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Synthesis of New Enantiopure Fluorinated Phenylcyclopropanecarboxylates – Potential Chiral Dopants for Liquid-Crystal Compositions

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The reaction of α-fluorostyrene (**1a**) with methyl phenyldiazoacetate in the presence of $Rh_2(OAc)_4$ gave a 64:36 mixture of diastereomeric monofluorinated cyclopropanes **5a** and **6a**. When using chiral Rh^{II} catalysts $Rh_2(TBSP)_4$ (**7**) and $Rh_2(DOSP)_4$ (**8**), the products were obtained enantioselectively in up to >99 % *ee* for both (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a**. The fluorocyclopropane derivatives are of interest as dopants to induce chirality in liquid-crystal mixtures.

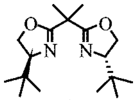
Introduction

For a long time compounds containing a cyclopropane ring have been of great interest. The unique bonding situation of the smallest carbocycle results in a specific geometry of substituents and in a unique reactivity, which makes it a valuable intermediate and starting material in organic chemistry.[1–3] Cyclopropane derivatives are also known for their strong biological activity, which is often related to the high ring strain.[4]

Numerous publications dealing with the synthesis of the cyclopropane moiety concentrate on convenient and enantioselective access to this useful building block.[5] One of the most widely applicable methods is the decomposition of diazo compounds in the presence of olefins, catalyzed by chiral transition-metal complexes.[6–9] Since Noyori et al.[10] and Pfaltz et al.[11] introduced the first asymmetric reactions of this type, much effort has been made to optimize this pathway.[12–14]

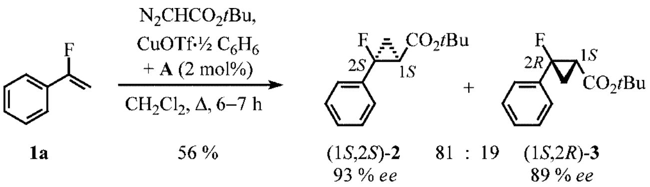
However, only a few attempts have yet been made to synthesize monofluorinated cyclopropanes[15,16] which promise an even greater potential for interesting biological activities since they combine the advantages of two known chemical leads, namely the strained ring and the fluorine substituent.

In addition to potential biomedical applications, fluorocyclopropane derivatives are also of interest as chiral dopants for liquid-crystal compositions in liquid-crystal displays (LCDs).[17–19] Some time ago, we reported an enantioselective cyclopropanation of α-fluorostyrene (**1a**) with *tert*-butyl diazoacetate and copper complexes of chiral bis(oxazoline)s such as **A** (Figure 1) to give the corresponding cyclopropanecarboxylic esters **2** and **3** with good diastereoselectivity and high enantioselectivity (see Scheme 1).[20]



A

Figure 1. Enantiopure ligand **A**.



Scheme 1. Enantioselective cyclopropanation of α-fluorostyrene (**1a**).[20]

These compounds have been converted into fluoro analogues of the antidepressant tranylcypromine.[21–25] They proved to be potent monoamine oxidase inhibitors, exhibiting significant selectivity as tyramine oxidase inhibitors compared to their potential to act as MAO A or MAO B inhibitors.

Besides these known reactions of monosubstituted diazoacetates with α-fluorostyrene (**1a**), products derived from disubstituted diazo compounds such as methyl phenyldiazoacetate may be attractive intermediates for the synthesis of complex molecules, as well. Here we present our recent results on the synthesis of polyfunctionalized cyclopropanes and their application as potent new enantiopure dopants for liquid-crystal compositions.

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Results and Discussion

Our first attempts at the cyclopropanation of α-fluorostyrene (**1a**) with methyl phenyldiazoacetate (**4**) dealt with the synthesis of racemic products (Scheme 2). We carried out the reaction with $Rh_2(OAc)_4$ as a catalyst and observed the diastereomeric products in 92% yield with a *cis*/*trans* ratio of 64:36.

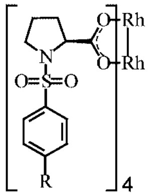
Comparison of our results with those of Zwanenburg et al.,[26] obtained with styrene (**1b**), showed that in terms of reactivity and yields the fluorinated and non-fluorinated substrates were similar, but they were different in diastereoselectivity (Scheme 2). The reaction of **1a** led to a low selectivity towards **5a**, whereas **5b** was present at a rate of 88%. When performing the reaction at ambient temperature, Davies et al. observed that **5b** was formed almost exclusively, but in lower yields.[27]

The high diastereoselectivity of the carbene transfer to non-fluorinated olefins was explained by Doyle et al.[28] Our results show that their hypothesis is not fully valid for reactions of vinyl fluorides such as **1a**. Additional factors seem to be relevant in the mechanism. The discrepancy in steric demand cannot be the only explanation for the different stereoselectivity, as fluorine and hydrogen are of similar size (van der Waals radii of 1.20 Å vs. 1.47 Å, respectively).[29] Another reason may be the ability of fluorine to stabilize a developing electron-deficient centre in the α-position,[30,31] which is the case for both the *cis* and *trans* transition states ($\mathbf{T}_{cis}$, $\mathbf{T}_{trans}$; see Figure 2). However, in $\mathbf{T}_{cis}$, the interaction of the lone pair of the carbonyl oxygen atom and the fluorinated electrophilic centre is weaker than it is in the non-fluorinated case. Consequently, the energy differences of the transition states $\mathbf{T}_{cis}$ and $\mathbf{T}_{trans}$ leading to **5a** and **6a**, respectively, are smaller than those leading to **5b** and **6b**, resulting in lower diastereoselectivity.

The lower *cis* selectivity in the case of α-fluorostyrene (**1a**) compared to that of the reaction with styrene (**1b**) provided both diastereomers as starting materials for further reactions after chromatographic separation. These promising results encouraged us to extend our studies of polyfunctionalized cyclopropanes towards enantioselective methods.

