Highly Improved Copper-Mediated Michael Addition of Ethyl Bromodifluoroacetate in the Presence of Protic Additive

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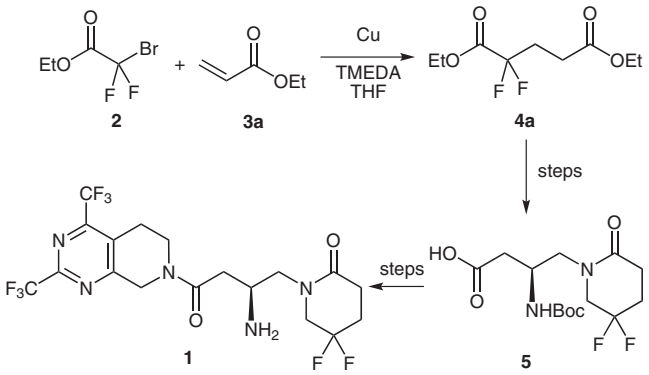
Abstract: Copper-mediated Michael addition of ethyl bromodifluoroacetate to Michael acceptors is accompanied by the formation of a substantial amount of byproducts. Elucidation of their structure hinted the cause of their formation, from which we discovered a highly improved and robust protocol by treatment with protic additives such as H_2O and AcOH. This modification led to significant increase of yield with concomitant decreased use of reagent.

Key words: copper, coupling, fluorine, Michael addition, protonation

Although organofluorine compounds are rarely found in nature,[1] the frequency of incorporation of fluorine into pharmaceuticals is increasing at an explosive rate.[2] As the most electronegative element, the inclusion of fluorine into a molecule commonly alters its metabolic stability, the basicity of basic groups when embedded within proximity, and occasionally its affinity toward a target protein.[3] It also induces delicate modifications in conformational behavior,[4] which can result in dramatic changes in physicochemical properties. Among various fluorine functional groups, a difluoromethylene (CF_2) unit is frequently incorporated into many biologically important compounds.[5] In particular, difluorinated piperidines have been embedded as an interesting pharmacophore fragment in the design of anticancer,[6] antiobesity,[7] and anticonvulsant agents.[8] The difluoro groups of difluoropiperidines are introduced via the deoxofluorination of the carbonyl group of piperidinone using (diethylamino)sulfur trifluoride (DAST)[9] or [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxofluor),[10] or morpholinesulfur trifluoride (Morph-DAST).[11] However, DAST and its derivatives are not a viable reagent in a large-scale production in terms of safety and cost.[12] As an alternative, CF_2 unit of ethyl bromodifluoroacetate (**2**) is incorporated as a difluoromethylene unit of piperidine derivatives. Beeler et al.[13] reported the synthesis of 4-hydroxy-4-phenyl-3,3-difluoropiperidine via SmI_2-mediated Reformatsky reaction and De Kimpe et al.[14] prepared 3,3-difluorolactam via Michael addition of **2** to acrylonitrile.

In the course of process development of Gemigliptin (**1**, Scheme 1),[15] which is a potent inhibitor of dipeptidyl peptidase-IV (DPP-IV) undergoing phase 3 clinical trials, we needed an efficient methodology for the preparation of the 5,5-difluoropiperidone subunit. At the discovery stage of preparation, DAST was used for the introduction of the CF_2 group from *N*-Boc 3-piperidone.[15] Because the protocol could not be applied to a large-scale preparation, our attention was turned to the copper-mediated Michael addition of **2** to ethyl acrylate (**3a**) developed by Kumadaki et al. for the introduction of the CF_2 group in **5**.[16] Although it is an improved version advantaged by ligand acceleration, its yield of ca. 50% was not satisfactory for a large-scale application. Herein, we describe a dramatically improved copper-mediated Michael addition of **2** to various Michael acceptors by selective quenching of the copper intermediates formed in the reaction using various protic sources.



