

New Perfluoroalkyl-Substituted Bisoxazolines as Chiral Ligands in Asymmetric Cu^{II}-Catalyzed Reactions

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Two new enantiomerically pure perfluoroalkyl-substituted bisoxazolines (F-Box) have been prepared by a reaction sequence that involves formation of the properly functionalized Box followed by introduction of one or two *n*-C₈F₁₇ residues. These ligands were employed for the first time in the Mukaiyama aldol addition of silylketene thioacetals to methylpyruvate promoted by Cu(OTf)₂ (up to 85% ee) and in the ene reaction between α -methylstyrene and ethylglyoxalate in the presence of Cu(OTf)₂ (up to 74% ee). We compared the reactivities of the new ligands with those of two other chiral

fluorous bisoxazolines that we have reported previously. In both cases, the F-Box that has the lower fluorine content performed better, in terms of chemical yield and enantioselectivity, than the more-fluorinated one. The recovery and recycling of the ligands is realized either by phase separation of the reaction solvents or by filtration through a short plug of fluorous silica gel.

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Introduction

The use of perfluorous solvents for liquid–liquid separation technologies is receiving a rapidly growing amount of attention.^[1] Fluorous biphasic reactions are based upon interactions between fluorous solvents and fluorous compounds, such as catalysts, reagents, and substrates; at the end of the reaction, non-fluorinated products are usually extracted from a fluorous phase into an organic phase, while fluorinated compounds are recovered from the fluorous phase.^[2] Although fluorous biphasic catalysis represents an environmentally attractive alternative to traditional catalytic methods, relatively few chiral fluorous ligands have been studied so far.^[3] Such ligands include salen-based derivatives that form cobalt and manganese complexes,^[3a,3b] BINOL compounds that act as titanium ligands,^[3c,3d] and iridium complexes of diimines and diamines,^[3e] BINAP and MOP derivatives.^[3a,3f,3g] Surprisingly, despite the recognized versatility of bis(oxazoline) (Box) ligands in asymmetric synthesis,^[4] only two reports so far have dealt with the synthesis and application of perfluorinated bis(oxazolines).^[5] In particular, we realized^[6] the synthesis of chiral fluorous bis(oxazolines), which we employed in Cu^I-promoted cyclopropanation and Cu^{II}-catalyzed ene

reactions, and Sinou's group reported^[7] the use of perfluorinated bis(oxazolines) in palladium-promoted allylic alkylations. Here we report the synthesis of two new enantiomerically pure perfluoroalkyl-substituted bisoxazolines (F-Box) and their use in asymmetric Mukaiyama aldol and ene-type reactions.

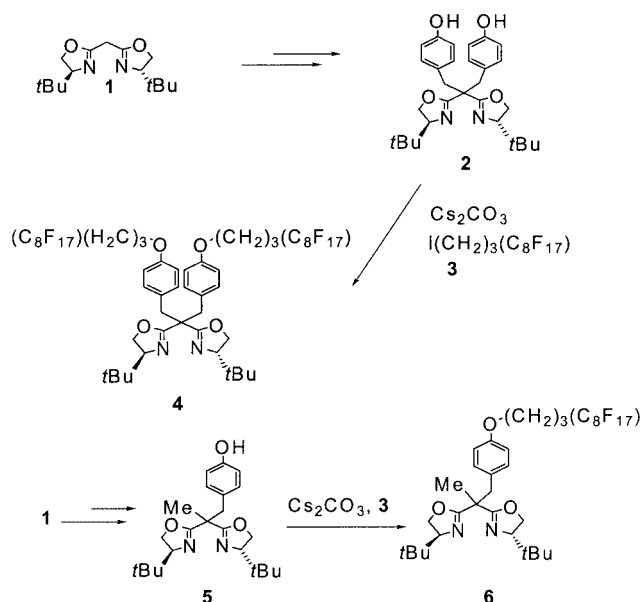
Results and Discussion

The synthesis of the new chiral fluorous bis(oxazolines), designed on the basis of our previous work with PEG-supported Box,^[8] is illustrated in Scheme 1. The *tert*-butyl-substituted, commercially available Box **1** was converted in two steps (70% overall yield) into the bis(phenol) **2**,^[8] which was reacted with 3-perfluorooctyl-1-iodopropane **3**,^[9] in presence of cesium carbonate, to give ligand **4** in 56% yield. Analogously, bis(oxazoline) **5**,^[6] prepared in 30% overall yield, was transformed into the perfluoroalkyl-substituted Box **6** (48% yield).

