In situ formation of ligand *and* catalyst—application in ruthenium-catalyzed enantioselective reduction of ketones

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Received (in Cambridge, UK) 20th April 2005, Accepted 30th June 2005
First published as an Advance Article on the web 12th July 2005
DOI: 10.1039/b505516d

The direct *in situ* formation of highly efficient ruthenium-catalysts for the asymmetric reduction of ketones was obtained by combining chiral ligand building blocks with a ruthenium precursor.

The use of transition-metal catalysts in asymmetric catalysis often involves tedious preparations of either the catalysts or more frequently, the chiral ligands surrounding the metal.[1] The process of finding a particular catalyst normally goes *via* an iterative examination of a number of chiral ligands. The evaluation of each individual ligand following a conventional catalyst optimization approach has to go through all the steps illustrated in Fig. 1a. In addition, the rate-limiting step in such an investigation is most often the formation of the chiral ligands. If these are made in several reaction steps, of which one might include an asymmetric transformation to incorporate chirality into the ligand core, the ability to construct and evaluate the often huge number of ligands necessary to find the best metal–ligand combination will be very limited. The use of combinatorial techniques creating libraries of ligands significantly speeds up this process but the generation of the ligands is still needed.[2] A more efficient route for the synthesis of a selective catalyst goes *via* the direct formation of the active metal complex simply by mixing together a metal precursor with suitable ligand *building blocks*.[3] In this way, there is no need for tedious ligand preparation and/or catalyst formation. In addition, if the ligand(s) and catalyst are formed in the reaction media used for the catalytic reaction, the whole process can be performed using a simple one-pot setup (Fig. 1b and c).

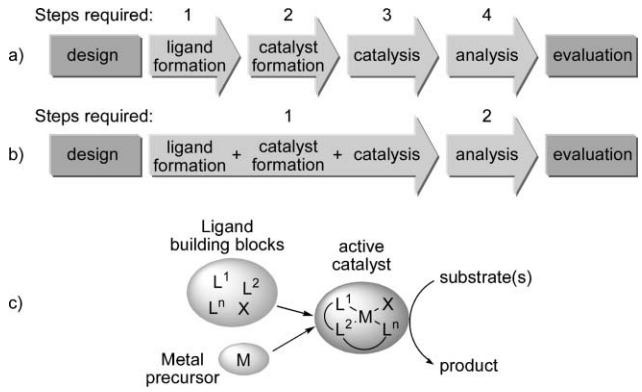

Fig. 1 a) Conventional experimental catalysis setup. b) Efficient one-pot procedure for *in situ* ligand and catalyst formation followed by catalysis. c) Schematic illustration of the process presented in b step 1.

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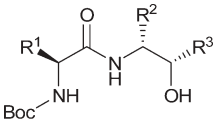
To demonstrate the effectiveness of this novel asymmetric catalysis strategy we decided to apply the concept to a valuable enantioselective reaction: the reduction of prochiral ketones.[4] Herein we present a highly convergent approach for a straightforward formation of efficient ruthenium-catalysts directly used in the asymmetric reduction of ketones under transfer hydrogenation conditions. The metal-catalyzed reduction of ketones with 2-propanol or formic acid as hydrogen source is a mild, safe and attractive route for the formation of secondary alcohols.[5] The combination of Ru(II)(η^6-arene) complexes with chiral amino alcohols or diamine ligands has resulted in some outstanding catalysts for this particular transformation.[6] We have recently reported on a new class of ligands for this particular transformation. We found that pseudo-dipeptides (**1**) when combined with a suitable ruthenium precursor resulted in excellent catalysts for enantioselective ketone reduction.[7] The use of simple amino acids and amino alcohols as building blocks for the formation of these pseudo-dipeptides allowed for the formation of small ligand libraries. Screening the libraries we found that the most efficient and selective catalysts were obtained using either of the alanine-based ligands **1a** (R^1 = CH_3, R^2 = Ph and R^3 = H) or **1b** (R^1 = R^3 = CH_3 and R^2 = H). In reductions of acetophenone using $[RuCl_2(p\text{-cymene})]_2$ and ligands **1a** or **1b** (1 mol%) as catalysts, we obtained the corresponding secondary alcohol in 94 and 96% ee respectively. The preparation of the ligands is a rather straightforward process, where the protected amino acid is coupled with the vicinal amino alcohol using an appropriate coupling reagent. Nevertheless, the synthesis of the ligand is a time-consuming step and we thought that a direct formation of not only the catalyst but also the ligand prior to the reduction reaction would be highly beneficial. The use of typical peptide building blocks in the preparation of ligands for asymmetric catalysis is most advantageous since there are a vast number of suitable activated derivatives available. To examine the possibility of directly generating *both* ligand and catalyst prior to the catalytic reduction reaction we chose to employ the formation of a ruthenium complex based on ligand **1b** as a model system. We initially considered that the metal precursor would be an appropriate template in the formation of the peptide bond. Beck and co-workers have previously shown that Ru(II)(η^6-arene) complexes can catalyze the formation of oligopeptides.[8] Thus, in an initial experiment we combined $[RuCl_2(p\text{-cymene})]_2$, the methyl ester of L-alanine and (*S*)-1-amino-2-propanol with the aim of forming the active reduction catalyst. This resulted, however, in a catalyst of low activity, and performing the reduction of

