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Catalytic asymmetric protonation of fluoro-enolic species: access to optically active 2-fluoro-1-tetralone

Markus A. Baur,[a,b] Abdelkhalek Riahi,[a] Françoise Hénin[a,*] and Jacques Muzart[a]

[a]*Unité mixte de recherche 'Réactions Sélectives et Applications', CNRS-Université de Reims Champagne-Ardenne, BP 1039, 51687, Reims Cedex 2, France*

[b]*Institut für Anorganische Chemie, Universitätsstraße 31, 93053 Regensburg, Germany*

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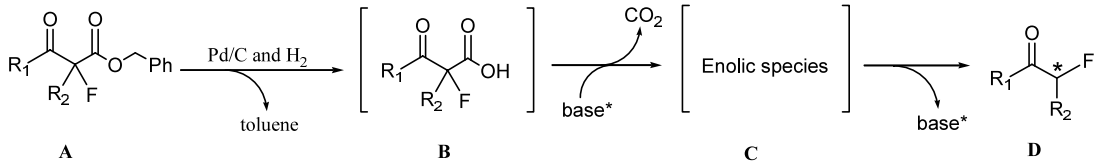
Abstract—Three racemic α-fluorinated benzyl β-ketoesters have been synthesized by electrophilic fluorination with Selectfluor™. They were submitted to our well established palladium-mediated cascade reaction (deprotection, decarboxylation and protonation of the resulting enolic species) producing optically active α-fluoro ketones. With benzyl 2-fluoro-1-tetralone-2-carboxylate as substrate, (*S*)-(−)-2-fluoro-1-tetralone with up to 65% enantiomeric excess was obtained using quinine as the chiral base and Pd/C type 807104 from Merck as the heterogeneous catalyst.

1. Introduction

The synthesis of cyclic and acyclic chiral fluoro-organic compounds is an important topic in modern pharmaceutical and agricultural chemistry;[1] non-racemic chiral α-fluoro ketones are also useful for asymmetric epoxydation of alkenes.[2] The generation of a quaternary fluoro stereogenic centre in the α-position to a carbonyl is now well developed using at least a stoichiometric amount of a chiral fluorinating agent[2,3] or a chiral substrate.[4] Catalytic methods have also been reported which consist of asymmetric alkylation of racemic α-fluoro carbonyl compounds under phase-transfer conditions,[5] and fluorination of β-ketoesters activated by chiral Lewis acid–TADDOL complexes[6] or under catalysis by chiral palladium complexes.[7] The enantioselective creation of a tertiary fluoro centre α to a carbonyl group is more problematic since most of the above methods work in media, which are not neutral enough to avoid racemisation of this centre bearing a hydrogen with enhanced acidity. For this purpose, only diastereoselective syntheses and a photochemical approach have been reported.[8] The development of catalytic procedures is highly desirable and we report here our studies dealing with the well established palladium/chiral base-catalysed cascade reaction[9] starting from a racemic α-fluoro-β-ketoesters such as **A**. The sequence could furnish optically active α-fluoroketone D, via oxoacid **B** and enolic species **C**, this latter being probably an enolate associated to the protonated base (Scheme 1).

2. Results and discussion

The first step of hydrogenolysis is a heterogeneous Pd-catalyzed reaction and it turned out that the type of the Pd on charcoal used not only influenced the benzyl



Scheme 1. The three steps of the cascade reaction.

* Corresponding author. Tel: +33-(0)3-2691-3310; fax: +33-(0)3-2691-3166; e-mail: francoise.henin@univ-reims.fr

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cleavage efficiency, but also the enantioselectivity of the protonation step.[10] the hydrogenolysis delivers the reactive β-ketoacid, the amount of which is probably kept low compared to that of the chiral base during the reaction. After the decarboxylation step, the stereoselectivity of the carbonyl compound is induced by the catalytically-active base which protonates the prochiral enolic species. Enantioselective decarboxylations starting directly from the free acids and leading to precursors of either the anti-inflammatory agent Naproxen or enantioenriched α-amino acids have also been recently reported.[11]

