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Synthesis of two new chiral fluorous bis(oxazolines) and their applications as ligands in catalytic asymmetric reactions

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Abstract—Two new chiral fluorous bis(oxazolines) with a fluorous content of 56.9% and 59.3%, respectively, have been prepared starting from (*S*)-serine and (*S*)-tyrosine. Applications of these compounds as fluorous box ligands in asymmetric alkylations gave ees up to 92%, and in allylic oxidations ees up to 50%. Recycling and reuse of the ligands in asymmetric alkylation and of the catalytic system in allylic oxidation gave the same enantioselectivities.

1. Introduction

The C_2-symmetric enantiopure bis(oxazolines) (box) have emerged as one of the most efficient classes of chiral ligands in the field of asymmetric organometallic catalysis.[1–7] The broad range of applications of these chiral ligands and the very high enantioselectivities obtained have stimulated an intense research activity concerning their immobilization on supports in order to recover and recycle the chiral catalyst.[8] This heterogenization has been performed using bonding to solid inorganic[9–15] or organic supports,[16,17] as well as to soluble organic polymers.[18–21] These different approaches gave enantioselectivities quite similar to those obtained using usual homogeneous conditions.

The fluorous biphase catalysis is quite a new concept.[22] In this approach, a soluble and easily recoverable ligand can be obtained by the introduction of fluorous ponytails in the molecule. This approach has been extended more or less successfully to some asymmetric organometallic catalysis in a two-phase system organic solvent–fluorous solvent. Some perfluoroalkyl-substituted chiral box ligands have been reported by us[23,24] and by Benaglia and co-workers,[25] and used as ligands in allylic alkylation, allylic oxidation, cyclopropanation, and ene reactions. In most cases, high enantioselectivities have been obtained, and the chiral catalysts, or at least the chiral ligands, were easily recovered and reused with the same enantioselectivities.

Herein, we report the synthesis of two new fluorous bis(oxazolines) having a fluorine content as high as 59% and their use as chiral ligands in three representative enantioselective catalytic reactions.

2. Results and discussion

In our paper concerning the use of chiral fluorous bis(oxazolines) in allylic alkylation and allylic oxidation, although enantioselectivities as high as those obtained using non-fluorous bi(oxazolines) were obtained, the main problem was the recycling of the catalyst. In order to try to circumvent this problem, one solution was to increase the fluorine content of the bis(oxazoline), by the introduction of more than two fluorous ponytails.

Treatment of (*S*)-serine with di-*tert*-butyl dicarbonate (Boc_2O) in dioxane in the presence of sodium hydroxide gave quantitatively (*S*)-*N*-Boc-serine **3**.[26] Amino acid **3** was reacted with sodium hydride (2.2 mol equiv) in DMF at room temperature, and then alkylated first with allyl bromide (1 mol equiv) and then with methyl iodide (1 mol equiv) according to a modified literature procedure[27,28] to afford the amino ester **4** in 53% isolated yield after column chromatography. Introduction of the fluorous ponytails was performed by the addition of

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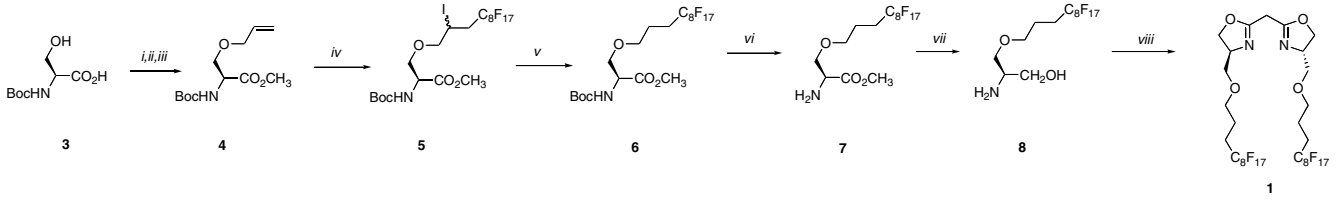
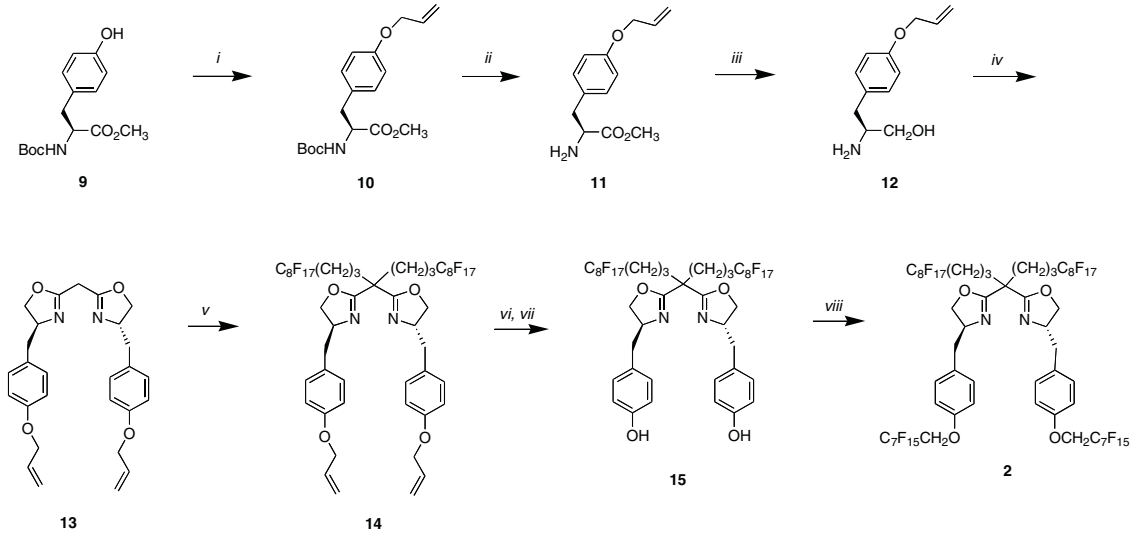
perfluorooctyl iodide to compound **4** in the presence of AIBN[29] to give the fluorous amino ester **5** as a mixture of epimers in 71% yield, whose reaction with tributyltin hydride in the presence of AIBN in trifluorotoluene at 80 °C gave the fluorous amino ester **6** in 78% isolated yield. Deprotection of the *N*-Boc was performed in the presence of CF_3CO_2H in CH_2Cl_2[30] to afford compound **7** in 92% yield. Reduction of the ester function of amino ester **7** using sodium borohydride in methanol according to the literature procedure[31] gave the fluorous amino alcohol **8** in 94% yield. Finally, condensation of amino alcohol **8** (2 M equiv) with malonimidate ethyl ester dihydrochloride in CH_2Cl_2 at room temperature[32] afforded the fluorous bis(oxazoline) **1** in 43% isolated yield. Unfortunately, all attempts to introduce two other fluorous ponytails on the methylene position of this bis(oxazoline) **1** by alkylation according to the methodology used previously[24] were unsuccessful; we always obtained a mixture of by-products whatever the conditions used (Scheme 1).

