New insights into the enantioselectivity in the hydrogenation of prochiral ketones†

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Received (in Cambridge, UK) 8th November 2006, Accepted 22nd January 2007
First published as an Advance Article on the web 12th March 2007
DOI: 10.1039/b616210j

The high enantioselectivity in the hydrogenation of acetophenone catalysed by *trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap) is explained in terms of the existence of a stable intermediate formed when the reactant enters the catalyst pocket fixing the molecular orientation.

The quest for economic methods for the preparation of enantiomerically pure alcohols continues as a result of the important role these intermediates serve in drug design. One of the most significant developments in this field was the discovery by Noyori and co-workers of highly efficient ruthenium catalysts for enantioselective hydrogenation of ketones.[1]

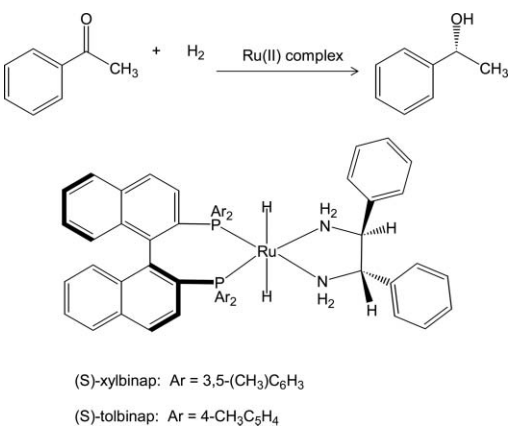
Among the best catalysts for carbonyl hydrogenation are octahedral complexes where Ru(II) is combined with a chiral diphosphine and a chiral diamine,[2] *e.g. trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap) **1** and *trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-tolbinap) **2** in Scheme 1 (dpen = 1,2-diphenylethylenediamine).

The high chemoselectivity of Noyori-type catalysts for the C=O function is based on the non-classical metal–ligand (M–L) bifunctional mechanism.[3] Hydride transfer from the metal center to the carbonyl atom has been considered to occur by a [2 + 2] mechanism: the hydridic Ru–H and protic N–H are simultaneously transferred to the C=O linkage *via* a six-membered pericyclic Transition State (TS). Several theoretical studies on model reactions have suggested that the M–L mechanism is the most favourable pathway.[4]

Concerning the enantioselectivity issue of *trans*-Ru(H)$_2$(diamine)(diphosphine) catalysts, experimental evidence shows that subtle modifications of the substituents at phosphorus can produce very significant changes in the enantioselectivity of the ketone hydrogenation reaction.[5] For example, acetophenone is reduced to phenylethanol with an ee of 99% if the reaction is catalysed by *trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap),[6] and with an ee of 82% if the reaction is catalysed by *trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-tolbinap).[6] However, geometry optimisation of the catalysts **1** and **2** at the Density Functional Theory (DFT) level[7] shows that the electronic nature of the atom directly involved in the reaction [Ru–H, N–H] as well as the structural parameters of the "core" of the catalysts do not differ between **1** and **2**.

The goal of this communication is to provide a qualitative theoretical characterization of the origin of enantioselectivity for the *trans*-Ru(H)$_2$(diphosphine)(diamine) catalysed hydrogenation reactions of prochiral ketones. We reason that the root of these effects may reside not only in changes at the transition state level but also in the "docking" of the substrate into the reactive pocket well before the bond breaking/forming interactions are established.

To investigate this hypothesis, we have applied a constrained geometry optimisation technique to model the approach of a ketone to the catalyst. Starting from separate non interacting reactants, at each stage, the geometry of the system is optimised with respect to the constraint, namely the (Ru–)H···C(=O) distance. The output from one simulation is used to generate the initial conformation of the next. The internuclear parameter (Ru–)H···C(=O) is intimately involved in the reaction as C and H are eventually bonded to one another in the alcohol product. Furthermore, a computational study of the hydrogen transfer acetone–isopropyl alcohol catalysed by a model *trans*-Ru(H)$_2$(diphosphine)(diamine) catalyst has demonstrated that (Ru–)H···C(=O) could be considered as the "pseudo" reaction coordinate for the M–L mechanism.[8]



Scheme 1 Hydrogenation of acetophenone to phenylethanol catalysed by *trans*-Ru(H)$_2$(diphosphine)(diamine) catalysts.