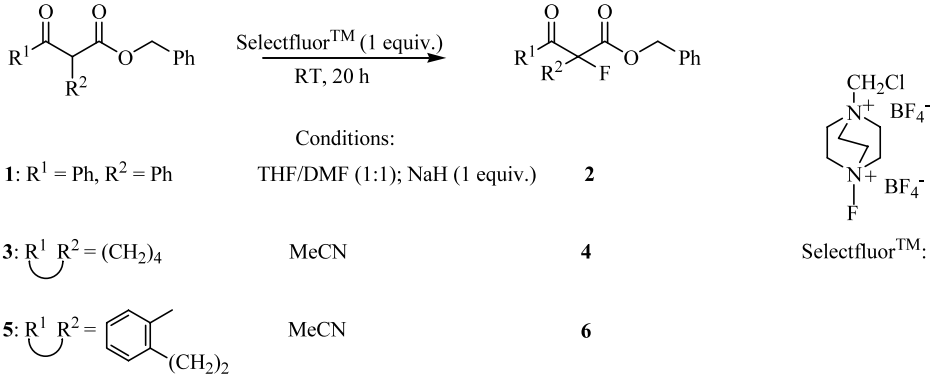
The substrates, β-oxoesters **2**, **4** and **6** were synthesized from the corresponding unsubstituted oxoesters **1**, **3** and **5**, by electrophilic fluorination with Selectfluor™ (Scheme 2). The transformation of the linear compound **1** requires a base such as NaH,[12] no conversion being observed under neutral conditions.[13] However, an unexpected competitive fluorination at the benzylic position occurred (THF, acetonitrile). In contrast, fluorination worked smoothly and selectively without base for the cyclic compounds **3** and **5**.

Employing the catalytic cascade reaction in order to obtain optically active fluoro ketones, the substrate (0.17 mmol) and the chiral base (0.3 equiv.) (Fig. 1) were dissolved in MeCN (10 mL). The Pd catalyst (0.025 equiv.) was added then and the hydrogen atmosphere provided by a gasbag. Starting from the linear compound **2** in the first experiment, we observed complete defluorination leading to deoxybenzoin as product. This was unexpected as the C–F bond is usually stable towards hydrogenolysis under Pd catalysis, but the presence of a base and the benzylic position of the fluorine atom facilitate dehalogenation.[14] A different problem occurred with **4**, since the reaction product, 2-fluorocyclohexanone, was too volatile for an effective work-up.[15] Fortunately, benzyl 2-fluoro-1-tetralone-2-carboxylate **6** was a suitable starting material for our studies. When submitted to the above conditions, the expected 2-fluoro-1-tetralone **7** was isolated besides small amounts of the defluorinated product **8** and the compound issued from the over-reduction of **7**: 2-fluoro-1-tetralol **9** (Scheme 3). The relative quantities of each product and the ee's of **7** were strongly dependent on the reaction conditions.

The nature of the catalyst used, palladium on charcoal, was especially crucial. The modification of the surface properties or the Pd and H_2O contents were sufficient to induce dramatic differences in reactivity or enantioselectivity. With the usually employed 5% Pd/C type Engelhard 5011,[16] the results were not reproducible (ee of **7** varied from 28 to 66% in presence of quinidine as a base and the yields of **8** from 0 to 30%). Pd/C Engelhard 5067[17] which initially delivered good results (Table 1, entry 1), later led also to reproductibility problems. Pd/C Fluka 75992[18] and 75990[19] gave inferior results (entries 2 and 3) to Pd/C Merck 807104[20] (entry 4). This latter catalyst led mainly to constant and reproducible results. With Pd(0) (prepared by $PdCl_2$ reduction), the reaction was slow (entry 5). The cleavage of the benzyl ester has been reported using the Wilkinson catalyst and a silane as hydrogen source,[21] but under hydrogen atmosphere this homogeneous catalyst resulted in both low reaction rate and ee (entry 6). Therefore, further experiments were carried out with Pd/C type 807104 from Merck.

The simple aminoalcohols **10**–**12** (Fig. 1) have previously led to good results in asymmetric protonation of tetralone enolic species[9a,10,22] and were tested in our experiments (Table 2). However, **10**–**12** as well as aminoalcohols **13** and **14**,[23] are not effective (Table 2, entries 7–11): poor ee's of **7** were observed and fair amounts of **8** were isolated in most cases. In contrast, the natural cinchona alkaloids **15**–**18** provided ee's up to 65% (entries 12–15) and produced low amounts of the defluorination product.