Thus, we turned our attention to another approach. Treatment of (*S*)-*N*-Boc-tyrosine methyl ester **9**[33] with allyl bromide in DMF at room temperature in the presence of potassium carbonate as the base afforded the amino ester **10** in 95% isolated yield. Sequential cleavage of the *N*-Boc group using CF_3CO_2H in CH_2Cl_2,[30] followed by reduction of the ester function of the amino ester using sodium borohydride in methanol,[31] afforded compounds **11** and **12** in 95% and 94% yields, respectively. Condensation of amino alcohol **12** (2 mol equiv) with malonimidate ethyl ester dihydrochloride in CH_2Cl_2 at room temperature[32] afforded the bis(oxazoline) **13** in 55% isolated yield. Treatment of bis(oxazoline) **13** with NaH (3 mol equiv) in DMF at 25 °C, followed by 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl iodide (2.3 mol equiv) in DMF at 80 °C,[24] afforded the fluorous bis(oxazoline) **14** in 72% isolated yield. Oxygen deprotection of compound **14** was carried out in ethanol at reflux with $Pd(OAc)_2$ and PPh_3 in the presence of SiO_2[25] to give fluorous bis(oxazoline) **15** in 72% yield. The introduction of two other perfluoroalkyl chains was achieved by alkylation of compound **15** with pentadecafluorooctyl nonafluorobutane sulfonate $C_7F_{15}CH_2OSO_2C_4F_{15}$ in DMF at 80 °C in the presence of cesium carbonate.[34] Fluorous bis(oxazoline) **21** bearing four ponytails was thus obtained in 66% unoptimized yield (Scheme 2).

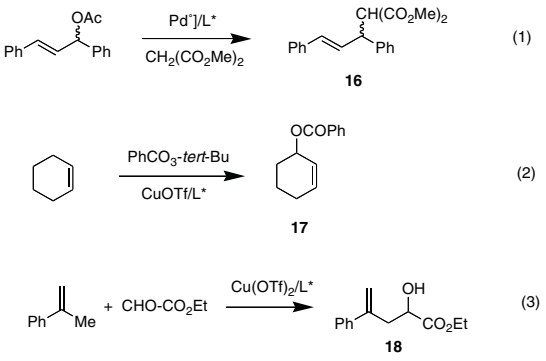
The fluorine contents of fluorous box ligands **1** and **2** were calculated as 56.9% and 59.3%, respectively. The partition coefficients P ($P = c_{FC72}/c_{organic\ solvent}$) of compounds **1** and **2** in CH_2Cl_2/FC72 (50:50, v/v) and CH_3CN/FC72 (50:50, v/v) were gravimetrically deter-



Scheme 1. Synthesis of bis(oxazoline) **1**. Reagents and conditions: (i) NaH, DMF, 0 °C; (ii) CH_2=CH–CH_2Br, rt; (iii) CH_3I, rt; (iv) $C_8F_{17}I$, AIBN, 75 °C; (v) AIBN, $HSnBu_3$, $C_6H_5CF_3$, 80 °C; (vi) CF_3CO_2H, CH_2Cl_2, rt; (vii) $NaBH_4$, CH_3OH, 35 °C; (viii) $C_2H_5OC(NH)CH_2C(NH)OC_2H_5$, 2HCl, CH_2Cl_2, rt.



Scheme 2. Synthesis of bis(oxazoline) **2**. Reagents and conditions: (i) CH_2=CH–CH_2Br, K_2CO_3, Bu_4NI, DMF, rt; (ii) CF_3CO_2H, CH_2Cl_2, rt; (iii) $NaBH_4$, CH_3OH, 35 °C; (iv) $C_2H_5OC(NH)CH_2C(NH)OC_2H_5$, 2HCl, CH_2Cl_2, rt; (v) $C_8F_{17}(CH_2)_3I$, NaH, DMF, rt; (vi) $Pd(OAc)_2$, PPh_3, C_2H_5OH, reflux; (vii) SiO_2, C_2H_5OH, rt; (viii) $C_7F_{15}CH_2OSO_2C_4F_9$, $CsCO_3$, DMF, 80 °C.



Scheme 3. Enantioselective reactions catalyzed by metal complexes of fluorous box ligands **1** and **2**.

mined as ca. 0.5 and 2.0, and 4.3 and 12.3, respectively. These values clearly show that bis(oxazoline) **2**, which has a fluorine content of 56.9% and bears four fluorous ponytails is more soluble in the fluorous solvent than bis(oxazoline) **1**, which bears only two fluorous ponytails.

Ligands **1** and **2** were tested in the representative enantioselective transformations reported in Scheme 3 (Eqs. 1, 2, and 3). The results are shown in Table 1.

