Expeditious Functionalization of Quinolines in Positions 2 and 8 via Polyfunctional Aryl- and Heteroarylmagnesium Intermediates

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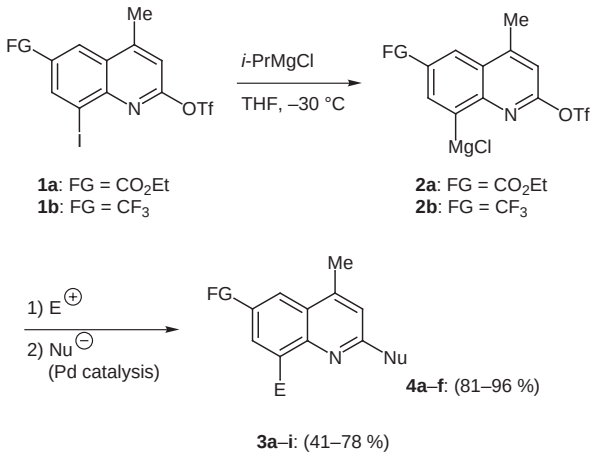
Abstract: An efficient way to prepare functionalized 8-iodo-2-trifluoromethanesulfonyloxyquinolines is presented. The iodo functionality could be selectively converted into other residues via an iodine–magnesium exchange reaction. In addition, the trifluoromethanesulfonate functionality was used as a leaving group in Negishi cross-coupling reactions.

Key words: functionalized organomagnesium reagents, iodine–magnesium exchange, functionalized heterocycles, cross-coupling, palladium catalysis

The preparation of functionalized heterocycles is an important synthetic goal since many of these molecules have unique biological and pharmaceutical properties.[1] Recently, we have shown that a range of polyfunctional aryl- and heteroarylmagnesium compounds can be readily prepared via an iodine– or bromine–magnesium exchange reaction.[2] Herein, we wish to report an efficient functionalization of iodoquinoline triflates of type **1** via the reactive quinolylmagnesium intermediates of type **2** obtained via an iodine–magnesium exchange reaction.[3] The successive reaction of the organometallics **2a**,**b** with an electrophile (E^+) and then with a nucleophile (Nu^-) provides a range of new quinolines of type **3** and **4** selectively functionalized in positions 8 and 2 (Scheme 1).



Scheme 1 Preparation of polyfunctional quinolines via the functionalized quinolylmagnesium species **2a**,**b**

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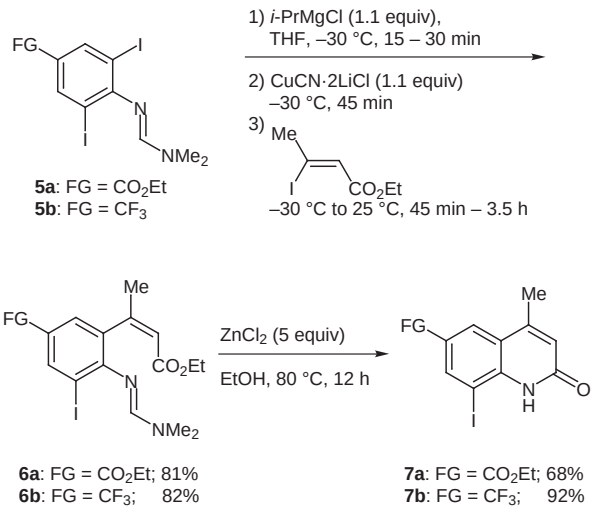
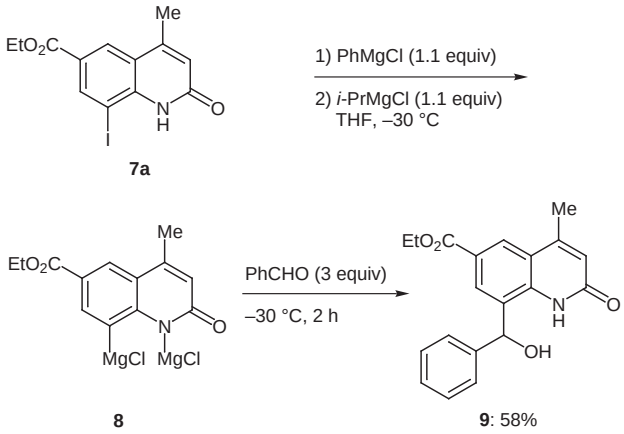
The conversion of **5a**,**b**, which were prepared according to literature procedures,[4] into the functionalized magnesium reagents is readily achieved by reaction with *i*-PrMgCl (–30 °C, 15–30 min), whereby only the monomagnesium reagent was formed.[5] After a transmetalation with the THF soluble copper salt CuCN·2LiCl,[6] the resulting functionalized arylcopper species undergoes an addition-elimination reaction with ethyl (*Z*)-3-iodobut-2-enoate,[7] providing the unsaturated esters **6a**,**b** in 81–82% yield.[8,9] These esters undergo a cyclization reaction to the heterocycles **7a**,**b** when heated in ethanol with $ZnCl_2$ at reflux for 12 hours (Scheme 2).



Scheme 2 Preparation of the starting heterocyles **7a**,**b**

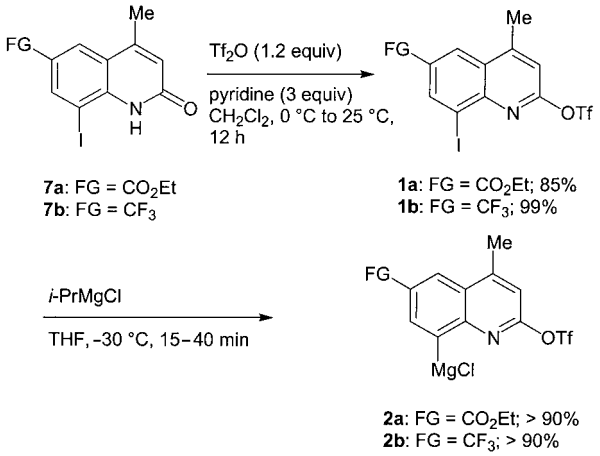
Preliminary results indicate that **7a** can be converted into the corresponding dimagnesium species **8** by successive treatment with PhMgCl (1.1 equiv) and *i*-PrMgCl (1.1 equiv) in THF at –30 °C. PhMgCl was chosen for the deprotonation of the amide functionalitiy of **7a**. This reagent is not reactive enough to perform the iodine–magnesium exchange, which is carried out by the subsequent addition of *i*-PrMgCl (1.1 equiv). The resulting dimagnesium compound **8** reacts with benzaldehyde, affording the expected benzhydryl alcohol **9** in 58% yield (Scheme 3).

In order to avoid the preparation of a bimetallic species and to allow further functionalization in position 2, we have prepared the iodoquinolinyl triflates **1a**,**b** by reacting **7a**,**b** with triflic anhydride (1.2 equiv) and pyridine (3 equiv) in CH_2Cl_2 (0 to 25 °C, 12 h). The reactions of **1a**,**b**



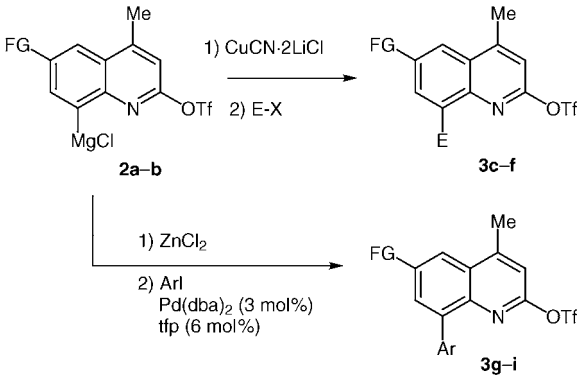
Scheme 3 Generation and reaction of dimagnesium intermediate **8**

with *i*-PrMgCl (1.1 equiv) in THF at –30 °C for 15–40 minutes lead in almost quantitative yield to the desired Grignard reagents **2a**,**b** (Scheme 4).



Scheme 4 Preparation of the polyfunctional quinolylmagnesium compounds **2a**,**b**

Thus, the ester-substituted Grignard reagent **2a** reacts directly with aldehydes such as anisaldehyde, furnishing in this case the corresponding alcohol **3a** in 52% yield (Table 1, entry 1). The bromination of **2a** with $(CCl_2Br)_2$ leads to the 8-bromoquinoline derivative **3b** in 78% yield (entry 2). After transmetalation with CuCN·2LiCl,[6] allylation with allyl bromide proceed smoothly affording the functionalized quinolines **3c** and **3d** in 77% and 70% yield, respectively (entries 3 and 4). The addition of *t*-butyl propiolate leads to the *E*-unsaturated ester **3e** in 41% yield (entry 5), whereas the addition of propargyl bromide to **2a** leads to the S_N2 substitution product **3f** accompanied by small amounts of the isomeric allene in 70% overall yield (entry 6). Palladium(0)-catalyzed cross-coupling reactions of the zinc reagents corresponding to **2a**,**b** (Negishi cross-coupling)[10] with various aromatic and heterocyclic iodides furnishes the expected cross-coupling products **3g–i** in 48–74% yield (entries 7–9) (Scheme 5).