Cinchona alkaloids **15**–**18** delivered promising results and some of their derivatives **19**–**28**[24] showed good catalytic performances during other asymmetric protonations.[11] With these modified alkaloids, defluorination and over-reduction were minor reactions (entries 16–25), but none of them was found to be superior to quinine and quinidine for the asymmetric process. The presence of a hydroxyl group is not crucial to observe enantioselectivity, since 9-amino(9-deoxy)epicinchonine **19** induced 19% ee (entries 12 and 16). However, the enantioselectivity never reached more than 25%, whatever the substitution at this amino group (entries 18–23). The transformation of the *C*-9-hydroxyl function



Scheme 2. Electrophilic fluorination of β-oxoesters **1**, **3** and **5**.

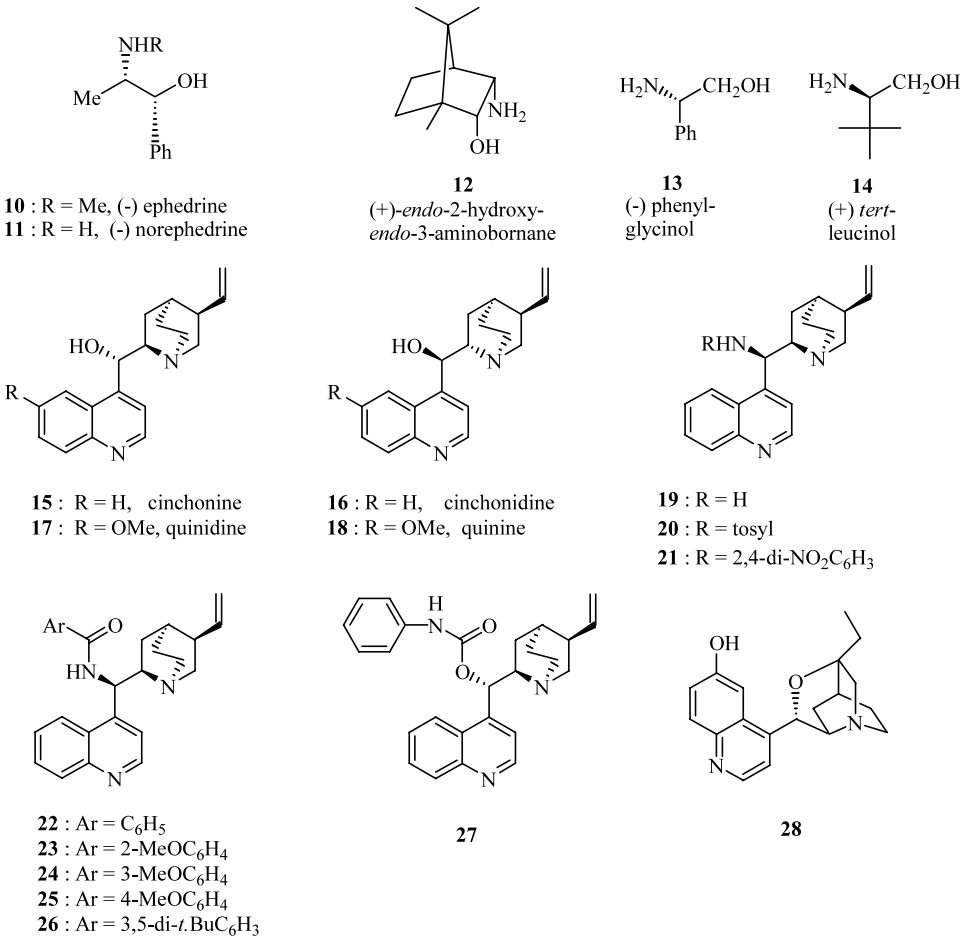
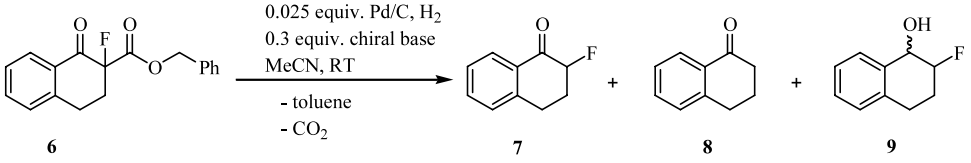


Figure 1. Chiral bases used as inductors.