These ligands were first assessed in the palladium-catalyzed allylic substitution of *rac*-(*E*)-1,3-diphenylpropenyl acetate with dimethyl malonate (Scheme 3, Eq. 1). The reaction was carried out in CH_2Cl_2 at rt in the presence of ligand **1** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol %), with BSA/KOAc being used as the base, to afford adduct **16** with only 39% conversion and 80% ee (Table 1, entry 1). When the same reaction was repeated using ligand **2**, the conversion was quantitative and the ee increased to 92% (Table 1, entry 2), quite close to the values obtained previously using similar fluorous bis(oxazolines).[24] Moreover, evaporation of the solvent at the end of the last reaction, followed by liquid–liquid extraction using FC72 as the fluorous solvent, allowed the quantitative recovery of bis(oxazoline) **2**; the reuse of this recovered ligand in another allylic alkylation afforded coupling product **16** in 98% conversion and 92% ee (Table 1, entry 3).

The enantioselective allylic oxidation of cyclohexene (Scheme 3, Eq. 2) was performed at 50 °C in $CHCl_3$/CH_3CN by forming the copper(I)triflate- or copper(I)hexafluorophosphate-bis(oxazoline) (5 mol %) and adding 80 equiv of cyclohexene followed by 20 equiv of *tert*-butyl perbenzoate. The catalyst obtained from Cu(OTf) and ligand **1** and ligand **2** gave cyclohexenyl benzoate **17** in 76% and 49% yield after 7 days at rt and 2 days at 50 °C, respectively, and with ee up to 43% and 50% ee (Table 1, entries 4 and 5). The catalyst obtained by mixing $[Cu(CH_3CN)_4]PF_6$ and ligand **2** only gave 12% yield after 3 days (Table 1, entry 7). Moreover, evaporation of the solvents using Cu(OTf) as the copper precursor and ligand **2**, followed by the addition of hexane, allowed the precipitation of the complex; this precipitated complex was reused in another allylic oxidation to give the allylic benzoate **17** in 43% yield and 50% ee after 2 days (Table 1, entry 6). The recycling of this catalyst gave higher conversion with similar ee than the previously described fluorous bis(oxazolines).[24]

Finally, the ene reaction between α-methylstyrene and ethyl glyoxalate (Scheme 3, Eq. 3) was carried out from 0 °C to room temperature for 24 h in CH_2Cl_2 in the presence of $[Cu(OTf)_2]$ and ligand **2** to afford adduct **18** in 32% yield and only 5% ee (Table 1, entry 8).

3. Conclusion

In conclusion, two new chiral fluorous bis(oxazolines) with a fluorous content of 56.9% and 59.3%, respectively, have been prepared starting from (*S*)-serine and (*S*)-tyrosine, the latter bearing four fluorous ponytails. Applications of these fluorous box ligands in asymmetric alkylation gave ee up to 92%, and in allylic oxidation ee up to 50%. Recycling and reuse of the ligand bearing the four ponytails (%F = 59.3%) in asymmetric alkylation, and of the catalytic system in allylic oxidation are now effective, the same enantioselectivities being obtained.

Table 1. Enantioselective reaction catalyzed by fluorous box ligands **1** and **2**

Entry	Equation in Scheme 3	Catalyst	Solvent	Time (h)	Yield (%)	ee (%) (config.)[a]
1	1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**1**	CH_2Cl_2	24	39[b] (**16**)	80 (*S*)
2	1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**2**	CH_2Cl_2	24	98[b] (**16**)	92 (*S*)
2 Bis[c]	1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**2**	CH_2Cl_2	24	98[b] (**16**)	92 (*S*)
3	2	CuOTf·0.5C_6H_6/**1**	$CHCl_3/CH_3CN$	168	76 (**17**)	43 (*S*)
4[d]	2	CuOTf·0.5C_6H_6/**2**	$CHCl_3/CH_3CN$	48	49 (**17**)	50 (*S*)
4 Bis[d,e]	2	CuOTf·0.5C_6H_6/**2**	$CHCl_3/CH_3CN$	48	43 (**17**)	50 (*S*)
5[d]	2	$[Cu(CH_3CN)_4]PF_6$/**2**	FC72/CH_3CN	72	12 (**17**)	nd
6	3	$Cu(OTf)_2$/**2**	CH_2Cl_2[f]	24	32 (**18**)	5 (*R*)

[a] The ee values were determined by HPLC using a chiral column Chiralpak AD, and the absolute configuration was determined by comparison of the HPLC retention time with the literature data.
[b] The conversion was determined by GC.
[c] Recycling of the ligand by liquid extraction.
[d] Reaction performed at 50 °C.
[e] Recycling of the catalyst by precipitation with hexane.
[f] THF (0.5 mL) was added.

4. Experimental

4.1. General

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer Model 241 polarimeter. The NMR spectra (^{1}H: 300 MHz, ^{13}C: 75 MHz, ^{19}F: 282 MHz) were recorded on a Bruker AM 300 instrument with Me_4Si, $CDCl_3$, and $CFCl_3$ as the internal standard, respectively. Exact mass spectra were recorded on a Finnigan Mat 95 XL spectrometer. Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). The reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere.

The solvents were purified by standard procedures, and commercial products used as received. Pentadecafluorooctyl nonafluorobutane sulfonate[34] and (*S*)-*N*-Boc-tyrosine methyl ester **9**[33] were prepared according to the literature procedure.

