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Iron-catalyzed C(sp^3)–H functionalization of methyl azaarenes with α-oxoesters: a facile approach to lactic acid derivatives

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ABSTRACT

A highly efficient method for the C(sp^3)–H functionalization of methyl azaarenes to α-oxoesters in the presence of iron(II) acetate as an inexpensive, nontoxic catalyst with moderate-to-excellent yields has been developed. This transformation represents a facile approach to medicinally important lactic acid derivatives.

1. Introduction

Development of new efficient functional group transformations based on atom-, and step-economic principle plays a crucial role in modern sustainable organic chemistry.[1] For this purpose, the functionalization of C(sp^3)–H bonds has received considerable attention in recent years.[2] Among them, the direct C(sp^3)–H bond functionalization of 2-alkyl azaarenes is a challenge task due to the lower activity of alkyl groups. This type of reaction is particularly valuable, because alkyl azaarene derivatives are important compounds in medicinal chemistry,[3] organic catalysis,[4] as well as material chemistry.[5]

Recently, a few reports have appeared on the direct C(sp^3)–H bond functionalization of 2-alkyl azaarenes without an activating group promoted by Lewis acid,[6] BrØnsted acid,[7] or under microwave-assisted catalyst free conditions.[8] For example, the addition of 2-alkyl azaarenes to the C=N double bond of *N*-sulfonyl aldimines,[6a–d,8a] the C=C double bond of conjugated alkenes,[6e,8c,8f] carbonyls,[6f,g,7a–c,8b,8d,e] and azodicarboxylate.[6h,i] Although azaarene-substituted lactic acid derivatives are medicinal important compounds, to the best of our knowledge, only two papers regarding the coupling of 2-alkyl azaarenes with α-oxoesters to provide lactic acid derivatives have been published,[6f–g] where one is $Yb(OTf)_3$ catalyzed C(sp^3)–H bond functionalization of methyl azaarenes with α-trifluoromethyl carbonyl compounds, another is the addition of α-alkyl azaarenes to ethyl glyoxylate in the presence of $Cu(OTf)_2$/1,10-phennanthroline catalytic system. Though the reported methods are satisfactory, they suffer from certain drawbacks like the use of expensive catalyst, toxic metal, and additional ligand, which hinder practical application. In view of this, the development of mild, high efficient, and applicable method for the synthesis of lactic acid derivatives from 2-alkyl azaarenes and α-oxoesters via C(sp^3)–H bond activation is desirable.

Iron is less-toxic, benign, and most abundant metal in Earth's crust after aluminium. Many iron salts and iron complexes are commercial available on a large scale or easy to synthesize, which results in low cost and ready accessibility. Iron seems to be promising catalyst in organic synthesis, and various iron-catalyzed organic transformations have been realized.[9] Herein, we report a simple and efficient approach for the synthesis of azaarene-substituted lactic acid derivatives via iron-catalyzed addition of methyl azaarenes to α-oxoesters.

2. Results and discussion

Initially, we chose the reaction of 2-methyl quinoline **1a** and ethyl 3,3,3-trifluoropyruvate **2a** in 1,4-dioxane at 120 °C for 24 h as a model reaction to evaluate the potential of iron salts in this transformation. As shown in Table 1, the results revealed that all the screened iron salts, such as $FeCl_2$, $FeCl_3$, $FeBr_3$, $Fe(OTf)_2$, $Fe(acac)_3$

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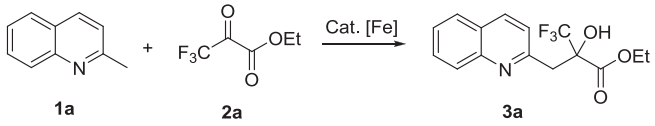
Table 1
Optimization of reaction conditions[a]



