Iron-Catalysed Reformatsky-Type Reactions

Muriel Durandetti,*[1] Jacques Périchon

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582, CNRS-Université Paris, 12 Val de Marne, 2 rue Henri-Dunant, 94320 Thiais, France
Fax +33(2)35522971; E-mail: muriel.durandetti@univ-rouen.fr
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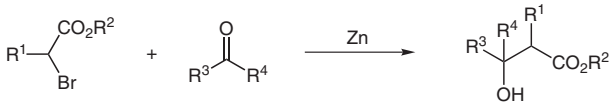
Abstract: A Reformatsky-type reaction has been developed using iron catalysis in acetonitrile or DMF. Reduction of iron(II) bromide by manganese metal in acetonitrile provides a low-valent iron catalyst, which is the active species; under these conditions, α-chloroesters or nitriles can both be converted into their corresponding derivatives. The method was applicable to both ketones and aldehydes, resulting in the formation of β-hydroxyesters under mild conditions.

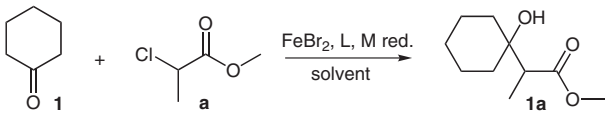
Key words: iron, Reformatsky reaction, α-haloester, carbonyl compounds, C–C coupling

In 1887, Reformatsky prepared β-hydroxyesters by the reaction of α-iodo or α-bromoesters with zinc metal in benzene and subsequent addition to carbonyl compounds.[2] (Equation 1)



Equation 1 The Reformatsky reaction

To extend the scope of this reaction, various parameters have been extensively investigated.[3] Since the reaction is initiated by the insertion of zinc into the halogen–carbon bond, the main emphasis has focused on the activation of zinc, such as, Rieke-Zn,[4] Zn–Cu couple,[5] Zn/Ag-graphite,[6] ultrasound[7] or sonoelectroreduction.[8] Recently, a Reformatsky-type reaction was developed, using $RhCl(PPh_3)_3$ and diethylzinc.[9] Another process has been performed, in aqueous THF, using $BF_3{\cdot}OEt_2$ and Zn dust but is limited to aldehydes.[10] In addition, a number of other metals and catalysts,[11] such as nickel,[12] manganese,[13] chromium[14] and indium[15] were also found to be active. An aqueous metal-free electrochemical Reformatsky reaction has also been reported recently.[16] We have already described some electrochemical processes for the Reformatsky reaction,[17] more recently, we reported an electrochemical method employing catalytic amounts of both chromium and nickel salts, using a sacrificial stainless-steel or an iron rod anode.[18] Under these conditions, β-hydroxyesters were obtained in good yields (60–80%) and moderate diastereoselectivity (*erythro*/*threo* ca. 60:40 to 70:30). With the purpose of devising a less toxic process, we then reported an original version of the Reformatsky reaction, by iron catalysis, associated with an electrochemical reaction.[19] This electrochemical method is as efficient with ketones as with aldehydes. In addition, as the process employs a simple iron complex in an undivided cell and sacrificial iron anode, the process is very easy, cheap, non-toxic and original. However, electrochemical reactions are often considered as being more difficult to handle than conventional classical methods. Electrochemical processes are not readily applicable on an industrial scale, therefore we now report a chemical method for an iron Reformatsky-type reaction, using $FeBr_2$ as a catalyst in the presence of an appropriate reducing metal (Equation 2),[20] taking advantage of cheap, non-toxic and environmentally benign iron salts. It was already reported that simple iron salts such as $Fe(acac)_3$ could catalyse the cross-coupling of Grignard reagents.[21] Herein we report the results of our investigations to realise a non-electrochemical iron-catalysed Reformatsky-type reaction, detailing the efficiency and scope of the procedure.



Equation 2 Iron Reformatsky-type reaction

We began by studying a range of parameters including the solvent, the ligand, and particularly the reducing metal (Table 1). The iron dibromide catalysed reaction of α-chloroesters is performed in a Barbier-type fashion.[22]

We have found that manganese is the best metal for the reduction of $FeBr_2$ (Table 1, entries 1–3, 6 and 7). With Zn as the reducing metal, the process occurs very slowly even when stoichiometric amounts of the iron salt are employed (Table 1, entries 4 and 8). Aluminium could not be used as a reducing metal, no cross-coupling occurs even after a reaction time of four days (Table 1, entries 5 and 9). Then depending on the solvent, two alternative sets of conditions can be used. The first one is derived from the electrochemical process, with DMF as the solvent, $FeBr_2$bipy as the catalyst (0.25 equiv) and the reaction is conducted at room temperature (Table 1, entry 1 and Equation 3). Under these conditions, β-hydroxyesters are obtained in good yields (65–95%) in four to seven hours. Decreasing the amount of $FeBr_2$bipy to 0.15 equivalents