The fluorine contents of the new F-Box ligands **4** and **6** were calculated to be 46.2 and 38.1%, respectively. As expected on the basis of the relatively low fluorine content, both of these new F-bis(oxazolines) are readily soluble in non-fluorinated solvents and may be classified as light fluorous substances.^[10] It is worth mentioning that the previously synthesized F-Box ligands **7** and **8**^[8] (Figure 1) had fluorine contents of 49.2 and 55.5%, respectively. While the former is soluble in organic solvents, **8** has a partition coefficient of 4.7 in *n*-perfluorooctane/dichloromethane (50:50, v/v) and of 17.5 in *n*-perfluorooctane/acetonitrile (50:50, v/v).

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Scheme 1. Synthesis of F-box ligands 4 and 6

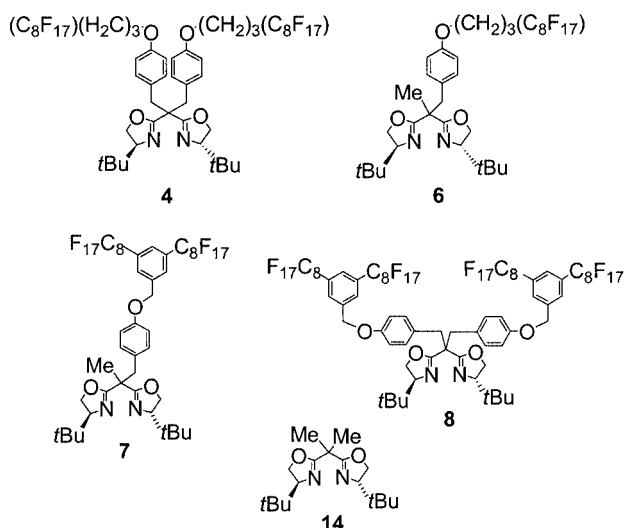
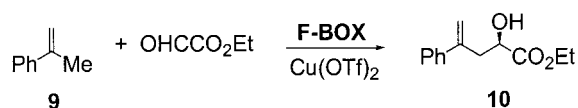


Figure 1. Structures of F-box ligands 4, 6–8, and 14

The copper(II) complexes of these four chiral F-Box ligands, which have different fluorine contents and solubility properties, were tested in two important enantioselective C–C bond-forming processes: the ene reaction and the Mukaiyama aldol addition.

The ene reaction^[11] (Scheme 2) between α -methylstyrene **9** (1 mol equiv.) and ethyl glyoxalate (50% solution in toluene, 10 mol equiv.), which we performed from 0 °C to room temp. over 18 h in CH_2Cl_2 in the presence of ligand **6** (11 mol%) and $\text{Cu}(\text{OTf})_2$ (10 mol%), afforded adduct **10** in 65% yield and 74% *ee*, as determined by the Mosher ester method (Table 1, entry 1). When the reaction was repeated under the same conditions, but using ligand **4**, the product was obtained in 73% chemical yield, but only 7% *ee* (Table 1, entry 2).



Scheme 2. Enantioselective ene reactions catalyzed by the metal complexes of F-box ligands 4 and 6–8

Thus the reactivity of the new ligand **6** compares favorably with that of ligand **7** (67% *ee*), and **8** (26% *ee* in a 1:1 CH_2Cl_2 /perfluorooctanes mixture; see entries 3–4 in Table 1).^[6]

Next we studied the enantioselective addition of enolsilane to pyruvate esters.^[12] We employed the Cu^{II} complexes of fluorinated bis-oxazolines, generated by stirring the ligand and $\text{Cu}(\text{OTf})_2$ in dry dichloromethane for 3 h at 25 °C, to promote the reaction between methyl pyruvate **11** and silylketene acetal **12**. Typically, methyl pyruvate (0.5 mmol) and silylketene acetal (0.6 mmol) were added to a solution of the catalyst (0.05 mmol, 10 mol%) in the appropriate solvent (2 mL) at 0 °C. The resulting mixture was stirred overnight while the temperature slowly increased from 0 °C to room temp.

