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# Asymmetric hydrogen transfer reduction of ketones using chiral perfluorinated diimines and diamines

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**Abstract**—Hydrogen transfer reduction of various ketones occurs in a mixture of perfluoroalkane/isopropanol using iridium complexes in association with chiral perfluorinated diimines or diamines as ligands. Enantioselectivity of up to 79% has been obtained. Recycling of the catalyst using chiral perfluorinated diamines as the ligands is possible with no loss of enantioselectivity and very low leaching of iridium in the organic phase. 

## 1. Introduction

The exploration of non-usual media such as water,[1,2] supercritical fluids,[3] and ionic liquids,[4,5] in organic chemistry and particularly in homogeneous organometallic catalysis is arousing increasing interest.[6] The first investigations in these fields were urged by the recycling of the costly and often toxic organometallic catalyst. However the use of such reaction media could be more safety and environment friendly than usual organic solvents. Moreover unusual selectivities could eventually be observed.

One of the most interesting recent advances in this field is based on the use of perfluorocarbons as solvents in organometallic catalysis. Perfluorocarbons have chemical and physical properties (chemical inertness, lack of toxicity, low miscibility with common organic solvents and water, low dielectric constant) that differ quite markedly from those of the corresponding hydrogenated compounds.[7] During the last years, a number of reagents and catalysts bearing appropriate perfluoroalkyl substituents have been used in 'Fluorous Biphasic Systems' ($FBS_S$). In the case of organometallic-catalyzed reaction using the FBS concept, the organometallic catalyst is solubilized in the fluorous phase via the use of perfluorinated ligands. At room temperature, the catalyst is segregated from the reagents and products, while the reaction can be performed in a homogeneous manner with all its advantages, and particularly high activity, the mass-transfer not being the limiting step. Several reviews described the principles and applications of fluorous biphasic systems, in a stoechiometric or a catalytic manner.[8–12] A number of organometallic-catalyzed reactions have been achieved in $FBS_S$: hydrogenation, hydroformylation, hydroboration, oligomerization, epoxidation, cyclopropanation of alkenes, hydrosilylation of ketones, oxidation of aldehydes, thioethers and hydrocarbons, Wacker oxidation of alkenes, palladium cross-coupling of organozinc bromides with aryl iodides as well as palladium allylic alkylation and Heck reaction.

Despite the fact that enantioselective homogeneous catalysis is now one of the most attractive methodology in asymmetric synthesis,[13] only few examples of asymmetric organometallic catalysis using chiral perfluoroligands have been reported. The first one concerned the asymmetric epoxidation of alkenes using manganese complexes of various chiral salen ligands bearing perfluoroalkyl substituents.[14–16] The usefulness of fluorinated ligands is not limited to $FBS_S$; an enantiopure (*R*)-(+)-2-diarylphosphino-2′-alkoxy-1,1′-binaphtyl bearing three fluorous ponytails freely soluble in common organic solvents has been prepared and it was shown to be an efficient ligand in the palladium-catalyzed asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with various methylene active compounds, affording chiral products of up to 87% ee.[17] Leitner and colleagues performed hydrogenation of various imines,[18] α-acetamidoacrylic acid and dimethyl itaconate,[19] as well as hydroformylation of alkenes,[19,20] in supercritical $CO_2$ in the presence of iridium or rhodium complexes associated with chiral fluorous ligands; enantioselectivities of up to 97% ee in hydrogenation and 95% ee in hydroformylation have been obtained.

The catalytic asymmetric transfer hydrogenation of ketones

*Keywords*: asymmetric reduction; iridium; perfluoroligands; perfluorosolvent; recycling.

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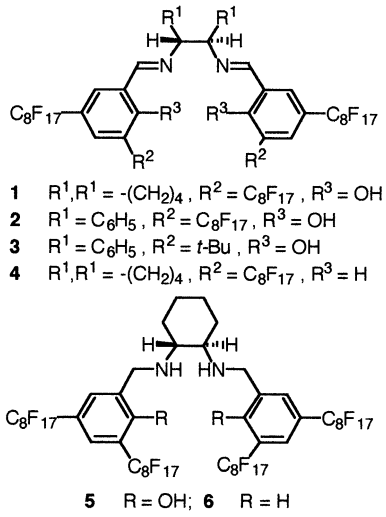
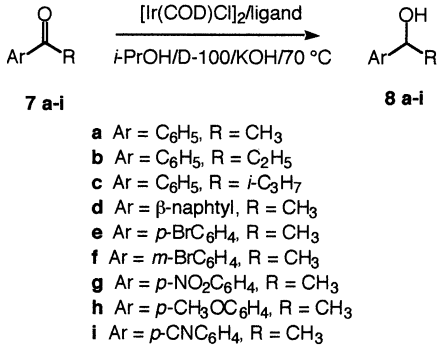