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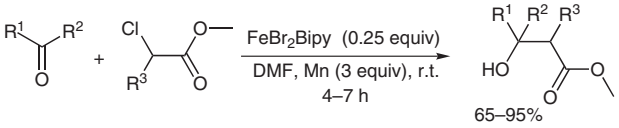
Table 1 Factors Affecting the Coupling Reaction between Cyclohexanone and Methyl 2-Chloro-propanoate Using $FeBr_2$ as a Catalyst

Entry	Catalyst (equiv)	Solvent	Metal	Time (h)	Yield (%)
1	$FeBr_2$bpy (0.25)	DMF[a]	Mn	7	95
2	$FeBr_2$bpy (0.15)	DMF[a]	Mn	30	64
3	$FeBr_2$bpy (0.15)	DMF[b]	Mn	28	71
4	$FeBr_2$bpy (0.50)	DMF[a]	Zn	100	55
5	$FeBr_2$bpy (0.25)	DMF[a]	Al	100	0
6	$FeBr_2$ (0.25)	MeCN[a]	Mn	17	88
7	$FeBr_2$ (0.15)	MeCN[b]	Mn	1.5	86
8	$FeBr_2$ (0.15)	MeCN[b]	Zn	24	5
9	$FeBr_2$ (0.15)	MeCN[b]	Al	100	0

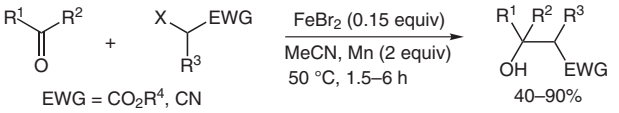
[a] Reaction conducted at r.t.
[b] Reaction conducted at 50 °C.



Equation 3 Iron Reformatsky-type reaction with DMF as solvent

resulted in a longer reaction time of 30 hours (Table 1, entry 2), even when the reduction was carried out at 50 °C (Table 1, entry 3).

Although this process is efficient, we have developed a second set of conditions, which was less expensive and less toxic, since the reactions are performed with only 0.15 equivalents of $FeBr_2$, without any ligand with acetonitrile as the solvent, at 50 °C (Equation 4). The chemical yields were similar (40–90%) but the reaction was complete in two to four hours.



Equation 4 Iron Reformatsky reaction in acetonitrile as solvent

We then extended this protocol to a large variety of carbonyl compounds (**1**–**10**), which were coupled with methyl 2-chloropropanoate (Table 2).

The process is efficient with ketones, whatever their structure (aromatic, aliphatic or cyclic), giving the desired cross-coupled products in good to excellent yields (55–93%) (Table 2, entries 1–8). With aldehydes the reaction is less efficient, as pinacolisation is the favoured reaction. However, if the aldehyde is added portionwise, the yields are increased (Table 2, entries 9 and 10). Lower yields were obtained with cyclohexenone **2** even though the ketone was completely consumed and no other products

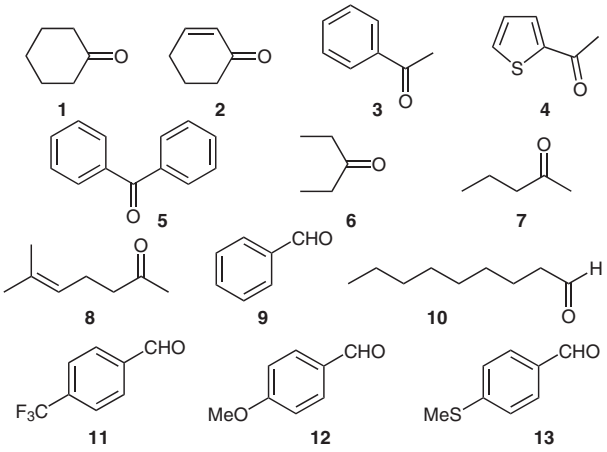


Figure 1 Carbonyl compounds used in the iron Reformatsky reaction

were detected; no conjugated addition was observed with this enone, thus indicating that the reaction is regiospecific.

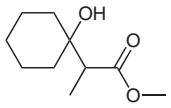
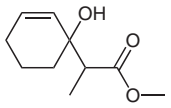
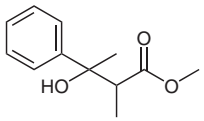
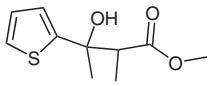
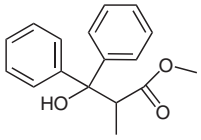
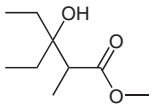
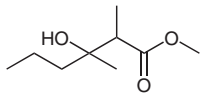
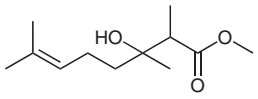
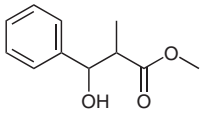
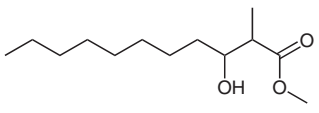
In the case of dissymmetric carbonyl compounds, we obtained the two diastereoisomers with moderate diastereoselectivity (Table 2, entries 2–4, 7–10), depending on the nature of the carbonyl compounds.

