IR spectroscopy as a high-throughput screening-technique for enantioselective hydrogen-transfer catalysts†

Daniëlle G. I. Petra, Joost N. H. Reek, Paul C. J. Kamer, Hans E. Schoemaker and Piet W. N. M. van Leeuwen*

Institute of Molecular Chemistry, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands. E-mail: pwnm@anorg.chem.uva.nl

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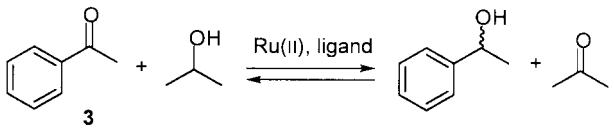
A new high-throughput screening-technique based on IR spectroscopy has been developed for ruthenium catalysed asymmetric transfer-hydrogenation by comparing the reaction rate of the reduction of ketones using (*R*)- *vs.* (*S*)-secondary alcohol as the hydrogen donor.

Combinatorial chemistry and rapid screening techniques are widely recognised as very promising tools in the development of novel catalysts.[1] Recent research has been focussed on two important aspects, *viz.* the parallel synthesis of new catalysts and the development of new rapid screening techniques. Most of the screening methods developed so far are based on UV–VIS, fluorescence spectroscopy and more recently also IR thermography[2] and involve screening of the activity of the catalyst only. The number of screening methods that have been reported involving enantioselective catalysis is rather small.[3–5] Here we report on a novel technique based on IR spectroscopy for the rapid screening of enantioselective transfer-hydrogenation catalysts.

Asymmetric transfer-hydrogenation is an efficient, mild and clean method for the synthesis of chiral alcohols.[6] Only a few examples are known of the enantioselective transfer-hydrogenation of functionalised ketones,[7] dialkyl ketones[8] and imines[9] that finally may lead to useful intermediates for the fine-chemical industries. Therefore, a combinatorial approach to develop efficient chiral transition metal catalysts for the transfer-hydrogenation of different substrates and a method to rapidly screen and optimise these catalysts is pivotal.

In order to test our proposed new rapid screening technique we used a known reaction: the reduction of acetophenone in propan-2-ol (Scheme 1) using (1*R*, 2*S*)-ephedrine **1** on (*R*)-phenylglycinol **2** in combination with ruthenium(II) as the catalyst.[10] The use of **1** gives rise to a high enantioselectivity (89%), whereas the use of **2** as the amino alcohol ligand results in a much lower enantioselectivity (24%) (Table 1).



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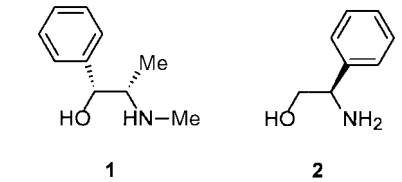
Scheme 1

The carbonyl of the aryl alkyl ketone absorbs at a different wavenumber in the IR than the dialkyl ketone (1682 and 1707 cm-1, respectively) which allows the reaction to be monitored by IR spectroscopy (Fig. 1). We performed a test reaction (reduction of acetophenone using propan-2-ol as the H-donor) that was followed both by IR and gas chromatography (GC) giving identical results. This indicates that IR is a reliable technique (Fig. A, ESI†).

A drawback of the transfer-hydrogenation reaction using an alcohol as the hydrogen source is its reversibility. At the same time, however, this property can be utilised for the kinetic resolution of secondary alcohols.[11] When the reduction of acetophenone occurs with an enantiofacial differentiation of $k_{Si}/k_{Re} \approx 100$, the dehydrogenation of (*R*)-1-phenylethanol is also *ca.* 100 times faster than that of (*S*)-phenylethanol. Here, we use the reversibility of the reaction to set up a rapid screening technique for enantioselective hydrogen transfer catalysts. Instead of monitoring the transfer-hydrogenation reaction we screen on the reverse reaction by determining the difference in dehydrogenation rate using (*R*)- and the (*S*)-1-phenylethanol. The difference in *dehydrogenation rate* between the (*R*)- and the (*S*)-alcohol is a measure of the enantioselectivity of the reaction and can be determined rapidly by IR spectroscopy. Table 1 shows the results of the ruthenium(II)-amino alcohol catalysts, containing ligands **1** and **2**, in the dehydrogenation of (*R*)- and (*S*)-1-phenylethanol (entries 3–6). These reactions were monitored with time by IR spectroscopy and Fig. 2 shows the results of experiments with **1** as ligand whereas Fig. B (ESI†) shows the results for ligand **2**.



1 **2**

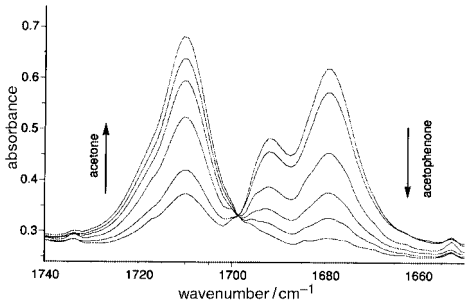


Fig. 1 The hydrogen transfer reaction followed by IR spectroscopy.

The reaction rate for the dehydrogenation of (*R*)-1-phenylethanol is much faster than the dehydrogenation of (*S*)-1-phenylethanol. The initial reaction rate calculated from the IR data is *ca.* 15 times higher for (*R*)-*cf.* (*S*)-1-phenylethanol (k_R/k_S = 15). This is in very good agreement with the k_{Si}/k_{Re} ratio of 17 calculated from the enantioselectivity in the hydrogenation reaction (entries 1 and 2). A smaller difference in dehydrogenation rate is observed for the Ru(II)–phenylglycinol catalyst (Table 1, Fig. B, ESI†). The much smaller k_R/k_S ratio of 2, calculated from the IR data, was again in very good agreement with the k_{Si}/k_{Re} ratio calculated from the enantioselectivity in the hydrogenation reaction.

