Mechanistic studies of an unusual epoxide-forming elimination of a β-hydroxyalkyl rhodium porphyrin

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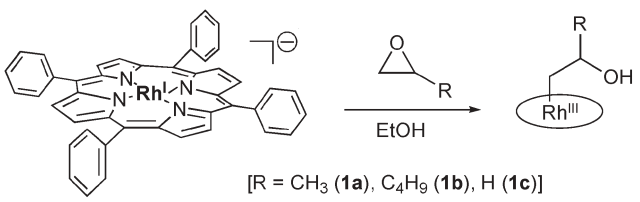
A new and remarkably facile sp^3-C–O bond forming reaction of β-hydroxyalkyl Rh porphyrins to form epoxides has been discovered and its mechanism investigated.

Carbon–oxygen bond formation at transition metal centers is a fundamental organometallic transformation that serves as the functionalization step in many important catalytic processes. For example, Pd-catalysed aryl etherification[1] and alkene alkoxycarbonylation,[2] Pt-[3] and Pd-catalysed[4] alkane oxidation, and Rh-mediated olefin hydrofunctionalization[5] all involve the formation of carbon–oxygen bonds as a key step in the catalytic cycle. However, despite the significance of this transformation, relatively few C–O coupling reactions at transition metal centers have been directly observed and studied, and most still require elevated temperatures, extended reaction times, and/or electronically/sterically constrained substrates.[4a,6–10] Such limitations hinder the development and scope of processes in which C–O bond formation is critical to product release and catalyst turnover. Furthermore, a significant and potentially important class of C–O coupling reactions—those involving the formation of sp^3-carbon–oxygen bonds—remain exceedingly rare.[8–10]

We report herein our preliminary investigations of a series of porphyrin Rh^{III} β-hydroxyalkyl complexes, which undergo clean and remarkably facile sp^3-C–O bond forming reactions upon the addition of base. Furthermore, we describe mechanistic investigations that implicate an S_N2 pathway for this unusual transformation.

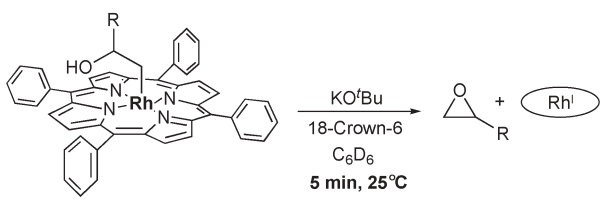
The nucleophilicity of square planar Rh^I porphyrins is well-documented, and these complexes react cleanly with many sterically unencumbered electrophiles *via* an S_N2 mechanism.[11] As such, a series of (TPP)Rh^{III} [TPP = tetraphenylporphyrin] β-hydroxyalkyl adducts was readily prepared by reaction of Na[(TPP)Rh^I] with unsubstituted or mono-substituted epoxide derivatives (Scheme 1).[11a,b] These reactions were complete within 30 min at 25 °C, and afforded complexes **1a–c** in 50–60% isolated yield.† The products were characterised by ^{1}H NMR spectroscopy based on the dramatic upfield shifts of the alkyl proton and OH resonances (resulting from the diamagnetic anisotropy associated with the porphyrin ligand). For example, the α-protons of complex **1b** appear at δ −4.57, while the hydroxyl proton resonates at δ −3.80 in C_6D_6.[12]



Scheme 1 Synthesis of (TPP)Rh^{III} β-hydroxyalkyl complexes.

Complexes **1a–c** showed no propensity toward inter- or intramolecular C–O bond formation under neutral conditions. However, the addition of several equivalents of base resulted in rapid intramolecular sp^3-C–O coupling to yield epoxides (Scheme 2). Under optimized reaction conditions (in C_6D_6 with 3 equiv. 18-Crown-6), complex **1b** reacted with KO^{t}Bu to produce 1,2-epoxyhexane and K[(TPP)Rh^I] in quantitative yield, as measured by ^{1}H NMR spectroscopy.[13] This reaction proceeded under unprecedentedly mild conditions,[4a,6–10] and was complete within 5 min *at room temperature*.

