

Carbene insertion into oxygen–hydrogen bonds by metalloporphyrin catalysts

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Abstract

Rhodium porphyrins, RhTPPI (1), RhTMPI (2) and RhOEPI (3), efficiently catalyze carbene insertion into O–H bonds, leading to ethers, by use of ethyl diazoacetate under mild condition. In a typical run, n-hexanol is converted to ethoxycarbonylmethyl n-hexyl ether in 79% yield in the presence of 2 as a catalyst in $C_2H_4Cl_2$ at 40°C for 4 h. The effect of the ligand structure of rhodium complexes on insertion reactions was examined for simple porphyrin complex 1, bulkier porphyrin complex 2 and $[Rh(OAc)_2]_2$ (4). The rhodium(III) complex 2 catalyzes carbene insertion into the O–H bond of alcohols in the order of prim > sec > tert, whereas the complex of the less bulky ligand 4 shows lower selectivity to the structure of alcohols. The stereoselective insertion reaction catalyzed by 2 was observed for menthol and neomenthol. In intramolecular competitive insertion of cholane-3,24-diol (5) and the bulkier 2, the prim-hydroxyl group also exhibits 5.6-fold preference for sec-hydroxyl group due to the steric hindrance between substrate and bulky ligand. It is clear that the bulkier TMP ligand of 2 plays an important role in the action of steric selectivity.

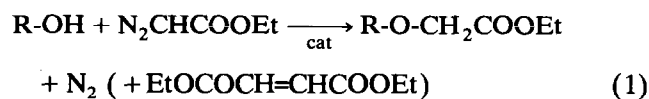
Key words: Alcohol; Carbene; Catalysis; Bulky ligands; Porphyrin; Rhodium

1. Introduction

The synthetic use of carbene species generated by transition metal catalysts has been the focus of much interest in organometallic chemistry [1]. In particular, the insertion of carbene into C–H or N–H bonds and cyclopropanation of various olefins by ethyl diazoacetate catalyzed by copper or rhodium complexes have been reported by many researchers [2]. In contrast, the insertion into O–H bonds seems to be noticeably underdeveloped compared with the above reactions. First, alkylation of alcohol with ethyl diazoacetate catalyzed by $CuCl_2$ was not sufficient in yield and selectivity [3]. A similar reaction with rhodium acetate, $[Rh(OAc)_2]_2$, as a catalyst proceeds more smoothly in alcohol solution [4,5]. However, to our knowledge, there are only a few useful reactions for ether bond formation by use of diazoacetate.

Recently, Callot and his co-workers have reported an efficient catalytic reaction for the C–H activation

and cyclopropanation of olefins by ethyl diazoacetate and particular catalysts, rhodium porphyrins [6]. Kodadek and his co-workers have extended this reaction further to catalytic asymmetric cyclopropanation by use of chiral wall porphyrin [7] and have discussed reaction mechanism [8]. In the last decade, we have also studied organic reactions, such as oxidation of olefins, reduction of ketones and Aldol condensation, catalyzed by metalloporphyrins, particularly rhodium porphyrins [9]. Callot reported that catalytic decomposition of ethyl diazoacetate in methanol with metalloporphyrin results in the O–H bond insertion [10,11]. In this paper, we describe efficient carbene insertion into the O–H bonds of a variety of alcohols with diazoacetate as a carbene precursor, catalyzed by rhodium porphyrins, and reaction selectivities controlled by the structural factors of the catalyst (eqn. (1)).



2. Results and discussion

Iodorhodium tetraphenylporphyrin (RhTPPI, 1), the much bulkier iodorrhodium tetramesitylporphyrin

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* Reference number with asterisk indicates a note in the list of references.

TABLE 1. O–H bond insertion of n-hexanol with ethyl diazoacetate as a carbene precursor ^a

Run	Catalyst (mol%)	Temperature (°C)	Time (h)	Conversion ^b (%)	Yield ^b (%)
1	RhTPPI (0.3)	40	3.5	> 95	76
2	RhTMPI (0.3)	40	4	> 95	79
3	RhTPPI (0.3)	60	1.5	> 95	73
4	RhTMPI (0.3)	60	3	> 95	78
5	RhOEPI (0.3)	60	4	> 95	73
6	RhTMPI (0.3)	25	72	60	45
7	RhTPPI (0.5)	25	72	70	57
8	No catalyst	40	4		9.7

^a All reactions were run in C₂H₄Cl₂ under nitrogen. Small portions of ethyl diazoacetate were added to solution monitored by GC and evolution of nitrogen (to a total of ca. 1.6 equiv.).