**Scheme 1.** Chiral perfluorinated diimines and diamines.

in the presence of soluble transition metal catalysts was developed several years ago.[21–23] In particular, a ruthenium catalyst bearing Noyori's ligand or mono N-tosylated diphenylethylenediamine gave enantioselectivities up to 99% ee.[24] In the hope of finding efficient recyclable catalysts, we focused our efforts on $FBS_S$. In a recent communication, we have shown that iridium complexes associated with chiral perfluorosalen ligands were effective catalysts in hydrogen transfer reduction of ketones in a mixture perfluoroalkane/isopropanol, enantioselectivity of up to 60% ee being obtained.[25] However an efficient recycling of the catalyst was not possible. Here we describe in detail this study, and moreover the use of chiral perfluorinated diamines in this asymmetric reduction of prochiral ketones, which allowed the recycling of the catalyst.

## 2. Results and discussion

The synthesis of salen ligands **1**–**4** (Scheme 1) was readily accomplished as previously described by condensation of two equivalents of benzaldehyde derivative bearing the perfluoroponytails with the corresponding chiral diamine.[15,16] The chiral perfluorous diamines **5** and **6** were obtained by reduction of the corresponding salen derivatives **1** and **4** with sodium borohydride in methanol for **5** or sodium triacetoxyborohydride in a mixture of acetic acid and FC-113 for **6**, in 15 and 95% yield, respectively; the very low yield obtained in the case of diamine **5** was due to the presence of a number of by-products which ended up in a tedious purification and was not optimized.




**Scheme 2.** Reduction of ketones by hydrogen transfer reaction.

The salen ligands **1**–**4** associated with $[Ir(COD)Cl]_2$ were tested in the asymmetric reduction of acetophenone **7a** with isopropanol as the hydride source (Scheme 2) in the presence of Galden D-100 (mainly *n*-perfluorooctane, bp 102°C) as the perfluorinated solvent (Table 1).

Ligands **1**–**4** showed quite good activities at 70°C, reduction of acetophenone being almost quantitative. The highest enantioselectivities were obtained using ligand **3** (ee=56%) (Table 1, entry 3) and ligand **4** (ee=47%) (Table 1, entry 5). These values are higher than those obtained by Alper et al. and Lemaire and colleagues who used non-perfluorinated aldimines.[26,27] By comparing the enantioselectivities obtained using ligands **3** and **4**, it seems that the presence of an hydroxyl function in the 2,2′-positions of the ligand is not necessary for the obtention of a high ee. Comparison of entries 2 and 3 indicates that the introduction of a bulky group *t*-butyl substituent instead of the $C_8F_{17}$ chain enhanced considerably the enantioselectivity when $R^1$ is a phenyl group.

It is to be noticed that reactions performed at room temperature gave very low conversion; however, reaction runs performed at 45°C in the presence of the catalyst obtained by mixing $[Ir(COD)Cl]_2$ and ligand **3** afforded quantitatively the reduced product with 46% ee when a small amount of diethyl ether was added in order to increase the miscibility of the two phases (Table 1, entry 4). In the case of ligand **3**, prolonged contact among reaction components resulted in increased conversions, but also in decreased enantioselectivities of the product (41% ee after 4 days) (Table 1, entry 3). This variation in enantioselectivity was not unexpected since the hydrogen transfer reaction catalyzed by metal complexes is reversible.[21,22]

We then used ligand **3** in the hydrogen transfer reduction of ethyl and *i*-propyl phenyl ketones **7b** and **7c**. Ethyl phenyl ketone **7b** was reduced quantitatively after 24 h affording the corresponding alcohol with 60% ee (Table 1, entry 6); when the reaction was allowed to proceed for 4 days the alcohol was obtained quantitavely with a little lower enantioselectivity (ee=57%). In the reduction of isopropyl phenyl ketone **7c**, the conversion was quantitative after 6 days, the alcohol being obtained with an enantioselectivity of up to 57% (Table 1, entry 7). However, in this case, the monitoring reaction surprisingly showed that the enantioselectivity increased with increasing conversion (Fig. 1). A possible reason might be the effective competition of the reaction product, the enantiomerically enriched phenyl isopropyl carbinol **7c**, with 2-propanol as a hydrogen donor in the reaction. This could lead to a match-pair with the chiral organometallic complex, and so afforded higher enantioselectivity.