1a 2a 3a

Entry	[Fe]	Solvent	T (°C)	Yield (%)[b]
1	$FeCl_2$	1,4-Dioxane	120	43
2	$FeCl_3$	1,4-Dioxane	120	68
3	$FeBr_3$	1,4-Dioxane	120	79
4	$Fe(OTf)_2$	1,4-Dioxane	120	62
5	$Fe(acac)_3$	1,4-Dioxane	120	57
6[c]	$Fe(ClO_4)_3$	1,4-Dioxane	120	65
7[c]	$Fe(BF_4)_2$	1,4-Dioxane	120	71
8	$Fe(OAc)_2$	1,4-Dioxane	120	86
9	—	1,4-Dioxane	120	NR[d]
10	$Fe(OAc)_2$	Toluene	120	79
11	$Fe(OAc)_2$	1,2-Dichloroethane	100	80
12	$Fe(OAc)_2$	CH_3CN	100	67
13	$Fe(OAc)_2$	THF	80	60
14	$Fe(OAc)_2$	CH_3NO_2	120	36
15	$Fe(OAc)_2$	PEG-400	120	74
16[e]	$Fe(OAc)_2$	1,4-Dioxane	120	73
17[f]	$Fe(OAc)_2$	1,4-Dioxane	120	87

[a] Reaction conditions: **1a** (0.70 mmol), **2a** (0.35 mmol), [Fe] catalyst (5 mol %) in 1 mL solvent under N_2 for 24 h.
[b] Yield after column chromatography.
[c] Iron salts are hexahydrate.
[d] NR: no reaction.
[e] 0.5 mmol **1a** was used.
[f] 10 mol % $Fe(OAc)_2$ was used.

were effective for this reaction, and $Fe(OAc)_2$ gave highest yield of product **3a** among them (Table 1, entries 1–8). When the reaction was carried out in the absent of iron salts, both starting materials were recovered unchanged (entry 9). A survey of solvents showed that 1,4-dioxane to be an optimal selection comparing to toluene, 1,2-dichloroethane, acetonitrile, tetrahydrofuran, nitromethane (entries 10–15). The proved green solvent polyethylene glycol-400 was also subjected in this transformation, and comparatively lower yield was obtained (entry 15). Decreasing of the amount of 2-methyl quinoline **1a** resulted in diminished yield (entry 16). Increasing the amount of iron acetate to 10 mol % didn't affect the yield of **3a** (entry 17).

The tolerance of this transformation to various 2-methyl quinolines bearing electron-donating or electron-withdrawing groups was examined under the optimized conditions (Table 2). The reaction of ethyl 3,3,3-trifluoropyruvate **2a** and 2-methyl quinolines proceed smoothly and gave corresponding products **3a**–**d** with yields of 76–86%. The 1-metyl isoquinoline was also applicable to this reaction and provided compound **3e** with lower yield of 60%. Next, the scope of 2-methyl pyridines was also examined, and desired product **3f**–**h** was obtained in lower yields of 24–54%, especially, the 2,6-dimethyl pyridine gave **3g** in 24% yield, which might be as a result of steric effect at C3 position of pyridine. The reaction of ethyl glyoxylate and 2-methyl quinolines was also examined, and the corresponding products **3i**–**n** was provided in higher yields of 72–90%. It was noted that the electron-deficient 2-methyl-8-nitroquinoline also gave the desired product **3n** in 72% yield. In contrast, the same product **3n** was obtained in 36% yield catalyzed by $Cu(OTf)_2$/1,10-phennanthroline.[6f] The reaction of 1-methyl quinoxaline and ethyl glyoxylate also proceeded smoothly and gave the product **3o** in 88% yield. The ethyl glyoxylate **2b** has higher reactivity in the reaction with 2-methyl pyridines comparing to ethyl 3,3,3-trifluoropyruvate **2a**, and gave the products **3p** and **3q** in 75% and 41% yield, respectively. The reaction of 2-methyl quinoline and ethyl pyruvate proceeded at higher reaction temperature (130 °C), with more amount of catalyst loading (10 mol %), and longer reaction time (48 h), to gave the desired product **3r** in 26% yield. It represents the first example about C(sp3)-H functionalization of methyl azaarene with ethyl pyruvate.

Encouraged by the success of the reaction with α-oxoesters, we attempted to extend the scope to other 1,2-dicarbonyl compounds. As shown in Scheme 1, *N*-benzyl-2-oxoacetamide (**2s**) and methylglyoxal (**2t**) were also compatible with this transformation, giving the products **3s** and **3t** in 79 and 76% yield, respectively, whereas phenylglyoxal (**4**) decomposed under the reaction conditions.

