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PAPER

Enantioselective Reformatsky reaction of ethyl iododifluoroacetate with ketones†

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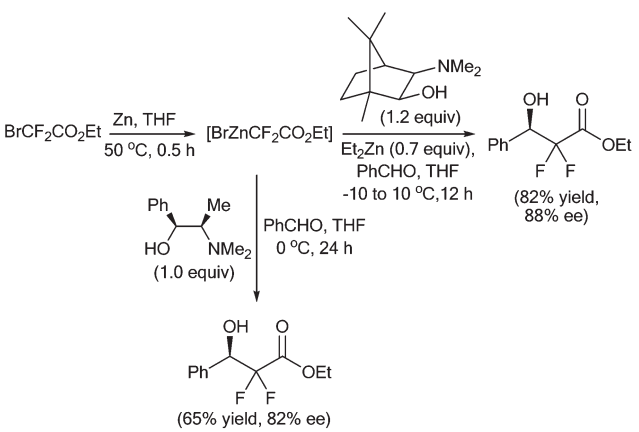
Two approaches have been developed for the enantioselective Reformatsky reaction of ethyl iododifluoroacetate with ketones to form a quaternary carbon centre using (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol as the chiral ligand. Good yields and high enantioselectivities (80–91% ee) were achieved with a range of alkyl aryl ketones in a convenient one-pot protocol using ethyl iododifluoroacetate and diethylzinc to form the difluorinated Reformatsky reagent homogeneously. In the traditional two-step Reformatsky reaction using the preformed Reformatsky reagent generated from ethyl iododifluoroacetate and zinc dust, good yields and good enantioselectivities (75–84% ee) were also obtained.

Introduction

Over the last 60 years fluorinated molecules have proved crucial in the development of new pharmaceuticals and ten of the top thirty best selling pharmaceutical products in 2008 contained at least one fluorine atom.[1] Although it is relatively straightforward to introduce fluorine regioselectively, one of the most demanding challenges in organofluorine chemistry is to design new methods for the enantioselective synthesis of fluorinated organic compounds. Outstanding progress has been made in recent years,[2] but further work is required for chiral fluorinated molecules to be increasingly used in medicinal chemistry.

The classical Reformatsky reaction between α-halogenated esters, zinc dust and carbonyl compounds provides a convenient synthesis of β-hydroxy esters.[3] Since the heterogeneous reaction conditions made the development of a catalytic asymmetric reaction difficult, stoichiometric amounts of chiral ligands were required to promote the enantioselective Reformatsky reaction until recently.[4] Homogeneous Reformatsky-type reactions have now been developed and can be promoted either by using α-bromoesters/α-iodoesters with dialkylzincs in the presence of catalysts or additives,[5] or by the direct iodine–zinc exchange between α-iodoesters with either diethylzinc or diisopropylzinc.[6] The first catalytic enantioselective Reformatsky reaction of ethyl iodoacetate was reported by Cozzi in 2006 using 20 mole% of a chiral manganese salen catalyst and dimethylzinc to generate the zinc reagent homogeneously.[7k] Since then, the catalytic enantioselective Reformatsky reactions of α-halogenated esters with aldehydes and ketones have been promoted by BINOL derivatives, chiral aminoalcohols, a chiral Schiff base and a chiral bisoxazolidine.[7]

The Reformatsky reaction of ethyl bromodifluoroacetate is one of the most efficient methods for the synthesis of medicinally-important compounds containing a difluoromethylene group.[8] In contrast to the enantioselective Reformatsky reaction with α-halogenated esters, there are only three reports of an enantioselective reaction with the difluorinated Reformatsky reagent giving α,α-difluoro-β-hydroxy esters in good enantiomeric excess in the presence of stoichiometric amounts of chiral aminoalcohols (Scheme 1).[4a,9] A two-step procedure is normally used and the Reformatsky reagent is prepared in the first step by refluxing ethyl bromodifluoroacetate with freshly-activated zinc



Scheme 1 Enantioselective Reformatsky reaction with benzaldehyde.[4a,9b]

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dust, before cooling to room temperature and adding the difluorinated Reformatsky reagent to a mixture of the aromatic aldehyde and the chiral aminoalcohol in the second step.

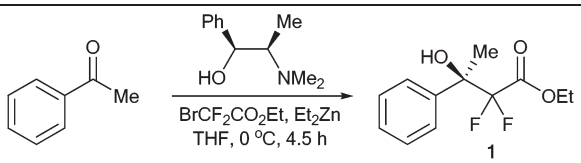
Since the enantioselective Reformatsky reaction of ethyl bromodifluoroacetate is limited to aldehydes, we were interested in extending this reaction to ketones in order to prepare quaternary stereocenters. The asymmetric synthesis of quaternary carbon centres is highly desirable, but it is a formidable goal because ketones are less reactive electrophiles than aldehydes, they often contain enolisable protons and there is less differentiation between the two groups on the carbonyl substrate compared to aldehydes.[10] We have developed and report herein the first enantioselective Reformatsky reaction of ethyl iododifluoroacetate with ketones by two distinct strategies: (i) firstly, using diethylzinc to generate the difluorinated Reformatsky reagent homogeneously and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol as the chiral aminoalcohol; (ii) secondly, using the same chiral ligand with the preformed Reformatsky reagent generated from ethyl iododifluoroacetate and zinc dust.[11] Good yields and high enantioselectivities (up to 91% ee) have been obtained for a broad range of alkyl aryl ketones.

Results and discussion

Optimisation of the enantioselective Reformatsky-type reaction with ethyl iododifluoroacetate and diethylzinc

We started our investigation with the reaction between acetophenone and ethyl bromodifluoroacetate using diethylzinc to generate the difluorinated Reformatsky reagent homogeneously and (1*S*,2*R*)-*N*-methylephedrine as a cheap, chiral ligand (Table 1). In run 1 a 100% conversion to ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **1** was obtained without any chiral aminoalcohol confirming that Wilkinson's catalyst was not required to form the

Table 1 Enantioselective Reformatsky-type reaction with ethyl bromodifluoroacetate and diethylzinc



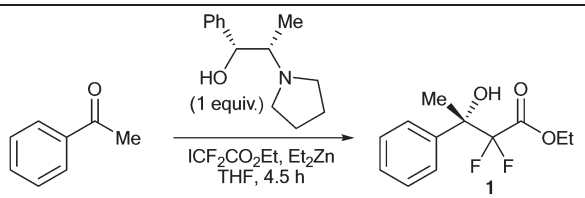
Run	$BrCF_2CO_2Et$ (equiv.)	Et_2Zn (equiv.)	*N*-Me-Eph (equiv.)	Yield[a] (%)	ee[b] (%)
1	1.5	1.5	0	100	NA
2	1.5	1.6	0.2	51	40
3	1.5	1.7	0.4	49	57
4	1.5	1.8	0.6	49	59
5	1.5	2.0	1.0	23	68
6[c]	1.5	2.0	1.0	60	50
7[d]	1.5 + 0.5	2.0 + 0.5	1.0	53	61
8[e]	1.5 + 0.5 + 0.5	2.0 + 0.5 + 0.5	1.0	72	57

[a] Determined by GC using ditolyl ether as the internal standard. [b] Determined by chiral HPLC. [c] Incorporation of Wilkinson's catalyst (1 mole%). [d] Further aliquots of ethyl bromodifluoroacetate (0.5 equiv.) and diethylzinc (0.5 equiv.) were added after 2 hours. [e] Further aliquots of ethyl bromodifluoroacetate (0.5 equiv.) and diethylzinc (0.5 equiv.) were added after 2 and 4 hours.

difluorinated Reformatsky reagent. This is in agreement with recent work by Jubault who has shown that the Reformatsky reaction between ethyl dibromofluoroacetate and carbonyl substrates can be promoted by diethylzinc without any rhodium catalyst in synthetic routes to α-fluoroacrylates and fluorinated glycidic esters.[12] In the enantioselective reactions (runs 2–8) the excess of diethylzinc was used to deprotonate the chiral aminoalcohol as well as to form the Reformatsky reagent *in situ* and there was no trace of the product resulting from the addition of diethylzinc to acetophenone in any of the reactions. As the amount of (1*S*,2*R*)-*N*-methylephedrine was increased from 0.2 to 1.0 equivalent in runs 2 to 5, the enantiomeric excess increased from 40 to 68% ee but the yield decreased from 51 to 23%. In order to improve the yield (23%) with 1 equivalent of (1*S*,2*R*)-*N*-methylephedrine, the reaction was repeated under exactly the same conditions but with 1 mole% of Wilkinson's catalyst incorporated (run 6). Although the yield increased to 60%, unfortunately, the enantiomeric excess dropped to only 50% ee. Consequently, Wilkinson's catalyst was not used in runs 7 and 8 when the addition of further aliquots of ethyl bromodifluoroacetate and diethylzinc had the desired effect of improving the yield to 53 and 72% respectively, but the enantiomeric excess decreased to 61 and 57% ee.