Optically active Rh^{II} carboxylate catalysts have efficiently been applied in the asymmetric cyclopropanation with aryldiazoacetates and a broad range of alkenes. Among them, *N*-(arylsulfonyl)prolinates proved to be the most selective ones for carbene transfers from phenyldiazoacetates to styrene (**1b**).[5]

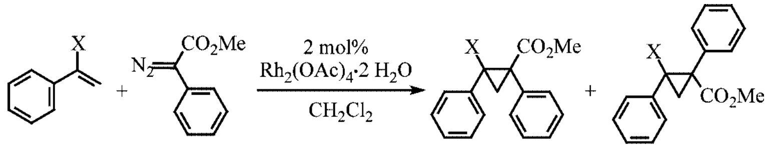
We applied the known catalysts $Rh_2(DOSP)_4$ (**7**) and $Rh_2(TBSP)_4$ (**8**) (see Figure 3),[32] which can be prepared by high-temperature ligand exchange from $Rh_2(OAc)_4$ and the corresponding (arylsulfonyl)prolinate in refluxing chlorobenzene with a modified Soxhlet apparatus (see Supporting Information) equipped with an Na_2CO_3-filled thimble for binding the excess acetic acid.



7 ($Rh_2(TBSP)_4$, R = *t*Bu)
8 ($Rh_2(DOSP)_4$, R = $C_{12}H_{25}$)

Figure 3. Optically active Rh^{II} (arylsulfonyl)prolinate catalysts **7** and **8**.[32]

The synthesized catalysts (0.01 equiv.) were used for the reaction of α-fluorostyrene (**1a**, 5.0 equiv.) with methyl phenyldiazoacetate (1.0 equiv.) at ambient temperature or –78 °C (see Table 1).



1a (X = F)	**4**	92 %	**5a**	64 : 36	**6a**
1b (X = H)		96 %	**5b**	88 : 12	**6b**[26]
1b (X = H)		69 %	**5b**	98 : 2	**6b**[27]

Scheme 2. Cyclopropanation of α-fluorostyrene (**1a**) and styrene (**1b**). Reagents and conditions: 1.0 equiv. of **1a**, 1.55 equiv. of **4** (added within 5–6 h), 2 mol-% of $Rh_2(OAc)_4$, refluxing CH_2Cl_2.

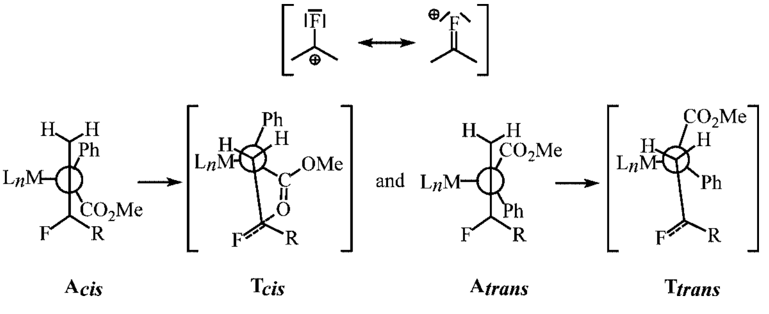
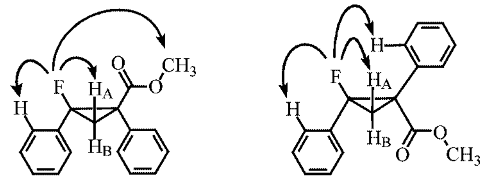


Figure 2. Transition states for the cyclopropanation of α-fluorostyrene (**1a**).

At room temperature, both catalysts showed similar diastereoselectivities of about 75:25 in favour of the *cis* isomer **5a**. The enantioselectivities were similar as well, giving 83–88% *ee* for **5a** and about 80% *ee* for **6a**. Compound **7** was less reactive than **8**. With $Rh_2(TBSP)_4$ (**7**) as a catalyst, the products were formed in a combined yield of 63%, while application of $Rh_2(DOSP)_4$ (**8**) furnished the products in 79% at ambient temperature. We observed an increase in yields to 81% with **7** and 91% with **8** at –78 °C due to longer reaction times. The diastereoselectivities did not differ from those observed at room temperature, but the enantioselectivities did. The effect of temperature and solvent on cyclopropanations with **7** and **8** has been discussed copiously in the literature.[32] These studies showed that the less polar the solvent and the lower the temperatures were, the higher was the *ee*. Our results agree with these conclusions (see Table 1). Reduction of the temperature to –78 °C and application of $Rh_2(DOSP)_4$ (**8**) as the catalyst caused a significant increase in enantioselectivity to >99% *ee* for both diastereomers. This catalyst is commonly mentioned to be the more selective one.[32,33]

The absolute stereochemistry in all cases was (1*R*,2*R*) for **5a** and (1*R*,2*S*) for **6a**, confirmed by X-ray data of the esters with abnormal dispersion. The crystal structures can be seen in Figure 4.

The X-ray data confirmed the ^1H-^{19}F heteronuclear NOE experiments (see Figure 5), which were performed to identify the diastereomers. Both compounds exhibited NOEs for H_A and the phenyl ring *ortho* protons. Only the spectrum of **5a** showed a strong enhancement for the ester signal, which leads to the conclusion that the ester group is in the vicinity of the fluorine atom.



5a **6a**

Figure 5. ^1H-^{19}F heteronuclear NOE analysis of **5a** and **6a**.