To use this technique for rapid screening of novel chiral catalysts, a single measurement per reaction mixture should suffice to determine an approximate ee value. Therefore the

† Electronic supplementary information (ESI) available: Fig. A, B and C; IR, GC, UV–VIS data and Experimental details (see text). See http://www.rsc.org/suppdata/cc/b0/b000479k/

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Table 1 Ru(II)-amino alcohol catalysed transfer hydrogenation[a]

Entry	Ligand	Ketone	H-donor	Conv. of ketone (%)[b]	Ee (%) alcohol[c,d]	k_{Si}/k_{Re}[e]	k_R/k_S[f]
1	**1**	**3**	Propan-2-ol	96	89	17	
2	**2**	**3**	Propan-2-ol	94	24	1.6	
3	**1**	**4**	(*R*)-1-Phenylethanol	95	—		15
4	**1**	**4**	(*S*)-1-Phenylethanol	15	—		
5	**2**	**4**	(*R*)-1-Phenylethanol	93	—		2
6	**2**	**4**	(*S*)-1-Phenylethanol	60	—		

[a] Reactions were carried out at room temperature using a 0.1 M ketone solution (33.3 mmol) in alcohol. Substrate : [$RuCl_2$(*p*-cymene)]2 : ligand : Bu^tOK = 400 : 1 : 5: 12.5. [b] Conversions were determined after 40 min by GLC analysis and/or IR spectroscopy. [c] Determined by capillary GLC analysis using a chiral cycloSil-B column. [d] The product configurations are (*R*). [e] k_{Si}/k_{Re} = (100 − *x*)/*x*; *x* = (100 − ee)/2. [f] Determined by IR spectroscopy after 5 min.

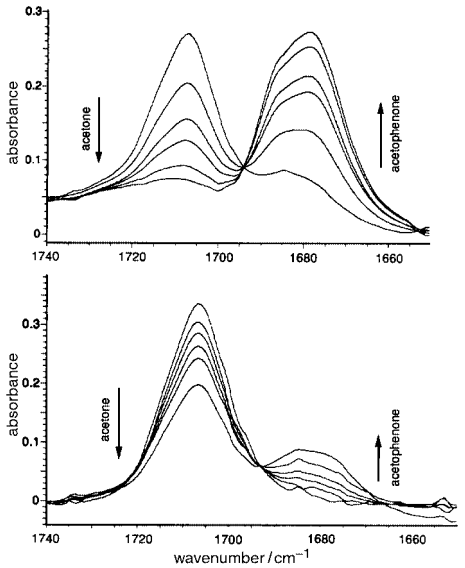

Fig. 2 Dehydrogenation of (*R*)- (top) and (*S*)-1-phenylethanol (bottom) using ligand **1**.

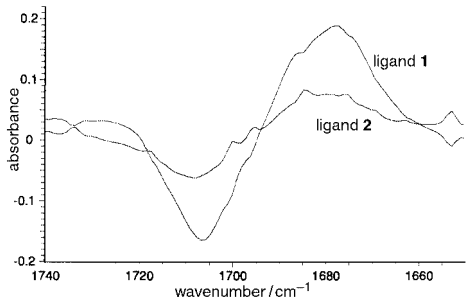

Fig. 3 IR-difference spectra of the dehydrogenation of (*R*)- and (*S*)-1-phenylethanol taken after 30 min reaction time, using **1** and **2** as the ligand.

difference in dehydrogenation rate between (*R*)- and (*S*)-1-phenylethanol was measured after 30 min and visualised as a difference spectrum (Fig. 3). Catalysts that give no chiral induction will give a flat line, whereas active and highly enantioselective catalysts will result in large peaks. Indeed the difference in reaction rate between the oxidation of (*R*)- and (*S*)-1-phenylethanol is much larger when Ru(II)–**1** is used than when Ru(II)–**2** is used as the catalyst. A good estimation of the enantioselectivity can be made simply from two IR measurements. Using an automated set up one could easily measure 100 IR spectra per hour,[12] which makes this rapid screening technique an order of magnitude faster than the known techniques as GC, HPLC and NMR.

Screening catalysts for reduction of dialkyl ketones using propan-2-ol as the donor using the above method is troublesome since the signals of acetone **4** and other dialkyl ketones overlap in the IR spectrum. Therefore acetophenone **3** and benzophenone **5** were used as substrates, using (*R*)- and (*S*)-hexan-2-ol as the H-donor, allowing the reaction to be followed by IR spectroscopy (Fig. C, ESI†). The k_{Si}/k_{Re} ratio calculated from the IR data was between 1 and 2 for both experiments, *i.e.* using ligands **1** and **2**. This is again in full agreement with the hydrogen transfer experiment, since only low ee values were obtained in the transfer-hydrogenation of hexanon using either ligand **1** or **2**.

In conclusion, IR spectroscopy proved to be a very useful technique to determine the performance of enantioselective transfer-hydrogenation catalysts. The reaction can be followed with time by performing it in the IR cell, or samples can be taken from a reaction mixture and subsequently analysed. The former method is especially interesting if non-linear effects are involved, whereas the single point measurements are more suited for rapid screening techniques. The difference in dehydrogenation rate between the (*R*)- and (*S*)-alcohol, *i.e.* the ratio k_R/k_S, serves as a reliable prefatory measure for the enantioselectivity of the transfer-hydrogenation of both aryl alkyl and dialkyl ketones.

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12 IR set-ups equipped with an autosampler that can handle between 100 and 180 samples per hour are nowadays commercially available.