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Linear Free Energy Correlation Analysis on the Electronic Effects of Rh(II) Carbene O−H Insertion

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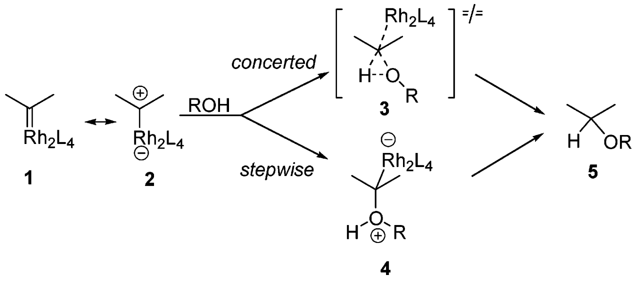
Abstract: The relative rate constants for the Rh(II)-catalyzed insertion of diazoacetone into the O−H bond have been measured through intermolecular competitions. The kinetic data were subjected to Hammett correlation analysis, and mechanistic implication of the results with respect to a stepwise vs a concerted O−H insertion pathway is discussed.

The Rh(II) complex catalyzed reaction of α-diazocarbonyl compounds generates Rh(II) carbene intermediates, which can subsequently undergo diverse synthetically useful transformations such as cyclopropanation, ylide formation, and insertion into C−H and X−H (X = O, S, N, Si, etc.) bonds. The Rh(II) carbene insertion into a polar X−H (X = O, S, N, etc.) bond, along with the insertion into C−H and Si−H bond, has attracted much attention in recent years. In the case of O−H insertion, the reaction provides an efficient and powerful method for generating new C−O bond.[1,2] Despite the practical value of O−H insertion in organic synthesis, its detailed reaction mechanism is not fully understood. In contrast to the generally accepted mechanism of concerted insertion of Rh(II) carbene into nonpolar C−H or Si−H bonds,[3] the insertion into the polar O−H bond is speculated to be stepwise (Scheme 1).[1,2b,d] Nevertheless, there exists little experimental evidence to support a stepwise mechanism, and a concerted pathway cannot be ruled out.

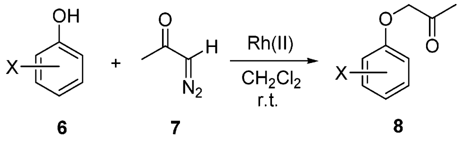
SCHEME 1



It is conceivable that the electronic effect imposed by the R group on the stepwise reaction mechanism should be significantly different from the concerted one due to the formation of the oxonium ylide intermediate in the stepwise pathway. Experimental study of such electronic effects may provide useful insights into the operating mechanism of O−H insertion.

To evaluate the electronic effects of O−H insertion, we studied a series of substituted phenol derivatives (**6a**−**h**, Scheme 2).[4] Diazoacetone **7** was used to generate the Rh(II) carbene instead of the traditional ethyl diazoacetate (EDA), because of the relatively low reactivity of EDA toward phenol O−H bond.[5]

SCHEME 2



a. X = *p*-OMe; **b.** X = *p*-Me; **c.** X = *p*-Ph;
d, X = H; **e.** X = *p*-Cl; **f.** X = *m*-Br
g. X = *m*-NO$_2$; **h**. X = *p*-NO$_2$

The relative reactivity of the O−H bond in **6a**−**h** can be measured by the product distribution during the intermolecular competition when a mixture of **6a**−**h** is allowed to react with **7**. This requires that the O−H insertion be clean and efficient. To establish a suitable protocol for this reaction, we examined four of the most common Rh(II) catalysts, namely rhodium(II) acetate [$Rh_2(OAc)_4$], rhodium(II) octanoate [$Rh_2(OOct)_4$], rhodium(II) acetamide [$Rh_2(acam)_4$], and rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$]. The reaction of **7** with **6a**−**h** in CH_2Cl_2 at room temperature, catalyzed by $Rh_2(OAc)_4$, gave O−H insertion products **8a**−**h** with isolated yields ranging from 65 to 88%. Similar results were obtained with $Rh_2(OOct)_4$ as the catalyst. The same reactions with $Rh_2(tfa)_4$ as the catalyst yielded clean O−H insertion products, but its rate is markedly slower than that with $Rh_2(OAc)_4$.[6] Unfortunately, the reactions with $Rh_2(acam)_4$

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(1) For comprehensive reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *44*, 1091.