Scheme 1 Synthesis of Gemigliptin (**1**)

When the Michael addition of ethyl bromodifluoroacetate (**2**) to ethyl acrylate (**3a**) was first conducted under the improved Kumadaki protocol using a bidentate ligand tetramethylethylenediamine (TMEDA), the 1,4-adduct **4a** was obtained in low yield (45–55%). To improve the yield, the effect of particle size of copper and ligand was initially tested. Copper of various particle sizes from granule (40 mesh) to dust (10 μm) was investigated. Smaller size (dust) showed very marginal rate acceleration compared to the bigger one and its variation did not show any significant influence on the yield and impurity profile. Next, diverse chelating ligands and the typical monoamine Et_3N were examined[17] in addition to TMEDA, but the reaction led to comparable or worse results in terms of yield and impurity profile.

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In the course of the investigation of copper source and ligand effect on this reaction, we recognized that there are always a number of unidentified side products in the reaction mixture. To pinpoint the root cause of their formation, the structures of side products were elucidated carefully by spectroscopic analysis (Figure 1).

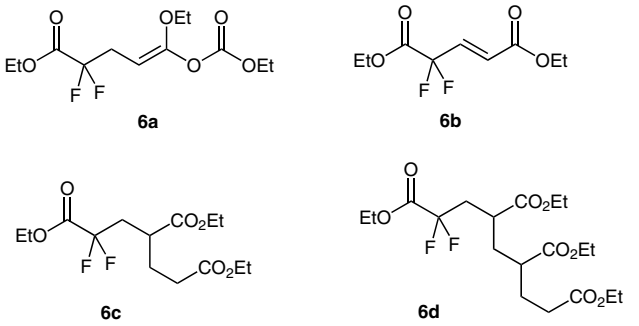


Figure 1 Structure of side products in copper-mediated Michael addition

Major side product **6a** (~15%) should have been formed from the reaction of the intermediates **B2** with **2** via haloform-type reaction, and the minor side products **6c** (<5%) and **6d** (<5%) obviously were derived from the further Michael addition of **B1** with acrylate **3a** (Scheme 2).

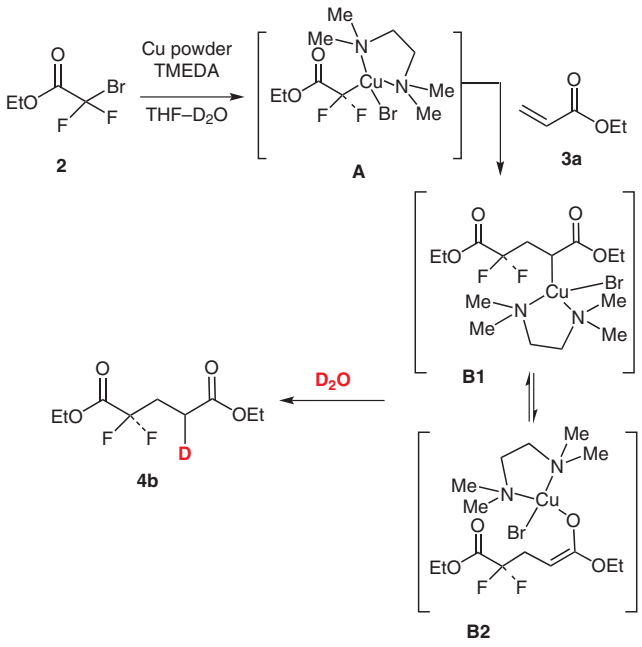
At this point, it was presumed that if we could selectively protonate **B1** or **B2** over **A**, the formation of side products could be minimized. Accordingly, a selective quench of the intermediate using stoichiometric amount of TMSCl was first attempted,[18] which resulted in a disappointing yield of <10%. After this attempt, we did not find for a while a suitable candidate for a selective quencher of **B1** or **B2** over **A**. However, an interesting observation serendipitously gave us a clue for this problem: aged copper powder of the same brand led to consistently a better result than freshly opened one by ca. 10–15% in the yield. Initially, the effect of copper oxide by air oxidation was checked, but it did not have any influence on the reaction. We envisaged that the different yield might be derived from water content in two different copper samples. If the water can quench the **B1** or **B2** species selectively over the intermediate **A**, our mission could be accomplished: we speculated that two difluoro atoms of the intermediate **A** would induce significant reactivity difference from the intermediate **B1** where only one hydrogen is attached to carbon bearing copper metal.

