Synthesis of Perfluoroalkyl-Substituted Bis(oxazolines) as Ligands for Catalytic Enantioselective Reactions

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Two chiral perfluoroalkyl-substituted bis(oxazolines) (F-box) have been prepared for the first time by a reaction sequence that involved formation of the properly functionalized box followed by introduction of two (ligand **9**) or four (ligand **6**) *n*-C_8F_{17} residues. The fluorine content of these F-box was 49.2 and 55.5%, respectively. These ligands were employed in the ene reaction between α-methylstyrene and ethylglyoxalate carried out in the presence of [Cu(OTf)$_2$] (up to 67% *ee*), and in the cyclopropanation of styrene in combination with CuOTf (up to 78% *ee*). In both cases the F-box with the lower fluorine content performed better than the more fluorinated one in terms of chemical yield and enantioselectivity. Ligand **9** was recovered by flash chromatography; ligand **6** by phase separation of the reaction solvents. Comparisons between the use of perfluoroalkyl groups and of soluble and insoluble polymers as solubility devices for the recovery and recycling of the bis(oxazoline) ligand are also reported.

Introduction

The versatility of chiral bis(oxazolines) (box) to act as ligands in a variety of catalytic enantioselective transformations[1] has stimulated intense research activity devoted to the immobilization of different representatives of this class of compounds on various supports. This effort lies within the framework of immobilization of ligands and catalysts on polymeric matrixes,[2] that is currently regarded as a viable tool to improve the efficiency of asymmetric catalysis[3] by allowing simple catalyst recovery and recycling.

Generally, insoluble supports have been selected for the immobilization of chiral box.[4] The immobilization of classic (Evans-type)[5] and structurally new[6] box on modified poly(ethyleneglycol)s (PEGs) of high molecular weight has been recently reported by Reiser's group[6] and ours.[5] The rationale behind the use of PEG as the support[7] stems from the ability of this inexpensive and readily functionalized polymer to act as a solubility device that combines the advantages of running a reaction under homogeneous (and likely best-performing) catalysis conditions with those of recovering and recycling a ligand or a catalyst as if it were bound to an insoluble support.[8] The PEG-supported species showed catalytic activity and stereocontrol ability very similar (and in some instances even superior) to those displayed by the nonsupported systems.[5]

In principle, a soluble and easily recoverable ligand can also be obtained by the fluorous-phase approach,[9] i.e. by the introduction of a sufficiently high number of perfluorinated "ponytails". To the best of our knowledge, no examples of perfluoroalkyl-substituted box (F-box) have been reported in the literature.[10] Here, we report the first synthesis of two derivatives of this class of compounds having different fluorine content, and describe their use as chiral ligands in two representative enantioselective catalytic reactions. We compare the results obtained with these new F-box with those obtained with related box, either nonsupported or supported on various polymers, paying particular attention to the recovery and recycling of the ligands.

Results

We designed the synthesis of the F-box ligands taking into account: (i) the convenience of starting from a commercially available box; (ii) the necessity of introducing a spacer to separate the perfluorinated residues from the coordination sites;[9f] and (iii) the need for disubstitution at the box bridging atom, a feature known to enhance the stereoselectivity of box-promoted reactions.[1] On the basis of our previous experience in the synthesis of PEG-supported box,[5] we performed the reaction sequence outlined in Scheme 1.

tert-Butyl-substituted box **1** was treated[4a] with MeLi (2.2 mol-equiv. in THF, −55 °C, 90 min) and then alkylated

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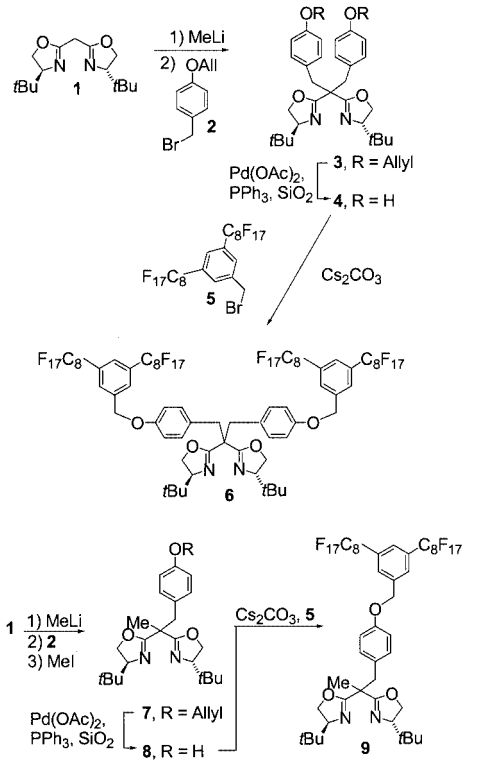


