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Enantioselective hydroxylation of benzylic C–H bonds by D_4-symmetric chiral oxoruthenium porphyrins†

Rui Zhang, Wing-Yiu Yu, Tat-Shing Lai and Chi-Ming Che*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong. E-mail: cmche@hku.hk

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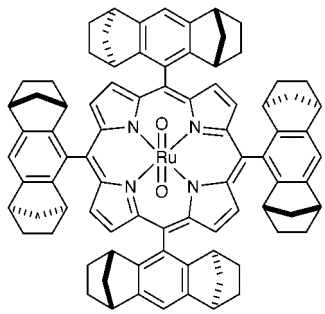
A D_4-symmetric chiral dioxoruthenium(VI) porphyrin can effect stoichiometric and catalytic enantioselective hydroxylation of benzylic C–H bonds to give enantioenriched aryl alcohols, the highest ee of 76% being attained in the catalytic oxidation of 4-ethyltoluene with 2,6-dichloropyridine *N*-oxide as terminal oxidant; the oxidations proceed *via* a rate-limiting H-atom abstraction to germinate a benzylic radical intermediate.

Despite significant advances in asymmetric alkene epoxidations,[1] the development of protocols for highly enantioselective hydroxylations of saturated C–H bonds has met with limited success. Groves and Viski first described the catalytic enantioselective benzylic C–H bond hydroxylations using a chiral iron porphyrin catalyst.[2] Recently, with the use of chiral Mn(salen) catalysts, ethylbenzene can be oxidized enantioselectively to 1-phenylethanol in 22% yield and 53% ee.[3] We herein describe a highly enantioselective benzylic C–H bond hydroxylation based on oxoruthenium complexes supported by a D_4-symmetric chiral porphyrin.

The [Ru^{II}(Por*)(CO)(EtOH)] and [Ru^{VI}(Por*)O_2] complexes {H_2Por* = 5,10,15,20-tetrakis[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracen-9-yl]-porphyrin} were prepared by the literature methods.[4] In a



[Ru^{VI}(Por*)O_2]

degassed CH_2Cl_2 solution (containing 2% w/w pyrazole), an excess of ethylbenzene reacted with [Ru^{VI}(Por*)O_2] to afford a mixture of 1-phenylethanol (32%) and acetophenone (33%) at room temperature; the (*S*)-1-phenylethanol was obtained in 45% ee (Table 1, entry 1). This features the first well-characterized chiral oxo-metal complex capable of hydroxylating saturated C–H bonds enantioselectively. Similarly, the stoichiometric oxidations of substituted ethylbenzenes, 2-ethylnaphthalene, indane and tetrahydronaphthalene by [Ru^{VI}(Por*)O_2] also furnished enantioenriched (*S*)-alcohols, and the oxidation of 2-ethylnaphthalene registered the highest ee of 58% ee (Table 1, entry 7). In all cases, a bis-pyrazolato-ruthenium(IV) porphyrin, [Ru^{IV}(Por*)$(pz)_2$], was isolated in > 85% yield at the end of the oxidation.

† Experimental and kinetic data, including UV-vis spectral traces, dual-parameter Hammett correlation studies and representative chiral GLC chromatograms, are available from the author at the address given above.

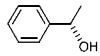
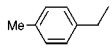
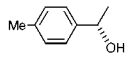
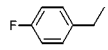
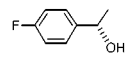
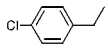
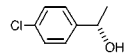
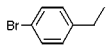
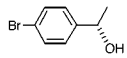
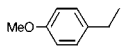
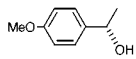
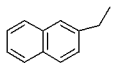
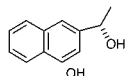
Under pseudo-first order conditions, the ethylbenzene oxidation by [Ru^{VI}(Por*)O_2] in 1,2-dichloroethane (with 2% w/w Hpz) exhibited isosbestic UV-vis spectral changes from Ru^{VI} to Ru^{IV} porphyrin (isosbestic points at 350, 415 and 444 nm). At 313 K, the second-order rate constant (k_2) is $(7.7 \pm 0.4) \times 10^{-4}$ dm^3 mol^{-1} s^{-1}. The second-order rate constants for the oxidation of *para*-substituted ethylbenzenes had been measured, and a linear dual-parameter Hammett correlation between log k_{rel} [$k_{rel} = k_2$(4-substituted ethylbenzene)/k_2(ethylbenzene)] and the $\sigma_{JJ}^{\cdot}$ and σ_p^+ constants[5] was established: log k_{rel} = + (0.57 ± 0.04) $\sigma_{JJ}^{\cdot}$ − (0.36 ± 0.01) σ_p^+ (R = 0.99; $|\rho_{JJ}^{\cdot}/\rho^+|$ = 1.58),† consistent with a rate-limiting benzylic radical intermediate formation. The primary kinetic isotope effect (k_H/k_D) for the oxidation of ethylbenzene-d_{10} was found to be 8.9 (313 K), in accord with a rate-limiting step involving substantial C–H bond cleavage.[6]

