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Novel simple and highly modular ligands for efficient asymmetric transfer-hydrogenation of ketones

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Novel simple and highly modular dipeptide-analogue ligands combined with [$RuCl_2$(*p*-cymene)]$_2$ were demonstrated to efficiently catalyze the reduction of ketones under hydrogen transfer conditions with enantioselectivities up to 96%.

The reduction of ketones using catalytic hydrogen-transfer conditions with 2-propanol or formic acid as hydrogen source is a mild and highly attractive route for the formation of secondary alcohols. The combination of Ru(II)(η^6-arene) complexes with chiral amino alcohols or diamine ligands have rendered some excellent catalysts for the asymmetric reduction of ketones.[1] Recently, amides derived from α-amino acids were reported as efficient chiral ligands for the above transformation.[2] In this context, we decided to investigate the effect of a novel class of amido-oxazoline ligands (**1**, Scheme 1) for the asymmetric reduction of ketones. These ligands, recently prepared in our laboratories, were employed in titanium-catalyzed enantioselective addition of diethylzinc to aldehydes.[3] Screening this class of ligands in the reduction of acetophenone using various Ru(II) precursors under transfer hydrogenation conditions (2-propanol) revealed that they performed rather poorly, giving the secondary alcohol in poor yield and low enantioselectivity. An interesting result, however, caught our attention. We discovered that a precursor to the oxazoline ligands gave much better selectivity than the parent ligand structure. The preparation of **1** starts with the formation of a dipeptide analogue from a Boc-protected α-amino acid and a 1,2-amino alcohol (**2**).

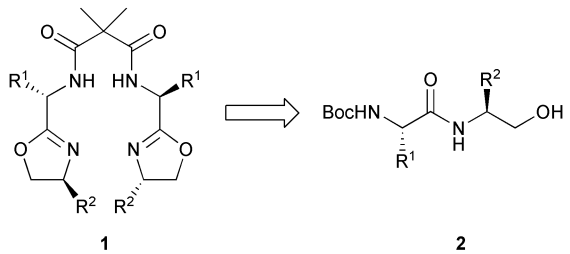
The coupling of *N*-Boc-protected L-valine with (*S*)-valinol generated a ligand (Scheme 1, **2a**, $R^1 = R^2 = i$-Pr) which together with [$RuCl_2$(*p*-cymene)]$_2$ catalyzed the reduction of acetophenone to (*S*)-1-phenylethanol with modest conversion (13% in 2 h) but in good enantioselectivity (93% ee) (Scheme 2). This encouraged us to further investigate other dipeptide analogues (*i.e.* combinations of amino acids and amino alcohols) as ligands for the ruthenium-catalyzed reduction of ketones under hydrogen-transfer conditions. Performing the reduction of acetophenone with a ligand containing (*S*)-phenylglycinol (**2b**) as the amino-alcohol part, resulted in slightly better conversion to (*S*)-1-phenylethanol (41% in 2 h, Table 1, entry 1). The enantioselectivity was in the same range (95% ee) as observed using ligand **2a**. The conversion to the secondary alcohol was, however, dramatically increased by employing the diastereomeric ligand **2c** (entry 2). The enantioselectivity of the reduction was unchanged (95%). Interestingly, the absolute configuration of the product alcohol stayed the same irrespectively of the chiral nature of the amino alcohol. Thus, regardless of the configuration of the amino alcohol, we obtained (*S*)-1-phenylethanol as the major product isomer. These results suggested that the stereocenter present in the amino acid part of the ligand was responsible for the stereochemical outcome of the reaction. To further investigate this, we prepared ligands **2d** and **2e**, starting from the non-natural D-valine. Performing the transfer-hydrogenation of acetophenone using these ligands resulted in high enantiomeric excess of (*R*)-1-phenylethanol (entries 3 and 4). Hence, the absolute configuration of the amino acid did indeed dictate the stereochemistry of the product.