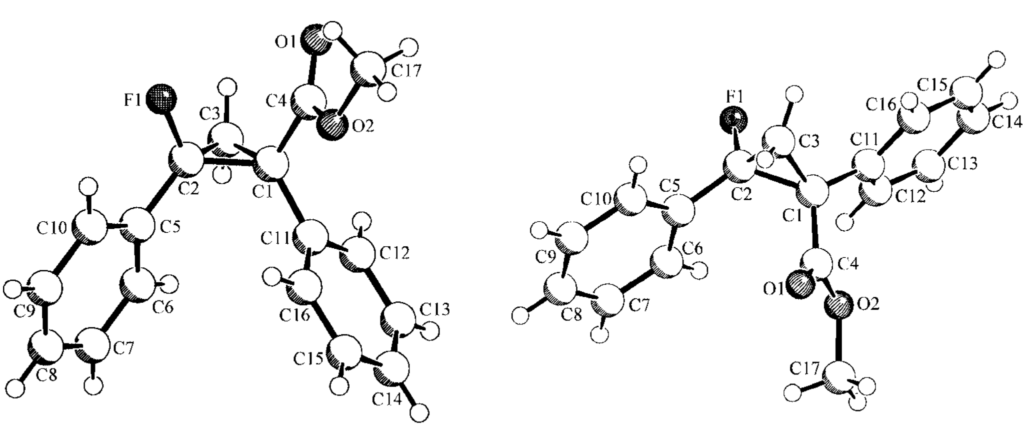
The absolute configurations we observed agree with the literature results for non-fluorinated compounds[33] considering that fluorine changes the priorities of substituents when introduced. Consequently, the mechanism proposed by Davies et al.[32] and other groups[34] is true for the fluorinated compounds, too. However, we found higher enantioselectivities at lower temperatures.

The D_2-symmetric catalyst $Rh_2(DOSP)_4$ forms a (carbene)metal complex with methyl phenyldiazoacetate, in which the phenyl ring is blocked from the backside by one of the chiral ligands. The ester group points back and is blocked itself by another ligand from the front. When α-fluorostyrene approaches the carbene complex, it can only attack from the front. For a long time it was presumed that

Table 1. Effect of temperature and catalyst on asymmetric induction.

Catalyst	*T*	Time	Solvent	Yield [%][a]	**5a/6a**	% *ee* (absolute configuration)[b] **5a**	**6a**
$Rh_2(TBSP)_4$ (**7**)	room temp.	5 h	pentane	63	75:25	83 (1*R*,2*R*)	78 (1*R*,2*S*)
$Rh_2(TBSP)_4$ (**7**)	–78 °C	5 d	CH_2Cl_2[c]	81	79:21	84 (1*R*,2*R*)	84 (1*R*,2*S*)
$Rh_2(DOSP)_4$ (**8**)	room temp.	5 h	pentane	79	74:26	88 (1*R*,2*R*)	80 (1*R*,2*S*)
$Rh_2(DOSP)_4$ (**8**)	–78 °C	5 d	pentane	91	75:25	>99 (1*R*,2*R*)	>99 (1*R*,2*S*)

[a] 5.0 equiv. of **1a**, 1.0 equiv. of **4** (added within 30 min) and 1 mol-% of $Rh_2(OAc)_4$. [b] The enantiomeric excess (*ee*) was determined by ^{19}F NMR spectroscopy within an error of ±1% after hydrolysis and subsequent esterification with (–)-menthol. Additionally, the *ee* of **5a** was determined by chiral GC with a Hydrodex®-β-PM column to confirm the ^{19}F NMR results. [c] Because of the poor solubility of **5** in pentane at –78 °C, dichloromethane was used as the solvent.



(1*R*,2*R*)-**5a** (1*R*,2*S*)-**6a**

Figure 4. Crystal structures of (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a**.

the alkene attacks in a side-on approach, preferentially over the ester group. Further studies showed that the alkene attacks in an end-on manner instead.[35] A bond is then formed between the β-carbon atom and the carbene carbon atom. Depending on the orientation of the phenyl ring of α-fluorostyrene towards the catalyst, the *cis* or *trans* transition state is formed. While the reaction proceeds, the rhodium bond becomes weaker, and the cyclopropane ring is built, leading to the products with the observed absolute configurations (Figure 6).

The known reaction with non-fluorinated styrene was carried out at room temperature, giving similar enantioselectivities for **5b** (91% *ee*)[27,33] as for **5a**, but a diastereoselectivity of 97:3. Consequently, fluorine does not significantly influence the enantioselectivity but changes the diastereoselectivity of the cyclopropanation reaction.

Having the diastereomeric methyl 2-fluorocyclopropanecarboxylates (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a** in hand, the corresponding acids were prepared by hydrolysis, which subsequently were transformed into esters substituted with typical alcohol components[17] known to exhibit positive effects on the properties of dopants for liquid-crystal compositions in LCDs (Scheme 3).

Chiral dopants are used to induce a cholesteric phase in otherwise achiral, nematic, liquid-crystal mixtures. The ability to induce a chiral pitch depends on the concentration of the dopant and on its so-called helical twisting power (HTP). For common technical applications such as displays based on the twisted nematic (TN) mode, a relatively small HTP (e.g. around 10–15 μm^{-1}) and a low dopant concentration (around 0.1%) are sufficient.[17,18] A higher HTP or increased concentrations are required for super-twisted nematic (STN) LCDs.[36,37] Also, LCDs based on ferroelectric liquid crystals in the smectic C* phase make use of chiral additives.[38] Some newer LCD modes such as the surface-stabilized cholesteric texture (SSCT) mode,[39,40] use nematic liquid crystals with an extremely short pitch in order to generate colour by the wavelength-selective reflection of visible light. Another important application of chiral dopants with very high HTP is cholesteric films (prepared by the polymerization of reactive mesogens including a chiral dopant) for improving, for example, the brightness of LCD panels or acting as polarizing reflectors.[41] For such applications, new dopants with very high HTP are in constant demand. Remarkably, although the first cholesteric liquid crystal was already reported in 1888,[42,43] the struc-