4.2. (*S*)-*N*-Boc-serine 3

Di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) in dioxane (10 mL) was added at 0 °C to a solution of (*S*)-serine (1 g, 9.5 mmol) in aqueous 1 M NaOH (10 mL). After being stirred at rt for 3 h, an aqueous 1 M solution of $KHSO_4$ (10 mL) was added at 0 °C. The aqueous phase was extracted with ethyl acetate (3×20 mL), and the combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave (*S*)-*N*-Boc-serine **3** (1.91 g, 98% yield) as an oil. $[\alpha]_D^{25} = -3.2$ (*c* 1.8, CH_3CO_2H); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H, CH_3), 3.86 (m, 1H, CH_2O), 4.03 (m, 1H, CH_2O), 4.37 (m, 1H, CHN), 5.83 (br s, 1H, NH). These physical data are in agreement with those published previously.[26]

4.3. (*S*)-*O*-Allyl-*N*-Boc-serine methyl ester 4

To a solution of amino ester **3** (1.92 g, 9.4 mmol) in DMF (20 mL) was added NaH (0.49 mg, 20.6 mmol). After being stirred for 30 min at 0 °C, allyl bromide (0.77 mL, 8.9 mmol) was added and the solution was stirred at 0 °C for 5 min, then at rt for 3 h. Methyl iodide (0.74 mL, 11.9 mmol) was added and the reaction stirred at rt for 1 h. The addition of a saturated aqueous solution of NaCl (30 mL) gave a solid that was filtered. The filtrate was extracted with diethyl ether (3×20 mL), and the combined organic phases were washed with a saturated aqueous solution of NaCl (20 mL). Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel, using a 4:1 mixture of petroleum ether/ethyl acetate as the eluent to give (*S*)-serine methyl ester **4** (1.29, 53% yield) as an oil. R_f 0.64 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{25} = +16.9$ (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, CH_3), 3.64 (dd, $J = 9.5$, 3.4 Hz, 1H, CH_2O), 3.76 (s, 3H, OCH_3), 3.85 (dd, $J = 9.5$, 3.4 Hz, 1H, CH_2O), 3.96–3.98 (m, 2H, OCH_2), 4.42 (m, 1 H, CHN), 5.17–5.27 (m, 2H, $=CH_2$), 5.36 (br s, 1H, NH), 5.77–5.90 (m, 1H, –CH=); ^{13}C NMR ($CDCl_3$): δ 28.7, 52.8, 54.4, 70.3, 72.6, 80.3, 117.7, 134.4, 155.5, 171.6. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16. Found: C, 55.21; H, 7.95.

4.4. (*S*)-*N*-Boc-*O*-(1*H*,1*H*,2*H*,3*H*,3*H*-2-iodo-perfluoroundecanyl)serine methyl ester 5

A mixture of (*S*)-serine methyl ester **4** (1.3 g, 5 mmol), perfluorooctyl iodide (2.7 g, 5 mmol), and AIBN (41.1 mg, 0.25 mmol) was warmed at 75 °C for 1 h. After being cooled at rt, AIBN (41.1 mg, 0.25 mmol) was added again and the mixture warmed at 75 °C for 1 h. This experiment was done once more and the mixture warmed for 24 h. After being cooled to rt, the mixture was directly purified by column chromatography on silica gel, using a 4:1 mixture of petroleum ether/ethyl acetate as the eluent to give fluoro amino ester **5** (2.86 g, 71% yield) as a white solid. Mp 68–70 °C; R_f 0.58 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{25} = +11.3$ (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.46 and 1.47 ($2 \times$ s, 9H, CH_3), 2.71–3.00 (m, 2H, CH_2CF_2), 3.74–3.82 (m, 3H, CH_2O), 3.76 and 3.78 ($2 \times$ s, 3H, OCH_3), 3.95 (m, 1H, CH_2O), 4.36 (m, 1H, CHI), 4.51 (m, 1H, CHN), 5.51 (br s, 1 H, CHN); ^{13}C NMR ($CDCl_3$): δ 13.9, 14.1, 28.2, 28.3, 37.7 (t, $J = 22.3$ Hz), 52.4, 52.5, 54.1, 71.2, 71.3, 75.9, 76.0, 80.1, 110.9–119.2, 155.6, 155.7, 170.9; ^{19}F NMR ($CDCl_3$): δ −127.3 (m, 2F), −124.5 (m, 2F), −123.0 (m, 2F), −122.6 (m, 6F), −114.6 (m, 2F), −82.2 (t, $J = 9.3$ Hz, 3F). Anal. Calcd for $C_{20}H_{21}F_{17}INO_5$: C, 29.83; H, 2.63. Found: C, 29.74; H, 2.62.

4.5. (*S*)-*N*-Boc-*O*-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecanyl)serine methyl ester 6

To a mixture of iodo derivative **5** (2.8 g, 3.48 mmol) and AIBN (52.2 mg, 0.35 mmol) in $C_6H_5CF_3$ (15 mL) was added under argon $HSnBu_3$ (1.4 mL, 5.22 mmol). After being stirred for 3 h at 80 °C, the solvent was evaporated and the residue purified by column chromatography on silica gel, using a 4:1 mixture of petroleum ether/ethyl acetate as the eluent to give fluoro amino ester **6** (1.84 g, 78% yield) as an oil. R_f 0.48 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{25} = +10.9$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, CH_3), 1.86–1.89 (m, 2H, CH_2), 2.12–2.15 (m, 2H, CH_2CF_2), 3.51–3.57 (m, 2H, CH_2O), 3.70 (dd, $J = 9.4$, 3.0 Hz, 1H, CH_2O), 3.75 (s, 3H, OCH_3), 3.85 (dd, $J = 9.4$, 3.0 Hz, 1H, CH_2O), 4.50 (m, 1H, CHN), 5.48 (br s, 1 H, CHN); ^{13}C NMR ($CDCl_3$): δ 20.7, 27.8 (t, $J = 21.6$), 28.2, 52.2, 54.1, 69.8, 70.9, 80.0, 115.4–118.7, 155.7, 171.2; ^{19}F NMR ($CDCl_3$): δ −127.4 (m, 2F), −124.5 (m, 2F), −123.9 (m, 2F), −122.9 (m, 6F), −115.5 (m, 2F), −82.3 (t, $J = 9.3$ Hz, 3F). Anal. Calcd for $C_{20}H_{22}F_{17}NO_5$: C, 35.36; H, 3.26. Found: C, 35.60; H, 3.20.