The proposed reaction pathway for the addition of 2-methylazaarenes and α-oxoesters was described in Scheme 2. The 2-methyl quinoline coordinates with $Fe(OAc)_2$ to generate iron-enamide species **A**, the active iron-enamide species **A** undergo nucleophilic attack to α-oxoester **2**, the electrophilicity of the α-carbonyl is dramatically enhanced by the complexation of carbonyl group with iron and the electron-withdrawing of the ester group, to give intermediate **C** via a transition state **B**. The product **3** is formed with regenerated iron catalyst after hydrolysis.

3. Conclusion

In summary, we have developed an iron-catalyzed straightforward, clean, atom-, step-economic synthesis of medicinally important azaarene-substituted lactic acid derivatives by the direct addition of 2-methylazaarenes and α-oxoesters. Investigations of the detailed reaction mechanism and further studies of iron-catalyzed sp^3 C–H bond functionalizations are currently underway.

4. Experimental section

4.1. General

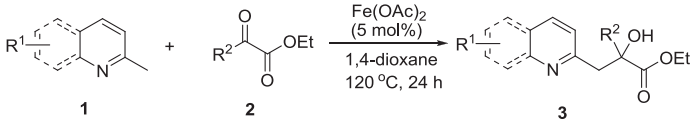
All reagents were obtained from commercial sources and used without further purification unless otherwise noted. Analytical thin layer chromatography (TLC) was carried out with silica gel GF 254 precoated plates. Visualization was accomplished with UV lamp. The reactions were carried out under N_2 atmosphere and products were isolated by column chromatography on silica gel (300–400 mesh) using petroleum ether (bp 60–90 °C) and ethyl acetate. All compounds were characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376.5 MHz), IR and HRMS.

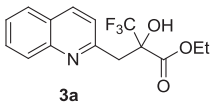
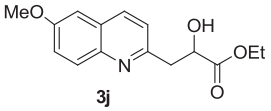
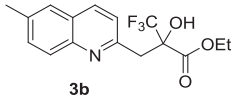
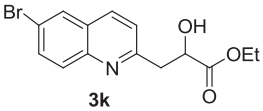
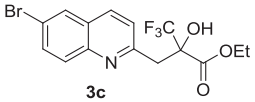
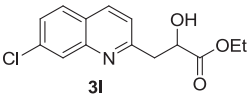
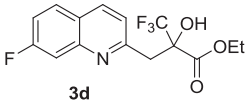
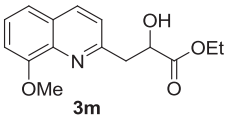
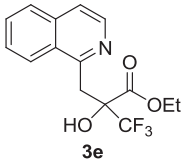
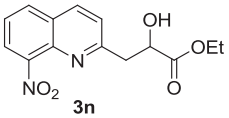
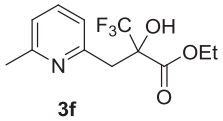
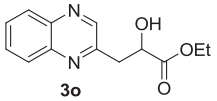
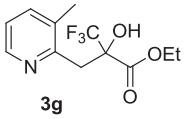
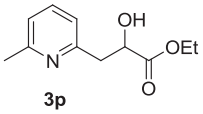
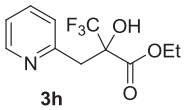
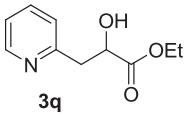
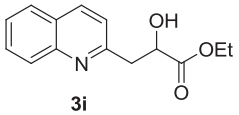
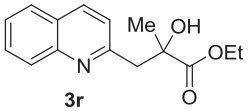
4.2. Typical procedure for the synthesis of ethyl 3,3,3-trifluoro-2-hydroxy-2-(quinolin-2-ylmethyl)propanoate (3a)

$Fe(OAc)_2$ (3.1 mg, 0.018 mmol), 2-methyl quinoline (100 mg, 0.70 mmol), ethyl 3,3,3-trifluoropyruvate (60 mg, 0.35 mmol) were added in a Schlenk tube, the tube was closed and degassed three times with nitrogen gas, 1.0 mL distilled 1,4-dioxane was injected by syringe, the mixture was stirred at 120 °C for 24 h, after completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the product **3a** (94 mg, 86%) as white solid.