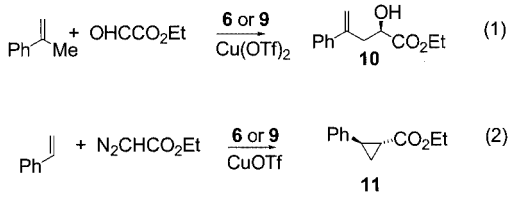
Scheme 1. Synthesis of F-box **6** and **9**

with 4-allyloxybenzyl bromide (**2**)[5] (2.0 mol-equiv., −10 °C, 4.5 h) to afford adduct **3** in 74% isolated yield. Oxygen deprotection was carried out at 90 °C with $Pd(OAc)_2$ and PPh_3 in EtOH in the presence of SiO_2 to give bis(phenol) **4** in 94% yield. Introduction of the perfluoroalkyl residues was achieved by alkylation of **4** (Cs_2CO_3, DMF, 50 °C, 60 h) with a slight molar deficiency[11] of α-bromo-3,5-bis(perfluorooctyl)toluene (**5**) (obtained in 60% yield from the corresponding alcohol[12] with PBr_3). Compound **6** was thus obtained in 37% unoptimized yield (26% overall yield from **1**).

Sequential treatment of similarly metallated **1**, first with the benzyl bromide **2** (1 mol-equiv., −10 °C, 40 min) and then with MeI (3 mol-equiv., from −10 °C to room temperature, 15 h), afforded box **7** in 40% yield along with box **3** (35% yield). These were readily separated by flash chromatography and adduct **7** was transformed into perfluoroalkyl-substituted box **9** via the two reactions described above, namely allyl removal (76% yield) and *O*-benzylation with **5** (54% yield). The unoptimized overall yield of **9** from **1** was 16.5%. Recovered **3** was recycled to produce F-box **6**.

The fluorine contents of F-box **6** and **9** were calculated as 55.5 and 49.2%, respectively, Despite these similar values, solubility studies revealed that while ligand **9** was readily soluble in non-fluorinated solvents, the partition coefficients of compound **6** in *n*-perfluorooctane/dichloromethane (50:50, v/v) and *n*-perfluorooctane/acetonitrile (50:50, v/v) were gravimetrically determined as ca. 4.7 and 17.5, respectively. Thus, the number of the perfluorinated ponytails, rather than the actual fluorine content, seems to be the discriminating factor in determining the solubility properties of perfluorinated compounds.[9]

Ligands **6** and **9** were then tested in the representative enantioselective transformations reported in Scheme 2 [Equations (1) and (2)]. The results are collected in Table 1 (see the Exp. Sect. for methods of *ee* determination).



Scheme 2. Enantioselective reactions catalyzed by metal complexes of F-box ligands **6** and **9**

The ene reaction[13] [Equation (1), Scheme 2; Entry 1, Table 1] between α-methylstyrene (1 mol-equiv.) and ethyl glyoxalate (50% solution in toluene, 10 mol-equiv.) carried out from 0 °C to room temp. for 18 h in CH_2Cl_2 in the presence of ligand **9** (11 mol%) and of $[Cu(OTf)_2]$ (10 mol%) afforded adduct **10** in 99% yield and 67% *ee* (as determined by the Mosher ester method). When the reaction was repeated under the same conditions using ligand **6** in a

Table 1. Enantioselective reactions catalyzed by F-box ligands **6** and **9**

Entry	Eq. in Scheme 2	Catalyst (10 mol%)	Product	Isolated yield (%)	*trans*/*cis*[a]	*ee* (%)[b]
1	(1)	**9**/$[Cu(OTf)_2]$	**10**	99	–	67
2	(1)	**6**/$[Cu(OTf)_2]$	**10**	64	–	26
3	(2)	**9**/CuOTf	**11**	68	65:35	78
4	(2)	**6**/CuOTf	**11**	55	73:27	60
5	(2)	**6**/CuOTf[c]	**11**	60	70:30	56
6	(2)	**6**/CuOTf[d]	**11**	65	77:23	3
7	(2)	**9**/CuOTf[e]	**11**	60	67:33	66
8	(2)	**6**/CuOTf[f]	**11**	50	65:35	44
9	(1)	**9**/$[Cu(OTf)_2]$[g]	**10**	96	–	65