We also studied the influence of the nature of the substituent Ar on the enantioselectivity of the reduction of ketones **7d**–**7i** using **3** and/or **4** as the chiral ligand (Table 1, entries

**Table 1.** Catalytic hydrogen transfer reduction of various ketones **7a**–**7i** using chiral diimines **1**–**4**

| Entry | Substrate | Ligand | Time (h) | Conversion (%)[a] | ee (%) (config.)[a] |
|---|---|---|---|---|---|
| 1 | **7a** | **1** | 0.5 | 94 | 15 (*S*) |
| 2 | **7a** | **2** | 0.5 | 95 | 11 (*S*) |
| 3 | **7a** | **3** | 24 | 84 | 56 (*S*) |
| | | | 48 | 91 | 56 (*S*) |
| | | | 96 | 96 | 41 (*S*) |
| 4 | **7a** | **3**[b] | 24 | 91 | 46 (*S*) |
| 5 | **7a** | **4** | 24 | 93 | 47 (*S*) |
| 6 | **7b** | **3** | 24 | 97 | 60 (*S*) |
| 7 | **7c** | **3** | 144 | 99 | 57 (*S*) |
| 8 | **7d** | **4** | 0.5 | 76 | 41 (*S*) |
| 9 | **7e** | **3** | 24 | 99 | 23 (*S*) |
| 10 | **7e** | **4** | 24 | 99 | 52 (*S*) |
| 11 | **7f** | **3** | 24 | 99 | 4 (*S*) |
| 12 | **7g** | **3** | 24 | 84 | 4 (*S*) |
| 13 | **7 g** | **4** | 24 | 98 | 32 (*S*) |
| 14 | **7 h** | **3** | 24 | 92 | 0 |
| 15 | **7 h** | **4** | 24 | 92 | 11 (*S*) |
| 16 | **7i** | **3** | 24 | 98 | 22 (*S*) |
| 17 | **7i** | **4** | 24 | 94 | 1 (*S*) |

Reaction conditions: 5 mL D-100; 5 mL *i*-PrOH; 70°C; [substrate]=$5\times10^{-3}$ mmol $L^{-1}$; [substrate]/[catalyst]=20; [KOH]/[catalyst]=5.
[a] Determined by capillary GC on a Cyclodex-B chiral column and by comparison with an authentic sample.
[b] 0.5 mL $Et_2O$ was added and the reaction was performed at 45°C.

8–17). All ketones were reduced quantitatively, although quite different enantioselectivities were observed, depending on the nature and the position of the substituent on the phenyl ring, and also the ligand used. The highest enantioselectivities were obtained using *p*-bromophenyl methyl ketone **7e** in the presence of ligand **3** (23% ee, Table 1, entry 9) or ligand **4** (52% ee, Table 1, entry 10). β-Naphtyl methyl ketone **7d** was also reduced to the corresponding alcohol **8d** with 41% ee in the presence of ligand **4** (Table 1, entry 8).

One of the goals of performing organometallic catalysis in a biphasic system organic solvent/perfluorosolvent is the recycling of the catalyst. We firstly used for this recycling the catalyst obtained from $[Ir(COD)Cl]_2$ and ligand **3** (%F=47.2) which gave the highest enantioselectivity in the reduction of acetophenone **7a**. The two phases were separated upon cooling at 0°C after the first reaction cycle was complete, and the fluorous phase containing the catalyst was used in a subsequent hydrogen transfer reaction. Low ketone conversion (37%) was observed after 21 h reaction, with very low enantioselectivity (6% ee), too. On the other hand, when the organic phase was used instead of the perfluorous phase, conversion as high as 89% was observed after 21 h reaction, but with no enantioselectivity at all. This implies that the catalytic species is probably very soluble in the organic phase, due to the very low fluorine content of the ligand (only 47.2%), and also that the ligand was probably hydrolized under our conditions. In order to prove that recycling is viable, we then used ligands **1** and **2** whose fluorine contents are higher: 64.8 and 61.7%, respectively. Indeed, the results summarized in Table 2 show that the perfluorous phase could be successfully reused. As expected, the catalytic system Ir/ligand **1** gave better results due to the high fluorine content of this ligand. For ligand **2**, with a lower fluorine content, the recycling gave a less active catalyst. It should be noted in both cases a significant iridium loss from the fluorous layer: 27 and 36% for the first cycle, 12 and 11% for the second cycle, with ligand **1** and ligand **2**, respectively.