^b Determined by GC analysis.

(RhTMPI, **2**), and iodorrhodium octaethylporphyrin (RhOEPI, **3**) are active catalysts for carbene insertion into O–H bonds using ethyl diazoacetate as a carbene source. The results of catalytic carbene insertion of n-hexanol (**5**) in the presence of 0.3 mol% (based on alcohol) of rhodium porphyrin are summarized in Table 1. In all runs, at first, 0.1 equiv. of ethyl diazoacetate was added to the solution and the reaction mixture was monitored by GC and evolution of nitrogen. Furthermore, additional small portions (0.1 equiv.) of ethyl diazoacetate were added (to a total of 1.5–2.0 equiv.), when the evolution of nitrogen stopped. This manipulation was required to decrease the formation of olefin resulting from catalytic decomposition of ethyl diazoacetate in higher concentration [12*]. The rate of catalytic insertion catalyzed by **2** is retarded due to the

TABLE 2. Yields of insertion into O–H bonds of prim-, sec- and tert-alcohols by use of three type of rhodium porphyrins ^a

Substrate	RhTPPI	RhTMPI	[Rh(OAc) ₂] ₂
n-C ₆ H ₁₃ -OH ^b	76	79	99
n-C ₆ H ₁₃ CH(CH ₃)-OH ^b	39	43	99
(ⁱ Pr) ₂ CHOH ^c	36	39	90
Et ₃ C-OH ^c	36	34	83

^a All reactions were run in C₂H₄Cl₂ at 40°C for 4 h. Yields were determined by GC analysis.

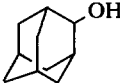
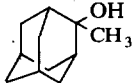
^b Total amount of ethyl diazoacetate was 2 equiv.

^c Total amount of ethyl diazoacetate was 3–4 equiv.

steric hindrance of the four mesityl groups of the ligand. The amount of catalyst at 0.3 mol% is sufficient for insertion of O–H bonds at 40°C or 60°C, although at ambient temperature, the rate of the reaction slows down due to the decomposition of catalyst. Furthermore, ether product from n-dodecanol, ethoxycarbonylmethyl n-dodecyl ether, was easily isolated in 73% yield by column chromatography.

Table 2 shows the comparison of yields of insertion into O–H bonds of prim-, sec- and tert-alcohols using either **1**, **2** or [Rh(OAc)₂]₂ (**4**) as a catalyst. Every rhodium complex acts as an efficient catalyst for carbene insertion into the O–H bond of prim-alcohol, however, the catalytic reaction of sec- and tert-alcohols does not proceed smoothly in the presence of rhodium porphyrin relative to **4**. An intermolecular competitive reaction was carried out in order to determine the selectivities of carbene insertion by use of ethyl dia-

TABLE 3. Competitive O–H insertion from representative alcohol pairs and ethyl diazoacetate in the presence of rhodium catalysts ^a


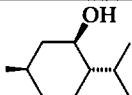

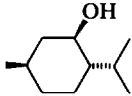
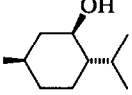
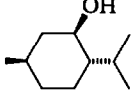
Alcohols ^b		Product ratio (¹ R-OCH ₂ CO ₂ Et / ² R-OCH ₂ CO ₂ Et) ^c		
¹ R-OH	² R-OH	RhTPPI	RhTMPI	[Rh(OAc) ₂] ₂
n-C ₆ H ₁₃ -OH	+ n-C ₆ H ₁₃ CH(CH ₃)-OH	1.4	1.7	1.1
n-C ₆ H ₁₃ -OH	+ ⁱ Pr-CH-OH	2.2	6.1	2.1
n-C ₆ H ₁₃ -OH	+ Et-C-OH	4.0	11.0	2.3
	+ 	1.2	3.6	2.0

^a All reactions were run in the presence of 0.3 mol% of rhodium porphyrin in C₂H₄Cl₂ at 40°C for 3 h. A 0.2 equiv. portion of ethyl diazoacetate was added to reaction mixture at first, and then additional 0.2 equiv. of ethyl diazoacetate was added, when the evolution of nitrogen (to a total of 1.2 equiv.).