*4.2.1. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(quinolin-2-ylmethyl propanoate (**3a**).*[6g] ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, J=7.2 Hz, 3H), 3.52 (d, J=15.2 Hz, 1H), 3.76 (d, J=15.2 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 6.79 (s, 1H), 7.31 (d, J=8.4 Hz, 1H), 7.51–7.55 (m, 1H), 7.68–7.72 (m, 1H), 7.79 (dd, J=8.4, 1.2 Hz, 1H), 7.94 (d, J=8.4 Hz, 1H), 8.14 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 29.7, 38.4, 62.8, 77.9 (q, J=29.1 Hz, CF_3), 122.1, 126.7, 126.9, 127.6, 128.4, 130.1, 137.3, 146.6, 156.3, 168.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.4 (s, 3F); IR (KBr): 3420, 2961, 1746, 1622, 1590, 1295, 1201, 1108, 750 cm^{-1};

Table 2
Scope of 2-methylazaarenes and α-oxoesters[a]



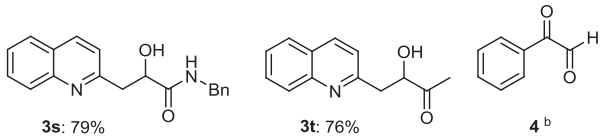
Product	Yield (%)	Product	Yield (%)
 **3a**	86	 **3j**	85
 **3b**	82	 **3k**	88
 **3c**	83	 **3l**	88
 **3d**	76	 **3m**	81
 **3e**	60	 **3n**	72
 **3f**	54	 **3o**	88
 **3g**	24	 **3p**	75
 **3h**	44	 **3q**	41
 **3i**	90	 **3r**	26[b]

[a] Reaction conditions: 2-methyl azaarene **1**(0.70 mmol), α-oxoesters **2a** (0.35 mmol), $Fe(OAc)_2$ (5 mol %) in 1,4-dioxane (1 mL) at 120 °C under N_2 for 24 h, yield after column chromatography.
[b] $Fe(OAc)_2$ (10 mol %), 130 °C, 48 h.

HRMS (ESI) calcd for $C_{15}H_{15}F_3NO_3$ $[M+H]^+$: 314.0998, found: 314.0996.

*4.2.2. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(6-methylquinolin-2-ylmethyl)propanoate (**3b**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (t, J=7.2 Hz, 3H), 2.52 (s, 3H), 3.49 (d, J=15.6 Hz, 1H), 3.72 (d, J=15.6 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 7.01 (s, 1H), 7.26 (d, J=8.4 Hz, 1H), 7.51–7.55 (m, 2H), 7.83 (d, J=8.4 Hz, 1H), 8.03 (dd, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 21.5, 38.2, 62.7, 78.2 (q, J=29.0 Hz, CF_3), 121.9, 122.0, 124.8, 126.4, 127.0, 128.0, 132.3, 136.6, 145.1, 155.3, 168.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.4 (s, 3F); IR (KBr): 3260, 2925, 2852, 1750, 1599, 1505, 1303, 1186, 1112, 995, 832, 660 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}F_3NO_3$ $[M+H]^+$: 328.1155, found: 328.1153.

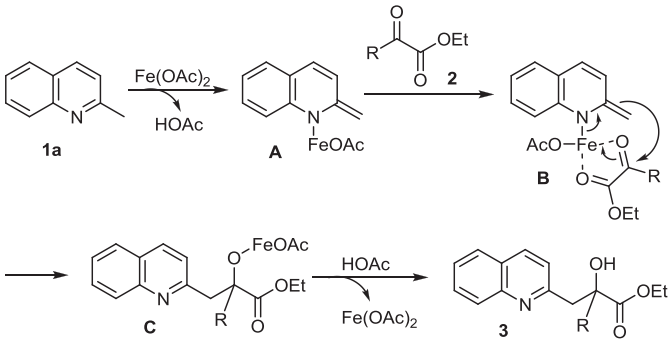
*4.2.3. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(6-bromoquinolin-2-ylmethyl)propanoate (**3c**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (t, J=7.2 Hz, 3H), 3.51 (d, J=15.2 Hz, 1H), 3.75 (d, J=15.6 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 6.14 (s, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.76–7.83 (m, 2H), 7.97 (d, J=2.0 Hz, 1H), 8.05 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$,



[a]Reaction conditions: 2-methyl quinoline **1** (0.70 mmol), α-oxoesters **2a** (0.35 mmol), $Fe(OAc)_2$ (10 mol%) in 1,4-dioxane (1 mL) at 120 °C under N_2 for 24 h, yield after column chromatography.