4.6. (*S*)-*O*-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluoroundecanyl)-serine methyl ester 7

To a solution of fluorous amino ester **6** (2.33 g, 3.42 mmol) in CH_2Cl_2 (10 mL) was slowly added trifluoroacetic acid (3.8 mL, 21.8 mmol). After being stirred for 1 h at rt, the solvent was evaporated, and a

saturated aqueous solution of $NaHCO_3$ (10 mL) added. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), and the combined organic phases dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel, using a 9:1 mixture of CH_2Cl_2/CH_3OH as the eluent to give (*S*)-serine methyl ester **7** (1.82 g, 92% yield) as an oil. R_f 0.54 (CH_2Cl_2/CH_3OH 9:1); $[\alpha]_D^{25} = +1.8$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.81 (br s, 2H, NH_2), 1.85–1.92 (m, 2H, CH_2), 2.03–2.25 (m, 2H, CH_2CF_2), 3.48–3.60 (m, 2H, CH_2O), 3.62–3.72 (m, 3H, CH_2O), 3.74 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 20.7, 27.9 (t, $J = 22.3$), 52.1, 55.0, 69.9, 72.9, 108.9–119.3, 174.4; ^{19}F NMR ($CDCl_3$): δ −127.4 (m, 2F), −124.6 (m, 2F), −124.0 (m, 2F), −123.1 (m, 6F), −115.6 (m, 2F), −82.3 (t, $J = 10.3$ Hz, 3F). Anal. Calcd for $C_{15}H_{14}F_{17}NO_3$: C, 31.10; H, 2.44. Found: C, 30.79; H, 2.08.

4.7. (*R*)-2-Amino-3-[(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecanyl)oxy]-propan-2-ol 8

To a solution of compound **7** (2.06 g, 3.56 mmol) in CH_3OH (15 mL) was added $NaBH_4$ (0.54 g, 14.25 mmol). After being stirred for 2 h at 35 °C, water was added, and the methanol was evaporated. The aqueous phase was extracted with $CHCl_3$ (3×20 mL), and chloroform solution was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography on silica gel, using a 2:1 mixture of CH_2Cl_2/CH_3OH as the eluent to afford **8** (1.84 g, 94% yield) as a yellow solid. Mp 62–64 °C; R_f 0.26 (CH_2Cl_2/CH_3OH 2:1); $[\alpha]_D^{25} = +0.6$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.76 (br s, 3H, NH_2, OH), 1.84–1.94 (m, 2H, CH_2), 2.12–2.21 (m, 2H, CH_2CF_2), 3.09 (m, 1H, CHN), 3.37–3.54 (m, 5H, CH_2O), 3.63 (m, 1H, CH_2O); ^{13}C NMR ($CDCl_3$): δ 19.7, 26.9 (t, $J = 22.3$), 51.4, 63.1, 68.8, 72.4, 110.1–118.7; ^{19}F NMR ($CDCl_3$): δ −126.8 (m, 2F), −124.0 (m, 2F), −123.3 (m, 2F), −122.5 (m, 6F), −115.0 (m, 2F), −81.5 (t, $J = 10.3$ Hz, 3F). Anal. Calcd for $C_{14}H_{14}F_{17}NO_2$: C, 30.50; H, 2.56. Found: C, 30.10; H, 2.60.

4.8. (4*S*,4′*S*)-2,2′-Methylene-bis[4-{(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecanyl)oxy} methyl]-4,5-dihydro-1,3-oxazole 1

To a solution of fluorous amino alcohol **8** (2.31 g, 4.2 mmol) in CH_2Cl_2 (20 mL) was added diethyl malonimidate dihydrochloride (0.49 g, 2.15 mmol) portionwise over 10 min. After being stirred at rt for 48 h, the solution was poured into water (20 mL), and the mixture extracted with CH_2Cl_2 (3×20 mL). The organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, using a 9:1 mixture of CH_2Cl_2/CH_3OH as the eluent to afford bis(oxazoline) **1** (1.24 g, 43% yield) as a yellow solid. Mp 52–54 °C; R_f 0.74 (CH_2Cl_2/CH_3OH 9:1); $[\alpha]_D^{25} = -8.3$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.81–1.83 (m, 4H, CH_2), 2.08–2.13 (m, 4H, CH_2CF_2), 3.33–3.68 (m, 10H, CH_2, CH_2O), 4.13–4.36 (m, 6H, OCH_2, CHN); ^{13}C NMR ($CDCl_3$): δ 21.0, 28.1 (t, $J = 22.3$), 28.5, 66.3, 70.1, 71.1, 72.7, 107.4–115.5, 163.5; ^{19}F NMR ($CDCl_3$): δ −126.6 (m, 4F), −123.9 (m, 4F), −123.2 (m, 4F), −122.4 (m, 12F), −114.8 (m, 4F), −81.2 (t, $J = 10.3$ Hz, 6F). Anal. Calcd for $C_{31}H_{24}F_{34}N_2O_4$: C, 32.82; H, 2.13. Found: C, 33.08; H, 2.03.

4.9. (*S*)-*O*-Allyl-*N*-Boc-tyrosine methyl ester 10

A mixture of (*S*)-*N*-Boc-tyrosine methyl ester **9**[33] (2.39 g, 8.11 mmol), K_2CO_3 (2.23 g, 16.1 mmol), Bu_4NI (0.3 g, 0.81 mmol), and allyl bromide (0.84 mL, 9.73 mmol) in DMF (20 mL) was stirred at rt for 18 h. After the addition of a 1 M aqueous solution of $KHSO_4$ (20 mL), the product was extracted with ethyl acetate (3×10 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), an aqueous saturated solution of NaCl (20 mL), and then dried over Na_2SO_4. Evaporation of the solvent afforded amino ester **10** (2.58 g, 95% yield) as an oil. R_f 0.4 (ethyl acetate/petroleum ether 1:5); $[\alpha]_D^{25} = +48.8$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.42 (s, 9H, CH_3), 3.00–3.02 (m, 2H, CH_2Ph), 3.71 (s, 3H, OCH_3), 4.51 (m, 1H, CHN), 4.51 (d, $J = 5{,}5$ Hz, 2H, OCH_2), 4.95 (br s, 1H, NH), 5.28 (dd, $J = 11.3$, 1.5 Hz, 1H, CH=CH_2), 5.40 (dd, $J = 17.3$, 1.5 Hz, 1H, CH=CH_2), 6.05 (m, 1H, CH=CH_2), 6.85 (d, $J = 8.7$ Hz, 2H, H_{arom}), 7.03 (d, $J = 8.7$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 28.7, 37.9, 52.6, 54.9, 69.2, 80.3, 115.2, 118.0, 128.5, 130.7, 133.7, 155.8, 158.1, 172.8. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51. Found: C, 64.42; H, 7.59.