To our delight, addition of water in the reaction mixture resulted in dramatic influence on the yield: use of 0.45–0.6 equivalent of water led to ca. 20% yield increase consistently (Table 1, entries 3 and 4).

Table 1 Effect of Amount of H_2O as an Additive on Michael Addition[a]

Entry	H_2O (equiv)	Starting **3a** (%)	**4a** (%)
1	0.00	15	48
2	0.30	13	61
3	0.45	16	70
4	0.60	19	69
5	1.20	44	52

[a] The reaction was carried out at r.t. and the conditions were as follows: **2** (1.2 equiv), TMEDA (1.1 equiv), **3a** (10 mmol, 1.0 equiv), and Cu (2.1 equiv) in THF (10 mL). The composition of starting **3a** and product **4a** was analyzed by ^{1}H NMR using 9-fluorenone as an internal standard.



Scheme 2 Proposed mechanism for copper-mediated Michael addition

However, the use of water (1.2 equiv) decreased the product yield due to quenching the difluoroacetate copper complex **A**, which is evidenced by the formation of ca. 10% of ethyl difluoroacetate in the reaction mixture from ^{1}H NMR analysis (entry 5). To further justify the proposed assumption, labeling experiment using D_2O (0.6 equiv) was performed. As expected, ca. 60% deuterated adduct **4b** was obtained in comparable 65% yield compared to that of H_2O addition (69%, Table 1, entry 4), which unambiguously support our assumption of selective quenching of intermediate **B1** or **B2** over **A** by water.

On the basis of these results, the reaction parameters were fine-tuned: reaction temperature, equivalents of **2**, TMEDA, and H_2O (Table 2). There was no significant reaction profile difference as the reaction temperature was raised to 50 °C. Only slight faster conversion was observed (Table 2, entries 1 and 2). At 50 °C, addition of water is critical for obtaining a good yield (entries 3–7): 1.2 equivalents of **2** and 0.6 equivalent of water are optimal amounts (entry 5). Excess **2** (1.6 and 1.8 equiv) in the presence of 0.9 equivalent of H_2O provided the desired **4a** in good (86%) to excellent (>97%) yield, respectively (entries 9, 10). Further increase of H_2O (1.2 equiv) slightly

reduced the yield (80%, entry 11). TMEDA amount could be reduced to 0.5 equivalent without any detrimental effect (entries 10 and 12). However, catalytic amount of TMEDA (10 mol%) resulted in sluggish reaction and low yield (12%, entry 14). At least 2.0 equivalents of copper should be employed for complete conversion: 1.0 equivalent of copper did not complete the reaction after prolonged reaction time to give 55% of **4a** along with 37% of the starting acrylate **3a** (entry 17).

Table 2 Optimization of Copper-Mediated Michael Addition of **2** to Ethyl Acrylate[a]

Entry	H_2O (equiv)	**2** (equiv)	TMEDA (equiv)	Temp (°C)	**4a** (%)[b]
1	0.00	1.2	1.1	r.t.	48
2	0.00	1.2	1.1	50	45
3	0.30	1.2	1.1	50	61
4	0.50	1.2	1.1	50	77
5	0.60	1.2	1.1	50	79
6	0.70	1.2	1.1	50	71
7	0.90	1.2	1.1	50	69
8	0.90	1.2	1.1	reflux	72
9	0.90	1.6	1.1	50	86
10	0.90	1.8	1.1	50	>97
11	1.20	1.8	1.1	50	80
12	0.90	1.8	0.5	50	96
13	0.90	1.8	0.3	50	60
14	0.90	1.8	0.1	50	12
15[c]	0.90	1.8	0.5	50	95
16[d]	0.90	1.8	0.5	50	67
17[e]	0.90	1.8	0.5	50	55