Coupling methyl 2-chloroacetate with ketones **1**–**7** also gave good yields of β-hydroxyesters (50–70% isolated yield, Table 3). As already observed in the case of electroreductive coupling carried out with α-chloroester,[23] the coupling with chloropropionate is more efficient than with chloroacetate. The excess of α-chloroester, necessary to consume the carbonyl compounds, is more important with methyl 2-chloroacetate than with methyl 2-chloropropanoate (1.5 equivalents instead of 1.3 equivalents are necessary).

We then looked at α-bromoesters, thus methyl 2-bromopropanoate was reacted with a range of ketones and aldehydes (Table 4). With ketones, chemical yields are similar using either α-chloroesters or α-bromoesters (compare Table 4, entry 1 with Table 2, entry 1). In the case of aldehydes, chemical yields are similar or better for α-bromoesters, the major benefit here was that it was not necessary to add the aldehyde in four portions (compare Table 4, entries 2 and 3 with Table 2, entries 9 and 10); this is probably due to the higher reactivity of the α-bromoester. We also demonstrated that the cross-coupling is efficient with aryl aldehydes bearing electron-donating (Table 4, entries 5-6) as well as electron-withdrawing groups (Table 4, entry 4).

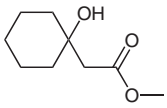
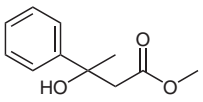
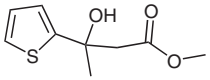
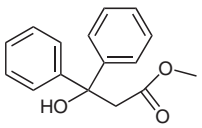
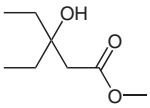
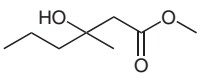
We then tried to realise the reaction between cyclohexanone **1** and the α-chloro- or bromoester without $FeBr_2$ as catalyst. In the case of α-chloroester, no coupling product was obtained even after a reaction time of five days, therefore iron catalysis is necessary to obtain the coupling product. However, with α-bromoester, we obtained 2% of β-hydroxyester after two hours, compared to 91% in the presence of $FeBr_2$ after the same reaction time (Table 4,

Table 2 Iron-Catalysed Cross-Coupling between Methyl 2-Chloropropanoate and Carbonyl Compounds[a]

Entry	Carbonyl compound	Product	Yield (%)[b]	*anti*/*syn*
1	**1**	 **1a**	86	–
2	**2**	 **2a**	55[c]	46:54
3	**3**	 **3a**	93	70:30
4	**4**	 **4a**	82	52:48
5	**5**	 **5a**	80	–
6	**6**	 **6a**	88	–
7	**7**	 **7a**	65	60:40
8	**8**	 **8a**	61	60:40
9	**9**[d]	 **9a**	64	65:35
10	**10**[d]	 **10a**	35	61:39

[a] Typical procedure: see experimental section.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.
[c] No 1,4-addition product was detected.
[d] RCHO was introduced in four portions to minimise direct reduction.

Table 3 Iron-Catalysed Cross-Coupling between Methyl 2-Chloroacetate and Carbonyl Compounds[a]

Entry	Carbonyl compound	Product	Yield (%)[b]
1	**1**	 **1b**	51
2	**3**	 **3b**	69
3	**4**	 **4b**	45[c]
4	**5**	 **5b**	50[d]
5	**6**	 **6b**	52
6	**7**	 **7b**	50

[a] Typical procedure: see experimental section.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.
[c] GC yield: 74%. Some spontaneous dehydration occurs during column chromatography on silica gel, thus, olefin **4d** was obtained in 29% yield.
[d] Yield of recovered ketone: 50%.

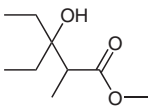
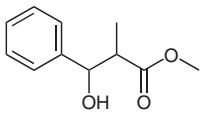
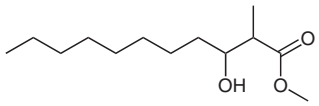
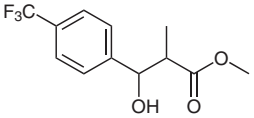
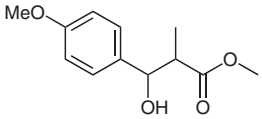
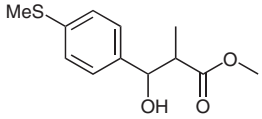
entry 1). When the reaction time was extended to three days a yield of 74% was achieved without iron catalysis, implying that insertion of manganese metal into the carbon–bromine bond was possible without iron catalysis.

We then extended the process to coupling ketones with α-chloronitrile under the same procedure described for α-chloroesters (Table 5).

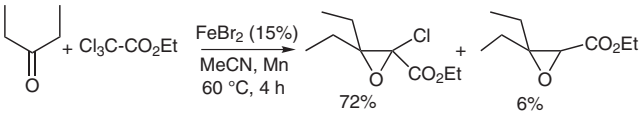
The method can also be applied to α,α′,α″-trichloroester. Thus, as a preliminary study, the coupling of 3-pentanone (**6**) with α,α′,α″-trichloroester proceeded in good yield (Equation 5), if the trichloroester is added slowly to minimise its direct reduction. Under these conditions two equivalents of trichloroester are necessary to obtain a good yield of coupling product.