^b In each case, the two alcohols were present at equivalent initial concentration.

^c Total yield of this insertion was approximately 30%. Yields were determined by GC analysis.

TABLE 4. Competitive O–H insertion from cyclohexanol pairs and ethyl diazoacetate in the presence of rhodium catalysts ^a

Alcohols ^b		Product ratio (¹ R–OCH ₂ CO ₂ Et / ² R–OCH ₂ CO ₂ Et) ^c		
¹ R–OH	² R–OH	RhTPPI	RhTMPI	[Rh(OAc) ₂] ₂
	+ 	1.5	1.5	1.4
	+ 	1.4	3.3	1.4
	+ 	1.0	2.4	1.0

^a All reactions were run in the presence of 0.3 mol% of rhodium porphyrin in C₂H₄Cl₂ at 40°C for 3 h. A 0.2 equiv. portion of ethyl diazoacetate was added to the reaction mixture at first, and then additional a 0.2 equiv. of ethyl diazoacetate was added, when the evolution of nitrogen occurred (to a total of 1.2 equiv.).

^b In each case, the two alcohols were present at equivalent initial concentration.

^c Total yield of this insertion was approximately 30%. Yields were determined by GC analysis.

zoacetate. Table 3 indicates the product ratios of the corresponding two ethoxycarbonylmethyl alkyl ethers. In each reaction, when the total yield reached about 30%, the competitive reaction was quenched at an earlier stage to determine the exact product ratio. The results of the competitive reaction are summarized as follows. Firstly, in each reaction, the O–H bond of primary alcohol, n-hexanol, is much more subject to insertion than that of secondary and tertiary alcohols. The prim-/tert-product ratio is higher than the prim-/sec- ratio. Secondly, the catalyst **2** shows the highest selectivity in competitive reactions. For the competitive reaction between n-hexanol and triethylcarbinol, the particular catalyst **2** greatly impedes the insertion to

the tertiary OH bond compared with those in catalysts **1** and **4**. Thirdly, the reactivity of carbene insertion into the O–H bond using rhodium porphyrin depends on the structure of the alcohol and the bulkiness of the porphyrin ligand, whereas the selectivity catalyzed by less hindered rhodium acetate is insensitive to the structure of the substrates. The present results lead us to conclude that the generation of the reactive metal–carbene complex occurs as has been proposed in the catalytic cyclopropanation of olefins with rhodium(III) porphyrin and ethyl diazoacetate [7(b)].

Several competitive runs with cyclohexanols as substrates were examined in order to further confirm the steric effect due to both catalyst and substrate. Table 4