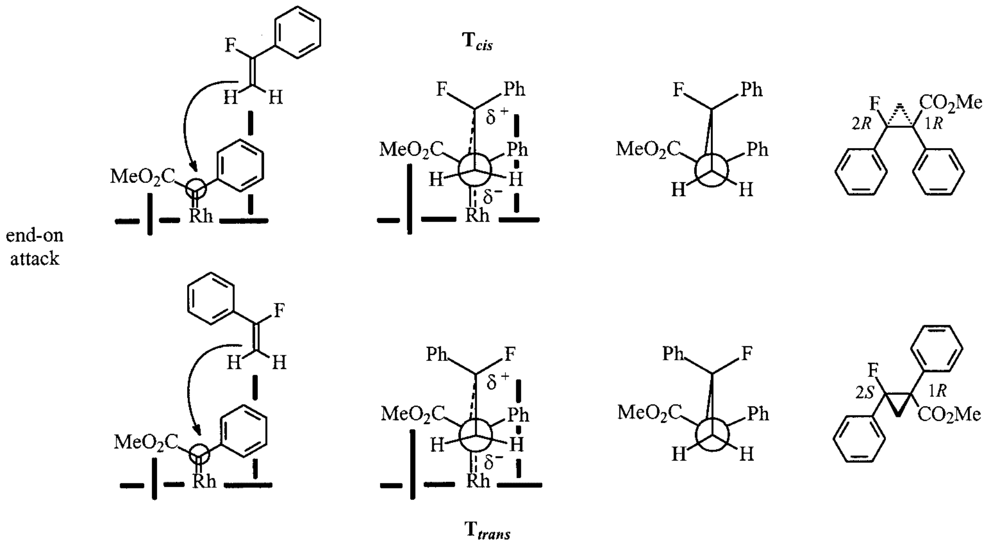
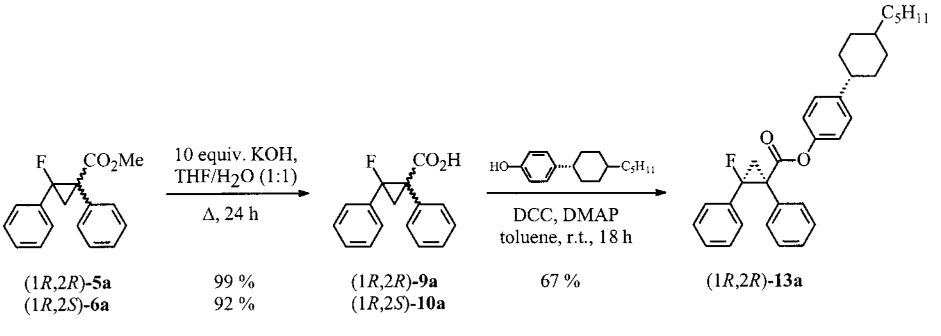


Figure 6. Mechanism of the enantioselective cyclopropanation of α-fluorostyrene (**1a**).



Scheme 3. Hydrolysis of diastereomeric methyl diphenylcyclopropanecarboxylates and esterification of the (1*R*,2*R*)-acid with a *p*-cyclohexylphenol.

ture-property relationships of chiral dopants are still not well understood. In general, molecules with a more liquid-crystal-like shape seem to be more effective in inducing chirality in a nematic host. Another rather general observation concerns the location of the chiral substructure within the dopant molecule; the more "central" the location, the higher is the HTP of the resulting chiral compound. Thus, we were interested to test the quality of enantiomerically pure, fluorinated diphenylcyclopropanecarboxylates as a new structural class of potential chiral dopants for liquid-crystal compositions.

The HTP (determined from a 1% w/w solution of the chiral component in the Merck liquid-crystal mixture MLC-6260) of the methyl esters (1*R*,2*R*)-**5a** (–8.7 μm^{-1}) and (1*R*,2*S*)-**6a** (–7.5 μm^{-1}) was found to be relatively small. However, the introduction of a more liquid-crystal-like phenol moiety into the ester afforded a significantly higher HTP of +24.0 μm^{-1} for (1*R*,2*R*)-**13a**. Although this value is higher than that of many commercially used chiral dopants,[18] there are several compounds known with an even higher HTP.[44–46] Nevertheless, esters of chiral diphenylcyclopropanecarboxylic acids show some promise as a versatile structural scaffold. So far, only modification of the ester group has been investigated to a very limited extent. The systematic exploration of the two phenyl moieties with combinatorial methodology may disclose even more efficient chiral dopants.

Experimental Section

General Remarks: Methyl phenyldiazoacetate, α-fluorostyrene (**1a**) and tetrakis[*N*-(phenylsulfonyl)-(*S*)-prolinato]dirhodium(II) catalysts $Rh_2(TBSP)_4$ (**7**) and $Rh_2(DOSP)_4$ (**8**) were prepared according to refs.[47–49] All other starting materials and reagents were obtained from ABCR, Acros, Fluka or Sigma–Aldrich. Dichloromethane was dried with and distilled from P_2O_5, whereas toluene was dried with and distilled from sodium with benzophenone as an indicator. Both solvents were stored over molecular sieves (0.4 nm). Mass spectra were measured with a Waters-Micromass GCT instrument operating at 70 eV or with a Waters-Micromass Quattro LC-Z instrument. NMR spectra were recorded with a Varian 600 Unity Plus (600.0 MHz for ^1H, 150.66 MHz for ^{13}C and 564.3 MHz for ^{19}F), Varian INOVA 500 (499.84 MHz for ^1H, 125.70 MHz for ^{13}C and 470.28 MHz for ^{19}F), Bruker ARX300 (300.13 MHz for ^1H, 75.48 MHz for ^{13}C and 282.37 MHz for ^{19}F) and Bruker AC250 (250.1 MHz for ^1H and 235.3 MHz for ^{19}F) in $CDCl_3$ solution with TMS or $CFCl_3$ as internal standards, respectively. Thin layer chromatography was performed with 60 F_{254} TLC plates (Merck). Column chromatography was performed with silica gel (Merck, particle size 0.063–0.200 mm, 70–230 mesh), and preparative MPLC was carried out on silica gel (Merck, particle size 0.040–0.063 mm, 230–400 mesh) with a solvent flow rate of 50 mL/min.

