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Synthesis of Recyclable Fluorous Chiral Ligands and Evaluation of Their Catalytic Activity toward Asymmetric Addition of Dimethylzinc to Aldehydes

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Abstract: The asymmetric addition of Me_2Zn to aldehydes is very slow and mostly gives low *ee* values. Previously, we reported the synthesis of a fluorous chiral ligand, (4*R*,5*S*,α′*R*)-2,2-dimethyl-α,α,α′-tris(perfluorooctyl)-2,3-dioxolane-4,5-dimethanol (**1a**), derived from tartarate as a chiral pool. Ligand **1a** showed high activity toward the addition of Me_2Zn to aldehydes with high enantiomeric excess. However, the very high content of fluorine makes **1a** difficult to dissolve in common solvents; hence, much solvent is required, which limits its use. This report describes the modification of **1a** by replacing either the perfluorooctyl groups with shorter perfluoroalkyl ones or the acetone ketal part with cyclohexanone ketal. The perfluorobutyl analogue **1c** is much more soluble than **1a** and shows comparable asymmetric induction toward the addition of Me_2Zn to aldehydes. Furthermore, **1c** has a much lower molecular weight than **1a**. This means that **1c** is used in smaller amounts (weight) than **1a**. The cyclohexanone ketal analogue **1d** is more soluble than **1a** and more easily synthesized owing to its high solubility and ease of crystallization. Ligand **1d** showed much higher asymmetric induction toward cyclohexanecarbaldehyde, a branched aldehyde, than **1a**. Thus, **1a** was modified into ligands with higher performance.

Keywords: aldehydes · asymmetric catalysis · asymmetric synthesis · fluorous ligands · zinc

Introduction

The C–F single bond is the strongest single bond known among organic compounds. Furthermore, the low polarizability and highly electron-attracting properties of fluorine gives the perfluoroalkyl group extraordinary stability and inertness under almost all reaction conditions.[1] Relative to common alkyl chains, perfluoroalkyl chains have superior steric effects: They are bulkier than the corresponding alkyl chains (cross-sections of around 30 and 20 $Å^2$, respectively), have a helical structure rather than the planar "zig-zag" structure of normal alkyl groups, and are more rigid than alkyl chains. Conformational freedom is strongly decreased; consequently, the occurrence of the gauche conformation is limited at equilibrium, which facilitates better stacking and ordering.[2] These differences promote the self-aggregation, phase separation, and exclusion of nonfluorinated molecules. Perfluoroalkyl chains are considerably more hydrophobic than alkyl chains, and have the unique property of being lipophobic (oleophobic) as well. These unique physical and chemical properties facilitated the emergence of "fluorous chemistry".[3] Fluorous techniques have been applied to many chemical transformations, thus replacing standard polymer-supported methods in the production of recyclable and reusable reagents. This is because fluorous tethered reagents are mostly easier to prepare, less labile to reaction conditions, and cheaper than polymer-supported ones. Special attention was given to chiral fluorous reagents because of their exceptionally high cost relative to nonchiral ones. Thus, an array of fluorous chiral catalysts and auxiliaries was reported recently in the literature,[4] although most of these catalysts have fluorous tethers far from their reaction centers.

Interestingly, the electron-withdrawing effect of the perfluoroalkyl group increases the acidity of the hydroxy group

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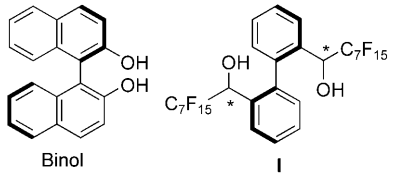
of perfluoroalkyl carbinols by about 10000 times compared with the usual hydroxy group. This exceptionally high acidity dramatically changes the properties of the hydroxy group. In other words, it increases the stability of the hydroxy group towards elimination and/or oxidation. It also enables the hydroxy group to form more-stable complexes with a variety of metals. These properties of the perfluoroalkyl carbinol group make it superior to the hydroxy group of non-fluorinated alkyl compounds involved in chiral ligands. However, owing to the lack of chiral starting materials with these groups, few examples of chiral ligands with chiral perfluoroalkyl carbinols have been synthesized. On the basis of these concepts, we reported the synthesis and application of C_2-dissymmetric fluorous chiral ligand **I**, which can be considered as a binol analogue with perfluoroalkyl carbinol as the coordinating center (Scheme 1).[5]



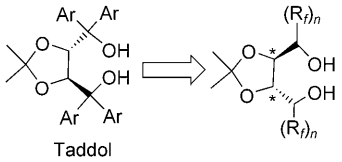
Scheme 1. Binol and our previously reported ligand **I**.

A characteristic of ligand **I**, which can be recycled with fluorous techniques, is the fact that the perfluoroheptyl groups work not only as fluorous tethers but also as activators of coordinating groups. The excellent results obtained by using these ligands encouraged us to challenge another target with the same concept.

