Anomalous Products from Intramolecular Insertion Reactions of Rhodium Carbenoids into the α-C−H Bonds of Ethers

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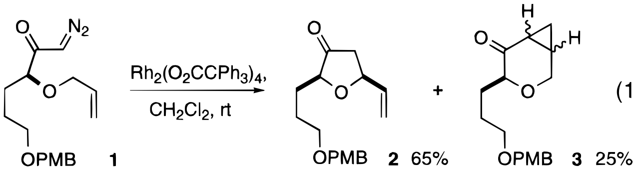
Intramolecular C−H insertion reactions of metal carbenoids are well known and have been widely used for the stereoselective construction of cyclopentanones, γ-lactones, and lactams.[1,2] The development of asymmetric variants of these reactions by Doyle and others has further extended their scope.[3,4] Recently, Adams and coworkers demonstrated that the intramolecular insertion reaction of a metal carbenoid into a C−H bond adjacent to an ether oxygen can be used for the stereoselective construction of 3(2*H*)-furanones.[5] This reaction has been adapted for the synthesis of tetrahydrofurans from diazo esters by Taber.[6] In addition, Lee has shown that the insertion of a carbenoid into a C−H bond adjacent to a silyl ether is especially favorable.[7]

In the course of our studies directed toward the synthesis of neoliacinic acid,[8] we prepared the 3(2*H*)-furanone **2** from the α-diazo ketone **1** by generation and subsequent intramolecular insertion of a rhodium carbenoid into the C−H bond of an allylic ether (eq 1).



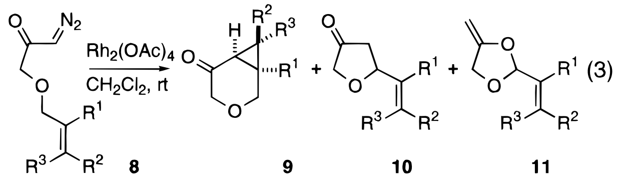
1 **2** 65% **3** 25% (1)

Although the yield for this transformation was reasonable, cyclopropanation was a significant competing process.[2,9] In an attempt to improve the selectivity for C−H insertion, we explored the cyclization reactions of some simple substrates related to **1**.

In order to identify the factors that influence the outcome of the intramolecular insertion reactions of carbenoids into the C−H bonds of allylic ethers, reactions of the α-diazo ketone **4** were investigated (eq 2). These reactions were performed using seven structurally diverse rhodium complexes as catalysts.[10] Analysis of the reaction mixtures by GC revealed that the cyclopropane **5** was the major product in all cases and that varying amounts of the expected 3(2*H*)-furanone **6** were also produced (Table 1). In addition to the expected products (**5** and **6**), significant amounts of a nonpolar product were also detected. Although this product proved to be too unstable to isolate and fully characterize, it was identified as the acetal **7** on the basis of NMR analysis of partially purified material. The acetal **7** is a very unusual product, and as far as we are aware, there is no literature precedent for the isolation of analogous products from the C−H insertion reactions of metal carbenoids. However, in previous studies, one of us isolated a similar product upon cyclization of a substrate related to the α-diazo ketone **1**.[11]

When electron-rich rhodium complexes were used to catalyze the reaction (entries 1−3 and 6, Table 1), the relative amounts of the anomalous product **7** and the 3(2*H*)-furanone **6** produced in each reaction were similar. However, when complexes bearing electron-withdrawing ligands were employed as catalysts (entries 4, 5, and 7, Table 1) there was a significant increase in the relative amount of the acetal **7** produced.

The $Rh_2(O_2CCH_3)_4$-catalyzed reactions of two other allylic ethers (**8a** and **8b**) were also investigated (eq 3).



(3)

	8	**9**	**10**	**11**
a	R^1 = H R^2,R^3 = –$(CH_2)_5$–	64%	2%	13%
b	R^1 = $(CH_2)_2$Ph R^2,R^3 = H	67%	15%	6%

These substrates were selected in order to explore the influence that alkene substituents have on the relative rates of cyclopropanation and C−H insertion, and on the amount of the anomalous C−H insertion product obtained. Cyclopropanation was the predominant reaction of both substrates, and the isolated ratio of cyclopropanation product to C−H insertion products was insensitive to the substitution pattern of the alkene. Treatment of the α-diazo ketone **8a** with $Rh_2(O_2CCH_3)_4$ afforded the acetal **11a** as the major C−H insertion product along with some of the aldehyde resulting from decomposition of this acetal. In contrast, the rhodium-catalyzed reaction of the substrate **8b** produced the 3(2*H*)-furanone **10a** as the major C−H insertion product. The result obtained upon cyclization of the substrate **4** using $Rh_2(O_2CCH_3)_4$ as the catalyst is also informative (entry 1, Table 1). These results demonstrate that the presence of alkyl

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(1) For the first examples of intramolecular C−H insertion of metal carbenoids to give cyclopentanones, see: (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.

