Molecular imprinting with an organometallic transition state analogue

Kurt Polborn and Kay Severin*

Institut für Anorganische Chemie, Ludwig-Maximilians-Universität, D-81377 München, Germany. E-mail: kse@cup.uni-muenchen.de

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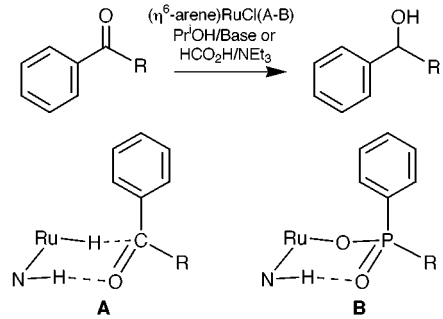
The microenvironment, and thus the activity and selectivity of an immobilised ruthenium catalyst, was modified in a controlled way using a transition state analogue as the catalyst precursor in combination with an imprinting technique.

Molecular recognition between enzymes and substrates, as well as subsequent catalytic transformation, is largely controlled by precisely positioned functional groups within cavities formed by the protein. The implementation of such cavities into artificial, biomimetic catalysts is one of the major challenges in this field. Current approaches are often based on organic host molecules (*e.g.* cyclodextrins) covalently attached to catalytically active groups but the synthetic effort required for the construction of such systems is generally substantial.[1] Alternatively, materials with cavities of molecular dimensions can be obtained by imprinting techniques.[2] Here, polymeric materials are generated in the presence of template molecules, removal of which creates cavities with complementary shapes. Several groups have tried to utilise this technology for the synthesis of catalytically active polymers using transition state analogues as templates but the observed activities were generally modest.[2] Recently, a very nice example of a synthetic esterase which shows a rate enhancement of 10^2 was reported by Wulff *et al.*[3] Nevertheless these values are several orders of magnitude lower than those observed for natural enzymes. Our goal is to produce *highly active* and *selective* enzyme mimics by combining the power of organometallic catalysts with the methodology of molecular imprinting.[4] Preliminary results are reported below.

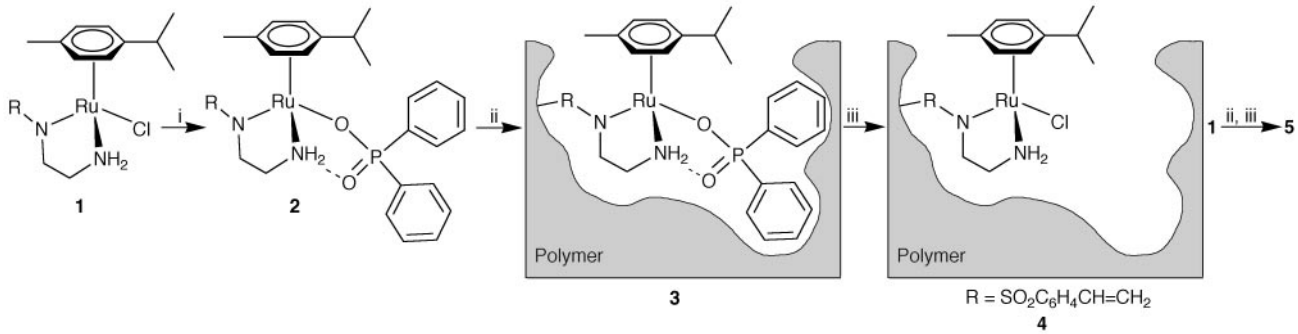
The transfer hydrogenation of aromatic ketones catalysed by ruthenium half-sandwich complexes has recently received much attention since with certain chiral amine-based ligands excellent enantioselectivities were obtained.[5] In these reactions propan-2-ol or formic acid serves as the hydrogen source (Scheme 1). In accordance with all experimental results a six-membered cyclic transition structure **A** was suggested for transformations of this kind.[5b] To imitate this structure with a coordinatively fixed pseudo-substrate we propose phosphinato complexes of the general formula **B** as organometallic transition state analogues (TSA). Our strategy for using such a TSA for the generation of an immobilised catalyst with a form-selective cavity in proximity to the catalytic centre is summarised in Scheme 2. A ruthenium complex **1** with a styrene side chain is synthesised from $[(\eta^6\text{-cymene})RuCl_2]_2$ and the respective amine ligand[6] in the presence of NaOMe (Ru:ligand:base = 1:2:2). The chloride ligand is then substituted with a diphenylphosphinato ligand to give complex **2** in good yield. The anticipated structure with a monodentate phosphinato ligand which shows a hydrogen bond to the amine group of the coligand was confirmed by the results of a single crystal X-ray analysis (Fig. 1).† To the best of our knowledge this complex represents the first structurally characterised organometallic TSA.[7] Complex **2** is copolymerised with ethylene glycol dimethacrylate (Ru:EGDMA = 1:99) in the presence of a porogen (chloroform) to give the highly crosslinked jet porous polymer **3**.[8] To initiate the reaction we employed 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) which allows the polymerisation to be carried out under very mild conditions.[9]

