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Stereoselective Intramolecular 1,3 C–H Insertion in Rh(II) Carbene Reactions

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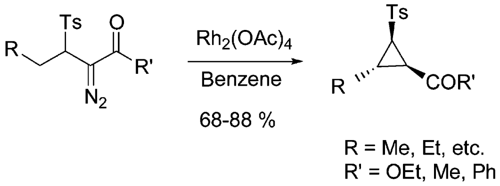
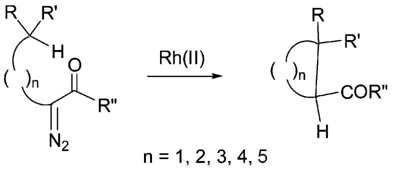
ABSTRACT



1,3 C–H insertion has been found to be a predominant reaction pathway in the Rh(II)-mediated reaction of *β*-tosyl α-diazo carbonyl compounds.

Rh(II)-mediated carbenoid intramolecular C−H insertion reactions have wide application in organic synthesis (Scheme 1).[1,2] The factors that govern the site selectivity of the C−H insertion include electronic, steric, and conformational factors.[3] In a freely rotating chain system, 1,5 C−H insertion is overwhelmingly predominant due to the entropically favorable six-membered transition state.[3,4] It has been known that steric or electronic factors may override this entropic preference for 1,5 insertions. 1,6 C−H insertions were sporadically reported for some structurally rigid systems,[5] while 1,4 and 1,7 C−H insertions occur when the C−H bond is activated by a neighboring heteroatom, in most cases oxygen or nitrogen.[6,7] Doyle et al. have reported a rare case in which a 14-membered ring macrolide is formed in Rh(II) carbene C−H insertion.[8] However, to the best of our knowl-

Scheme 1



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[3] For mechanistic investigations on Rh(II) carbene C−H insertions, see: (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686−7693. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958−964. (c) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994J. Am. Chem. S** **2002**, *124*, 7181−7192. (j) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165−4169. (k) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276−4278.

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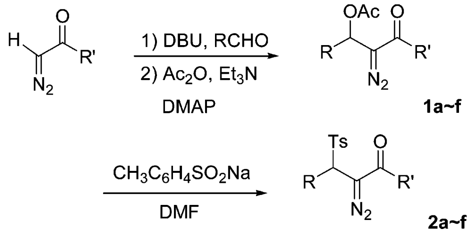
[6] For examples, see: (a) Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247−250. (b) Nanada, M.; Hashimoto, S.-i. *Tetrahedron Lett.* **1998**, *39*, 9063−9066. (c) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539−3542. (d) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837−8846.

[7] Lee, E.; Choi, I.; Song, S. Y. *Chem. Commun.* **1995**, 321−322.

10.1021/ol051130l CCC: $30.25

Scheme 2



edge, 1,3 C−H insertion has not been observed in Rh(II)-catalyzed reactions of α-diazo carbonyl compounds.[9] We report here the first examples of 1,3 intramolecular C−H insertion in freely rotating chain systems.

We have recently studied various reactions of β-hydroxy α-diazo carbonyl compounds, which are easily available by the deprotonation of acyldiazomethane and the subsequent addition of the resulting anion to aldehydes or ketones.[10] It has been observed that these diazo compounds react with TsNHN═CHCOCl/Et_3N to give β-(*p*-tolylsulfonyl) α-diazo esters.[11] Further investigation revealed that the β-position of α-diazo carbonyl compounds are susceptible to nucleophilic substitution.[12] Thus, the β-hydroxyl group is converted to a β-acetoxy group, and the resulting β-acetoxy α-diazo carbonyl compounds were treated with *p*-$MeC_6H_4SO_2Na$ to give β-tosyl α-diazo compounds in good yields (Scheme 2, Table 1).

