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Screening method for the evaluation of asymmetric catalysts for the reduction of aliphatic ketones

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ABSTRACT

ATH reductions of aliphatic ketones in water catalyzed by ruthenium coordinated by prolinamide ligands produce alcohols with moderate enantiomeric excesses in most cases. A set of seven aliphatic ketones is proposed for a rapid evaluation of the enantioselectivity of catalysts by one-pot multi-substrates reduction. The screening of a library of prolinamides shows that according to the structure of the ketones different ligands give the best asymmetric inductions.

1. Introduction

New methodologies for preparing chiral compounds are required to meet the criteria of green chemistry, such as the use of safe reagents and solvents, the recyclability of catalysts and the easy separation of reaction products.[1] In such a concern asymmetric transfer hydrogenation (ATH), which allows the easy preparation of enantiomerically enriched alcohols avoiding the use of hydrogen gas under high pressure has been the focus of numerous work.[2] ATH reactions in water were developed more recently.[3] The first system described by Chung involved ruthenium catalysts coordinated by amides derived from (*S*)-proline.[4] Rhodium, iridium or ruthenium associated to different types of ligands such as bidendate diamines,[5] or aminoalcohol ligands[6] proved to be highly enantioselective for the reduction of aromatic ketones in water. Performing reactions in water with the same ligand than in organic solvents led to chiral alcohols with high enantiomeric excesses and many times with higher reaction rates.[3,5b–d,5l] However although the transformation of aromatic ketones into alcohols by asymmetric catalysed reactions is well documented, catalytic reductions of aliphatic ketones with comparable enantioselectivities are rare and in most cases are efficient for only a few substrates. Thus the development of new asymmetric catalysts for the reduction of a wide range of aliphatic ketones with high enantiomeric excesses remains nowadays a challenging goal.

In the course of our previous investigations we have studied asymmetric transfer hydrogenation (ATH) of aromatic ketones in water using a catalyst obtained by the addition of *N*-phenyl-(L)-proline amide ligand **3a** to $[RuCl_2(p\text{-cymene})]_2$ in water under nitrogen.[8] This catalyst could be reused either for the reduction of the same ketone (fifteen reuses) or using a different ketone for each cycle. Seven ketones could thus be successively reduced with the same enantiomeric excess than in individual reactions. Next for improving the enantioselectivity of our catalytic system we studied a method affording a rapid selection of ligands by multi-substrate screening.[9] Such method first developed by Kagan,[10] is based on single-pot reactions with several substrates followed by the measurement of enantiomeric excesses on the mixture of products.[11] We studied water ruthenium-catalyzed reductions of a mixture of six aromatic ketones with a library of ligands and selected the proline amide prepared from (1*R*,2*S*)-*cis*-aminoindanol as the best ligand. The latter afforded also high enantiomeric excesses for the reduction of other aromatic ketones. We now report water ATH reductions of aliphatic ketones and multi-substrate reduction of several aliphatic ketones for a rapid evaluation of ligands.

2. Results

The study of one-pot multi-substrate reductions requires choosing several ketones and checking that enantiomeric excesses

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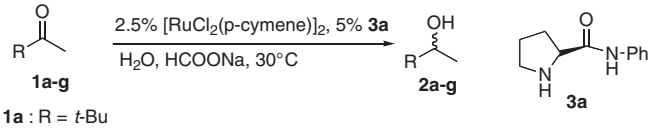
of the corresponding alcohols can be easily measured. A series of seven methyl ketones **1a–g** substituted by alkyl groups with different steric demand was considered. Indeed we found conditions for the evaluation of the enantiomeric excesses of all the corresponding alcohols **2a–g** by a single GC analysis on a chiral column. All pairs of enantiomeric alcohols were separated without overlap of the peaks. The chromatogram of an equimolecular mixture of the seven racemic alcohols is represented in Figure 1. For the reduction of ketones **1a–g** we first investigated the catalyst that we had previously used for the reduction of aromatic ketones or ketoesters,[12] that is, ruthenium coordinated to *N*-phenyl-(L)-prolinamide. The water ATH reduction of each of these ketones has been examined prior to the one-pot reduction of the seven substrates. An aqueous solution of *N*-phenylprolinamide **3a** and ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ was stirred for one hour at room temperature before the addition of sodium formate and ketone (Scheme 1). Reactions were monitored by GC and enantiomeric excesses were determined by GC using a chiral column. Results are indicated in Table 1.

The catalytic system showed satisfying activity for the reduction of ketones **1a–g** since a total conversion in alcohol was observed for all the substrates. Reaction times were dependent on the bulkiness of ketones varying from 17 h for substrates with linear chains to 48 h for ketone **1g** including the bulky adamantyl group. Enantiomeric excesses varied similarly with the steric hindrance close to the ketone functionality. Good asymmetric inductions have been observed for alcohols **2a** and **2g** bearing a tertiary group (70% and 68%, respectively, Table 1, entries 1 and 7). Moderate enantiomeric excess was observed for alcohol **2d** including a cyclohexyl group (entry 4). As might be expected the reduction of linear ketones was less enantioselective (entries 2 and 3). The presence of phenyl substituents (entries 5 and 6) did not improve the asymmetric induction.

