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# Ni-catalyzed activation of α-chloroesters: a simple method for the synthesis of α-arylesters and β-hydroxyesters

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**Abstract**—Coupling reactions of α-chloroesters with aryl halides (α-arylation) or carbonyl compounds (Reformatsky) using nickel catalyst allow, under mild conditions, the preparation of various functionalized aryl propionic acid derivatives or β-hydroxyesters. In the synthesis of aryl propionic acid derivatives, the process is efficient with aryl halides bearing either electron-withdrawing or electron-donating groups.
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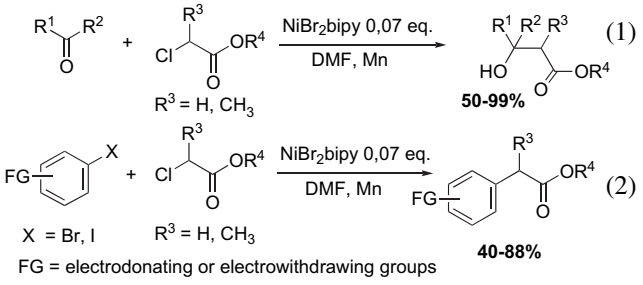
## 1. Introduction

The nucleophilic character coupled with low basicity of Reformatsky reagents has resulted in their renewed interest as enolates sources. For example, they have been found to be effective in nucleophilic addition to carbonyl compounds,[1] and more recently as nucleophilic partners in coupling reactions with aryl halides mediated by palladium.[2] Since the Reformatsky reaction is initiated by the insertion of zinc into halogen–carbon bond, most efforts have been focused on the activation of zinc. In addition a number of other metals and catalysts,[3] such as nickel,[4] manganese,[5] chromium,[6] indium,[7] … were also found active. In our laboratory, we have already described some electrochemical processes for the Reformatsky reaction.[8]

Aryl propanoic acids, like ibuprofen, are known to be non-steroidal anti-inflammatory drugs.[9] A mild and an efficient procedure to obtain functionalized aryl acetic or propanoic acid is thus of great interest. Many routes to selected structures of therapeutic interest have been described, from either a benzylic[10] or an aromatic derivative,[11] or by rearrangement of propiophenone,[9] but the obtention of this products by an arylation-type reaction will be much interesting, taking into consideration that variously substituted aryl halides are commonly available. We have developed the electrochemical cross-coupling reaction between aryl halides and methyl chloroacetate or methyl 2-chloropropanoate, using $NiBr_2$bipy as catalyst.[12] In all cases, isolated yields were good to excellent, whatever the functional group in aryl halides was. However electrochemical reactions are often considered as being more difficult to handle than conventional classical methods. Thus, electrochemical processes are poorly applied in industrial scale and therefore we developed pure 'chemical' processes instead of electrochemical processes.[8d,e,13] We now report a chemical method for a nickel-catalyzed activation of α-chloroesters, leading to aryl propanoic esters (Eq. 2) and β-hydroxyesters (Eq. 1), using $NiBr_2$bipy as catalyst in the presence of an appropriate reducing metal (Scheme 1). The usual chemical routes to the arylnickel compounds however require the tedious preparation of Ni(0) complexes such as $Ni(cod)_2$. But we developed an interesting alternative, which is the in situ generation of Ni(0) complexes in the presence of both the aromatic halide and the electrophile. The main advantages of the method are the use of an easily prepared Ni(II)bipy complex in catalytic amounts and the easy control of the overall reactions.




**Scheme 1**. Nickel-catalyzed activation of α-chloroesters.

## 2. Results and discussion

At first we studied different parameters such as the solvent, the ligands, and particularly the reducing metal. Results are

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**Table 1**. Optimization of the cross-coupling reaction between cyclohexanone and methyl 2-chloropropanoate using $NiBr_2$ salt as catalyst

| Entry | Catalyst | Solvent | M | Time | Yields (%) |
|---|---|---|---|---|---|
| 1 | $NiBr_2$ 10% | MeCN | Mn | 24 h | 76 |
| 2 | $NiBr_2$bipy 10% | DMF | Mn | 1 h | 88 |
| 3 | $NiBr_2$bipy 10% | DMF | Mg | 30 min | 11[a] |
| 4 | $NiBr_2$bipy 10% | DMF | Zn | 100 h | 50[b] |
| 5 | $NiBr_2$bipy 10% | DMF | Al | 100 h | 0 |

[a] Claisen product is obtained as the major product.
[b] Ketone (48%) is recovered.

reported in Table 1, concerning the Reformatsky reaction and in Table 2 for the syntheses of aryl propanoic esters.

We have found that manganese is the best metal for the reduction of $NiBr_2$bipy (Table 1, entries 1 and 2 and Table 2, entries 1 and 2) in both reactions. The use of manganese as a benign reducing agent in combination with an effective metal salt has already been originally described.[8e,13a,14] The decrease in the chemical yield with magnesium metal can be explained by the occurrence of Claisen condensation as side reaction (Table 1, entry 3 and Table 2, entry 4). This reaction could be minimized by adding a large excess of α-chloroester using the portionwise addition (Table 2, entry 5). With Zn as the reducing metal, the Reformatsky reaction occurs very slowly (Table 1, entry 4), but Zn cannot be employed for the cross-coupling with aryl halides (Table 2, entry 3). Aluminum could not be used as a reducing metal, no cross-coupling occurred in both reactions even after four days (Table 1, entry 5 and Table 2, entry 6). With manganese metal, we observed at first that the Reformatsky reaction is best performed at room temperature using $NiBr_2$bipy in DMF, than $NiBr_2$ in acetonitrile (Table 1, entries 1 and 2). However, the cross-coupling with aryl halide occurs faster at 50 °C than at room temperature (Table 2, entries 1 and 2). The amount of nickel salt could be decreased to 3%, but in these conditions reaction times are sometimes longer.