acetophenone in 2-propanol gave 1-phenylethanol in moderate yield and low ee. In a control experiment employing only the amino alcohol as ligand we obtained similar results, indicating that the active catalyst in the above reaction simply was the ruthenium complex of (*S*)-1-amino-2-propanol.[9] Apparently the peptide was not formed, and we therefore changed the methyl ester used above for the corresponding more reactive 4-nitrophenyl analogue.



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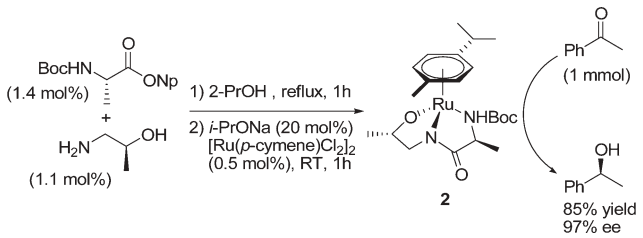
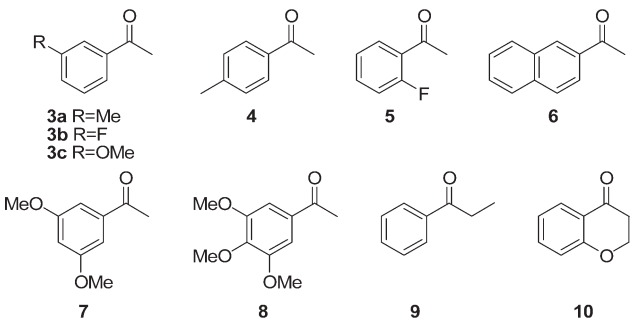
The initial transfer hydrogenation experiments performed using the 4-nitrophenyl ester of Boc-protected L-alanine as one of the ligand building blocks were sluggish and we obtained rather irreproducible results. The outcome of the reduction reaction proved to be sensitive towards the order of reagent addition, and the amount of base (NaOPr^i) used to activate the catalyst. A key difference with this methodology as compared to reactions performed with a preformed ligand is the amount of acidic by-products formed in the *in situ* generation of the dipeptide ligand. The typical quantity of base used in transfer-hydrogenations with this class of ligands is 5 mol%, and performing the reaction with this amount of NaOPr^i led to lower conversion of the starting ketone. Increasing the amount of base to 20 mol% assured the formation of the active catalyst and higher conversion was obtained. In addition, we found that performing the ligand formation using a 1 : 1 stoichiometry between the ligand building blocks led to incomplete formation of dipeptide **1b**. The remaining amino acid did not affect the catalytic reaction,[10] however, the vicinal amino alcohol can act as a ligand for ruthenium in the ketone reduction and this resulted in a diminished enantiomeric excess of the product alcohol.[9] This obstacle was overcome by employing a slight excess of the amino acid. Hence, after some optimizations we found appropriate conditions which allowed for the direct formation of 1-phenylethanol in high yield and with excellent enantiomeric excess. In fact, the ee turned out to be slightly better than what we previously obtained using the preformed and isolated ligand **1b**.[7c] The optimized one-pot procedure for the reduction of acetophenone using the *in situ* formed ligand **1b** *and* catalyst **2** is shown in Scheme 1.[11]

Having established reaction conditions for efficient one-pot generation of the pseudo-dipeptides and ruthenium(II)-catalysts based on these ligands, we employed this novel technology in the formation of a small library of structurally similar catalysts. The evaluation of the results obtained in the reduction of acetophenone showed, not surprisingly, that the catalyst based on ligand **1b** was



Scheme 1 Reduction of acetophenone with *in situ* formed ligand and catalyst.

indeed superior to the other Ru(II)-complexes formed.[12] With these results in hand we selected a series of different ketones (**3–10**) for the evaluation of this novel catalytic reduction approach.† In accordance with the previously reported results, we obtained good conversions and excellent ee's with simple mono-substituted derivatives of acetophenone (Table 1). Interestingly, a significant rate-enhancement was observed using the one-pot *in situ* method. The reactions were in almost all cases over after 60 minutes. This should be compared to the substantially longer reaction times (2–3 h) which we found using the corresponding preformed ligand. The reduction of 3-fluoroacetophenone was remarkably fast under these new conditions (entry 2). In fact, already after 15 minutes this reaction had reached 73% conversion, with a product ee of 97%. As the reaction was allowed to reach the full equilibrium conversion, a small drop in enantioselectivity was observed. The small decrease is most likely due to the reversible reaction conditions involved in transfer hydrogenation reactions when 2-propanol is used as the hydride source. Electron rich substrates like ketones **7**, **8** and **10**, were reduced with excellent selectivity although the latter two in somewhat lower conversion (entries 7, 8 and 10 respectively).