General Procedure for Rh^{II}-Catalyzed Decompositions of Methyl Phenyldiazoacetate in the Presence of α-Fluorostyrene: α-Fluorostyrene (**1a**, 1–5 equiv.) and Rh^{II} catalyst [$Rh_2(OAc)_4 \cdot 2H_2O$, $Rh_2(TBSP)_4$ (**7**) or $Rh_2(DOSP)_4$ (**8**), 0.01–0.02 equiv., relative to the diazo compound] were dissolved in absolute dichloromethane or pentane under argon at room temperature or –78 °C. A solution of methyl phenyldiazoacetate (1–1.55 equiv.) was added with a syringe pump. When $Rh_2(OAc)_4 \cdot 2H_2O$ was used, the addition took place at reflux within 5–6 h, followed by another 12 h of refluxing. When chiral Rh^{II} catalysts were used, the diazo compound was added within 30 min at room temperature or –78 °C, and the mixture was stirred for 5 h or 5 d, respectively, at the same temperature. Subsequently, the reaction mixture was diluted with dichloromethane and treated with a saturated sodium carbonate solution and water. The organic layer was dried with magnesium sulfate before removing the solvent under reduced pressure. The reactions carried out at –78 °C were quenched at that temperature with silica gel before concentrating the mixture in vacuo. The crude product was then purified by column chromatography on silica gel with pentane/diethyl ether (20:1) as the eluent to give the diastereomeric product as a white solid. The amounts of α-fluorostyrene, catalyst, diazo compound and solvent are presented in that order in abbreviated form. Diastereomeric ratios were determined by gas chromatography (GC). After hydrolysis of **5a** or **6a** and esterification with (–)-menthol, ^{19}F NMR spectroscopy at 282 MHz was used to determine the *ee* within an error of ±1%, calculated with racemic **5a** and **6a**. Additionally, the *ee* of **5a** was determined by chiral GC using a Hydrodex®-β-PM column from Macherey–Nagel, giving the same results as obtained by ^{19}F NMR spectroscopy.

General Procedure for the Determination of Enantiomeric Excesses: A diastereomeric mixture of **5a** and **6a** (50 mg, 0.18 mmol) and KOH (99 mg, 1.8 mmol, 10 equiv.) were dissolved in THF/H_2O (1:1, 3 mL) and heated for 24 h. The reaction mixture was then cooled to room temperature and subsequently acidified with HCl (pH = 1). The aqueous phase was extracted with dichloromethane, and the combined organic layers were dried before removing the solvent under reduced pressure. The crude product, dicyclohexylcarbodiimide (DCC, 0.05 g, 0.22 mmol), (–)-menthol (0.09 g, 0.6 mmol) and some grains of DMAP were dissolved in absolute dichloromethane (2 mL) and stirred at room temperature overnight. The precipitate was filtered and washed with dichloromethane before removing the solvent in vacuo. The resulting product was analyzed by ^{19}F NMR spectroscopy.

(±)-Methyl 2α-Fluoro-1β,2β-diphenylcyclopropanecarboxylate [(±)-5a] and (±)-Methyl 2α-Fluoro-1α,2β-diphenylcyclopropanecarboxylate [(±)-6a]: α-Fluorostyrene (**1a**, 610 mg, 5 mmol) was treated with $Rh_2(OAc)_4 \cdot 2H_2O$ (68 mg, 0.155 mmol) and methyl phenyldiazoacetate (**4**, 1.365 g, 7.75 mmol) in dichloromethane (20 mL). Purification of the crude diastereomeric product gave 1.232 g (92% yield) of a mixture of (±)-**5a** and (±)-**6a** (64:36). The diastereomers were separated by MPLC with pentane/diethyl ether (20:1) and each isomer was recrystallised from pentane, giving 682 mg (50% yield) of (±)-**5a** as colourless, tetragonal columns and 328 mg (24% yield) of (±)-**6a** as colourless, hexagonal plates, respectively. (±)-**5a**: M.p. 93 °C (pentane). ^1H NMR (600 MHz, $CDCl_3$): δ = 2.10 (dd, *J* = 7.8 and 11.7 Hz, 1 H), 2.77 (dd, *J* = 7.7 and 21.9 Hz), 3.73 (s, 3 H), 6.97–7.15 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3 (dt, *J* = 21.3 Hz), 42.6 (ds, *J* = 13.8 Hz), 52.8 (q), 83.7 (ds, *J* = 224.3 Hz), 125.6 (dd, *J* = 7.2 Hz), 127.4 (d), 127.7 (dd, *J* = 0.9 Hz), 127.8 (d), 128.0 (dd, *J* = 1.4 Hz), 130.9 (dd, *J* = 2.2 Hz), 134.0 (ds, *J* = 3.7 Hz), 134.2 (s), 168.6 (ds, *J* = 3.7 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –176.95 (dd, *J* = 12.1 and 24.3 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 270 $[M]^+$ (25), 251 (4), 250 (38), 235 (35), 218 (14), 209 (23), 191 (47), 189 (41), 178 (28), 165 (22), 140 (10), 139 (100), 133 (55), 115 (13), 109 (33), 105 (71), 89 (24), 77 (57), 63 (37), 51 (45). $C_{17}H_{15}FO_2$ (270.30): calcd. C 75.54, H 5.59; found C 75.49; H 5.34. (±)-**6a**: M.p. 68 °C (pentane). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.01 (dd, *J* = 7.3 and 20.1 Hz, 1 H), 2.62 (dd, *J* = 7.3 and 12.9 Hz, 1 H), 3.27 (s, 3 H), 7.31–7.56 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4 (dt, *J* = 9.4 Hz), 41.7

(ds, J = 14.2 Hz), 52.4 (q), 84.0 (ds, J = 227.4 Hz), 127.9 (d), 128.2 (d), 128.2 (dd, J = 0.6 Hz), 128.3 (dd, J = 1.1 Hz), 129.2 (dd, J = 2.6 Hz), 131.3 (d), 133.8 (ds, J = 21.1 Hz), 134.3 (ds, J = 3.2 Hz), 169.4 (ds, J = 1.9 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –156.87 (dd, J = 12.7 and 20.8 Hz, 1 F) ppm. MS (EI): m/z (%) = 270 $[M]^+$ (66), 251 (5), 250 (75), 235 (35), 219 (11), 218 (30), 210 (43), 209 (49), 191 (73), 189 (48), 178 (38), 165 (36), 163 (14), 139 (100), 133 (80), 115 (23), 109 (90), 105 (63), 89 (39), 77 (67), 63 (52), 51 (66). $C_{17}H_{15}FO_2$ (270.30): calcd. C 75.54, H 5.59; found C 75.41, H 5.39.