The mechanism of the reaction is under investigation,[24] but it appears that manganese metal has two roles. It is believed that reduction of Fe(II) to Fe(0) is effected by man-

Table 4 Iron-Catalysed Cross-Coupling between Methyl 2-Bromopropanoate and Carbonyl Compounds[a]

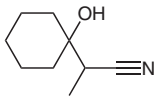
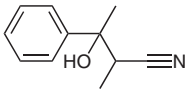
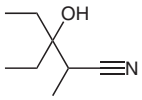
Entry	Carbonyl compound	Product	Yield (%)[b]	*anti*/*syn*
1	**1**	 **1a**	91	–
2	**9**	 **9a**	78	67:33
3	**10**	 **10a**	36	62:38
4	**11**	 **11a**	67	78:22
5	**12**	 **12a**	60	75:25
6	**13**	 **13a**	68	68:32

[a] Typical procedure: see experimental section.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.



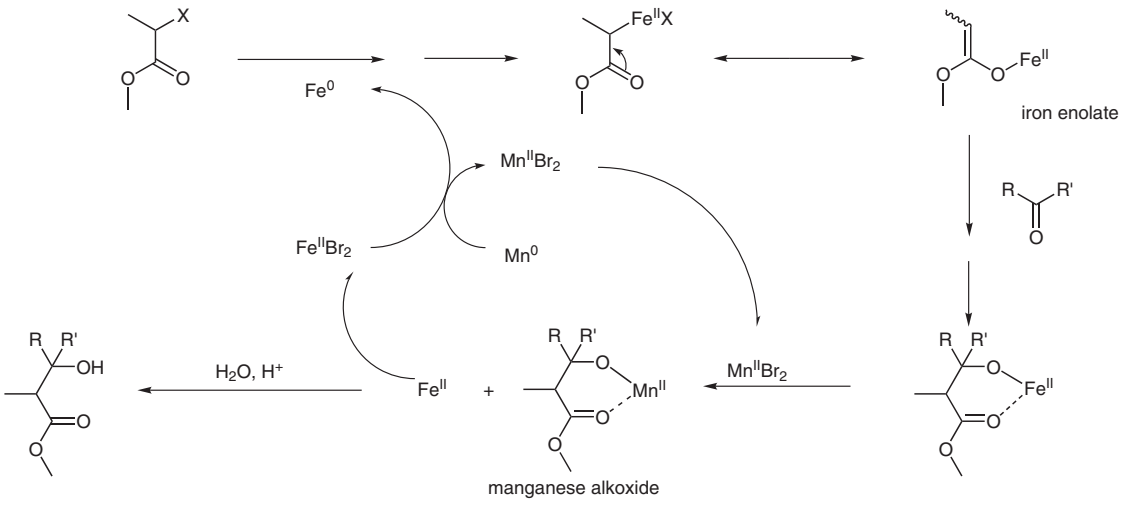
Equation 5 The addition of α,α′α″-trichloroester to 3-pentanone via iron catalysis

Table 5 Iron-Catalysed Cross-Coupling between α-Chloropropionitrile and Carbonyl Compounds[a]

Entry	Carbonyl compound	Product	Yield (%)[b]	*anti*/*syn*
1	**1**	 **1c**	46	–
2	**3**	 **3c**	57	66:34
3	**6**	 **6c**	66	–

[a] Typical procedure: see experimental section.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.

ganese metal; Fe(0) is stabilised by acetonitrile itself and can react with an α-chloroester. Then, the addition of the organoiron species to the carbonyl compound leads to an iron alkoxide. The process will be catalytic in iron only if the Mn(II) obtained during the redox reaction between Mn(0) and Fe(II), reacts with the alkoxide to lead a manganese alkoxide (Scheme 1).



Scheme 1 Proposed mechanism of the iron-catalysed Reformatsky-type reaction

In conclusion, we have reported an efficient cross-coupling of carbonyl compounds and activated alkyl halides, enabling the preparation of valuable target molecules such as β-hydroxyesters. A broad range of organic compounds can be applied, such as, α-chloro- or α-bromoesters and α-chloronitrile. The method is applicable to both ketones and aldehydes (portionwise addition with chloroesters). The efficiency of iron salts in this process has been clearly demonstrated. The method is also very easy, cheap, non-toxic and totally original.

To the best of our knowledge this is the first chemical iron-catalysed Reformatsky-type reaction reported so far. Further investigations are necessary to determine the organoiron species involved in this mechanism.

GC analysis was carried out using a 4-m capillary column. MS were recorded with a spectrometer coupled to a GC. Column chromatography was performed on silica gel 60, 70–200 μm. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, with TMS as internal standard.

All solvents and reagents were purchased and used without further purification. DMF and MeCN were stored under argon. 2,2′-Bipyridine was used as obtained.