Scheme 3. Reaction of benzyl 2-fluoro-1-tetralone-2-carboxylate **6**.

Table 1. Influence of the supported catalyst on the transformation of **6**[a]

Entry	Catalyst (equiv.)	Time (h)	Products[b]		
			7 (%)[c]	**8** (%)[c]	ee of **7** (%)[d]
1	5% Pd/C Engelhard 5067 (0.025)	1	96; 94	4; 6	62.6; 56.9
2	5% Pd/C Fluka 75992 (0.025)	1	98; 99	2; 1	63.1; 59.9
3	10% Pd/C Fluka 75990 (0.025)	1	98; 92	2; 8	50.7; 65.6
4	10% Pd/C Merck 807104 (0.025)	1	95; 74	Traces[e]	66.0; 67.9[f]
5	Pd(0) (0.25)	2	14; 17	Traces[e]	59.8; 51.2
6	$Rh(PPh_3)_3Cl$ (0.025)	2	2; 2	Traces[e]	20.5; 18.3

[a] *Conditions*: **6**, MeCN, rt, **18** (0.3 equiv.), H_2 delivered by a gasbag except entry 6 (40 bar).
[b] The expressed results correspond to two experiments (entries 5 and 6) or to the extreme values of several experiments (entries 1–4).
[c] Yields are determined by HPLC, using 2-methoxynaphthalene as standard.
[d] 2-Fluorotetralone of (*S*) configuration, ee determined by HPLC analysis.
[e] Yields <0.4%.
[f] Overall, nine experiments were carried out with this Pd/C, in seven cases the ee was 59–68%, in two cases only 48% and 50% ee were found.

Table 2. Reaction of **6** in the presence of chiral bases **10**–**28**[a]

Entry	Base	Time (h)	Products[b]		
			7[c] (%)	**8**[c] (%)	ee of **7**[d] (%) (config.)
7	**10**	0.5	60; 74	40; 26	1.5; 1.7 (*R*)
8	**11**	0.5	71; 71	29; 29	0.6; 1.1 (*R*)
9	**12**	0.5	69; 73	31; 27	0[e]
10	**13**	0.5	52; 71	1; 5	3.4; 0.8 (*S*)
11	**14**	0.5	40; 53	60; 46	0.6; 1.3 (*S*)
12	**15**[g]	2	97; 98	3; 3	51.4; 51.5 (*R*)
13	**16**[g]	2	95; 97	5; 3	50.0; 50.1 (*S*)
14	**17**	2	99; 87	Traces[f]; 13	64.7; 64.8 (*R*)
15	**18**	2	94; 93	6; 7	62.5; 64.4 (*S*)
16	**19**	2	96; 95	2; 2	20.4; 17.9 (*S*)
17	**20**	2	95; 94	1; 1	24.1; 14.7 (*S*)
18	**21**	2	86; 85	3; 2	6.7; 1.5 (*S*)
19	**22**	2	97; 93	3; 7	20.0; 25.1 (*S*)
20	**23**	2	96; 97	2; 3	2.7; 2.4 (*S*)
21	**24**	2	98; 96	2; 1	17.4; 19.4 (*S*)
22	**25**	2	97; 95	1; 1	24.9; 20.7 (*S*)
23	**26**	2	95; 89	1; Traces[f]	8.1; 8.0 (*S*)
24	**27**	2	97; 97	1; 1	5.9; 1.7 (*S*)
25	**28**	2	97; 96	2; 2	20.9, 21.1 (*S*)

[a] *Conditions*: **6**, Pd/C Merck 807104 (0.025 equiv.), base (0.3 equiv.), MeCN, rt, H_2 delivered by a gasbag.
[b] The expressed results correspond to two experiments.
[c] Yields are determined by HPLC, using 2-methoxynaphthalene as standard; the yield of **9** was low (0–4%), therefore it is not listed in Table 2.
[d] Ee determined by HPLC analysis.
[e] Not detected by HPLC ($\lambda = 254$ nm).
[f] Yields <0.4%.
[g] Not fully soluble in MeCN.

into carbamate **27** or ether **28** also gave disappointing results[25] (entries 24 and 25).