(1*R*,2*R*)-Methyl 2α-Fluoro-1β,2β-diphenylcyclopropanecarboxylate [(1*R*,2*R*)-5a] and (1*R*,2*S*)-Methyl 2α-Fluoro-1α,2β-diphenylcyclopropanecarboxylate [(1*R*,2*S*)-6a]. Method A [with $Rh_2(TBSP)_4$ (7)]: α-Fluorostyrene (**1a**, 610 mg, 5 mmol) was treated with $Rh_2(TBSP)_4$ (**7**, 14 mg, 0.01 mmol) and methyl phenyldiazoacetate (**4**, 176 mg, 1 mmol) in dichloromethane (–78 °C) or pentane (room temp., 4 mL). The reaction at room temp. furnished 170 mg (63% yield) of diastereomeric (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a** [75:25, 83% *ee* (1*R*,2*R*)-**5a** and 78% *ee* (1*R*,2*S*)-**6a**], while the reaction at –78 °C yielded 220 mg (81% yield) of (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a** [79:21, 84% *ee* (1*R*,2*R*)-**5a** and 84% *ee* (1*R*,2*S*)-**6a**]. **Method B [with $Rh_2(DOSP)_4$ (8)]:** α-Fluorostyrene (**1a**, 610 mg, 5 mmol) was treated with $Rh_2(DOSP)_4$ (**8**, 19 mg, 0.01 mmol) and methyl phenyldiazoacetate (**4**, 176 mg, 1 mmol) in pentane (4 mL). The reaction at room temp. furnished 214 mg (79% yield) of diastereomeric (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a** [74:26, 88% *ee* (1*R*,2*R*)-**5a** and 80% *ee* (1*R*,2*S*)-**6a**], while the reaction at –78 °C yielded 246 mg (91% yield) of (1*R*,2*R*)-**5a** and (1*R*,2*S*)-**6a** [75:25, >99% *ee* (1*R*,2*R*)-**5a** and >99% *ee* (1*R*,2*S*)-**6a**]. (1*R*,2*R*)-**5a**: $[\alpha]_D^{20}$ = +62.7 (c = 1.0, $CHCl_3$), >99% *ee*. (1*R*,2*S*)-**6a**: $[\alpha]_D^{20}$ = +287.5 (c = 1.0, $CHCl_3$), >99% *ee*.

General Procedure for Hydrolysis: KOH (1.12 g, 20 mmol, 10 equiv.) was added to a solution of methyl 2-fluoro-1,2-diphenylcyclopropanecarboxylate **5a** or **6a** (0.541 g, 2 mmol) in THF/H_2O (1:1, 60 mL). The resulting mixture was heated to reflux for 24 h. Subsequently, it was poured into iced water (60 mL), and the phases were separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL) and then acidified with HCl (pH = 1) and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were dried with sodium sulfate and concentrated in vacuo. Crystallization from cyclohexane/ethyl acetate (10:1) furnished the corresponding acids.

(1*R*,2*R*)-2α-Fluoro-1β,2β-diphenylcyclopropanecarboxylic Acid [(1*R*,2*R*)-9a]: Compound (1*R*,2*R*)-**5a** (0.541 g, 2 mmol) gave 515 mg (>99% yield) of (1*R*,2*R*)-**9a** as colourless needles. M.p. 189 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20}$ = +71.3 (c = 1.0, $CHCl_3$, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (dd, J = 7.9 and 11.8 Hz, 1 H), 2.79 (dd, J = 7.7 and 21.8 Hz, 1 H), 6.97–7.16 (m, 10 H), 10.81 (br. s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (dt, J = 9.6 Hz), 42.3 (ds, J = 12.4 Hz), 84.4 (ds, J = 227.0 Hz), 125.7 (dd, J = 9.0 Hz), 127.7 (d), 127.8 (d), 128.2 (d), 131.0 (d), 133.6 (s), 133.9 (ds, J = 22.2 Hz), 174.4 (ds, J = 4.3 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –176.95 (dd, J = 10.0 and 19.6 Hz, 1 F) ppm. MS (ESI/daughter ion experiment): m/z (%) = 257 (12) $[M + H]^+$, 219 (100), 191 (15), 105 (8). MS (EI, as trimethylsilyl ester): m/z (%) = 328 (14) $[M]^+$, 313 (3), 308 (39), 239 (4), 238 (60), 236 (9), 235 (1), 218 (3), 210 (27), 209 (36), 197 (2), 192 (9), 191 (38), 189 (32), 179 (15), 178 (13), 165 (8), 163 (2), 152 (2), 133 (13), 131 (9), 115 (2), 109 (15), 105 (72), 103 (37), 102 (2), 89 (11), 77 (58), 75 (36), 73 (100), 65 (1), 63 (9), 62 (1), 47 (9), 45 (27). $C_{16}H_{13}FO_2$ (256.28): calcd. C 74.99, H, 5.11; found C 74.50, H 5.03.