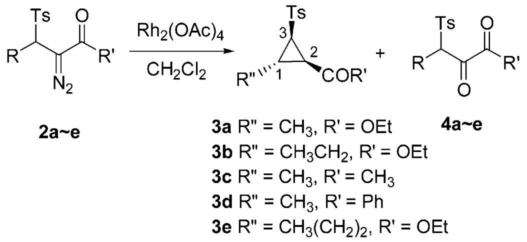
Table 1. Preparation of Diazo Compounds **2a**−**f** by Nucleophilic Substitution

entry	diazo substrate **1**	product	yield (%)[a]
1	**a**, R = CH_3CH_2, R′ = OEt	**2a**	65
2	**b**, R = $CH_3(CH_2)_2$, R′ = OEt	**2b**	90
3	**c**, R = CH_3CH_2, R′ = CH_3	**2c**	80
4	**d**, R = CH_3CH_2, R′ = Ph	**2d**	88
5	**e**, R = $CH_3(CH_2)_3$, R′ = OEt	**2e**	87
6	**f**, R = $CH_3(CH_2)_5$, R′ = OEt	**2f**	82

[a] Isolated yields after silica gel column chromatography.

To our knowledge, α-diazo compounds with β-tosyl substituents have not been reported in the literature. We have been interested in the Rh(II) complex catalyzed reaction of these novel diazo compounds. From our knowledge of the Rh(II)-catalyzed reaction of β-substituted α-diazo carbonyl compounds, we had expected that 1,2-hydride migration could occur to give the corresponding α,β-unsaturated compounds.[10,12] However, contrary to this expectation, the $Rh_2(OAc)_4$-catalyzed reaction (CH_2Cl_2, rt, 12 h) of **2a** gave two products, neither of which was the 1,2-hydride migration product (Scheme 3). One of the products (isolated in 45% yield) was the α-oxo ester **4a**, which was generated through Rh(II)-catalyzed oxidation in the presence of trace oxygen. The spectral data of the other product (isolated in 40% yield) showed it was a cyclopropane derivative. Its structure was unambiguously confirmed as **3a** by single-crystal X-ray analysis, as shown in Figure 1. The X-ray structure reveals that the tosyl group and the ester group are *cis* to one another, while the methyl is *trans*. The formation of a cyclopropane derivative is obviously due to an intramolecular 1,3 C−H insertion, and the insertion proceeded with high stereoselectivity because only one diastereoisomer was observed.

Scheme 3



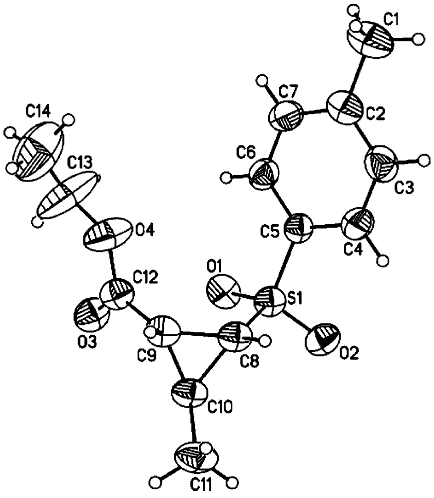


Figure 1. X-ray structure of **3a**.

When the oxidation product **4a** was minimized by applying strict oxygen-free reaction conditions, the yield of **3a** increased to 73%. The 1,3 C−H insertion was found to be general, as shown in Table 2. For substrates **2b**, **2c**, and **2d**,

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(8) Doyle, M. P.; Protopopova, M. N.; Poulter, C. D.; Rogers, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 7281−7282.

(9) 1,3 C−H insertion was reported in the Cu-catalyzed reaction of a structurally rigid diazo compound: Yates, P.; Danishefsky, S. *J. Am. Chem. Soc.* **1962**, *84*, 879−880.

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(11) Shi, W.; Zhang, B.; Liu, B.; Xu, F.; Xiao, F.; Zhang, J.; Zhang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 4563−4566.

(12) Xu, F.; Shi, W.; Wang, J. *J. Org. Chem.* **2005**, *70*, 4191−4194.

the Rh(II)-catalyzed reaction gave the corresponding cyclopropane derivatives **3b**, **3c**, and **3d**, respectively, in modest isolated yields, together with the oxidized products **4b**, **4c**, and **4d** in various amounts. All of the reactions gave a cyclopropane derivative as a single diastereoisomer. Since the ^{1}H NMR spectra data are all similar to that of **3a** (coupling constants 1-H and 2-H are around 9 Hz), it is reasonable to assume that these products should have the same configuration as **3a**. When the reaction was carried out in refluxing benzene, the reaction time was shortened (4 h), and the oxidation reaction could be further minimized (entries 2, 4, and 6).