The effects of adding different substrates dropwise, as well as different orders of substrate addition, were investigated but despite many different combinations, there were no further improvements in the reaction. The first real step forward was when ethyl iododifluoroacetate was used instead of ethyl bromodifluoroacetate and the yield improved dramatically from 23 to 72% with only a small drop in the enantiomeric excess from 68 to 63% ee (Table 2,

Table 2 Enantioselective Reformatsky-type reaction with ethyl iododifluoroacetate and diethylzinc



Run	ICF_2CO_2Et (equiv.)	Et_2Zn (equiv.)	Temp. (° C)	Yield[a,b] (%)	ee[c] (%)
1[d]	1.5	2.0	0	72 (59)	63[e]
2[d,f]	1.5 + 0.5	2.0 + 0.5	0	97 (87)	58[e]
3	1.5	2.0	0	61 (54)	76
4[f]	1.5 + 0.5	2.0 + 0.5	0	94 (66)	74
5	2.0	2.5	0	99 (92)	71
6	2.0	2.5	−20	98 (95)	80
7	**2.0**	**2.5**	**−40**	**98 (95)**	**87**
8[g]	2.0	2.5	−40	88	70
9	2.0	2.5	−50	56 (46)	91
10	2.0	2.5	−78	50 (41)	91

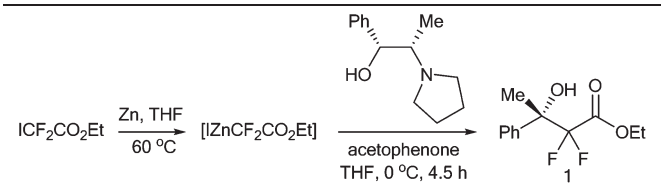
[a] Determined by GC using ditolyl ether as the internal standard in runs 1–5 and by ^1H NMR spectroscopy in runs 6–9. [b] Isolated yield in parenthesis. [c] Determined by chiral HPLC. [d] (1*S*,2*R*)-*N*-Methylephedrine (1.0 equiv.) was used as the chiral aminoalcohol. [e] Major enantiomer formed was (*R*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate. [f] Further aliquots of ethyl iododifluoroacetate (0.5 equiv.) and diethylzinc (0.5 equiv.) were added after 2 hours. [g] 0.2 Equivalents of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol were used.

run 1). The better yields are presumably due to a more efficient iodine–zinc exchange reaction between ethyl iododifluoroacetate and diethylzinc than the bromine–zinc exchange reaction between ethyl bromodifluoroacetate and diethylzinc. When further aliquots of ethyl iododifluoroacetate and diethylzinc were added after 2 hours in run 2 the yield increased to 97% but the enantiomeric excess decreased to 58% ee. By changing the chiral aminoalcohol to (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol the enantiomeric excess increased to 76% ee in run 3 albeit with a slightly lower yield. However, the yield was improved to 94% by adding further aliquots of ethyl iododifluoroacetate and diethylzinc in run 4. A more convenient protocol was used in runs 5 to 10 when 2 equivalents of ethyl iododifluoroacetate and 2.5 equivalents of diethylzinc were added in one portion at the beginning of the reaction. As the reaction temperature was lowered from 0 to −78 °C, the yield decreased but the enantiomeric excess increased to an excellent 91% ee. Run 7 gave the best result providing an excellent isolated yield (95%) with an excellent enantiomeric excess (87% ee) at −40 °C. Although the reaction can be performed with a catalytic amount of chiral ligand (0.2 equivalents) at −40 °C, the enantiomeric excess decreased to 70% ee (run 8) probably because of the competitive uncatalysed pathway.

Comparison of the heterogeneous and homogeneous Reformatsky reactions

The classical two-step reaction using the preformed difluorinated Reformatsky reagent, generated from ethyl iododifluoroacetate and zinc dust, was also investigated with the same chiral ligand in THF at 0 °C (Table 3) for a direct comparison with the homogeneous one-step protocol. The difluorinated Reformatsky reagent was prepared by the procedure described by Knochel *et al.*[4a] and a large excess was used in order to deprotonate the chiral aminoalcohol as well as to react with acetophenone. Without chiral aminoalcohol (run 1), ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **1** was obtained in only a 19% yield (*vide supra*). However, the yield increased as the amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol was increased from 0.4 to 1.4 equivalents and the same enantiomeric excess (83% ee) was obtained whether 0.6, 0.8, 1.0 or 1.4 equivalents of the chiral aminoalcohol were used. Surprisingly, a lower enantiomeric excess (73% ee) and a lower yield (81%) was obtained with ethyl bromodifluoroacetate in run 6 compared to using ethyl iododifluoroacetate in run 5. When the reaction was carried out at −10 °C in run 7, the yield decreased dramatically and disappointingly, there was no improvement in the enantiomeric excess. Similar to the one-pot protocol, the optimum yield and enantiomeric excess was obtained when the reaction was mediated with 1 equivalent of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (run 5). However, even the best conditions for the two-step protocol still required a larger excess of ethyl iododifluoroacetate, gave a lower yield and a lower enantiomeric excess than the best one-step protocol described above (Table 2, run 7).

Table 3 Enantioselective Reformatsky reaction with ethyl iododifluoroacetate and Zn dust



Run	ICF_2CO_2Et (equiv.)	Chiral ligand (equiv.)	Yield[a,b] (%)	ee[c] (%)
1	1.5	0	19	NA
2	1.9	0.4	62 (58)	76
3	2.1	0.6	69 (61)	83
4	2.3	0.8	78 (63)	83
5	**2.5**	**1.0**	**91 (75)**	**84**
6[d]	2.5	1.0	81 (70)	73
7[e]	2.5	1.0	26 (22)	84
8	2.9	1.4	92 (87)	82

[a] Determined by GC using ditolyl ether as the internal standard. [b] Isolated yield in parenthesis. [c] Determined by chiral HPLC. [d] Reaction with ethyl bromodifluoroacetate. [e] Reaction at −10 °C.

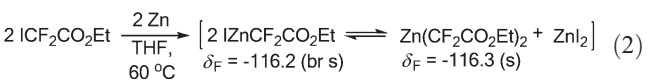
Since the homogeneous and heterogeneous protocols gave different yields in the uncatalysed Reformatsky reaction (Table 1, run 1 *versus* Table 3, run 1), preliminary experiments directed towards differentiating between the mechanisms of these reactions were undertaken. Firstly, ^{19}F NMR spectroscopy was used to probe the active zinc intermediates formed in the reactions between ethyl iododifluoroacetate and either zinc dust or diethylzinc, and secondly, both enantioselective Reformatsky reactions were monitored at 0 °C in the presence of 1 equivalent of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol.

Initially, two singlets were observed in the ^{19}F NMR spectrum of the Reformatsky reagent, generated from ethyl bromodifluoroacetate and zinc dust in THF, showing that carbon-metallated enolates were formed as reported in similar work by Burton and Easdon (eqn (1)) and there was no sign of an AB pattern for oxygen-metallated enolates.[13] In addition, there were also two minor singlets at −120.7 and −127.9 ppm corresponding to the Wurtz coupled by-product, $(CF_2CO_2Et)_2$ and difluoroacetate respectively (see Fig. S5 in the ESI†).