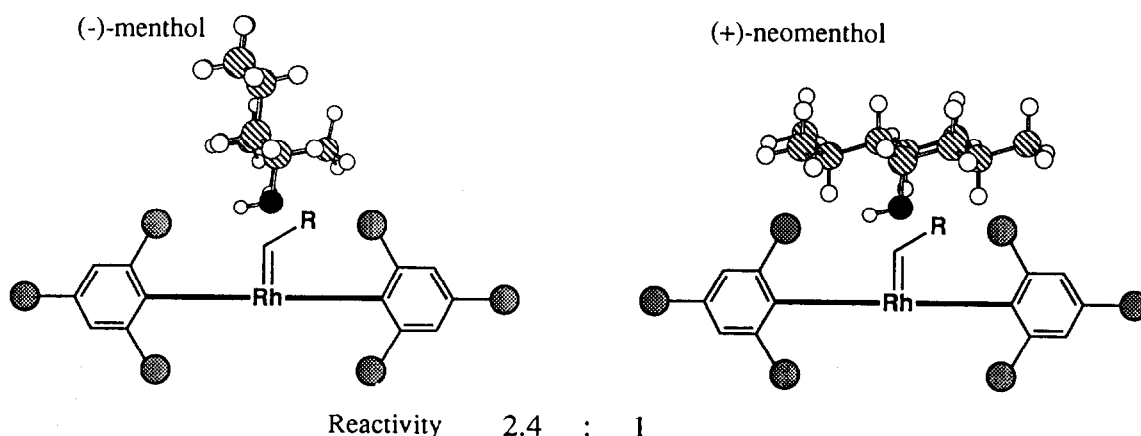
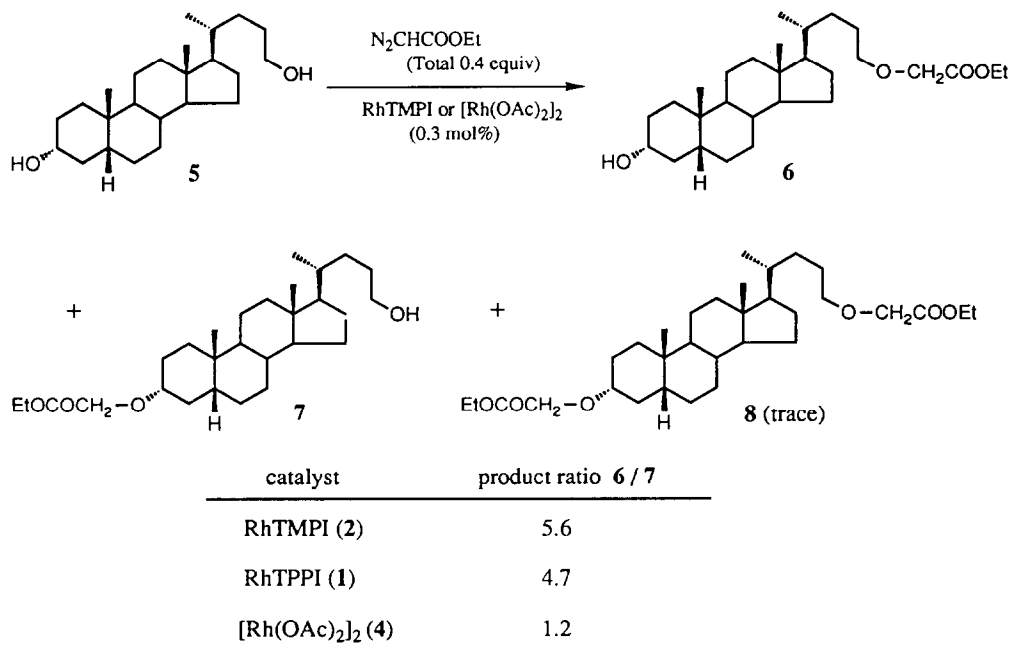


Fig. 1. Plausible approach for menthol and neomenthol to the RhTMPI 2-carbene complex.



Scheme 1.

shows the product ratios of the corresponding two ethers from cyclohexanol pairs. The carbene insertions to cyclohexanol and (–)-menthol proceeded in a similar way, and selectivity for rhodium acetate 4 and both rhodium porphyrins, 1 and 2 was low. In contrast, rhodium catalysts, 1 and 4, gave 1.4–1.5 ratios of ether products derived from cyclohexanol and (+)-neomenthol; however, in the presence of 2, cyclohexanol is more reactive than neomenthol by a factor of 3.3. Competitive insertion into O–H bonds from menthol and neomenthol with 1 or 4 shows both alcohols to be quite equally reactive, while neomenthol is less reactive in the presence of 2. It is evident that the reactivity in the bulkier RhTMPI catalyst depends on the substituent and its conformation at the vicinal position relative to the hydroxyl group. In fact, Fig. 1 proposes that neomenthol has steric repulsion with mesityl groups of 2 compared to menthol. Thus, in the carbene insertion into O–H bonds, the steric factors between substrate and catalyst seem to preferentially contribute to the reactivity of the hydroxyl group.

Furthermore, we carried out the reaction between cholane-3,24-diol (5) and ethyl diazoacetate (2.5 : 1 molar ratio) at 40°C by three catalysts, 1, 2 and 4 as shown in Scheme 1. Large substrate 5 has sec-hydroxyl and prim-hydroxyl groups at the 3 and 24 positions, respectively. The ratio of ethers 6 and 7 obtained was determined from the ¹H NMR spectrum of the reaction mixture after usual work-up. Signals due to the methylene group (–O–CH₂–CO₂Et) of 6 and 7 were ob-

served at 4.045 and 4.100 ppm, respectively. In addition to two ethers, a trace amount of diether 8 was detected by TLC analysis. The product ratio of 6/7 was found to be 5.6 in the presence of 2, while small differences in the insertion ratio were observed with 4. The insertion catalyzed by porphyrin complexes 1 and 2 shows a larger preference for the prim-hydroxyl group due to marked steric repulsion between both the porphyrin and the steroid framework.