Diazo compound **2e** provides an interesting situation in which intramolecular 1,5 C−H insertion can compete with the 1,3 insertion. The Rh$_2$(OAc)$_4$-catalyzed reaction of **2e** gave 1,3 C−H insertion product **3e** as a single stereoisomer, together with the formation of 1,5 C−H insertion products in approximately the same amount.[13] The ratio of 1,5 insertion versus 1,3 insertion is affected by the ligands of the Rh(II) catalyst (Table 3). The Rh(II) catalysts with electron-withdrawing ligands favor 1,3 insertion (entries 4, 5, and 7). The solvent, however, does not affect the product ratio (compare entries 5 and 7).

Intramolecular 1,3 C−H insertion also occurs efficiently for diazo compounds **7a** and **7b**, in which spiro compounds containing the cyclopropane moiety are obtained (Scheme 4). The structure of **8b** was confirmed by single-crystal X-ray diffraction (Figure 2). Again, the 1,3 C−H insertion proceeds with high diastereoselectivity with the tosyl group and the ester group *cis* to one another.

There are two unusual aspects about the $Rh_2(OAc)_4$-catalyzed reaction of **2a**−**e**. The first is that 1,2-hydride migration, which is usually a very feasible process, does not occur. The second is the unprecedented formation of the three-membered ring through Rh(II) carbene 1,3 C−H bond insertion.

The unique reactivity of β-tosyl diazo compounds may be interpreted from both steric and electronic considerations. The strongly electron-withdrawing tosyl group should be responsible for the inhibition of 1,2-hydride migration. These results can be compared with the Rh(II)-catalyzed reaction of β-trichloroacetylamino substituted α-diazo carbonyl compounds, in which case aryl, vinyl, and 1,2-alkynyl migrations occur exclusively even in the presence of a β-hydrogen.[10e]

Re-examination of the X-ray structure of **2b**[11] reveals some interesting features. The $O{=}C{-}C{=}N_2$ group is found to possess the *s-Z* conformation, while the other β-substituted α-diazo carbonyl compounds that we have studied all have *s-E* conformation.[14] The diazo group and the carbonyl group are almost coplanar with a dihedral angle of −0.93°. The dihedral angle between the C−H bond and the diazo group is −169.5°. Thus, the C−H is in nearly antiperiplanar position. The diazo compounds **2a**−**f** are found to be exceptionally stable. In EI-MS spectra, they all give a molecular ion peak. In the absence of $Rh_2(OAc)_4$, they are stable when heated in 1,2-dichloroethane.

The intramolecular 1,3 C−H insertions are likely to be due to conformational factors. In the X-ray structure of **2b**, it is noted that one of the 3-H bonds is in close proximity to the diazo carbon. If one assumes that this is the stable conformation of the diazo compounds and the corresponding Rh(II) carbene intermediates in CH_2Cl_2 solution, then the 1,3 C−H insertion might be simply explained by steric proximity. This interpretation is supported by the fact that $Rh_2(tfa)_4$ and $Rh_2(pfb)_4$ were found to favor 1,3 C−H insertion in the competition study of 1,3 versus 1,5 C−H insertion (Table 3, entries 4 and 5). Rh(II) catalysts with strongly electron-withdrawing ligands are known to make the Rh(II) carbene more reactive, and thus, the subsequent reaction proceeds through a earlier, more starting-material-like transition state.[3b] Further study is needed to elucidate the detailed mechanism of 1,3 C−H insertions.

In conclusion, we report here the first examples of 1,3 C−H insertion in freely rotating chain systems. This unusual 1,3 insertion reaction may find utility in organic synthesis as a new entry to the substituted cyclopropane derivatives. This study further demonstrates the dramatic effect of neighboring groups on Rh(II) carbene reactions.

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Supporting Information Available: Experimental details and characterization data for all new compounds, X-ray crystallographic data of **2b**, **3a**, and **8b** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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