$FeBr_2$-Catalysed Synthesis; General Procedure

Carbonyl compound (10 mmol) and α-haloester or nitrile (13 mmol) in MeCN (15 mL) were stirred in a flask under argon at 50 °C. Then Mn (1.10 g, 20 mmol) was introduced, followed by $FeBr_2$ (0.32 g, 1.5 mmol) and then CF_3CO_2H (20 μL) to activate Mn metal. The reaction is conducted at 50 °C and monitored by GC (reaction time, ca. 2 h). The mixture was then hydrolysed with 1 N HCl (30 mL) and diluted with Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL), the combined organic layers were washed with H_2O (30 mL) and a sat. solution of NaCl, dried over $MgSO_4$ and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give the desired compounds.

Methyl (1-Hydroxy-α-methylcyclohexane)acetate (1a)

^{1}H NMR: δ = 3.70 (s, 3 H), 3.04 (s, 1 H), 2.52 (q, *J* = 7.1 Hz, 1 H), 1.48 (m, 10 H), 1.19 (d, *J* = 7.1 Hz, 3 H).

MS: *m*/*z* (%) = 187 (M^+ + 1), 169 (M^+ – OH), 155 (M^+ – OMe), 143, 130, 113, 99, 81 (100), 55.

Methyl (1-Hydroxy-α-methyl-2-cyclohexene)acetate (2a)

^{1}H NMR (*anti*): δ = 5.50–5.92 (m, 2 H), 3.70 (s, 3 H), 2.98 (s, 1 H), 2.63 (q, *J* = 7.2 Hz, 1 H), 2.10–1.50 (m, 6 H), 1.22 (d, *J* = 7.2 Hz, 3 H).

^{1}H NMR (*syn*): δ = 5.90–5.50 (m, 2 H), 3.70 (s, 3 H), 3.00 (s, 1 H), 2.60 (q, *J* = 7.4 Hz, 1 H), 2.10–1.50 (m, 6 H), 1.18 (d, *J* = 7.4 Hz, 3 H).

MS: *m*/*z* (%) = 184 (M^+), 156 (M^+ – CO), 124 (M^+ – CO_2Me), 97 (100), 79, 55.

Methyl 3-Hydroxy-2-methyl-3-phenylbutanoate (3a)

^{1}H NMR (*anti*): δ = 7.41 (m, 2 H), 7.20 (m, 3 H), 4.15 (s, 1 H), 3.33 (s, 3 H), 2.98 (q, *J* = 7.07 Hz, 1 H), 1.42 (s, 3 H), 1.23 (d, *J* = 7.07 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.40 (m, 2 H), 7.25 (m, 3 H), 3.91 (s, 1 H), 3.70 (s, 3 H), 2.86 (q, *J* = 7.12 Hz, 1 H), 1.55 (s, 3 H), 0.95 (d, *J* = 7.12 Hz, 3 H).

MS: *m*/*z* (%) = 209 (M^+ + 1), 191 (M^+ – OH), 121 (100), 105, 77.

Methyl 3-Hydroxy-2,3-dimethyl-3-thienylpropanoate (4a)

^{1}H NMR (*anti*): δ = 7.17–7.14 (m, 1 H), 6.92–6.85 (m, 2 H), 4.40 (s, 1 H), 3.57 (s, 3 H), 2.99 (q, *J* = 7.13 Hz, 1 H), 1.54 (s, 3 H), 1.28 (d, *J* = 7.13 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.70–7.60 (m, 1 H), 7.20–7.10 (m, 2 H), 4.09 (s, 1 H), 3.70 (s, 3 H), 2.87 (q, *J* = 6.7 Hz, 1 H), 1.62 (s, 3 H), 1.11 (d, *J* = 6.7 Hz, 3 H).

MS: *m*/*z* (%) = 214 (M^+), 197 (M^+ – OH), 127 (M^+ – $C_2H_7O_2$, 100), 111, 97, 85, 57.

Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.58, S, 14.96. Found: C, 56.17; H, 6.53, S, 15.04.

Methyl 3,3-Diphenyl-3-hydroxy-2-methylpropanoate (5a)

^{1}H NMR: δ = 7.50 (m, 4 H), 7.20 (m, 6 H), 4.68 (s, 1 H), 3.66 (q, *J* = 7.1 Hz, 1 H), 3.00 (s, 3 H), 1.16 (d, *J* = 7.1 Hz, 3 H).

MS: *m*/*z* (%) = 270 (M^+), 253 (M^+ – OH), 183 (100), 105, 77.

Methyl 3-Ethyl-3-hydroxy-2-methylpentanoate (6a)

^{1}H NMR: δ = 3.71 (s, 3 H), 3.20 (s, 1 H), 2.61 (q, *J* = 7.2 Hz, 1 H), 1.50 (m, 4 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.4 Hz, 3 H), 0.82 (t, *J* = 7.6 Hz, 3 H).