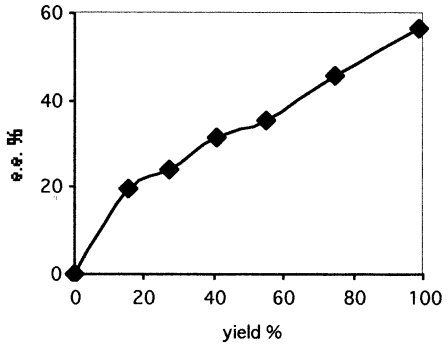



**Figure 1.** Enantioselectivity observed in the reduction of ketone **7c** as a function of the conversion.

As we suspected the perfluorinated diimines ligands to be unstable under our reaction conditions, the two chiral perfluorinated diamines **5** and **6** were also tested in the reduction of acetophenone **7a** in the presence of $[Ir(COD)Cl]_2$ and also $[Ru(p\text{-cymene})Cl_2]_2$ (Table 3). The catalyst obtained by mixing $[Ir(COD)Cl]_2$ and **5** (%F=64.7%) reduced almost quantitatively acetophenone, but with low enantioselectivity (23%) (Table 3, entry 1). Moreover, the iridium leaching in the organic phase was very important (51%), possibly due to the presence of two reactive hydroxyl groups in the ligand. Recycling of the catalyst was attempted, but as a consequence of the pronounced leaching of iridium in the first cycle, the catalytic system showed lower activity and also enantioselectivity (17% ee); iridium leaching in this first recycling was only 4%.

We then used the catalyst $[Ir(COD)Cl]_2$ in association with diamine **6** (%F=65.7) bearing no hydroxyl function. Acetophenone **7a** was reduced after 0.5 h in 92% yield and 69% enantioselectivity (Table 3, entry 3); the measured

**Table 2.** Recycling of the catalyst in the hydrogen transfer of acetophenone **7a** using chiral diimines **1** and **2**

| Entry | Ligand | Cycle | Time (h) | Conversion (%)[a] | ee (%)[a] | Ir leaching (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1** | 1 | 0.5 | 94 | 15 | 27 |
| 2 | | 2 | 0.5 | 95 | 13 | 12 |
| 3 | | 2 | 2 | 98 | 7 | |
| 4 | **2** | 1 | 0.5 | 95 | 11 | 36 |
| 5 | | 2 | 0.5 | 58 | 23 | 11 |
| 6 | | 2 | 2 | 85 | 23 | |
| 7 | | 2 | 19 | 95 | 18 | |

Reaction conditions: 5 mL D-100; 5 mL *i*-PrOH; 70°C; [substrate]=$5\times10^{-3}$ $L^{-1}$; [substrate]/[catalyst]=20; [KOH]/[catalyst]=5.
[a] Determined by capillary GC on a Cyclodex-B chiral column.
[b] Determined by ICP-AES.

**Table 3.** Catalytic hydrogen transfer reduction of acetophenone **7a** using chiral diamines **5** and **6**

| Entry | Catalyst | Cycle | Time (h) | Conversion (%)[a] | ee (%)[a] | Metal leaching (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Ir/**5** | 1 | 5 | 95 | 23 | 51 |
| 2 | | 2 | 25 | 80 | 17 | 4 |
| 3 | Ir/**6** | 1 | 0.5 | 92 | 69 | 4 |
| 4 | | 2 | 0.5 | 90 | 79 | 1 |
| | | | 16 | 97 | 47 | |
| 5 | | 3 | 1 | 86 | 59 | |
| | | | 44 | 98 | 35 | |
| 6 | | 4 | 1 | 43 | 56 | |
| | | | 2 | 69 | 58 | |
| | | | 18 | 96 | 53 | |
| 7 | Ru/**6** | 1 | 2 | 98 | 9 | 46 |
| | | 2 | 24 | 98 | 22 | 8 |

Reaction conditions: 5 mL D-100; 5 mL *i*-PrOH; 70°C; [substrate]=$5\times10^{-3}$ mmol $L^{-1}$; [substrate]/[catalyst]=20; [KOH]/[catalyst]=5.
[a] Determined by capillary GC on a Cyclodex-B chiral column.
[b] Determined by ICP-AES.