After optimization the best conditions are found to be 0.07 equiv of $NiBr_2$bipy versus carbonyl compounds or aryl halides in the presence of manganese metal in DMF as solvent at room temperature for the Reformatsky reaction and 50 °C for the synthesis of arylesters, and yields 40–99% of coupling product in 15 min to 2 h depending on the substrate (Scheme 1).

**Table 2**. Optimization of the cross-coupling reaction between *m*-trifluoromethyl bromobenzene and methyl 2-chloropropanoate using $NiBr_2$bipy (10%) as catalyst

| Entry | Solvent | M | Time | Yields (%) |
|---|---|---|---|---|
| 1 | DMF[a] | Mn | 5 h | 82 |
| 2 | DMF[b] | Mn | 1 h | 78 |
| 3 | DMF[b] | Zn | 24 h | 4 |
| 4 | DMF[b] | Mg | 30 min | 11[c] |
| 5 | DMF[b] | Mg[d] | 1 h | 39[c] |
| 6 | DMF[b] | Al | 100 h | 0 |

[a] Reaction is carried out at room temperature.
[b] Reaction is carried out at 50 °C.
[c] Claisen product and *m*-$CF_3$PhCHO were obtained as major products.
[d] α-Chloroesters (5 equiv) were introduced in five portions to minimize the Claisen condensation.

Concerning the Reformatsky reaction, this process was applied to a large variety of carbonyl compounds (**1–10**) (Fig. 1). Results for the coupling with methyl 2-chloropropanoate are given in Table 3.

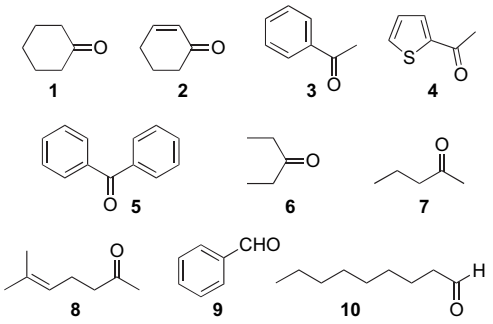
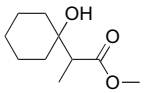
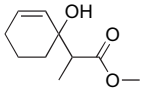
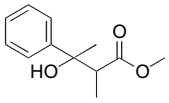
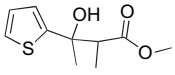
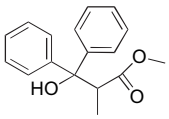
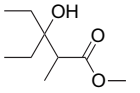
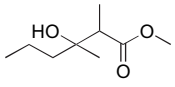
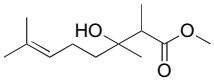
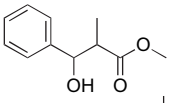
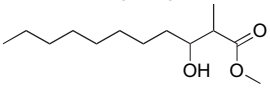



**Figure 1**. Carbonyl compounds used in the nickel Reformatsky reaction.

**Table 3**. Nickel-catalyzed cross-coupling between methyl 2-chloropropanoate and carbonyl compounds[a]

| Entry | Carbonyl compounds | Isolated yields (%) of coupling product[b] | | *anti*/*syn* |
|---|---|---|---|---|
| 1 | **1** |  | 88 | — |
| 2 | **2** |  | 61[c] | 63/37 |
| 3 | **3** |  | 69 | 72/28 |
| 4 | **4** |  | 92 | 54/46 |
| 5 | **5**[d] |  | 33[e] | — |
| 6 | **6** |  | 90 | — |
| 7 | **7** |  | 99 | 60/40 |
| 8 | **8** |  | 92 | 60/40 |
| 9 | **9**[d] |  | 46 | 59/41 |
| 10 | **10**[d] |  | 19 | 58/42 |

[a] Typical procedure: see Section 3.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.
[c] No 1,4-addition product was detected.
[d] Reaction is carried out at 50 °C.
[e] Ketone (60%) is recovered.

Results in Table 3 show that the cross-coupling is efficient with ketones, whatever their structures are (aromatic, aliphatic or cyclic) (Table 3, entries 1–8). Chemical yields are good to excellent (61–99%), except for benzophenone **5**, which needs a higher temperature. With aldehydes the efficiency is less due to a major pinacolization reaction. No conjugated addition was observed with enone **2**, thus indicating that the reaction is regioselective.

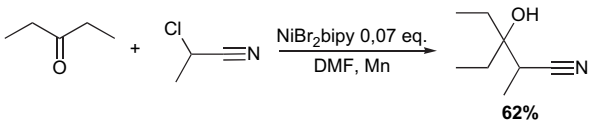
In the case of dissymmetric carbonyl compounds, we obtained the two diastereoisomers with moderate diastereoselectivities (Table 3, entries 2–4, 7–10), depending on the nature of the carbonyl compound.