[a] TMEDA (1.1 equiv), **3a** (10 mmol, 1.0 equiv), and Cu (2.1 equiv) were used in THF (10 mL).
[b] Isolated yield.
[c] Amount of Cu used: 3.0 equiv.
[d] Amount of Cu used: 1.5 equiv.
[e] Amount of Cu used: 1.0 equiv.

Next, our attention was turned to the investigation on other protic additives having various pK_a values in copper-mediated Michael addition (Table 3). Several alcohol additives revealed inferior results than that of H_2O (Table 3, entries 2–5) under an optimized condition. Noteworthy is the rate acceleration by AcOH, which completed the reaction within a half-hour – in water it took two hours (entry 6 vs. entry 1). Interestingly, treatment of ammonium acetate salt (0.5 equiv of TMEDA and 0.9 equiv of AcOH) also led to **4a** in comparable yield (>96%, entry 7).

Table 3 Effect of Various Protic Additives on Michael Addition[a]

Entry	Additive	pK_a[b] (DMSO)	Time (h)	Yield (%)[c]
1	H_2O	15.7 (32)	2.0	96
2	MeOH	15.5 (27.9)	1.5	68
3	EtOH	15.9 (29.8)	1.5	73
4	*i*-PrOH	16.5 (30.3)	1.5	68
5	*s*-BuOH	17.0 (32.2)	1.5	68
6	AcOH	4.8 (12.6)	0.5	97
7[d]	AcOH	4.8 (12.6)	0.5	97

[a] Reaction conditions: **2** (1.8 equiv), **3a** (10 mmol, 1.0 equiv), TMEDA (0.5 equiv), Cu (2.1 equiv), and additive (0.9 equiv) in THF (10 mL) at 50 °C.
[b] In H_2O.
[c] Isolated yield.
[d] To a stirred mixture of **2**, **3a**, and Cu in THF was added a solution of TMEDA (0.5 equiv) and AcOH (0.9 equiv) under the same condition. The salt formation was confirmed by obvious downfield shift of protons around nitrogen in the ^{1}H NMR spectrum.

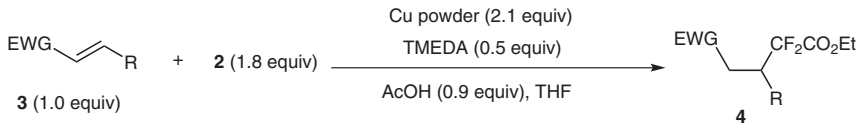
With optimized conditions determined, the substrate scope[19] was examined and a head-to-head comparison with the data reported by Kumadaki et al. is outlined in Table 4.[16]

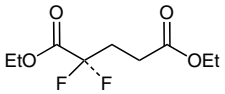
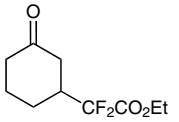
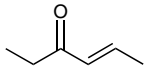
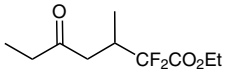
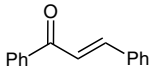
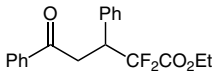
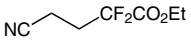
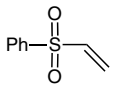
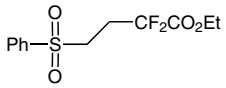
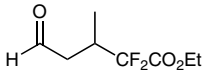
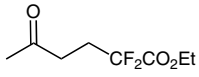
All the substrates tested showed significantly better results to the reported ones.[14,16] Moreover, the optimized conditions generally required less amounts of reagents and reactants: 1.8 equivalents versus 3.0 equivalents of **2**, 2.1 equivalents versus 6.6 equivalents of copper, and 0.5 equivalent versus 0.9 equivalent of TMEDA.