In conclusion, we have introduced a novel concept for the execution of catalytic reactions. The *in situ* formation of the active catalyst by mixing together the chiral ligand with a suitable metal precursor is a common strategy often applied in asymmetric catalysis. However, herein we have demonstrated that it is possible to perform an *in situ* formation of the chiral ligand *and* the catalyst in the same reaction media used for the catalytic reaction. The

Table 1 Enantioselective transfer hydrogenation of different aromatic ketones[a]

Entry	Ketone	*t* (min)	Conv. (%)[b]	ee (%)[c]
1	**3a**	60	83	97 (*S*)
2	**3b**	30	95	96 (*S*)
3	**3c**	60	86	97 (*S*)
4	**4**	60	66	96 (*S*)
5	**5**	60	90	92 (*S*)
6	**6**	60	64	97 (*S*)
7	**7**	60	82	97 (*S*)
8	**8**	60	45	99 (*S*)
9	**9**	60	64	97 (*S*)
10	**10**	60	31	> 99 (*S*)

[a] Reaction conditions: Ketone (1 equiv., 0.2 M in 2-propanol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol% in Ru), *in situ* formed ligand **1b** (1.1 mol%) and *i*-PrONa (20 mol%). All reactions were performed at ambient temperature. [b] Conversion was determined by GLC analysis. The products can be isolated in high yields as reported in ref. 7b and c. [c] Enantiomeric excess and absolute configuration were determined by chiral GC (CP Chirasil DEX CB).

concept was exemplified in the asymmetric reduction of ketones under transfer hydrogenation conditions using a ruthenium-based catalyst. By the careful choice of appropriate ligand building blocks and reaction conditions we obtained a highly efficient and enantioselective catalyst for the reduction of variously substituted aryl alkyl ketones. Under optimized conditions it was possible to form the product alcohols in up to > 99% ee. The simplicity of this method in combination with its excellent performance in the transfer hydrogenation reaction suggests that the concept of forming ligand(s) and the active metal-catalyst in a one-pot procedure prior to the catalytic reaction can be applied to other asymmetric transformations.

We gratefully acknowledge the Swedish Research Council for financial support.

Notes and references

† *General procedure for the in situ formation of ligand* ***1b*** *and ruthenium complex* ***2*** *followed by the direct reduction of ketones presented in Table 1.* Boc-L-Ala-ONp (0.01375 mmol) and (*S*)-1-amino-2-propanol (0.011 mmol) were mixed in 2-propanol (1 mL) and refluxed for 1 hour in a dry Schlenck tube, under inert atmosphere (N_2). The mixture was cooled to ambient temperature before *i*-PrONa (0.20 mmol in 2 mL 2-propanol) was added followed by acetophenone (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol) and additional 2-propanol (2 mL). The reaction mixture was stirred at ambient temperature. Aliquots were taken at different time intervals and quenched with diluted brine (1 mL), extracted with EtOAc (1 mL), passed through a pad of silica and washed with EtOAc. The resulting solution was analyzed by GLC (CP Chirasil DEX CB).

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9 The reduction of acetophenone, catalyzed by $[RuCl_2(p\text{-cymene})]_2$ and (*S*)-1-amino-2-propanol, gave the corresponding secondary alcohol in 83% conversion and 67% ee (*S*-isomer).

10 In control experiments using acetophenone and a catalyst based on either Boc-L-Ala-ONp or Boc-L-Ala and $[RuCl_2(p\text{-cymene})]_2$ we observed no product formation. However, Ru-complexes based on unprotected amino acids are reported to act as catalysts in the transfer hydrogenation of aryl alkyl ketones, see: (*a*) T. Ohta, S.-I. Nakahara, Y. Shigemura, K. Hattori and I. Furukawa, *Chem. Lett.*, 1998, 491–492; (*b*) T. Ohta, S.-I. Nakahara, Y. Shigemura, K. Hattori and I. Furukawa, *Appl. Organomet. Chem.*, 2001, **15**, 699–709; (*c*) A. Katho, D. Carmona, F. Viguri, C. D. Remacha, J. Kovács, F. Joó and L. A. Oro, *J. Organomet. Chem.*, 2000, **593–594**, 299–306.

11 The proposed structure of catalyst **2** is displayed in Scheme 1. Attempts to isolate and analyze this complex have so far been unsuccessful.

12 As an example, the reduction of acetophenone using the *in situ* formed catalyst based on Boc-L-Val-ONp, (*S*)-1-amino-2-propanol and $[RuCl_2(p\text{-cymene})]_2$ gave 1-phenylethanol in merely 29% conversion with 96% ee (*S*-isomer, reaction time 1 h). See Scheme 1 for the result obtained with ligand **1b**.