Scheme 5 Reaction of the Grignard reagents **2a**,**b** with electrophiles after transmetalation reactions

The products **3a–i** bear a triflate group in position 2 which can participate in a further Negishi cross-coupling reaction. Thus, the three triflates **3c**, **3d** and **3h** react with various organozinc reagents in the presence of $Pd(dba)_2$ (3 mol%), *tris*-*o*-furylphosphine (tfp, 6 mol%) at 25 °C in 1.5–4 hours, leading to the expected polyfunctional quinoline derivatives **4a–f** in 81–96% yield (Table 2 and Scheme 1).

Table 1 Products of Type **3** Obtained by the Reaction of **2a**,**b** with Electrophiles Directly or after Transmetalation with CuCN·2LiCl,[6] $ZnCl_2$, or $ZnBr_2$

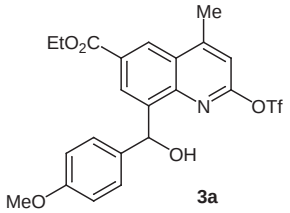
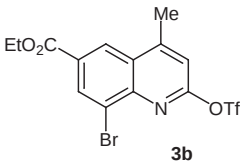
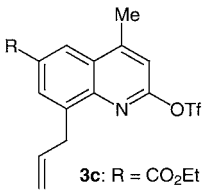
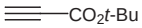
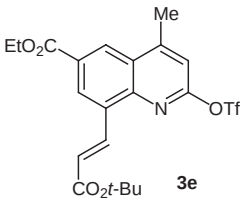
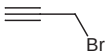
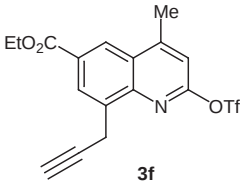
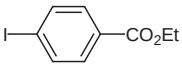
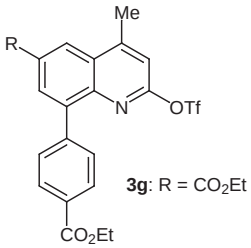
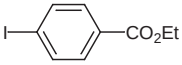
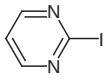
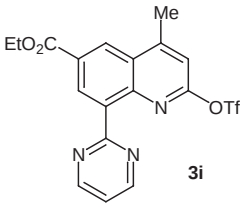
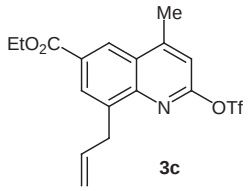
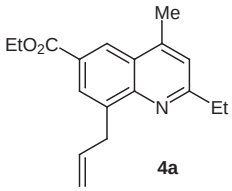
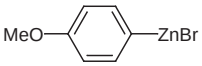
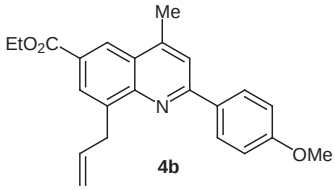
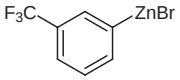
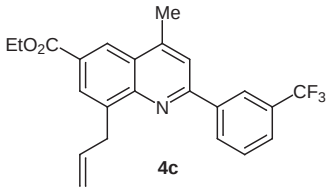
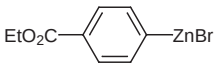
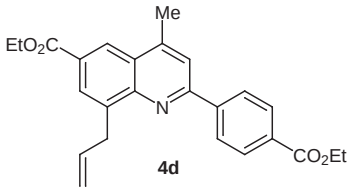
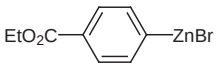
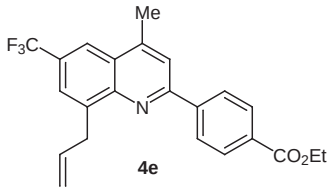
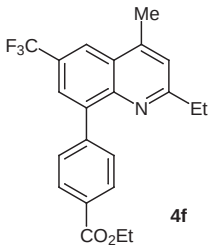
Entry	Grignard Reagent	Electrophile	Product of Type **3**	Yield (%)[a]
1	**2a**	*p*-$MeOC_6H_4CHO$	 **3a**	52

Table 1 Products of Type **3** Obtained by the Reaction of **2a**,**b** with Electrophiles Directly or after Transmetalation with CuCN·2LiCl,[6] $ZnCl_2$, or $ZnBr_2$ (continued)

Entry	Grignard Reagent	Electrophile	Product of Type **3**	Yield (%)[a]
2	**2a**	$(CCl_2Br)_2$	 **3b**	78
3	**2a**	allyl bromide	 **3c**: R = CO_2Et	77[b]
4	**2b**	allyl bromide	**3d**: R = CF_3	70[b]
5	**2a**		 **3e**	41[b]
6	**2a**		 **3f**	70[b,c]
7	**2a**		 **3g**: R = CO_2Et	74[d]
8	**2a**		**3h**: R = CF_3	63[d]
9	**2b**		 **3i**	48[d]

[a] Isolated yields of analytically pure products.
[b] The Grignard reagent was treated with CuCN·2LiCl (1.1 equiv) prior to the addition of the electrophile.
[c] This product contains approximately 10% of the corresponding allene (see experimental section).
[d] The Grignard reagent was treated with $ZnCl_2$ (1.0 equiv) prior to the addition of the electrophile.

Table 2 Polyfunctional Quinolines **4a–f** Obtained by Pd(0)-Catalyzed Cross-Coupling of Quinolinyl Triflates with Various Organozinc Reagents

Entry	Quinolyl Triflate	Organozinc Reagent	Product of Type **4**	Yield (%)[a]
1	 **3c**	Et_2Zn	 **4a**	82
2	**3c**		 **4b**	96
3	**3c**		 **4c**	81
4	**3c**		 **4d**	92
5	**3d**		 **4e**	89
6	**3h**	Et_2Zn	 **4f**	84

[a] Isolated yields of analytically pure products.

In summary, we have shown that functionalized amino-substituted arylmagnesium reagents can be efficiently used to prepare 8-iodo-2-trifluoromethanesulfonyloxy-quinolines which can be selectively functionalized in position 2 and 8 by the use of intermediate quinolylmagnesium species.

Melting points were measured on a Büchi B 540 apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin-Elmer 1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker ARX 300 spectrometer in $CDCl_3$ or pyridine-d_5 and referenced to the solvent signal. Low resolution mass spectra were recorded on a HP 6890/MSD 5973 spectrometer fitted with a HP-5 column (30 m × 0.25 mm × 0.25 μm). High resolution mass spectra were run on a Varian MAT 711 spectrometer at an ionizing potential of 70 eV. Microanalyses were performed using a Heraeus CHN-Rapid-Elementaranalysator. Flash chromatography was accomplished using Merck Kieselgel 60 (230–400 mesh ASTM).

Commercially available compounds were used without further purification. All reactions were carried out in anhydrous solvents under argon. All organometallic compounds and salts were used as solutions in THF, if not stated otherwise.

Ethyl 8-Iodo-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (1a)

To a mixture of **7a** (6.76 g, 19.0 mmol) and anhyd pyridine (15 mL) in CH_2Cl_2 (50 mL) was added Tf_2O (22.8 mmol, 3.8 mL) dropwise at 0 °C. The reaction mixture was stirred for 12 h and allowed to warm to r.t. After complete conversion, determined by TLC analysis, the mixture was poured into aq sat. $NaHCO_3$ solution (100 mL) and extracted with Et_2O (4 × 300 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The product **1a** (7.31 g, 79%) precipitated as light brown solid, which was filtered, and washed with a small amount of Et_2O. The filtrate was purified by flash chromatography (pentane–EtOAc, 67:33) to yield a further amount of **1a** (577 mg, 6%; total yield: 7.89 g, 85%); mp 176 °C.

IR (KBr): 3436 (m), 1714 (m), 1420 (m), 1276 (m), 1231 (m), 1128 (w), 979 (w), 862 (w), 831 (w), 765 (w), 607 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.94 (d, 1 H, *J* = 1.8 Hz, ArH-7), 8.74 (d, 1 H, *J* = 1.8 Hz, ArH-5), 7.18–7.16 (m, 1 H, ArH-3), 4.48 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.85 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.47 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 155.4, 154.0, 147.6, 141.1, 130.1, 127.2, 127.0, 120.8, 115.0, 101.9, 62.0, 19.3, 14.3.

MS (EI): *m*/*z* (%) = 489 (M^+, 100), 461 (10), 444 (29), 380 (12), 328 (23), 300 (12), 173 (15), 129 (14), 128 (18), 69 (11).

HRMS: *m*/*z* calcd for $C_{14}H_{11}F_3INO_5S$: 488.9355; found: 488.9388.

Anal. Calcd for $C_{14}H_{11}F_3INO_5S$ (489.21): C, 34.37; H, 2.27; N, 2.86. Found: C, 34.55; H, 2.22; N, 2.89.