(2) For reviews concerning the C−H insertion reactions of metal carbenoids, see: (a) Taber, D. F. In *Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 4.2, p 1045. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 5.2, p 421.

(3) Doyle, M. P. *Aldrichim. Acta* **1996**, *29*, 3 and references therein.

(4) (a) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983. (b) Müller, P.; Polleux, P. *Helv. Chim. Acta* **1994**, *77*, 645. (c) Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995**, *36*, 1491.

(5) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.

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(8) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605.

(9) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1992**, *48*, 9767.

(10) The complexes $Rh_2(O_2CCH_3)_4$, $Rh_2(O_2CC_7H_{15})_4$, and $Rh_2(O_2CCF_3)_4$ are commercially available. For the preparation of the other catalysts used, see: (a) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709 [$Rh_2(O_2CCPh_3)_4$]. (b) Drago, R. S.; Long, J. R.; Cosmano, R. *Inorg. Chem.* **1982**, *21*, 2196 [$Rh_2(O_2CC_3F_7)_4$]. (c) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906 [$Rh_2(NHCOCH_3)_4$]. (d) Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522 [$Rh_2(NHCOCF_3)_4$].

(11) Russell, C. A. Unpublished results.

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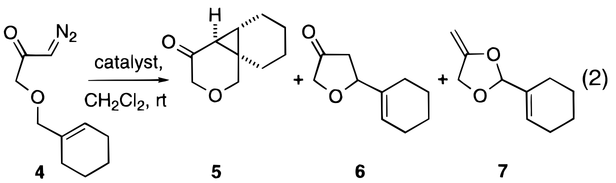
Table 1. Rhodium-Catalyzed Cyclization Reactions of the α-Diazo Ketone 4

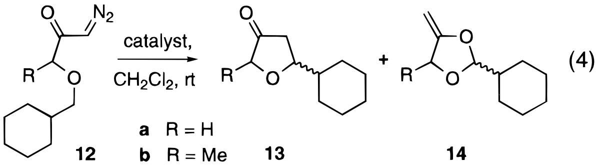


4 **5** **6** **7**

entry	catalyst^a	product ratio^b (isolated yields, %)^c 5	6	7
1	$Rh_2(O_2CCH_3)_4$	78 (51)	13 (10)	9
2	$Rh_2(O_2CC_7H_{15})_4$	82	13	5
3	$Rh_2(O_2CCPh_3)_4$	46 (23)	30 (23)	24
4	$Rh_2(O_2CCF_3)_4$	74 (72)	8 (8)	18
5	$Rh_2(O_2CC_3F_7)_4$	77	6	17
6	$Rh_2(NHCOCH_3)_4$	65	20	15
7	$Rh_2(NHCOCF_3)_4$	55	19	26

[a] Catalysts $Rh_2(O_2CCH_3)_4$, $Rh_2(O_2CC_7H_{15})_4$, and $Rh_2(O_2CCF_3)_4$ are available commercially. The other catalysts were prepared using literature procedures (see ref 10). [b] Relative ratio of major products as determined by capillary GC analysis prior to purification. [c] Yields after purification by chromatography on neutral alumina (Brockmann grade 3).

Table 2. Rhodium-Catalyzed Cyclization Reactions of the α-Diazo Ketones 12a and 12b



12 **13** **14**

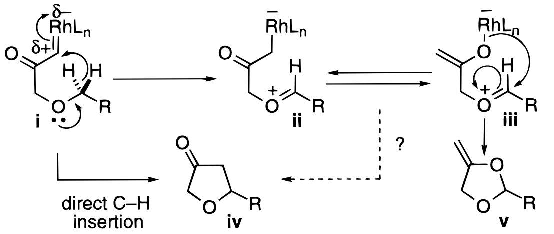
entry	substrate	catalyst^a	isolated yield^b (%) 13	14	ratio^c
1	**12a**	$Rh_2(O_2CCH_3)_4$	55	8	(96:4)
2	**12a**	$Rh_2(O_2CCF_3)_4$	35	40	(36:64)
3	**12b**	$Rh_2(O_2CCH_3)_4$	62	14	
4	**12b**	$Rh_2(O_2CCF_3)_4$	18	40	