As quinine **18** delivered the best results, variations of the experimental conditions were carried out with this base (Table 3). Switching to THF as solvent decreased the ee from 65 to 60% (entry 26). With EtOAc, ee may increase, but the result was not reproducible (entry 27). Furthermore, defluorination increased in both solvents. At 45°C, ee's are identical to standard conditions, but more defluorination was observed (entry 28). Ee's of **7** were almost unchanged for a reaction time between 0.25 h (entry 29) and 16 h (entry 30); the amount of **9** remained low, while that of **8** increased and it became the main product after 52 h (91%), ee of **7** decreasing to 8% (entry 31). A reaction carried out under 40 bar led to an ee similar to the standard conditions (entry 32). A tenfold amount of Pd/C induced a high degree of defluorination and the ee dropped to 25% (entry 33). With a threefold quantity of quinine, results were simi-

Table 3. Variation of the catalysis parameters with **6** as substrate and **18** as a base

Entry	Change/standard conditions[a]	Products[b]			
		7[c] (%)	**8**[c] (%)	**9**[c] (%)	ee of **7**[d] (%)
26	Solvent: THF	81; 77	11; 23	8; n.d.[e]	59; 61.8
27	Solvent: EtOAc	86; 97	14; 2	n.d.[e]; 1	70.3; 59.2
28	$T = 45$°C	60; 86	32; 14	8; n.d.[e]	65.9; 68.0.
29	Time = 0.25 h	4; 5	Traces[f]	0; 0	64.4; 66.6
30	Time = 16 h	53; 64	35; 36	12; n.d.[e]	69.8; 51.8
31	Time = 52 h	9	91	n.d.[e]	8.2
32	H_2 pressure = 40 bar, time = 0.25 h	12; 16	Traces[f]	0; 0	64; 60
33	Pd/C, 0.25 equiv.	5; 3	57; 62	38; 35	24.6; 26
34	0.9 equiv. of **18**	98	2	n.d.[e]	55.0

[a] *Standard conditions*: **6**, Pd/C Merck 807104 (0.025 equiv.); **18** (0.3 equiv.); MeCN, rt, H_2 delivered by a gasbag, reaction time, 2 h.
[b] The expressed results correspond to two experiments.
[c] Yields are determined by HPLC, using 2-methoxynaphthalene as standard.
[d] (*S*) Configuration.
[e] Not detected by HPLC ($\lambda = 254$ nm).
[f] Yields <0.4%.

lar to standard catalysis (entry 34). It could be logical to correlate the decrease of the ee with the liberation of racemizing HF issued from the defluorination (entries 31 and 33), but this was not observed in all cases (entries 26, 27, 28, 30).

Further reactions have been carried out in order to approach the mechanism of the different reactions (Table 4). Stirring enantioenriched **7** under standard conditions (Pd/C, quinine, MeCN, H_2, rt), the ee of **7** stayed constant, but **8** and **9** were formed (entry 35). Without hydrogen, no by-product was detected and a longer reaction time led to a drop of the ee (entry 36). Analogous experiments performed from racemic **7** under a hydrogen atmosphere did not lead to enantioenrichment of **7** but by-products **8** and **9** were formed (entry 37). No transformation was observed in the absence of hydrogen (entry 38). Thus, deracemisation of **7** was excluded during its reduction to **8** or **9**. As expected, racemic **6** was stable under standard conditions in the absence of hydrogen (entry 39). From these experiments, it appears that defluorination is probably a hydrogenolysis (compare runs 35 and 36) and that liberated HF did not racemise **7** (see above). On the contrary, the supported palladium catalyst racemizes even without hydrogen (entry 36).

3. Conclusions

In conclusion, the use of the catalytic cascade reaction with benzyl 2-fluoro-1-tetralone-2-carboxylate as substrate showed that switching from α-alkylated β-ketoesters to comparable fluoro substituted compounds is not a simple analogous application. The reaction is much more sensitive to the nature of the Pd catalyst generating reproducibility problems. The aminoalcohols we previously used proved to be inappropriate catalysts in regard to the ee's, furthermore they may promote fast defluorination. Not only is the chiral inductor important, but the adapted conditions are essential for success and to avoid defluorination or racemisation. Associated to Pd/C catalyst type 807104 from Merck and the commercial quinine and quinidine turned out to be the most successful catalytically active bases for this reaction, leading to enantiomeric excesses up to 65%.