Although the stereoselectivity using either of the ligands **2b**–**e** remained on an equally high level, the enantiomeric ligand pair **2c** and **2d** appear to be the matched cases regarding the reactivity of the formed catalysts. The other pair of ligands (**2b** and **2e**) can thus be considered as the mis-matched cases

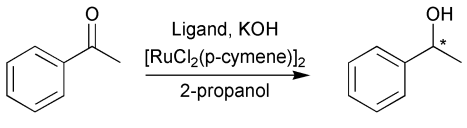
Table 1 Enantioselective reduction of acetophenone using transfer hydrogenation conditions[a]

Entry	Ligand	Conv.[b] (%)	Ee[c] (%)
1	**2b**	41	95 (*S*)
2[d]	**2c**	78	95 (*S*)
3	**2d**	75	95 (*R*)
4	**2e**	32	95 (*R*)
5	**2f**	63	83 (*S*)
6	**2g**	62	83 (*R*)

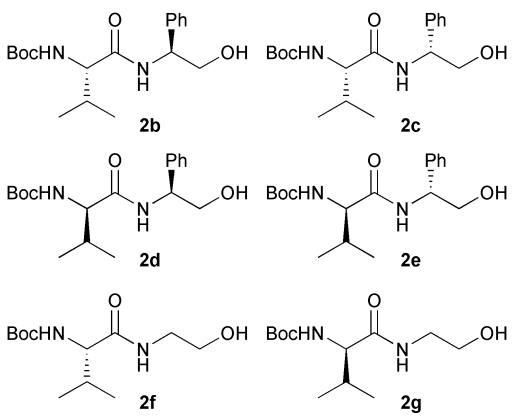
[a] *Reaction conditions*: acetophenone (1 eq., 0.2 M in 2-propanol), [$RuCl_2$(*p*-cymene)]$_2$ (1 mol% in Ru), ligand (3 mol%) and NaOH (5 mol%). All reactions were performed at ambient temperature for 2 h. [b] Conversion was determined by GLC analysis. [c] Enantiomeric excess and absolute configuration were determined by GLC (CP Chirasil DEX CB). [d] Conversion after 5 h; > 96% (94% ee).



Scheme 1



Scheme 2



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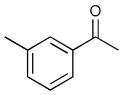
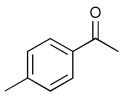
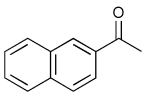
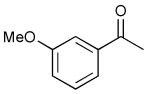
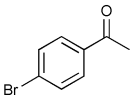
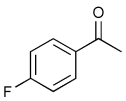
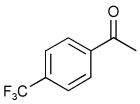
resulting in significantly lower conversions to the secondary alcohol. Replacing the ruthenium source with $[RuCl_2(benzene)]_2$ in the above protocol resulted in complementary conversions and enantioselectivities. The reaction carried out in the presence of ligand **2c** gave 81% conversion to the alcohol and 80 enantiomeric excess ((*S*)-isomer) within 2 h. Employing ligand **2d** resulted in 65% conversion and 81% ee of the (*R*)-isomer. The same trend was observed with the mis-matched pair (*i.e.* comparable low conversions and moderate enantioselectivities). As observed by others, the nature of the η^6-arene ligand is important for the catalytic activity.[4] In our case the ruthenium precursor containing *p*-cymene provides a catalyst which is equally active as its less hindered benzene analogue, although the former precursor transforms into a more stereoselective catalyst. To investigate the chiral influence of the amino alcohol moiety of the ligands, we prepared compounds **2f** and **2g** from *N*-Boc-protected L- and D-valine, respectively, and 2-aminoethanol. Employing these ligands in the above described procedure for the reduction of acetophenone, resulted in good conversion albeit moderate enantioselectivity of the formed alcohol (entries 5 and 6, Table 1). From these results it is evident that the chiral information supplied by the amino alcohol assists in increasing the enantiomeric excess of the product, although the important stereochemical information comes from the amino acid.† This implies that the structure of the active ruthenium catalyst probably involves coordination of the amino acid part of the ligand. The structural investigation is, however, still under consideration. The *N*-Boc protection of the ligand turned out to be crucial for the outcome of the reaction. Removal of the protecting group from ligand **2c** and thereafter performing the reduction of acetophenone resulted in no conversion to the alcohol. From the above results we concluded that compounds **2c**/**2d** are the most efficient ligands for the asymmetric reduction of acetophenone.‡ To investigate the scope of the transfer-hydrogenation a number of aromatic prochiral ketones were subjected to the protocol containing $[RuCl_2(p\text{-cymene})]_2$ and ligand **2c** (Table 2).§ As presented in Table 2, all the examined substrates were transformed to their corresponding secondary alcohols with good to excellent conversion and in high enantioselectivities. Notably, the reduction of the electron-rich 3-methoxyacetophenone proceeded smoothly to yield the corresponding secondary alcohol in high enantiomeric excess (entry 4, Table 2). Aromatic ketones substituted with electron-withdrawing groups, Br, F and CF_3, were reduced in high conversions (entries 5–7). The electrophilic nature of these substrates favor a rapid hydride transfer, a process typically connected with low stereoselectivity. This was, however, not the case since the secondary alcohols were obtained in excellent enantioselectivities.