To determine the mechanism of this transformation, the stereospecifically deuterated substrate **1b–d** was synthesized *via* reaction of Na[(TPP)Rh^I] with *trans*-1,2-oxido[1-D]hexane. The ^{1}H NMR spectra of **1b–d** and **1b** are compared in Fig. 1. Trace (A) is the spectrum of complex **1b** and trace (B) is the decoupled spectrum of complex **1b** obtained upon irradiation of H_c at δ −2.43. The very high-field positions of H_c and the –OH proton (δ −3.8) with respect to the highest field CH_2 protons (δ −1.4 and −0.9) and the gradually descending shifts of the other alkyl resonances indicate that the conformation of **1b** is as shown, with the larger *n*-butyl group *anti* to the rhodium, similar to **1a**.[12] Very similar chemical shifts have been reported for analogous *gauche* β-hydroxy-N-alkyl porphyrins.[11e] Accordingly, the following coupling constants in **1b** can be obtained from spectra (A) and (B): $^2J_{ab}$ = 9.34 Hz, $^3J_{ac}$ = 8.45 Hz, $^3J_{bc}$ = 1.47 Hz, $^2J_{Rh–H}$ = 2.93 Hz. The ^{1}H NMR spectrum of compound **1b–d** is shown in spectrum (C), indicating that H_a is the deuterated position in **1b–d**. This identification confirms that the formation of β-hydroxyalkylrhodium(III) porphyrin complex **1b** occurred with inversion of stereochemistry at C_α,[11] presumably *via* S_N2 attack of Na[(TPP)Rh^I] on the epoxide.



Scheme 2 C–O bond forming reactions of complexes **1a–c**.

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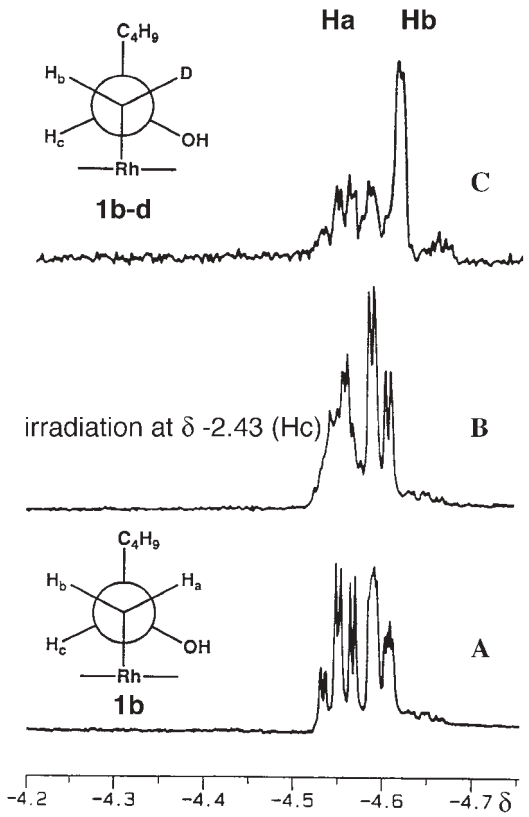


Fig. 1 ^{1}H NMR spectra of alkyl-rhodium(III) complex **1b**. Integration of trace C indicates *ca.* 60% deuteration.

The subsequent addition of KO^{t}Bu/18-crown-6 to complex **1b** led to rapid C–O bond formation to produce the corresponding epoxide. The cyclized product was analysed *via* ^{1}H NMR spectroscopy (Fig. 2, Spectra A, B, and C). Spectrum A shows the spectrum of an authentic sample of 1-hexene oxide, while spectrum B shows that of *trans*-1,2-oxido[1-D]hexane (containing 24% unlabelled 1-hexene oxide). Finally, spectrum C shows the spectrum of the volatile components of the reaction mixture from **1b–d** following trap-to-trap distillation.