[a] Determined by 300 MHz ^1H NMR analysis of the crude reaction products. [b] Determined by the Mosher ester method (compound **10**), or by HPLC on a chiral stationary phase (compound **11**). In the case of adducts **11** the reported *ee* is that of the major isomer.[c] See ref.[14]. [d] Reaction carried out in a 1:1 mixture of acetonitrile/perfluorooctanes as solvent.[e] With a sample of ligand **9** recycled from the reaction of entry 3 (see text). [f] With a sample of ligand **9** recycled from the reaction of entry 4 (see text). [g] With a sample of ligand **9** recycled from the reaction of entry 1 (see text).

CH_2Cl_2/perfluorooctanes (1:1) mixture, the yield and the *ee* dropped to 64 and 26%, respectively (Entry 2, Table 1).

The cyclopropanation[14] [Equation (2), Scheme 2; Entry 3, Table 1] of styrene (5 mol-equiv.) carried out with ethyl diazoacetate (1 mol-equiv., addition time ca. 10 h) in the presence of ligand **9** (11 mol%) and CuOTf (10 mol%) in CH_2Cl_2 (12 h from the end of the addition of diazoacetate, room temp.) gave a 65:35 mixture of the *trans*/*cis* cyclopropane adducts in 68% yield. The major *trans* isomer **11** had a 78% *ee* (as determined by HPLC on a chiral stationary phase). The use of ligand **6** in a CH_2Cl_2/perfluorooctanes (1:1) mixture of solvent led to a 55% yield of the *trans*/*cis* (73:27) mixture, with the *trans* isomer being obtained in 60% *ee* (Entry 4, Table 1).[15] When ligand **6** was used in a mixture of acetonitrile/perfluorooctanes (1:1) (Entry 6, Table 1), the *ee* of the *trans* adduct **11** was only 3% (65% yield, *trans*/*cis* = 77:23).

Discussion

The data collected in Table 1 showed that ligand **9** (the one with two perfluorinated ponytails) performed consistently better than ligand **6** (four perfluorinated ponytails) in terms of enantioselectivity. Working with ligand **9**, *ee* values about 20% lower than those obtained with the best ligands reported in the literature[13,14] were observed.[16] Indeed, the use of F-box **9** in the ene reaction led to product **10** in 67% *ee* compared with 89% *ee* obtained by Evans using the catalyst derived from the *gem*-dimethyl-substituted box (**1** with two methyl groups at the bridging carbon atom) at identical concentration.[13] In the cyclopropanation reaction a 78% *ee* was achieved for **11** working with ligand **9**, while the same product was isolated in 99% *ee*[14] with the catalyst derived from the *gem*-dimethyl-substituted box.

To attempt a rationalization of the obtained results, we considered the influences exerted by the substitution pattern at the box-bridging carbon atom, and by the introduction of the perfluoroalkyl ponytails. We studied the influence of the substitution pattern in the case of ligand **6**, i.e. the less effective one. By running the ene reaction of Equation (1) (Scheme 1) in the presence of the catalyst derived from C_2-symmetric box **3** and [Cu(OTf)$_2$], adduct **11** was obtained in 71% yield and 82% *ee*.[17] Although slightly poorer than that obtained with the best performing box under similar conditions (89%),[13] the observed *ee* was clearly higher than that obtained with either F-box **6** or **9** as ligands.

