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Asymmetric hydrogen transfer reduction of ketones using chiral perfluorinated ligands

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Abstract

Hydrogen transfer reduction of ketones occurs in a mixture of perfluoroalkane/isopropanol using iridium complexes in association with chiral perfluorosalen ligands. An enantioselectivity of up to 60% was obtained.

One of the most studied fields in homogeneous catalysis to date is the exploration of non-traditional reaction media such as water,[1] supercritical carbon dioxide (sc CO_2),[2] ionic liquids[3] and perfluorocarbons.[4] The use of such reaction media could induce new selectivities; it is also an entry to new catalyst immobilization or recovery strategies to facilitate their reuse. One of the most interesting recent advances in this field is based on the use of perfluorocarbons as solvents in organometallic catalysis.

In Fluorous Biphasic Systems (FBSs) recently disclosed by Horvàth and Ràbai,[4] the organometallic catalyst is solubilized in the fluorous phase via the use of perfluorinated ligands; at room temperature, the catalyst is segregated from reagents and products, although the reaction can be performed in a homogeneous manner with all its advantages, in particular, high activities. Thus, performing organometallic catalysis in perfluorosolvent is currently attracting the attention of many researchers. Several catalytic reactions have been achieved in FBSs: the hydrogenation of alkenes,[5–7] the hydroformylation of olefins,[4,8,9] the hydroboration of alkenes,[10,11] the hydrosilylation of ketones,[12] the oligomerization of ethylene,[13] the epoxidation of alkenes,[14–17] the cyclopropanation of alkenes,[18] the oxidation of aldehydes,[14] thioethers[14] and hydrocarbons,[19,20] the Wacker oxidation of alkenes,[21] the cross-coupling palladium of organozinc bromides with aryl iodides[22] as well as the palladium allylic alkylation[23] and Heck reaction.[24]

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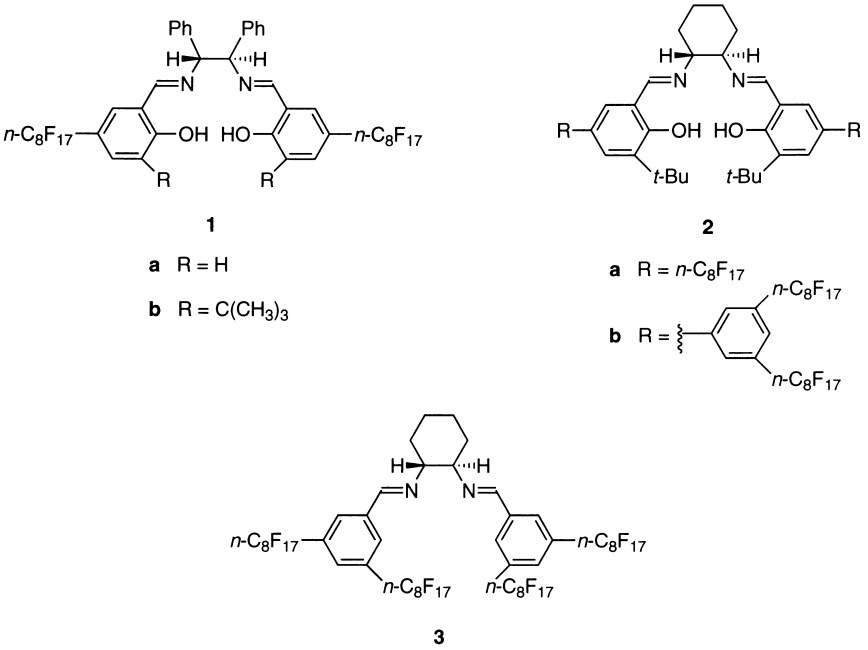
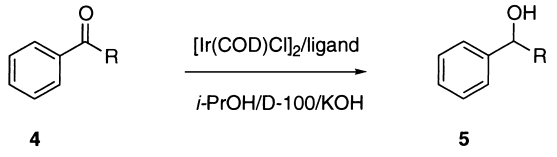
Although asymmetric organometallic catalysis is now a well-used methodology in organic synthesis, there are only two examples of asymmetric organometallic catalysis using perfluoroligands described in the literature. The first concerns the asymmetric epoxidation of alkenes using various chiral salen ligands bearing perfluoro-alkyl substituents in association with manganese;[16,17] enantioselectivities of up to 92% were obtained. The second example of asymmetric organometallic catalysis using perfluoroligands is the iridium-catalyzed hydrogenation of imines in supercritical dioxide, enantioselectivities of up to 81% being obtained.[25]

Lemaire and co-workers showed that aldimines, associated with iridium complexes, were efficient catalysts for the asymmetric reduction of acetophenone via hydrogen transfer: e.e.s up to 22% were obtained in a homogeneous system, while e.e.s up to 72% were achieved using heterogenized dialdimine ligands.[26] In this paper we describe some preliminary results on the use of chiral salen perfluoroligands **1**–**3** in association with iridium complexes in the hydrogen transfer reduction of some ketones.