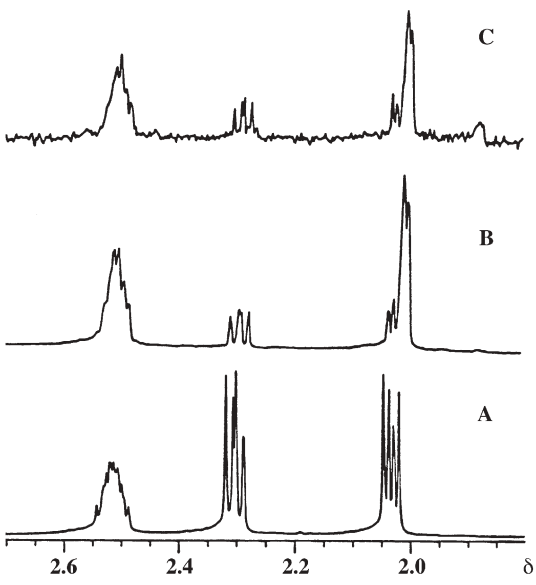
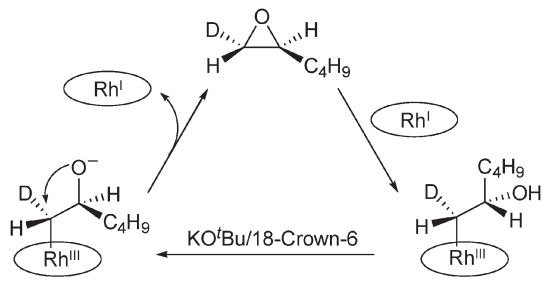


Fig. 2 ^{1}H NMR (300 MHz) spectrum (C_6D_6) of (A) authentic 1-hexene oxide, (B) authentic *trans*-1,2-oxido[1-D]hexane (containing 24% unlabelled 1-hexene oxide), and (C) product obtained from treatment of complex **1b–d** with 3 equiv. KO^{t}Bu/ 3 equiv. 18-crown-6.

The ^{1}H NMR spectra of the epoxide product (C) and of *trans*-1,2-oxido[1-D]hexane (B) are clearly identical, indicating that the epoxide ring opening/ring closing sequence led to overall retention of stereochemistry. Based on this data, it is clear that C–O coupling proceeded with *inversion* of configuration at C_α, implicating an S_N2 mechanism (Scheme 3). Alternate mechanisms, including pre-coordination of the alkoxide[6,7] or radical chain pathways[11d] can be ruled out, as they would involve retention or scrambling of stereochemistry, respectively. Notably, the proposed mechanism is consistent with conclusions of Collman *et al.* that a closely related Rh^I/Rh^{III} alkyl exchange reaction proceeds by an S_N2 pathway.[14,15] Similar mechanisms have also been observed in C–O bond forming reductive elimination from Pt^{IV} centers, which serve as the product forming step in the Shilov reaction.[3c] By extension, it can be inferred that the anti-Markovnikov hydrofunctionalization of olefins we have recently described for oxygen, nitrogen, and carbon nucleophiles[5] all proceed *via* such an S_N2 displacement of a rhodium(I) porphyrin leaving group. Accordingly, efforts to make this transformation truly catalytic will need to address (i) the factors that affect the leaving group ability of the Rh^I as well as (ii) the compatability of other elementary steps of the catalytic cycle with the basic reaction medium required for the C–O coupling process.

The carbon–oxygen bond-forming reaction described herein is particularly notable in light of the diverse and unique reactivity of Rh porphyrins. For example, [Por]Rh complexes are well-known to promote the C–H activation of methane and toluene[16a] as well as to mediate highly regioselective alkene/CO insertion reactions[16b] under extremely mild conditions. Developing methods to couple such transformations (which produce [Por]Rh σ-alkyl and σ-formyl products) with subsequent functionalization steps could provide novel insights and solutions to many challenges in catalysis, including alkane oxidation, regioselective olefin hydrofunctionalization, and the Fisher–Tropsch synthesis of hydrocarbons. Efforts towards these applications are currently underway in our laboratories.[5]

In conclusion, this report describes a new, base-promoted sp^3-C–O coupling reaction of β-hydroxyalkyl Rh^{III} porphyrins. Mechanistic investigations reveal that this transformation proceeds *via* deprotonation of the β-hydroxyalkyl ligand followed by nucleophilic displacement of K[(TPP)Rh^I] by an S_N2 pathway.



Scheme 3 Mechanism of reductive C–O bond formation for **1b–d**.