(1*R*,2*S*)-2α-Fluoro-1α,2β-diphenylcyclopropanecarboxylic Acid [(1*R*,2*S*)-10a]: Compound (1*R*,2*S*)-**6a** (0.100 g, 0.37 mmol) gave 88 mg (92% yield) of (1*R*,2*S*)-**10a** as colourless needles. M.p. 131 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20}$ = +249.6 (c = 1.0, $CHCl_3$, >99% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (dd, J = 7.3 and 19.8 Hz, 1 H), 2.53 (dd, J = 7.2 and 13.4 Hz, 1 H), 7.30–7.52 (m, 10 H) ppm. ^{13}C NMR (75 MHz $CDCl_3$): δ = 22.0 (dt, J = 8.3 Hz), 41.0 (ds, J = 13.4 Hz), 84.6 (ds, J = 228.3 Hz), 128.0 (d), 128.2 (d), 128.3 (d), 128.4 (d), 129.3 (dd, J = 2.8 Hz), 131.2 (d), 133.1 (ds, J = 19.4 Hz), 134.8 (ds, J = 2.7 Hz), 174.5 (s) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –153.79 (dd, J = 13.6 and 21.6 Hz, 1 F) ppm. MS (ESI/daughter ion experiment): m/z (%) = 257 (22) $[M + H]^+$, 237 (4), 219 (100), 191 (5), 105 (4). MS (EI, as trimethylsilyl ester): m/z (%) = 328 (11) $[M]^+$, 313 (1), 308 (13), 239 (4), 238 (51), 236 (1), 218 (2), 210 (20), 209 (23), 192 (9), 191 (38), 189 (17), 179 (2), 178 (2), 165 (3), 163 (1), 133 (7), 131 (4), 115 (1), 109 (7), 105 (76), 103 (23), 102 (1), 89 (5), 77 (31), 75 (14), 73 (100), 63 (4), 63 (9), 47 (4), 45 (17). $C_{16}H_{13}FO_2$ (256.28): calcd. C 74.99, H, 5.11; found C 74.37, H 4.94.

General Procedure for Esterification with (–)-Menthol: Compound (1*R*,2*R*)-**9a** or (1*R*,2*S*)-**10a** (1 mmol), *N*,*N*-dicyclohexylcarbodiimide (DCC, 1.25 mmol, 1.25 equiv.), (–)-menthol (1.1 mmol, 1.1 equiv.) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were dissolved in absolute dichloromethane (6 mL). The reaction mixture was stirred at room temp. overnight before the precipitate formed was filtered and washed with dichloromethane (2 mL). The filtrate was concentrated in vacuo. After determination of the ratio of diastereomers by ^{19}F NMR spectroscopy, the crude product was purified by column chromatography.

(–)-Menthyl (1*R*,2*R*)-2-Fluoro-1,2-diphenylcyclopropanecarboxylate [(1*R*,2*R*)-11a]: Compound (1*R*,2*R*)-**9a** (182 mg, 80% *ee*, 0.71 mmol) gave 146 mg (80% *de*, 52% yield) of (1*R*,2*R*)-**11a** as a colourless oily liquid after column chromatography with pentane/dichloromethane (5:1) as the eluent. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76–0.91 (m, 2 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 1.02–1.11 (m, 1 H), 1.37–1.50 (m, 2 H), 1.63–1.69 (m, 2 H), 1.88–1.92 (m, 1 H), 2.02 (m, 1 H), 2.06 (dd, J = 7.6 and 11.4 Hz, 1 H), 2.72 (dd, J = 7.8 and 21.7 Hz, 1 H), 4.74 (ddd, J = 4.4, 11.0 and 11.0 Hz, 1 H), 6.96–7.18 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6 (q), 20.7 (q), 21.0 (dt, J = 10.5 Hz), 21.9 (q), 23.7 (t), 26.6 (d), 31.3 (d), 34.2 (t), 40.3 (t), 43.2 (ds, J = 14.2 Hz), 46.9 (d), 76.0 (d), 83.5 (ds, J = 224.2 Hz), 125.5 (dd, J = 6.5 Hz), 127.3 (d), 127.7 (d), 127.8 (d), 128.0 (d), 130.8 (d), 134.3 (s), 134.6 (s), 180.5 (s) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –176.55 (dd, J = 22.1 and 11.5 Hz, 1 F) ppm. MS (EI): m/z (%) = 394 (0) $[M]^+$, 374 (2), 372 (15), 341 (1), 313 (1), 255 (1), 231 (1), 199 (1), 189 (4), 163 (27), 162 (100), 150 (21), 131 (29), 129 (22), 115 (16), 103 (34), 91 (17), 77 (6), 69 (7), 57 (11), 55 (14), 43 (16).

(–)-Menthyl *trans*-(1*R*,2*S*)-2-Fluoro-1,2-diphenylcyclopropanecarboxylate [(1*R*,2*S*)-12a]: Compound (1*R*,2*S*)-**10a** (0.039 g, 94% *ee*, 0.15 mmol) gave 29 mg (94% *de*, 49% yield) of (1*R*,2*S*)-**12a** as a white solid after column chromatography with pentane/diethyl ether (80:1) as the eluent. M.p. 95 °C (pentane/diethyl ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.24 (dd, J = 12.2 and 23.2 Hz, 1 H), 0.43 (d, J = 6.9 Hz, 3 H), 0.70 (d, J = 6.5 Hz, 3 H), 0.76 (d, ^3J = 7.0 Hz, 3 H), 0.67 (m, 1 H), 0.85 (m, 1 H), 1.08 (m, 1 H), 1.21 (m, 1 H), 1.34–1.39 (m, 1 H), 1.45 (m, 1 H), 1.51 (m, 2 H), 2.02 (dd, J = 7.3 and 20.3 Hz, 1 H), 2.64 (dd, J = 7.3 and 13.3 Hz, 1 H), 4.29 (ddd, J = 4.4, 10.9 and 10.9 Hz, 1 H), 7.32–7.57 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0 (q), 20.7 (q), 20.9 (dt, J = 9.3 Hz), 21.8 (q), 23.0 (t), 25.8 (d), 31.0 (d), 33.9 (t), 39.6

(t), 42.0 (ds, $J = 14.2$ Hz), 46.4 (d), 75.3 (d), 84.0 (ds, $J = 226.9$ Hz), 127.7 (d), 128.1 (d), 128.2 (d), 128.3 (d), 129.1 (ds, $J = 2.7$ Hz), 131.3 (d), 134.0 (ds, $J = 21.3$ Hz), 134.8 (ds, $J = 3.3$ Hz), 168.3 (s) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -156.63$ (dd, $J = 19.8$ and 13.4 Hz, 1 F) ppm. MS (GCToF/EI): m/z (%) = 394 (0) $[M]^+$, 256 (4), 237 (4), 236 (24), 220 (8), 218 (21), 207 (6), 202 (10), 193 (1), 192 (15), 191 (24), 189 (34), 178 (6), 165 (6), 163 (4), 139 (4), 138 (23), 131 (10), 123 (23), 121 (9), 109 (9), 105 (18), 95 (100), 93 (11), 82 (15), 81 (86), 79 (21), 77 (14), 76 (4), 68 (10), 67 (57), 57 (5), 55 (31), 53 (10), 50 (4), 44 (10), 41 (24).