The polymer was ground and wet-sieved to obtain uniform particle sizes of between 25 and 100 μm. The phosphinato ligand was selectively cleaved off using a solution of $BnNEt_3Cl$ in methanol (0.1 M) to give polymer **4** containing a ruthenium chloro complex.[10] The polymer was finally washed with methanol and dried *in vacuo*. To determine the influence of the cavity generated this way we made the polymer **5** using complex **1** instead of the TSA **2** following an otherwise identical protocol.

When tested for their ability to catalyse the reduction of benzophenone both polymers displayed a high activity indicating good incorporation and accessibility of the ruthenium



Scheme 1 Transfer hydrogenation of aromatic ketones catalysed by ruthenium half-sandwich complexes (A–B represents an anionic chelate ligand). The proposed transition structure **A** is mimicked by the phosphinato complex **B**.



Scheme 2 *Reagents and conditions*: i, AgO_2PPh_2, CH_2Cl_2, room temp., 96 h; ii, EGDMA, $CHCl_3$ (Ru:$CHCl_3$:EGDMA = 1:100:99), V-70 (1.5%), 35 °C, 20 h; then 65 °C, 4 h; iii, $[BnNEt_3]Cl$ in MeOH (0.1 M).

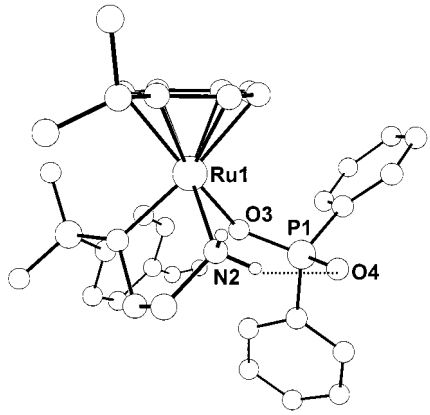


Fig. 1 The molecular structure of **2** in the crystal (most hydrogen atoms are omitted for clarity). Selected bond distances (Å) and angles (°): Ru(1)–N(2) 2.135(3), Ru(1)–O(3) 2.155(3), P(1)–O(4) 1.499(3), P(1)–O(3) 1.518(3), N(2)–O(4) 2.972(3); N(2)–Ru(1)–O(3) 82.81(12), O(4)–P(1)–O(3) 116.5(2), P(1)–O(3)–Ru(1) 131.9(2).

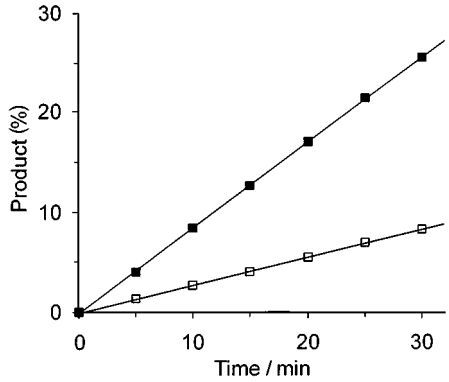


Fig. 2 Product formation as a function of time for reactions carried out at 70 °C with 500 μl of azeotropic HCO_2H/NEt_3, 500 μl of MeCN, 100 μmol of benzophenone and 1 μmol of catalyst **4** (■) or catalyst **5** (□), respectively. To calculate the amount of catalyst, a quantitative incorporation of complex **1** and **2** into the polymer was assumed. Every 5 min a sample of 100 μl was removed from the reaction vessel, quenched with $MeCN/MeCO_2H$ (3:1), filtered and analysed by capillary GC. The data represent averaged values from two independent experiments; the errors are < 0.2 %.

complexes. To quantify the activity the initial turnover frequencies (TOF) were determined. The experiments revealed that the molecularly imprinted polymer (MIP) **4** was significantly more active than polymer **5** [TOF(**4**) = 51.4 h^{-1}, TOF(**5**) = 16.5 h^{-1}, Fig. 2]. The rate enhancement of greater than a factor of three is remarkable considering that both polymers contain the same amount of ruthenium complexes having an identical first coordination sphere.