MS: *m*/*z* (%) = 175 (M^+ + 1), 157 (M^+ – OH), 145 (M^+ – Et), 113, 97, 88, 57 (100).

Methyl 3-Hydroxy-2,3-dimethylhexanoate (7a)

^{1}H NMR (*anti*): δ = 3.71 (s, 3 H), 3.12 (s, 1 H), 2.57 (q, *J* = 7.15 Hz, 1 H), 1.42–1.25 (m, 4 H), 1.19 (d, *J* = 7.15 Hz, 3 H), 1.18 (s, 3 H), 0.91–0.79 (m, 3 H).

^{1}H NMR (*syn*): δ = 3.70 (s, 3 H), 3.10 (s, 1 H), 2.54 (q, *J* = 7.1 Hz, 1 H), 1.40–1.20 (m, 4 H), 1.20 (d, *J* = 7.1 Hz, 3 H), 1.10 (s, 3 H), 0.90–0.80 (m, 3 H).

MS: *m*/*z* (%) = 175 (M^+ + 1), 157 (M^+ – OH, 100), 131 (M^+ – C_3H_7), 99, 71, 57.

Methyl 3-Hydroxy-2,3,7-trimethyl-6-octenoate (8a)

^{1}H NMR (*anti*): δ = 5.13–5.05 (m, 1 H), 3.70 (s, 3 H), 3.24 (s, 1 H), 2.59 (q, *J* = 7.1 Hz, 1 H), 2.08–2.01 (m, 2 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.53–1.43 (m, 2 H), 1.21 (s, 3 H), 1.20 (d, *J* = 7.1 Hz, 3 H).

^{1}H NMR (*syn*): δ = 5.13–5.05 (m, 1 H), 3.70 (s, 3 H), 3.24 (s, 1 H), 2.57 (q, *J* = 7.09 Hz, 1 H), 2.08–2.01 (m, 2 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.53–1.43 (m, 2 H), 1.15 (s, 3 H), 1.20 (d, *J* = 7.09 Hz, 3 H).

MS: *m*/*z* (%) = 215 (M^+ + 1), 196 (M^+ – OH), 136, 121, 109 (100), 99, 93, 81, 67, 57.

Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate (9a)

^{1}H NMR (*anti*): δ = 7.23 (m, 5 H), 4.97 (d, *J* = 5.1 Hz, 1 H), 3.76 (s, 1 H), 3.53 (s, 3 H), 2.73 (qd, *J* = 7.0, 5.1 Hz, 1 H), 1.10 (d, *J* = 7.0 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.28 (m, 5 H), 4.68 (d, *J* = 8.7 Hz, 1 H), 3.65 (s, 3 H), 3.51 (s, 1 H), 2.76 (dq, *J* = 8.7, 7.2 Hz, 1 H), 0.91 (d, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* (%) = 195, 177 (100), 121, 107, 88, 79, 57.

Methyl 3-Hydroxy-2-methylundecanoate (10a)

^{1}H NMR (*anti*): δ = 3.88 (m, 1 H), 3.69 (s, 3 H), 2.54 (dq, *J* = 7.1, 4.5 Hz, 1 H), 1.45–1.28 (m, 15 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{1}H NMR (*syn*): δ = 3.7 (m, 1 H), 3.69 (s, 3 H), 2.3 (m, 1 H), 1.45–1.28 (m, 15 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

MS: *m*/*z* (%) = 231 (M^+ + 1), 215 (M^+ – CH_3), 197, 181, 163, 117, 88 (100), 57.

Methyl 3-Hydroxy-2-methyl-3-(4-trifluoromethylphenyl)propanoate (11a)
^{1}H NMR (*anti*): δ = 7.62 (d, *J* = 8.2 Hz, 2 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 5.19 (d, *J* = 3.9 Hz, 1 H), 3.89 (s, 1 H), 3.71 (s, 3 H), 2.79 (qd, *J* = 7.1, 3.9 Hz, 1 H), 1.11 (d, *J* = 7.1 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.62 (d, *J* = 8.2 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 4.81 (d, *J* = 8.1 Hz, 1 H), 3.72 (s, 1 H), 3.13 (s, 3 H), 2.79 (dq, *J* = 8.1, 7.2 Hz, 1 H), 1.05 (d, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* (%) = 260 (M^+), 242 ($M^+ - H_2O$), 228, 213, 173 (100), 145, 125, 95.

Methyl 3-Hydroxy-2-methyl-3-(4-methoxyphenyl)propanoate (12a)
^{1}H NMR (*anti*): δ = 7.23 (d, *J* = 8.3 Hz, 2 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 4.97 (s, 1 H), 3.77 (s, 3 H), 3.61 (s, 3 H), 2.84–2.74 (m, 2 H), 1.19 (d, *J* = 6.7 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.21 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.50 (s, 1 H), 2.79–2.71 (m, 2 H), 0.91 (d, *J* = 7.1 Hz, 3 H).

MS: *m*/*z* (%) = 224 (M^+), 206 (M – H_2O), 193 (M^+ – OMe), 151, 137 ($M^+ - C_4H_7O_2$, 100), 109, 94, 77.