The ligands **1**–**3** (Scheme 1) were first tested in the asymmetric reduction of acetophenone **4a** (Eq. (1)) with isopropanol as the hydride source in the presence of Galden D-100 (mainly *n*-perfluorooctane, b.p. 102°C) as the perfluorinated solvent. As the catalyst prepared from $[Rh(COD)Cl]_2$ and ligand **1a** or **1b** gave no conversion at all, we focused on the use of the $[Ir(COD)Cl]_2$ complex in association with the various ligands **1a**–**b**, **2a**–**b** and **3** (Table 1).



Scheme 1.

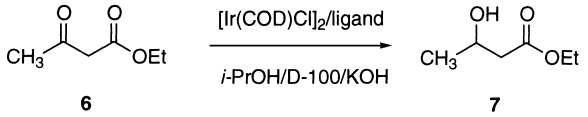


(1)

Table 1
Catalytic hydrogen transfer reduction of various ketones[a]

Entry	Substrate	Ligand	Temperature (°C)	Time (h)	Conversion (%)[b]	e.e. (%) (Config.)[b]
1	**4a**	**1a**	40[c]	24	60	0
2	**4a**	**1b**	45	150	7	18 *(S)*
3	**4a**	**1b**	45[c]	24	91	46 *(S)*
4	**4a**	**1b**	70	24	84	56 *(S)*
5	**4a**	**1b**	70	47	91	56 *(S)*
6	**4a**	**2a**	40[c]	24	46	5 *(S)*
7	**4a**	**2b**	40[c]	24	86	10 *(S)*
8	**4a**	**3**	70	24	93	47 *(S)*
9	**4b**	**1b**	70	24	97	60 *(S)*
10	**4b**	**1b**	70	144	99	57 *(S)*
11	**6**	**1b**	40[c]	24	74	15 *(S)*
12	**6**	**1b**	70	24	14	18 *(S)*

[a] Reaction conditions: 5 mL D-100; 5 mL *i*-PrOH; [substrate] = 5 x 10^{-3} mmol.L^{-1}; [substrate]:[catalyst] = 20; [KOH]:[catalyst] = 5.
[b] Determined by capillary GC on a Cyclodex-B chiral column.
[c] 0.5 mL Et_2O was added.



6 7 (2)

Ligand **1b** showed low activity at 45°C (Table 1, entry 2); performing the reaction at 70°C or adding a small amount of diethyl ether in order to increase the miscibility of the two phases increases the activity, reduction being almost quantitative (Table 1, entries 3–5). Ligands **1a**, **2a** and **2b** gave catalysts with moderate activities (Table 1, entries 1, 6 and 7), although ligand **3**, without hydroxyl function, is as active as ligand **1b** (Table 1, entry 8).

The highest enantioselectivities were obtained using ligand **1b** (e.e. = 56%) (Table 1, entries 4 and 5) or ligand **3** (e.e. = 47%) (Table 1, entry 8). It is to be noted that these values are higher than those obtained by Lemaire et al. using non-perfluorinated aldimines as ligands.[26]

We then used ligand **1b** in the hydrogen transfer reduction of other ketones. Ethyl phenyl ketone **4b**, isopropyl phenyl ketone **4c** and also ethyl acetoacetate **6** (Eq. (2)) were reduced in 60, 57, and 18% enantioselectivity, respectively (Table 1, entries 9–12). In the case of ethyl acetoacetate, addition of a small amount of diethyl ether increases the activity of the catalyst, without any influence on the enantioselectivity.

The test of catalyst recycling was performed with ligand **1b** in the reduction of acetophenone **4a**. The fluorous phase was carefully separated from the reaction mixture at 0°C, and reused in a new reduction. Unfortunately, we noticed a significant loss of activity (29% conversion after 21 h)

and the alcohol was obtained with only 6% e.e. The organic phase was also active in the reduction of acetophenone, since 89% conversion was observed after 21 h, but with no enantioselectivity at all. It seems that the ligand is destroyed under these conditions.

In conclusion, this work shows that hydrogen transfer reduction of ketones can be performed in an asymmetric way in a perfluorosolvent/isopropanol mixture with chiral perfluoroaldimines in association with iridium complexes. The enantioselectivities obtained are higher than those obtained in isopropanol alone using dialdimines ligands.[27] Work is in progress to extend the scope of this asymmetric reduction and to circumvent the problem of the recycling of the catalyst by preparing more robust perfluoroligands.

Acknowledgements

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27. Typical experiment: The catalyst was prepared in a Schlenk tube by stirring $[Ir(COD)Cl]_2$ (14 mg, 0.02 mmol) and the ligand (0.04 mmol) in D-100 (5 mL) at 70°C for 2 h. To this solution cooled to 0°C was added a solution of the substrate (0.4 mmol) and KOH (5.9 mg, 0.1 mmol) in *i*-PrOH (5 mL). The mixture was stirred at 70°C. The conversion and the enantioselectivity were determined by gas chromatography using a capillary Cyclodex-B chiral column.