On the other hand, among the chiral functionalities, the methyl carbinol moiety is involved in a great number of biologically active natural products.[6] Most of these compounds show potent biological activity. Thus, the construction of this group is of great importance for medicinal chemists. The addition of Me_2Zn to aldehydes might provide a very important methodology for the construction of chiral methyl carbinol moieties, as it involves the simultaneous formation of both a new C–C bond and a new chiral center. However, only a small number of studies on the asymmetric addition of Me_2Zn to aldehydes have been reported,[7] probably owing to the lower reactivity of Me_2Zn than its higher homologues.[8] Only a very limited number of ligands can catalyze this reaction with remarkable activity. Even taddol (Scheme 2), which was chosen to be among the three most effective ligands toward the addition of Et_2Zn to aldehydes, is less effective for the addition of Me_2Zn. Only two examples that utilize taddol for the addition of Me_2Zn to aldehydes have recently been reported in the literature.[9] The protocols used in these examples suffer from complexity, long reaction time, and high catalyst loading.

Taddol, a tartarate-derived ligand, is one of "the privileged chiral ligands"[10] that have a variety of applications in asymmetric synthesis. However, to the best of our knowledge, no fluorous analogue of taddol has yet been synthesized, although a variety of polymer-supported analogues has been reported.[11]

On the basis of this information, we tried to synthesize a new type of ligand containing bulky perfluoroalkyl groups in place of the aryl groups of taddol (Scheme 2). We thought



Scheme 2. Taddol-based design of the new fluorous ligand. R_f = perfluoroalkyl group.

that the new ligands might have better catalytic activity towards Me_2Zn than taddol. We expected this approach to have the following advantages: 1) Perfluoroalkyl groups are sterically large enough to induce high *ee* values, 2) their electronic effect would increase the Lewis acidity of the metal coordinated and hence increase the activity of the complex, and 3) the high fluorine content would facilitate the recycling of the ligand with fluorous techniques.

By applying this concept, we reported the synthesis of the novel fluorous recyclable chiral ligand **1a** (Scheme 3). Ligand **1a** has the advantage of containing the relatively acidic perfluoroalkyl carbinol based on the tartarate chiral backbone. This ligand showed excellent catalytic activity toward the addition not only of Et_2Zn but also of Me_2Zn to aldehydes.[12] However, in spite of its remarkably high catalytic activity, **1a** still has some drawbacks due to its extraordinarily high fluorine content. The high fluorine content of **1a** allows good recyclability but at the same time decreases its solubility in common solvents, and the high molecular weight requires a large amount (weight) of **1a** to be used, although it is highly effective on the molar level. Therefore, we planned to synthesize new ligands with shorter perfluoroalkyl groups and to study the effect of the length of the perfluoroalkyl chains on both activity and recyclability. Furthermore, replacement of the acetone ketal part with cyclo-

Abstract in Japanese:

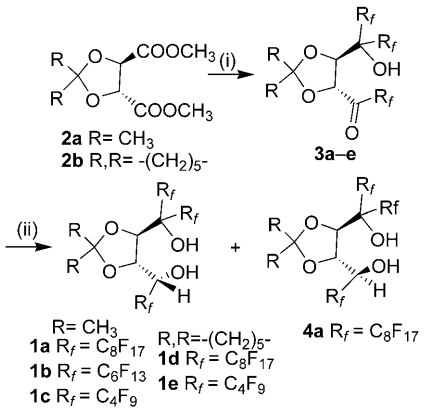
Me_2Znのアルデヒドへの付加は非常に遅く，その効率的不斉付加反応は余り知られていない．我々は既にフルオラスなキラルリガンド，(4*R*,5*S*,α'*R*)-2,2-dimethyl-α,α,α'-tris(perfluorooctyl)-2,3-dioxolane-4,5-dimethanol(**1a**)を合成し，これが長鎖のアルキル亜鉛のみならずMe_2Znの反応でも高い不斉誘導能を示すことを明らかにした．しかし，**1a**はそのフッ素含有量が非常に高いために，フルオラス溶媒を用いなくても回収再利用が可能である反面，通常の溶媒には溶け難く利用面で制約を受ける．また，分子量が非常に大きいためにモル比では少量も，重量的には多量を必要とする点も利用上の欠点であった．本研究で，**1a**のペルフルオロオクチル基をペルフルオロブチル基に換えた**1c**が不斉誘導能を余り下げることなく溶解性に改善が見られ，しかも分子量が小さく使用する質量や溶媒の量を大幅に削減できること，**1a**のアセトンケタール部をシクロヘキサノンケタールにした**1d**では，溶解性の向上のほかに**1a**で若干不斉誘導が低かったシクロヘキサンカルバルデヒドでも高い不斉誘導が認められるなど，そのリガンドの性質に著しい改善が認められた．

hexanone ketal may increase the solubility. In this report, we discuss our recent efforts to synthesize fluorous chiral-ligand analogues of **1a** derived from the tartarate chiral pool with various perfluoroalkyl groups and the effect of various perfluoroalkyl groups on catalytic activity and recyclability.

