Synthesis A. B. Bellan et al. Paper

Chromium-Catalyzed Cross-Coupling Reactions of Alkylmagnesium Reagents with Halo-Quinolines and Activated Aryl Chlorides

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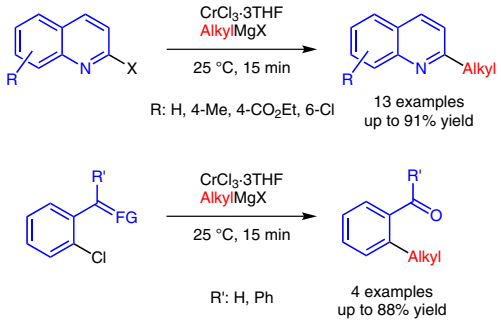
Dedicated to Professor Dieter Enders on the occasion of his 70th birthday and in recognition of his outstanding contribution to asymmetric catalysis.



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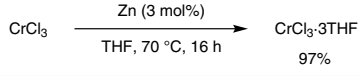
Abstract An efficient protocol for chromium(III)-catalyzed C(sp^2)–C(sp^3) cross-coupling is reported. The alkylations of halo-quinoline and phenacyl derivatives proceed at room temperature within minutes using the tetrahydrofuran-soluble chromium(III) complex $CrCl_3$·3THF. The reactions occur without the formation of homo-coupling side products, which are common for the related iron-, cobalt- or manganese-catalyzed cross-coupling reactions.

Key words magnesium, chromium, quinolines, cross-coupling, Grignard reagents

Although, palladium- and nickel-catalyzed cross-couplings using Grignard reagents are well known, alternative cross-couplings using transition-metal catalysts such as iron, cobalt or copper salts are cost efficient options and have therefore been studied with great attention.[1–9]

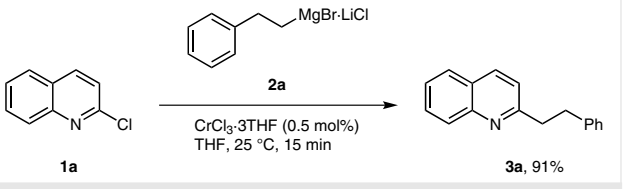
Recently, we reported that chromium(II) chloride catalyzes the cross-coupling of various aryl- and heteroarylmagnesium reagents with electron-deficient aryl and heteroaryl halides.[10–12] We showed also that $CrCl_2$ catalyzes the direct oxidative arylation of pyridines, aryl oxazolines, and imines with aryl Grignard reagents.[13] In addition, $CrCl_2$ catalyzes the amination of N-heterocyclic chlorides.[14]

Herein, we report a simple procedure allowing the cross-coupling of alkylmagnesium reagents with electron-deficient unsaturated substrates using $CrCl_3$·3THF, a chromium(III) catalyst that is well soluble in THF.[15] This complex was prepared by Soxhlet extraction of $CrCl_3$ with THF and a catalytic amount of zinc powder (Scheme 1).



Scheme 1 Preparation of THF-soluble $CrCl_3$·3THF

In a preliminary experiment, we treated 2-chloroquinoline (**1a**) with phenylethylmagnesium bromide (**2a**) (1.5 equiv), prepared from the corresponding bromide and Mg/LiCl, in the presence of $CrCl_3$·3THF (3 mol%) at 25 °C.[16] We observed full conversion after 15 minutes of reaction time and obtained 91% yield of the desired cross-coupling product **3a**. In contrast to other transition metals such as iron or cobalt, no homo-coupling byproducts were observed. We were also able to reduce the amount of $CrCl_3$·3THF from 3 mol% to 0.5 mol% with no decrease in the yield using this Grignard reagent (Scheme 2).