In all of cases, 1.3 equiv of α-chloroester is necessary.

Coupling methyl 2-chloroacetate with the same ketones **1**–**8** also gave moderate to good yields of β-hydroxyesters (50–90% isolated yield, Table 4).

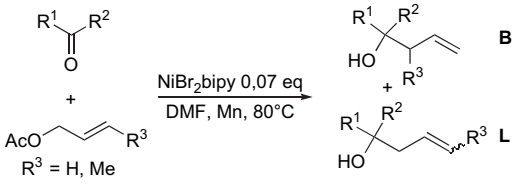
As already observed in the case of electroreductive coupling between aryl halide and α-chloroester with a nickel catalyst,[12] the coupling with chloroacetate (Table 4) is less efficient than with chloropropionate (Table 3). Furthermore the excess of α-chloroester, necessary to consume totally the carbonyl compounds, is more important with methyl 2-chloroacetate than with methyl 2-chloropropanoate (1.7–2 instead of 1.3 equiv are necessary).

We have then extended the process to α-chloronitrile. Thus, as a preliminary study, the coupling between 3-pentanone **6** and α-chloropropionitrile proceeds in good yield (Scheme 2).




**Scheme 2**. The addition of α-chloropropionitrile to 3-pentanone via nickel catalyst.

To extend the scope of this process, we intend to show that this method can be suitable for the activation of allyl acetates. The first results show that the method can also be applied to the preparation of homoallylic alcohols (Scheme 3, and Table 5).

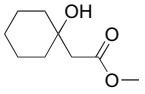
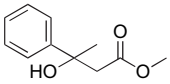
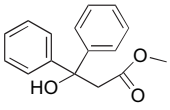
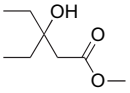
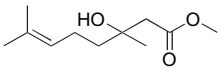



**Scheme 3**. The Addition of allyl acetates to ketones via nickel catalyst.

Thus, as a preliminary study, the coupling between ketones and allylic acetates proceeds in good yields, if the reaction is carried out at 80 °C (Table 5, entries 1 and 2). Then we wanted to test the regioselectivity of this coupling reaction. So we have run experiment using crotyl acetate. Reactions involving allylic derivatives generally give two isomeric products due to allylic transposition (Scheme 3). The ratio of branched to linear alcohol (**B/L**) is known to depend mainly on the nature of the metal in the organometallic reagent.[15] However, in this method, the major product formed seems to be the branched product **B**, with a ratio **B/L** of 95/5 (Table 5, entry 3).

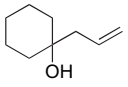
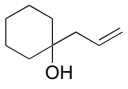
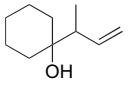
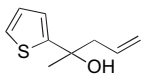
We have then focused on the second reaction, leading directly the ester of the desired aryl acetic and α-aryl-propanoic acid, in a simple and an efficient process compared to

**Table 4**. Nickel-catalyzed cross-coupling between methyl 2-chloroacetate and carbonyl compounds[a]

| Entry | Ketones | Isolated yields (%) of coupling product[b] | |
|---|---|---|---|
| 1 | **1** |  | 64 |
| 2 | **3** |  | 62 |
| 3 | **5** |  | 46[c] |
| 4 | **6** |  | 52[d] |
| 5 | **8** |  | 92 |

[a] Typical procedure: see Section 3.
[b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data.
[c] Ketone (50%) is recovered.
[d] Ketone (20%) is recovered and 6% of methyl 3,3-diethyl-2-oxiranecarboxylate is obtained.

**Table 5**. Allylation of ketones using $NiBr_2$bipy as catalyst[a]

| Entry | Ketone | Reaction time (h) | Isolated yields (%) of coupling product[b] | | Ratio **B/L** |
|---|---|---|---|---|---|
| 1 | **1** | 9 |  | 59[c] | — |
| 2 | **1** | 2 |  | 74[d] | — |
| 3 | **1** | 3 |  | 69[d] | 95/5 |
| 4 | **4** | 5 |  | 54[d,e] | — |

[a] Typical procedure: see Section 3.
[b] Isolated yields, based on initial ketones. All products gave satisfactory analytical data.
[c] Reaction is carried out at room temperature.
[d] Reaction is carried out at 80 °C.
[e] Ketone (20%) is recovered.

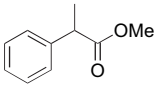
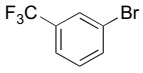
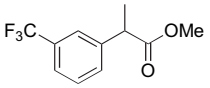
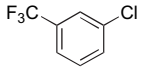
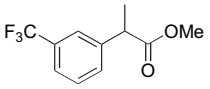
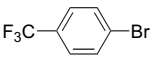
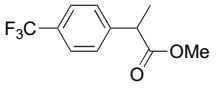
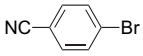
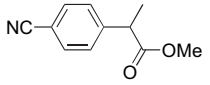
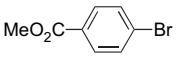
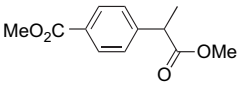
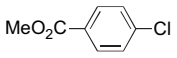
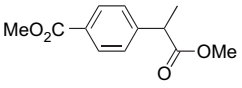
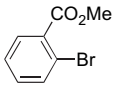
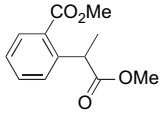
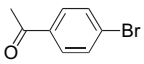
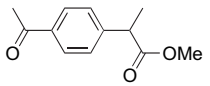
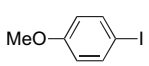
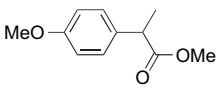
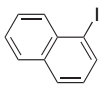
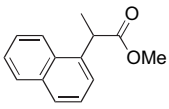
other describes routes (Scheme 1, Eq. 2). Results for the cross-coupling reaction between aryl halides and methyl 2-chloropropanoate, using $NiBr_2$bipy as catalyst, are given in Table 6.