Results and Discussion

Synthesis and Evaluation of Ligands with Shorter Perfluoroalkyl Groups

First, we tried to replace the bulky perfluorooctyl chains of **1a** with less bulky perfluorohexyl (**1b**) or perfluorobutyl (**1c**) chains. Thus, we treated dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**2a**) with perfluorohexyl or perfluorobutyl Grignard reagents to give keto alcohols **3b** or **3c** along with side products in 63 and 67% yield, respectively (Scheme 3). Interestingly, although we used



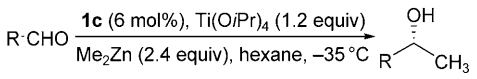
Scheme 3. Synthesis of ligands **1a**–**e**. Reaction conditions: i) R_fMgBr (4 equiv), Et_2O, −65 to −30°C; ii) $CeCl_3{\cdot}7H_2O$ (2 equiv), $NaBH_4$ (4 equiv), MeOH (+Et_2O).

excess Grignard reagents, we obtained only the tris addition products **3**, not the tetrakis addition products, which are the exact taddol analogues.

Reduction was achieved by using a mixture of excess $NaBH_4/CeCl_3$ to produce diols **1b** or **1c** in good yield (63% for both) and with excellent selectivity. The low solubility of ketone **3a** in Et_2O/MeOH at low temperature forced us to carry out the reaction at higher temperature (0°C–RT); hence, the selectivity of the reduction was low, and inactive diastereomer **4a** was obtained as an inseparable side product.[12] In the case of **3b** and **3c**, their good solubility allowed the reaction to proceed in methanol alone at low temperature (−30°C–RT) and hence improved the selectivity of the reaction. Thus, their diastereomers **4b** and **4c** were not formed in detectable amounts.

Next, we examined the effect of the size of the perfluoroalkyl groups on the catalytic activity of the new ligands towards titanium-catalyzed addition of Me_2Zn to aldehydes. We utilized exactly the same procedure previously reported with **1a** except for the amount of solvent. Owing to the difficult availability and the high price of perfluorohexyl iodide, we examined only two examples for the perfluorohexyl analogue **1b**. Ligand **1b** catalyzed the addition reaction effectively with excellent yields and *ee* values comparable to those for **1a**. In the case of benzaldehyde, *ee* values of up to 95% were achieved. For aliphatic aldehydes, **1b** gave 88% *ee* with octanal. The yields in both cases were up to quantitative. This means that shortening of the perfluoroalkyl groups does not affect the catalytic activity of the ligand. To examine this concept carefully, we made a full investigation into the catalytic activity of the perfluorobutyl analogue **1c**. Results obtained for ligand **1c** are summarized in Table 1.

Table 1. Catalytic activity of **1c** toward Me_2Zn addition to aldehydes.



Entry	R	*t* [h]	Yield [%][a]	*ee* [%][b]
1	C_6H_5	3	99	95
2	*p*-CH_3O-C_6H_4	3	92	90
3	*p*-CF_3-C_6H_4	3	97	92
4	2-naphthyl	2	98	94
5	*o*-F-C_6H_4	3	98	88
6	2-furyl	1	99	98
7	C_7H_{15}	2	98	87[c]
8	Ph-CH_2-CH_2	6	85	85
9	C_6H_{11}	8	90	87[c]
10	Ph-CH=CH	3	92	90
11	heptyn-1-yl	2	98	92

[a] Yield of isolated product. [b] Determined by HPLC with an OD-H column. All products were of *R* configuration. Absolute configurations were established by the signs of the optical rotation reported. [c] Determined by chiral HPLC analysis of the dinitrobenzoyl ester.

We note here that the molecular weights of **1a**, **1b**, and **1c** are 1416, 1116, and 816, respectively. The molecular weight of **1c** is only 57.6% of **1a**, and **1b** is 21.1% lighter than **1a**. This means that the newly formed ligands could be used effectively in lesser amounts (weight) than **1a**. Another important point is the higher solubility of the new ligands relative to the parent. Ligand **1a** has low solubility in most organic solvents such as toluene, alcohols, and THF. It is partially soluble in hydrocarbons such as hexane, but freely soluble only in Et_2O and fluorous solvents. Although this poor solubility of **1a** makes it an excellent recyclable ligand, it widely limits its further application. On the other hand, **1c** and, to a less extent, **1b** have better solubility in $CHCl_3$, toluene, alcohols, and hydrocarbons. The higher solubility of **1b** and **1c** would allow us to expand the application of this type of ligand and to decrease the amount of solvent used for reactions catalyzed by them.