Conversion of cyclohexenone (**3b**), in sharp contrast to other Michael acceptors, required relatively harsh reaction conditions: 5.0 equivalents of copper at reflux (Table 4, entry 2) and interestingly, when H_2O was used as an additive, only 15% of **4b** was obtained compared to 97% using AcOH. Sterically hindered crotonaldehyde (**3g**) and ketone **3c** also required reflux conditions with 5–6 equivalents of copper (entries 3 and 7). Michael acceptor **3f** bearing sulfone group reacted much slower rate (3 h vs 0.5 h of acrylate) to give **4f** in 85% yield (entry 6). Some limitation was also observed: conjugated Michael acceptor **3d** yielded the desired **4d** in low yield (35%) with a number of byproducts (entry 4).

In summary, we have discovered proton additives as a selective quencher of intermediate **B1** or **B2** over **A** in the copper-mediated Michael addition of **2** to **3a**. This protocol dramatically improved the yield with concomitant significant reduction of the amount of reagents. It is highly practical, reproducible, applicable to broad substrates, and excellent in yield. Further investigations on the more detailed aspect of rate acceleration by acetic acid and pK_a value effect with various substrates are under progress and will be published in due course.

Table 4 Scope of Copper-Mediated Michael Addition Using AcOH as an Additive of **2** toward Michael Acceptors **3**



Entry	Michael acceptor **3**	Time (h)	Temp (°C)	Product **4**	Yield (%)[a]	Yield (%) reported by Kumadaki et al.[b]
1	ethyl acrylate (**3a**)	15 0.5	r.t. 50	 (**4a**)	93 97	not reported 45[c]
2[d]	cyclohex-2-enone (**3b**)	8	reflux	 (**4b**)	97	73
3	 (**3c**)	1	reflux	 (**4c**)	92[e]	68
4	 (**3d**)	1	reflux	 (**4d**)	35	23
5	acrylonitrile (**3e**)	1	r.t.	 (**4e**)	91	40
6	 (**3f**)	3	50	 (**4f**)	85	73
7	crotonaldehyde (**3g**)	1	reflux	 (**4g**)	58	23
8	methyl vinyl ketone (**3h**)	1	r.t.	 (**4h**)	90	62

[a] Isolated yield.
[b] Kumadaki's protocol: Michael acceptor (5.0 mmol, 1.0 equiv), **2** (3.0 equiv), Cu powder (6.6 equiv), and TMEDA (0.9 equiv) in THF (6 mL) at reflux.
[c] According to Kumadaki's protocol, **4a** was obtained in 45% yield.
[d] Amount of Cu used: 5.0 equiv.
[e] Amount of Cu used: 6 equiv.

All reactions were performed under a nitrogen atmosphere. All commercially available reagents and solvents were used without further purification unless otherwise noted. Column chromatography was performed with silica gel (0.040–0.0063 mm, Merck). NMR spectra were recorded on Bruker 400 MHz and Jeol 500 MHz spectrometers. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Coupling constants (*J* values) are reported in hertz. MS experiments were performed on an Agilent 5973 GC/MS and 6460 Triple Quad LC/MS system.