In all cases, the reactions are conducted in the presence of 1.3 equiv or less of the chloroester relative to the aryl halide. Reactions involving aryl iodides were run at room temperature approximately for 1 h to give good yields (Table 6, entries 1, 10, and 11). With aryl bromides, even if the reaction is efficient at room temperature, a faster reaction is obtained at 50 °C (vide supra) (Table 2, entries 1 and 2). The yields are good to excellent and do not seem to greatly depend on the nature of the ring substituents. Reaction is as efficient with electron-donating (Table 6, entry 10) than with electron-withdrawing group (Table 6, entries 2–9). With electron-donating substituents, aryl iodides are best performed (lower yields were obtained with aryl bromides). With electron-withdrawing groups aryl bromides or iodides could be used. However, aryl chlorides are not enough reactive to allow good yields of coupling product (Table 6, entries 3 and 7). With an ortho-substituent, a lower yield is obtained due to steric effects (Table 6, entry 8). The reaction is highly chemoselective, as no addition products with ketones groups are detected (Table 6, entry 9), even if acetophenone **3** allows good yields with methyl 2-chloropropanoate in the Reformatsky reaction (Table 3, entry 3).

Coupling methyl chloroacetate with aryl halides also gave good yields of aryl acetic esters (55–88% isolated yield, Table 7), using the same procedure.

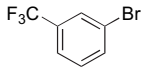
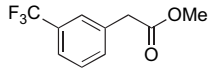
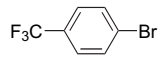
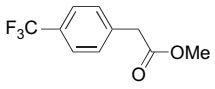
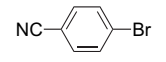
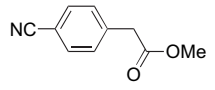
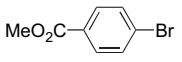
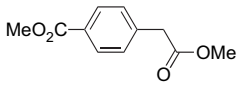
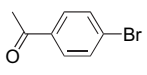
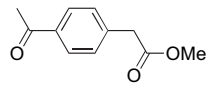
During these studies, a minor biaryl by-product (less than 10%) was observed arising from homocoupling of the aryl halide. This homocoupled by-product has been observed previously in other aryl halide cross-coupling reaction.[8b,12,16] Optimization of the coupling reaction allowed the major formation of the desired heterocoupled product. However, we thought that it would also be possible to refine conditions that would facilitate the formation of the homocoupling product. The chemical process was first optimized with 1-bromonaphthalene because its homocoupling was generally limited, and 1,1′-binaphthyl, when substituted in the 2,2′-positions, is a good candidate for the formation of atropisomers.[17] Using the same process, 92% of binaphthyl is obtained in 2 h at 50 °C using 7 mol % of $NiBr_2$bipy (Scheme 4).

**Table 6**. Nickel-catalyzed cross-coupling between methyl 2-chloropropanoate and aryl halides[a]

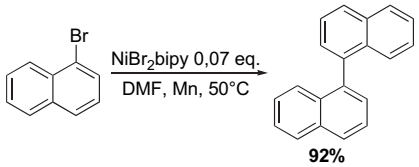
| Entry | Aryl halides | Isolated yields (%) of coupling product[b] |
|---|---|---|
| 1 |  |  87 |
| 2 |  |  78 |
| 3 |  |  20 |
| 4 |  |  70 |
| 5 |  |  75 |
| 6 |  |  65 |
| 7 |  |  20 |
| 8 |  |  40 |
| 9 |  |  70 |
| 10 |  |  69 |
| 11 |  |  82 |

[a] Typical procedure: see Section 3.
[b] Isolated yields, based on initial aryl halides. All products gave satisfactory analytical data.

**Table 7**. Nickel-catalyzed cross-coupling between methyl 2-chloroacetates and aryl halides[a]

| Entry | Aryl halides | Isolated yields (%) of coupling product[b] |
|---|---|---|
| 1 |  |  62 |
| 2 |  |  88 |
| 3 |  |  55 |
| 4 |  |  72 |
| 5 |  |  77 |

[a] Typical procedure: see Section 3.
[b] Isolated yields, based on initial aryl halides. All products gave satisfactory analytical data.




**Scheme 4**. Homocoupling reaction of 1-bromonaphthalene.

In conclusion, we have reported in this paper an efficient cross-coupling of aryl halides and α-chloroesters, as well as the Refortmatsky reaction, enabling the preparation of valuable target molecules such as aryl propanoic acid derivatives or β-hydroxyesters. The scope of the method is wide concerning the type of organic compounds involved as α-chloroesters can be used. For the Reformatsky reaction, the method is efficient with ketones. Aryl propanoic acid derivatives could be obtained with a large variety of functional groups (electron-donating as well as electron-withdrawing groups), using aryl bromides or iodides. The method is also very easy, cheap, and totally original.