4. Experimental

4.1. General

IR spectra were measured on a Beckman Acculab 3. ^1H, ^{13}C and ^{19}F spectra were recorded on Bruker AC 250, Avance 300 or Avance 600. Mass spectra were obtained by electronic impact (EI-MS; Finnigan MAT 311A) or by chemical ionization (GC-CI; JEOL D-300). Flash chromatography: silica gel Merck 9385 (230–400 mesh); (ordinary) chromatography: silica gel 60 Merck (70–230 mesh). The melting point is uncorrected (Büchi SMP 20). Elemental analysis was done with Perkin–Elmer CHN 2400. HPLC were recorded on a Hewlett–Packard HP1090M, column thermostat Agilent 1100 Series, column Daicel OD-H (length 250 mm, 5 μm inner diameter), using 2-methoxynaphtalene as internal standard for quantitative analysis. The solvents used for synthesis and catalysis were dried by standard procedures. Preparation of starting material was performed under argon or nitrogen atmosphere.

The precursors for fluorination were prepared as described for **1**[9c] and by transesterification[26] with benzyl alcohol of the corresponding ethyl oxo-ester, commercially available for **3** or synthezised following reported procedures.[27]

4.2. Fluorination of oxoesters

4.2.1. Fluoro-3-oxo-2,3-diphenylpropionic acid benzyl ester 2. To a suspension of NaH (60% in mineral oil; 120 mg; 3.00 mmol) in THF (10 mL), 3-oxo-2,3-diphenylpropionic acid benzyl ester[9c] (990 mg, 3.00 mmol) in THF (20 mL) was added slowly at 0°C. The mixture was stirred for 0.5 h at 0°C and then 1 h at rt. After dilution with DMF (30 mL), Selectfluor® (1.06 g, 3.00 mmol) was added in one portion. The mixture was stirred overnight. After addition of water, it was extracted with Et_2O (3×50 mL); the organic extracts were dried over $MgSO_4$ and evaporated. The crude product was successively purified by flash chromatography (petroleum ether:EtOAc 95:5) and chromatography (CH_2Cl_2). This procedure did not allow to remove a low amount of by-product fluorinated at the benzylic position (about 3%). Colorless oil (570 mg, 55%). ^1H NMR ($CDCl_3$, 250 MHz): δ 5.33 (d, 1H, $J=10.0$ Hz, CH*H*Ph), 5.38 (d, 1H, $J=10.0$ Hz, C*H*HPh), 7.28–7.67 (m, 13H, aromatics), 7.92–7.99 (m, 2H, aromatics) ppm; ^{13}C DEPT135 NMR ($CDCl_3$, 62.9 MHz): δ 68.7

Table 4. Further experiments[a]

Entry	Substrate	H_2	Time (h)	Products			
				7 (%)	**8** (%)	**9** (%)	ee of **7** (%)
35	**7** (50/55% ee)	Yes	16	10/68	74/25	16/6	50.6/53.6
36	**7** (62.6/65.9% ee)	No	48	100/100	0/0	0/0	23.0/34.5
37	**7** (racemic)	Yes	16	71/94	27/4	2/2	Racemic
38	**7** (racemic)	No	16	100/100	0/0	0/0	Racemic
39	**6** (racemic)	No	48	–	–	–	–

[a] *Reaction conditions*: **6**, Pd/C Merck 807104 (0.025 equiv.); **18** (0.3 equiv.); MeCN, rt, H_2 delivered by a gasbag.

(s, CH_2Ph), 126.1 (d, $J=8.8$ Hz), 128.6 (s), 129.0 (s), 129.8 (s), 130.6 (d, $J=5.0$ Hz), 134.3 (s) ppm: *C*H aromatic; ^{19}F NMR (235 MHz, $CDCl_3$): δ −157.2 (s) ppm; GC–MS (CI): 6.8 min, m/z (%)=91 (22) [Ph–CH_2], 108 (42) [$PhCH_2OH$], 244 (36) [M^+–PhCO], 262 (100) [M^+–PhCO+NH_4].