Finally we conclude that iodorrhodium porphyrins efficiently catalyze the carbene insertion into O–H bonds by use of ethyl diazoacetate. In particular, it is noted that the bulkier catalyst 2 is able to recognize the structure of substrate molecules in the moiety of the catalytic reaction center. Thus, the large steric selectivity of insertion by use of 2 might be of synthetic utility for site-specific alkylation of alcohol derivatives of natural products. Further work on the improvement in selectivity, applications of this reaction and details on the reaction mechanism are in progress.

3. Experimental details

3.1. General

RhTPPI (1), RhTMPI (2) and RhOEPI (3) were prepared by a slight modification of the published procedures [10,13]. Ethyl diazoacetate was prepared according to the literature [14] and purity was checked before use by ¹H NMR. Cholane-3,24-diol (5) was prepared by the protection of hydroxyl groups of litho-

cholic acid [15], followed by reduction by lithium aluminum hydride. Products were monitored on a Shimadzu GC-8A Gas Chromatograph equipped with 10% SE-30 or 5% PEG 20M 3-m packed column. In order to determine the yields, reference ether products were prepared from corresponding alcohols and ethyl diazoacetate in the presence of **4**. ^1H NMR data were obtained at 90 MHz and 500 MHz using Jeol FX90-Q and α -500 spectrometers with residual CHCl_3 (7.25 ppm) as a reference.

3.2. Carbene insertion into the O-H bond with rhodium catalyst

In a typical run, rhodium catalyst (0.003 mmol), alcohol (1.0 mmol), $\text{C}_2\text{H}_4\text{Cl}_2$ (1.0 ml) were placed in a 5-ml Schlenk tube equipped with a nitrogen collector. Ethyl diazoacetate was added to the reaction tube *via* microsyringe. The resulting mixture was stirred at 40°C and additional small portions (0.1 equiv.) of ethyl diazoacetate were added (to a total of 1.5–2.0 equiv.), after the evolution of nitrogen stopped. After the reaction finished, hexadecane or heptadecane (GC standard, 0.1 mmol) was added to the reaction mixture. Yields were determined by chromatography. After usual workup and column chromatography on silica gel, the pure ether product was obtained.

3.3. Typical representative spectra of products

5: ^1H NMR (CDCl_3): δ 0.634 (s, 3H); 0.907 (s, 3H); 0.913 (d, $J = 6.1$ Hz, 3H); 0.930–1.970 (m, 30H); 3.613 (m, 3H).

6: ^1H NMR (CDCl_3): δ 0.626 (s, 3H); 0.902 (d, $J = 6.5$ Hz, 3H); 0.904 (s, 3H); 0.919–1.968 (m, 29H); 1.277 (t, $J = 7.3$ Hz, 3H); 3.475 (m, 2H); 3.609 (m, 1H); 4.05 (s, 2H); 4.208 (q, $J = 7.3$ Hz, 2H).

7: ^1H NMR (CDCl_3): δ 0.619 (s, 3H); 0.891 (s, 3H); 0.899 (d, $J = 8.0$ Hz, 3H); 0.922–1.954 (m, 28H); 1.267 (t, $J = 7.1$ Hz, 3H); 3.335 (m, 1H); 3.593 (m, 2H); 4.098 (s, 2H); 4.201 (q, $J = 7.1$ Hz, 2H).

8: ^1H NMR (CDCl_3): δ 0.622 (s, 3H); 0.901 (s, 3H); 0.907 (d, $J = 5.5$ Hz, 3H); 0.925–1.952 (m, 28H); 1.273 (t, $J = 7.2$ Hz, 3H); 1.277 (t, $J = 7.2$ Hz, 3H); 3.337 (m, 1H); 3.476 (m, 2H); 4.043 (s, 2H); 4.100 (s, 2H); 4.206 (q, $J = 7.2$ Hz, 2H); 4.209 (q, $J = 7.2$ Hz, 2H).

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