8-Iodo-4-methyl-6-(trifluoromethyl)-2-quinolinyl Trifluoromethanesulfonate (1b)

To a mixture of **7b** (662 mg, 1.88 mmol) and anhyd pyridine (437 mg, 5.50 mmol) in CH_2Cl_2 (5 mL) was added Tf_2O (2.21 mmol, 0.37 mL) dropwise at 0 °C. The reaction mixture was stirred for 13 h and allowed to warm to r.t. After complete conversion, determined by GC, the mixture was poured into aq sat. $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The product **1b** (910 mg, 99%) was obtained as pale yellow solid; mp 112 °C.

IR (KBr): 3436 (w), 1601 (w), 1460 (w), 1424 (m), 1393 (m), 1293 (s), 1218 (s), 1129 (s), 1091 (m), 981 (m), 889 (m), 857 (m), 796 (m), 765 (w), 656 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, 1 H, *J* = 1.8 Hz, ArH-7), 8.32–8.29 (m, 1 H, ArH-5), 7.23–7.21 (m, 1 H, ArH-3), 2.84 (d, 3 H, *J* = 0.9 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 153.5, 147.0, 137.3 (q, J_{CF} = 2.9 Hz), 130.2 (q, J_{CF} = 33.5 Hz), 127.0, 122.2 (q, J_{CF} = 4.1 Hz), 120.9 (q, J_{CF} = 5.3 Hz), 116.6, 115.6, 103.1, 19.2.

MS (EI): *m*/*z* (%) = 485 (M^+, 100), 421 (20), 324 (26), 294 (12), 266 (10), 225 (12), 198 (11), 197 (93), 196 (12), 176 (10), 170 (10), 169 (15), 147 (11), 69 (21).

HRMS: *m*/*z* calcd for $C_{12}H_6F_6INO_3S$: 484.9017; found: 484.9002.

Ethyl 8-[Hydroxy(4-methoxyphenyl)methyl]-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3a); Typical Procedure

To a mixture of **1a** (342 mg, 0.70 mmol) and tetradecane (3 drops, internal standard) in THF (1 mL) at –30 °C was added *i*-PrMgCl (0.94 M, 0.82 mL, 0.77 mmol). After the exchange was complete (15 min, determined by GC), anisaldehyde (143 mg, 1.05 mmol) was then added and the reaction mixture was stirred for 1.5 h, after which time TLC analysis indicated complete conversion. The reaction was quenched with aq sat. NH_4Cl solution, poured into aq NH_4Cl solution and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$) and purified by flash chromatography (pentane–EtOAc, 86:14, then 50:50). The functionalized quinoline **3a** (181 mg, 52%) was obtained as a yellow solid; mp 132 °C.

IR (KBr): 3437 (m), 2965 (w), 1715 (s), 1592 (m), 1512 (s), 1418 (s), 1224 (s), 1174 (m), 1136 (s), 1033 (m), 974 (s), 863 (m), 824 (m), 769 (m), 613 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, 1 H, *J* = 1.8 Hz, ArH-5), 8.43 (d, 1 H, *J* = 1.8 Hz, ArH-7), 7.41 (dm, 2 H, *J* = 8.6 Hz, ArH-2′,6′), 7.11–7.09 (m, 1 H, ArH-3), 6.85 (dm, 2 H, *J* = 8.6 Hz, ArH-3′,5′), 6.59 (d, 1 H, *J* = 5.3 Hz, C*H*OH), 4.46 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.77 (s, 3 H, OCH_3), 2.83 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.45 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 158.0, 153.0, 152.8, 144.1, 141.5, 133.9, 128.0, 127.5, 126.9, 126.4, 124.9, 117.5 (q, J_{CF} = 320.4 Hz), 112.7, 112.5, 71.8, 60.7, 54.2, 18.6, 13.3.

MS (EI): *m*/*z* (%) = 499 (M^+, 0.2), 367 (17), 366 (74), 259 (16), 258 (100), 230 (34), 135 (11).

HRMS: *m*/*z* calcd for $C_{22}H_{20}F_3NO_7S$: 498.0834 $[M - H]^+$; found: 498.0841 $[M - H]^+$.

Ethyl 8-Bromo-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3b)

Compound **3b** was synthesized following the typical procedure as described for compound **3a** by reacting **1a** (489 mg, 1.0 mmol) with *i*-PrMgCl (0.94 M, 1.17 mL, 1.1 mmol) for 15 min at –30 °C. 1,2-Dibromo-1,1,2,2-tetrachloroethane (977 mg, 3.00 mmol) dissolved in THF (1 mL) was then added, the cooling bath was removed and the reaction mixture was stirred at r.t. The conversion was complete after 1.5 h. After workup and purification by flash chromatography (pentane–EtOAc, 88:12), **3b** (344 mg, 78%) was obtained as a white solid; mp 182 °C.

IR (KBr): 3430 (w), 1712 (s), 1592 (m), 1456 (w), 1420 (m), 1388 (m), 1328 (w), 1279 (s), 1231 (s), 1209 (m), 1128 (m), 980 (m), 918 (w), 864 (m), 837 (m), 806 (w), 766 (w), 737 (w), 607 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.72 (d, 1 H, *J* = 1.8 Hz, ArH-5), 8.69 (d, 1 H, *J* = 1.8 Hz, ArH-7), 7.21–7.18 (m, 1 H, ArH-3), 4.48 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.85 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.47 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 154.4, 152.8, 144.5, 133.2, 128.6, 127.1, 125.0, 123.9, 119.8, 114.0, 61.0, 18.5, 14.5.

MS (EI): *m*/*z* (%) = 443/441 (M^+, 100/99), 415 (20), 413 (20), 398 (47), 396 (45), 334 (31), 332 (31), 282 (16), 280 (16), 254 (22), 252 (21), 236 (10), 229 (11), 210 (10), 208 (15), 157 (12), 156 (10), 129 (19), 128 (28), 101 (13), 69 (19).

HRMS: *m*/*z* calcd for $C_{14}H_{11}BrF_3NO_5S$: 440.9493; found: 440.9496.

Anal. Calcd for $C_{14}H_{11}BrF_3NO_5S$ (442.21): C, 38.03; H, 2.51; N, 3.17. Found: C, 37.94; H, 2.48; N, 3.17.

Ethyl 8-Allyl-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3c)

Compound **3c** was synthesized following the typical procedure as described for compound **3a** by reacting **1a** (3.42 g, 7.00 mmol) with *i*-PrMgCl (0.94 M, 8.2 mL, 7.7 mmol) for 10 min at –30 °C. Following the addition of CuCN·2LiCl (1.0 M, 7.7 mL, 7.7 mmol), allyl bromide (2.54 g, 21.0 mmol) was added as the electrophile. The

cooling bath was removed and the reaction mixture was stirred at r.t. After 1 h, the mixture was worked up and purified by flash chromatography (pentane–EtOAc, 93:7) to yield **3c** (2.16 g, 77%) as an orange solid; mp 81 °C.

IR (KBr): 3414 (w), 3073 (w), 2990 (w), 1716 (vs), 1590 (s), 1515 (m), 1460 (m), 1418 (vs), 1323 (m), 1282 (s), 1230 (s), 1130 (s), 1031 (m), 1011 (m), 981 (s), 928 (m), 912 (m), 868 (s), 834 (m), 802 (w), 792 (m), 754 (m), 676 (w), 608 (s), 504 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, 1 H, *J* = 1.8 Hz, ArH-5), 8.23 (d, 1 H, *J* = 1.8 Hz, ArH-7), 7.14–7.11 (m, 1 H, ArH-3), 6.19–6.05 (m, 1 H, CH_2CH=CH_2), 5.21–5.13 (m, 1 H, CH_2CH=CH_{trans}H), 5.13–5.07 (m, 1 H, CH_2CH=CH_{cis}H), 4.47 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.95 (d, 2 H, *J* = 6.6 Hz, CH_2CH=CH_2), 2.83 (d, 3 H, *J* = 0.9 Hz, ArCH_3), 1.46 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 154.4, 153.2, 146.3, 140.3, 136.4, 129.9, 128.9, 127.3, 124.8, 120.8, 116.6, 113.6, 61.6, 35.6, 19.5, 14.4.

MS (EI): *m*/*z* (%) = 403 (M^+, 28), 358 (21), 270 (65), 242 (29), 240 (19), 226 (14), 209 (14), 208 (17), 207 (77), 198 (100), 197 (64), 196 (20), 180 (28), 168 (28), 167 (30), 154 (16), 69 (17), 64 (15).

HRMS: *m*/*z* calcd for $C_{17}H_{16}F_3NO_5S$: 403.0701; found: 403.0693.

Anal. Calcd for $C_{17}H_{16}F_3NO_5S$ (403.37): C, 50.62; H, 4.00; N, 3.47. Found: C, 50.62; H, 4.06; N, 3.53.

