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

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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 Noxide as terminal oxidant; the oxidations proceed *via* a ratelimiting 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[(1S,4R,5R,8S)-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



degassed CH₂Cl₂ solution (containing 2% w/w pyrazole), an excess of ethylbenzene reacted with [Ru^{VI}(Por*)O₂] 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-ethyl-naphthalene, indane and tetrahydronaphthalene by [Ru^{VI-}(Por*)O₂] 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-pyrazolatoruthenium(IV) porphyrin, [Ru^{IV}(Por*)(pz)₂], was isolated in >85% yield at the end of the oxidation.

Under pseudo-first order conditions, the ethylbenzene oxidation by [Ru^{VI}(Por*)O₂] 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 $(7.7 \pm 0.4) \times 10^{-4}$ dm³ 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 σ_{IJ} and σ_p^+ constants⁵ was established: log $k_{rel} = +$ (0.57 ± 0.04) σ_{JJ} – (0.36 ± 0.01) σ_p^+ (R = 0.99; $|\rho_{JJ}/\rho^+| =$ 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 (Cl₂pyNO) 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 CH₂Cl₂ led to a lower ee of 62% (Table 1, entry 1). Likewise, other parasubstituted ethylbenzenes were oxidized to their (S)-1-arylethanols in 62-76% ee and 28-72% yields under the rutheniumcatalyzed 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 σ_{JJ} and σ_{p}^{+} substituent constants:⁵ $\log k_{rel} = + (0.78 \pm 0.05) \sigma_{JJ} - (0.71 \pm 0.02) \sigma_{p}^{+} (R = 0.99,$ $|\rho_{JJ}/\rho^{+}| = 1.1$, Fig. 1). A primary kinetic isotope effect ($k_{\rm H}/k_{\rm D}$) 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 com-plexes 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 {[RuII-(Por*)(CO)(EtOH)] (0.5 µmol) and Cl₂pyNO (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

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

Entry	Substrate	Product	$[\operatorname{Ru}^{\vee I}(\operatorname{Por}^*)O_2]^a$			[RuII(Por*)(CO)(EtOH)] + Cl2pyNOe				
			Alcohol yield (%) ^b	Ee (%)	Ketone yield (%) ^c	<i>t/</i> h	Conv. (%)	Alcohol yield (%) ^f	Ee (%)	Ketone yield (%) ^f (total turnovers)
1		С	32 30 ^d	45 (S) 37 (S) ^d	33 34 ^d	$\frac{12}{12^g}$	13 10 ^g	62 67 ^g	72 (<i>S</i>) 62 (<i>S</i>) ^g	37 (112) 32 ^g
2	Me	Ме-	31	51 (S)	32	30	20	72	76 (<i>S</i>)	24 (224)
3	F	F-	36	58 (S)	30	10	11	60	72 (<i>S</i>)	38 (129)
4	CI-	CI-	35	55 (<i>S</i>)	31	18	23	28	74 (<i>S</i>)	70 (262)
5	Br	Br	27	41 (<i>S</i>)	34	8	14	63	74 (<i>S</i>)	36 (164)
6	MeO	MeO-	44	55 (<i>S</i>)	26	8	15	65	62 (<i>S</i>)	32 (190)
7		ОН	32	58 (S)	31	20	15	62	75 (<i>S</i>)	38 (168)
8	\bigcirc		48	9 (<i>S</i>)	25	6	54	65	12 (<i>S</i>)	34 (551)
9		Ц Ц	47	18 (S)	24	2	42	60	12 (S)	40 (475)

^{*a*} Stoichiometric oxidation: to a degassed CH₂Cl₂ solution (2 cm³) containing pyrazole (0.05 g) and alkane (1.0 mmol) was added [Ru^{VI}(Por^{*})O₂] (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 C₆H₆. ^{*e*} Catalytic oxidations: a mixture of alkane (0.5 mmol), [Ru^{II}(Por^{*})(CO)(EtOH)] (0.5 µmol) and Cl₂pyNO (0.55 mmol) was stirred in dry and degassed C₆H₆ (5 cm³). 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 CH₂Cl₂.



Fig. 1 Dual-parameter Hammett correlation for the ruthenium catalyzed enantioselective hydroxylation of *para*-substituted ethylbenzenes (p-YC₆H₄Et; Y = MeO, Me, F, Cl and H).



consumption. The low degree of kinetic resolution for the catalytic (\pm) -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

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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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