By employing the F-Box **7** in dry CH_2Cl_2 , we obtained the product **13** in 55% yield and 83% *ee* (Table 1, entry 5). Running the reaction in THF resulted in a slight increase in the yield (from 55 to 63%), but also to a decrease in the enantiomeric excess (from 83 to 65%; Table 1, entry 6). Surprisingly, the reaction employing the C_2 -symmetric F-Box **4** in dichloromethane and **8** in a 1:1 CH_2Cl_2 /perfluorooctanes mixture afforded the product in very low yields and with practically no enantioselectivity (Table 1, entries 7 and 8). Finally, the use of ligand **6** in dry dichloromethane led to the hydroxy ester **13** being obtained in 65% yield and 85% *ee* (Table 1, entry 9). It is worth mentioning that under the same reaction conditions, Evans' bis-oxazoline **14** (see Figure 1) promoted the Mukaiyama aldol reaction in 71% yield and 92% *ee*.^[13]

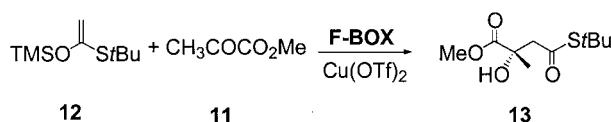
The data collected in Table 1 indicate that the C_1 -symmetric ligands **6** and **7** performed constantly better than the C_2 -symmetric ligands **4** and **8** in terms of enantioselectivity. In the best case for the ene reaction, we observed the *ee* to be ca. 15% lower than those obtained with the best ligands reported in the literature.^[11,14] Indeed, the use of F-Box **6** in the ene reaction led to product **10** in 74% *ee*; Evans obtained an 89% *ee* by using the catalyst derived from Box **14**. In the aldol reaction, the use of ligands **4** and **8** afforded an essentially racemic product in low chemical yields; once again, **6** and **7** clearly performed better (83 and 85% *ee*). It is noteworthy that the enantiomeric excess obtained using F-Box **6** (85% *ee*) is only slightly inferior to that obtained using Box **14** (92% *ee*).

These findings seem to suggest some negative effects exerted by the perfluorinated “ponytails”.^[15] An explanation of these effects is not easy to provide, however, because there is no clear inverse relationship between the fluorine loading of the ligands and the enantioselectivity observed in

Table 1. Enantioselective reactions catalyzed by F-box ligands **4** and **6–8** in dry dichloromethane.

Entry	Equation	Catalyst (10 mol %)	Product	Isolated yield%	ee % ^[a]	Recov. yield %
1	1	6 /Cu(OTf) ₂	10	65	74	78 ^[b]
2	1	4 /Cu(OTf) ₂	10	73	7	80 ^[b]
3	1	7 /Cu(OTf) ₂	10	99	67	77 ^[b]
4 ^[c]	1	8 /Cu(OTf) ₂	10	64	26	89 ^[d]
5	2	7 /Cu(OTf) ₂	13	55	83	80 ^[b]
6 ^[e]	2	7 /Cu(OTf) ₂	13	63	65	77 ^[b]
7	2	4 /Cu(OTf) ₂	13	15	7	84 ^[b]
8 ^[c]	2	8 /Cu(OTf) ₂	13	10	4	85 ^[d]
9	2	6 /Cu(OTf) ₂	13	65	85	85 ^[b]
10 ^[f]	2	6 /Cu(OTf) ₂	13	63	82	74 ^[b]
11 ^[g]	1	6 /Cu(OTf) ₂	10	62	71	72 ^[b]

^[a] Determined by the Mosher ester method (in the case of compound **10**) or by HPLC on a chiral stationary phase (in the case of compound **13**). ^[b] Ligand recovered by fluorous-phase silica gel chromatography. ^[c] Reaction run in a 1:1 CH₂Cl₂/perfluorooctanes mixture. ^[d] Ligand recovered by phase separation. ^[e] Reaction run in dry tetrahydrofuran. ^[f] Reaction performed using a sample of ligand **6** recycled from the reaction of entry 9 (see text). ^[g] Reaction performed using a sample of ligand **6** recycled from the reaction of entry 1 (see text).