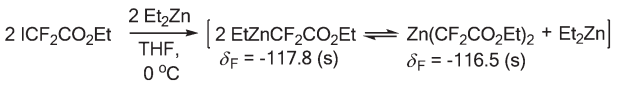
$$2\ BrCF_2CO_2Et \xrightarrow[\text{THF, } 60\ ^oC]{2\ Zn} \left[2\ BrZnCF_2CO_2Et \underset{\delta_F = -116.4\ (s)}{\overset{\delta_F = -115.8\ (br\ s)}{\rightleftharpoons}} Zn(CF_2CO_2Et)_2 + ZnBr_2\right] \quad (1)$$

In the reactions between ethyl iododifluoroacetate and either zinc dust or diethylzinc, singlets were observed in the ^{19}F NMR spectra showing that carbon-metallated enolates were formed in both protocols. The proposed zinc intermediates and their Schlenk equilibria are summarised in eqn (2) and (3), whilst the ^{19}F NMR spectra are shown in Fig. S6 and S7 in the ESI.† As expected, $IZnCF_2CO_2Et$ was the main species formed in the zinc insertion method with only small amounts of the diorganozinc reagent present (eqn (2)). In the iodine–zinc exchange reaction using diethylzinc, however, there was a 70–30 mixture of $EtZnCF_2CO_2Et$ and $Zn(CF_2CO_2Et)_2$ respectively (eqn (3)).[14] The latter reaction using diethylzinc also gave a cleaner reaction with no organic by-products formed, whilst small amounts of $(CF_2CO_2Et)_2$ and difluoroacetate were observed in the zinc insertion method (eqn (2)). These data confirm that different zinc intermediates are formed by the two different procedures and account for their different reactivity since it is well-established

that diorganozinc reagents (R_2Zn) are more reactive than organozinc halides (RZnX).[15]



(2)



(3)

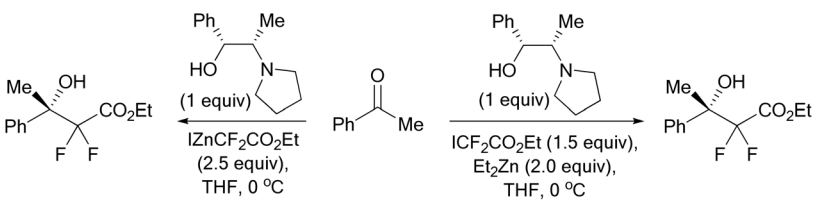
In the one-step and two-step enantioselective Reformatsky reactions the reaction monitoring began with the addition of diethylzinc and the preformed Reformatsky reagent, $IZnCF_2CO_2Et$, respectively and the results are shown in Fig. 1. There was a dramatic difference in the profiles for the two reactions and the homogeneous protocol was a surprisingly fast reaction which was complete after 30 min at 0 °C. In fact, when the homogeneous Reformatsky-type reaction was repeated under identical conditions and quenched 10 min after the addition of diethylzinc, a 74% conversion and 75% ee was obtained showing that the reaction was finished in just 10 min. Therefore, the chiral zinc catalyst generated in the homogeneous protocol is different to the chiral catalyst generated from $IZnCF_2CO_2Et$ and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol.

Results from screening a range of ketones in both enantioselective Reformatsky reactions

The scope of both enantioselective Reformatsky reactions with ethyl iododifluoroacetate was investigated with a broad range of alkyl aryl ketones under the optimum reaction conditions (Table 4). Overall, the homogeneous enantioselective Reformatsky-type reaction gave higher enantioselectivities (Method A: 81–91% ee) than the heterogeneous protocol (Method B: 75–84% ee) and both methods gave good isolated yields. For the iodine–zinc exchange reaction using diethylzinc, the excellent enantiomeric excess was maintained at 85–91% ee when the aromatic ring was substituted with either electron-donating or electron-withdrawing substituents (entries 1–4). The reaction also worked well when the methyl group was substituted either by an ethyl (81% ee), propyl (81% ee) or even a relatively bulky *iso*-butyl group (84% ee). In addition, good yields and excellent enantiomeric excesses (84–89% ee) were obtained with the two cyclic ketones, indanone and tetralone (entries 9–10). As expected from Kumadaki *et al.*'s work,[16] the reaction with the α,β-unsaturated ketone, *trans*-4-phenyl-3-buten-2-one, did not work with the one-pot protocol and only a very low enantiomeric excess (13% ee) was obtained in the two-step asymmetric Reformatsky reaction.

A number of crystals of the product esters suitable for X-ray crystallography were grown by slow evaporation from either hexane or 10% ethyl acetate in hexane and the molecular structures of ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **5**, ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate **6**, ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate **7** and ethyl-3-(2,3-dihydro-1*H*-inden-1-yl)-2,2-difluoro-3-hydroxybutanoate **9** are reported in the ESI (Fig. S9–S12†).

In order to determine the absolute configuration of the product esters, ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **1** (72% ee) and ethyl-2,2-difluoro-3-hydroxy-3-phenylpentanoate **5** (78% ee) were reacted with the lithium salt of (*S*)-(1-phenylethyl)amine to form the two diastereomers (Scheme 2). In each



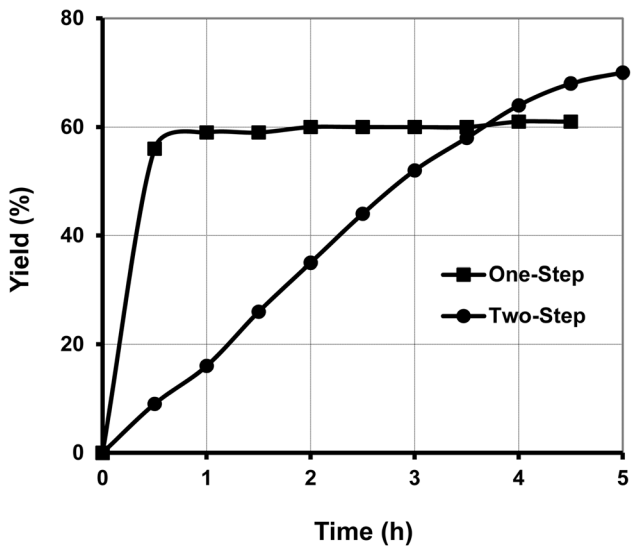
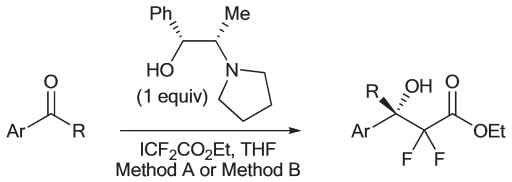


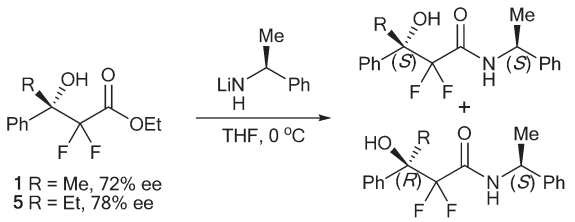
Fig. 1 Reaction monitoring of the one-step and two-step protocols at 0 °C.