[b]Compound **4** was decomposed under the reaction conditions.

Scheme 1. Reaction of **1a** with other linear 1,2-dicarbonyls.[a]



Scheme 2. Proposed reaction pathway.

100 MHz) δ: 13.9, 38.7, 63.0, 77.8 (q, *J*=29.1 Hz, CF_3), 120.5, 123.1, 124.7, 128.0, 129.7, 130.2, 133.5, 136.1, 145.3, 156.6, 168.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.5 (s, 3F); IR (KBr): 3462, 2953, 2918, 1743, 1602, 1489, 1466, 1310, 1225, 1193, 1147, 1077, 886, 828, 696, 618 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}BrF_3NNaO_3$ $[M+Na]^+$: 413.9923, found: 413.9921.

*4.2.4. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(7-fluoroquinolin-2-ylmethyl)propanoate (**3d**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.22 (t, *J*=7.6 Hz, 3H), 3.52 (d, *J*=15.2 Hz, 1H), 3.76 (d, *J*=15.2 Hz, 1H), 4.27 (q, *J*=7.2 Hz, 2H), 6.22 (s, 1H), 7.29–7.35 (m, 2H), 7.55–7.58 (m, 1H), 7.78–7.82 (m, 1H), 8.12 (d, *J*=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 38.7, 63.0, 77.9 (q, *J*=29.6 Hz, CF_3), 112.2, 112.3, 117.1, 117.3, 121.6, 124.0, 129.7, 129.8, 137.1, 147.7, 157.4, 162.0, 164.6, 168.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.5 (s, 3F), −108.4 (s, 1F); IR (KBr): 3241, 2973, 2929, 1743, 1629, 1606, 1513, 1431, 1291, 1240, 1166, 1022, 964, 874, 695, 633, 508 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}F_4NNaO_3$ $[M+Na]^+$: 354.0724, found: 354.0723.

*4.2.5. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(isoquinolin-1-ylmethyl) propanoate (**3e**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (t, *J*=6.4 Hz, 3H), 3.75 (d, *J*=16.4 Hz, 1H), 4.14–4.22 (m, 3H), 6.99 (s, 1H), 7.58 (d, *J*=6.0 Hz, 1H), 7.66 (t, *J*=8.0 Hz, 1H), 7.74 (t, *J*=7.2 Hz, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 8.31 (d, *J*=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 34.2, 62.6, 78.1 (q, *J*=28.7 Hz, CF_3), 120.5, 122.1, 124.6, 127.3, 127.6, 127.9, 130.8, 136.3, 140.1, 156.1, 168.9; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.4 (s, 3F); IR (KBr): 3249, 2996, 2984, 2922, 1739, 1626, 1568, 1416, 1299, 1236, 1147, 1061, 968, 824, 758, 691 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}F_3NO_3$ $[M+H]^+$: 314.0999, found: 314.0997.

*4.2.6. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(6-methylpyridin-2-ylmethyl)propanoate (**3f**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, *J*=6.8 Hz, 3H), 2.49 (s, 3H), 3.29 (d, *J*=14.8 Hz, 1H), 3.47 (d, *J*=14.8 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 7.01 (d, *J*=7.6 Hz, 1H), 7.06 (d, *J*=7.6 Hz, 1H), 7.55 (t, *J*=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 23.9, 37.6, 62.5, 78.1 (q, *J*=28.8 Hz, CF_3), 121.3, 121.9, 124.8, 137.5, 154.8, 157.3, 168.7; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.3 (s, 3F); IR (KBr): 3475, 2988, 2938, 2284, 1747, 1602, 1579, 1455, 1373, 1194, 1139, 1069, 1011, 797, 699 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}F_3NO_3$ $[M+H]^+$: 278.0999, found: 278.0997.