4.10. (*S*)-*O*-Allyl-tyrosine methyl ester 11

To (*S*)-*O*-allyl-*N*-Boc-tyrosine methyl ester **10** (1.40 g, 4.18 mmol) dissolved in CH_2Cl_2 (15 mL) was slowly added CF_3CO_2H (4.6 mL, 26.3 mmol). After being stirred for 1 h at rt, the solvent was evaporated, and a saturated aqueous solution of $NaHCO_3$ (10 mL) added. The aqueous solution was extracted with CH_2Cl_2 (3×20 mL). Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography on silica gel, using ethyl acetate as the eluent to give compound **11** (930 mg, 95% yield) as a yellow oil. R_f 0.36 (ethyl acetate); $[\alpha]_D^{25} = +10$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.50 (br s, 2H, NH_2), 2.81 (dd, $J = 13.6$, 7.7 Hz, 1H, CH_2Ph), 3.02 (dd, $J = 13.6$, 5.2 Hz, 1H, CH_2Ph), 3.68 (m, 1H, CHN), 3.72 (s, 3H, OCH_3), 4.51 (d, $J = 5.3$ Hz, 2H, OCH_2), 5.29 (dd, $J = 10.4$, 1.3 Hz, 1H, CH=CH_2), 5.40 (dd, $J = 17.3$, 1.3 Hz, 1H, CH=CH_2), 6,05 (m, 1H, CH=CH_2), 6.85 (d, $J = 8{,}7$ Hz, 2H, H_{arom}), 7.09 (d, $J = 8.7$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 40.6, 52.3, 56.3, 69.2, 115.2, 118.0, 129.7, 130.6, 133.7, 157.9, 175.9. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.24; H, 7.23. The ^1H NMR data are in agreement with those published previously.[35]

4.11. (*S*)-3-[4-Allyloxyphenyl]-2-aminopropanol 12

To a solution of compound **11** (840 mg, 3.56 mmol) in CH_3OH (15 mL) was added $NaBH_4$ (0.54 g, 14.25 mmol). After being stirred for 2 h at 35 °C, water was

added, and the methanol evaporated. The aqueous phase was extracted with $CHCl_3$ (3×20 mL), and the chloroform solution was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was purified by column chromatography on silica gel, using a 4:1 CH_2Cl_2/CH_3OH mixture to give amino alcohol **12** (650 mg, 88% yield) as a white solid. Mp 76–78 °C [lit[36] mp 77–79 °C]; R_f 0.26 (CH_2Cl_2/CH_3OH 4:1); $[\alpha]_D^{25} = -14.5$ (*c* 1, $CHCl_3$); ^1H NMR (300 MHz): δ 1.80 (br s, 3H, NH_2, OH), 2.46 (dd, $J = 13.6$, 8.7 Hz, 1H, C*H*$_2$Ph), 3.07 (dd, $J = 13.6$, 5.3 Hz, 1H, C*H*$_2$Ph), 3.07 (m, 1H, CHN), 3.38 (dd, $J = 10.5$, 7.2 Hz, 1H, C*H*$_2$OH), 3.62 (dd, $J = 10.5$, 3.8 Hz, 1H, C*H*$_2$OH), 4.51 (d, $J = 5.3$ Hz, 2H, OCH_2), 5.27 (dd, $J = 10.6$, 1.5 Hz, 1H, CH=C*H*$_2$), 5.41 (dd, $J = 17.0$, 1.5 Hz, 1H, CH=C*H*$_2$), 6.05 (m, 1H, C*H*=CH_2), 6.85 (d, $J = 8.6$ Hz, 2H, H_{arom}), 7.10 (d, $J = 8.6$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 40.3, 54.6, 66.6, 69.2, 115.2, 118.0, 130.5, 131.2, 133.7, 157.6. HRMS: Calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$: 208.1338. Found: 208.1333.

4.12. (4*S*,4′*S*)-2,2′-Methylenebis[4-(4-allyloxybenzyl)-4,5-dihydro-1,3-oxazole] 13

To amino alcohol **12** (700 mg, 3.38 mmol) dissolved in CH_2Cl_2 (10 mL) was slowly added malonimidate ethyl ester dihydrochloride (390 mg, 1.72 mmol). After being stirred for 48 h at rt, water (10 mL) was added and the organic product extracted with CH_2Cl_2 (3×10 mL). The organic phase was washed with a saturated aqueous solution of NaCl (20 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was purified by flash-chromatography on silica gel, using ethyl acetate as the eluent to afford bis(oxazoline) **13** (377 mg, 55% yield) as an oil. R_f 0.51 (CH_2Cl_2/CH_3OH 9:1); $[\alpha]_D^{25} = -16.9$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.62 (dd, $J = 13.8$, 8.3 Hz, 2H, C*H*$_2$Ph), 3.02 (dd, $J = 13.8$, 5.3 Hz, 2H, C*H*$_2$Ph), 3.31 (s, 2H, CH_2), 3.97–4.02 (m, 2H, CH_2O), 4.19–4.25 (m, 2H, CH_2O), 4.34–4.41 (m, 2H, CHN), 4.50 (d, $J = 5.3$ Hz, 4H, OC*H*$_2$–CH=), 5.27 (dd, $J = 10.5$, 1.5 Hz, 2H, –CH=C*H*$_2$), 5.39 (dd, $J = 17.2$, 1.5 Hz, 2H, –CH=C*H*$_2$), 6.00–6.09 (m, 2H, –C*H*=CH_2), 6.83 (d, $J = 8.5$ Hz, 4H, H_{arom}), 7.10 (d, $J = 8.5$ Hz, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 28.8, 40.9, 67.9, 69.2, 72.6, 115.1, 118.0, 130.3, 130.6, 133.8, 157.7, 162.4. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77. Found: C, 72.44; H, 6.84.