The MIP-catalyst **4** was also expected to display an increased selectivity for benzophenone, the substrate which was imitated during the polymerisation process by the pseudo-substrate diphenylphosphinate. We therefore performed a series of competition experiments with equimolar amounts of benzophenone and a cosubstrate, chosen to differ in size, shape and reactivity. The selectivity was determined comparing the initial rates of product formation (Table 1). In all cases catalyst **4** showed a substantially higher specificity for benzophenone than the control catalyst **5**. The relative increase in selectivity was slightly larger for aliphatic ketones (entries 1–3) as compared to aromatic ketones (entries 4–6).

These results show that the activity and selectivity of an immobilised catalyst can be enhanced using organometallic TSAs as templates in combination with an imprinting technique. Currently we are trying to apply this methodology to other catalytic transformations including enantioselective reactions. Further results will be reported in due course.

Table 1 Substrate-selectivity of the MIP-catalyst **4** and the control polymer **5**

		Selectivity[b]	
Entry[a]	Cosubstrate	**4**	**5**
1	2-Norbornanone	4.3	2.2
2	2-Adamantanone	4.9	2.5
3	Cyclohexyl methyl ketone	14.2	7.4
4	Acetophenone	2.8	1.8
5	α-Tetralone	3.8	2.2
6	Phenyl isopropyl ketone	20.6	13.8

[a] The reactions were carried out with 50 μmol of benzophenone, 50 μmol of the cosubstrate and 1 μmol of the respective catalyst. [b] The selectivity was calculated by dividing the initial rate of diphenylmethanol formation by the initial rate of product formation for the reduction of the cosubstrate. For norborneol the sum of isomers was used.

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Notes and references

† *Crystal data* for $C_{32}H_{37}N_2O_4PS \cdot 0.5CH_3OH$ **2**: M = 693.76, triclinic, space group $P\bar{1}$, a = 10.387(2), b = 11.762(5), c = 14.362(2) Å, α = 88.05(3), β = 81.10(2), γ = 73.33(3)°, U = 1660.6(8) Å^3, Z = 2, μ = 0.622 mm^{-1}, T = 298 K, 5196 independent reflections, 5439 collected (R_{int} 0.0221). Final R indices [$I > 2\sigma(I)$] R_1 0.0471, wR_2 0.1233. The vinyl group was disordered and two independent positions for the two C-atoms were refined. CCDC 182/1474. See http://www.rsc.org/suppdata/cc/1999/2481/ for crystallographic files in .cif format.

1 A. J. Kirby, *Angew. Chem.*, 1996, **108**, 770; *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707; J. K. M. Sanders, *Chem. Eur. J.*, 1998, **4**, 1378; Y. Murakami, J. Kikuchi, Y. Hisaeda and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721.
2 K. Haupt and K. Mosbach, *Trends Biotech.*, 1998, **16**, 468; G. Wulff, *Angew. Chem.*, 1995, **107**, 1958; *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1812.
3 G. Wulff, T. Groß and R. Schönfeld, *Angew. Chem.*, 1997, **109**, 2050; *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1962.
4 A similar concept was recently proposed by Gagné and coworkers but so far only preliminary results have been presented: B. P. Santora, A. O. Larsen and M. R. Gagné, *Organometallics*, 1998, **17**, 3138.
5 (*a*) M. J. Palmera and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045; (*b*) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97.
6 The ligand was prepared by reaction of *p*-styrenesulfonyl chloride with ethylenediamine in dichloromethane. Complexes **1** and **2**, as well as the ligand, were characterised by ^1H, ^{13}C NMR and elemental analysis.
7 For the production of Diels–Alder catalytic antibodies a cyclopentadienyl iron complex was used as a haptenic group: J. T. Yli-Kauhaluoma, J. A. Ashley, C.-H. Lo, L. Tucker, M. M. Wolfe and K. D. Janda, *J. Am. Chem. Soc.*, 1995, **117**, 7041.
8 The morphology of EGDMA polymers in the presence of various porogens was investigated in detail: B. Sellergren and K. J. Shea, *J. Chromatogr.*, 1993, **635**, 31.
9 So far, 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) has rarely been used as the thermal initiator in molecular imprinting studies although low polymerisation temperatures are generally advantageous.
10 NMR experiments have shown that addition of $[BnNEt_3]Cl$ to a solution of **2** in MeOH leads to a quantitative exchange of the phosphinato ligand.

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