For aromatic aldehydes, **1c** gave excellent yields and *ee* values. Yields were above 90% for all aromatic aldehydes and almost quantitative in some cases (Table 1, entries 1 and 4–6). The *ee* values were also above 90%, except in the case of *o*-fluorobenzaldehyde (Table 1, entry 5). Furfural, a heter-

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ocyclic aldehyde, gave 98% *ee*. For aliphatic aldehydes, the yields were also excellent, except for hydrocinnamaldehyde (Table 1, entry 8). The *ee* values were also very good to excellent. An excellent result was obtained with cyclohexanecarbaldehyde (Table 1, entry 10), with up to 90% *ee*. A comparison of the catalytic activities of **1a** and **1c** should be carried out to examine the effect of shortening of the perfluoroalkyl group on activity. The difference between the two ligands can best be exemplified by comparing the *ee* values of the products obtained by both ligands (Figure 1).

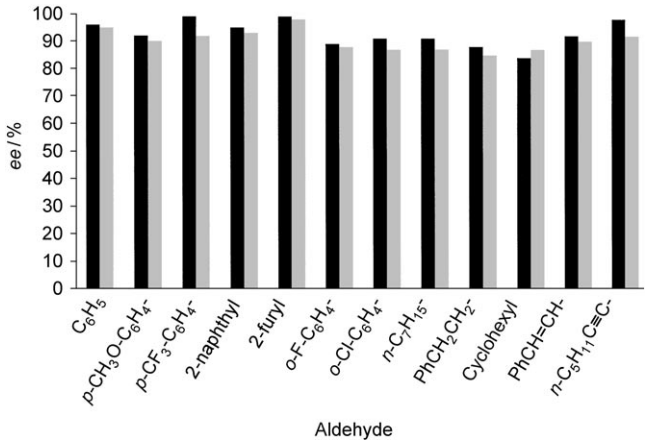


Figure 1. Comparison of the catalytic activities of perfluorooctyl-derived ligand **1a** and the perfluorobutyl-derived ligand **1c**. Black = **1a**, gray = **1c**.

From the graph, we conclude that both ligands have very similar activities toward most aldehydes, but the more bulky ligand **1a** showed slightly higher *ee* values, except for cyclohexanecarbaldehyde, which gave a better yield and *ee* value with **1c**, although the reaction time was extended. This means that shortening of the perfluoroalkyl group affected neither the catalytic activity nor the ability of asymmetric induction of this class of ligands. Importantly, the better solubility of **1c** allowed us to lower the amount of solvent used for the addition of Me_2Zn to aldehydes. For this reason, the reaction with **1c** decreased the amount of solvent used (hexane) to half. The amount of solvent can be further decreased to only 25% of the original amount used in case of **1a** without any effect on yield or *ee*.[13]

A decrease in the molecular weight of the ligand and the amount of solvent could strongly improve the economy of this reaction. However, another important factor should be taken into consideration: the effect of shortening the perfluoroalkyl group on the recyclability of the ligand. Thus, the good solubility of **1c** limited its recyclability slightly relative to **1a**. Whereas **1a** could be recycled without the use of fluorous extraction, it was necessary to use a fluorous solvent for the recycling of **1c**. For the latter, partitioning between perfluorohexane and CH_2Cl_2 (which was chosen because the ligand showed the lowest solubility in it) was used. The results of recycling are shown in Table 2.

Table 2. Recycling of **1c**.

Cycle	Ligand recovered [%]	Yield [%][a]	*ee* [%][b]
1	–	100	95
2	90	100	91
3	80	100	87
4	80	96	81

[a] Yield determined by GC. [b] Determined by HPLC with an OD-H column.

The recovered ligand was used in the next recycling step without any purification. The amount of ligand recovered decreased consistently throughout the recycling steps; this was attributed to its escape into the organic phase, which was confirmed by GC. For each cycle, the yield was not affected; however, the *ee* values declined slightly, which might be due to the decrease in ligand loading. When the amount of substrate was decreased to keep the substrate/ligand ratio constant, the decrease in *ee* was negligible. The recycling of ligand **1c** was not as effective as **1a** owing to the better solubility of **1c** in organic solvents. For further study on the effect of perfluoroalkyl chains on the activity of the ligands, we tried to prepare the trifluoromethyl analogue. Unfortunately, we could not obtain it owing to instability of the trifluoromethyl Grignard reagent.

Synthesis and Evaluation of Ligands with a Cyclohexanone Ketal Moiety

Next, we tried to replace the acetone ketal group with cyclohexanone. We thought that an increase in the size of the aliphatic part may improve the solubility of the ligand in common organic solvents and may also lead to better performance due to the change in bond angles, which leads to a different architecture of the complex.[14]

We utilized the same general procedure for the synthesis of these ligands (Scheme 3). Instead of acetone ketal **2a**, we started with the cyclohexanone ketal of dimethyl tartarate, **2b**, which was prepared according to the literature.[14] Ketal **2b** was treated with excess perfluoroalkyl magnesium bromide to afford keto alcohol **3d** in 60% yield or **3e**. Reduction of **3d** or **3e** by $NaBH_4/CeCl_3$ afforded the products **1d** or **1e**, respectively, in pure form after crystallization. Ligand **1d** was crystallized from $CHCl_3$ in moderate yield (65%). Ligand **1e** was difficult to crystallize because of its relatively high solubility in most of the solvents, so we could obtain it only in poor yield (10% over 2 steps). Although some byproducts were observed by GC during the reduction of **3d** or **3e**, we could not isolate any of them in pure form for further identification.