Table 4 Enantioselective Reformatsky reaction with ethyl iododifluoroacetate



Entry	Ar	R	Product	Method A Et$_2$Zn, −40 °C, 4.5 hours Yield[a,b] (%)	Method A Et$_2$Zn, −40 °C, 4.5 hours Ee[c,d] (%)	Method B Zn, 0 °C, 6.5 hours Yield[a,b] (%)	Method B Zn, 0 °C, 6.5 hours ee[c,d] (%)
1	Ph	Me	**1**	97 (90)	86 (*S*)	98 (94)	80 (*S*)
2	2-MeOC$_6$H$_4$	Me	**2**	66 (57)	91	76 (63)	82
3	4-MeOC$_6$H$_4$	Me	**3**	93 (78)	89	95 (94)	84
4	4-ClC$_6$H$_4$	Me	**4**	99 (79)	85	88 (81)	80
5	Ph	Et	**5**	72 (59)	80 (*S*)	46 (40)	79 (*S*)
6	Ph	Propyl	**6**	85 (62)	81	95 (69)	80
7	Ph	*iso*-Butyl	**7**	79 (62)	84	46 (29)	75
8	Ph	H	**8**	100 (88)	76 (*S*)	100 (71)	78 (*S*)
9	1-Indanone		**9**	88 (85)	84	100 (99)	82
10	1-Tetralone		**10**	80 (69)	89 (*S*)	100 (86)	83 (*S*)

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield in parenthesis. [c] Determined by chiral HPLC. [d] In entries 1, 5 and 10 the product esters were reacted with the lithium salt of (*S*)-(1-phenylethyl)amine and the absolute configuration was determined by X-ray crystallographic analysis; the absolute configuration for ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate in entry 8 was determined by comparing retention times of HPLC analysis with those reported by Knochel *et al.*;[4a] the stereochemistry of the other product esters was tentatively assumed by analogy.



Scheme 2 Determination of the absolute configuration of ethyl 2,2-difluoro-3-hydroxy-3-phenylbutanoate and ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate.

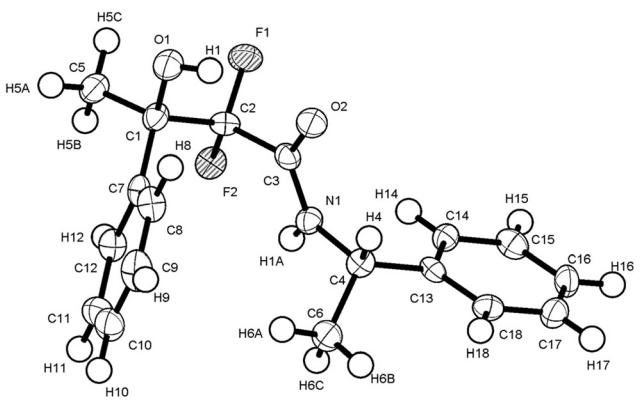


Fig. 2 Molecular structure of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide showing 50% displacement ellipsoids.

reaction the two diastereomers were separated by column chromatography and a single crystal of the minor diastereomer was obtained. There is intramolecular hydrogen bonding between O

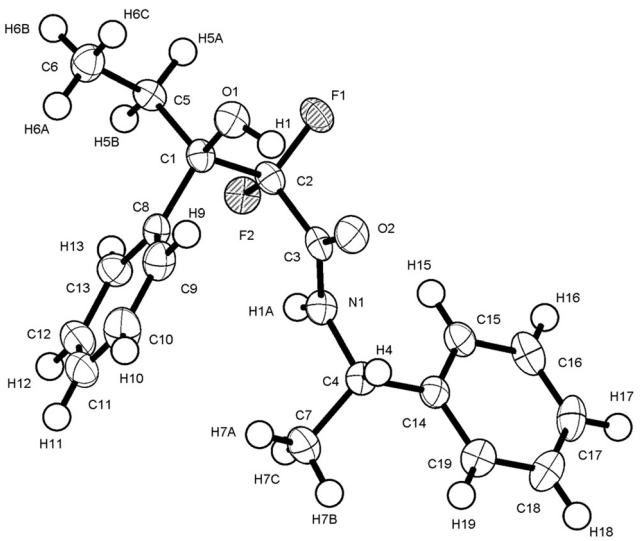


Fig. 3 Molecular structure of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide showing 50% displacement ellipsoids.

(1)–H(1) and O(2) in both molecular structures which are shown in Fig. 2 and 3. Both structures revealed that the minor diastereomer has the (1′*S*,3*R*)-configuration and so, the major enantiomer formed in the enantioselective Reformatsky reactions mediated by (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol is the (*S*)-enantiomer resulting from nucleophilic addition to the *Re* face of the ketone. This facial selectivity is the same as that obtained in the asymmetric Reformatsky reaction between ethyl bromodifluoroacetate and benzaldehyde[9] and in the catalytic enantioselective Reformatsky reaction with ethyl iodoacetate,[7c–f] as well as in the aminoalcohol promoted additions of dialkylzinc to

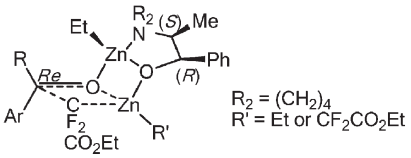


Fig. 4 Proposed transition state for the enantioselective Reformatsky-type reaction using diethylzinc.

aldehydes.[17] Consequently, we have proposed that the stereoselectivity in the enantioselective Reformatsky-type reaction using diethylzinc can be accounted for by Noyori's classic *anti* transition state (Fig. 4).[17]

Conclusions

The first enantioselective Reformatsky reaction between ethyl iododifluoroacetate and ketones has been accomplished by two different procedures using (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol as the chiral ligand. Good yields and high enantioselectivities (up to 91% ee) were achieved with a range of alkyl aryl ketones using ethyl iododifluoroacetate and diethylzinc to form the difluorinated Reformatsky reagent homogeneously. The heterogeneous Reformatsky reaction using ethyl iododifluoroacetate and zinc dust was also investigated, but proved inferior requiring more ethyl iododifluoroacetate and giving lower enantioselectivity (up to 84% ee) compared to the homogeneous protocol.

Experimental

Proton, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer at 400.13, 376.46 and 100.62 MHz respectively and were referenced to external $SiMe_4$ (^{1}H), external $CFCl_3$ (^{19}F) and to external $SiMe_4$ (^{13}C) using the high frequency positive convention. Elemental analyses were performed by the Elemental Analysis Service at the University of North London. Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos concept 1 H, double focussing, forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for the FAB spectra. Electrospray mass spectra were obtained on a Micromass Quatro LC. High performance liquid chromatography was carried out on a Perkin Elmer HPLC Liquid Chromatograph supported with either an OD-H (Daicel) or an AS (Daicel) column and a UV-VIS detector. X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Optical rotation data were collected on a Perkin Elmer 341 Polarimeter and the concentration of the samples were 1g per 100 mL.

THF was obtained dry from a distillation machine model Puresolve^{TM}, and was stored in sealed ampoules over 4 Å molecular sieves under an atmosphere of dry nitrogen. (1*S*,2*R*)-*N*-Methylephedrine and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol were dried using the Kugelröhr oven at 100 °C under oil pump vacuum for 30 min. After cooling, the crystals of the chiral aminoalcohols were dissolved in dry diethyl ether and the solvent was removed under vacuum. The second step was not a purification process and the only aim was to obtain small crystals that were convenient to use. The dry aminoalcohols were stored in a flushbox under nitrogen. The zinc dust (<10 μm, 98+%), purchased from Aldrich, was washed with 17% HCl for 10 seconds and the acid was removed by suction filtration. The zinc dust was washed with water, ethanol and diethyl ether before it was dried under vacuum at 120 °C for 2 hours. The activated zinc dust was stored and handled under a nitrogen atmosphere.