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Notes and references

† **Preparation of β-hydroxy-alkyl(tetraphenylporphyrinato)-rhodium(III) complexes (1a–c)**. To a solution of 10 mg RhTPPI in 10 mL of degassed ethanol, 0.5 mL of 0.5 N aqueous NaOH solution containing 5 mg $NaBH_4$ was added. The mixture was stirred under nitrogen at 55–65 °C for 1 h and then cooled to 25 °C. The appropriate epoxide (2 mL) was added and the mixture was stirred for 1 h under nitrogen. **1a–c** were isolated by preparative TLC (silica/CH_2Cl_2) in 50–60% yield. **1a** NMR ($CDCl_3$): δ 8.76 (s, *pyr*-H, 8H); 8.2 (m, *o*-H, 8H); 7.8 (m, *m*,*p*-H, 12H); −1.43 (d, 3H); −2.31 (m, 1H); −4.11 (br.s, -OH, 1H); −4.88 (m, 2H). FAB MS (*m*-nitrobenzyl alcohol matrix; M^+): *m*/*z* Found: 774 (100), 775(63), 776(22), 777(8). Calcd: 774 (100), 775(55), 776(15), 777(4); +HR FAB MS (3-NBA/Li matrix),[17] M + Li *m*/*z* Found: 781.2019, calcd: 781.2026 (−88); **1b** NMR (C_6D_6): δ 8.85 (s, 8H); 8.24–8.11 (m, 8H); 7.50 (m, 12H); 0.16 (t, 3H); 0.05 (m, 2H); −0.45 (m, 2H); −0.90 (m, 1H); −1.4 (m, 1H); −2.43 (m, $1H_c$); −3.80 (s, 1H); −4.55 (td, $1H_a$) −4.60 (dm, $1H_b$); $^2J_{ab}$ = 9.34 Hz, $^3J_{ac}$ = 8.45 Hz, $^3J_{bc}$ = 1.47 Hz, $^2J_{Rh-H}$ = 2.93 Hz. FAB MS (*m*-nitrobenzyl alcohol matrix; M^+): *m*/*z* Found: 816(100), 817(59), 818(42), 819(12). Calcd: 816(100), 817(59), 818(17), 819(5); +HR FAB MS (3-NBA/Li matrix), M + H *m*/*z* Found: 817.2400, calcd: 817.2414 (−1.66); **1c** NMR (C_6D_6): δ 8.79 (s, *pyr*-H, 8H); 8.16 (m, *o*-H, 4H); 8.00 (d, *o'*-H, 4H); 7.47–7.32 (m, *m*,*p*-H, 12H); −2.00 (q, *b*-H, 2H); −2.94 (t, -OH, 1H); −4.78 (dt, α-H, 2H). FAB MS (*m*-nitrobenzyl alcohol matrix; M^+): *m*/*z* Found: 760 (100), 761(70), 762(25), 763(10). Calcd: 760 (100), 761(53), 762(12), 763(5); +HR FAB MS (3-NBA/Li matrix), M + Li *m*/*z* Found: 767.1847, calcd: 767.1869 (−2.92). **β-Hydroxy-1-deuterio-*n*-hexyl(tetraphenylporphyrinato)-rhodium(III) TPPRhCHDCH(OH)C_4H_9 (1b–d)** was prepared in a similar fashion as **1b** from *trans*-1,2-oxido[1-D]hexane. The high field region of the ^{1}H NMR spectrum of **1b–d** displayed the expected *J*-coupling collapse and a characteristic upfield shift of H_b due to deuterium substitution of H_a,[11d] which partially obscures the residual H_b. Integration of this region indicated approximately 60% deuteration of the H_a site and small amounts of impurities in the sample. NMR (C_6D_6): δ 8.85 (s, 8H); 8.24–8.1 (m, 8H); 7.50 (m, 12H); 0.16 (t, 3H); 0.05 (m, 2H); −0.45 (m, 2H); −0.90 (m, 1H); −1.4 (m, 1H); −2.43 (m, 1H); −3.80 (s, 1H); −4.58 (m, H_a, 0.4H; H_b, 1H). FAB MS (*m*-nitrobenzyl alcohol matrix; M^+): *m*/*z* Found: 816(35), 817(100), 818(65), 819(26), 820(12). Calcd: 816(26), 817(100), 818(54), 819(16), 820(4). **The reaction of β-hydroxylalkyl rhodium (III) porphyrins with potassium *t*-butoxide. 1a–c** and **1b–d** (4 mg) were dissolved in 0.7 mL of C_6D_6 in a dry box, 2–3 equiv. of 18-crown-6 and excess potassium *t*-butoxide were added. The reactions were followed by ^{1}H NMR. The reaction mixtures were then transferred to 50 mL flasks, the volatile components were isolated by bulb-to-bulb distillations (liquid N_2 trap) and analyzed by ^{1}H NMR.