(2) For reviews on carbene and carbenoids O−H insertions, see: (a) Kirmse, W. In *Advances in Carbene Chemistry*; Brinker, U., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 1; pp 1−57. (b) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811. For recent examples of carbenoid O−H insertions, see: (c) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem.* **1995**, *60*, 4449. (d) Doyle, M. P.; Yan, M. *Tetrahedron Lett.* **2002**, *43*, 5929. (e) Davies, H. M. L.; Yokota, Y. *Tetrahedron Lett.* **2000**, *41*, 4851. (f) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630. (g) Schils, R.; Simal, F.; Demonceau, A.; Noels, A. F.; Eremenko, I. L.; Sidorov, A. A.; Nefedov, S. E. *Tetrahedron Lett.* **1998**, *39*, 7849. (h) Kettle, J. G.; Faull, A. W.; Fillery, S. M.; Flynn, A. P.; Hoyle, M. A.; Hudson, J. A. *Tetrahedron Lett.* **2000**, *41*, 6905.

(3) For mechanistic investigations on Rh(II) carbene C−H insertion and Si−H insertion, see: (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (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. (c) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (d) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (e) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853. (f) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181. (g) Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *Tetrahedron Lett.* **1997**, *38*, 229. (h) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.

(4) For an earlier report on the Rh(II) carbene O−H insertion with phenols, see: Haigh, D. *Tetrahedron* **1994**, *50*, 3177.

(5) Ethyl diazoacetate failed to react when it was treated with catalytic $Rh_2(OAc)_4$ in CH_2Cl_2 in the presence of phenol at room temperature.

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TABLE 1. Relative Rate Constants of the Rh(II) Carbene Insertion into Phenol O−H Bond

		$Rh_2(OAc)_4$			$Rh_2(OOct)_4$			$Rh_2(tfa)_4$		
entry	**6** (X =)	GC yield (%)	ratio[a]	k_{rel}[b]	GC yield (%)	ratio[a]	k_{rel}[b]	GC yield (%)	ratio[a]	k_{rel}[b]
1	*p*-OMe	71.6	1.26	1.33	79.2	1.51	1.70	18.0	0.96	0.96
2	*p*-Me	67.3	0.82	0.78	47.4	0.86	0.84	16.1	0.85	0.84
3	*p*-Ph	60.5	0.93	0.92	71.4	0.91	0.89	24.0	0.99	0.99
4	H	-	-	1.00	-	-	1.00	-	-	1.00
5	*p*-Cl	61.6	0.86	0.83	70.5	0.90	0.88	19.2	0.92	0.92
6	*m*-Br	66.9	0.67	0.61	52.0	0.66	0.62	19.3	0.78	0.77
7	*m*-NO_2	50.8	0.66	0.62	54.5	0.64	0.59	21.0	1.18	1.19
8	*p*-NO_2	70.9	0.54	0.46	61.2	0.60	0.54	18.1	0.63	0.62

[a] The product ratio of **8a**−**c** and **8e**−**h** to **8d** in each competition experiment. [b] Relative rate constant k_{rel} is calculated from the yields; see the Supporting Information.

TABLE 2. Hammett Correlation Data of Relative Rate k_{rel}

substituent constant[a]	$\rho(r)$[b]		
	$Rh_2(OAc)_4$	$Rh_2(OOct)_4$	$Rh_2(tfa)_4$
σ^+	−0.25 (−0.91)	−0.28 (−0.93)	−0.09 (−0.70)
σ	−0.32 (−0.88)	−0.35 (−0.86)	−0.13 (−0.74)
σ^-	−0.25 (−0.89)	−0.26 (−0.82)	−0.11 (−0.83)

[a] Substituent constants were taken from ref. 7. [b] ρ = reaction constants. r = correlation coefficient.

gave a complex mixture of products and no effort was made to identify them. Based on these results, we limited our study of the electronic effect to three Rh(II) catalysts: $Rh_2(OAc)_4$, $Rh_2(OOct)_4$, and $Rh_2(tfa)_4$.