By-product (3-oxo-2,3-diphenylpropionic acid fluorobenzyl ester): ^1H NMR ($CDCl_3$, 250 MHz): 5.85 (d, 0.03H, $^2J_{H,F}=47.8$ Hz, CF*H*Ph); ^{19}F NMR (235 MHz, $CDCl_3$): δ −179.87 (d, $^2J_{H,F}=47.8$ Hz, C*F*HPh); GC–MS (CI): 7.1 min, m/z (%)=91 (27) [Ph–CH_2], 106 (97), 108 (86) [$PhCH_2OH$], 116 (28), 134 (22) [$PhCH_2COO$], 220 (11) [PhCOCHPhCOO], 268 (100); $C_{22}H_{17}FO_3$ (348.4).

4.2.2. Benzyl 2-fluorocyclohexanone-2-carboxylate 4. To benzyl cyclohexanone-2-carboxylate **3** (1.50 g, 6.46 mmol) in acetonitrile (65 mL), Selectfluor® (2.29 g, 6.46 mmol) was added in one portion and the reaction mixture was stirred for 20 h at rt. After removal of the solvent, the residue was taken up in CH_2Cl_2/H_2O and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with water and dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether:EtOAc 90:10). Colorless liquid (1.30 g, 80%). IR (neat): ν 2980, 2890, 1760, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74–1.98 (m, 4H), 2.08–2.24 (m, 1H), 2.36–2.63 (m, 2H), 2.65–2.79 (m, 1H), 5.24 (d, 1H, $J=12.1$ Hz, C*H*HPh), 5.29 (d, 1H, $J=12.1$ Hz, CH*H*Ph), 7.30–7.42 (m, 5H, aromatics) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8 (d, $J=5.2$ Hz), 26.6 (s), 36.0 (d, $J=21.4$ Hz), 39.6 (s), 67.8 (s), 96.4 (d, $J=196.8$ Hz, *C*F), 128.3 (s), 128.6 (s), 128.7 (s), 134.8 (s), 166.8 (d, $J=25.1$ Hz, *C*=O ester), 201.8 (d, $J=19.9$ Hz, *C*=O oxo) ppm; ^{19}F NMR (235 MHz, $CDCl_3$): δ 160.97 (ddd, $J=21.9$, 13.7, 5.1 Hz) ppm; GC–MS (CI): 7.1 min, m/z (%)=91 (10) [Ph–CH_2], 108 (29) [$PhCH_2OH$], 134 (5) [C_6H_9FO+NH_4], 250 (4) [M], 268 (100) [M^++NH_4]; $C_{14}H_{15}FO_3$ (250.3).

4.2.3. Benzyl 2-fluoro-1-tetralone-2-carboxylate 6. To benzyl 1-tetralone-2-carboxylate **4** (2.34 g, 8.35 mmol) in acetonitrile (100 mL), Selectfluor® (2.96 g, 8.35 mmol) was added in one portion. The reaction mixture was stirred for 19 h at rt. After evaporation of the solvent, the remaining residue was taken up (H_2O/CH_2Cl_2) and extracted three times with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash-chromatography (petroleum ether:EtOAc 90:10) afforded an orange oil. Recrystallisation from Et_2O gave a colorless solid (1.72 g, 69%). Mp=64–65°C; IR (KBr): ν 1760, 1600, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.55 (dddd, 1H, $J=13.8$, 11.3, 8.0, 5.2 Hz), 2.72 (dddd, 1H, $J=13.8$, 11.3, 7.4, 5.0 Hz), 3.00 (ddd, 1H, $J=17.3$, 7.8, 5.2 Hz), 3.17 (dt, 1H, $J=17.3$, 6.2 Hz), 5.22 (d, 1H, $J=12.3$ Hz, C*H*HPh), 5.30 (d, 1H, $J=12.3$ Hz, CH*H*Ph), 7.22–7.33 (m, 6H, aromatics), 7.37 (t, 1H, $J=8.1$ Hz, aromatic), 7.55 (td, 1H, $J=7.5$, 1.4 Hz, aromatic), 8.08 (dd, 1H, $J=7.8$, 1.2 Hz, aromatic) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.8 (d, $J=7.3$ Hz); 31.9 (d, $J=22.1$ Hz), 67.7 (s), 93.3 (d, $J=193.9$ Hz, *C*F), 127.3 (s), 128.0 (s), 128.5 (d, $J=2.9$ Hz), 128.6 (s), 128.8 (s), 134.6 (s), 132.7 (d, $J=193.9$ Hz, C), 143.1 (s), 167.2 (d, $J=26.5$ Hz, C=O ester), 188.5 (d, $J=19.2$ Hz, C=O oxo) ppm; ^{19}F NMR (235 MHz, $CDCl_3$): δ −164.94 (dd, $J=22.4$, 10.3 Hz) ppm; MS (PI–EI) m/z (%)=91 (100) [$PhCH_2$], 118 (26), 164 (43) [$C_{10}H_9FO$], 298.1 (27) [M]; $C_{18}H_{15}FO_3$ (298.3); HPLC: [Chiralcel OD-H, hexane:isopropanol 97:3, 0.6 mL/min, 25°C, 210 nm, 35.8 min and 42.9 min]. Anal. calcd: C, 72.47; H, 5.07. Found: C, 72.21; H, 4.84%.