8-Allyl-4-methyl-6-(trifluoromethyl)-2-quinolinyl Trifluoromethanesulfonate (3d)

Compound **3d** was synthesized following the typical procedure as described for compound **3a** by reacting **1b** (445 mg, 0.92 mmol) with *i*-PrMgCl (0.94 M, 1.07 mL, 1.01 mmol) for 40 min at –30 °C. Following the addition of CuCN·2LiCl (1.0 M, 1.01 mL, 1.01 mmol), allyl bromide (333 mg, 2.75 mmol) was added as the electrophile, the cooling bath was removed and the reaction mixture was stirred at r.t. for 1 h. Workup and purification by flash chromatography (pentane–EtOAc, 95:5) yielded **3d** (366 mg, 70%) as a pale yellow solid; mp 81 °C.

IR (KBr): 3436 (w), 1594 (w), 1515 (w), 1466 (w), 1416 (m), 1307 (m), 1245 (m), 1220 (m), 1166 (m), 1128 (s), 1094 (m), 972 (m), 932 (w), 869 (w), 804 (w), 666 (w), 610 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, ArH-5), 7.84–7.80 (m, 1 H, ArH-7), 7.19–7.17 (m, 1 H, ArH-3), 6.18–6.03 (m, 1 H, CH_2CH=CH_2), 5.23–5.16 (m, 1 H, CH_2CH=CH_{trans}H), 5.18–5.12 (m, 1 H, CH_2CH=CH_{cis}H), 3.98 (d, 2 H, *J* = 6.6 Hz, CH_2CH=CH_2), 2.83 (d, 3 H, *J* = 0.9 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 152.7, 145.5, 141.6, 135.8, 129.1 (q, J_{CF} = 32.9 Hz), 127.1, 126.0 (q, J_{CF} = 2.9 Hz), 121.4 (q, J_{CF} = 93.3 Hz), 119.9 (q, J_{CF} = 4.7 Hz), 117.2, 116.6, 114.2, 35.5, 19.4.

MS (EI): *m*/*z* (%) = 399 (M^+, 28), 380 (11), 267 (35), 266 (100), 265 (17), 264 (28), 248 (15), 236 (23), 235 (16), 222 (18), 197 (13), 69 (12).

HRMS: *m*/*z* calcd for $C_{15}H_{11}F_6NO_3S$: 399.0364; found: 399.0398.

Anal. Calcd for $C_{15}H_{11}F_6NO_3S$ (399.31): C, 45.12; H, 2.78; N, 3.15. Found: C, 45.37; H, 2.87; N, 3.50.

Ethyl 8-[(1*E*)-3-*tert*-butoxy-3-oxoprop-1-enyl]-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3e)

Compound **3e** was synthesized following the typical procedure as described for compound **3a** by reacting **1a** (342 mg, 0.70 mmol) at –30 °C with *i*-PrMgCl (0.94 M, 0.82 mL, 0.77 mmol) for 15 min. Following the addition of CuCN·2LiCl (1.0 M, 0.77 mL, 0.77 mmol), *tert*-butyl propiolate (132 mg, 1.05 mmol) in THF (1 mL) was added very slowly over 5 min. After 1 h the reaction mixture was allowed to warm to r.t. and stirred for 3.5 h until the starting material was completely consumed (determined by TLC analysis). Workup and purification by flash chromatography (pentane–EtOAc, 93:7) afforded **3e** (142 mg, 41%) as a yellow solid; mp 140 °C.

IR (KBr): 3432 (m), 2984 (m), 2936 (w), 1723 (s), 1692 (s), 1589 (m), 1509 (m), 1459 (m), 1419 (s), 1370 (m), 1286 (s), 1224 (s), 1158 (s), 1132 (s), 1021 (m), 974 (s), 910 (w), 858 (m), 830 (m), 767 (m), 682 (w), 600 (m), 510 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.76 (d, 1 H, *J* = 1.4 Hz, ArH-5), 8.64 (d, 1 H, *J* = 1.4 Hz, ArH-7), 8.59 (d, 1 H, *J* = 16.1 Hz, ArC*H*=CH), 7.19 (s, 1 H, ArH-3), 6.71 (d, 1 H, *J* = 16.1 Hz, ArCH=C*H*), 4.50 (q, 2 H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 2.86 (s, 3 H, ArCH_3), 1.58 [s, 9 H, $C(CH_3)_3$], 1.48 (t, 3 H, *J* = 7.2 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 165.4, 154.7, 153.3, 145.6, 137.6, 134.0, 129.0, 128.1, 127.6, 127.5, 124.2, 118.7 (q, J_{CF} = 321.6 Hz), 114.4, 80.7, 61.9, 28.1, 19.5, 14.4.

MS (EI): *m*/*z* (%) = 489 (M^+, 1), 416 (15), 388 (21), 257 (16), 256 (100), 255 (28), 228 (15), 210 (36), 154 (19), 57 (55).

HRMS: *m*/*z* calcd for $C_{21}H_{22}F_3NO_7S$: 489.1069; found: 489.1078.

Anal. Calcd for $C_{21}H_{22}F_3NO_7S$ (489.46): C, 51.53; H, 4.53; N, 2.86. Found: C, 51.18; H, 4.78; N, 2.70.

Ethyl 4-Methyl-8-(prop-2-ynyl)-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3f)

Compound **3f** was synthesized following the typical procedure as described for compound **3a** by reacting **1a** (342 mg, 0.70 mmol) with *i*-PrMgCl (0.94 M, 0.82 mL, 0.77 mmol) for 25 min at –30 °C. Following the addition of CuCN·2LiCl (1.0 M, 0.77 mL, 0.77 mmol), propargyl bromide (250 mg, 2.10 mmol) was added as the electrophile, the cooling bath was removed and the mixture was stirred at r.t. After 30 min the reaction mixture was quenched with aq sat. NH_4Cl solution. Workup and purification by flash chromatography (pentane–EtOAc, 93:7) gave the quinoline derivative **3f** (196 mg, 70%) as a pale yellow solid. The product was contaminated with the corresponding allene (approximately 10%, determined by ^1H NMR spectroscopy); mp 118 °C.

IR (KBr): 3278 (m), 2998 (w), 1708 (s), 1597 (m), 1513 (m), 1460 (m), 1422 (s), 1325 (m), 1302 (s), 1261 (s), 1209 (vs), 1170 (m), 1128 (s), 1029 (m), 983 (s), 914 (w), 858 (m), 827 (s), 770 (m), 752 (m), 674 (m), 601 (s), 511 (m) cm^{-1}; for the isomeric allene: 1956 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.69–8.65 (m, 1 H, ArH-7), 8.65–8.60 (m, 1 H, ArH-5), 7.15–7.13 (m, 1 H, ArH-3), 4.48 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.16 (d, 2 H, *J* = 3.1 Hz, $CH_2C{\equiv}CH$), 2.84 (d, 3 H, *J* = 0.9 Hz, ArCH_3), 2.32 (t, 1 H, *J* = 3.1 Hz, $CH_2C{\equiv}CH$), 1.47 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$); for the isomeric allene: δ = 5.30 (2 dm, 2 H, *J* = 6.6 Hz, CH=C=CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 154.4, 153.3, 145.6, 135.7, 129.4, 129.0, 127.0, 125.4, 118.7 (q, J_{CF} = 321.0 Hz), 113.9, 80.9, 71.8, 61.7, 20.8, 19.4, 14.4; for the isomeric allene: δ = 210.9.

MS (EI): *m*/*z* (%) = 401 (M^+, 20), 356 (13), 269 (13), 268 (68), 241 (17), 240 (100), 211 (16), 195 (13), 167 (24), 166 (19), 139 (15).

HRMS: *m*/*z* calcd for $C_{17}H_{14}F_3NO_5S$: 401.0545; found: 401.0547.

Anal. Calcd for $C_{17}H_{14}F_3NO_5S$ (401.36): C, 50.87; H, 3.52; N, 3.49. Found: C, 50.63; H, 3.56; N, 3.46.

Ethyl 8-[4-(Ethoxycarbonyl)phenyl]-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3g); Typical Procedure

Compound **1b** was dissolved in THF (2 mL) with tetradecane as an internal standard and the reaction mixture was cooled to –30 °C. *i*-PrMgBr (0.94 M, 0.82 mL, 0.77 mmol) was added and the mixture

was stirred for 30 min, then $ZnCl_2$ (1.5 M, 0.51 mL, 0.77 mmol) was added and the temperature was allowed to warm to r.t. (mixture A). In a syringe, the active catalyst was preformed from $Pd(dba)_2$ (1 mol%, 3.45 mg, 6 μmol) and tfp (2 mol%, 2.8 mg, 12 μmol) in THF (1 mL) and added to ethyl 4-iodobenzoate (190 mg, 0.70 mmol). To this was canulated mixture A and the reaction mixture was stirred for 1.5 h at r.t. Then the mixture was quenched with aq sat. NH_4Cl solution, poured into aq NH_4Cl solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (pentane–EtOAc, 86:14) yielded the product **3g** (307 mg, 74%) as a white solid; mp 152 °C.