1 For recent reviews, see: (*a*) D. Prim, J. M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041; (*b*) J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852.

2 J. Wolowska, G. R. Eastham, B. T. Heaton, J. A. Iggo, C. Jacob and R. Whyman, *Chem. Commun.*, 2002, 2084 and references therein.

3 For examples, see: (*a*) A. E. Shilov and G. B. Shul'pin, *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*, Kluwer, Dordecht, 2000; (*b*) R. A. Periana, D. J. Taube, S. Gamble, H. Taube, T. Satoh and H. Fujii, *Science*, 1998, **280**, 560; (*c*) S. S. Stahl, J. A. Labinger and J. E. Bercaw, *Angew. Chem., Int. Ed.*, 1998, **37**, 2181; (*d*) G. A. Luinstra, L. Wang, S. S. Stahl, J. A. Labinger and J. E. Bercaw, *J. Organomet. Chem.*, 1995, **504**, 75.

4 (*a*) A. R. Dick, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 12790; (*b*) L. V. Desai, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 9542; (*c*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300.

5 M. S. Sanford and J. T. Groves, *Angew. Chem.*, 2004, **43**, 588.

6 (*a*) Q. Shelby, N. Kataoka, G. Mann and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10718; G. Mann, C. Incarvito, A. L. Rheingold and J. F. Hartwig, *J. Am. Chem. Soc.*, 1999, **121**, 3224; G. Mann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 13109; (*b*) R. A. Widenhoefer and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 6504; R. A. Widenhoefer, H. A. Zhong and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 6787.

7 Y.-S. Lin and A. Yamamoto, *Organometallics*, 1998, **17**, 3466.

8 (*a*) B. S. Williams and K. I. Goldberg, *J. Am. Chem. Soc.*, 2001, **123**, 2576; B. S. Williams, A. W. Holland and K. I. Goldberg, *J. Am. Chem. Soc.*, 1999, **121**, 252; (*b*) A. J. Canty and H. Jin, *J. Organomet. Chem.*, 1998, **565**, 135; A. J. Canty, H. Jin, B. W. Skelton and A. H. White, *Inorg. Chem.*, 1998, **37**, 3975.

9 Y.-S. Lin, S. Takeda and K. Matsumoto, *Organometallics*, 1999, **18**, 4897.

10 Oxidatively induced C–O coupling is more common. For examples, see: (*a*) K. Koo and G. L. Hillhouse, *Organometallics*, 1998, **17**, 2924; (*b*) J. E. Bäckvall, *Acc. Chem. Res.*, 1983, **16**, 335.

11 (*a*) H. Ogoshi, J.-I. Setsune and Z.-I. Yoshida, *J. Organomet. Chem.*, 1980, **185**, 95; (*b*) B. B. Wayland, S. L. Van Voorhees and K. J. Del Rossi, *J. Am. Chem. Soc.*, 1987, **109**, 6513; (*c*) R. Guilard and K. M. Kadish, *Chem. Rev.*, 1988, **88**, 1121; (*d*) J. P. Collman, J. I. Brauman and A. M. Madonik, *Organometallics*, 1986, **5**, 310; (*e*) J. P. Collman, P. D. Hampton and J. I. Brauman, *J. Am. Chem. Soc.*, 1986, **108**, 7862.

12 The connectivity of complex **1a** was also verified by X-ray crystallography. However, the structure showed considerable disorder, particularly, in the β-hydroxyalkyl ligand, Y.-Z. Han, PhD Thesis, Princeton University, 1992.

13 The identity of the products was confirmed by comparison of their ^{1}H NMR spectra with those of authentic samples.

14 J. P. Collman, J. I. Brauman and A. M. Madonik, *Organometallics*, 1986, **5**, 215.

15 Solvent and steric effects in related C–O coupling reactions of Rh^{III} porphyrins are also consistent with an S_N2 mechanism (ref. 5).

16 (*a*) K. J. Delrossi, X. X. Xhang and B. B. Wayland, *J. Organomet. Chem.*, 1995, **504**, 47; (*b*) B. B. Wayland, S. J. Ba and A. E. Sherry, *J. Am. Chem. Soc.*, 1991, **113**, 5305; (*c*) R. S. Paonessa, N. C. Thomas and J. Halpern, *J. Am. Chem. Soc.*, 1985, **107**, 4333.

17 Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).