The intermolecular competition was carried out with a solution of equimolar phenol **6d**, substituted phenols **6a**−**c**,**e**−**h**, and diazoacetone **7** in CH_2Cl_2 containing 0.1 mol % Rh(II) catalyst. After the reaction was stirred for 12 h at room temperature, biphenyl was added as the internal standard and the reaction mixture was directly analyzed by GC. To ensure the reproducibility, at least two GC runs were performed for each experiment. The relative rate constants for each phenol can then be derived from the yield of each insertion product (for detailed kinetic treatment, see the Supporting Information). The experimental results and the derived rate constants (relative to the unsubstituted phenol, **6d**) are displayed in Table 1. It is worth noting that no products other than **8a**−**h** could be detected and all unreacted phenols were recovered quantitatively. Control experiments indicated that without Rh(II) catalysts, no reaction occurred. Therefore, the O−H insertion is Rh(II) complex catalyzed and presumably occurs through the Rh(II) carbene intermediate.

Next, we proceeded to correlate the relative rate constants with Hammett substituent constants (σ, σ^+, and σ^-). The Hammett plots are included in the Supporting Information, and the linear fit results are summarized in Table 2 along with the correlation coefficients. Clearly, the rate constants correlate better with σ^+ for the $Rh_2(OAc)_4$- and $Rh_2(OOct)_4$-catalyzed reactions than with σ^+ and σ^-. For the $Rh_2(tfa)_4$-catalyzed reaction, however, the rates correlate better with σ^-. Even though the linearity is not excellent in general, the Hammett reaction constants do provide useful insights into the reaction mechanism. First, the relatively small magnitude of the reaction constants, ρ, in all three catalytic systems indicates that the O−H insertion is only slightly sensitive to the change in the electronic nature of the substituents on the phenyl ring. This finding contradicts the stepwise mechanism in which a much greater electronic effect would have been expected due to the fully developing positive charge in the oxonium ylide intermediate (Scheme 1). Second, our observed small negative reaction constants indicate that the Rh(II) carbene insertion into the O−H bond is slightly accelerated by electron-donating groups on the phenyl ring. This result is consistent with the model of a concerted insertion[1a] in which the p orbital of the electrophilic carbene overlaps more efficiently with the more electron-rich O−H bond.

If the O−H insertion follows a concerted mechanism as C−H and Si−H insertions, then the small reaction constants are also in agreement with a relatively early three-center two-electron transition state **3** (Scheme 1),[3b] where little positive charge is being developed. The stronger electron-withdrawing ligand in $Rh_2(tfa)_4$, as compared to that in $Rh_2(OAc)_4$ and $Rh_2(OOct)_4$, increases the electrophilicity of the carbene and results in an even earlier transition state. As a result, there would be less positive charge developing on the oxygen due to the greater distance between the carbene and the O−H bond in this transition state. This is in good agreement with our observed trend of reaction constant magnitude (−0.13 for $Rh_2(tfa)_4$ vs −0.32 for $Rh_2(OAc)_4$ and −0.35 for $Rh_2(OOct)_4$). We notice that for Rh(II) carbene insertion into C−H bonds, $Rh_2(tfa)_4$-catalyzed reaction also gives a smaller reaction constant compared to the corresponding C−H insertion catalyzed by $Rh_2(OAc)_4$.[3e]

The concerted insertion mechanism is also consistent with the observation that the O−H bond of aliphatic alcohols has a higher reactivity than that of phenols.[8] Because of the small positive charge being developed on the oxygen in the concerted mechanism, the electron density of the O−H bond becomes crucial. The inductive effect of alkyl groups is electron-donating, while that of a phenyl group is weakly electron-withdrawing. Consequently, an alkyl group enhances the O−H bond electron density, thus accelerating the O−H insertion. Previous reports also suggest that the O−H insertion is insensitive to steric effects,[8] which is in accordance with an early transition state of a concerted mechanism.

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(6) Moody et al. have observed the same phenomena that electron-withdrawing ligands on Rh(II) retard the O−H insertions. It is rationalized that the alcohol coordinates more strongly to the more electron-demanding catalysts. See ref 8.

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For $Rh_2(OAc)_4$-catalyzed C−H and Si−H insertion, reaction constants of −1.26 and −0.31 (both against σ)[3e,g] have been reported, respectively. It is well-known that O−H bonds and Si−H bonds are much more reactive toward Rh(II) carbene insertion than C−H bonds. The insertion of Rh(II) carbene into a C−H bond is also known to be sensitive to steric hindrance.[3a] If all insertions follow a similar concerted mechanism, then the Hammett reaction constants clearly reflect this trend of reactivity. The more reactive O−H and Si−H bonds cause an early transition state while the less reactive C−H bond results in a relatively late transition state (thus more sensitive to electronic and steric effect). An early transition state may also be responsible for the fact that the asymmetric O−H insertion is much less successful than the corresponding C−H insertion.[1]