iridium leaching was only 4%. The perfluorous solution was separated and used in the reduction of a new sample of acetophenone **7a** to give methylphenyl carbinol **8a** in 90% yield and 79% enantioselectivity after 0.5 h (Table 3, entry 4); the iridium leaching for this first recycling was less than 1%. It is to be noticed that stirring the reaction mixture for 16 h gave higher yield (97%), but lower enantioselectivity (47% ee), as in the case of reactions carried out in the presence of ligand **3**. Two further recyclings of the fluorous layer gave the carbinol with enantioselectivities of up to 59 and 58% ee, respectively (Table 3, entries 5 and 6), although a decrease in activity was observed.

One experiment was also performed using a ruthenium catalyst obtained by mixing $[Ru(p\text{-cymene})Cl_2]_2$ with the perfluorinated diamine **6** (Table 3, entry 7). Although the catalyst showed a very high activity, conversion of acetophenone **7a** being quantitative after 2 h, the obtained enantioselectivy was very low (9%). Moreover an important loss of ruthenium (46%) was observed, which lower the catalytic activity of the recycled layer.

## 3. Conclusion

Hydrogen transfer reduction of ketones can be performed in an asymmetric way in a perfluorosolvent/isopropanol mixture using chiral perfluorinated diimines or diamines in association with iridium complexes. The enantioselectivities are higher than those obtained in isopropanol only using non-perfluorinated ligands: enantioselectivity of up to 79% has been obtained. Iridium complexes associated with perfluorinated dimines ligands did not seem to be very stable, thus compromising the recycling of the catalyst. On the other hand, the use of perfluorinated diamines allowed an easy recycling of the catalyst with no loss of enantioselectivity and only a very low leaching of iridium.

## 4. Experimental

### 4.1. General

Solvents were purified by standard methods and dried if necessary, except perfluorocarbons that were used as received. All commercially available reagents were used as received. The preparation of diimines **1**,[15] **2**,[15] **3**,[16] has already been described. Galden D-100 (mainly perfluorooctane) was a gift from Ausimont. Reactions involving organometallic catalysis were carried out in Schlenk tube under an inert atmosphere. TLC was carried out on silica gel 60 $F_{254}$. Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). Melting points (uncorrected) were determined with a capillary melting point apparatus Büchi SMP-20. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. Gas chromatography was performed on a Perkin Elmer Autosystem XL GC apparatus using a capillary Cyclodex-B chiral column. The metal leaching was determined using ICP-AES (Inductive Coupled Plasma-Atomic Emission Spectrometry). The NMR spectra ($^1H$: 300 MHz, $^{13}C$: 75.4 MHz, $^{19}F$: 282 MHz) were recorded on a Bruker

AC-300 spectrometer with $SiMe_4$, $CDCl_3$, and $CFCl_3$ as the internal standard, respectively.

**4.1.1. *N,N′*-Bis[3,5-bis(*n*-heptadecafluorooctyl)benzylidene]-cyclohexane-(1*R*,2*R*)-1,2-diamine 4.** To a suspension of 3.5-bis(*n*-heptadecafluorooctyl)benzaldehyde[28] (1.88 g, 2.0 mmol) in benzene (100 mL) was added under nitrogen (1*R*,2*R*)-1,2-diaminocyclohexane (0.12 g, 1.0 mmol). The stirred suspension was refluxed for 5 h in a Dean–Stark apparatus and then cooled to room temperature. After evaporation of the solvent under reduced pressure, the residue was crystallized from hexane (40 mL) affording the diimine **4** as a white solid (1.55 g, 79%). $[\alpha]_D^{20}=-59.0$ ($c$=0.5, $Et_2O$); mp=89°C; $^1H$ NMR ($CDCl_3$): $\delta$ 1.54–1.90 (m, 8H), 3.46 (m, 2H), 7.72 (bs, 4H), 7.97 (bs, 2H), 8.19 (s, 2H); $^{19}F$ NMR ($CDCl_3$): $\delta$ −81.3 (t, $J$=10 Hz, 6F), −111.7 (bs, 4F), −121.8 (bs, 4F), −122.3 (bs, 12F), −123.4 (bs, 4F), −126.7 (bs, 4F); $^{13}C$ NMR ($CDCl_3$): $\delta$ 24.6, 32.7, 74.1, 105–120 (m, $C_8F_{17}$), 127.2, 129.7, 130.9, 138.2, 158.1. Anal. Calcd for $C_{52}H_{18}F_{68}N_2$ (1962.63): C, 31.82; H, 0.92; N, 1.43%. Found: C, 32.05; H, 1.06; N, 1.45%.