IR (KBr): 3436 (m), 1719 (m), 1610 (w), 1416 (m), 1285 (m), 1220 (m), 1108 (m), 974 (w), 865 (w), 817 (w), 767 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, 1 H, *J* = 1.8 Hz, ArH-7), 8.43 (d, 1 H, *J* = 1.8 Hz, ArH-5), 8.16 (dm, 2 H, *J* = 8.4 Hz, ArH-2′,6′), 7.75 (dm, 2 H, *J* = 8.4 Hz, ArH-3′,5′), 7.18–7.15 (m, 1 H, ArH-3), 4.50 (q, 2 H, *J* = 7.1 Hz, $ArCO_2CH_2CH_3$), 4.43 (q, 2 H, *J* = 7.1 Hz, $Ar'CO_2CH_2CH_3$), 2.89 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.47 (t, 3 H, *J* = 7.1 Hz, $ArCO_2CH_2CH_3$), 1.44 (t, 3 H, *J* = 7.1 Hz, $Ar'CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 165.7, 154.7, 153.2, 145.3, 142.1, 140.4, 131.2, 130.7, 129.8, 129.0, 128.9, 127.8, 126.4, 118.5 (q, J_{CF} = 319.8 Hz), 114.1, 61.8, 61.0, 19.7, 14.3.

MS (EI): *m*/*z* (%) = 511 (M^+, 22), 466 (29), 380 (11), 379 (44), 378 (100), 350 (40), 334 (19), 332 (15), 306 (39), 305 (12), 278 (23), 260 (18), 234 (13), 233 (10), 204 (24), 203 (11).

HRMS: *m*/*z* calcd for $C_{23}H_{20}F_3NO_7S$: 511.0913; found: 511.0897.

Anal. Calcd for $C_{23}H_{20}F_3NO_7S$ (511.47): C, 54.01; H, 3.94; N, 2.74. Found: C, 53.85; H, 3.90; N, 2.76.

Ethyl 4-(4-Methyl-6-(trifluoromethyl)-2-{[(trifluoromethyl)-sulfonyl]oxy}-8-quinolinyl)benzoate (3h)

Compound **3h** was synthesized following the typical procedure as described for compound **3g** by reacting **1b** (400 mg, 0.83 mmol) with *i*-PrMgCl (0.94 M, 0.97 mL, 0.91 mmol) for 40 min at –30 °C. After the addition of $ZnBr_2$ (1.5 M, 0.61 mL, 0.91 mmol), the reaction mixture was warmed to r.t. (mixture A). The catalyst was preformed from $Pd(dba)_2$ (2 mol%, 7.9 mg, 14 μmol) and tfp (4 mol%, 6.38 mg, 28 μmol) in THF (1 mL) and added to ethyl 4-iodobenzoate (190 mg, 0.69 mmol). To this solution was canulated mixture A and the reaction mixture was stirred for 3.5 h at r.t., then quenched with aq sat. NH_4Cl solution and worked up in the usual way. Purification by flash chromatography (pentane–EtOAc, 97:3) yielded the product **3h** (221 mg, 63%) as a white solid; mp 128 °C.

IR (KBr): 3436 (m), 2987 (w), 1706 (s), 1610 (m), 1465 (m), 1418 (s), 1370 (m), 1284 (s), 1225 (s), 1132 (s), 1062 (m), 1024 (m), 976 (m), 898 (m), 865 (m), 802 (m), 766 (m), 708 (m), 653 (m), 607 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.37–8.34 (m, 1 H, ArH-7), 8.16 (d, 2 H, *J* = 8.8 Hz, ArH-2′,6′), 8.02 (d, 1 H, *J* = 1.8 Hz, ArH-5), 7.74 (d, 2 H, *J* = 8.8 Hz, ArH-3′,5′), 7.22 (d, 1 H, *J* = 0.9 Hz, ArH-3), 4.43 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.88 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.44 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 154.7, 152.7, 141.6, 141.4, 130.7, 130.2, 130.1, 129.9 (q, J_{CF} = 19.4 Hz), 129.6 (q, J_{CF} = 33.5Hz), 127.7, 127.3 (q, J_{CF} = 2.9 Hz), 127.2, 121.5 (q, J_{CF} = 4.1 Hz), 118.5 (q, J_{CF} = 321.0 Hz), 114.6, 61.1, 19.5, 14.3.

MS (EI): *m*/*z* (%) = 507 (M^+, 18), 462 (16), 374 (38), 346 (43), 330 (11), 328 (17), 303 (19), 392 (100), 301 (25), 300 (11).

HRMS: *m*/*z* calcd for $C_{21}H_{15}F_6NO_5S$: 507.0575; found: 507.0577.

Ethyl 4-Methyl-8-(2-pyrimidinyl)-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (3i)

Compound **3i** was synthesized following the typical procedure as described for compound **3g** by reacting **1a** (342 mg, 0.70 mmol) with *i*-PrMgCl (0.94 M, 0.82 mL, 0.77 mmol) for 10 min at –30 °C. Following the addition of $ZnCl_2$ (1.0 M, 0.77 mL, 0.77 mmol) the reaction mixture was warmed to r.t. (mixture A). The catalyst was preformed from $Pd(dba)_2$ (6 mol%, 20.7 mg, 36 μmol) and tfp (12 mol%, 16.8 mg, 72 μmol) in THF (1 mL) and added to 2-iodopyrimidine[11] (122 mg, 0.6 mmol). To this solution was canulated mixture A and the reaction mixture was stirred for 4 h at r.t. Then the reaction was quenched with aq sat. NH_4Cl solution and worked up in the usual way. Purification by flash chromatography (pentane–EtOAc, 86:14) yielded **3i** (128 mg, 48%) as a pale yellow solid; mp 151 °C.

IR (KBr): 3432 (m), 3072 (w), 2987 (w), 1711 (s), 1593 (m), 1569 (m), 1559 (s), 1420 (s), 1401 (s), 1300 (m), 1278 (s), 1227 (vs), 1137 (s), 1026 (w), 962 (s), 912 (w), 871 (m), 834 (m), 767 (m), 752 (m), 713 (w), 679 (m), 651 (w), 609 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, 2 H, *J* = 4.9 Hz, ArH-3′,5′), 8.89 (d, 1 H, *J* = 1.8 Hz, ArH-7), 8.86 (d, 1 H, *J* = 1.8 Hz, ArH-5), 7.37 (t, 1 H, *J* = 4.9 Hz, ArH-4′), 7.16–7.13 (m, 1 H, ArH-3), 4.47 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.88 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.44 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 165.3, 156.9, 155.1, 153.0, 145.7, 138.9, 131.5, 128.7, 127.8, 127.6, 119.4, 118.4 (q, J_{CF} = 321.0 Hz), 113.9, 61.8, 19.5, 14.3.

MS (EI): *m*/*z* (%) 396 ($[M - OEt]^+$, 5), 309 (22), 308 (100), 280 (29).

HRMS: *m*/*z* calcd for $C_{18}H_{14}F_3N_3O_5S$: 442.0685 $[M + H]^+$; found: 442.0712 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{14}F_3N_3O_5S$ (441.38): C, 48.98; H, 3.20; N, 9.52. Found: C, 49.06; H, 3.10; N, 9.36.

Ethyl 8-Allyl-2-ethyl-4-methyl-6-quinolinecarboxylate (4a)

According to the typical procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (1 mol%, 2.9 mg, 5 μmol) and tfp (2 mol%, 2.3 mg, 10 μmol) in THF (0.7 mL) and added to **3c** (202 mg, 0.50 mmol). To this mixture was canulated Et_2Zn (1.0 M in Et_2O, 1.05 mL, 1.05 mmol) and the reaction mixture was stirred for 35 min at r.t., then quenched with aq sat. NH_4Cl solution. Workup in the usual way and purification by flash chromatography (pentane–EtOAc, 96:4) yielded the product **4a** (115 mg, 82%) as a white solid; mp 69 °C.

IR (KBr): 3426 (w), 2977 (m), 2933 (w), 1713 (vs), 1604 (m), 1570 (w), 1497 (w), 1468 (w), 1418 (m), 1366 (w), 1271 (s), 1240 (m), 1222 (m), 1199 (m), 1144 (w), 1114 (w), 1033 (m), 995 (w), 915 (m), 904 (m), 869 (w), 766 (m), 512 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, 1 H, *J* = 1.8 Hz, ArH-5), 8.11 (d, 1 H, *J* = 1.8 Hz, ArH-7), 7.18–7.15 (m, 1 H, ArH-3), 6.29–6.14 (m, 1 H, $CH_2CH=CH_2$), 5.24–5.16 (m, 1 H, $CH_2CH=CH_{trans}H$), 5.11–5.06 (m, 1 H, $CH_2CH=CH_{cis}H$), 4.45 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.09 (d, 2 H, *J* = 6.6 Hz, $CH_2CH=CH_2$), 2.97 (q, 2 H, *J* = 7.5 Hz, $ArCH_2CH_3$), 2.72 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.45 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.41 (t, 3 H, *J* = 7.5 Hz, $ArCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 164.5, 148.0, 145.5, 139.6, 137.6, 127.7, 126.5, 126.0, 125.0, 122.4, 115.7, 61.1, 36.0, 32.1, 19.0, 14.4, 13.1.