4.3. Hydrogenolysis–decarboxylation–protonation

Benzyl-2-fluoro-1-tetralone-2-carboxylate **6** (50.4 mg, 0.17 mmol) and the chiral base (0.3 equiv., 0.051 mmol) were dissolved in acetonitrile (10 mL). Then the Pd catalyst (0.025 equiv., 4.25 μmol) was added and the hydrogen atmosphere was provided by a gasbag.

After the time indicated in Tables 1–4, the reaction mixture was filtered through a pad of Celite 545 (10 cm, CH_2Cl_2 as solvent) to remove the palladium catalyst and through a short SiO_2 column (CH_2Cl_2) to remove the base. The solvents were eliminated at rt.

4.3.1. 2-Fluoro-1-tetralone 7[28]. ^1H NMR (300 MHz, $CDCl_3$): δ 2.20–2.38 (m, 1H), 2.53 (dddd, 1H, $J=16.8$, 9.8, 5.3, 4.2 Hz), 3.08 (dd, 2H, $J=9.8$, 4.2 Hz), 5.10 (ddd, 1H, $J=47.9$, 12.8, 5.3 Hz, FC*H*), 7.22 (d, 1H, $J=7.7$ Hz), 7.30 (t, 1H, $J=7.5$ Hz), 7.48 (td, 1H, $J=7.5$, 1.4 Hz), 8.01 (dd, 1H, $J=8.0$, 1.1 Hz) ppm; ^{19}F NMR (235 MHz, $CDCl_3$): δ −191.36–190.25 (m) ppm; $C_{10}H_9FO$ (164.2); $[\alpha]_D^{20}=-35.5$ (*c* 0.42, dioxane) (*S*) configuration, $ee_{[HPLC]}$ 59%; lit.[29] +64.9 (*c* 0.43, dioxane) (*R*) configuration, ee >95%). HPLC: [Chiralcel OD-H, hexane: isopropanol 97:3, 0.6 mL/min, 25°C, 210 nm, (*R*)-(+): 22.2 min, (*S*)-(−): 23.5 min].

4.3.2. 1-Tetralone 8. HPLC: [Chiralcel OD-H, hexane:isopropanol 97:3, 0.6 mL/min, 25°C, 210 nm, 13.4 min].

4.3.3. 2-Fluoro-1-tetralol 9. This compound is identical to a sample issued from the $NaBH_4$ reduction of 2-fluorotetralone leading to a 70/30 mixture of diastereomers, where a OH, F-*cis*-relative configuration has been attributed to the major diastereomer by comparison of ^1H NMR spectra with those described in the literature.[30] MS (EI) m/z (%)=91 (36), 119 (100), 148 (70) [M–H_2O], 166 (42) [M]; $C_{10}H_{11}FO$ (166.2); HPLC: [Chiralcel OD-H, hexane:isopropanol 97:3, 0.6 mL/min, 25°C, 210 nm, 25.8 min and 28.4 min (*cis*-isomers); 27.6 min and 30.0 min (*trans*-isomers)].[31]

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