Further investigations to exploit the mechanism are in progress.

## 3. Experimental

### 3.1. Analytical methods

GC analysis was carried out using a 4-m capillary column. Mass spectra were recorded with a spectrometer coupled to a gas chromatograph. Column chromatography was performed on silica gel 60, 70–230 mesh. $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded in $CDCl_3$ at 200, 50, and 188 MHz, respectively, with TMS as an internal standard. All solvents and reagents were purchased and used without further purification. DMF is stored under argon. The catalyst precursor $NiBr_2$bipy was either prepared separately according to the literature.[18]

**3.1.1. General procedure for the Reformatsky reaction (Scheme 1, Eq. 1).** Carbonyl compounds (10 mmol) and 13 mmol of α-chloroester were added in a stirred flask under argon at room temperature with 15 mL of DMF. Then 1.1 g of Mn (20 mmol) is introduced, followed up by 0.26 g of $NiBr_2$bipy (0.7 mmol) and finally 20 μL of $CF_3CO_2H$ to activate manganese metal. The reaction is conducted at room temperature. The reaction was monitored by GC and stopped after carbonyl compound was consumed (ca. 1 h). The mixture was then hydrolyzed with 1 N hydrochloric acid and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water and saturated NaCl solution, dried over $MgSO_4$ and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give desired compounds.

**3.1.2. General procedure for the synthesis of aryl propanoic esters (Scheme 1, Eq. 2).** Aryl halides (10 mmol) and 13 mmol of α-chloroester were added in a stirred flask under argon at room temperature with 15 mL of DMF. Then 1.1 g of Mn (20 mmol) is introduced, followed up by 0.26 g of $NiBr_2$bipy (0.7 mmol) and finally 20 μL of $CF_3CO_2H$ to activate manganese metal. The reaction is conducted at room temperature for aryl iodide or 50 °C for aryl bromide. The reaction was monitored by GC and stopped after aryl halide was consumed (ca. 1 h). The mixture was then hydrolyzed with 1 N hydrochloric acid and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water and saturated NaCl solution, dried over $MgSO_4$, and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give desired compounds.

**3.1.2.1. Methyl (1-hydroxy-α-methylcyclohexane)acetate.** *$^{1}H$ NMR*: 3.70 (s, 3H); 3.04 (s, 1H); 2.52 (q, *J*=7.1 Hz, 1H); 1.48 (m, 10H); 1.19 (d, *J*=7.1 Hz, 3H).

*MS*: 187 (M+1), 169 (M–OH), 155 (M–OMe), 143, 130, 113, 99, 81 (base), 55.

**3.1.2.2. Methyl (1-hydroxy-α-methyl-2-cyclohexene)-acetate.** *$^{1}H$ NMR*: *anti*: 5.50–5.92 (m, 2H); 3.70 (s, 3H); 2.98 (s, 1H); 2.63 (q, *J*=7.2 Hz, 1H), 2.10–1.50 (m, 6H); 1.22 (d, *J*=7.2 Hz, 3H).

*syn*: 5.9–5.5 (m, 2H); 3.7 (s, 3H); 3 (s, 1H); 2.60 (q, *J*=7.4 Hz, 1H), 2.10–1.50 (m, 6H); 1.18 (d, *J*=7.4 Hz, 3H).

*MS*: 184 (M), 156 (M−CO), 124 (M−$CO_2$Me), 97 (base), 79, 55.

**3.1.2.3. Methyl 3-hydroxy-2-methyl-3-phenylbutanoate.** *$^{1}H$ NMR*: *anti*: 7.41 (m, 2H); 7.20 (m, 3H); 4.15 (s, 1H); 3.33 (s, 3H); 2.98 (q, *J*=7.07 Hz, 1H); 1.42 (s, 3H); 1.23 (d, *J*=7.07 Hz, 3H).

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

*MS*: 209 (M+1), 191 (M−OH), 121 (base), 105, 77.

**3.1.2.4. Methyl 3-hydroxy-2,3-dimethyl-3-thienylpropanoate.** *$^{1}H$ NMR*: *anti*: 7.17–7.14 (m, 1H); 6.92–6.85 (m, 2H); 4.4 (s, 1H); 3.57 (s, 3H); 2.99 (q, *J*=7.13 Hz, 1H); 1.54 (s, 3H); 1.28 (d, *J*=7.13 Hz, 3H).

*syn*: 7.7–7.6 (m, 1H); 7.2–7.1 (m, 2H); 4.09 (s, 1H); 3.7 (s, 3H); 2.87 (q, *J*=6.7 Hz, 1H); 1.62 (s, 3H); 1.11 (d, *J*=6.7 Hz, 3H).

*MS*: 214 (M), 197 (M−OH), 127 (M−$C_2H_7O_2$, base), 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.

**3.1.2.5. Methyl 3,3-diphenyl-3-hydroxy-2-methylpropanoate.** *$^{1}H$ NMR*: 7.50 (m, 4H); 7.20 (m, 6H); 4.68 (s, 1H); 3.66 (q, *J*=7.1 Hz, 1H); 3.00 (s, 3H); 1.16 (d, *J*=7.1 Hz, 3H).

*MS*: 270 (M); 253 (M−OH), 183 (base), 105, 77.