[a] Catalysts $Rh_2(O_2CCH_3)_4$ and $Rh_2(O_2CCF_3)_4$ are commercially available. [b] Yields after purification by chromatography on neutral alumina (Brockmann grade 3). [c] Relative ratio of major products as determined by capillary GC analysis prior to purification.

substituents at the terminus of the alkene promotes formation of the acetal product (**11a**/**b** or **7**) at the expense of the 3(2*H*)-furanone (**10a**/**b** or **6**).

At this juncture, it was important to establish if the formation of anomalous products is a general phenomenon during the intramolecular C–H insertion reactions of ethers or is restricted to allylic ethers. It was also desirable to explore the two C–H insertion reaction manifolds without the complication of competitive cyclopropanation. Hence, the cyclization reactions of the substrates **12a** and **12b** were investigated (eq 4, Table 2). The cyclization of the α-diazo ketone **12a** catalyzed by either $Rh_2(O_2CCH_3)_4$ or $Rh_2(O_2CCF_3)_4$ provided the expected C–H insertion product **13a** along with the acetal **14a**. However, the outcome of this reaction was strongly influenced by the complex used for carbenoid generation. When $Rh_2(O_2CCH_3)_4$ was used as the catalyst, the 3(2*H*)-furanone **13a** was isolated in 55% yield along with 8% of the acetal **14a**. However, when $Rh_2(O_2CCF_3)_4$ was employed as the catalyst, analysis of the crude reaction mixture by GC indicated an approximately 1:2 ratio of products (**13a**:**14a**), although roughly equivalent amounts of the two products were isolated. The acetal **14a** proved to be relatively stable in comparison to the acetals obtained by cyclization of the allylic ethers and could be isolated in good yield. The relative ratio of the acetal **14a** to the 3(2*H*)-furanone **13a** was lower than that obtained from the reaction of the corresponding allyl ether **4a** (entry 4, Table 1), which suggests that although the presence of a π-system is not a prerequisite for acetal formation, it does promote this reaction.

Scheme 1



The presence of an additional substituent in substrate **12b** was found to increase the amount of the acetal **14b** relative to 3(2*H*)-furanone **13b** in both reactions, but especially in the reaction catalyzed by $Rh_2(O_2CCF_3)_4$.

The results above suggest that the intramolecular insertion of metal carbenoids into C–H bonds adjacent to ethers may proceed by a more complex mechanism than previously recognized.[6,12] One possible mechanistic rationale which accounts for our data is shown in Scheme 1. In this mechanism, the acetal product arises by oxygen-assisted hydride transfer to the electrophilic carbon of the carbenoid **i**.[13] This affords a reactive intermediate (**ii**), which contains both an enolate and oxonium ion. Intramolecular attack of the oxonium ion by the oxygen atom of the enolate (**ii** or **iii**) then affords the acetal **v**. In principle, the 3(2*H*)-furanone **iv** could also be produced from the enolate. However, further experiments are required to ascertain whether or not the 3(2*H*)-furanone **iv** is produced in this manner. The intermediacy of an oxonium ion is supported by the trends observed upon treatment of the substrates **4**, **8a**, and **8b** with $Rh_2(O_2CCH_3)_4$. The highest proportion of the anomalous product relative to the expected insertion product is obtained upon cyclization of the α-diazo ketone **8a**. This is consistent with our postulated reaction mechanism because alkyl substituents on the alkene would stabilize development of incipient positive charge in the allyl system during formation of the oxonium ion. In addition, electron-deficient catalysts favor formation of the anomalous product. This can be accounted for by an increase in the rate of hydride transfer to the more electrophilic carbenoid generated and stabilization of the rhodium enolate (**ii** or **iii**) by electron withdrawal from the metal center.

We are currently performing further experiments in order to fully elucidate the mechanism by which carbenoids undergo insertion into ether C–H bonds, and the results of these studies will be reported in due course.

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Supporting Information Available: Details of the experimental procedures for the preparation and cyclization of diazo ketones **4**, **8a**,**b**, and **12a**,**b** and spectroscopic data for compounds **4**–**14** (10 pages).

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(13) Hydride transfer has been proposed to account for the formation of other anomalous products during C–H insertion reactions of rhodium carbenoids: Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619.