General procedure for Table 1

Each reaction was run in duplicate and the average yield and enantiomeric excess is reported. A THF solution of acetophenone (0.600 g, 5.0 mmol) and ditolyl ether (0.496 g, 2.5 mmol) was made up in a 10 mL volumetric flask and was transferred into a Schlenk flask. Under argon a three neck round bottom flask was charged with THF (6 mL) and the THF solution (2 mL) of acetophenone (0.12 mL, 1.0 mmol) and tolyl ether (0.099 g, 0.5 mmol). After cooling the reaction mixture to 0 °C, ethyl bromodifluoroacetate (0.19 mL, 1.5 mmol) and the required amount of (1*S*,2*R*)-(+)-*N*-methylephedrine (0.179 g, 1.0 mmol for runs 5–8) were added. The reaction mixture was then stirred at 0 °C for 30 min before the required amount of diethylzinc (2.0 mL, 1.0 M solution in hexane, 2.0 mmol for runs 5–8) was added. Two hours after the initial injection of diethylzinc, a further aliquot of ethyl bromodifluoroacetate (0.06 mL, 0.5 mmol) followed by an aliquot of diethylzinc (0.5 mL, 0.5 mmol) were added in run 7. In run 8 further aliquots of both ethyl bromodifluoroacetate (0.06 mL, 0.5 mmol) and diethylzinc (0.5 mL, 0.5 mmol) were added after two and four hours. The reaction mixture was quenched with 1 M HCl (10 mL) 4.5 hours after the first addition of diethylzinc, was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulfate. A sample (1.0 mL) from the crude product was filtered through a short plug of silica gel (1 g) and the conversion was determined by GC. The product was purified by column chromatography (25% EtOAc in hexane) on silica gel to give ethyl-2,2-difluoro-3-hydroxy-3-phenylbutanoate **1** as a colourless oil. The characterisation data was in agreement with the literature.[18,19] The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 8.55 min ((*R*)-enantiomer), 12.37 min ((*S*)-enantiomer). The enantiomers were also separated on a chiralcel OD-H column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 7.65 min ((*R*)-enantiomer), 8.35 min ((*S*)-enantiomer).

General procedure for Table 2

Each reaction was run in duplicate and the average yield and enantiomeric excess is reported. A three neck round bottom flask was charged with THF (8 mL) and acetophenone (0.12 mL, 1.0 mmol) under argon. After cooling to the required temperature (0 to −78 °C), ethyl iododifluoroacetate (0.22 mL, 1.5 mmol) and either (1*S*,2*R*)-(+)-*N*-methylephedrine (0.179 g, 1.0 mmol) or (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol

(0.205 g, 1.0 mmol) were added. The reaction mixture was then stirred at the required temperature for 30 min before diethylzinc (2.0 mL, 1.0 M solution in hexane, 2.0 mmol) was added. Two hours after the initial injection of diethylzinc, a further aliquot of ethyl iododifluoroacetate (0.07 mL, 0.5 mmol) followed by an aliquot of diethylzinc (0.5 mL, 0.5 mmol) were added in runs 2 and 4. The reaction mixture was quenched with 1 M HCl (10 mL) 4.5 hours after the first addition of diethylzinc, was extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulfate. A sample (0.8 mL) from the crude product was filtered through a short plug of silica gel (1 g) and the conversion was determined by GC in runs 1–5. In runs 6–9 the solvent was removed and the conversion was determined by ^{1}H NMR spectroscopy on the crude product. The product was purified by column chromatography (10% EtOAc in hexane) on silica gel to give a colourless oil.

General procedure for Table 3

Preparation of the solution of Reformatsky reagent. A two neck round bottom flask was charged with acid-washed zinc dust (0.565 g, 5.7 mmol) and dry THF (15.2 mL). The suspension was heated to 60 °C, and the heating was stopped before ethyl iododifluoroacetate (0.83 mL, 5.7 mmol) was added dropwise over 2–3 min. The Reformatsky reagent was used after a further 2 min of stirring.

The asymmetric Reformatsky reaction with acetophenone. A three neck round bottom flask was charged with THF (1 mL), acetophenone (0.12 mL, 1 mmol) and the required amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol (0.205 g, 1.0 mmol in runs 5–7) under argon. After cooling to 0 °C, the required amount of the solution of the Reformatsky reagent (7 mL, 2.5 mmol in runs 5–7) was added and the reaction mixture was stirred for 4.5 hours at 0 °C. The reaction mixture was quenched with 1 M HCl (10 mL), extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulfate. The solvent was removed and the product was purified by column chromatography (EtOAc–hexane = 1 : 9) on silica gel to give a colourless oil. Each reaction was run in duplicate and the average yield and enantiomeric excess is reported.

General procedure for Table 4

Method A. Each reaction was run in duplicate and the average yield and enantiomeric excess is reported. A three neck round bottom flask under argon was charged with ketone (1.0 mmol) and THF (8 mL). After cooling the reaction mixture to −40 °C, ethyl iododifluoroacetate (0.29 mL, 2.0 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol (0.205 g, 1.0 mmol) were added. The reaction mixture was then stirred for a further 30 min at −40 °C before diethylzinc (2.5 mL, 1.0 M solution in hexane, 2.5 mmol) was added. After 4.5 hours the reaction mixture was quenched with 1 M HCl (10 mL), extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulfate. The solvent was removed and the product was purified by column chromatography (EtOAc–hexane) on silica gel.

Ethyl 2,2-difluoro-3-hydroxy-3-(2′-methoxyphenyl)butanoate 2. The crude product was purified by column chromatography (20% EtOAc in hexane) to give ethyl 2,2-difluoro-3-hydroxy-3-(2′-methoxyphenyl)butanoate as a colourless oil (0.157 g, 57%, 91% ee). $[\alpha]_D$ ($CHCl_3$) −14.5° (c = 1); δ_H ($CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ 7.2 Hz, OCH_2CH_3), 1.72 (3H, t, $^4J_{HF}$ 2.0 Hz, $CF_2C(OH)CH_3$), 3.84 (3H, s, OCH_3), 4.19 (2H, q, $^3J_{HH}$ 7.2 Hz, OCH_2CH_3), 5.88 (1H, br s, OH), 6.89 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 6.94 (1H, td, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.2 Hz, ArH), 7.22 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.26 (1H, m, ArH); δ_F ($CDCl_3$) −113.50 (1F, d, $^2J_{FF}$ 246.5 Hz, CF_AF_B), −115.60 (1F, d, $^2J_{FF}$ 246.5 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 23.0 (CH_3), 56.2 (CH_3), 62.6 (CH_2), 77.8 (t, $^2J_{CF}$ 25.2 Hz, C), 112.3 (CH), 115.9 (t, $^1J_{CF}$ 260.6 Hz, CF_2), 121.5 (CH), 126.6 (C), 129.5 (CH), 130.0 (CH), 158.2 (C), 163.7 (t, $^2J_{CF}$ 32.2 Hz, CO); m/z (FAB) 297.0918 (MNa^+. $C_{13}H_{16}F_2O_4Na$ requires 297.0914). The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 7.76 min (minor enantiomer), 8.73 min (major enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-3-(4′-methoxyphenyl)butanoate 3. The crude product was purified by column chromatography (10% EtOAc in hexane) to give ethyl 2,2-difluoro-3-hydroxy-3-(4′-methoxyphenyl)butanoate as a colourless oil (0.214 g, 78%, 89% ee). $[\alpha]_D$ ($CHCl_3$) 17.5° (c = 1). The characterisation data is reported in the literature.[19] The enantiomers were separated on a chiralcel OD-H column eluted with 2% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 14.68 min (major enantiomer), 16.41 min (minor enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-3-(4′-chlorophenyl)butanoate 4. The crude product was purified by column chromatography (20% EtOAc in hexane) to give ethyl 2,2-difluoro-3-hydroxy-3-(4′-chlorophenyl)butanoate as a colourless oil (0.219 g, 79%, 85% ee). $[\alpha]_D$ ($CHCl_3$) 14.7° (c = 1). The characterisation data is reported in the literature.[19] The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 10.17 min (minor enantiomer), 16.80 min (major enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate 5. The crude product was purified by column chromatography (10% EtOAc in hexane) to give ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate as white crystals (0.152 g, 59%, 81% ee). $[\alpha]_D$ ($CHCl_3$) 5.5° (c = 1); mp 38–39 °C; anal. calcd for $C_{13}H_{16}F_2O_3$: C 60.5, H 6.2%; found: C 60.5, H 6.3%. δ_H ($CDCl_3$) 0.69 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.00 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.02 (1H, m, $CH_AH_BCH_3$), 2.13 (1H, m, $CH_AH_BCH_3$), 2.92 (1H, s, OH), 4.02 (2H, q, $^3J_{HH}$ 7.0, OCH_2CH_3), 7.21–7.34 (3H, m, ArH), 7.41 (2H, d, $^3J_{HH}$ 7.0 Hz, ArH); δ_F ($CDCl_3$) −115.43 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −116.14 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 6.6 (CH_3), 13.6 (CH_3), 27.1 (CH_2), 62.8 (CH_2), 78.5 (t, $^2J_{CF}$ 23.6 Hz, C), 115.1 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.5 (CH), 128.0 (CH), 128.1 (CH), 137.3 (C), 163.6 (t, $^2J_{CF}$