Scheme 3. Enantioselective aldol reactions catalyzed by the metal complexes of F-box ligands **4** and **6–8**

their reactions. It is possible that the two highly fluorinated substituents positioned at the bridging carbon atom in the F-Box ligands may experience strong steric repulsions that reduce the “bite angles” of the Box moieties and lead to the ligands having greater difficulty in complexing with copper ions; this situation, consequently, leads to poorly enantioselective transformations.^[16] This negative effect should be especially evident in reactions catalyzed by Box/Cu^{II} complexes that adopt a square-planar geometry; these reactions are known to be particularly sensitive to the Box “bite angle”.^[17] Indeed, the bridging substitution in the C₁-symmetric ligands **6** and **7** is less sterically demanding than it is in **4** and **8**, and the ligand–copper cation complexation should be similar to that of the commercially available Box **14**. The very different behavior of ligands that have similar fluorine content, such as **7** (49.2%) and **4** (46.2%), suggests that the spatial arrangement of the fluorous “ponytails” plays a major role in determining the efficiency of the chiral ligands.^[18]

Next, we studied the recovery of the fluorous bis-oxazolines. First, the ligands were released from the copper cation in the crude reaction mixture by decomplexation with an aqueous solution containing cyanide ions.^[19] After standard workups of both the Mukaiyama aldol and ene reactions, we recovered ligand **8** by separation of the CH₂Cl₂/perfluorooctanes mixture and evaporation of the latter solvent. The ligands recovered from both reactions were stable under the reaction and recovery conditions, as evidenced by their ¹H and ¹⁹F NMR spectra being identical to those of fresh samples. Although ligand **8** was not an efficient pro-

moter of the aldol condensation, its recovery was accomplished successfully in 85% yield, which is similar to its 89% recovered yield after the ene reaction.^[6]

The low fluorine content of the other F-Box does not allow us to use the same procedure. It has already been demonstrated that **7** can be recovered chromatographically using a short silica gel column.^[6] In the present work, fluorous solid-phase extraction (FSPE) made the recovery of the ligands even easier.^[20] Indeed, in the Mukaiyama aldol reaction, the ligands **4**, **6**, and **7** were isolated in 84, 85, and 80% yields, respectively, by simple filtration through a very short plug of fluorous reverse-phase silica gel (see Exp. Sect.).^[21] The F-Box ligands we recovered from both the ene and aldol reactions were pure compounds to within the detection limits of ¹H and ¹⁹F NMR spectroscopic analysis.

We reused the recovered ligands in new reactions; for example, recycling of **6** in the aldol condensation (Table 1, entry 10) afforded product **13** in 63% yield and 82% ee; these values are very similar to those obtained when we used a fresh sample of ligand (entry 9). The ligand recovered in the ene reaction was also recycled with good results (entry 11): the product **10** was isolated in 62% yield and 71% ee; these values are similar to those obtained when using the fresh ligand (65% yield, 74% ee; Table 1, entry 1).

Conclusions

In conclusion, the synthesis of two new perfluorinated bisoxazoline (F-Box) ligands having different fluorine contents and solubility properties is described. We employed the Cu^{II} triflate complexes of these compounds in two catalytic enantioselective transformations to afford the products in good chemical yields; the enantiomeric excesses are only slightly inferior to those reported in the literature.^[11,12]

Recovery of the F-Box is possible by either of two procedures: phase separation in one case and a very easy filtration through a short plug of fluorous silica gel in the

other. The recovered ligands can be recycled to afford reaction products in chemical yields and enantioselectivities that are almost identical to those obtained in the first cycle.

Experimental Section

General: ^1H NMR spectra were recorded at 300 MHz in CDCl_3 unless otherwise stated, and were referenced to tetramethylsilane (TMS) at $\delta = 0.00$ ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to CDCl_3 at $\delta = 77.0$ ppm. ^{19}F NMR spectra were recorded at 282 MHz in CDCl_3 and were referenced to hexafluorobenzene at $\delta = 0.0$ ppm. Optical rotations were measured at the Na-D line in a 1-dm cell at 22 °C. IR spectra were recorded using thin films or solutions in CH_2Cl_2 .

Adducts **10** and **13** are known compounds having established absolute configurations.^[11,12] The *ee* of compound **10** was determined by analyzing the ^1H NMR spectra of the corresponding Mosher ester obtained by reaction with the (*R*)-enantiomer of the Mosher acid chloride. The esters gave signals identical to those reported by Evans (see the Supporting Information of ref.^[11]). The diagnostic signals were those of the vinyl protons that resonate at $\delta = 5.40$ and 5.22 ppm for the major (*R,R*)-isomer and at $\delta = 5.23$ and 5.02 ppm for the minor (*S,R*)-isomer. The *ee* of compound **13** was determined by performing HPLC on a chiral stationary phase: Chiralcel OD column; eluent, hexane/ *i*PrOH (99:1); flow rate, 1 mL/min; $\lambda = 210$ nm. Minor enantiomer: $T_R = 7.64$ min; major enantiomer: $T_R = 8.39$ min.