Methyl 3-Hydroxy-2-methyl-3-(4-sulfanylphenyl)propanoate (13a)
^{1}H NMR (*anti*): δ = 7.15 (m, 4 H), 4.96 (d, *J* = 4.3 Hz, 1 H), 3.59 (s, 3 H), 2.92 (s, 1 H), 2.68 (qd, *J* = 7.3, 4.3 Hz, 1 H), 2.39 (s, 3 H), 1.04 (d, *J* = 7.3 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.16 (m, 4 H), 4.62 (d, *J* = 7.9 Hz, 1 H), 3.64 (s, 3 H), 2.89 (s, 1 H), 2.72 (dq, *J* = 7.9, 6.8 Hz, 1 H), 2.40 (s, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H).

MS: *m*/*z* (%) = 240 (M^+), 209 (M^+ – SMe), 166, 153 ($M^+ - C_4H_7O_2$, 100), 109, 125, 77.

Methyl (1-Hydroxycyclohexyl)acetate (1b)
^{1}H NMR: δ = 3.70 (s, 3 H), 3.38 (s, 1 H), 2.48 (s, 2 H), 1.68–1.36 (m, 10 H).

MS: *m*/*z* (%) = 173 (M^+ + 1), 155 (M^+ – OH), 130, 123, 116, 97, 79 (100), 69, 55.

Methyl 3-Hydroxy-3-phenylbutanoate (3b)
^{1}H NMR: δ = 7.45–7.40 (m, 2 H), 7.39–7.15 (m, 3 H), 4.35 (s, 1 H), 3.53 (s, 3 H), 2.96 (d, *J* = 15.9 Hz, 1 H), 2.77 (d, *J* = 15.9 Hz, 1 H), 1.52 (s, 3 H).

MS: *m*/*z* (%) = 195 (M^+ + 1), 179 (M^+ – Me, 100), 177 (M^+ – OH), 121 ($M^+ - CH_2CO_2CH_3$), 105, 91, 77, 51.

Methyl 3-Hydroxy-3-(2-thienyl)butanoate (4b)
^{1}H NMR: δ = 7.26–7.19 (m, 1 H), 7.13–6.80 (m, 2 H), 5.07 (s, 1 H), 3.59 (s, 3 H), 2.94 (d, *J* = 16.0 Hz, 1 H), 2.76 (d, *J* = 16.0 Hz, 1 H), 1.57 (s, 3 H).

MS: *m*/*z* (%) = 200 (M^+), 185 ($M^+ - CH_3$), 127 ($M^+ - C_3H_5O_2$, 100), 112, 97.

Methyl 3-(2-Thienyl)but-2-enoate (4d)
^{1}H NMR: δ = 7.26–7.19 (m, 1 H), 7.13–6.80 (m, 2 H), 6.19 (d, *J* = 1.1 Hz, 1 H), 3.67 (s, 3 H), 2.54 (d, *J* = 1.1 Hz, 3 H).

MS: *m*/*z* (%) = 182 (M^+), 150 ($M^+ - OCH_3$, 100), 123 (M^+ – CO_2Me), 79.

Methyl 3-Hydroxy-3,3-diphenylpropanoate (5b)
^{1}H NMR: δ = 7.40–7.20 (m, 10 H), 5.04 (s, 1 H), 3.63 (s, 3 H), 3.28 (s, 2 H).

MS: *m*/*z* (%) = 256 (M^+), 239 (M^+ – OH), 183 ($M^+ - CH_2CO_2CH_3$), 105 (100), 77, 51.

Methyl 3-Ethyl-3-hydroxypentanoate (6b)
^{1}H NMR: δ = 3.69 (s, 3 H), 3.46 (s, 1 H), 2.46 (s, 2 H), 1.54 (q, *J* = 7.2 Hz, 4 H), 0.88 (t, *J* = 7.2 Hz, 6 H).

MS: *m*/*z* (%) = 161 (M^+ + 1, 100), 143 (M^+ – OH), 131 ($M^+ - C_2H_5$), 111, 99, 83, 69, 57.

Methyl 3-Hydroxy-3-methylhexanoate (7b)
^{1}H NMR: δ = 4.63 (s, 1 H), 3.72 (s, 3 H), 2.54 (d, *J* = 15.3 Hz, 1 H), 2.44 (d, *J* = 15.3 Hz, 1 H), 1.53–1.32 (m, 4 H), 1.23 (s, 3 H), 0.92 (t, *J* = 6 Hz, 3 H).

MS: *m*/*z* = 161 (M^+ + 1), 145 (M^+ – OH), 117 ($M^+ - C_3H_7$), 85 (100), 71, 55.

2-(1-Hydroxycyclohexyl)propionitrile (1c)
^{1}H NMR: δ = 2.67 (q, *J* = 7.2 Hz, 1 H), 2.50 (s, 1 H), 1.79–1.34 (m, 10 H), 1.33 (d, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* (%) = 154 (M^+ + 1), 136 (M^+ – OH), 99 ($M^+ - C_3H_4N$), 81 (100), 71 ($M^+ - C_6H_{10}$), 55.