This finding pointed to some negative effects exerted by the perfluorinated ponytails. Any explanation of these effects must also account for the observed inverse relationship existing between the fluorine loading of the ligands and the enantioselectivity of their reactions. In a first hypothesis we can surmise that the fluorinated ponytails of **6** and **9** prevent copper chelation by altering the electronic availability (and, hence, the chelating ability) of the box nitrogen atoms. However, it seems likely that the long spacer (two phenyl rings and four saturated atoms) separating the perfluoroalkyl chains from the sites of chelation should effectively prevent this effect.[9f,18]

Alternatively, we can hypothesize that the two heavily fluorinated substituents at the bridging carbon atom in ligand **6** experience a strong repulsion, both steric and electronic in origin. This should result in a reduced "bite angle" for the box moiety, and more difficult complexation of the copper ion.[19] Under this hypothesis, an undetermined amount of catalytically active copper(II) cations noncomplexed by **6** could be present in the reaction medium, promoting a poorly enantioselective transformation. This negative effect should be felt more in the case of the ene reaction, which is known[20] to be catalyzed by a box/Cu^{II} complex adopting a square-planar geometry particularly sensitive to the box "bite angle".[21] Since in ligand **9** the bridging substitution is sterically less demanding than in **6**, ligand/copper cation complexation should be easier and this should result in more enantioselective reactions. It must be noted that this behavior is not a general feature of chiral F-catalysts since in other cases they were found to perform as efficiently as their non-fluorinated counterparts.[10]

We then studied the recovery of ligands **6** and **9**. The solubility properties of these F-box (see above) required the use of different procedures. First, both ligands were released from the copper cation by decomplexation with an aqueous solution containing cyanide ions, carried out on the crude reaction mixture. After a standard workup, ligand **9** was then recovered by filtration through a short silica-gel column, whereas ligand **6** was recovered by separation of the CH_2Cl_2/perfluorooctanes mixture and evaporation of the latter solvent. The ligands recovered from both the cyclopropanation and the ene reaction were shown to be stable under the reaction and recovery conditions (they gave ^1H and ^{19}F NMR spectra identical to those of fresh samples).

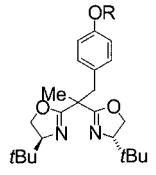
However, F-box **6** and **9** recovered from the cyclopropanation reaction were found (by ^1H NMR spectroscopy) to be contaminated by considerable amounts of ethyl diazoacetate derived decomposition products.[22] Indeed, recycling of the recovered ligand **9** in a second cyclopropanation reaction (Entry 7, Table 1) led to the isolation of a *trans*/*cis* (67:33) mixture in 60% yield, with adduct **11** having a 66% *ee*. Further recovery/recycling showed a fast decrease of both the chemical yields and the *ee* of the product, as the results of accumulation of the contaminants in recovered **9** (at the fourth cycle level: 40% yield, 37% *ee*). Similarly, one recycling of the recovered ligand **6** (Entry 8, Table 1), led to adduct **11** in 44% *ee*.

In contrast, the F-box recovered from the ene reaction were shown to be pure compounds (within the detection limits of ^1H and ^{19}F NMR analysis). The recovery yields were 89% and 64% for compounds **6** and **9**, respectively.[23] As expected, recycling of the latter in the reaction of Equation (1) (Entry 9, Table 1) afforded product **10** in 96% yield and 65% *ee*; these values were very similar to those obtained with a fresh sample of ligand (Entry 1, Table 1).

Finally, we compared different solubility devices employed for the recovery and recycling of chiral box ligands. The behavior of the soluble polymer-supported PEG-box

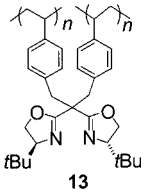
12[5] (Figure 1) was considered an excellent term of comparison to that of F-box **9**. These ligands share: (i) the substitution pattern at the bridging carbon atom and at the stereocenters; (ii) the location and the chemical nature of the site of attachment of the solubility device; and (iii) the ready solubility in CH_2Cl_2. Comparison of the data included in Figure 1 and reported in Table 1 (Entries 1 and 9) for the ene reaction [Equation (1)] shows that, at the same loading of catalyst, adduct **10** was obtained in very high yield in both the first and the second cycles. As far as the enantioselectivity is concerned, however, the reactions carried out with PEG-box **12** gave a higher *ee* than those carried out with F-box **9** (95 and 90% vs. 67 and 65%, for the first and second runs, respectively). The trend was the same, although with a smaller difference in enantioselectivity, for the cyclopropanation reaction [Equation (2); with **12**/CuOTf: 91% *ee*, Figure 1; with **9**/CuOTf: 78% *ee*, Entry 3, Table 1]. It is also worth mentioning that **12** was recovered by precipitation and filtration, whereas **9** was recovered by flash chromatography.