The catalytic activity of the new ligand was examined for the addition of Me_2Zn to aldehydes. Ligand **1d** was tested on a variety of aldehydes to evaluate its catalytic activity and generality. The results are shown in Table 3.

Benzaldehyde gave excellent yield and *ee* similar to that obtained with **14a** (Table 3, entry 1). More-bulky aldehydes such as 2-naphthylaldehyde also gave an excellent result

Table 3. Catalytic activity of **1d** toward Me_2Zn addition to aldehydes.

Entry	R	*t* [h]	Yield [%][a]	*ee* [%][b]
1	C_6H_5	3	99	95
2	2-naphthyl	2	95	95
3	*o*-Cl-C_6H_4	4	96	93
4	*o*-F-C_6H_4	2	99	91
5	2-furyl	2	98	98
6	C_7H_{15}	3	97	91[c]
7	C_6H_{11}	6	95	93[c]
8	Ph-CH=CH	3	92	92

[a] Yield of isolated product. [b] Determined by HPLC with an OD-H column. All products were of *R* configuration. Absolute configurations were established by the signs of the optical rotation reported. [c] Determined by chiral HPLC analysis of the dinitrobenzoate ester.

comparable to that of **1a** (Table 3, entry 2). With the *ortho*-substituted aldehydes, **1d** gave superior results to those of **1a** (Table 3, entry 3), especially for *o*-fluorobenzaldehyde, which gave up to 93% *ee*. Linear and unsaturated aldehydes gave *ee* values comparable to those of **1a** (Table 3, entries 6 and 8). Interestingly, the branched aldehyde cyclohexanecarbaldehyde, which was reported to give low *ee* values with **1a**, gave excellent *ee* of up to 93% with **1d** (Table 3, entry 7).

Ligand **1e** also showed very good activity. It gave 94% *ee* with benzaldehyde and 90% *ee* with cyclohexanecarbaldehyde. We concluded that the cyclohexanone ketal improved the activity of the ligand with respect to the acetone ketal. Another positive effect of the cyclohexanone ketal is the fact that it improves the solubility of the ligand; thus, the reaction catalyzed by **1d** could be carried out in 60% of the solvent required for **1a.**

Next, we attempted the recycling of ligand **1d**. We utilized the same method reported for the recycling of **1a** while taking the advantage of the low solubility of **1d** in cold toluene. Upon cooling a solution of the crude reaction product in toluene, the ligand precipitated and was separated from the products by filtration. By this simple method, we could recycle the ligand up to four times. The ligand could be used in the next step without any purification. The recycling data are shown in Table 4. When the amount of substrate was adjusted to keep the substrate/**1d** ratio constant, the *ee* values were not decreased significantly.

Table 4. Recycling of **1d**.

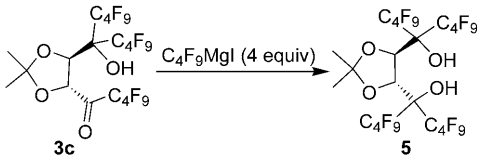
Cycle	Ligand recovered [%]	Yield [%][a]	*ee* [%][b]
1	–	100	96
2	99	100	94
3	81	100	91
4	80	96	88

[a] Yield determined by GC. [b] Determined by HPLC with an OD-H column.

Thus, owing to its better solubility in organic solvents, the recycling of **1d** with the same technique as **1a** was slightly less effective than that of **1a**. We conclude that changing the ketal part from acetone ketal to cyclohexanone ketal improves both the activity and the solubility of the ligand, but as a result the recyclability is slightly decreased.

Tetrakis(perfluoroalkyl)-Substituted Ligands

As mentioned before, we failed to obtain the tetrakis(perfluoroalkyl) analogues of taddol by using the single-step addition technique; in all cases, the tris adduct keto alcohols **3** were formed, accompanied by various side products. We tried to prepare the tetrakis(perfluoroalkyl)-substituted derivatives in two steps: separation of the tris addition product followed by treatment with excess perfluoroalkyl Grignard reagent. Application of this technique for **3a** did not give the desired product. We thought that this might be related to steric effects. Therefore, we applied the same method to the smaller keto alcohol **3c**. Thus, the adduct **3c** was treated with excess perfluorobutyl Grignard reagent, and we obtained the tetrakis(perfluorobutyl)-substituted derivative **5** in very low yield (9%; Scheme 4).



Scheme 4. Synthesis of the tetrakis(perfluorobutyl)-derived ligand **5**.

Unfortunately, this ligand was shown to be completely inactive toward the addition of Me_2Zn. The reason for this inactivity is not clear. This result shows that we were lucky: If we had obtained the tetrakis(perfluoroalkyl) analogue of taddol first, we would not have found the highly efficient ligands **1**.