4.13. (4*S*,4′*S*)-2,2′-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluorotricosane-12,12-diyl)bis[4-(4-allyloxy benzyl)-4,5-dihydro-1,3-oxazole] 14

Bis(oxazoline) **13** (430 mg, 0.96 mmol) dissolved in DMF (4 mL) was slowly added at 0 °C to a suspension of NaH (69 mg, 2.86 mmol) in dry DMF (8 mL). After being stirred for 1 h at rt, $C_8F_{17}(CH_2)_3I$ (1.29 g, 2.19 mmol) in DMF (4 mL) was slowly added. After being stirred at 80 °C for 16 h, half of the solvent was evaporated, and water (10 mL) added. The organic product was extracted using diethyl ether (4×10 mL), and the ether solution was washed with a saturated aqueous solution of NaCl (2×20 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was purified by flash-chromatography on silica gel, using ethyl acetate/petroleum ether (2:1) as the eluent to give the fluorous bis(oxazoline) **14** (748 mg, 57% yield) as an oil. R_f 0.44 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25} = -9.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.53–1.56 (m, 4H, CH_2), 2.04–2.10 (m, 8H, CH_2, CH_2CF_2), 2.60 (dd, $J = 13.7$, 8.3 Hz, 2H, C*H*$_2$Ph), 3.30 (dd, $J = 13.7$, 4.9 Hz, 2H, C*H*$_2$Ph), 3.98–4.02 (m, 2H, CH_2O), 4.16–4.22 (m, 2H, CH_2O), 4.37–4.40 (m, 2H, CHN), 4.49 (d, $J = 5.1$ Hz, 4H, OC*H*$_2$–CH=), 5.26 (dd, $J = 10.4$, 1.3 Hz, 2H, –CH=C*H*$_2$), 5.39 (dd, $J = 17.2$, 1.3 Hz, 2H, –CH=C*H*$_2$), 5.98–6.10 (m, 2H, –*CH*=CH_2), 6.84 (d, $J = 8.7$ Hz, 4H, H_{arom}), 7.10 (d, $J = 8.7$ Hz, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 15.6, 31.3 (t, $J = 21.0$ Hz), 33.2, 40.9, 46.0, 67.7, 69.1, 72.2, 115.1, 117.8, 130.0, 130.7, 133.7, 157.7, 167.2; ^{19}F NMR ($CDCl_3$): δ −127.0 (m, 4F, CF_2), −124.2 (m, 4F, CF_2), −123.5 (m, 4F, CF_2), −122.7 (m, 12F, CF_2), −114.9 (m, 4F, CF_2), −81.7 (t, $J = 9.3$ Hz, 6F, CF_3). Anal. Calcd for $C_{49}H_{40}F_{34}N_2O_4$ (1366.8): C, 43.06; H, 2.95. Found: C, 43.08; H, 3.02.

4.14. (4*S*,4′*S*)-2,2′-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluorotricosane-12,12-diyl)bis-[4-(4-hydroxy benzyl)-4,5-dihydro-1,3-oxazole] 15

A mixture of fluorous bis(oxazoline) **14** (770 mg, 0.56 mmol), $Pd(OAc)_2$ (23.5 mg, 0.11 mmol), and PPh_3 (130 mg, 0.50 mmol) in ethanol (10 mL) was refluxed for 1.5 h. After cooling, SiO_2 (1.13 g) was added and the resulting mixture stirred for 45 min at rt. Filtration over Celite followed by evaporation of the solvent gave a residue that was purified by flash-chromatography on silica gel, using ethyl acetate/petroleum ether (1:1) as the eluent to give the fluorous bis(oxazoline) **15** (518 mg, 72% yield) as a yellow solid. Mp 67–69 °C; R_f 0.6 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D = -19.3$ (*c* 1.02, acetone); ^1H NMR (CD_3COCD_3): δ 1.48–1.52 (m, 4H, CH_2), 1.89–1.95 (m, 4H, CH_2), 2.06–2.19 (m, 4H, CH_2CF_2), 2.46 (dd, J = 13.9, 7.6 Hz, 2H, C*H*$_2$Ph), 2.73 (dd, $J = 13.9$, 6.0 Hz, 2H, C*H*$_2$Ph), 3.80–3.86 (m, 2H, CH_2O), 4.05–4.11 (m, 2H, CH_2O), 4.14–4.22 (m, 2H, CHN), 6.62 (d, $J = 8.6$ Hz, 4H, H_{arom}), 6.95 (d, $J = 8.6$ Hz, 4H, H_{arom}); ^{13}C NMR (CD_3COCD_3): δ 16.5, 31.8 (t, $J = 22.0$ Hz), 34.1, 41.8, 46.8, 68.7, 72.9, 116.3, 130.1, 131.6, 157.2, 167.7; ^{19}F NMR (CD_3COCD_3): δ −126.6 (m, 4F, CF_2), −123.9 (m, 4F, CF_2), −123.2 (m, 4F, CF_2), −122.3 (m, 12F, CF_2), −114.6 (m, 4F, CF_2), −81.2 (m, 6F, CF_3). Anal. Calcd for $C_{43}H_{32}F_{34}N_2O_4$: C, 40.12; H, 2.51. Found: C, 40.32; H, 2.57.