The identification of a supported counterpart of F-box **6** was less straightforward. Among the examples reported in the literature,[4] the insoluble homopolymeric ligand **13** of Luis and Mayoral[4a] (Figure 1) seemed the best choice. Indeed, **13** and **6** have identical substituents at the bridging carbon atom and at the stereocenters, and a very similar mode of attachment of the solubility device. The major difference between these two systems resides in their solubility. The data reported in Figure 1 showed that using **13**/CuOTf in the cyclopropanation reaction led to product in lower yields (36%), different *trans*/*cis* ratio (37:63), and higher *ee* (for the *trans* isomer **11**: 78%) compared with those obtained with F-box **6** (Entry 4, Table 1). Two recyclings of the *catalyst* derived from **13**, recovered by filtration, were possible with only marginal decrease in chemical yield and *ee*,[4a] whereas recycling of **6**, recovered by phase separation, was prevented by ligand contamination (see above).



12, R = -$(CH_2)_3$-C_6H_4-$OPEG_{5000}$OMe

Eq.	Cycle	Product	Yield (%)	*ee* (%)
(1)	1	**10**	96	95
(1)	2	**10**	91	90
(2)	1	**11**	63	91



13

Eq.	Cycle	Product	Yield (%)	*ee* (%)
(2)	1	**11**	36	78
(2)	2	**11**	33	75

Figure 1. Structure of polymer-supported box **12** and **13**

Conclusions

The synthesis of two perfluorinated bis(oxazolines) (F-box) with different fluorine contents and solubility properties has been described for the first time. When these compounds were employed as ligands in combination with Cu^{I} and Cu^{II} triflates in two catalytic enantioselective transformations (ene reaction and cyclopropanation), the products were obtained in similar chemical yield and about 20% lower *ee* compared with the reactions carried out with the best performing ligands. Recovery of the F-box was possible by two procedures, involving chromatography in one case and phase separation in the other. While the ligands recovered from the cyclopropanation reaction were contaminated by decomposition products, those recovered from the ene reaction could be recycled, affording the product in chemical yield and enantioselectivity almost identical to those observed in the first cycle. The F-box were compared to structurally related box supported on soluble and insoluble polymers, in terms of chemical and stereochemical efficiency, and of simplicity of recovery and recycling. As a whole, the collected data indicated that the identification of a "good-for-all" approach toward the development of an easily recyclable enantioselective catalyst still requires an extensive research effort.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz in [D]chloroform ($CDCl_3$) 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 $\delta = 77.0$ ppm in $CDCl_3$. ^{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 from thin films or solutions in CH_2Cl_2. Compounds **2**, **7**, and **8** were prepared as described.[5] Adducts **10** and **11** are known compounds of established absolute configurations.[13,14] The *ee* of compound **10** was determined by ^{1}H NMR spectroscopy of the corresponding Mosher's ester obtained by reaction with the (*R*) enantiomer of the Mosher's acid chloride. The esters gave signals identical to those reported by Evans (see the Supporting Information of ref.[13]). The diagnostic signals were those of the vinyl protons that resonated 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 **11** was determined by HPLC on a chiral stationary phase: column Chiracel OD; eluent: hexane/*i*PrOH (85:15); flow rate: 1 mL/min; $\lambda = 210$ nm. t_R of the major enantiomer: 4.83 min; t_R of the minor enantiomer: 5.53 min.

1-(Bromomethyl)-3,5-bis(*n*-perfluorooctyl)benzene (5): PBr_3 (0.3 mL, 3.2 mmol) was added by syringe over 5 min to a stirred solution of 3,5-bis(*n*-perfluorooctyl)benzyl alcohol[12] (3.78 g, 4.0 mmol) in dry THF (40 mL), kept under nitrogen at 0 °C. The turbid mixture was stirred at 0 °C for 1 h, then at room temp. for a further 3 h. ^{1}H NMR spectroscopy of the mixture showed complete