Conclusions

We have synthesized a series of fluorous ligands **1a–e**, which were originally designed as the first fluorous analogues of taddol. Unlike taddol, which has four aromatic substituents, our new ligands have only three perfluoroalkyl substituents. However, they showed unprecedented activity towards the addition of Me_2Zn to aldehydes. We studied the effect of structure modification on both activity and recyclability. The replacement of the perfluorooctyl groups of the original ligand **1a** with shorter groups did not affect the activity of the ligand, but cut down the amount of solvent used for the reaction owing to better solubility in common solvents than **1a**. Although the recyclability was partly decreased by this higher solubility, the ligands could still be reused without purification after extraction with fluorous solvent. We prepared cyclohexanone ketal analogues of **1a**, which were shown to give higher *ee* than **1a** with cyclohexanecarbaldehyde. The perfluorooctyl analogue with cyclohexanone ketal, **1d**, seems to be most effective and easiest to prepare

owing to its moderate solubility. This compound could be recycled without fluorous solvent, as its high fluorine content makes it very insoluble in common solvents. The tetrakis-(perfluorobutyl)-substituted analogue of taddol was also synthesized, but it was found to be inactive toward the addition of Me_2Zn to aldehydes.

We cannot show the reaction mechanism clearly at this stage, but we observed peaks for a complex of titanium/2× **1c** in the mass spectrum (see Supporting Information). Seebach et al. showed that the spiro titanium bis(taddol)ate can act as the active complex.[15] Our mechanistic study is still ongoing.

Experimental Section

General

^{1}H NMR spectra were recorded on JNM-GX400 and JEOL-ECA-600SN spectrometers. Chemical shifts are reported in ppm with respect to tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), relative integration value. Mass spectra were obtained on JEOL JMS-700T spectrometers. Chromatographic purification was done with 230–400-mesh silica gel. Analytical GC was performed on a Hitachi 3500 gas chromatograph equipped with a flame ionization detector, a split-mode capillary injection system, and a TC-5 column (0.25 mm, 15 m, GL Sciences, Inc.) or a chiral column (GAMMA DEX 225TM, 0.25 mm, 30 m, Spelco). Peak areas were calculated with a Hitachi D-2500 Chromato-Integrator. Analytical HPLC was performed on a Jasco TRI-ROTAR-VITM liquid chromatograph equipped with a variable-wavelength UV detector (Jasco UVIDEC-100-VI), a Daicel Chiralcel™ OD-H column (0.46 cm I.D.× 25 cm) (Daicel, Inc.), and a HITACHI L-6000 pump system. Peak areas were calculated with a Shimadzu C-R1B™ Chromato-Integrator. HPLC-grade isopropanol and hexane were used as the eluting solvents. All reactions were carried out under argon atmosphere in flame-dried glassware with standard inert-atmosphere techniques for introducing reagents and solvents. All aldehydes were purified before use. Me_2Zn (1 M in hexane) was purchased from Kanto. Titanium tetraisopropoxide was purchased from Wako and distilled before use. Hexane was distilled over P_2O_5 and stored over 4-Å molecular sieves. Diethyl ether, THF, and toluene were distilled over benzophenone ketyl sodium just before use. IR spectra were recorded on a HITACHI 270-30 infrared spectrophotometer.

Syntheses

General procedure for the preparation of keto alcohols **3b–e**: A solution of the corresponding perfluoroalkyl iodide (20 mmol) in Et_2O (20 mL) was added slowly to a vigorously stirred solution of EtMgBr (6.67 mL, 3 M in Et_2O, 20 mmol) in Et_2O (100 mL) at −65 °C. After complete addition, the mixture was warmed to −40 °C within 30 min. When the temperature reached −40 °C, a solution of dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (0.92 mL, 5 mmol) in Et_2O (20 mL) was added. After the mixture was allowed to warm further to −30 °C, it was vigorously stirred for 4 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the organic phase was separated. The aqueous phase was extracted with Et_2O (3×30 mL), and the combined organic phase was dried over anhydrous $MgSO_4$ and concentrated to give a red oil, which was purified by silica-gel column chromatography.

3b: Yellow oil, yield: 3.5 g (63 %). $[\alpha]_D^{23} = +4.00$ ($c = 1.15$, Et_2O); IR (neat): $\tilde{\nu} = 3600$, 1760 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): $\delta = 5.30$ (d, $J = 6.3$ Hz, 1H), 5.15 (d, $J = 6.3$ Hz, 1H), 3.75 (s, 1H, overlapped with D_2O), 1.53 (s, 3H), 1.32 ppm (s, 3H); MS (FAB^-): $m/z = 1113$ $[M-1]^-$; HRMS (FAB^-): m/z calcd for $C_{25}H_8F_{39}O_4$: 1112.980 $[M-1]^-$; found: 1112.980.