1,4-Conjugated Michael Addition Reaction; Diethyl 2,2-Difluoropentanedioate (4a); Typical Procedure

To a stirred mixture of Cu powder (665 mg, 10.48 mmol), ethyl acrylate (**3a**; 500 mg, 4.99 mmol), and ethyl bromodifluoroacetate (**2**; 1.83 g, 8.98 mmol) in THF (5.8 mL) was added at 50 °C TMEDA (290 mg, 2.50 mmol) and AcOH (270 mg, 4.49 mmol) in sequence. The reaction mixture was stirred for 0.5 h at 50–55 °C and cooled to 25 °C. Aq 10% NH_4Cl (5.8 mL) and MTBE (8.7 mL) were added. After stirring for 30 min, the organic phase was separated and fil-

tered on a pad of Celite to remove the insoluble materials. The filtrate was washed with aq 10% NH_4Cl (5.8 mL) and concentrated under reduced pressure to give crude **4a** as a light yellow oil (1.19 g) in 96% yield with >98% purity by ^1H NMR analysis using 9-fluorenone as an internal standard. No column chromatography was carried out.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (q, *J* = 7.2 Hz, 2 H), 4.15 (q , *J* = 7.2 Hz, 2 H), 2.52 (m, 2 H), 2.41 (m, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 163.9 (t, *J* = 40.0 Hz), 115.7 (t, *J* = 251.6 Hz), 64.8, 63.1, 61.0, 30.0 (t, *J* = 20.1 Hz), 26.7, 13.9 (t, *J* = 20.1 Hz).

GC/MS (EI): *m*/*z* = 224 [M^+].

Ethyl 2,2-Difluoro-2-(3-oxocyclohexyl)acetate (4b)
Yield: 1.07 g (97%); pale yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.35 (q, *J* = 7.0 Hz, 2 H), 2.70–1.66 (m, 9 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 163.6 (t, *J* = 32.4 Hz), 116.1 (t, *J* = 252.6 Hz), 63.1, 42.5 (t, *J* = 23.4 Hz), 40.9, 39.7 (t, *J* = 3.6 Hz), 24.0, 23.4 (t, *J* = 4.2 Hz), 14.0.

GC/MS (EI): *m*/*z* = 220 [M^+].

Ethyl 2,2-Difluoro-3-methyl-5-oxoheptanoate (4c)
Yield: 1.02 g (92%); pale yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.32 (q, *J* = 7.0 Hz, 2 H), 2.97–2.84 (m, 1 H), 2.77 (dd, *J* = 17.7, 4.0 Hz, 1 H), 2.48–2.38 (m, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 1.07 (t, *J* = 7.3 Hz, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6, 164.2 (t, *J* = 30.2 Hz), 117.5 (t, *J* = 251.6 Hz), 63.2, 41.8, 36.7, 33.9 (t, *J* = 22.1 Hz), 14.2, 13.3 (t, *J* = 4.5 Hz), 7.9.

GC/MS (EI): *m*/*z* = 222 [M^+].

Ethyl 2,2-Difluoro-5-oxo-3,5-diphenylhexanoate (4d)
Yield: 0.59 g (35%); white solid; mp 65–66 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.92 (m, 2 H), 7.57–7.53 (m, 1 H), 7.46–7.43 (m, 2 H), 7.37–7.35 (m, 2 H), 7.29–7.23 (m, 3 H), 4.36–4.24 (m, 1 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 3.67 (s, 1 H), 3.65 (d *J* = 2.4 Hz, 1 H), 1.14 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 163.9 (t, *J* = 30.2 Hz), 136.9, 135.6, 135.5, 134.3, 133.9, 130.1, 129.1, 128.9, 117.0 (t, *J* = 256.6 Hz), 63.3, 45.6 (t, *J* = 20.1 Hz), 37.9, 14.1.

LC/MS (ESI): *m*/*z* = 333 [M + H^+].

Ethyl 4-Cyano-2,2-difluorobutanoate (4e)
Yield: 0.81 g (91%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.37 (q, *J* = 7.0 Hz, 2 H), 2.63 (m, 2 H), 2.48 (m, 2 H), 1.38 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2 (t, *J* = 35.2 Hz), 118.1, 114.6 (t, *J* = 50.3 Hz), 63.4, 30.8 (t, *J* = 25.2 Hz), 14.1, 10.6 (t, *J* = 7.0 Hz).