MS (EI): *m*/*z* (%) = 283 (M^+, 58), 282 (22), 269 (20), 268 (100), 254 (23), 241 (11), 240 (63), 238 (18), 225 (14), 210 (13), 195 (15), 180 (10).

HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1582.

Anal. Calcd for $C_{18}H_{21}NO_2$ (283.36): C, 76.29; H, 7.47; N, 4.94. Found: C, 76.29; H, 7.31; N, 4.92.

Ethyl 8-Allyl-2-(4-methoxyphenyl)-4-methyl-6-quinolinecarboxylate (4b)

To a solution of 4-iodoanisole (342 mg, 0.70 mmol) in THF (0.2 mL), was added slowly *n*-BuLi (1.7 M in hexane, 0.7 mL, 1.2 mmol) at –78 °C and the reaction mixture was stirred for 30 min. $ZnCl_2$ (1.0 M, 1.2 mL, 1.2 mmol) was then added and the mixture was warmed to r.t. and stirred for a further 30 min (mixture A). According to the typical procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (1 mol%, 2.9 mg, 5 μmol) and tfp (2 mol%, 2.3 mg, 10 μmol) in THF (0.7 mL) and added to **3c** (202 mg, 0.50 mmol). To this was canulated mixture A, the reaction mixture was stirred for 1.25 h at r.t., then quenched with aq sat. NH_4Cl solution. Workup in the usual way and purification by flash chromatography (pentane–EtOAc, 96:4) yielded the product **4b** (173 mg, 96%) as a pale brown solid; mp 99 °C.

IR (KBr): 3436 (m), 2977 (w), 1705 (s), 1603 (m), 1560 (w), 1496 (w), 1462 (w), 1354 (w), 1252 (m), 1181 (m), 1153 (w), 1035 (w), 901 (w), 833 (w), 764 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, 1 H, *J* = 2.0 Hz, ArH-5), 8.24 (d, 2 H, *J* = 8.8 Hz, ArH-2′,6′), 8.14 (d, 1 H, *J* = 2.0 Hz, ArH-7), 7.76–7.73 (m, 1 H, Ar*H*-3), 7.04 (d, 2 H, *J* = 8.8 Hz, ArH-3′,5′), 6.34–6.19 (m, 1 H, CH_2CH=CH_2), 5.28–5.19 (m, 1 H, CH_2CH=CH_{trans}H), 5.14–5.09 (m, 1 H, CH_2CH=CH_{cis}H), 4.46 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.17 (d, 2 H, *J* = 6.6 Hz, CH_2CH=CH_2), 3.90 (s, 3 H, OCH_3), 2.80 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.46 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 161.1, 156.7, 148.3, 146.2, 140.0, 137.7, 131.9, 128.9, 128.1, 126.7, 126.3, 125.1, 119.1, 115.8, 114.2, 61.2, 55.4, 36.1, 19.3, 14.5.

MS (EI): *m*/*z* (%) = 361 (M^+, 30), 360 (100), 346 (22), 332 (15), 318 (15).

HRMS: *m*/*z* calcd for $C_{23}H_{23}NO_3$: 360.1600 $[M – H]^+$; found: 360.1588 $[M – H]^+$.

Anal. Calcd for $C_{23}H_{23}NO_3$ (361.43): C, 76.43; H, 6.41; N, 3.88. Found: C, 75.41; H, 6.30; N, 3.84.

Ethyl 8-Allyl-4-methyl-2-[3-(trifluoromethyl)phenyl]-6-quinolinecarboxylate (4c)

To a solution of 1-iodo-3-(trifluoromethyl)benzene (342 mg, 0.70 mmol) in THF (0.2 mL) was added slowly BuLi (1.58 M in hexane, 0.44 mL, 0.70 mmol) at –78 °C and the reaction mixture was stirred for 30 min. $ZnBr_2$ (1.05 M, 0.70 mL, 0.74 mmol) was added and the mixture was warmed to r.t. and stirred for 30 min (mixture A). According to the typical procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (1 mol%, 2.9 mg, 5 μmol) and tfp (2 mol%, 2.3 mg, 10 μmol) in THF (0.7 mL) and added to **3c** (202 mg, 0.50 mmol). To this solution was canulated mixture A and the reaction mixture was stirred for 2 h at r.t., then quenched with aq sat. NH_4Cl solution. Workup in the usual way and purification by flash chromatography (pentane–EtOAc, 96:4) yielded the product **4c** (161 mg, 81%) as a pale yellow solid; mp 105 °C.

IR (KBr): 3436 (m), 3077 (m), 2982 (m), 1706 (s), 1604 (m), 1564 (w), 1416 (m), 1350 (m), 1328 (s), 1244 (s), 1127 (s), 1076 (m), 1033 (w), 914 (m), 900 (m), 802 (m), 764 (m), 694 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (d, 1 H, *J* = 1.8 Hz, Ar*H*-5), 8.51 (s, 1 H, Ar*H*-2′), 8.44 (d, 1 H, *J* = 8.0 Hz, Ar*H*-4′), 8.20 (d, 1 H, *J* = 1.8 Hz, Ar*H*-7), 7.80 (s, 1 H, Ar*H*-3), 7.73 (d, 1 H, *J* = 8.0 Hz, Ar*H*-6′), 7.64 (t, 1 H, *J* = 8.0 Hz, Ar*H*-5′), 6.30–6.15 (m, 1 H, CH_2CH=CH_2), 5.29–5.20 (m, 1 H, CH_2CH=CH_{trans}H), 5.17–5.10 (m, 1 H, CH_2CH=CH_{cis}H), 4.47 (q, 2 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.17 (d, 2 H, *J* = 6.6 Hz, CH_2CH=CH_2), 2.84 (s, 3 H, $ArCH_3$), 1.47 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 154.4, 147.2, 146.1, 139.5, 139.1, 136.4, 130.4, 130.0, 129.7, 128.3, 127.5, 126.7, 125.8, 125.3 (q, J_{CF} = 3.5 Hz), 124.1, 123.3 (q, J_{CF} = 4.1 Hz), 118.3, 115.0, 60.3, 35.2, 18.4, 13.4.

MS (EI): *m*/*z* (%) = 399 (M^+, 38), 398 (100), 184 (33), 370 (26), 356 (41), 326 (11).

HRMS: *m*/*z* calcd for $C_{23}H_{20}F_3NO_2$: 398.1368 $[M – H]^+$; found: 398.1406 $[M – H]^+$.

Ethyl 8-Allyl-2-[4-(ethoxycarbonyl)phenyl]-4-methyl-6-quinolinecarboxylate (4d)

To a solution of ethyl 4-iodobenzoate (276 mg, 0.75 mmol) in THF (1 mL) was added slowly *i*-PrMgCl (0.94 M, 0.88 mL, 0.83 mmol) at –30 °C and the reaction mixture was stirred for 30 min. $ZnCl_2$ (1.0 M, 0.83 mL, 0.83 mmol) was added and the mixture was warmed to r.t. and stirred for a further 30 min (mixture A). According to the typical procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (1 mol%, 2.9 mg, 5 μmol) and tfp (2 mol%, 2.3 mg, 1 μmol) in THF (0.7 mL) and added to **3c** (202 mg, 0.50 mmol). To this was canulated mixture A and the reaction mixture was stirred for 1 h at r.t., then quenched with aq sat. NH_4Cl solution. Workup in the usual way and purification by flash chromatography (pentane–EtOAc, 95:5) yielded the product **4d** (186 mg, 92%) as a white solid; mp 159 °C.

IR (KBr): 3435 (m), 2981 (w), 1717 (s), 1602 (m), 1558 (w), 1496 (w), 1475 (w), 1422 (w), 1366 (w), 1350 (w), 1277 (s), 1222 (m), 1155 (w), 1110 (m), 1026 (m), 911 (w), 862 (w), 776 (m), 709 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.65–8.63 (m, 1 H, ArH-5), 8.32 (dm, 2 H, *J* = 8.4 Hz, ArH-2′, 6′), 8.19 (dm, 2 H, *J* = 8.4 Hz, ArH-3′, 5′), 8.17 (s, 1 H, ArH-7), 7.82 (s, 1 H, ArH-3), 6.33–6.18 (m, 1 H, CH_2CH=CH_2), 5.28–5.19 (m, 1 H, CH_2CH=CH_{trans}H), 5.16–5.09 (m, 1 H, CH_2CH=CH_{cis}H), 4.47 (q, 2 H, *J* = 7.1 Hz, $ArCO_2CH_2CH_3$), 4.43 (q, 2 H, *J* = 7.1 Hz, $Ar'CO_2CH_2CH_3$), 4.18 (d, 2 H, *J* = 7.1 Hz, CH_2CH=CH_2), 2.83 (d, 3 H, *J* = 0.9 Hz, $ArCH_3$), 1.47 (t, 3 H, *J* = 7.1 Hz, $ArCO_2CH_2CH_3$), 1.44 (t, 3 H, *J* = 7.1 Hz, $Ar'CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 166.4, 155.8, 148.2, 146.9, 143.3, 140.5, 137.5, 131.2, 130.0, 128.3, 127.6, 127.4, 126.8, 125.1, 119.7, 116.0, 61.3, 61.1, 36.1, 19.4, 14.4, 14.3.