*4.2.7. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(3-methylpyridin-2-ylmethyl)propanoate (**3g**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, *J*=7.2 Hz, 3H), 2.33 (s, 3H), 3.24 (d, *J*=15.6 Hz, 1H), 3.57 (d, *J*=15.6 Hz, 1H), 4.21 (q, *J*=7.6 Hz, 2H), 7.10–7.13 (m, 1H), 7.49–7.51 (m, 1H), 8.25–8.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 18.5, 34.2, 62.5, 78.2 (q, *J*=28.6 Hz, CF_3), 122.3, 124.9, 132.4, 138.5, 145.3, 154.6, 169.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.5 (s, 3F); IR (KBr): 3362, 2922, 2852, 1735, 1614, 1459, 1388, 1167, 1143, 1014, 730 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}F_3NO_3$ $[M+H]^+$: 278.0998, found: 278.0997.

*4.2.8. Ethyl 3,3,3-trifluoro-2-hydroxy-2-(pyridin-2-ylmethyl)propanoate (**3h**).*[6g] ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (t, *J*=7.2 Hz, 3H), 3.35 (d, *J*=15.2 Hz, 1H), 3.54 (d, *J*=15.2 Hz, 1H), 4.23 (q, *J*=7.2 Hz, 2H), 6.57 (s, 1H), 7.20–7.23 (m, 2H), 7.65–7.69 (m, 2H), 8.45–8.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.8, 38.0, 62.8, 77.8 (q, *J*=28.8 Hz, CF_3), 122.4, 124.5, 137.2, 148.4, 155.5, 168.7; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ: −78.3 (s, 3F); IR (KBr): 3015, 2918, 2848, 2766, 1758, 1598, 1571, 1478, 1136, 1011, 848, 758, 602 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}F_3NNaO_3$ $[M+Na]^+$: 286.0661, found: 286.0658.

*4.2.9. Ethyl 2-hydroxy-3-(quinolin-2-yl)propanoate (**3i**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, *J*=7.5 Hz, 3H); 3.52–3.39 (m, 2H), 4.22 (q, *J*=7.5 Hz, 2H), 4.77 (dd, J_1=7.5 Hz, J_2=3.5 Hz, 1H), 7.31 (d, *J*=8.5 Hz, 1H), 7.53–7.51 (m, 1H), 7.72–7.68 (m, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 8.00 (d, *J*=8.0 Hz, 1H), 8.11 (d, *J*=9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 40.9, 61.3, 70.4, 122.0, 126.2, 126.9, 127.5, 128.7, 129.7, 136.7, 147.1, 158.8, 173.6; IR (neat): 3065, 2979, 1732, 1599, 1508, 1287, 1161, 1040, 831, 763, 626 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0950, found: 268.0952.

*4.2.10. Ethyl 2-hydroxy-3-(6-methoxyquinolin-2-yl)propanoate (**3j**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, *J*=7.0 Hz, 3H), 3.48–3.34 (m, 2H), 3.93 (s, 3H), 4.21 (q, *J*=7.5 Hz, 2H), 4.74 (dd, J_1=7.0 Hz, J_2=4.0 Hz, 1H), 7.05 (d, *J*=3.0 Hz, 1H), 7.25 (d, *J*=8.0 Hz, 1H), 7.35 (dd, J_1=9.0 Hz, J_2=2.5 Hz, 1H), 7.89 (d, *J*=9.0 Hz, 1H), 8.01 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 40.6, 55.5, 61.2, 70.5, 105.1, 122.2, 122.3, 127.8, 130.1, 135.5, 143.2, 156.1, 157.6, 173.6; IR (neat): 3074, 2979, 1726, 1599, 1504, 1383, 1238, 1023, 831, 610 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_4$ $[M+Na]^+$: 298.1055, found: 298.1064.