32.2 Hz, CO); *m/z* (EI) 258.10641 (M^+. $C_{13}H_{16}F_2O_3$ requires 258.10635), 229 (18%), 201 (23%), 135 (100%). Crystals suitable for X-ray crystallography were grown on the side of a round bottom flask from the pure product without using solvent. The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 6.77 min ((*R*)-enantiomer), 11.49 min ((*S*)-enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate 6. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate as white crystals (0.165 g, 62%, 81% ee). $[\alpha]_D$ ($CHCl_3$) 15.5 ° (*c* = 1). mp 41–43 °C; anal. calcd for $C_{14}H_{18}F_2O_3$: C 61.75, H 6.7%; found: C 61.85, H 6.65%. δ_H ($CDCl_3$) 0.80 (3H, t, $^3J_{HH}$ 7.0 Hz, $CH_2CH_2CH_3$), 0.90 (1H, m, $CH_2CH_AH_BCH_3$), 1.00 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.31 (1H, m, $CH_2CH_AH_BCH_3$), 1.94 (1H, ddd, $^2J_{HH}$ 14.0 Hz, $^3J_{HH}$ 11.5 Hz, $^3J_{HH}$ 4.5 Hz, $CH_CH_DCH_AH_BCH_3$), 2.07 (1H, m, $CH_CH_DCH_AH_BCH_3$), 2.96 (1H, br s, OH), 4.04 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 7.21–7.31 (3H, m, ArH), 7.41 (2H, d, $^3J_{HH}$ 7.0 Hz, ArH); δ_F ($CDCl_3$) −115.46 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −116.16 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.6 (CH_3), 14.3 (CH_3), 15.7 (CH_2), 36.4 (CH_2), 62.8 (CH_2), 78.3 (t, $^2J_{CF}$ 24.1 Hz, C), 115.0 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.4 (CH), 128.0 (CH), 128.1 (CH), 137.8 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); *m/z* (FAB) 273.1306 (MH^+. $C_{14}H_{19}F_2O_3$ requires 273.1302). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of ethyl 2,2-difluoro-3-hydroxy-3-phenylhexanoate in hexane. The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 5.76 min (minor enantiomer), 10.44 min (major enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate 7. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate as white crystals (0.179 g, 62%, 84% ee). $[\alpha]_D$ ($CHCl_3$) 3.8 ° (*c* = 1); mp 63–64 °C; anal. calcd for $C_{15}H_{20}F_2O_3$: C 62.9, H 7.0%; found: C 63.1, H 6.9%; δ_H ($CDCl_3$) 0.61 (3H, d, $^3J_{HH}$ 6.7 Hz, $CHCH_3$), 0.86 (3H, d, $^3J_{HH}$ 6.7 Hz, $CHCH_3$), 0.98 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 1.50 (1H, m, $CH(CH_3)_2$), 1.82 (1H, dd, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 7.4 Hz, $CH_AH_BCH(CH_3)_2$), 2.09 (1H, ddt, $^2J_{HH}$ 14.5 Hz, $^3J_{HH}$ 5.1 Hz, $^4J_{HF}$ 1.6 Hz, $CH_AH_BCH(CH_3)_2$), 2.95 (1H, br s, OH), 4.02 (2H, q, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 7.21–7.31 (3H, m, ArH), 7.42 (2H, d, $^3J_{HH}$ 7.0 Hz, ArH); δ_F ($CDCl_3$) −116.02 (2F, s, CF_2); δ_C ($CDCl_3$) 13.5 (CH_3), 23.5 (CH_3), 24.0 (CH_3), 24.4 (CH), 41.9 (CH_2), 62.8 (CH_2), 78.8 (t, $^2J_{CF}$ 23.1 Hz, C), 114.9 (t, $^1J_{CF}$ 263.6 Hz, CF_2), 126.6 (CH), 127.98 (CH), 128.02 (CH), 137.9 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); *m/z* (TOF) 285.1311 ($(M - H)^+$. $C_{15}H_{19}F_2O_3$ requires 285.1302). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of ethyl 2,2-difluoro-3-hydroxy-5-methyl-3-phenylhexanoate in hexane. The enantiomers were separated on a chiralpak AS column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 4.81 min (minor enantiomer), 7.14 min (major enantiomer).

Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate 8. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate as a colourless oil (0.202 g, 88%, 76% ee). $[\alpha]_D$ ($CHCl_3$) 12.5 ° (*c* = 1). The characterisation data is reported in the literature.[18] The enantiomers were separated on a chiralpak AS column eluted with 10% IPA in hexane. The flow rate of the mobile phase was set at 1 mL min^{-1}. R_t = 11.09 min ((*S*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate), 15.74 min ((*R*)-ethyl-2,2-difluoro-3-hydroxy-3-phenylpropanoate).

Ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl) acetate 9. The crude product was purified by column chromatography (2% EtOAc in hexane) to yield ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate as white crystals (0.216 g, 85%, 84% ee). $[\alpha]_D$ ($CHCl_3$) −7.7° (*c* = 1); mp 56–58 °C; anal. calcd for $C_{13}H_{14}F_2O_3$: C 60.9, H 5.5%; found: C 61.0, H 5.5%. δ_H ($CDCl_3$) 1.23 (3H, t, $^3J_{HH}$ 7.0 Hz, OCH_2CH_3), 2.11 (1H, m, $CF_2C(OH)CH_AH_B$), 2.72–3.04 (4H, m, $CF_2C(OH)CH_AH_BCH_2$ and O*H*), 4.25 (2H, m, OCH_2CH_3), 7.17–7.23 (2H, m, ArH), 7.27 (1H, t, $^3J_{HH}$ 7.4 Hz, ArH), 7.42 (1H, d, $^3J_{HH}$ 8.2 Hz, ArH); δ_F ($CDCl_3$) −114.57 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), −117.59 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.8 (CH_3), 29.9 (CH_2), 35.7 (CH_2), 63.1 (CH_2), 84.7 (t, $^2J_{CF}$ 24.1 Hz, C), 115.3 (t, $^1J_{CF}$ 259.1 Hz, CF_2), 124.9 (CH), 125.1 (CH), 126.9 (CH), 129.8 (CH), 139.8 (C), 145.0 (C), 163.8 (t, $^2J_{CF}$ 32.2 Hz, CO); *m/z* (EI) 256.09065 (M^+. $C_{13}H_{14}F_2O_3$ requires 256.09075), 165 (10%), 133 (100%). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of ethyl 2,2-difluoro-2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate in 20% EtOAc in hexane. The enantiomers were separated on a chiralcel OD-H column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 8.40 min (major enantiomer), 10.79 min (minor enantiomer).