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† Electronic supplementary information (ESI) available: Electronic energy variation of the system [*trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap) + acetophenone] along the [(Ru–)H···C(=O)] internuclear distance for the Q1 appraoch. See DOI: 10.1039/b616210j

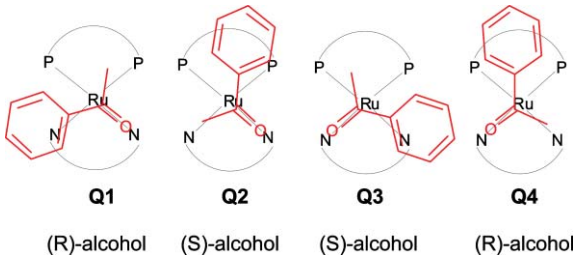

Fig. 1 Definition of the possible reaction paths with the subsequent stereochemical configuration of the alcohol product.

The reduction of acetophenone catalysed by **1** has been considered in this preliminary study. To investigate the selectivity of the reactions, we have computed all different pathways in which the acetophenone can approach the active site (Ru–H, N–H) of the catalyst. These different paths are classified according to the criteria depicted in Fig. 1. When the approach of the ketone is Q1 or Q4 the product is (*R*)-phenylethanol; when the approach is Q2 or Q3 the product is (*S*)-phenylethanol.

Fig. 2 shows the energy variation, calculated using DFT,[7] of the system [**1** + acetophenone] as a function of the internuclear distance (Ru–)H···C(=O) for each possible approach (Q1, Q2, Q3, Q4). Only the electronic energy is included and no account taken of thermal and entropic effects. Energetically, the four alternative pathways display very different trends. It is evident that the Q1 approach is the most energetically favourable for the approach of acetophenone along the (Ru–)H···C(=O) direction and all four pathways display a maximum energy centered at approximately 2 Å. The structure corresponding to the maximum along the "pseudo" reaction coordinate (Ru–)H···C(=O) can be considered as a good approximation to the transition state for the hydrogen transfer acetophenone–phenylethanol reaction (Hydrog. TS). This approximation is supported by a frequency mode analysis on the maximum point along the (Ru–)H···C(=O) distance for the system [**1** + cyclohexyl methyl ketone], which shows that the single negative frequency corresponds to the transfer of the hydride between Ru and C of the carbonyl, and to the hydrogen transfer between N and O.

The energies of the Hydrog. TS like structures relative to that of the separated reactants (considered at 8 Å) are: −5.98 kJ mol^{-1} for Q1, +14.34 kJ mol^{-1} for Q2, +24.31 kJ mol^{-1} for Q3 and +34.61 kJ mol^{-1} for Q4. Since the reaction will proceed mostly through the lowest energy saddle point, it is evident that the approach of the acetophenone in the Q2, Q3 approaches (which give the *S*-alcohol as resulting product) are not kinetically competitive with the Q1 approach (which gives the *R*-alcohol as resulting product). This result is in agreement with the experimental evidence.

The energy profiles in Fig. 2 have an interesting analogy with enzyme-catalysed reactions. In fact, before the hydrogen transfer reaction has taken place, it is likely that there is a "recognition step" in which the ketone is bound to a specific region of the catalyst. From the energy profiles in Fig. 2, we observe that the

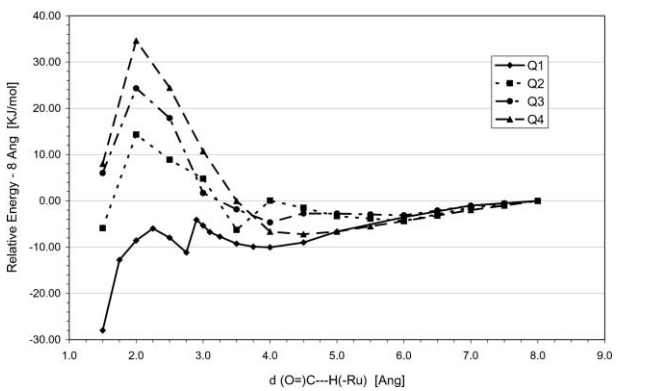

Fig. 2 Electronic energy variation of the system [*trans*-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap) + acetophenone] along the [(Ru–)H···C(=O)] internuclear distance for each possible approach (Q1, Q2, Q3, Q4).

