Diureas as Ligands in Asymmetric Reduction of Ketones

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Although phosphines have received more attention during the last three decades, recent papers have demonstrated the usefulness of nitrogen-containing ligands in asymmetric catalysis. Sharpless[1] and Jacobsen[2] have nicely illustrated the potential uses of such ligands in C−O bond formation. More recently, Pfaltz,[3] Noyori,[4] Mukaiyama,[5] as well as reports from our laboratory[6] have shown that nitrogen-containing ligands can be used in asymmetric reductions with similar or even higher enantioselectivities than those obtained with the best chiral phosphines. The hydride transfer reduction of ketones is one of the reactions where they have been used.[7] We recently reported on the successful utilization of polyureas as ligands and as supports in a heterogeneous reduction of ketones.[8] On the basis of these results, we chose to prepare and evaluate the monomeric analogs of the polymers (i.e., diureas) with the aim of attaining solution phase chemistry. Indeed, considering the diurea function as an efficient ligand for hydride transfer reduction, the possibility to associate different commercially available diisocyanates with diamines allows a rapid preparation of a great number of new ligands.

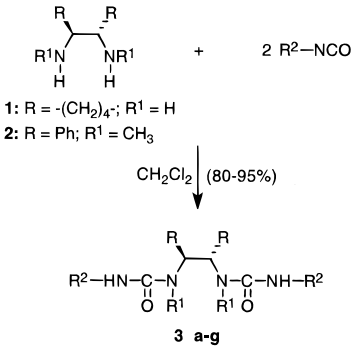
Diureas were prepared by the sequence depicted in Scheme 1. Treatment of diamine **1** or **2** in the presence of an isocyanate (2 equiv) in dichloromethane overnight under argon gave diureas **3** in 80−95% yields.[9]

Asymmetric reductions using **3a** and **3b** as ligands were performed on a series of aromatic ketones (Scheme 2), and the results are collected in Table 1.

Entries 1−4 (Table 1) highlight the utilization of a rhodium−ligand **3a** complex as catalyst. Reduction of acetophenone (Table 1, entry 1) led to a 43% ee of (*R*)-1-phenylethanol. The best result was obtained with propiophenone (Table 1, entry 2), which was reduced in 80% ee. Except for the 2,2-dimethylpropiophenone (Table 1, entry 4), a (*S*,*S*) ligand configuration resulted in (*R*)-alcohols (the hydride addition occurs by the *Si* face of the ketones). This result can be explained by a bulky *tert*-butyl group forcing the substrate to approach the rhodium catalyst by its *Re* face (Scheme 3, **A** and **B**). The use of ligand **3b** in the reduction of propiophenone (Table 1, entry 5) showed a decrease of enantioselectivity from 80 to 37%, although better catalytic efficacy (Table 1, entries 2 and 5) was noted. This lower enantioselectivity may be due to a steric effect of the naphthyl group leading to a weak complexation of rhodium. An attempt using iridium as the metal was explored with propiophenone (Table 1, entry 6) showing that the catalytic iridium complex was both less active and enantioselective.

We also evaluated the diureas synthesized from diamines **1** and **2** and optically pure isocyanates. The use of such diastereoisomeric ligands permitted us to study

Scheme 1



Scheme 2

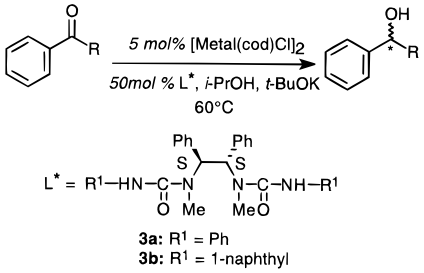


Table 1. Hydride Transfer Reduction of Ketones Using 3a and 3b as Ligands[10]

entry	R	metal	L*	convsn (time, d)	ee,[a] % (confign)
1	Me	Rh	**3a**	97 (7)	43 (*R*)[b]
2	Et	Rh	**3a**	87 (7)	80 (*R*)[b]
3	$(CH_3)_2CH$	Rh	**3a**	93 (11)	74 (*R*)[b]
4	$(CH_3)_3C$	Rh	**3a**	100 (4)	28 (*S*)[c]
5	Et	Rh	**3b**	98 (1)	37 (*R*)
6	Et	Ir	**3a**	97 (9)	57 (*R*)

[a] Enantiomeric excesses were determined by GC (estimated error: ±1%) on a chiral Cydex B SGE column (25m × 0.25 mm ∅). [b] Absolute configurations were determined by GC by comparison with the commercial optically pure products ((*R*)-1-phenylethanol, (*R*)-1-phenyl-1-propanol, (*R*)-2-methyl-1-phenyl-1-propanol: Aldrich). [c] Absolute configuration of (*R*)-2,2-dimethyl-1-phenyl-1-propanol was determined by polarimetry ($[\alpha]^{23}_D$ +30.6° (*c* 4, acetone)).[11]

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(9) **Urea Synthesis.** Typical procedure is described in the supporting information.