It is interesting to note the comparable reaction constants [−0.32 (σ) vs −0.31 (σ)] for $Rh_2(OAc)_4$-catalyzed O−H and Si−H insertion, respectively. Further comparison of these two types of insertion discloses other similarities.[3g] For Si−H insertion, the rate of arylsilanes is slower than that of alkylsilanes [$k(^iPr_3Si{-}H)$:$k(Ph_3Si{-}H)$=1.17:1], while phenols are less reactive than alcohols in O−H insertion. Moreover, the effect of steric hindrance on Si−H insertion is quite small [$k(ClMe_2Si{-}H)$:$k(Cl^tBu_2Si{-}H)$ = 1:2], just as in O−H insertion. These similarities further support the idea that O−H and Si−H insertions follow similar concerted reaction mechanisms with early transition states, in which the Rh(II) carbene and O−H or Si−H bond are relatively far away from each other.

Although our study of electronic effect does not provide conclusive evidence on the mechanism of Rh(II) carbene insertion into the O−H bond, the Hammett correlation data are in favor of a concerted insertion process, as in the case of corresponding C−H or Si−H bond insertion. Further experimental evidence is needed to eventually solve this mechanistic puzzle.

Experimental Section

Caution: Diazoketone **7** is presumed to be toxic and potentially explosive. It should be handled with care in a well-ventilated fumehood.

General Procedure for $Rh_2(OAc)_4$-Catalyzed Reaction of Diazoketone 7 with Phenols 6a−h. To a solution of phenol **6a−h** (1 mmol) and $Rh_2(OAc)_4$ (0.4 mg, 0.1 mmol %) in CH_2Cl_2 (10 mL) was added dropwise a solution of diazoketone **7** (92 mg, 1.1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 10−12 h under N_2. The solution was washed with 10% aqueous NaOH to remove unreacted phenol, washed with water and brine, and finally dried over $MgSO_4$. Solvent was removed by rotavap, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 5:1) to give O−H insertion products **8a−h**: **8a**, 83%; **8b**, 78%; **8c**, 76%; **8d**, 88%; **8e**, 67%; **8f**, 65%; **8g**, 78%; **8h**, 72%. The products were characterized or confirmed by spectra data.

1-(*p*-Phenyl)phenoxypropan-2-one (8c): IR 3080, 3035, 1723, 1686, 1606, 1524, 1489 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.58 (s, 2H), 6.93−6.98 (m, 2H), 7.38−7.57 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.65, 73.14, 114.79, 116.00, 126.77, 126.88, 128.38, 128.75, 134.89, 157.24, 205.75; MS (*m*/*z*, relative intensity) 226 (M^+, 100), 183 (62), 153 (71), 115 (18), 43 (58). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.63; H, 6.24.

General Procedure for Kinetic Competition Experiments. Each insertion product is mixed with the reference compound biphenyl in different molar ratios (10:1, 5:1, 2:1, and 1:1). The samples were then analyzed on GC to obtain the detector responding factors [a standard working line of lg(molar ratio) versus lg(GC peak area ratio) of insertion product to biphenyl].

Phenol **6d** (94 mg, 1 mmol) and a substituted phenol (1 mmol) were dissolved in CH_2Cl_2 (10 mL), followed by the addition of Rh(II) catalyst (0.1 mmol %). Under N_2 atmosphere and with stirring was added a solution of diazoacetone **7** (84 mg, 1 mmol) in CH_2Cl_2 (5 mL) dropwise. The reaction mixture was stirred overnight. Biphenyl (31 mg, 0.2 mmol) was added as the internal standard, and the reaction mixture was directly subjected to GC analysis. The product ratio and the yields were obtained from the responding factors. The relative rate constants were then calculated from the product yields and ratios (see the Supporting Information for details).

GC Conditions. The reaction mixture was analyzed by a flame ionization detector (FID) and a HP-5 analytical column (30-m fused silica column with an internal diameter of 0.32 mm and a film thickness of 0.25 μm). The initial oven temperature was 70 °C, which was ramped by 10 °C/min to the final temperature of 270 °C. At least two GC runs were performed for each sample to ensure reproducibility.

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Supporting Information Available: Kinetic treatments and the Hammett plots with σ, σ^+, and σ^-. This material is available free of charge via the Internet at http://pubs.acs.org.

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