4.15. (4*S*,4′*S*)-2,2′-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluorotricosane-12,12-diyl)bis-[4-(4-(1*H*,1*H*-perfluoroctyloxybenzyl))-4,5-dihydro-1,3-oxazole] 2

A mixture of bis(oxazoline) **15** (450 mg, 0.35 mmol), pentadecafluorooctyl nonafluorobutane sulfonate (610 mg, 0.90 mmol), and $CsCO_3$ (380 mg, 1.17 mmol) in dry DMF (7 mL) was stirred at 80 °C for 18 h. After cooling to rt, water (10 mL) was added, the aqueous phase extracted with diethyl ether (3×10 mL), and the

organic phase dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue that was dissolved in FC72 (10 mL). The fluorous phase was washed with ethanol (2×10 mL), and acetonitrile (2×10 mL). Evaporation of the fluorous solvent gave the fluorous bis(oxazoline) **2** (474 mg, 66% yield) as a brown solid. Mp 65–67 °C; R_f 0.32 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25} = -21.6$ (c 0.5, $C_6H_5CF_3$); ^1H NMR ($CDCl_3$): δ 1.56–1.59 (m, 4H, CH_2), 1.94–2.06 (m, 8H, CH_2, CH_2CF_2), 2.71 (dd, $J = 13.8$, 7.4 Hz, 2H, CH_2Ph), 2.94 (dd, $J = 13.8$, 5.5 Hz, 2H, CH_2Ph), 3.94–3.99 (m, 2H, CH_2O), 4.18–4.24 (m, 2H, CH_2O), 4.41 (t, $J = 12.8$ Hz, 4H, OCH_2CF_2), 4.37–4.45 (m, 2H, CHN), 6.85 (d, $J = 8.5$ Hz, 4H, H_{arom}), 7.14 (d, $J = 8.5$ Hz, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 15.6, 31.6 (t, $J = 22.8$ Hz), 33.6, 40.7, 46.0, 65.6 (t, $J = 26.5$ Hz), 67.4, 72.0, 115.2, 131.1, 131.9, 156.7, 161.7; ^{19}F NMR ($CDCl_3$): δ −126.8 (m, 8F, CF_2), −124.1 (m, 8F, CF_2), −124.0 (m, 8F, CF_2), −122.6 (m, 20F, CF_2), −120.2 (m, 4F, CF_2), −114.7 (m, 4F, CF_2), −81.4 (t, $J = 9.3$ Hz, 12F, CF_3). Anal. Calcd for $C_{59}H_{34}F_{64}N_2O_4$: C, 34.55; H, 1.67. Found: C, 34.53; H, 1.90.

4.16. General procedure for the catalytic allylic alkylation

Ligand (31.2 μmol, 6.5 mol %) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4.6 mg, 12.5 μmol, 2.5 mol %) were dissolved in the solvent (1.5 mL) under nitrogen in a Schlenk tube. The reaction mixture was stirred for 1 h at 50 °C, and *rac*-(*E*)-1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol) in the solvent (1.5 mL) was transferred to this Schlenk tube. After 20 min, this solution was transferred into another reaction vessel containing *N*,*O*-bis(trimethylsilyl)acetamide (305 mg, 1.5 mmol), KOAc (4.9 mg, 0.05 mmol), and the nucleophile (1.5 mmol) in the corresponding solvent (2 mL). The reaction mixture was stirred at the desired temperature for the appropriate time. The mixture was then diluted with diethyl ether, and the organic layer was washed with a saturated aqueous NH_4Cl solution (2×5 mL), and then dried over Na_2SO_4. Evaporation of the solvent under a reduced pressure gave a residue that was purified by chromatography on silica gel affording the alkylated product **16**. The enantioselectivity was determined by HPLC using a Chiralpak AD column (25 cm × 0.46 cm) and eluting with hexane/*i*-PrOH (6:4).

4.16.1. Recycling of the ligand. At the end of the reaction, the solvent was removed under reduced pressure, and the residue was extracted with the fluorous solvent FC72 (3×2 mL). The combined fluorous phases were washed with CH_3CN (2×2 mL), and the fluorous solvent was evaporated to afford the fluorous bis(oxazoline) that was directly used for another reaction.

4.17. General procedure for the catalytic allylic oxidation

To a stirred solution of $CuOTf{\cdot}0.5C_6H_6$ (4 mg, 16 μmol, 5 mol %) or $[Cu(CH_3CN)_4]PF_6$ (5.9 mg, 16 μmol, 5 mol %) in $CHCl_3$ (2 mL) was added the fluorous bis(oxazoline) (25 μmol, 8 mol %). This solution was warmed at 50 °C for 1 h. Cyclohexene (105 mg, 1.28 mmol) in CH_3CN (2 mL) was added to the solution cooled at rt, followed by dropwise addition of *tert*-butyl perbenzoate (61.3 mg, 0.32 mmol). The resulting solution was then stirred at rt for the time indicated. The mixture was then diluted with ether (10 mL), and the organic solution was washed with water (5 mL), HCl 2 N (5 mL), and water (5 mL). The solvent was removed in vacuo to afford a residue that was purified by column chromatography on silica gel, to give the corresponding allylic benzoate **17**. The ee was determined by HPLC using a Chiralpak AD column (25 cm × 0.46 cm) and eluting with hexane/*i*-PrOH (150:1).

4.17.1. Recycling of the catalyst. After the reaction, the solvent was removed and hexane (3×2 mL) added. The catalyst, which precipitated as a blue-green solid, was recovered by simple decantation of the supernatant liquid. The catalyst was reused in another catalytic oxidation without further addition of copper or ligand. Evaporation of hexane afforded a residue that was purified by chromatography on silica, to give the allylic benzoate **17**.

4.18. General procedure for the catalytic ene reaction

To a solution of $Cu(OTf)_2$ (11.2 mg, 31 μmol, 10 mol %) in CH_2Cl_2 (2 mL) was added the fluorous bis(oxazoline) **2** (63.6 mg, 31 μmol, 10 mol %). After being stirred for 3 h, α-methylstyrene (39 μL, 0.3 mmol) and a 50% solution of ethyl glyoxalate (0.60 mL, 3 mmol) in toluene were added. After being stirred for 24 h at rt, the solvent was evaporated, and the residue purified by column chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as the eluent. The ee of compound **18** was determined by HPLC using a Chiralpak AD column (25 cm × 0.46 cm) and eluting with hexane/*i*-PrOH (95:5).

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