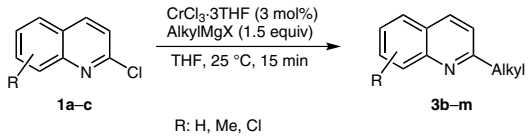
Scheme 2 First example of the chromium(III)-catalyzed coupling of alkylmagnesium reagents and (hetero)aryl chlorides

We extended this coupling reaction to primary alkylmagnesium derivatives such as **2b**,**c** and obtained the alkylated quinolines **3b**,**c** in 65–79% yield under the same reaction conditions (Table 1, entries 1 and 2). In these cross-couplings, we used Grignard reagents complexed with LiCl.[16] Control experiments using alkylmagnesium reagents in the absence of LiCl led to no differences in the yield or reaction time. The related 2-chloro-4-methylquinoline (**1b**) reacted similarly with the Grignard reagents **2a**–**e** leading, within 15 minutes at 25 °C, to the 2-alkylated quinolines **3d**–**h** in 56–82% yield (Table 1, entries 3–7). Electron-deficient 2,6-dichloroquinoline (**1c**) underwent a regioselective

cross-coupling with various primary alkylmagnesium reagents **2a**–**e** furnishing the expected 2-alkylated-6-chloroquinolines **3i**–**m** in 58–84% yield (Table 1, entries 8–12).[17]

The reaction scope could be somewhat extended and functionalized 2-bromoquinoline **1d** as well as 1-iodoisoquinoline (**1e**) reacted well with the alkylmagnesium reagent **2a** producing the expected products **3n**,**o**, both in 50% yield (Scheme 3).

Table 1 Chromium-Catalyzed Cross-Coupling Reactions of Alkylmagnesium Reagents **2a**–**e** with Bicyclic Heteroarenes **1a**–**c**



1a–c **3b–m**

R: H, Me, Cl

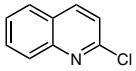
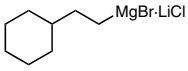
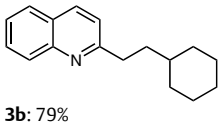
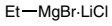
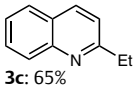
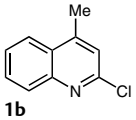
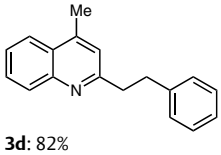
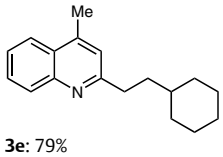
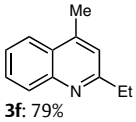
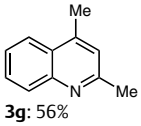
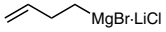
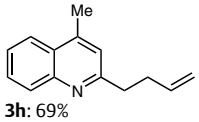
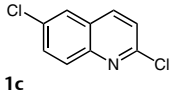
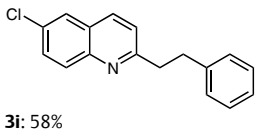
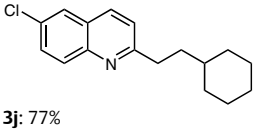
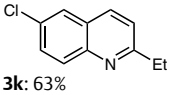
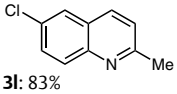
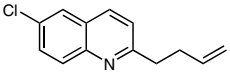
Entry	Electrophile	Magnesium reagent	Product/Yield[a]
1	 **1a**	 **2b**	 **3b**: 79%
2	**1a**	 **2c**	 **3c**: 65%
3	 **1b**	**2a**	 **3d**: 82%
4	**1b**	**2b**	 **3e**: 79%
5	**1b**	**2c**	 **3f**: 79%
6	**1b**	 **2d**	 **3g**: 56%
7	**1b**	 **2e**	 **3h**: 69%
8	 **1c**	**2a**	 **3i**: 58%

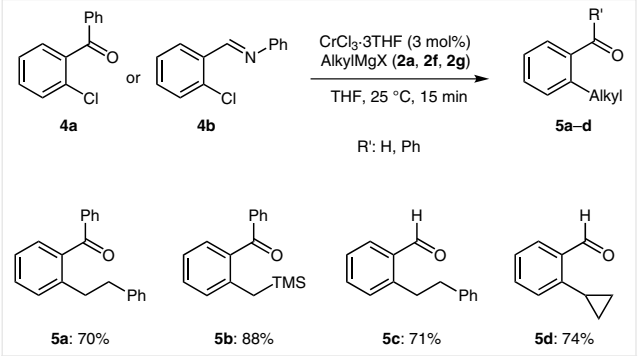
Table 1 (continued)