conversion of the starting alcohol. Concentration under reduced pressure afforded a white solid that was dissolved in Et_2O (40 mL). The organic solution was washed with H_2O (2 × 15 mL) and brine (15 mL), and dried with Na_2SO_4. Column chromatography of the crude product with a hexanes/Et_2O (85:15) mixture as eluent afforded the product (2.49 g, 2.48 mmol, yield 62%) as a colorless solid. M.p. 46−47 °C. ^{1}H NMR: δ = 4.58 (s, 2 H, CH_2), 7.76 (s, 1 H, aromatic H *para* to CH_2), 7.86 (s, 2 H, aromatic H *ortho* to CH_2) ppm. ^{13}C NMR: δ = 29.8, 119.5−106.5 (m, fluorinated C), 125.4, 130.0 (t, $^2J_{C,F}$ = 22.5 Hz), 131.0, 140.2 ppm. ^{19}F NMR: δ = −81.2 (t, $^3J_{F,F}$ = 10 Hz, 6 F), −111.5 (t, $^3J_{F,F}$ = 14 Hz, 4 F), −121.6 (br. s, 4 F), −122.3 (br. s, 12 F), −123.2 (br. s, 4 F), −126.6 (br. s, 4 F) ppm. $C_{23}H_5BrF_{34}$ (1007.1): calcd. C 27.43, H 0.50; found C 27.58, H 0.51.

Synthesis of F-box 6 and 9: These compounds were prepared by a multistep synthesis starting from the commercially available box **1** and the known benzyl bromide **2**.

2,2-Bis[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl]-1,3-bis[4-(prop-2-en-1-yloxy)phenyl]propane (3): MeLi in Et_2O (0.52 mL of a 1.6 M solution, 0.826 mmol) was added dropwise to a stirred solution of box **1** (0.100 g, 0.375 mmol) in dry THF (5 mL) cooled to −55 °C under nitrogen. After 1 h of stirring at −55 °C, compound **2** (0.188 g, 0.826 mmol) in THF (3 mL) was added dropwise and the reaction mixture was stirred for 4.5 h at −10 °C. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography with a hexanes/EtOAc (9:1) mixture as eluent to afford the product (0.155 g, 0.2775 mmol, 74% yield) as a thick pale-yellow oil. $[\alpha]_D^{22}$ = −73.8 (*c* = 2.77 in $CHCl_3$). IR: ṽ = 2928, 2853, 1655, 1510, 1262 cm^{-1}. ^{1}H NMR: δ = 0.86 (s, 18 H, *t*Bu), 3.11 (A part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.39 (B part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.81 (dd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 8.6 Hz, 2 H, 1 H of isoxazoline CH_2), 4.00 (t, $^3J_{H,H}$ = 8.6 Hz, 2 H, CH*t*Bu), 4.09 (dd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 8.6 Hz, 2 H, 1 H of isoxazoline CH_2), 4.53 (dt, $^3J_{H,H}$ = 5.2, $^4J_{H,H}$ = 1.5 Hz, 4 H, OCH_2C=C), 5.36 (dq, $^2J_{H,H}$ = 1.5, $^3J_{H,H}$ = 10.2, $^4J_{H,H}$ = 1.5 Hz, 2 H, H *cis* to H in CH=CH_2), 5.42 (dq, $^2J_{H,H}$ = 1.5, $^3J_{H,H}$ = 17.2, $^4J_{H,H}$ = 1.5 Hz, 2 H, H *trans* to H in CH=CH_2), 6.06 (m, 2 H, CH=CH_2), 6.82 (A part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 4 H, aromatic H *ortho* to O), 7.17 (B part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 4 H, aromatic H *meta* to O) ppm. ^{13}C NMR: δ = 25.8, 33.9, 38.6, 48.5, 68.3, 68.8, 75.1, 114.2, 117.4, 129.4, 131.5, 133.5, 157.3, 166.3 ppm. $C_{35}H_{46}N_2O_4$ (558.8): calcd. C 75.23, H 8.30, N 5.01; found C 75.62, H 8.51, N 4.92.

