the *cis* isomer (**8**). Presumably, this leads to a more fully developed carbon–hydrogen bond in **12** relative to carbon–carbon bond formation.^{10,12} In contrast, carbon–carbon bond formation precedes carbon–hydrogen bond formation in transition state structure **13**. This analysis explains why the KIEs leading to **7** (via **12**) are larger relative to the KIEs for **8** (via **13**) (Fig. 1).

The cyclization of diazoester **6** to *trans*-**7** and *cis*-**8** promoted by rhodium(II) or copper(I) catalysts is generally non-stereoselective (entries a–e).¹² The one exception is Rh₂(cap)₄ which affords *cis*-**8** with modest stereoselectivity (entry b). However, this reaction required a temperature of 70°C to proceed at a reasonable rate suggesting a leakage through a thermal carbene manifold that displays high *cis*

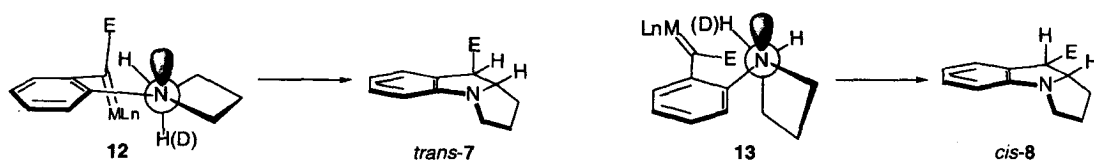


Figure 1. Proposed transition state structures **12** and **13** leading to *trans*-**7** and *cis*-**8**, respectively

stereoselectivity (entry g).^{5a} Next, we attribute the lack of a deuterium kinetic isotope effect in the case of the thermal and photochemical reactions (entries f and g) to a higher barrier to carbon–nitrogen bond rotation relative to the activation barrier to C–H bond insertion of the intermediate carbene. Finally, we note that the deuterium kinetic isotope effects in the copper(I) catalyzed reactions (entries d and e) were higher relative to the rhodium(II) catalysts. This can be attributed to a greater extent of C–H bond breaking in the copper(I) mediated case relative to the corresponding rhodium(II) catalyzed reaction.

In conclusion, our study supports a concerted insertion of a metal carbene into a C–H bond rather than a stepwise mechanism proceeding by way of an enolate–immonium ion intermediate. Our results also suggest a significant stereoelectronic effect in the insertion reaction leading to *trans* isomer **8**.

Acknowledgements

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- The analysis shown in Fig. 1 would suggest high *trans* stereoselectivity for the metal carbene mediated cyclization of **6**. However, this is not the case (cf. Table 1). Our only explanation at this time is that a combination of other unfavorable interactions offsets the favorable stereoelectronic effect shown in **12** leading to an overall non-stereoselective cyclization.