Chromatographic analysis on the chiral column of a mixture of the seven racemic alcohols **2a–g** indicated different retention times for all enantiomers. This allowed the measurement of the enantiomeric excesses of the seven alcohols by a single analysis. One-pot reduction of the mixture of ketones **1a–g** using the same catalyst, *N*-phenylprolinamide ligand **3a** and the ruthenium precursor $[RuCl_2(p\text{-cymene})]_2$ was then examined. We checked that enantiomeric excesses of all alcohols had similar values to those obtained in the individual reductions (Table 2, entry 1) as previously observed for the reduction of aromatic ketones. A variety of ligands was investigated for the one-pot reduction of this mixture of ketones with ruthenium to try to improve asymmetric inductions. The different ligands are indicated in Scheme 2.



1a : R = *t*-Bu
1b : R = *n*-C_4H_9
1c : R = 4-methyl-pent-3-enyl
1d : R = cyclohexyl
1e : R = benzyl
1f : R = 2-phenyl-ethyl
1g : R = 1-adamantyl

Scheme 1. Enantioselective reduction of ketones **1a–g** catalyzed by $[RuCl_2(p\text{-cymene})]_2$ coordinated by *N*-phenyl prolinamide **3a**.

Table 1
ATH reduction of ketones catalyzed by ruthenium complex coordinated by *N*-phenylprolinamide **3a**

Entry	Product	t^a (h)	Yield[b] (%)	ee[c] (%)	Conf.[d]
1	**2a**	35	40	70	*R*
2	**2b**	20	54	20	*R*
3	**2c**	18	60	29	*R*
4	**2d**	24	49	42	*R*
5	**2e**	17	80	13	*R*
6	**2f**	17	85	35	*R*
7	**2g**	48	93	68	*R*

[a] Reactions were performed with 2.5% $[RuCl_2(p\text{-cymene})]_2$ and 5% ligand **3a** in water at 30 °C for total conversion.[13]
[b] Isolated yields.
[c] Enantiomeric excesses (%) have been determined by GC using Chiraldex β-PM column.
[d] Configurations were determined by comparison with literature (see Experimental part).

The ligands which led to the more enantioselective catalysts for the reduction of aromatic ketones in our former investigations, **3b**, **3c,** or **3d** were first examined for the one-pot reduction of the mixture of aliphatic ketones **1a–g**. The comparison of *N*-aminoindanol prolinamide **3b** with ligand **3a** indicated a decrease of the enantiomeric excesses obtained from all substrates with the former (Table 2, entry 2). Ligand 2-hydroxyphenyl prolinamide **3c** led to similar values than **3a** for enantiomeric excesses of all alcohols except **2a** and **2g** which were obtained with lower ee (entry 3). Reaction was slower with aminoindanol **3d** than with phenyl prolinamide **3a** and all alcohols were obtained under racemic form except alcohols **2d** and **2e** (40% ee) (entry 4). Hydroxyl substituents on the amido groups of ligands **3b**, **3c**, had no positive effect on enantio-

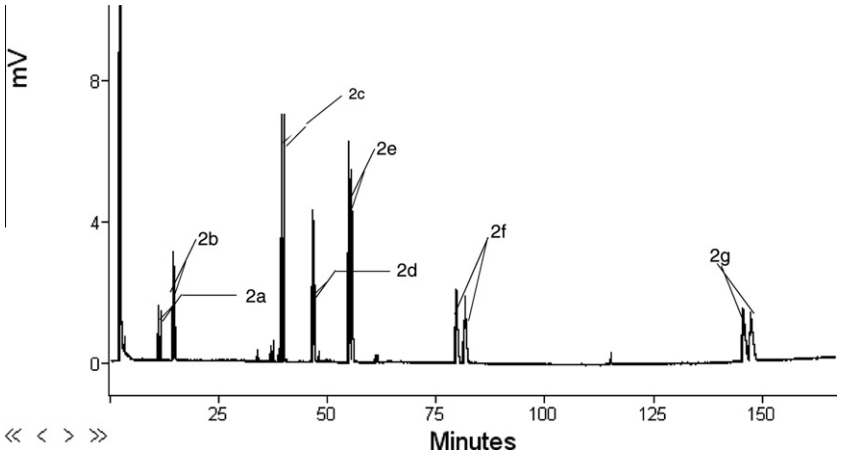


Figure 1. Analysis of the mixture of enantiomers of alcohols **2a–g** by chiral GC (Chiraldex β-PM column (50 m × 0.25 mm), hydrogen as the carrier gas (1.0 mL/min); oven temperature : 50 °C during 30 min, heated to 100 °C (5 °C/min) and maintained at 100 °C during 65 min, heated to 120 °C (5 °C/min) and maintained at 120 °C during 100 min.