Ethyl 2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate 10. The crude product was purified by column chromatography (10% EtOAc in hexane) to give ethyl 2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate as a colourless oil (0.187 g, 69%, 90% ee). $[\alpha]_D$ ($CHCl_3$) 1.3° (*c* = 1); anal. calcd for $C_{14}H_{16}F_2O_3$: C 62.2, H 6.0%; found: C 62.3, H 6.0%. δ_H ($CDCl_3$) 1.26 (3H, t, $^3J_{HH}$ 7.4 Hz, OCH_2CH_3), 1.85 (1H, m, $CF_2C(OH)CH_AH_B$), 2.05 (2H, m, $CH_AH_BCH_2CH_2$), 2.30 (1H, m, $CF_2C(OH)CH_AH_B$), 2.85 (3H, m, $ArCH_2$ and OH), 4.29 (2H, m, OCH_2CH_3), 7.16 (1H, m, ArH), 7.22–7.31 (2H, m, ArH), 7.69 (1H, d, $^3J_{HH}$ 7.4 Hz, ArH); δ_F ($CDCl_3$) −111.58 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −113.24 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.7 (CH_3), 18.7 (CH_2), 29.5 (CH_2), 33.2 (CH_2), 63.0 (CH_2), 73.7 (t, $^2J_{CF}$ 22.6 Hz, C), 116.0 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.2 (CH), 127.9 (CH), 128.6 (CH), 129.1 (CH), 133.7 (C), 138.9 (C), 163.8 (t, $^2J_{CF}$ 32.2 Hz, CO); *m/z* (EI) 270.10642 (M^+. $C_{14}H_{16}F_2O_3$ requires 270.10635), 147 (100%). The enantiomers were separated on a chiralcel OD-H column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 8.20 min ((*S*)-enantiomer), 9.88 min ((*R*)-enantiomer).

General procedure for Table 4

Method B – Preparation of the solution of Reformatsky reagent. A two neck round bottom flask was charged with acid-washed zinc dust (0.565 g, 5.7 mmol) and dry THF (10 mL). The suspension was heated to 60 °C and the heating was stopped before ethyl iododifluoroacetate (0.83 mL, 5.7 mmol) in THF (5.2 mL) was added dropwise over 2–3 min. The Reformatsky reagent was used after a further 2 min of stirring.

Method B – The asymmetric Reformatsky reaction with ketones. A three neck round bottom flask was charged with THF (1 mL), ketone (1 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)1-propanol (0.205 g, 1.0 mmol) under argon. After cooling to 0 °C, the solution of the Reformatsky reagent (7 mL, 2.5 mmol) was added and the reaction mixture was stirred for 6.5 hours at 0 °C. The reaction mixture was quenched with 1 M HCl (10 mL), extracted with ethyl acetate (3 × 10 mL) and the organic layer was washed with 1 M HCl (30 mL), brine (30 mL) and water (30 mL) before being dried over magnesium sulfate. The solvent was removed and the product was purified by column chromatography (EtOAc–hexane) on silica gel. Each reaction was run in duplicate and the average yield and enantiomeric excess is reported.

Ethyl (*E*)-2,2-difluoro-3-hydroxy-3-methyl-5-phenylpent-4-enoate 11. The crude product was purified by column chromatography (10% EtOAc in hexane) to give a colourless oil (0.263 g, 97%); anal. calcd for $C_{14}H_{16}F_2O_3$: C 62.22, H 5.97%; found: C 62.12; H 5.87%. δ_H ($CDCl_3$) 1.28 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 1.46 (3H, t, $^4J_{HF}$ 1.6 Hz, $CF_2C(OH)CH_3$), 2.50 (1H, br s, OH), 4.24 (2H, q, $^3J_{HH}$ 7.0, OCH_2CH_3), 6.21 (1H, dt, $^3J_{HH}$ 16.0 Hz, $^4J_{HF}$ 1.6 Hz, ArCH=C*H*C(OH)), 6.75 (1H, d, $^3J_{HH}$ 16.0 Hz, ArC*H*), 7.17–7.22 (1H, m, ArH), 7.23–7.28 (2H, m, ArH), 7.30–7.34 (2H, m, ArH); δ_F ($CDCl_3$) −116.52 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B), −117.82 (1F, d, $^2J_{FF}$ 260.2 Hz, CF_AF_B); δ_C ($CDCl_3$) 13.9 (CH_3), 21.8 (CH_3), 63.1 (CH_2), 75.1 (t, $^2J_{CF}$ 25.2 Hz, C), 114.8 (t, $^1J_{CF}$ 260.6 Hz, CF_2), 126.8 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 131.3 (CH), 136.0 (C), 163.6 (t, $^2J_{CF}$ 32.2 Hz, CO); *m*/*z* (FAB) 293.0960 (MNa^+. $C_{14}H_{16}F_2O_3Na$ requires 293.0965). The characterisation data was in agreement with literature.[16] The enantiomers were separated on a chiralcel OD-H column eluted with 4% IPA in hexane. The flow rate of the mobile phase was set at 1.0 mL min^{-1}. R_t = 10.18 min (minor enantiomer), 11.55 min (major enantiomer).

Determination of the absolute configuration of the new chiral centre in ethyl 2,2-difluoro-3-hydroxy-3-phenylbutanoate

Under an argon atmosphere a dry three neck flask was charged with THF (30 mL), (*S*)-(1-phenylethyl)amine (0.81 mL, 6.3 mmol) and *n*-butyllithium (5.7 mL, 1.6 M in hexane, 9.1 mmol). After 30 min of stirring at 0 °C, a solution of (*S*)-ethyl 2,2-difluoro-3-hydroxy-3-phenylbutanoate **1** (0.60 g, 2.5 mmol, 72% ee) in THF (2 mL) was added. The dropping funnel was washed with THF (2 mL) and the reaction mixture was stirred for 24 hours at 0 °C. After quenching the reaction mixture with 1 M HCl (20 mL), it was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with 1 M HCl (20 mL), brine (20 mL) and water (20 ml) before being dried over magnesium sulphate. The solvent was removed and the crude product consisted of a 6 : 1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (15% EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-3(*S*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide as colourless crystals (0.50 g, 63%); mp 81–85 °C; $[\alpha]_D$ ($CHCl_3$) −42.5° (*c* = 1); anal. calcd for $C_{18}H_{19}F_2NO_2$: C 67.7, H 6.0, N 4.4%; found: C 67.85, H 5.6, N 4.3%. δ_H ($CDCl_3$) 1.46 (3H, d, $^3J_{HH}$ 7.0 Hz, $CHCH_3$), 1.74 (3H, s, $CF_2C(OH)CH_3$), 4.72 (1H, s, OH), 4.96 (1H, quintet, $^3J_{HH}$ 7.0 Hz, C*H*CH_3), 6.40 (1H, br s, NH), 6.79–6.82 (2H, m, ArH), 7.19–7.25 (3H, m, ArH), 7.31–7.36 (3H, m, ArH), 7.49–7.53 (2H, m, ArH); δ_F ($CDCl_3$) −115.40 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −117.96 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 20.9 (CH_3), 22.5 (CH_3), 48.7 (CH), 76.1 (t, $^2J_{CF}$ 24.1 Hz, C), 114.4 (t, $^1J_{CF}$ 262.6 Hz, CF_2), 125.7 (CH), 126.3 (CH), 127.5 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 140.1 (C), 140.9 (C), 163.5 (t, $^2J_{CF}$ 29.2 Hz, CO); *m*/*z* (ES^+) 320.1465 (MH^+. $C_{18}H_{20}F_2NO_2$ requires 320.1462).

The pure diastereomer 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide was obtained as colourless crystals (0.04 g, 5%); mp 84–86 °C; $[\alpha]_D$ ($CHCl_3$) −38.6° (*c* = 1); anal. calcd for $C_{18}H_{19}F_2NO_2$: C 67.7, H 6.0, N 4.4%; found: C 67.6, H 5.8, N 4.2%. δ_H ($CDCl_3$) 1.03 (3H, d, $^3J_{HH}$ 7.0 Hz, $CHCH_3$), 1.63 (3H, t, $^4J_{HF}$ 1.2 Hz, $CF_2C(OH)CH_3$), 4.49 (1H, br s, OH), 4.83 (1H, quintet, $^3J_{HH}$ 7.0 Hz, C*H*CH_3), 6.30 (1H, br s, NH), 7.08 (2H, dm, $^3J_{HH}$ 8.0 Hz, ArH), 7.16–7.30 (6H, m, ArH), 7.41–7.46 (2H, m, ArH); δ_F ($CDCl_3$) −116.55 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −117.45 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 20.6 (CH_3), 22.6 (CH_3), 48.9 (CH), 76.1 (t, $^2J_{CF}$ 24.0 Hz, C), 114.5 (t, $^1J_{CF}$ 262.6 Hz, CF_2), 126.1 (CH), 126.3 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.9 (CH), 140.1 (C), 141.2 (C), 163.3 (t, $^2J_{CF}$ 29.2 Hz, CO); *m*/*z* (TOF) 320.1465 (MH^+. $C_{18}H_{20}F_2NO_2$ requires 320.1462). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)butanamide in 20% EtOAc in hexane.