3c: Yellow oil, yield: 2.72 g (67 %). $[\alpha]_D^{23} = +6.20$ ($c = 1.36$, Et_2O); IR (neat): $\tilde{\nu} = 3600$, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta = 5.31$ (d, $J = 6.4$ Hz, 1H), 5.15 (d, $J = 6.4$ Hz, 1H), 3.78 (s, 1H, overlapped with D_2O), 1.55 (s, 3H), 1.32 ppm (s, 3H); MS (FAB^-): $m/z = 813$ $[M-1]^-$; HRMS (FAB^-): m/z calcd for $C_{19}H_8F_{27}O_4$: 812.999 $[M-1]^-$; found: 813.000.

3d: A further 30 mL of Et_2O was added to avoid precipitation of the perfluorooctyl Grignard reagent. In place of dimethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate, dimethyl (2*R*,3*R*)-1,4-dioxaspiro-[4.5]decane-2,3-dicarboxylate was used. Pale-yellow oil, which was crystallized from hexane to give white crystals, yield: 4.3 g (60 %). M.p.: 61–62 °C; $[\alpha]_D^{23} = -1.73$ ($c = 1.48$, Et_2O); IR (KBr): $\tilde{\nu} = 3650$, 1745 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): $\delta = 5.30$ (d, $J = 6.4$ Hz, 1H), 5.14 (d, $J = 6.3$ Hz, 1H), 3.71 (s, 1H, overlapped with D_2O), 1.72–1.35 ppm (m, 10H); MS (EI^+): $m/z = 1454$ $[M]^+$; HRMS (EI^+): m/z calcd for $C_{34}H_{13}F_{51}O_4$: 1454.000 $[M]^+$; found: 1454.001.

3e: In place of (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate, dimethyl 1,4-dioxaspiro[4.5]decane-2,3-dicarboxylate was used. Compound **3e** could not be obtained in a form pure enough for characterization. The crude product was reduced in the procedure described below, and the diol **1e** was fully characterized.

General procedure for the preparation of catalysts **1b–e**: A mixture of $CeCl_3{\cdot}7H_2O$ (684 mg, 2 mmol) and the corresponding keto alcohol **3b–e** (1 mmol) in CH_3OH (15 mL) was stirred for 15 min at −30 °C. $NaBH_4$ (144 mg, 4 mmol) was added to this solution portionwise. The mixture was allowed to warm slowly to reach room temperature. The mixture was stirred for a further 3 h at room temperature. The excess $NaBH_4$ was decomposed with acetone, the reaction was quenched with NH_4Cl, and the mixture was extracted with Et_2O. The Et_2O layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude product as an oily mass, which was purified by crystallization.

1b: White crystals (hexane), yield: 703 mg (63 %). M.p.: 64–65 °C; $[\alpha]_D^{23} = -1.51$ ($c = 0.73$, Et_2O); IR (KBr): $\tilde{\nu} = 3500$ cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): $\delta = 4.75$ (d, $J = 8.0$ Hz, 1H), 4.62 (d, $J = 8.0$ Hz, 1H), 4.35–4.28 (m, 1H), 3.76 (s, 1H, overlapped with D_2O), 2.81 (d, $J = 10.33$ Hz, 1H, overlapped with D_2O), 1.52 (s, 3H), 1.50 ppm (s, 3H); MS (FAB^+): $m/z = 1117$ $[M+1]^+$; HRMS (FAB^+): m/z calcd for $C_{25}H_{12}F_{39}O_4$: 1117.011 $[M+1]^+$; found: 1117.011.

1c: White crystals (hexane), yield: 513 mg (63 %). M.p.: 56–57 °C; $[\alpha]_D^{23} = -1.62$ ($c = 0.73$, Et_2O); IR (KBr): $\tilde{\nu} = 3500$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 4.74$ (d, $J = 8.0$ Hz, 1H), 4.60 (d, $J = 8.0$ Hz, 1H), 4.37–4.28 (m, 1H), 3.81 (s, 1H, overlapped with D_2O), 2.88 (d, $J = 12.6$ Hz, 1H, overlapped with D_2O), 1.52 (s, 3H), 1.0 ppm (s, 3H); MS (FAB^+): $m/z = 817$ $[M+1]^+$; HRMS (FAB^+): m/z calcd for $C_{19}H_{12}F_{27}O_4$: 817.030 $[M+1]^+$; found: 817.030.

1d: A small amount of Et_2O (3 mL) was added during the reaction to retain the solubility of the starting material. White crystals (chloroform), yield: 946 mg (65 %). M.p.: 99–100 °C; $[\alpha]_D^{23} = -10.8$ ($c = 0.8$, Et_2O); IR (KBr): $\tilde{\nu} = 3500$ cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): $\delta = 4.78$ (d, $J = 8.0$ Hz, 1H), 4.61 (d, $J = 8.0$ Hz, 1H), 4.35–4.28 (m, 1H), 3.79 (s, 1H, overlapped with D_2O), 2.80 (d, $J = 12.6$ Hz, 1H, overlapped with D_2O), 1.73–1.38 ppm (m, 10H); MS (EI^+): $m/z = 1456$ $[M]^+$; HRMS (FAB^+): m/z calcd for $C_{34}H_{15}F_{51}O_4$: 1456.016 $[M]^+$; found: 1456.016.

