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Synthesis of α -fluoro- β -hydroxy esters by an enantioselective Reformatsky-type reaction[†]

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The first enantioselective Reformatsky-type reaction of ethyl iodofluoroacetate has been accomplished with alkyl aryl ketones. High diastereoselectivities and excellent enantioselectivities for the major diastereomer (93–95% ee) were achieved with large alkyl groups. For smaller alkyl groups the diastereoselectivities were moderate, but excellent enantioselectivities were obtained for both diastereomers (79–94% ee).

The incorporation of fluorine into the organic framework is an important strategy for the development of new pharmaceutical products because of the beneficial properties imparted by fluorine.¹ Recently, there has been a surge of interest in the field of asymmetric fluorination because of the increasing demand for enantiopure pharmaceutical products.² We were interested in designing an enantioselective synthesis of α -fluoro- β -hydroxy esters which are important building blocks for the preparation of monofluorinated analogues of amino acids and carbohydrates.³

The classical Reformatsky reaction provides a convenient synthesis of β -hydroxy esters by the nucleophilic addition of the Reformatsky reagent, prepared by the direct insertion of zinc into α -halogenated esters, to carbonyl compounds.⁴ It is an excellent alternative to the base-catalysed aldol reaction because of the high tolerance towards functional groups and the mild reaction conditions. Until recently, stoichiometric amounts of chiral ligands were required to promote the enantioselective Reformatsky reaction because of the heterogeneous reaction conditions.⁵ Following the development of homogeneous Reformatsky-type reactions,^{6,7} Cozzi reported the first catalytic enantioselective Reformatsky reaction in 2006 using 20 mol% of a chiral manganese salen catalyst and dimethylzinc to generate the zinc reagent homogeneously.8h Since then, BINOL derivatives, chiral aminoalcohols and a chiral bisoxazolidine have been used to promote the catalytic enantioselective Reformatsky reactions of a-halogenated esters with aldehydes and ketones.8

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In stark contrast to these reports on the enantioselective Reformatsky reaction of α -halogenated esters, there are only three reports of an enantioselective reaction with the difluorinated Reformatsky reagent^{5a,9} and no reports of an asymmetric reaction with the monofluorinated Reformatsky reagent. The Reformatsky reaction of ethyl bromofluoroacetate is one of the oldest and most efficient methods for preparing α -fluoro- β -hydroxy esters.¹⁰ Presumably, an enantioselective version has not been developed because the reaction only proceeds in the presence of both the zinc dust and the carbonyl substrate in a one-step procedure whereas a two-step zinc insertion procedure is normally used for the enantioselective Reformatsky reaction with ethyl bromodifluoroacetate. In this paper we will report the first example of an enantioselective Reformatsky-type reaction of ethyl iodofluoroacetate with ketones using diethylzinc to generate the Reformatsky reagent homogeneously and (1R,2S)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol as the chiral ligand.¹¹

Previously, the Reformatsky reaction of ethyl bromofluoroacetate with carbonyl substrates had only been reported using zinc dust under heterogeneous conditions.¹⁰ We now show that the Reformatsky reaction of ethyl iodofluoroacetate and ethyl bromofluoroacetate can also be performed under homogeneous conditions (Table 1, entries 1-3). The reaction with ethyl iodofluoroacetate (entry 1) gave 100% conversion to ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate 1 which was obtained as a 63:37 mixture of the (2S,3S)/(2R,3R)- and (2R,3S)/(2S,3R)-diastereomers. The solid-state structure of the major diastereomer confirmed that it was a mixture of the (2S,3S)- and (2R,3R)-enantiomers which is in agreement with the literature.^{10a} The bromine-zinc exchange reaction between ethyl bromofluoroacetate and diethylzinc was less efficient than the iodine-zinc exchange reaction resulting in only a 29% conversion to ethyl 2-fluoro-3-hydroxy-3-phenylbutanoate 1 (entry 2). The conversion could be improved substantially to 76% (entry 3) when the reaction with ethyl bromofluoroacetate was catalysed by 1 mol% of [RhCl(PPh₃)₃].