3-Hydroxy-2-methyl-3-phenylbutyronitrile (3c)
^{1}H NMR (*anti*): δ = 7.41–7.20 (m, 5 H), 2.96 (q, *J* = 7.2 Hz, 1 H), 2.88 (s, 1 H), 1.73 (s, 3 H), 1.16 (d, *J* = 7.2 Hz, 3 H).

^{1}H NMR (*syn*): δ = 7.50–7.30 (m, 5 H), 2.96 (q, *J* = 7.2 Hz, 1 H), 2.81 (s, 1 H), 1.70 (s, 1 H), 1.14 (d, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* (%) = 175 (M^+), 158 (M^+ – OH), 121 (M – C_3H_4N, base), 115, 105, 91, 77, 51.

3-Ethyl-3-hydroxy-2-methylpentanenitrile (6c)
^{1}H NMR: δ = 2.90 (s, 1 H), 2.79 (q, *J* = 7.2 Hz, 1 H), 1.66 (q, *J* = 7.1 Hz, 2 H), 1.61 (q, *J* = 7.7 Hz, 2 H), 1.29 (d, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 7.7 Hz, 3 H).

MS: *m*/*z* (%) = 142 (M^+ + 1), 124 (M^+ – OH), 112, 87, 69, 56 (100).

Methyl 3,3-Diethyl-2-oxiranecarboxylate
^{1}H NMR: δ = 3.78 (s, 3 H), 3.37 (s, 1 H), 1.71 (q, *J* = 7.5 Hz, 2 H), 1.67 (q, *J* = 7.7 Hz, 2 H), 0.94 (t, *J* = 7.7 Hz, 3 H), 0.95 (t, *J* = 7.5 Hz, 3 H).

MS: *m*/*z* (%) = 159, 141 (M^+ – OH), 129, 101 (100), 67, 59.

References

(1) New address: Dr. M. Durandetti, Laboratoire des Fonctions Azotées & Oxygénées Complexes de L'IRCOF, UMR 6014 CNRS, Université de Rouen, 76821 Mont Saint-Aignan Cedex, France.
(2) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210.
(3) For recent reviews on the Reformatsky reaction, see: (a) Ocampo, R.; Dolbier, W. R. Jr. *Tetrahedron* **2004**, *60*, 9325. (b) Fürstner, A. *Synthesis* **1989**, 571. (c) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Elsevier: New York, **1991**, 277–299. (d) Fürstner, A. In *Organozinc Reagents*; Knochel, P.; Jones, P., Eds.; Oxford University Press: New York, **1999**, 287–305.
(4) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.
(5) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.
(6) Csuk, R.; Fürster, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775.
(7) (a) Han, B.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030. (b) Nishiyama, T.; Woodhall, J. F.; Lawson, E. N.; Kitching, W. *J. Org. Chem.* **1989**, *54*, 2184.

(8) Durant, A.; Delplanche, J.; Libert, V.; Reisse, J. *Eur. J. Org. Chem.* **1999**, 2845.
(9) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549.
(10) Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561.
(11) Orsini, F.; Sello, G. *Curr. Org. Synth.* **2004**, *1*, 111.
(12) Inab, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155.
(13) (a) Kahiga, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807. (b) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373.
(14) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772.
(15) (a) Hirashita, T.; Kinoshita, K.; Yamamura, H.; Kawai, M.; Araki, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, *5*, 825. (b) Lee, P. H.; Bang, K.; Sung, S.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781.
(16) Areias, M. C. C.; Bieber, L. W.; Navarro, M.; Diniz, F. B. *J. Electroanal. Chem.* **2003**, *558*, 125.
(17) (a) Rollin, Y.; Gebehenne, C.; Derien, S.; Dunach, E.; Périchon, J. *J. Orgonomet. Chem.* **1993**, *461*, 9. (b) Connan, A.; Sibille, S.; Périchon, J. *J. Org. Chem.* **1991**, *56*, 2018.
(18) Durandetti, M.; Nédelec, J.-Y.; Périchon, J. *Org. Lett.* **2001**, *3*, 2073.
(19) Durandetti, M.; Meignein, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 317.
(20) Durandetti, M.; Périchon, J. Patent application FR 2004-7230, **2004**.
(21) (a) Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547. (c) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131. (d) Bogdanovic, B.; Schwickardi, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.
(22) Blomberg, C. *The Barbier Reaction and Related One-Step Processes*; Springer: Berlin, **1993**.
(23) (a) Durandetti, M.; Périchon, J. *Synthesis* **2004**, 3079. (b) Durandetti, M.; Nédelec, J.-Y.; Périchon, J. *J. Org. Chem.* **1996**, *61*, 1748.
(24) The insertion of a low valent iron salt into an α-haloester is already reported: Buriez, O.; Durandetti, M.; Périchon, J. *J. Electroanal. Chem.* **2005**, *578*, 63.