A catalytic quantity of either [Ru^{II}(Por*)(CO)(EtOH)] or [Ru^{VI}(Por*)O_2] can effect hydroxylation of ethylbenzene using 2,6-dichloropyridine *N*-oxide (Cl_2pyNO) as terminal oxidant to produce (*S*)-1-phenylethanol in 62% yield and 72% ee at 25 °C (Table 1, entry 1). More importantly, the catalytic reactions afforded the alcohols in much higher enantioselectivity. Benzene is the solvent of choice, while the use of CH_2Cl_2 led to a lower ee of 62% (Table 1, entry 1). Likewise, other *para*-substituted ethylbenzenes were oxidized to their (*S*)-1-arylethanols in 62–76% ee and 28–72% yields under the ruthenium-catalyzed conditions (entries 2–6). Notably, the catalytic asymmetric 2-ethylnaphthalene oxidation afforded 1-naphthylethanol in 75% ee and 66% yield (Table 1, entry 7). In all cases, only alcohols and ketones were formed, and the combined alcohol and ketone yields have a mass balance of 98% of the amount of substrate consumed.

The effect of *para*-substituents on the chiral ruthenium porphyrin-catalyzed asymmetric hydroxylation of ethylbenzenes has been examined. Both electron-donating and -withdrawing substituents can promote the reaction, and the relative rate constants (log k_{rel}), established by competitive experiments, correlate linearly with the $\sigma_{JJ}^{\cdot}$ and σ_p^+ substituent constants:[5] log k_{rel} = + (0.78 ± 0.05) $\sigma_{JJ}^{\cdot}$ − (0.71 ± 0.02) σ_p^+ (R = 0.99, $|\rho_{JJ}^{\cdot}/\rho^+|$ = 1.1, Fig. 1). A primary kinetic isotope effect (k_H / k_D) of 11.2 (298 K) was found for the catalytic oxidation of ethylbenzene-d_{10}.

It is known that ruthenium porphyrin-catalyzed alkane oxidations using 2,6-dichloropyridine *N*-oxide proceed through a reactive oxoruthenium intermediate.[7] Thus, the high ee observed in the catalytic ethylbenzene hydroxylations would suggest that the chiral 'Ru=O' intermediate should preferentially abstract the *pro-S* hydrogen atom of ethylbenzene, if a hydrogen atom abstraction mechanism is operative.[2a] Because oxidation of benzyl alcohol by reactive oxoruthenium complexes involves a rate-limiting C–H bond cleavage analogous to the hydroxylation of aromatic hydrocarbons,[6d,8] the (*S*)-isomer of racemic 1-phenylethanol is expected to be more readily oxidized to acetophenone, leaving an excess of (*R*)-1-phenylethanol. However, when racemic 1-phenylethanol (1 mmol) was subjected to the ruthenium-catalyzed conditions {[Ru^{II}(Por*)(CO)(EtOH)] (0.5 μmol) and Cl_2pyNO (3 mmol) in C_6H_6}, we found that only a 4% excess of (*R*)-1-phenylethanol and 97% yield of acetophenone were produced at 42% alcohol