MS (EI): *m*/*z* (%) = 403 (M^+, 32), 402 (100), 388 (17), 374 (11), 346 (11), 332 (14).

HRMS: *m*/*z* calcd for $C_{25}H_{25}NO_4$: 402.1705 $[M – H]^+$; found: 402.1694 $[M – H]^+$.

Ethyl 4-[8-Allyl-4-methyl-6-(trifluoromethyl)-2-quinolinyl]-benzoate (4e)

To a solution of ethyl 4-iodobenzoate (239 mg, 0.86 mmol) in THF (1 mL) at –30 °C was added slowly *i*-PrMgCl (0.94 M, 1.01 mL, 0.95 mmol) and the reaction mixture was stirred for 1 h. $ZnBr_2$ (THF, 1.5 M, 0.63 mL, 0.95 mmol) was then added, the mixture was warmed to r.t. and stirred for a further 30 min (mixture A). According to the procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (7 mol%, 32.2 mg, 40 μmol) and tfp (14 mol%, 18.56 mg, 80 μmol) in THF (0.7 mL) and added to **3d** (230 mg, 0.58 mmol). To this solution was canulated mixture A and the reaction mixture was stirred for 4 h at r.t., then quenched with aq sat. NH_4Cl solution. Workup and purification by flash chromatography (pentane–EtOAc, 97:3) yielded the product **4e** (203 mg, 89%) as a white solid; mp 119 °C.

IR (KBr): 3434 (m), 2982 (w), 1716 (s), 1604 (m), 1466 (w), 1421 (m), 1368 (w), 1316 (s), 1271 (s), 1225 (m), 1157 (s), 1121 (s), 1064 (w), 1024 (w), 896 (m), 858 (w), 777 (m), 711 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.32 (dm, 2 H, *J* = 8.8 Hz, ArH-2′,6′), 8,19 (dm, 2 H, *J* = 8.8 Hz, ArH-3′,5′), 8.17 (s, 1 H, ArH-3), 7.86 (s, 1 H, ArH-5), 7.76–7.73 (m, 1 H, ArH-7), 6.23–6.15 (m, 1

H, CH_2CH=CH_2), 5.29–5.21 (m, 1 H, CH_2CH=CH_{trans}H), 5.19–5.13 (m, 1 H, CH_2CH=CH_{cis}H), 4.43 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.19 (d, 2 H, J = 6.6 Hz, CH_2CH=CH_2), 2.81 (d, 3 H, J = 0.9 Hz, $ArCH_3$), 1.44 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 155.9, 147.3, (q, J_{CF} = 1.2 Hz), 146.3, 143.1, 141.8, 136.9, 131.6, 130.0, 127.7 (q, J_{CF} = 32.3 Hz), 127.4, 126.6, 124.4 (q, J_{CF} = 2.9 Hz), 122.5, 120.1, 119.9 (q, J_{CF} = 4.7 Hz), 116.6, 61.1, 36.0, 19.3, 14.3.

MS (EI): *m*/*z* (%) = 399 (M^+, 32), 398 (100), 384 (18), 371 (10), 370 (41), 356 (27), 326 (12).

HRMS: *m*/*z* calcd for $C_{23}H_{20}F_3NO_2$: 399.1446; found: 399.1410.

Anal. Calcd for $C_{23}H_{20}F_3NO_2$ (399.41): C, 69.16; H, 5.05; N, 3.51. Found: C, 69.18; H, 4.93; N, 3.45.

Ethyl 4-[2-Ethyl-4-methyl-6-(trifluoromethyl)-8-quinolinyl]-benzoate (4f)

According to the typical procedure described for compound **3g**, the active catalyst was preformed from $Pd(dba)_2$ (3 mol%, 5.8 mg, 10 μmol) and tfp (6 mol%, 4.6 mg, 20 μmol) in THF (0.7 mL) and added to **3h** (160 mg, 0.32 mmol). To this mixture was canulated Et_2Zn (1.0 M in Et_2O, 0.47 mL, 0.47 mmol) and the reaction mixture was stirred for 30 min at r.t., then quenched with aq sat. NH_4Cl solution. Workup in the usual way and purification by flash chromatography (pentane–EtOAc, 97:3) yielded the product **4f** (106 mg, 84%) as a pale yellow solid; mp 86 °C.

IR (KBr): 3416 (m), 2982 (m), 2936 (m), 1714 (vs), 1610 (s), 1570 (m), 1471 (m), 1416 (s), 1369 (m), 1312 (s), 1276 (vs), 1213 (m), 1186 (s), 1160 (vs), 1122 (vs), 1058 (m), 1023 (m), 897 (s), 858 (s), 809 (m), 772 (m), 710 (s), 630 (w), 507 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H, ArH-7), 8.16 (dm, 2 H, J = 8.4 Hz, ArH-2′,6′), 7.91–7.88 (dm, 1 H, J = 1.8 Hz, ArH-5), 7.84 (d, 2 H, J = 8.4 Hz, ArH-3′,5′), 7.25 (s, 1 H, ArH-3), 4.43 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.92 (q, 2 H, J = 7.5 Hz, $ArCH_2CH_3$), 2.75 (s, 3 H, $ArCH_3$), 1.44 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.33 (t, 3 H, J = 7.5 Hz, $ArCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.4, 144.2 (q, J_{CF} = 106.8 Hz), 140.8, 131.0, 130.1, 129.4, 128.9, 127.1, 126.8 (q, J_{CF} = 32.3 Hz), 126.5, 125.4 (q, J_{CF} = 2.9 Hz), 124.3 (q, J_{CF} = 272.3 Hz), 122.8, 121.5 (q, J_{CF} = 4.7 Hz), 60.9, 32.0, 19.0, 14.4, 12.8.

MS (EI): *m*/*z* (%) = 387 (M^+, 96), 386 (100), 359 (12), 358 (42), 342 (12), 314 (30), 299 (16), 298 (13).

HRMS: *m*/*z* calcd for $C_{22}H_{20}F_3NO_2$: 387.1446; found: 387.1463.

Anal. Calcd for $C_{22}H_{20}F_3NO_2$ (387.39): C, 68.21; H, 5.20; N, 3.62. Found: C, 68.42; H, 5.30; N, 3.44.

Ethyl 4-{[(*E*)-(Dimethylamino)methylidene]amino}-3-[(1*Z*)-3-ethoxy-1-methyl-3-oxoprop-1-enyl]-5-iodobenzoate (6a)

To a solution of **5a** (7.08 g, 15.0 mmol) in THF (7 mL) with tetradecane (10 drops) as internal standard was added *i*-PrMgCl (0.94 M, 17.6 mL, 16.5 mmol) at –30 °C. The reaction mixture was stirred for 15 min, then CuCN·2LiCl (1.0 M, 16.5 mL, 16.5 mmol) was added followed by ethyl (*Z*)-3-iodobut-2-enoate (5.40 g, 22.5 mmol) and the mixture was warmed to r.t. After 45 min, the reaction was quenched with aq sat. NH_4Cl solution. The mixture was poured into aq NH_4Cl solution (200 mL) and extracted with EtOAc (3 × 400 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. An aliquot was removed from the crude product (2% of the crude product, determined by weighing, corresponding to 0.27 mmol) and purified by flash chromatography (pentane–EtOAc, 88:12). The product **6a** (100 mg, 81%) was obtained as a yellow oil.

IR (film): 3430 (w), 2980 (w), 1715 (m), 1643 (m), 1581 (m), 1369 (w), 1265 (m), 1104 (w), 768 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, 1 H, J = 1.8 Hz, ArH-6), 7.61 (d, 1 H, J = 1.8 Hz, ArH-2), 7.23 (s, 1 H, N=CH), 5.90–5.87 (m, 1 H, C=C$H$$CO_2CH_2CH_3$), 4.32 (q, 2 H, J = 7.1 Hz, $ArCO_2CH_2CH_3$), 4.00 (q, 2 H, J = 7.1 Hz, C=$CHCO_2CH_2CH_3$), 2.99 (s, 3 H, NCH_3), 2.96 (s, 3 H, NCH_3), 2.04 (d, 3 H, J = 1.3 Hz, CCH_3), 1.36 (t, 3 H, J = 7.1 Hz, $ArCO_2CH_2CH_3$), 1.09 (t, 3 H, J = 7.01 Hz, C=$CHCO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 165.3, 155.5, 153.9, 139.3, 139.3, 133.7, 129.1, 129.1, 125.3, 120.1, 93.5, 60.8, 59.8, 24.5, 14.3, 14.1.

MS (EI): *m*/*z* (%) 458 (M^+, 9), 386 (18), 385 (100), 357 (13).

HRMS: *m*/*z* calcd for $C_{18}H_{23}IN_2O_4$: 458.0703; found: 458.0723.