**4.1.2. *N,N′*-Bis[3,5-bis(*n*-heptadecafluorooctyl)benzyl]-cyclohexane-(1*R*,2*R*)-1,2-diamine 6.** To diimine **1** (0.98 g, 0.5 mmol) dissolved in 1,1,2-trichloro-trifluoroethane (15 mL) was added under nitrogen at room temperature $NaBH(OAc)_3$ (0.30 g, 1.4 mmol) followed by AcOH (0.06 mL). After being stirred for 7 h, aqueous NaOH (1 M, 3 mL) was added. The mixture was stirred for 30 min and extracted with $Et_2O$ (3×10 mL). The combined organic layers were washed with water, brine and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded the diamine **6** as a white solid (0.98 g, 95%). $[\alpha]_D^{20}=-45.5$ ($c$=0.1, $Et_2O$); mp=105 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 0.94–1.10 (m, 2H), 1.16–1.28 (m, 2H), 1.67–1.79 (m, 2H), 2.06–2.29 (m, 4H), 3.91 (d, $J$=14 Hz, 2H), 4.02 (d, $J$=14 Hz, 2H) 7.66 (bs, 2H), 7.76 (bs, 4H); $^{19}F$ NMR ($CDCl_3$): $\delta$ −81.3 (t, $J$=10 Hz, 6F), −111.5 (t, $J$=14 Hz, 4F), −121.7 (bs, 4F), −122.3 (bs, 12F), −123.2 (bs, 4F), −126.6 (bs, 4F). Anal. Calcd for $C_{52}H_{22}F_{68}N_2$ (1966.66): C, 31.76; H, 1.13; N, 1.42%. Found: C, 31.98; H, 1.33; N, 1.41%.

**4.1.3. *N,N′*-Bis[3,5-bis(*n*-heptadecafluorooctyl)-2-hydroxyben-zyl]-cyclohexane-(1*R*,2*R*)-1,2-diamine 5.** To a suspension of salen ligand **1** (0.64 g, 0.32 mmol) in refluxing methanol (50 mL) was added $NaBH_4$ (0.04 g, 1.05 mmol) in four identical portions under nitrogen over 1 h. When the addition was over, the mixture was refluxed for 1 h. After evaporation of the solvent under reduced pressure, the residue was taken up in $Et_2O$ (70 mL), and the ether solution was washed with water, brine and dried over $Na_2SO_4$. The solvent was evaporated affording a residue from which 96 mg of the diamine **5** was isolated by column chromatography (silica gel, $Et_2O$/MeOH 96/4) as a a pale yellow foam (yield 15%). $^1H$ NMR (CDCl3): $\delta$ 1.05–1.31 (m, 4H), 1.69 (bs, 2H), 2.11–2.17 (m, 2H), 2.36–2.49 (m, 2H), 4.04 (d, $J$=14 Hz, 2H), 4.16 (d, $J$=14 Hz, 2H) 7.40 (bs, 2H), 7.61 (bs, 2H); $^{19}F$ NMR ($CDCl_3$): $\delta$ −81.3 (t, $J$=10 Hz, 6F), −111.5 (t, $J$=14 Hz, 4F), −121.8 (bs, 4F), −122.3 (bs, 12F), −123.1 (bs, 4F), −126.6 (bs, 4F).

### 4.2. Typical experiment

The catalyst was prepared in a Schlenk tube by stirring $[Ir(COD)Cl]_2$ (14 mg, 0.02 mmol) or $[Ru(p\text{-cymene})Cl_2]_2$ (12.2 mg, 0.02 mmol) and the perfluorinated ligand (0.04 mmol) in D-100 (5 mL) at 70°C for 3 h. To this solution cooled to room temperature was added a solution of the substrate **7** (0.4 mmol) and KOH (5.7 mg, 0.1 mmol) in *i*-PrOH (5 mL). The mixture was stirred at 70°C. The conversion and the enantiomeric excess were determined by gas chromatography using a capillary Cyclodex-B chiral column. For the recycling, the organic phase was separated from the fluorous phase at 0°C, and a solution of acetophenone and KOH in *i*-PrOH was added.

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