Entry	Electrophile	Magnesium reagent	Product/Yield[a]
9	**1c**	**2b**	 **3j**: 77%
10	**1c**	**2c**	 **3k**: 63%
11	**1c**	**2d**	 **3l**: 83%
12	**1c**	**2e**	 **3m**: 84%

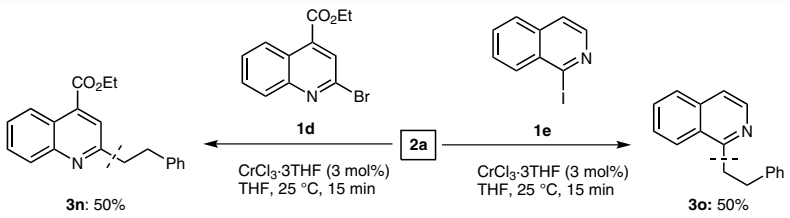
[a] Yield of isolated pure product.

Interestingly, alkylmagnesium halides also reacted smoothly with aryl chlorides bearing an electron-withdrawing function, such as a phenacyl group or an imine, at the *ortho* position. Thus, the Grignard reagent **2a** coupled with 2-chlorobenzophenone (**4a**) in the presence of 3 mol% $CrCl_3$·3THF within 15 minutes at 25 °C furnishing the alkylated benzophenone **5a** in 70% yield. Using the less reactive Grignard reagent, Me_3SiCH_2MgCl·LiCl[18] (**2f**) provided the benzophenone **5b** in 88% yield. Also, imine **4b** was readily alkylated with **2a** producing, after acidic hydrolysis, the *ortho*-alkylated benzaldehyde **5c** in 71% yield. Although, secondary alkylmagnesium halides normally undergo these cross-couplings in moderate yield, cyclopropylmagnesium bromide complexed with lithium chloride (**2g**) underwent a rapid cross-coupling with **4b** leading to the aldehyde **5d** in 74% yield (Scheme 4).

In summary, we have shown that primary alkylmagnesium reagents rapidly undergo cross-couplings with chloroquinolines, iodoisoquinolines, and activated aryl chlorides at 25 °C within 15 minutes leading to the corresponding alkylated products. These cross-couplings do not show any traces of homo-coupling, which are typical in iron- or cobalt-mediated cross-couplings. Further investigations on extending the reaction scope are underway in our laboratory.



Scheme 4 Chromium-catalyzed cross-couplings of activated aryl chlorides



Scheme 3 Cross-coupling of bromide **1d** and iodide **1e** with the Grignard reagent **2a**

Unless otherwise stated, all reactions were carried out with magnetic stirring and in flame-dried glassware under argon. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Reactions were monitored by gas chromatography or by thin-layer chromatography. TLC was performed using aluminum plates coated with SiO_2 (Merck 60, F-254) and visualized by UV radiation. Purification by column chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh, ASTM from Merck). Commercially available starting materials were used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone. Commercially available Grignard reagents were titrated against iodine in THF prior to use. Other Grignard reagents were prepared from the corresponding bromides by insertion of magnesium in the presence of lithium chloride, and were titrated against iodine in THF prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC analysis. Melting points were measured with a Büchi B-540 apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin Elmer spectrum BX-59343 instrument. For detection, a Smiths Detection DuraSamplIR II Diamond ATR sensor was used. IR data are reported in frequency of absorption (cm^{-1}). NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer in $CDCl_3$ and chemical shifts are reported in parts per million (ppm). H–H coupling constants are reported in Hz. Mass spectra and high-resolution mass spectra (HRMS) were recorded on Finnigan MAT 90 or Finnigan MAT 95 instruments using electron ionization (EI).

$CrCl_3$·3THF (0.1 M)

A dry, argon-flushed Soxhlet extraction apparatus was charged with anhydrous $CrCl_3$ (5.0 g, 31.6 mmol, 1.0 equiv) and Zn dust (62 mg, 0.95 mmol, 0.03 equiv).[15] The reaction mixture was extracted for 24 h with refluxing THF (250 mL). The mixture was allowed to cool to r.t. and the THF was removed in vacuo. The violet solid (11.5 g, 97%) was stored in a Schlenk flask under argon. THF (10 mL) was added and the Cr(III) complex partially dissolved. This solution was transferred into a tared Schlenk flask under argon and the THF was removed in vacuo. The weight of the resulting solid was determined and enough THF was added to obtain a 0.1 M solution.