Ethyl (2*Z*)-3-[2-{[(*E*)-(Dimethylamino)methylidene]amino}-3-iodo-5-(trifluoromethyl)phenyl]but-2-enoate (6b)

Compound **6b** was synthesized following the same procedure as described for compound **6a** by reacting compound **5b** (1.87 g, 4.0 mmol) with *i*-PrMgCl (0.94 M, 4.68 mL, 4.4 mmol) for 30 min at –30 °C. Following the addition of CuCN·2LiCl (1.0 M, 4.4 mL, 4.4 mmol), ethyl (*Z*)-3-iodobut-2-enoate (1.44 g, 6.0 mmol) was added as the electrophile, the cooling bath was removed and the mixture was stirred at r.t. for 3.5 h. Workup and flash chromatography (pentane–EtOAc, 90:10) yielded **6b** (1.49 g, 82%) as a yellow oil.

IR (film): 2981 (m), 2938 (m), 1715 (s), 1645 (vs), 1593 (s), 1435 (s), 1415 (m), 1371 (s), 1305 (vs), 1241 (s), 1203 (s), 1121 (s), 1076 (s), 1047 (s), 887 (m), 771 (m), 686 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.94 (m, 1 H, ArH-4), 7.21 (s, 1 H, ArH-6), 7.19–7.15 (m, 1 H, N=CH), 5.91–5.87 (m, 1 H, C=C$H$$CO_2CH_2CH_3$), 4.00 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 2.97 (s, 3 H, NCH_3), 2.96 (s, 3 H, NCH_3), 2.04 (d, J = 1.3 Hz, 3 H, CCH_3), 1.07 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 154.7, 154.1, 134.7 (q, J_{CF} = 3.5 Hz), 134.1, 124.9, 124.8 (q, J_{CF} = 3.5 Hz), 121.6, 120.5, 95.4, 59.9, 24.3, 13.9.

MS (EI): *m*/*z* (%) = 454 (M^+, 6), 382 (17), 381 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{18}F_3IN_2O_2$: 454.0365; found: 454.0387.

Anal. Calcd for $C_{16}H_{18}F_3IN_2O_2$ (454.23): C, 42.31; H, 3.99; N, 6.17. Found: C, 42.06; H, 3.77; N, 6.23.

Ethyl 8-Iodo-4-methyl-2-oxo-1,2-dihydro-6-quinolinecarboxylate (7a)

A quantity of the crude product **6a** (14.4 g, corresponding to 29.7 mmol, relative to the amount of starting meterial, assuming 100% conversion) was dissolved in a solution of $ZnCl_2$ (1.5 M, 99 mL, 149 mmol). The solvent was removed under reduced pressure and the remaining mixture was taken up in EtOH (100 mL), and stirred overnight at 80 °C. The mixture was then cooled to r.t. and **7a** (7.18 g, 68%) precipitated as a white solid which was washed with a small amount of EtOH; mp 224 °C.

IR (KBr): 3435 (w), 1719 (w), 1675 (m), 1596 (w), 1271 (m), 762 (w) cm^{-1}.

^{1}H NMR (300 MHz, pyridine-d_5): δ = 10.38 (s, 1 H, NH), 8.76 (d, 1 H, J = 1.8 Hz, Ar*H*-7), 8.36 (d, 1 H, J = 1.8 Hz, ArH-5), 6.64 (s, 1 H, ArH-3), 4.39 (q, 2 H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.27 (s, 3 H, $ArCH_3$), 1.28 (t, 3 H, J = 7.2 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, pyridine-d_5): δ = 164.8, 162.4, 148.6, 142.8, 141.2, 127.3, 125.6, 122.6, 120.9, 86.4, 61.6, 18.5, 14.4.

MS (EI): *m*/*z* (%) = 357 (M^+, 100), 329 (23), 312 (85), 256 (9), 207 (25), 157 (15), 129 (20), 102 (13).

HRMS: *m*/*z* calcd for $C_{13}H_{12}INO_3$: 356.9862; found: 356.9856.

Anal. Calcd for $C_{13}H_{12}INO_3$ (357.14): C, 43.72; H, 3.39; N, 3.92. Found: C, 44.04; H, 3.20; N, 3.81.

8-Iodo-4-methyl-6-(trifluoromethyl)-2(1*H*)-quinolinone (7b)
Compound **6b** (1.35 g, 2.97 mmol) was dissolved in a solution of $ZnCl_2$ (1.15 M, 13 mL, 15.0 mmol). The solvent was removed under reduced pressure and the remaining mixture was redissolved in EtOH (10 mL), and stirred overnight at 80 °C. The mixture was then cooled to r.t. and **7b** (896 mg, 85%) precipitated as a white solid which was washed with small amounts of EtOH. Flash chromatography (pentane–EtOAc, 33:67) yielded an additional amount of **7b** (75 mg, 7%, total yield: 971 mg, 92%); mp 241 °C.

IR (KBr): 3436 (m), 3338 (s), 3057 (w), 1683 (vs), 1602 (s), 1440 (w), 1382 (m), 1369 (m), 1302 (vs), 1219 (m), 1153 (s), 1122 (s), 1099 (s), 1082 (m), 959 (w), 891 (m), 766 (m), 727 (w), 706 (w), 666 (m), 632 (m), 615 (m), 580 (w), 520 (m), 490 (w) cm^{-1}.

^1H NMR (300 MHz, pyridine-d_5): δ = 8.38 (d, J = 1.8 Hz, 1 H, ArH-7), 7.92–7.89 (m, 1 H, ArH-5), 6.70 (d, J = 1.3 Hz, 1 H, ArH-3), 2.29 (d, J = 1.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, pyridine-d_5): δ = 162.4, 148.3, 142.5, 136.8 (q, J_{CF} = 3.5 Hz), 124.3 (q, J_{CF} = 32.9 Hz), 123.0, 122.8 (q, J_{CF} = 3.5 Hz), 121.1, 113.4, 18.4.

MS (EI): *m*/*z* (%) = 353 (M^+, 100), 324 (38), 198 (16), 197 (19).

HRMS: *m*/*z* calcd for $C_{11}H_7F_3INO$: 352.9524; found: 352.9554.

Anal. Calcd for $C_{11}H_7F_3INO$ (353.08): C, 37.42; H, 2.00; N, 3.97. Found: C, 37.34; H, 1.93; N, 3.92.

Ethyl 8-[Hydroxy(phenyl)methyl]-4-methyl-2-oxo-1,2-dihydro-6-quinolinecarboxylate (9)
Compound **7a** (178 mg, 0.50 mmol) was suspended in anhyd THF (1 mL) and cooled to –30 °C. PhMgCl (1.9 M, 0.29 mL, 0.55 mmol) was added and the reaction mixture was stirred for 15 min, then *i*-PrMgCl (0.94 M, 0.59 mL, 0.35 mmol) was added and the mixture was stirred for a further 30 min. Benzaldehyde (159 mg, 1.5 mmol) was then added and the incomplete reaction was was quenched after 2 h by the addition of aq sat. NH_4Cl solution. The mixture was poured into aq NH_4Cl solution (50 mL), extracted with EtOAc (3 × 200 mL), washed with brine (25 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (pentane–EtOAc–pyridine, 49:49:2) afforded **9** (169 mg, 58%) as a white solid; mp 237 °C.

IR (KBr): 3422 (m), 2981 (m), 1713 (s), 1660 (vs), 1603 (s), 1576 (m), 1453 (m), 1392 (m), 1365 (m), 1281 (s), 1212 (s), 1147 (s), 1025 (m), 975 (w), 913 (w), 864 (m), 767 (m), 705 (m), 611 (m), 500 (w) cm^{-1}.

^1H NMR (300 MHz, pyridine-d_5): δ = 8.49 (d, 1 H, J = 1.6 Hz, ArH-7), 8.38 (d, 1 H, J = 1.6 Hz, ArH-5), 7.77 (d, 2 H, J = 7.5 Hz, ArH 2′,6′), 7.55–7.54 (m, 1 H, ArH-4′), 7.38–7.31 (m, 2 H, ArH-3′,5′), 7.27–7.22 (m, 1 H, ArH-3), 6.67 (s, 1 H), 6.56 (s, 1 H), 4.36 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.22 (d, 3 H, J = 1.3 Hz, $ArCH_3$), 1.24 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$).

^{13}C NMR (75 MHz, pyridine-d_5): δ = 166.1, 161.7, 148.7, 143.9, 140.8, 130.4, 129.9, 129.0, 127.9, 126.7, 126.5, 123.7, 122.2, 121.0, 74.8, 61.2, 19.0, 14.4.

MS (EI): *m*/*z* = (%) 337 (M^+, 20), 336 (18), 335 (62), 334 (30), 322 (22), 321 (100), 320 (31), 319 (43), 318 (27), 306 (23), 292 (23), 291 (14), 290 (36), 276 (24), 262 (13), 248 (23), 217 (11), 105 (10), 77 (12).

HRMS: *m*/*z* calcd for $C_{20}H_{19}NO_4$: 337.1314; found: 337.1331.

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