**3.1.2.6. Methyl 3-ethyl-3-hydroxy-2-methylpentanoate.** *$^{1}H$ NMR*: 3.71 (s, 3H); 3.20 (s, 1H); 2.61 (q, *J*=7.2 Hz, 1H); 1.50 (m, 4H); 1.17 (d, *J*=7.2 Hz, 3H); 0.88 (t, *J*=7.4 Hz, 3H); 0.82 (t, *J*=7.6 Hz, 3H).

*MS*: 175 (M+1), 157 (M−OH), 145 (M−Et), 113, 97, 88, 57 (base).

**3.1.2.7. Methyl 3-hydroxy-2,3-dimethyl hexanoate.** *$^{1}H$ NMR*: *anti*: 3.71 (s, 3H); 3.12 (s, 1H); 2.57 (q, *J*=7 Hz, 1H); 1.42 (m, 4H); 1.19 (d, *J*=7 Hz, 3H); 1.18 (s, 3H); 0.91 (m, 3H).

*syn*: 3.7 (s, 3H); 3.1 (s, 1H); 2.54 (q, $J$=7 Hz, 1H); 1.4 (m, 4H); 1.2 (d, $J$=7 Hz, 3H); 1.1 (s, 3H); 0.9 (m, 3H).

*MS*: 175 (M+1), 157 (M−OH, base), 131 (M−$C_3H_7$), 99, 71, 57.

**3.1.2.8. Methyl 3-hydroxy-2,3,7-trimethyl-6-octenoate.** *$^1$H NMR*: *anti*: 5.13–5.05 (m, 1H); 3.70 (s, 3H); 3.24 (s, 1H); 2.59 (q, $J$=7.1 Hz, 1H); 2.08–2.01 (m, 2H); 1.67 (s, 3H); 1.61 (s, 3H); 1.53–1.43 (m, 2H); 1.21 (s, 3H); 1.20 (d, $J$=7.1 Hz, 3H).

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

*MS*: 215 (M+1), 196 (M−OH), 136, 121, 109 (base), 99, 93, 81, 67, 57.

**3.1.2.9. Methyl 3-hydroxy-2-methyl-3-phenylpropanoate.** *$^1$H NMR*: *anti*: 7.23 (m, 5H); 4.97 (d, $J$=5.1 Hz, 1H); 3.76 (s, 1H); 3.53 (s, 3H); 2.73 (qd, $J_1$=7.0 Hz, $J_2$=5.1 Hz, 1H); 1.10 (d, $J$=7.0 Hz, 3H).

*syn*: 7.28 (m, 5H); 4.68 (d, $J$=8.7 Hz, 1H); 3.65 (s, 3H); 3.51 (s, 1H); 2.76 (qd, $J_1$=8.7 Hz, $J_2$=7.2 Hz, 1H); 0.91 (d, $J$=7.2 Hz, 3H).

*MS*: 195, 177 (base), 121, 107, 88, 79, 57.

**3.1.2.10. Methyl 3-hydroxy-2-methylundecanoate.** *$^1$H NMR*: *anti*: 3.88 (m, 1H); 3.69 (s, 3H); 2.54 (dq, $J_1$=7.1 Hz, $J_2$=4.5 Hz, 1H); 1.45–1.28 (m, 15H); 1.18 (d, $J$=7.1 Hz, 3H); 0.88 (t, $J$=6.4 Hz, 3H).

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

*MS*: 231 (M+1), 215 (M−$CH_3$), 197, 181, 163, 117, 88 (base), 57.

**3.1.2.11. Methyl (1-hydroxycyclohexyl)acetate.** *$^1$H NMR*: 3.7 (s, 3H); 3.38 (s, 1H); 2.48 (s, 2H); 1.68–1.36 (m, 10H).

*MS*: 173 (M+1), 155 (M−OH), 130, 123, 116, 97, 79 (base), 69, 55.

**3.1.2.12. Methyl 3-hydroxy-3-phenylbutanoate.** *$^1$H NMR*: 7.45–7.40 (m, 2H); 7.39–7.15 (m, 3H); 4.35 (s, 1H), 3.53 (s, 3H); 2.96 (d, $J$=15.9 Hz, 1H); 2.77 (d, $J$=15.9 Hz, 1H); 1.52 (s, 3H).

*MS*: 195 (M+1), 179 (M−$CH_3$, base), 177 (M−OH), 121 (M−$CH_2CO_2CH_3$), 105, 91, 77, 51.

**3.1.2.13. Methyl 3-hydroxy-3,3-diphenylpropanoate.** *$^1$H NMR*: 7.4–7.2 (m, 10H); 5.04 (s, 1H); 3.63 (s, 3H); 3.28 (s, 2H).

*MS*: 256 (M), 239 (M−OH), 183 (M−$CH_2CO_2CH_3$), 105 (base), 77, 51.

**3.1.2.14. Methyl 3-ethyl-3-hydroxypentanoate.** *$^1$H NMR*: 3.69 (s, 3H); 3.46 (s, 1H); 2.46 (s, 2H); 1.54 (q, $J$=7.2 Hz, 4H); 0.88 (t, $J$=7.2 Hz, 6H).

*MS*: 161 (M+1, base), 143 (M−OH), 131 (M−$C_2H_5$), 111, 99, 83, 69, 57.