4-(*trans*-4-*n*-Pentylcyclohexyl)phenyl (1*R*,2*R*)-2α-Fluoro-1β,2β-diphenylcyclopropanecarboxylate : A solution of (1*R*,2*R*)-**9a** (2.00 g, 7.7 mmol), 4-(*trans*-4-*n*-pentylcyclohexyl)phenol (1.90 g, 7.7 mmol) and DMAP (120 mg) in absolute toluene (30 mL) was treated dropwise at 10 °C with DCC (1.75 g, 8.48 mmol) in toluene (10 mL). The mixture was stirred at room temp. for 18 h. Oxalic acid dihydrate (200 mg) was added. After stirring for 1 h, the precipitate was filtered off, washed with toluene, and the solution was concentrated in vacuo to give a viscous yellow oil. The crude product was chromatographed with toluene on a short silica gel column and crystallized from ethanol after the addition of a small amount of toluene, yielding 2.5 g (67% yield, 99.4% pure by HPLC) of a colourless solid. M.p. 113 °C (ethanol). $[\alpha]_D^{20} = -48.6$ ($c = 1.0$, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): $\delta = 0.89$ (t, $J = 6.8$ Hz, 3 H), 0.95–1.08 (m, 2 H), 1.21–1.50 (m, 11 H), 1.93–1.87 (m, 4 H), 2.20 (dd, $J = 8.0$ and 11.7 Hz, 1 H), 2.44 (mc, 1 H), 2.87 (dd, $J = 7.8$ and 21.9 Hz, 1 H), 6.94–7.00 (m, 2 H), 7.03–7.07 (m, 2 H), 7.12–7.25 (m, 10 H) ppm. ^{19}F NMR (235 MHz, $CDCl_3$, 300 K): $\delta = -176.23$ (dd, $J = 11.4$ and 21.8 Hz, 1 F) ppm. MS (EI): m/z (%) = 484 (13) $[M]^+$, 420 (5), 238 (100), 219 (6), 210 (9), 191 (14), 133 (12), 109 (13), 104 (21).

X-ray Crystal Structure Analysis for Compound (1*R*,2*R*)-5a: $C_{17}H_{15}FO_2$, $M = 270.29$, colourless crystal, $0.30 \times 0.10 \times 0.10$ mm, $a = 5.705(1)$ Å, $b = 15.307(1)$ Å, $c = 15.496(1)$ Å, $V = 1353.2(3)$ Å^3, $\rho_{calcd.} = 1.327$ g cm^{-3}, $\mu = 0.782$ mm^{-1}, empirical absorption correction ($0.799 \leq T \leq 0.926$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and φ scans, 6020 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.58$ Å^{-1}, 2073 independent ($R_{int} = 0.032$) and 2051 observed reflections [$I \geq 2\sigma(I)$], 182 refined parameters, $R = 0.031$, $wR^2 = 0.080$, Flack parameter 0.23(16), max. residual electron density 0.12 (–0.12) e·Å^{-3} and hydrogen atoms calculated and refined as riding atoms.

X-ray Crystal Structure Analysis for Compound (1*R*,2*S*)-6a: $C_{17}H_{15}FO_2$, $M = 270.29$, colourless crystal, $0.35 \times 0.35 \times 0.15$ mm, $a = 8.127(1)$ Å, $b = 10.301(1)$ Å, $c = 16.501(1)$ Å, $V = 1381.4(2)$ Å^3, $\rho_{calcd.} = 1.300$ g cm^{-3}, $\mu = 0.766$ mm^{-1}, empirical absorption correction ($0.775 \leq T \leq 0.894$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and φ scans, 9078 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 2451 independent ($R_{int} = 0.031$) and 2427 observed reflections [$I \geq 2\sigma(I)$], 182 refined parameters, $R = 0.031$, $wR^2 = 0.085$, Flack parameter 0.03(13), max. residual electron density 0.12 (–0.14) e·Å^{-3} and hydrogen atoms calculated and refined as riding atoms.

X-ray Crystal Structure Analysis for Compound (1*R*,2*R*)-9a: $C_{16}H_{13}FO_2$, $M = 256.26$, colourless crystal, $0.20 \times 0.10 \times 0.03$ mm, $a = 9.219(5)$ Å, $b = 5.743(2)$ Å, $c = 12.429(6)$ Å, $\beta = 90.07(4)°$, $V = 658.0(5)$ Å^3, $\rho_{calcd.} = 1.293$ g cm^{-3}, $\mu = 0.776$ mm^{-1}, empirical absorption correction ($0.860 \leq T \leq 0.977$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223$ K, ω and φ scans, 6406 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.58$ Å^{-1}, 1748 independent ($R_{int} = 0.042$) and 1640 observed reflections [$I \geq 2\sigma(I)$], 173 refined parameters, $R = 0.055$, $wR^2 = 0.154$, Flack parameter –0.5(3), max. residual electron density 0.15 (–0.14) e·Å^{-3} and hydrogen atoms calculated and refined as riding atoms.

Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection: COLLECT (Nonius B.V., 1998); data reduction: Denzo-SMN;[50] absorption correction: SORTAV[51] and DENZO;[52] structure solution: SHELXS-97;[53] structure refinement: SHELXL-97;[54] graphics: SCHAKAL.[55] CCDC-610521 to -610523 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Synthesis of catalysts **7** and **8**, ^{1}H,^{19}F-Hetero-NOE experiments, extended X-ray data of compounds (1*R*,2*R*)-**5a**, (1*R*,2*S*)-**6a** and (1*R*,2*S*)-**9a**.

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