The scope of the reaction with ethyl iodofluoroacetate was established with a series of ketones and the α -fluoro- β -hydroxy esters were isolated in good yields (Table 1, entries 4–11). The (2S,3S)/(2R,3R)- and (2R,3S)/(2S,3R)-diastereomers of products **2**, **4**, **5** and **7** were separated by column chromatography. In each case the major diastereomer was confirmed as the (2S,3S)/(2R,3R)-diastereomer by X-ray crystallography and the molecular structures are shown in the ESI. The (2S,3S)/(2R,3R)- and

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[†] Electronic supplementary information (ESI) available: Table 4, experimental procedures, NMR spectra and crystallographic data for 2a, 4a, 5a, 7a, 10b and 10d. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17985g

Table 1 Reformatsky-type reaction with ethyl iodofluoroacetate



^{*a*} Determined by ¹H NMR spectroscopy. ^{*b*} Determined by ¹⁹F NMR spectroscopy for crude product. ^{*c*} Isolated yield. ^{*d*} Confirmed as (*SS/RR*)-diastereomer by X-ray crystallography. ^{*e*} BrCHFCO₂Et was used instead of ICHFCO₂Et. ^{*f*} Incorporation of [RhCl(PPh₃)₃] (1 mol%). ^{*g*} 5% of (*SS/RR*)-diastereomer, 20% of (*RS/SR*)-diastereomer, 45% mixture of both diastereomers.

(2R,3S)/(2S,3R)-diastereomers are easy to distinguish by ¹⁹F NMR spectroscopy because the chemical shift for the (2S,3S)/(2R,3R)-diastereomer is always at a lower field than that exhibited by the (2R,3S)/(2S,3R)-diastereomer (Table 4, ESI†). This data was used to assign the diastereomers of products **3**, **6**, **8** and **9**. With the exception of compounds **5** and **8**, it was also observed that the (2S,3S)/(2R,3R)-diastereomers had a typical one bond carbon–fluorine coupling constant of 191–194 Hz, whilst the one bond carbon–fluorine coupling constants for the (2R,3S)/(2S,3R)-diastereomers tended to be larger (196–201 Hz). Only low levels of diastereoselectivity were observed in all of the reactions and a similar lack of diastereoselectivity had also been reported for the heterogeneous Reformatsky reaction with ethyl bromofluoroacetate and ethyl chlorofluoroacetate.¹⁰

In Table 2 acetophenone was used as the model substrate for optimising the enantioselective Reformatsky-type reaction of ethyl iodofluoroacetate in the presence of (1R,2S)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol as the chiral ligand.^{8c,d} In entry 1 the uncatalysed reaction was repeated using 2.5 equivalents of diethylzinc and the results were identical to the uncatalysed reaction using a stoichiometric amount of diethylzinc in Table 1 (entry 1). In the enantioselective reactions (entries 2–7) an excess of diethylzinc was always used to deprotonate the chiral aminoalcohol as well as to form the Reformatsky reagent homogeneously and there was no trace of the product resulting from the addition of diethylzinc to acetophenone in any of the reactions. When 1 equivalent of (1R,2S)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol was used to catalyse the reaction in entry 2, the conversion dropped to 84% and the diastereomeric ratio increased from 63:37 to 79:21. A good enantiomeric excess (80% ee) was obtained for the major (2S,3S)/(2R,3R)diastereomer whilst a much lower enantiomeric excess (46% ee) was observed for the minor (2R,3S)/(2S,3R)-diastereomer.

 Table 2
 Optimisation of the enantioselective Reformatsky-type reaction with ethyl iodofluoroacetate



^{*c*} Determined by ¹H NMR spectroscopy. ^{*c*} Isolated yield in parenthesis. ^{*c*} Determined by ¹⁹F NMR spectroscopy for crude product. ^{*d*} Determined by chiral HPLC. ^{*e*} No chiral aminoalcohol.

On increasing the amount of ethyl iodofluoroacetate to 2.0 equivalents in entry 3, the conversion increased to 100%and the enantiomeric excess for the minor diastereomer increased to 51% ee, but the enantioselectivity for the major diastereomer decreased to 73% ee. As the reaction temperature was lowered from 0 to -40 °C (entries 3–5), the conversion decreased to 66% and the diasteromeric ratio dropped slightly to 75:25 whilst the enantioselectivity increased for both diastereomers giving 90% ee and 72% ee for the major and minor diastereomers respectively. In an attempt to enhance the conversion 3.5 equivalents of diethylzinc were used in entry 6. The conversion was increased successfully to 99% and the enantiomeric excess for the minor diastereomer increased to 82% ee, but the enantiomeric excess for the major diastereomer dropped slightly (87% ee). In entry 7 the amount of ethyl iodofluoroacetate was increased to 3.0 equivalents and the high conversion (100%) was maintained but the enantiomeric excess for both diastereomers decreased. Therefore, entry 6 gave the best result providing an excellent isolated yield (97%) with excellent enantiomeric excess for the major diastereomer (87% ee) and a good enantiomeric excess for the minor diastereomer (82% ee). Finally, the uncatalysed reaction under identical conditions in entry 8 gave 100% conversion with a lower 60:40 diastereomeric ratio demonstrating that it would not be possible to catalyse the enantioselective reaction with a catalytic amount of the chiral aminoalcohol.