2,2-Bis[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl]-1,3-bis(4-hydroxyphenyl)propane (4): A solution of compound **3** (0.559 g, 1 mmol) in ethanol (15 mL) containing $Pd(OAc)_2$ (0.045 g, 0.2 mmol) and PPh_3 (0.231 g, 0.88 mmol) was refluxed for 90 min. The resulting mixture was cooled to room temperature and SiO_2 (2 g) was added in one portion. After stirring at room temperature for 40 min, the mixture was filtered through a Celite plug, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography with a CH_2Cl_2/EtOAc (6:4) mixture as eluent to give the product (0.45 g, 0.94 mmol, 94% yield). M.p. 200 °C (dec). $[\alpha]_D^{22}$ = +129.3 (*c* = 0.65 in $CHCl_3$). $[\alpha]_D^{22}$ = −99.1 (*c* = 0.6 in MeOH). IR: ṽ = 3583, 3054, 1648, 1515, 1438, 1266 cm^{-1}. ^{1}H NMR ([D$_6$]EtOH): δ = 0.88 (s, 18 H, *t*Bu), 3.07 (A part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.31 (B part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.76 (dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 7.6 Hz, 2 H, 1 H of isoxazoline CH_2), 4.08 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH*t*Bu), 4.16 (dd, $^2J_{H,H}$ = 9.8, $^3J_{H,H}$ = 7.6 Hz, 2 H, 1 H of isoxazoline CH_2), 6.74 (A part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 4 H, aromatic H *ortho* to O), 7.07 (B part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 4 H, aromatic H *meta* to O) ppm. ^{13}C NMR: δ = 25.1, 33.5, 38.0, 48.5, 68.2, 75.1, 114.6, 127.0, 131.1, 156.0, 166.5 ppm. $C_{29}H_{38}N_2O_4$ (478.6): calcd. C 72.77, H 8.00, N 5.85; found C 72.70, H 8.21, N 5.77.

1,3-Bis(4-{[3,5-bis(perfluorooctyl)phenyl]methoxy}phenyl)-2,2-bis[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl]propane (6): Cesium carbonate (0.344 g, 1.057 mmol), and benzyl bromide **5** (0.257 g, 0.272 mmol) were added to a solution of bis(phenol) **4** (0.072 g, 0.151 mmol) in DMF (2 mL) stirred under nitrogen at 50 °C. The mixture was stirred at 50 °C for 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 with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography with a hexanes/Et_2O (8:2) mixture as eluent to give the product (0.128 g, 0.056 mmol, 37% yield). M.p. 48−50 °C. $[\alpha]_D^{22}$ = −17.2 (*c* = 0.9 in $CHCl_3$). IR: ṽ = 3051, 2955, 1657, 1510, 1266, 741 cm^{-1}. ^{1}H NMR: δ = 0.86 (s, 18 H, *t*Bu), 3.12 (A part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.40 (A part of an AB system, $^2J_{H,H}$ = 14.2 Hz, 2 H, 1 H of PhCH_2), 3.83 (dd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 10.0 Hz, 2 H, 1 H of oxazoline CH_2), 4.00 (t, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 8.6 Hz, 2 H, 1 H of oxazoline CH_2), 4.07 (dd, $^3J_{H,H}$ = 8.6, 10.0 Hz, 2 H, CH*t*Bu), 5.18 (s, 4 H, ArCH_2O), 6.88 (A part of an AB system, $^3J_{H,H}$ = 8.7 Hz, 4 H, aromatic H *ortho* to O), 7.21 (B part of an AB system, $^3J_{H,H}$ = 8.7 Hz, 4 H, aromatic H *meta* to O), 7.79 (s, 2 H, aromatic H *para* to CH_2O), 7.92 (s, 4 H, aromatic H *ortho* to CH_2O) ppm. ^{13}C NMR: δ = 25.7, 33.9, 38.8, 48.4, 68.3, 68.5, 75.6, 114.3, 119.5−106.5 (m, C_8F_{17}), 124.9, 129.0, 130.4 (t, $^2J_{C,F}$ = 22.0 Hz), 131.7, 139.7, 156.8, 166.2 ppm. ^{19}F NMR: δ = −81.3, −111.4, −121.6, −122.3, −123.2, −126.6 ppm. $C_{75}H_{46}F_{68}N_2O_4$ (2331.1): calcd. C 38.64, H 1.99, N 1.20; found C 38.43, H 2.03, N 1.24.