**3.1.2.15. Methyl 3-hydroxy-3,7-dimethyloct-6-enoate.** *$^1$H NMR*: 5.13–5.05 (m, 1H); 3.69 (s, 3H); 3.50 (s, 1H); 2.57 (d, $J$=15.8 Hz, 1H); 2.38 (d, $J$=15.8 Hz, 1H); 2.08–2.01 (m, 2H); 1.67 (s, 6H); 1.53–1.43 (m, 2H); 1.31 (s, 3H).

*MS*: 201 (M+1), 182 (M−$H_2O$), 123, 109 (base), 57.

**3.1.2.16. 3-Ethyl-3-hydroxy-2-methylpentanenitrile.** *$^1$H NMR*: 2.9 (s, 1H); 2.79 (q, $J$=7.2 Hz, 1H); 1.66 (q, $J$=7.1 Hz, 2H); 1.61 (q, $J$=7.7 Hz, 2H); 1.29 (d, $J$=7.2 Hz, 3H); 0.92 (t, $J$=7.1 Hz, 3H); 0.89 (t, $J$=7.7 Hz, 3H).

*MS*: 142 (M+1), 124 (M−OH), 112, 87, 69, 56 (base).

**3.1.2.17. (Propenyl-2)-1-cyclohexanol.** *$^1$H NMR*: 5.9 (ddt, $J$=16.8 Hz, $J$=10.8 Hz, $J$=7.5 Hz, 1H); 5.11 (d, $J$=16.8 Hz, 1H); 5.09 (d, $J$=10.8 Hz, 1H); 2.34 (s, 1H); 2.2 (d, $J$=7.5 Hz, 2H); 2.04–0.84 (m, 10H).

*MS*: 139 (M−H), 123 (M−OH), 99, 81 (base), 55.

**3.1.2.18. 1-(1-Methyl-2-propenyl)-cyclohexanol.** *$^1$H NMR*: 5.92–5.74 (m, 1H); 5.09–5.01 (m, 2H); 2.17 (dq, $J$=7.7 Hz, $J$=7 Hz, 1H); 1.62 (s, 1H); 1.56–1.3 (m, 10H); 1.0 (d, $J$=7 Hz, 3H).

*MS*: 154, 137 (M−OH), 99 (M−$C_4H_7$), 81 (base), 55.

**3.1.2.19. 2-Thienyl-pent-4-en-2-ol.** *$^1$H NMR*: 7.27–7.17 (m, 1H); 6.97–6.89 (m, 2H); 5.80–5.63 (m, 1H); 5.19–5.11 (m, 2H); 2.75–2.54 (m, 2H); 2.32 (s, 1H); 1.62 (s, 3H).

*MS*: 168 (M), 151 (M−OH), 127 (M−$C_3H_5$, base), 111, 97, 85 (M−$C_4H_3S$), 71, 57.

**3.1.2.20. Methyl 2-phenylpropanoate.** *$^1$H NMR*: 7.26 (s, 5H); 3.69 (q, $J$=7.3 Hz, 1H); 3.58 (s, 3H); 1.46 (d, $J$=7.3 Hz, 3H).

*MS*: 164 (M), 105 (M−$CO_2$Me, base).

**3.1.2.21. Methyl 2-(3-(trifluoromethyl)phenyl)-propanoate.** *$^1$H NMR*: 7.61 (s, 1H); 7.53–7.36 (m, 3H); 3.79 (q, $J$=7.16 Hz, 1H); 3.63 (s, 3H); 1.51 (d, $J$=7.16 Hz, 3H).

*$^{19}$F NMR*: −62.59 (s, 3F)/$CFCl_3$.

*$^{13}$C NMR*: 174.0–141.6–130.83 (q, $J_{CCF}$=32 Hz)–130.82–129.0 (q, $J_{CCCF}$=3.9 Hz)–124.4 (q, $J_{CCCF}$=3.9 Hz)–124.13–124.09 (q, $J_{CF}$=272 Hz, $CF_3$)–51.7–45.1–18.1.

*MS*: 232 (M), 213 (M−F), 182, 173 (M−$CO_2$Me, base), 154.

**3.1.2.22. Methyl 2-(4-(trifluoromethyl)phenyl)propanoate.** *$^1$H NMR*: 7.59 and 7.42 (2H each, AA′-BB′ system $J$=8.2 Hz); 3.80 (q, $J$=7.1 Hz, 1H); 3.67 (s, 3H); 1.52 (d, $J$=7.1 Hz, 3H).

*$^{19}$F NMR*: −62.33 (s, 3F)/$CFCl_3$.

*MS*: 232 (M), 213 (M−F), 173 (M−$CO_2$Me, base), 154.

**3.1.2.23. Methyl 2-(4-cyanophenyl)propanoate.** *$^1$H NMR*: 7.63 and 7.44 (2H each, AA′-BB′ system, $J$=8.2 Hz); 3.81 (q, $J$=7.2 Hz, 1H); 3.68 (s, 3H); 1.53 (d, $J$=7.2 Hz, 3H).

*MS*: 189 (M), 174 (M−Me), 158 (M−OMe), 130 (M−$CO_2$Me, base), 115.

**3.1.2.24. Methyl 4-(1-methoxy-1-oxopropan-2-yl)benzoate.** *$^1$H NMR*: 8.00 and 7.37 (2H each, AA′-BB′ system, $J$=8.36 Hz); 3.91 (s, 3H); 3.79 (q, $J$=7.19 Hz, 1H); 3.67 (s, 3H); 1.52 (d, $J$=7.19 Hz, 3H).