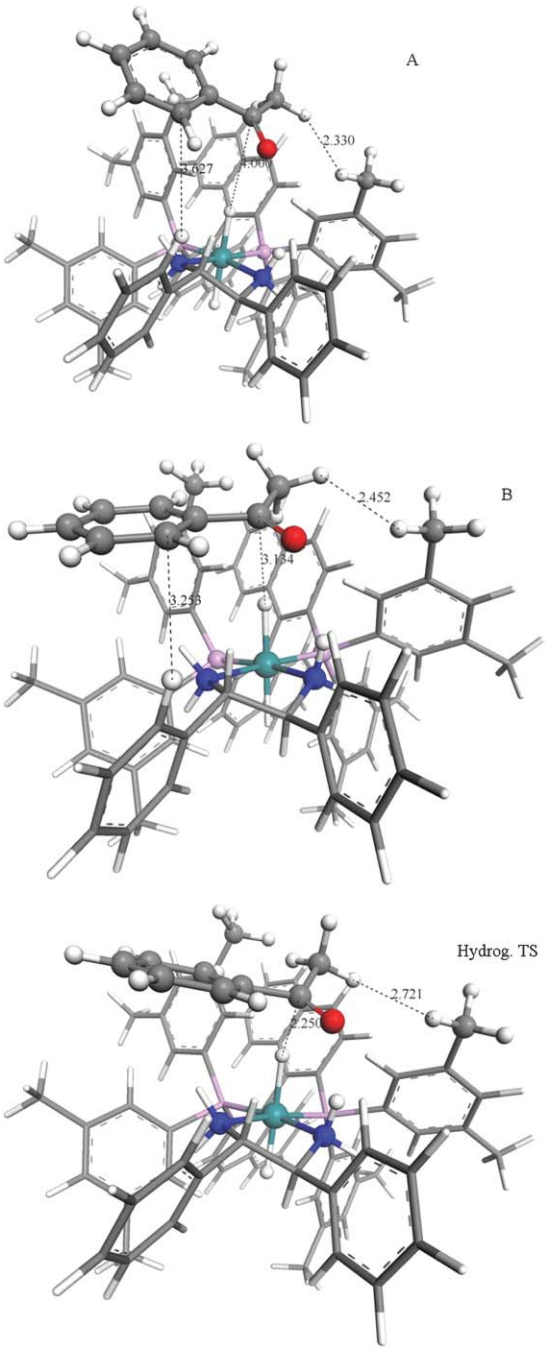

Fig. 3 Minima (**A**, **B**) and transition state like (Hydrog. TS) structures for acetophenone entry in the Q1 approach. Bond lengths reported in Å.

Table 1 Energetic and structural characterisation of the minima (**A**, **B**) and transition-state like (Hydrog. TS) structures associated with the entrance of the acetophenone in the Q1 approach. Energies in kJ mol^{-1}, distances in Å and angles in degrees

			trans-Ru(H)$_2$(*S*,*S*-dpen)(*S*-xylbinap)				Acetophenone				
	ΔE	r(CH$_1$)	r(RuH$_1$)	r(RuH$_2$)	r(RuN)	r(RuP)	r(N–H)	r(CO)	r(OH)	τ	γ
A	−10.14	4.000	1.727	1.726	2.220	2.269	1.023	1.232	3.667	1.09	1.63
B	−15.74	3.134	1.728	1.725	2.230	2.269	1.024	1.234	2.761	0.05	15.40
TS	−5.98	2.250	1.771	1.693	2.209	2.283	1.030	1.247	2.093	18.99	18.93

[a] ΔE: electronic energy difference with respect to the energy at 8 Å separation; τ: out-of-plane bending of the carbonyl carbon; γ: torsional angle of the phenyl group along the C–C(=O) bond.