With the reaction conditions optimised, the scope of the enantioselective Reformatsky-type reaction with ethyl iodo-fluoroacetate was evaluated with a series of alkyl aryl ketones (Table 3). In contrast to the achiral reaction (Table 1, entries 1, 4–6), when the aliphatic side of the ketone was extended to an ethyl, propyl and *iso*-butyl group (Table 3, entries 1–4), the diastereomeric ratio increased stepwise from 74:26 for acetophenone to an excellent 92:8 for 3-methyl-1-phenylbutan-1-one. In each reaction excellent enantioselectivity was achieved for the major (2S,3S)/(2R,3R)-diastereomer (93–95% ee) with

 Table 3
 Scope of the enantioselective Reformatsky-type reaction with ethyl iodofluoroacetate

Me HO (1.0 equiv) OF ICHFCO₂Et (2.0 equiv) ĥ Et₂Zn (3.5 equiv) THF, -40 °C, 4.5 h (2S,3S)/(2R,3R)-(2R,3S)/(2S,3R)diastereomer diastereomer SS/RR: Yield^{a,b} $ee^{d,e}$ (%) $ee^{d,e}$ (%) RS/SRR Entry Ar (%)ratio (SS/RR)(RS/SR)82 (3*S*) Me 99 (97) 1 Ph 74:26 87 (3S) 100 (71:13) 87:13 95 56 2 Ph Et 3 Pr 100 (95) 93 65 Ph 89.11 4 Ph iso-Bu 96 (94) 92:8 94 61 5 2-MeOC₆H₄ Me 100(51:34)58:42 84 85 6 4-MeOC₆H₄ Me 100 (99) 81:19 93 81 7 100 (96) 71:29 88 79 4-ClC₆H₄ Me 8 80 1-indanone 98 (97) 38:62 86 100 (84) 9 1-tetralone 40:60 88 94

^{*a*} Determined by ¹H NMR spectroscopy. ^{*b*} Isolated yield in parenthesis. ^{*c*} Determined by ¹⁹F NMR spectroscopy for crude product. ^{*d*} Determined by chiral HPLC. ^{*e*} Esters **1a** and **1b** were reacted with the lithium salt of (*S*)-(1-phenylethyl)amine and absolute configuration determined by X-ray crystallographic analysis; stereochemistry of the other product esters was tentatively assumed by analogy.

moderate enantioselectivity for the minor (2R,3S)/(2S,3R)diastereomer (56–65% ee). On the other hand, when the aromatic ring was substituted with either electron-donating or electron-withdrawing substituents (entries 5–7), moderate diastereoselectivities were obtained ranging from 58:42 to 81:19. In these reactions excellent enantioselectivities were achieved for both the major (84–93% ee) and the minor diastereomers (79–85% ee). Although the diastereomeric ratio was reversed for the cyclic ketones, 1-indanone and 1-tetralone, once again excellent enantiomeric excesses were obtained for both diastereomers (80–94% ee).

The absolute configuration of the new chiral centre formed at the 3-position for both the major (2S,3S)/(2R,3R)-diastereomer **1a** and the minor (2R,3S)/(2S,3R)-diastereomer **1b** (see ESI†) was determined to be the (S)-enantiomer resulting from nucleophilic addition to the *Re* face of the ketone. This facial selectivity is the same as that observed in the asymmetric Reformatsky reaction between ethyl bromodifluoroacetate and aromatic aldehydes,^{5a,9} as well as in the catalytic enantioselective Reformatsky reaction of ethyl iodoacetate with aldehydes and ketones using the same chiral ligand, (1*R*,2*S*)-1-phenyl-2-(pyrrolidin-1-yl)propan-1-ol.^{8c,d}

In conclusion, we have reported the first example of an enantioselective Reformatsky-type reaction with ethyl iodofluoroacetate. High diastereoselectivies (up to 92:8) and enantioselectivities for the major diastereomers (93–95% ee) were achieved with PhC(O)R derivatives ($R = Et, Pr, {}^{i}Bu$). With 1-indanone, 1-tetralone and ArC(O)Me derivatives, moderate diastereoselectivities and excellent enantioselectivities for both diastereomers (79–94% ee) were obtained.

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