1e: White crystals (pentane), total yield over 2 steps: 86 mg (10 %). M.p.: 68–70 °C; $[\alpha]_D^{23} = -14.5$ ($c = 0.74$, Et_2O); IR (KBr): $\tilde{\nu} = 3500$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.79$ (d, $J = 8.0$ Hz, 1H), 4.62 (d, $J = 8.0$ Hz, 1H), 4.36–4.29 (m, 1H), 3.82 (s, 1H, overlapped with D_2O), 2.77 (d, $J = 12.6$ Hz, 1H, overlapped with D_2O), 1.73–1.38 ppm (m, 10H); MS (FAB^+): $m/z = 857$ $[M+1]^+$; HRMS (FAB^+): m/z calcd for $C_{22}H_{16}F_{27}O_4$: 857.062 $[M+1]^+$; found: 857.061.

Typical procedure for addition of Me_2Zn to aldehydes with **1c** as catalyst (Table 1): Freshly distilled titanium tetraisopropoxide (361 μL, 1.22 mmol) was added to a solution of **1c** (0.06 mmol) in dry hexane (5 mL), and the mixture was stirred for 30 min at room temperature. Me_2Zn (2.44 mL, 1 M in hexane, 2.44 mmol) was added to this mixture, and the resulting mixture was stirred for a further 15 min. The mixture was cooled to −35 °C, and the appropriate aldehyde (1.02 mmol) was

added slowly. The mixture was kept stirring at this temperature and checked by GC. After the peak of the starting aldehyde disappeared, the reaction was quenched with NH_4Cl, and the whole mixture was filtered through sintered glass. The product was extracted with an appropriate solvent and purified by flash column chromatography. The *ee* value was checked by chiral HPLC. Racemic α-methyl carbinols were prepared by the reaction of methyl magnesium bromide with the corresponding aldehydes and used to confirm the separation of the racemates by HPLC. The absolute configuration of each product was estimated by the sign of the optical rotation in the literature. The above procedure was used for the rest of catalysts **1b**–**e** with the same amounts of ligands and solvents. In the case of **1d**: A further 1 mL of dry hexane was added to ensure the solubility of the catalyst, and the reaction proceeded by the same procedure.

Procedure for recycling of ligand **1c**: The residue obtained by concentration of the organic phase after workup of the addition reaction with benzaldehyde was dissolved in CH_2Cl_2 (2 mL) and extracted with perfluorohexane (3×3 mL). The fluorous phase was re-extracted several times with CH_2Cl_2 (1 mL each) until no product contamination was observed with GC. After the solid was dried, the purity of ligand **1c** was checked by GC and ^{1}H NMR spectroscopy, and the weight was measured to determine the recovery. The ligand was used in the next cycle without further purification. The recovery of **1c** and the yield and *ee* of the product are summarized in Table 2.

Procedure for recycling of ligand **1d**: The residue obtained by evaporation of the solvent from the organic phase after workup of the above reaction with benzaldehyde was treated with toluene (2 mL) and cooled to −40 °C. Ligand **1d**, which was precipitated as a white solid, was separated by filtration. The white solid was washed with cold toluene (2×2 mL) to remove any impurities. After the solid was dried, ligand **1d** was checked by GC and ^{1}H NMR spectroscopy to determine the purity, and the weight was measured to check the yield of recycling. The ligand was used in the next cycle without further purification. The recovery of **1d** and the yield and *ee* of the product are summarized in Table 4.

5: A solution of perfluorobutyl iodide (0.84 mL, 4 mmol) in Et_2O (10 mL) was added slowly to a vigorously stirred solution of EtMgBr (1.3 mL, 3 M in Et_2O, 4 mmol) in Et_2O (25 mL) at −65 °C. After complete addition, the mixture was allowed to warm to −40 °C in 45 min. When the temperature reached −40 °C, a solution of ketone **3c** (814 mg, 1 mmol) in Et_2O (10 mL) was added. After the mixture was warmed further to −30 °C, the mixture was stirred for 12 h at the same temperature, the temperature was raised slowly to room temperature, and the mixture was stirred for a further 24 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, the organic phase was separated, and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil, which was purified by silica-gel column chromatography followed by crystallization from chloroform to yield tetrakis(perfluorobutyl)-substituted ligand **5** (94 mg, 9%) as white crystals. M.p. 120 °C; $[\alpha]_D^{23} = +0.96$ ($c = 0.83$, Et_2O); IR (KBr): $\tilde{\nu} = 3350\ cm^{-1}$; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): $\delta = 7.82$ (s, 1H, overlapped with D_2O), 5.11 (s, 1H, overlapped with D_2O), 5.03 (s, 2H), 1.45 ppm (s, 6H); MS (FAB^-): $m/z = 1033$ $[M-1]^-$; HRMS (FAB^-): m/z calcd for $C_{23}H_9F_{36}O_4$: 1032.992 $[M-1]^-$; found: 1032.992.

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