[catalyst **1**–acetophenone] complex is likely to be a stable intermediate when the ketone approaches as Q1, while the formation of this intermediate seems to be hindered for the Q2, Q3 and Q4 approaches.

In Fig. S1 (ESI†) the variation in the electronic energy with acetophenone entrance in the Q1 orientation is considered in detail. There are two clear energy barriers that the reactant must overcome before arriving at the active site of the catalyst. The minima at 4 Å and at 2.75 Å have been freely optimised. The freely optimised minima (**A** and **B**) and the transition state like structure (Hydrog. TS) for the Q1 pathway are shown in Fig. 3 and described in Table 1.

We observe that in **A**, the ketone is outside the "pocket" made by the bulky groups of the catalyst **1**. From the structure in Fig. 3, we see that the energy barrier along the (Ru–)H···C(=O) coordinate is attributable to the increasing steric interaction of the methyl group of the acetophenone with the methyl group in the *meta* position of the phosphorus aryl substituent. (Note that in TolBINAP the –CH_3 group is only in the *para* position and therefore the steric interaction should be less discriminating between Q1 and Q2, Q3, Q4 approaches). The minimum **B** in Fig. 3 clearly corresponds to the situation where the acetophenone enters into the "pocket". The phenyl group of the acetophenone rotates (in Table 1, γ changes from 1.63° in **A** to 15.40° in **B**) in order to fit into the active site of the catalyst. Table 1 shows that the torsional angle of the phenyl group is the only structural parameter that changes significantly on going from **A** to **B**; in particular the out-of-plane angle τ indicates that the carbonyl carbon still has an sp^2 character. The large stabilisation of the intermediate **B** compared with **A** (and in general with acetophenone and **1** separated) should be connected to: (i) electronic effects, due to the formation of a π–π attractive interaction between the phenyl group of the ketone and the aryl groups of the catalyst which can be established when the acetophenone enters into the "pocket"; (ii) steric effects: the minimum distance between the methyl group of the acetophenone and the methyl group of the aryl group in the *meta* position increases from **A** (2.330 Å) to **B** (2.452 Å).

We finally consider the structure of the Hydrog. TS (see Fig. 3 and Table 1). In particular, we note that the torsional angle in Hydrog. TS (γ = 18.93°) is close to the one observed in the intermediate **B** (γ = 15.40°). This corroborates the hypothesis that the formation of a stable [catalyst **1**–acetophenone] complex is induced by the rearrangement of the phenyl group [rotation along the C–C(=O)] in order to have a conformation closer to the one of the Hydrog. TS. With regards to the other parameters of the Hydrog. TS like structure, the lengthening of the Ru–H_1, N–H, C=O bonds, the shortening of the Ru–H_2, Ru–N, Ru–P bonds, and the change of C hybridisation (τ = 0.05° in **B** to 18.99° in Hydrog. TS) indicate forming and breaking of bonds at the transition state level, in agreement with previous studies on hydrogen transfer ketone–alcohol reactions catalysed by model Ru(H)$_2$(diphosphine) (diamine) catalysts.[8–10] Furthermore, the activation energy between the intermediate **B** and the Hydrog. TS (9.76 kJ mol^{-1}) is in close agreement with those calculated for hydrogen transfer ketone/alcohol reactions catalysed by small model[8] and extended model[9] Ru(H)$_2$(diphosphine)(diamine) catalysts employing the same level of theory used in the present study.

To conclude, the present computational study on the hydrogenation of acetophenone catalysed by *trans*-Ru(H)$_2$(*S*,*S*-dpen)-(*S*-xylbinap) shows that the high ee of the (*R*)-phenylethanol product could be explained in terms of the existence of a stable intermediate along the reaction pathway associated with the (*R*) product (Q1 channel), which is hindered for the competitive Q2, Q3, Q4 pathways.

This work is funded by the DTI "Manufacturing Molecules Initiative" with contributions from AstraZeneca, GlaxoSmithKline, Johnson Matthey and Pfizer. Dr Erika Palin, Prof. Jianliang Xiao and Dr Andreas Danopoulos are thanked for useful discussions.

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