2,2-Bis{2-[(4*S*)-(1,1-dimethylethyl)-1,3-oxazoliny]}-1,3-bis{4-[3-(perfluorooctyl)propoxy]phenyl}propane: Cesium carbonate (0.344 g, 1.057 mmol) and 3-perfluorooctyl-1-iodopropane^[16] (0.160 g, 0.272 mmol) were added to a solution of 2,2-bis{2-[(4*S*)-(1,1-dimethylethyl)-1,3-oxazoliny]}-1,3-bis(4-hydroxyphenyl)propane^[6] (0.072 g, 0.151 mmol) in DMF (2 mL) that was stirred under nitrogen at 50 °C. The mixture was then stirred at 50 °C for a further 60 h. The cooled mixture was poured into water (5 mL) and extracted with Et_2O (4 $\times$ 10 mL). The combined organic phases were washed with water (5 mL), dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash chromatography (hexanes/ Et_2O , 8:2) to give the product (0.106 g, 0.076 mmol, 56% yield). M.p. > 150 °C dec. $[\alpha]_D^{25} = -19.5$ ($c = 0.8$ in CHCl_3). IR: $\tilde{\nu} = 3051, 2955, 1656\text{ cm}^{-1}$. ^1H NMR: $\delta = 0.86$ (s, 18 H, *t*Bu), 2.10 (m, 4 H, $\text{ArOCH}_2\text{CH}_2$), 2.33 (m, 4 H, $\text{C}_8\text{F}_{17}\text{CH}_2$), 3.11 (A part of AB system, $^2J_{\text{H,H}} = 14.2$ Hz, 2 H, one proton of ArCH_2), 3.39 (B part of AB system, $^2J_{\text{H,H}} = 14.2$ Hz, 2 H, one proton of ArCH_2), 3.83 (dd, $^3J_{\text{H,H}} = 7.6, 10.1$ Hz, 2 H, $\text{CHBu-}t$), 3.98–4.10 (m, 8 H, two protons of oxazoline CH_2 and two protons of ArOCH_2), 6.79 (A part of AB system, $^3J_{\text{H,H}} = 8.6$ Hz, 4 H, aromatic protons *ortho* to O), 7.19 (B part of AB system, $^3J_{\text{H,H}} = 8.6$ Hz, 4 H, aromatic protons *meta* to O) ppm. ^{13}C NMR: $\delta = 21.6, 26.5$ (t, $^2J_{\text{C,F}} = 20.0$ Hz), 33.6, 33.9, 41.2, 43.5, 68.5, 74.5, 75.5, 114.4, 119.5–106.5 (m, C_8F_{17}), 129.3, 130.2 (t, $^2J_{\text{C,F}} = 22.5$ Hz), 156.9, 167.7 ppm. ^{19}F NMR: $\delta = -126.6, -123.2, -122, 118, 115-106, 81.3$ ppm. $\text{C}_{51}\text{H}_{48}\text{F}_{34}\text{N}_2\text{O}_3$ (1382.51): calcd. C 43.79, H 3.46, N 2.00; found C 43.70, H 3.39, N 2.02.

2,2-Bis{2-[(4*S*)-(1,1-dimethylethyl)-1,3-oxazoliny]}-1-{4-[3-(perfluorooctyl)propoxy]phenyl}propane: Cesium carbonate (0.130 g, 0.400 mmol) and 3-perfluorooctyl-1-iodopropane^[16] (0.067 g, 0.114 mmol) were added to a solution of 2,2-bis{2-[(4*S*)-(1,1-dimethylethyl)-1,3-oxazoliny]}-1-(4-hydroxyphenyl)propane^[6] (0.044 g, 0.114 mmol) in DMF (2 mL) that was stirred under nitrogen at 50 °C. The mixture was stirred at 50 °C for an additional 60 h. The