Determination of the absolute configuration of the new chiral centre in ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate

The procedure above was repeated using (*S*)-(1-phenylethyl) amine (0.22 mL, 1.7 mmol), *n*-butyllithium (1.6 mL, 1.6 M in hexane, 2.6 mmol), (*S*)-ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **5** (0.18 g, 0.7 mmol, 78% ee) and THF (8 mL). The crude product consisted of a 7.3 : 1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (10% EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-3(*S*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide as white crystals (0.18 g, 77%); mp 88–90 °C. $[\alpha]_D$ ($CHCl_3$) −44.5° (*c* = 1); δ_H ($CDCl_3$) 0.66 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.36 (3H, d, $^3J_{HH}$ 7.0 Hz, $CHCH_3$), 2.07 (2H, q, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 4.55 (1H, br s, OH), 4.83 (1H, quintet, $^3J_{HH}$ 7.4 Hz, C*H*CH_3), 6.29 (1H, br s, NH), 6.64–6.69 (2H, m, ArH), 7.07–7.16 (3H, m, ArH), 7.22–7.27 (3H, m, ArH), 7.36–7.41 (2H, m, ArH); δ_F ($CDCl_3$) −115.35 (1F, d, $^2J_{FF}$ 257.5 Hz, CF_AF_B), −118.65 (1F, d, $^2J_{FF}$ 257.5 Hz, CF_AF_B); δ_C ($CDCl_3$)

6.5 (CH_3), 20.9 (CH_3), 26.7 (CH_2), 48.6 (CH), 78.6 (t, $^2J_{CF}$ 23.1 Hz, C), 114.7 (t, $^1J_{CF}$ 263.6 Hz, CF_2), 125.7 (CH), 126.8 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 128.7 (CH), 138.0 (C), 140.9 (C), 163.7 (t, $^2J_{CF}$ 28.2 Hz, CO); *m*/*z* (ES^+) 334.1620 (MH^+. $C_{19}H_{22}F_2NO_2$ requires 334.1619).

The procedure above was repeated using (*S*)-(1-phenylethyl) amine (0.77 mL, 5.9 mmol), *n*-butyllithium (5.4 mL, 1.6 M in hexane, 8.6 mmol), racemic ethyl 2,2-difluoro-3-hydroxy-3-phenylpentanoate **5** (0.31 g, 1.2 mmol) and THF (28 mL). The crude product consisted of a 1 : 1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (10% EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)pentanamide as colourless crystals (0.06 g, 15%); mp 131–132 °C. $[\alpha]_D$ ($CHCl_3$) −40.7° (*c* = 1); δ_H ($CDCl_3$) 0.78 (3H, t, $^3J_{HH}$ 7.4 Hz, CH_2CH_3), 1.14 (3H, d, $^3J_{HH}$ 6.7 Hz, $CHCH_3$), 2.07–2.23 (2H, m, CH_2CH_3), 4.49 (1H, br s, OH), 4.91 (1H, quintet, $^3J_{HH}$ 7.0 Hz, $CHCH_3$), 6.34 (1H, br s, NH), 7.17–7.21 (2H, m, ArH), 7.27–7.42 (6H, m, ArH), 7.49–7.54 (2H, dm, $^3J_{HH}$ 8.0 Hz, ArH); δ_F ($CDCl_3$) −116.69 (1F, d, $^2J_{FF}$ 254.7 Hz, CF_AF_B), −118.40 (1F, d, $^2J_{FF}$ 254.7 Hz, CF_AF_B); δ_C ($CDCl_3$) 6.6 (CH_3), 20.5 (CH_3), 26.6 (CH_2), 48.8 (CH), 78.6 (t, $^2J_{CF}$ 23.1 Hz, C), 114.8 (t, $^1J_{CF}$ 262.6 Hz, CF_2), 126.1 (CH), 126.9 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.9 (CH), 138.0 (C), 141.1 (C), 163.5 (t, $^2J_{CF}$ 28.2 Hz, CO); *m*/*z* (ES^+) 334.1621 (MH^+. $C_{19}H_{22}F_2NO_2$ requires 334.1619). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of 2,2-difluoro-3(*R*)-hydroxy-3-phenyl-*N*-((*S*)-1-phenylethyl)-pentanamide in 10% EtOAc in hexane.

Determination of the absolute configuration of the new chiral centre in ethyl 2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate

The procedure above was repeated using (*S*)-(1-phenylethyl) amine (0.32 mL, 2.5 mmol), n-butyllithium (2.3 mL, 1.6 M in hexane, 3.7 mmol), racemic ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate **10** (0.14 g, 0.5 mmol) and THF (12 mL). The crude product consisted of a 1 : 1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to the ^{1}H NMR spectrum. The diastereoisomers were separated by silica gel column chromatography (10% EtOAc in hexane) to give diastereomerically pure 2,2-difluoro-3(*S*)-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenylethyl)acetamide as colourless crystals (0.03 g, 17%); mp 153–155 °C; $[\alpha]_D$ ($CHCl_3$) −20.4° (*c* = 1); anal. calcd for $C_{20}H_{21}F_2NO_2$: C 69.55, H 6.1, N 4.05%; found: C 69.4, H 6.2, N 4.1%. δ_H ($CDCl_3$) 1.44 (3H, d, $^3J_{HH}$ 7.0 Hz, CH_3), 1.66–1.78 (1H, m, $CF_2COHCH_AH_B$), 1.88 (2H, d, $^3J_{HH}$ 11.0 Hz, $CH_2CH_2CH_2$), 2.24 (1H, m, $CF_2COHCH_AH_B$), 2.62–278 (2H, m, $ArCH_2$), 4.05 (1H, br s, OH), 5.04 (1H, quintet, $^3J_{HH}$ 7.0 Hz, $CHCH_3$), 6.52 (1H, br s, NH), 7.02–7.06 (2H, m, ArH), 7.12–7.32 (6H, m, ArH), 7.51 (1H, d, $^3J_{HH}$ 7.8 Hz, ArH); δ_F ($CDCl_3$) −112.76 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B), −113.65 (1F, d, $^2J_{FF}$ 257.4 Hz, CF_AF_B); δ_C ($CDCl_3$) 19.0 (CH_2), 21.2 (CH_3), 29.5 (CH_2), 33.2 (CH_2), 49.3 (CH), 73.7 (t, $^2J_{CF}$ 23.1 Hz, C), 115.7 (t, $^1J_{CF}$ 261.6 Hz, CF_2), 126.2 (2 × CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 134.0 (C), 139.1 (C), 141.4 (C), 163.6 (t, $^2J_{CF}$ 29.2 Hz, CO); *m*/*z* (ES^+) 346.1628 (MH^+. $C_{20}H_{22}F_2NO_2$ requires 346.1619). Crystals suitable for X-ray crystallography were grown on the side of a round bottom flask from the pure product without using solvent. The molecular structure is shown in Fig. S8 in the ESI.†

The procedure above was repeated using (*S*)-(1-phenylethyl) amine (0.28 mL, 2.25 mmol), *n*-butyllithium (2.0 mL, 1.6 M in hexane, 3.2 mmol), (*S*)-ethyl-2,2-difluoro-2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate **10** (0.24 g, 0.9 mmol, 88% ee) and THF (11 mL). The crude product consisted of a 10 : 1 mixture of (*S*,*S*)- and (*R*,*S*)-diastereomers according to the ^{19}F NMR spectrum and the ^{19}F NMR data revealed that the crystal structure was obtained from the major diastereomer, 2,2-difluoro-3(*S*)-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-((*S*)-1-phenyl-ethyl)acetamide.

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