*MS*: 222 (M), 207 (M−Me), 191 (M−OMe), 163 (M−$CO_2$Me, base), 131, 117, 103, 92.

**3.1.2.25. Methyl 2-(1-methoxy-1-oxopropan-2-yl)benzoate.** *$^1$H NMR*: 7.90 (dd, $J$=7.79 Hz, $J$=1.32 Hz, 1H); 7.51–7.24 (m, 3H); 4.65 (q, $J$=7.16 Hz, 1H); 3.86 (s, 3H); 3.62 (s, 3H); 1.52 (d, $J$=7.16 Hz, 3H).

*$^{13}$C NMR*: 174.5–167.4–141.8–132.0–130.5–129.0–128.2–126.5–51.6–51.5–41.8–17.9.

*MS*: 222 (M), 190 (M−OMe), 162 (M−$CO_2$Me, base), 147, 131, 103, 77.

**3.1.2.26. Methyl 2-(4-acetylphenyl)propanoate.** *$^1$H NMR*: 7.91 and 7.39 (2H each, AA′-BB′ system, $J$=8.36 Hz); 3.80 (q, $J$=7.17 Hz, 1H); 3.64 (s, 3H); 2.56 (s, 3H); 1.51 (d, $J$=7.17 Hz, 3H).

*MS*: 206 (M), 191 (M−Me, base), 147 (M−$CO_2$Me), 103.

**3.1.2.27. Methyl 2-(4-methoxyphenyl)propanoate.** *$^1$H NMR*: 7.19 and 6.82 (2H each, AA′-BB′ system, $J$=8.68 Hz); 3.70 (s, 3H); 3.64 (q, $J$=7.1 Hz, 1H); 3.59 (s, 3H); 1.44 (d, $J$=7.1 Hz, 3H).

*MS*: 194 (M), 163 (M−OMe, base), 135 (M−$CO_2$Me), 132, 104.

**3.1.2.28. Methyl 2-(naphthalen-1-yl)propanoate.** *$^1$H NMR*: 8.02 (d, $J$=8.26 Hz, 1H); 7.76–7.62 (m, 2H); 7.47–7.29 (m, 4H); 4.42 (q, $J$=7.2 Hz, 1H); 3.49 (s, 3H); 1.59 (d, $J$=7.2 Hz, 3H).

*MS*: 214 (M), 183 (M−OMe), 155 (M−$CO_2$Me, base).

**3.1.2.29. 1,1′-Binaphthyl.** *$^1$H NMR*: 8.17 (s, 2H); 7.98–7.86 (m, 8H); 7.56–7.46 (m, 4H).

*MS*: 254 (M), 127 (base).

**3.1.2.30. Methyl 2-(3-(trifluoromethyl)phenyl)acetate.** *$^1$H NMR*: 7.57 (s, 1H); 7.49–7.32 (m, 3H); 3.67 (s, 3H); 3.66 (s, 2H).

*MS*: 218 (M), 199 (M−F), 159 (M−$CO_2$Me, base), 140, 109.

**3.1.2.31. Methyl 2-(4-(trifluoromethyl)phenyl)acetate.** *$^1$H NMR*: 7.55 and 7.38 (2H each, AA′-BB′ system, $J$=8.16 Hz); 3.69 (s, 2H); 3.67 (s, 3H).

*$^{13}$C NMR*: 171.0–138.0–129.7 (2C)–129.2 (q, $J_{CCF}$= 32.2 Hz)–125.1 (q, $J_{CCCF}$=3.9 Hz, 2C)–124.1 (q, $J_{CF}$= 271.8 Hz, $CF_3$)–51.8–40.5.

*MS*: 218 (M), 199 (M−F), 168, 159 (M−$CO_2$Me, base), 140.

**3.1.2.32. Methyl 2-(4-cyanophenyl)acetate.** *$^1$H NMR*: 7.80 and 7.40 (2H each, AA′-BB′ system, $J$=8.3 Hz); 3.70 (s, 3H); 3.65 (s, 2H).

*MS*: 175 (M), 160 (M−Me), 144 (M–OMe), 116 (M–$CO_2$Me, base), 89.

**3.1.2.33. Methyl 4-(2-methoxy-2-oxoethyl)benzoate.** *$^1$H NMR*: 7.99 and 7.35 (2H each, AA′-BB′ system, $J$=8.14 Hz); 3.89 (s, 3H); 3.69 (s, 3H); 3.68 (s, 2H).

*$^{13}$C NMR*: 171.1–166.6–139.0–129.7 (2C)–129.3 (2C)–129.0–52.0–51.8–40.9.

*MS*: 208 (M), 177 (M−OMe, base), 149 (M−$CO_2$Me), 121, 89.

**3.1.2.34. Methyl 2-(4-acetylphenyl)acetate.** *$^1$H NMR*: 7.90 and 7.36 (2H each, AA′-BB′ system, $J$=8.22 Hz); 3.68 (s, 5H); 2.56 (s, 3H).

*$^{13}$C NMR*: 197.2–170.9–139.1–135.7–129.3 (2C)–128.3 (2C)–51.8–40.6–26.4.

*MS*: 192 (M), 177 (M−Me, base), 133 (M−$CO_2$Me), 89.

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