Table 1 Enantioselective oxoruthenium mediated benzylic hydroxylations

			$[Ru^{VI}(Por^*)O_2]$[a]			$[Ru^{II}(Por^*)(CO)(EtOH)] + Cl_2pyNO$[e]				
Entry	Substrate	Product	Alcohol yield (%)[b]	Ee (%)	Ketone yield (%)[c]	*t*/h	Conv. (%)	Alcohol yield (%)[f]	Ee (%)	Ketone yield (%)[f] (total turnovers)
1			32 30[d]	45 (*S*) 37 (*S*)[d]	33 34[d]	12 12[g]	13 10[g]	62 67[g]	72 (*S*) 62 (*S*)[g]	37 (112) 32[g]
2			31	51 (*S*)	32	30	20	72	76 (*S*)	24 (224)
3			36	58 (*S*)	30	10	11	60	72 (*S*)	38 (129)
4			35	55 (*S*)	31	18	23	28	74 (*S*)	70 (262)
5			27	41 (*S*)	34	8	14	63	74 (*S*)	36 (164)
6			44	55 (*S*)	26	8	15	65	62 (*S*)	32 (190)
7			32	58 (*S*)	31	20	15	62	75 (*S*)	38 (168)
8			48	9 (*S*)	25	6	54	65	12 (*S*)	34 (551)
9			47	18 (*S*)	24	2	42	60	12 (*S*)	40 (475)

[a] Stoichiometric oxidation: to a degassed CH_2Cl_2 solution (2 cm^3) containing pyrazole (0.05 g) and alkane (1.0 mmol) was added $[Ru^{VI}(Por^*)O_2]$ (30 μmol) under argon; the mixture was then stirred at room temperature for 12 h. The ruthenium complex was removed by filtration through a short alumina column. After addition of 1,4-dichlorobenzene as internal standard, aliquots were analyzed by GLC for product identification and quantification. [b] Yields were based on the ruthenium oxidant used. [c] The ketone yields were calculated based on a stoichiometric ratio of oxidant-to-ketone = 2:1. [d] In C_6H_6. [e] Catalytic oxidations: a mixture of alkane (0.5 mmol), $[Ru^{II}(Por^*)(CO)(EtOH)]$ (0.5 μmol) and Cl_2pyNO (0.55 mmol) was stirred in dry and degassed C_6H_6 (5 cm^3). Aliquots were analyzed by chiral capillary GC equipped with J & W scientific Cyclodex-B or B-PM chiral column for quantification and ee determination. [f] Yields were based on the amount of alkane consumed. [g] In CH_2Cl_2.

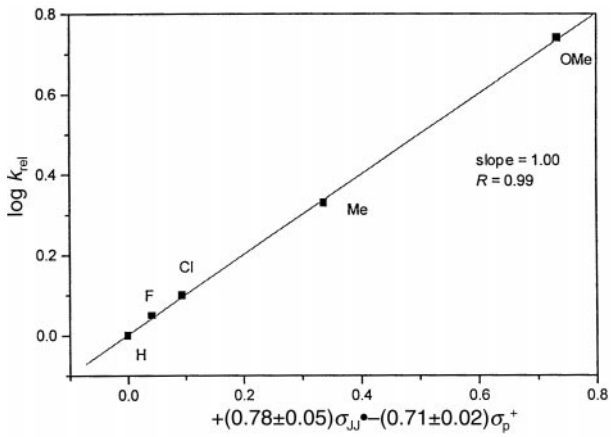
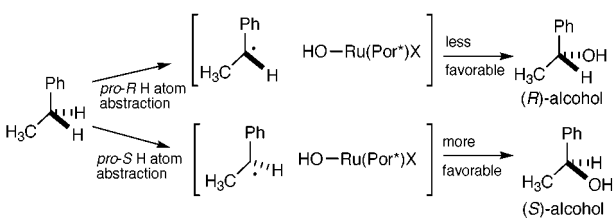


Fig. 1 Dual-parameter Hammett correlation for the ruthenium catalyzed enantioselective hydroxylation of *para*-substituted ethylbenzenes (*p*-YC_6H_4Et; Y = MeO, Me, F, Cl and H).



Scheme 1

consumption. The low degree of kinetic resolution for the catalytic (±)-1-phenylethanol oxidation is in constrast to the high ee of the catalytic ethylbenzene hydroxylation reactions. Assuming an oxygen rebound mechanism (Scheme 1),[9] we postulate that the production of enantioenriched alcohols may arise from the preferential collapse of the benzylic radical on the *pro-S* face *versus* the *pro-R* face at the oxygen atom rebound step, due to the good fit of the substrate into the chiral cavity.

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Notes and references

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