*4.2.11. Ethyl 3-(6-bromoquinolin-2-yl)-2-hydroxypropanoate (**3k**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, *J*=7.0 Hz, 3H), 3.51–3.37 (m, 2H), 4.22 (q, *J*=7.0 Hz, 2H), 4.75 (dd, J_1=7.0 Hz, J_2=4.0 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 1H), 7.77–7.43 (m, 1H), 7.86 (d, *J*=8.5 Hz, 1H), 7.95 (d, *J*=2.0 Hz, 1H), 8.01 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 41.2, 61.3, 70.1, 119.9, 122.8, 127.9, 129.5, 130.3, 133.0, 135.5, 145.7, 159.1, 173.5; IR (neat): 3133, 2982, 1729, 1593, 1490, 1289, 1029, 832, 638 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}BrNNaO_3$ $[M+Na]^+$: 348.0055, found: 348.0066.

*4.2.12. Ethyl 3-(7-chloroquinolin-2-yl)-2-hydroxypropanoate (**3l**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, *J*=7.0 Hz, 3H), 3.52–3.38 (m, 2H), 4.23 (q, *J*=7.0 Hz, 2H), 4.76–4.74 (m, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.47 (dd, J_1=9.0 Hz, J_2=2.0 Hz, 1H), 7.73 (d, *J*=8.5 Hz, 1H), 8.01 (d, *J*=2.0 Hz, 1H), 8.08 (d, *J*=8.5 Hz, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ: 14.1, 41.1, 61.4, 70.1, 122.2, 125.2, 127.3, 127.7, 128.7, 135.5, 136.4, 147.5, 159.8, 173.6; IR (neat): 3095, 2979, 1735, 1615, 1499, 1279, 1161, 1033, 847, 628 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}ClNNaO_3$ $[M+Na]^+$: 302.0560, found: 302.0560.

*4.2.13. Ethyl 2-hydroxy-3-(8-methoxyquinolin-2-yl)propanoate (**3m**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, J=7.0 Hz, 3H), 3.54–3.36 (m, 2H), 4.04 (s, 3H), 4.22 (q, J=7.0 Hz, 2H), 4.78 (dd, J_1=7.5 Hz, J_2=3.5 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.37–7.34 (m, 2H), 7.43 (t, J=8.0 Hz, 1H), 8.08 (d, J=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 40.7, 55.9, 61.2, 70.6, 108.0, 119.2, 122.3, 126.4, 127.9, 136.6, 138.9, 154.9, 157.6, 173.5; IR (neat): 3152, 1739, 1600, 1505, 1257, 1103, 845, 759 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_4$ $[M+Na]^+$: 298.1055, found: 298.1058.

*4.2.14. Ethyl 2-hydroxy-3-(8-nitroquinolin-2-yl)propanoate (**3n**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.28 (t, J=7.5 Hz, 3H), 3.59–3.50 (m, 2H), 4.26–4.20 (m, 2H), 4.77 (m, 1H), 7.47 (d, J=8.5 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 8.03 (d, J=8.5 Hz, 1H), 8.11 (dd, J_1=8.0 Hz, J_2=1.0 Hz, 1H), 8.21 (d, J=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 41.1, 61.5, 69.8, 123.8, 124.6, 124.9, 127.6, 132.2, 136.6, 138.4, 147.1, 161.6, 173.3; IR (neat): 3390, 3067, 1712, 1600, 1520, 1349, 1248, 1026, 842, 775, 660 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_5$ $[M+Na]^+$: 313.0800, found: 313.0798.

*4.2.15. Ethyl 2-hydroxy-3-(quinoxalin-2-yl)propanoate (**3o**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.27 (t, J=7.0 Hz, 3H), 3.57–3.42 (m, 2H), 4.29–4.23 (m, 2H), 4.77 (dd, J_1=7.0 Hz, J_2=4.0 Hz, 1H), 7.78–7.72 (m, 2H), 8.03–8.01 (m, 1H), 8.10–8.08 (m, 1H), 8.78 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 39.5, 61.7, 69.8, 128.7, 129.1, 129.4, 130.1, 141.4, 141.6, 146.1, 153.1, 173.5; IR (neat): 3244, 3054, 1727, 1495, 1279, 1095, 957, 864, 762 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3$ $[M+Na]^+$: 269.0902, found: 269.0897.