GC/MS (EI) *m*/*z* = 177 [M^+].

Ethyl 2,2-Difluoro-4-(benzenesulfonyl)butanoate (4f)
Yield: 1.24 g (85%); viscous oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.96 (m, 2 H), 7.82–7.78 (m, 1 H), 7.72–7.65 (m, 2 H), 4.27 (q, *J* = 7.0 Hz, 2 H), 3.57–3.48 (m, 2 H), 2.50–2.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (t, *J* = 30.2 Hz), 138.7, 134.7, 130.0, 128.4, 114.7 (t, *J* = 251.6 Hz), 63.9, 49.3 (t, *J* = 10.1 Hz), 28.6 (t, *J* = 251.6 Hz), 14.2.

GC/MS (EI): *m*/*z* = 219 [$M^+ - CO_2Et$].

Ethyl 2,2-Difluoro-3-methyl-5-oxopentanoate (4g)
Yield: 0.56 g (58%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.01–2.88 (m, 1 H), 2.84 (dd, *J* = 18.1, 4.0 Hz, 1 H), 2.46 (ddd, *J* = 18.1, 8.9, 1.6 Hz, 1 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.08 (d, *J* = 4.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 163.9 (t, *J* = 33.0 Hz), 117.2 (t, *J* = 251.6 Hz), 63.2, 43.6 (t, *J* = 3.4 Hz), 32.6 (t, *J* = 21.8 Hz), 15.4, 14.1 (t, *J* = 4.4 Hz).

GC/MS (EI): *m*/*z* = 194 [M^+].

Ethyl 2,2-Difluoro-5-oxohexanoate (4h)
Yield: 0.88 g (90%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.32 (q, *J* = 7.0 Hz, 2 H), 2.69 (t, *J* = 7.9 Hz, 2 H), 2.43–2.31 (m, 2 H), 2.19 (s, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.1, 164.3 (t, *J* = 35.0 Hz), 116.0 (t, *J* = 251.6 Hz), 63.3, 35.7 (t, *J* = 10.1 Hz), 30.1, 28.8 (t, *J* = 20.1 Hz), 14.2.

GC/MS (EI): *m*/*z* = 194 [M^+].

Major Byproduct 6a
Yield: 0.222 g (15%); oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (q, *J* = 7.1 Hz, 2 H), 4.15 (dq, *J* = 7.2, 2.0 Hz, 4 H), 3.69 9 (t, *J* = 6.4 Hz, 1 H), 2.78 (dt, *J* = 16.8, 6.4 Hz, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 163.1 (t, *J* = 32.1 Hz), 114.6 (t, *J* = 249.8 Hz), 63.0, 61.8, 45.5, 33.2 (t, *J* = 23.8 Hz), 13.6, 13.5.

GC/MS (EI): *m*/*z* = 296 [M^+].

HRMS (EI): *m*/*z* [$M]^+$ calcd for $C_{12}H_{18}F_2O_6$: 206.1072; found: 205.1066.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are spectroscopic data (^1H and ^{13}C NMR spectra of the Michael adducts, **4a**–**h**, and byproduct **6a**).

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(17) The ligands shown in Figure 2 were examined. In the case of Et_3N, no desired adduct of **3a** was obtained.

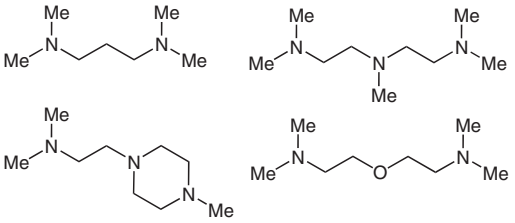

Figure 2 Ligands examined

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(19) Ethyl bromoacetate and ethyl bromofluoroacetate as Michael donors were subjected to the optimized Michael addition to provide no desired product and ca. 15% adduct, respectively.