cooled mixture was poured into water (5 mL) and extracted with Et_2O (4 $\times$ 10 mL). The combined organic phases were washed with water (5 mL), dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash chromatography (hexanes/ Et_2O , 9:1) to give the product (0.046 g, 0.054 mmol, 48% yield) as a thick pale-yellow oil. $[\alpha]_D^{25} = -44.7$ ($c = 0.58$ in CHCl_3). IR: $\tilde{\nu} = 3054, 2981, 1673\text{ cm}^{-1}$. ^1H NMR: $\delta = 0.86$ (s, 18 H, *t*Bu), 1.4 (s, 3 H), 2.0–2.4 (m, 4 H), 3.11 (A part of AB system, $^2J_{\text{H,H}} = 14.2$ Hz, 2 H, one proton of ArCH_2), 3.39 (B part of an AB system, $^2J_{\text{H,H}} = 14.2$ Hz, 2 H, one proton of ArCH_2), 3.7–4.2 (m, 8 H, two protons of oxazoline CH_2 and two protons of ArOCH_2), 6.75 (A part of an AB system, $^3J_{\text{H,H}} = 8.6$ Hz, 4 H, aromatic protons *ortho* to O), 7.05 (B part of an AB system, $^3J_{\text{H,H}} = 8.6$ Hz, 4 H, aromatic protons *meta* to O) ppm. ^{13}C NMR: $\delta = 20.6, 25.8, 28$ (t, $^2J_{\text{C,F}} = 22.0$ Hz), 33.9, 38.6, 48.7, 66.3, 68.3, 75.6, 113.9, 120.5–105.5 (m, C_8F_{17}), 129.6, 131.6, 157.3, 162.2, 166.2 ppm. ^{19}F NMR: $\delta = -126.3, -122.2, -121.8, 118.5, 113-106, 81.3$ ppm. $\text{C}_{34}\text{H}_{39}\text{F}_{17}\text{N}_2\text{O}_3$ (846.66): calcd. C 48.23, H 4.64, N 3.31; found C 48.14, H 4.59, N 3.27.

Stereoselective Syntheses Promoted by Chiral F-Box Ligands

Ene Reaction: A solution was prepared by dissolving the chiral ligand (0.030 mmol) and $\text{Cu}(\text{OTf})_2$ (0.012 g, 0.033 mmol) under nitrogen in dry CH_2Cl_2 (2 mL). The resulting dark-green solution was stirred at room temp. for 4 h and then it was added to a mixture of α -methylstyrene (0.039 mL, 0.3 mmol) and ethylglyoxalate (0.595 mL of a 50% solution in toluene, 3.0 mmol) that had been cooled to 0 °C. The resulting mixture was stirred overnight while the temperature slowly increased to room temp. The mixture was then concentrated under vacuum; the residue was dissolved in CH_2Cl_2 (5 mL), dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a crude product that was purified by flash chromatography (hexanes/ Et_2O , 7:3). Yields and values of *ee* of the product are reported in Table 1.

Mukaiyama Aldol Reaction: A solution was prepared by dissolving the chiral ligand (0.030 mmol) and $\text{Cu}(\text{OTf})_2$ (0.012 g, 0.033 mmol) in dry CH_2Cl_2 (2 mL) under nitrogen. The resulting dark-green solution was stirred at room temp. for 3 h, cooled to 0 °C, and added to a mixture of methyl pyruvate (0.035 g, 0.30 mmol) and trimethylsilyl *tert*-butylthio ketene acetal (0.082 g, 0.40 mmol) in dry CH_2Cl_2 (2 mL) that had been cooled to 0 °C. After stirring at that temperature for 1 h, the temperature of the stirring reaction mixture was increased slowly to room temp. The mixture was then filtered through a short plug of silica gel and concentrated under vacuum to give a crude product that was analyzed by GC. The crude silyl ether was then hydrolyzed with 1 N HCl in THF to yield the hydroxy ester, which was purified by flash chromatography. The values of *ee* were determined by HPLC analysis on a Chiralcel OD column (hexane/2-propanol, 99:1; flow rate: 1 mL/min; minor enantiomer: $T_R = 7.64$ min; major enantiomer: $T_R = 8.39$ min).

In the ligand recovery procedure, the crude reaction mixture dissolved in CH_2Cl_2 was treated with a aqueous solution of KCN; the organic phase was separated, dried over Na_2SO_4 , filtered, and concentrated under vacuum to give the crude product, which was loaded onto a short plug of fluoros reverse-phase silica gel (diameter: 0.7 cm, length: 5–7 cm). The product was recovered upon eluting with CH_3CN (10–15 mL); in a few cases, the product was contaminated by traces of the fluoros ligand. The chiral F-Box was then recovered by eluting with CH_2Cl_2 (15 mL). The recovered chiral ligands exhibited NMR spectra identical to those of the freshly synthesized samples.

Acknowledgments

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