(10) **Hydride Transfer Reduction.** Typical procedure is described in the supporting information.

(11) Mc Leod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876−880.

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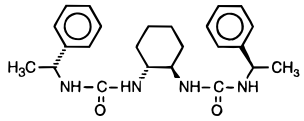
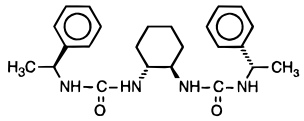
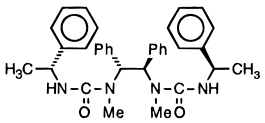
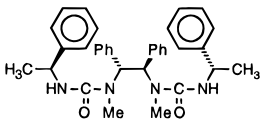
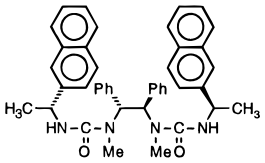
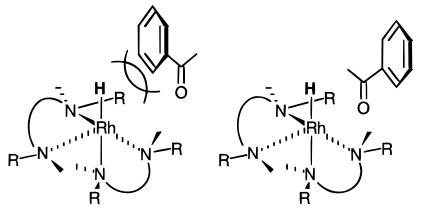
Table 2. Reduction of Propiophenone Using Ligands 3c−g. Match/Mismatch Effect

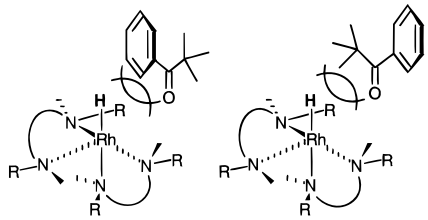
Entry	Diurea*	Inductor Config.	Conv., %	Time, d	ee, %[a] (Config.)
1	 **3c**	(*R*,*R*,*R*,*R*)	7	5	56 (*S*)
2	 **3d**	(*R*,*R*,*S*,*S*)	3	5	45 (*S*)
3	 **3e**	(*R*,*R*,*R*,*R*)	100	14	72 (*S*)
4	 **3f**	(*R*,*R*,*S*,*S*)	98	14	51 (*S*)
5	 **3g**	(*R*,*R*,*R*,*R*)	95	14	68 (*R*)

[a] Ee determined by GC on a chiral column.

Scheme 3



A: Usual prochiral ketone approach



B: Case of the *tert*-butyl phenyl ketone

a match/mismatch double induction effect. Several examples were examined in the reduction of propiophenone by a rhodium catalyst at 60 °C, and the results are illustrated in Table 2.

Initially, we utilized diureas obtained from the commercial (1*R*,2*R*)-1,2-diaminocyclohexane **1** and (*R*)-(+)- or (*S*)-(−)-α-methylbenzyl isocyanate. With the (*R*,*R*,*R*,*R*) diastereoisomer, a 7% conversion in 5 days and 56% ee of (*S*)-1-phenylpropanol (Table 2, entry 1) was observed. Unlike all previous reductions (Table 1), this reaction could take place in the heterogeneous phase, **3c** being insoluble in 2-propanol. The lower activity observed with this type of ligand could be ascribed to a low concentration of active catalyst in solution and/or to a lower activity of the insoluble complex. The use of the (*R*,*R*,*S*,*S*) diastereoisomer led to similar activity with a 11% loss in enantioselectivity, which could be due to a mismatch effect (Table 2, entry 2). Ligands **3e**−**g** derived from *N*,*N*′-dimethyl-1,2-diphenylethanediamine (**2**)[12] and different optically pure diisocyanates were also evaluated. Diastereoisomeric ligands **3e** and **3f** allowed for complete reduction of propiophenone in 2 weeks with a 21% difference in enantioselectivity (Table 2, entries 3 and 4). The last diurea **3g** was made in order to observe the influence on ee of enhanced steric bulk (Table 2, entry 5). No influence of the naphthyl group was apparent as a 68% ee was obtained as compared to 72% with the phenyl group (Table 2, entries 3 and 5).

In summary, we have shown that the urea function could be used as a ligand in asymmetric catalysis. In addition, this new class of ligand is easy and versatile to synthesize. Further experiments are under investigation in order to improve enantiomeric excesses and to determine the scope of applications of diurea ligands.

Supporting Information Available: General experimental procedures, including synthesis and characterization of the diureas **3a**−**g** (14 pages).

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(12) *N*,*N*′-Dimethyl-1,2-diphenylethanediamine (**2**) was synthesized according to: Mangeney, P.; Tejero, T.; Alexakis, A.; Normant, J. F. *Synthesis* **1988**, 255.