Table 2 Enantioselective transfer hydrogenation of aromatic ketones[a]

Entry	Substrate	Conv.[b] (%)	E.e.[c] (%)
1		72	92
2		65	95
3		99	96
4		75	95
5		97	95
6		83	94
7		98	94

[a] *Reaction conditions*: substrate:ligand **2c**:[Ru]:NaOH = 100:3:1:5 in 2-propanol ([substrate] = 0.2 M) at ambient temperature. Reaction time: 2 h. [b] Conversion was determined by GLC analysis. [c] Enantiomeric excess and absolute configuration were determined by GLC (CP Chirasil DEX CB).

In conclusion, we have demonstrated that simple dipeptide analogues can be employed as ligands for the ruthenium-catalyzed asymmetric transfer-hydrogenation of ketones. Although the ligands contain more than one center of chirality, the absolute configuration of the amino acid dictates the stereochemical outcome of the reduction. The simplicity and high modularity of the ligand structure, in combination with inexpensive ligand starting material, makes this class of ligands particularily attractive for asymmetric catalytic reactions.

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Notes and references

† This is in direct contrast to the transfer-hydrogen reduction protocols employing chiral 1,2-amino alcohols as ligands. In these systems the asymmetric induction originates from the chirality imposed by the amino alcohol.

‡ It should be noted that active catalyst is formed simply by mixing the ligand and the ruthenium-source at ambient temperature in the presence of NaOH, thus no heating is required.

§ *General experimental procedure* for the reduction of ketones: ligand **2c** (0.03 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol) and NaOH (5 mol%) were dissolved in 2-propanol (5 mL) in a dry Schlenck tube, under inert atmosphere (N_2). The solution was stirred for 15 min and the substrate (1 mmol) added. The reaction mixture was stirred at ambient temperature for 2 h and thereafter quenched by the addition of NH_4Cl (10 mL, sat. aq. solution). An aliquot of the crude product was passed through a pad of silica and washed with Et_2O. The resulting solution was analyzed by GLC (CP Chirasil DEX CB).

1 R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; M. J. Palmer and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045.

2 Amino acids: D. Carmona, F. J. Lahoz, R. Atencio, L. A. Oro, M. Pilar Lamata, F. Viguri, E. San Jose, C. Vega, J. Reyes, F. Joó and Á. Kathó, *Chem. Eur. J.*, 1999, **5**, 1544; A. Kathó, D. Carmona, F. Viguri, C. D. Remacha, J. Kovács, F. Joó and L. A. Oro, *J. Organomet. Chem.*, 2000, **593–594**, 299; T. Ohta, S. Nakahara, Y. Shigemura, K. Hattori and I. Furukawa, *Appl. Organometal. Chem.*, 2001, **15**, 699. Amino acid amides: H. Y. Rhyoo, Y. A. Yoon, H. J. Park and Y. K. Chung, *Tetrahedron Lett.*, 2001, **42**, 5045; H. Y. Rhyoo, H. J. Park and Y. K. Chung, *Chem. Commun.*, 2001, 2064; J. W. Faller and A. R. Lavoie, *Organometallics*, 2001, **20**, 5245.

3 I. M. Pastor and H. Adolfsson, *Tetrahedron Lett.*, 2002, **43**, 1743.

4 J. Takehara, S. Hashiguchi, A. Fujii, S. Inoue, T. Ikariya and R. Noyori, *Chem. Commun.*, 1996, 233.