*4.2.16. Ethyl 2-hydroxy-3-(6-methylpyridin-2-yl)propanoate (**3p**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, J=7.0 Hz, 3H); 2.51 (s, 3H), 3.28–3.12 (m, 2H), 4.20 (q, J=7.0 Hz, 2H), 4.63 (dd, J_1=7.5 Hz, J_2=4.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 24.3, 40.1, 61.1, 70.7, 120.7, 121.4, 137.0, 157.4, 157.5, 173.6; IR (neat): 3078, 2982, 1730, 1600, 1459, 1198, 1040, 792, 583 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NNaO_3$ $[M+Na]^+$: 232.0949, found: 232.0943.

*4.2.17. Ethyl 2-hydroxy-3-(pyridin-2-yl)propanoate (**3q**).*[6f] ^1H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, J=7.0 Hz, 3H); 3.34–3.16 (m, 2H), 4.20 (q, J=7.0 Hz, 2H), 4.66–4.64 (m, 1H), 7.20–7.17 (m, 2H), 7.65–7.62 (m, 1H), 8.50 (d, J=5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 40.6, 61.3, 70.5, 121.9, 123.9, 136.8, 148.7, 158.0, 173.7; IR (neat): 3403, 2979, 1732, 1595, 1475, 1205, 1091, 764 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}NNaO_3$ $[M+Na]^+$: 218.0793, found: 218.0804.

*4.2.18. Ethyl 2-hydroxy-2-methyl-3-(quinolin-2-yl)propanoate (**3r**).* ^1H NMR (500 MHz, $CDCl_3$) δ: 1.10 (t, J=7.0 Hz, 3H); 1.58 (s, 3H), 3.27 (d, J=15.0 Hz, 1H), 3.56 (d, J=16.0 Hz, 1H), 4.09 (q, J=7.0 Hz, 2H), 7.27 (d, J=8.5 Hz, 1H), 7.53–7.49 (m, 1H), 7.71–7.67 (m, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.98 (d, J=8.5 Hz, 1H), 8.09 (d, J=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 26.4, 46.3, 61.1, 75.1, 122.2, 126.2, 126.8, 127.5, 128.6, 129.7, 136.7, 146.8, 159.1, 176.0; IR (neat): 3391, 2980, 1725, 1599, 1506, 1426, 1291, 1190, 1107, 1018, 823, 752 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_3$ $[M+Na]^+$: 282.1106, found: 282.1105.

*4.2.19. N-Benzyl-2-hydroxy-3-(quinolin-2-yl)propanamide (**3s**).* ^1H NMR (500 MHz, $CDCl_3$) δ: 3.39–3.43 (m, 1H), 3.54–3.58 (m, 1H), 4.31–4.35 (m, 1H), 4.52–4.57 (m, 1H), 4.69 (dd, J_1=7.5 Hz, J_2=4.0 Hz, 1H), 7.04–7.12 (m, 2H), 7.13–7.18 (m, 3H), 7.34 (d, J=8.5 Hz, 1H), 7.53–7.56 (m, 1H), 7.67–7.72 (m, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.4, 42.8, 71.6, 122.3, 126.4, 126.9, 127.2, 127.3, 127.6, 127.7, 128.3, 128.4, 128.7, 129.9, 137.2, 138.0, 146.5, 160.0, 173.0; IR (neat): 3300, 3060, 2816, 1651, 1599, 1505, 1310, 1074, 830, 691, 624 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_2$ $[M+Na]^+$: 329.1266, found: 329.1271.

*4.2.20. 3-Hydroxy-4-(quinolin-2-yl)butan-2-one (**3t**).* ^1H NMR (500 MHz, $CDCl_3$): δ2.39 (s, 3H), 3.38–3.34 (m, 1H), 3.49–3.45 (m, 1H), 4.61–4.58 (m, 1H), 7.32 (d, J=8.5 Hz, 1H), 7.54–7.51 (m, 1H), 7.70 (t, J=7.5 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.98 (d, J=8.5 Hz, 1H), 8.10 (d, J=8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.3, 40.1, 76.8, 122.1, 126.2, 126.9, 127.6, 128.5, 129.7, 136.8, 147.0, 158.9, 211.1; IR (neat): 3064, 2933, 1702, 1599, 1506, 1427, 1359, 1309, 1069, 834, 750, 625 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{13}NNaO_2$ $[M+Na]^+$: 238.0844, found: 238.0849.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.069.

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