1-(4-{[3,5-Bis(perfluorooctyl)phenyl]methoxy}phenyl)-2,2-bis{2-[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl}propane (9): Cesium carbonate (0.152 g, 0.468 mmol) and benzyl bromide **5** (0.156 g, 0.156 mmol) were added to a solution of phenol **8** (0.060 g, 0.156 mmol) in DMF (2 mL), stirred under nitrogen at 50 °C. The mixture was stirred at 50 °C for 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 with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography with a CH_2Cl_2/Et_2O (8:2) mixture as eluent to give the product (0.111 g, 0.084 mmol, 54% yield) as a pale yellow viscous oil. $[\alpha]_D^{22}$ = −18.8 (*c* = 0.48 in $CHCl_3$). IR: ṽ = 3054, 2981, 1657, 1510, 1266, 741 cm^{-1}. ^{1}H NMR: δ = 0.85 (s, 9 H, *t*Bu), 1.43 (s, 3 H, *Me* at bridging C), 3.17 (A part of an AB system, $^2J_{H,H}$ = 14.0 Hz, 1 H, 1 H of PhCH_2), 3.37 (A part of an AB system, $^2J_{H,H}$ = 14.0 Hz, 1 H, 1 H of PhCH_2), 3.82 (dd, $^3J_{H,H}$ = 8.5, 10.0 Hz, 1 H, CH*t*Bu), 3.90 (dd, $^3J_{H,H}$ = 8.5, 10.0 Hz, 1 H, CH*t*Bu), 4.05 (t, $^3J_{H,H}$ = 8.5, $^2J_{H,H}$ = 8.5 Hz, 1 H, remaining H of 2 CH_2O of oxazolines), 4.23−4.12 (m, 3 H, 3 H of 2 CH_2O of oxazolines), 5.17 (s, 2 H, ArCH_2O), 6.87 (A part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 2 H, aromatic H *ortho* to O), 7.13 (B part of an AB system, $^3J_{H,H}$ = 8.5 Hz, 2 H, aromatic H *meta* to O), 7.77 (s, 1 H, aromatic H *para* to CH_2O), 7.91 (s, 2 H, aromatic H *ortho* to CH_2O) ppm. ^{13}C NMR: δ = 21.1 25.7, 33.7, 33.9, 41.2, 43.5, 68.5, 68.7, 75.4, 75.6, 114.4, 119.5−106.5 (m, C_8F_{17}), 124.9, 129.0, 129.3, 130.2 (t, $^2J_{C,F}$ = 22.5 Hz), 131.8, 139.7, 156.9, 167.2, 167.7 ppm. ^{19}F NMR: δ = −81.3, −111.4, −121.6,

−122.3, −123.2, −126.6 ppm. $C_{46}H_{38}F_{34}N_2O_3$ (1312.8): calcd. C 42.09, H 2.92, N 2.13; found C 42.33, H 2.96, N 2.11.

Stereoselective Syntheses Promoted by F-box Ligands 6 and 9: The reactions carried out with ligand **9** are illustrative of the procedure.

Ene Reaction: A solution was prepared by dissolving under nitrogen ligand **9** (0.039 g, 0.030 mmol) and $[Cu(OTf)_2]$ (0.012 g, 0.033 mmol) in dry CH_2Cl_2 (2 mL). The resulting dark-green solution was stirred at room temperature for 4 h and then 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), cooled to 0 °C. The resulting mixture was stirred overnight while the temperature was allowed to slowly increase from 0 °C to room temperature. The mixture was then concentrated under vacuum, and the residue was dissolved in CH_2Cl_2 (5 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum to give the crude product, which was purified by flash chromatography with a hexanes/Et_2O (7:3) mixture as eluent. Yields and *ee* of adduct **10** are reported in Table 1.

Cyclopropanation: A solution was prepared by stirring under nitrogen ligand **9** (0.039 g, 0.030 mmol) and commercially available CuOTf·0.5PhH (0.008 g, 0.033 mmol) in dry CH_2Cl_2 (2 mL) at room temperature for 2 h. To the resulting pale-yellow solution, freshly distilled styrene (0.157 mL, 1.5 mmol) was added. Ethyl diazoacetate (0.034 mL, 0.3 mmol), dissolved in CH_2Cl_2 (1 mL), was added over a period of 10 h by a syringe pump, and the mixture was stirred for 20 h at room temperature. The mixture was then concentrated under vacuum, and the residue was dissolved in CH_2Cl_2 (5 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum to give the crude product, which was purified by flash chromatography with a hexanes/EtOAc (95:5) mixture as eluent. Yields and *ee* of adduct **11** are reported in Table 1.

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marginally different results were observed (60% yield, *trans*/*cis* = 70:30, 56% *ee*; see Entry 5, Table 1).

[16] When the [Cu(OTf)$_2$] complexes of ligands **6** and **9** were employed to catalyze the Diels−Alder cycloaddition between cyclopentadiene and *N*-acryloyloxazolidinone, the corresponding cycloadducts were obtained in high yield, excellent *endo* diastereoselectivity, and low *ee*.

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