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

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Keywords: Biphasic catalysis / Chiral bisoxazolines / Fluorous ligands / Fluorous silica gel chromatography / Homogeneous catalysis

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*-C_8F_{17} 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.

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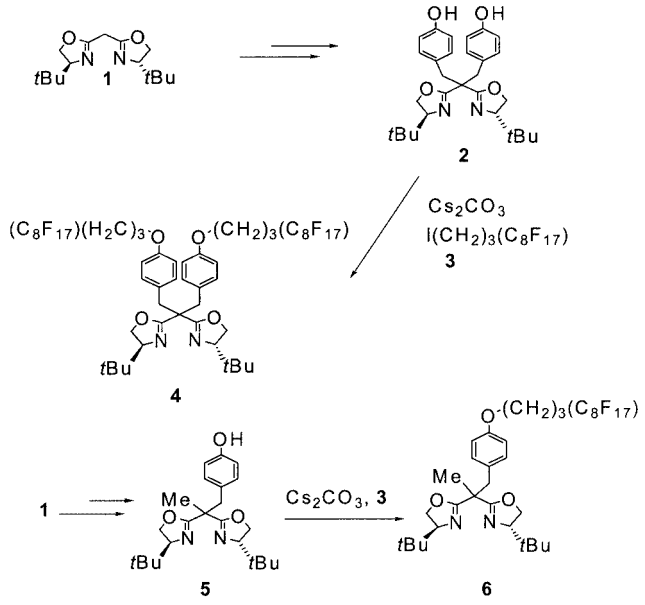
Results and Discussion

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).



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

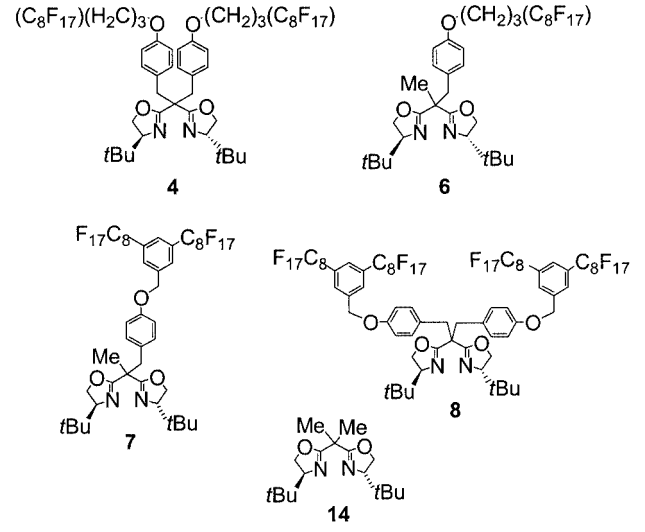
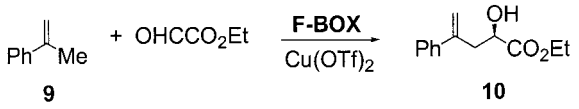


Figure 1. Structures of F-box ligands **4**, **6**–**8**, and **14**

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 $Cu(OTf)_2$ (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).



9 10

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 fluorous bis-oxazolines, generated by stirring the ligand and $Cu(OTf)_2$ 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

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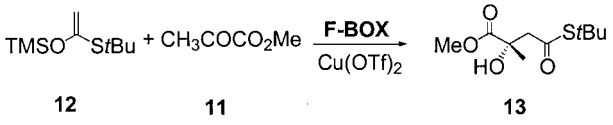
Table 1. Enantioselective reactions catalyzed by F-box ligands **4** and **6**−**8** in dry dichloromethane.

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 CH_2Cl_2/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 C_1-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 CH_2Cl_2/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 ^{19}F NMR spectra being identical to those of fresh samples. Although ligand **8** was not an efficient promoter 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 ^{19}F 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

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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: ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise stated, and were referenced to tetramethylsilane (TMS) at δ = 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to $CDCl_3$ at δ = 77.0 ppm. ^{19}F NMR spectra were recorded at 282 MHz in $CDCl_3$ and were referenced to hexafluorobenzene at δ = 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 ^{1}H 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 δ = 5.40 and 5.22 ppm for the major (*R*,*R*)-isomer and at δ = 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: Chiracel OD column; eluent, hexane/ *i*PrOH (99:1); flow rate, 1 mL/min; λ = 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-oxazolinyl]}-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-oxazolinyl]}-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 × 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. $[\alpha]_D^{22}$ = −19.5 (*c* = 0.8 in $CHCl_3$). IR: $\tilde{\nu}$ = 3051, 2955, 1656 cm^{-1}. ^{1}H NMR: δ = 0.86 (s, 18 H, *t*Bu), 2.10 (m, 4 H, ArOCH$_2$CH$_2$), 2.33 (m, 4 H, $C_8F_{17}CH_2$), 3.11 (A part of AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, one proton of ArCH_2), 3.39 (B part of AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, one proton of ArCH_2), 3.83 (dd, $^3J_{H,H}$ = 7.6, 10.1 Hz, 2 H, *CH*Bu-*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, $^3J_{H,H}$ = 8.6 Hz, 4 H, aromatic protons *ortho* to O), 7.19 (B part of AB system, $^3J_{H,H}$ = 8.6 Hz, 4 H, aromatic protons *meta* to O) ppm. ^{13}C NMR: δ = 21.6, 26.5 (t, $^2J_{C,F}$ = 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, $^2J_{C,F}$ = 22.5 Hz), 156.9, 167.7 ppm. ^{19}F NMR: δ = −126.6, −123.2, −122, 118, 115−106, 81.3 ppm. $C_{51}H_{48}F_{34}N_2O_3$ (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-oxazolinyl]}-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-oxazolinyl]}-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 × 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. $[\alpha]_D^{22}$ = −44.7 (*c* = 0.58 in $CHCl_3$). IR: $\tilde{\nu}$ = 3054, 2981, 1673 cm^{-1}. ^{1}H NMR: δ = 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, $^2J_{H,H}$ = 14.2 Hz, 2 H, one proton of ArCH_2), 3.39 (B part of an AB system, $^2J_{H,H}$ = 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, $^3J_{H,H}$ = 8.6 Hz, 4 H, aromatic protons *ortho* to O), 7.05 (B part of an AB system, $^3J_{H,H}$ = 8.6 Hz, 4 H, aromatic protons *meta* to O) ppm. ^{13}C NMR: δ = 20.6, 25.8, 28 (t, $^2J_{C,F}$ = 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: δ = −126.3, −122.2, −121.8, 118.5, 113−106, 81.3 ppm. $C_{34}H_{39}F_{17}N_2O_3$ (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 $Cu(OTf)_2$ (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 $Cu(OTf)_2$ (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 piruvate (0.035 g, 0.30 mmol) and trimethylsilyl *tert*-butylthioketene 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 Chiracel 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 fluorous 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 fluorous 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.

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Acknowledgments

This work was supported by MIUR (Progetto Nazionale Stereoselezione in Sintesi Organica; Metodologie ed Applicazioni), C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi), and CNR-ISTM.

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[14] When the $Cu(OTf)_2$ complexes of ligands **4** and **6** were employed to catalyze the Diels−Alder cycloaddition between cyclopentadiene and *N*-acryloyloxazolidinone, the corresponding cycloadducts were obtained with low *ee*; the chemical yield when using **6** was good, but it was very poor when using **4**.

[15] We note that this behavior is not a general feature of chiral fluorinated catalysts because in other cases they perform as efficiently as their non-fluorinated counterparts. See ref.[3]

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Received January 19, 2004

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