Chromium-Mediated Cross-Coupling; Typical Procedure

A dry, argon-flushed Schlenk tube (10 mL), equipped with a stirring bar and a septum, was charged with a solution of $CrCl_3$·3THF (0.15 mL, 0.1 M in THF, 0.015 mmol, 0.03 equiv), the corresponding (hetero)aryl halide (0.5 mmol, 1.0 equiv) and THF (2.5 mL). The alkylmagnesium bromide solution (0.75 mmol, 1.5 equiv) was added dropwise over 2 min via syringe at r.t. After 15 min, the reaction mixture was quenched with sat. NH_4Cl solution (1 mL) and diluted with H_2O (4 mL). The phases were separated and the aq phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude residue was purified by flash column chromatography to give the respective cross-coupled product.

2-Phenethylquinoline (3a)

A cross-coupling was performed according to the typical procedure between 2-chloroquinoline (**1a**) (81 mg) and Grignard reagent **2a** (0.85 mL, 0.88 M) with $CrCl_3$·3THF (2.5 µmol, 25 µL, 0.5 mol%). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3a** (106 mg, 91%) was obtained as a yellow oil.

IR (ATR): 3026, 2923, 2856, 1618, 1599, 1502, 1452, 1425, 1310, 819, 748, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.5 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.1 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 7.39–7.21 (m, 6 H), 3.34 (dd, *J* = 9.8, 6.3 Hz, 2 H), 3.21 (dd, *J* = 9.7, 6.3 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.9, 148.0, 141.6, 136.3, 129.5, 128.9, 128.6, 128.5, 127.6, 126.9, 126.1, 125.9, 121.6, 41.1, 36.0.

MS (EI, 70 eV): *m*/z (%) = 233 (95) [M]$^+$, 232 (100), 217 (17), 156 (55), 129 (23), 128 (14), 115 (11), 91 (15).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{15}N$: 233.1204; found: 233.1204.

2-(2-Cyclohexylethyl)quinoline (3b)

A cross-coupling was performed according to the typical procedure between 2-chloroquinoline (**1a**) (81 mg) and Grignard reagent **2b** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3b** (95 mg, 79%) was obtained as a yellow oil.

IR (ATR): 2919, 2848, 1600, 1561, 1502, 1447, 1425, 824, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 10.9, 8.7 Hz, 2 H), 7.74 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.45 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 3.01–2.92 (m, 2 H), 1.85–1.76 (m, 2 H), 1.75–1.60 (m, 5 H), 1.39–1.29 (m, 1 H), 1.29–1.08 (m, 3 H), 1.04–0.90 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.5, 147.9, 136.2, 129.3, 128.9, 127.5, 126.7, 125.6, 121.4, 37.8, 37.8, 36.9, 33.3, 26.7, 26.4.

MS (EI, 70 eV): *m*/z (%) = 156 (38) [M–cyclohex]$^+$, 144 (10), 143 (100).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{17}H_{20}N$: 238.1590; found: 238.1592.

2-Ethylquinoline (3c)

A cross-coupling was performed according to the typical procedure between 2-chloroquinoline (**1a**) (81 mg) and Grignard reagent **2c** (0.65 mL, 1.15 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3c** (51 mg, 65%) was obtained as a yellow oil.

IR (ATR): 2969, 2933, 1618, 1602, 1504, 1426, 839, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.3 Hz, 1 H), 8.03 (d, *J* = 8.6 Hz, 1 H), 7.76 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.67 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 7.30 (d, *J* = 8.5 Hz, 1 H), 3.00 (q, *J* = 7.6 Hz, 2 H), 1.39 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 147.9, 136.4, 129.4, 128.9, 127.6, 126.8, 125.7, 120.9, 32.5, 14.2.

MS (EI, 70 eV): *m*/*z* (%) = 157 (55) [M]$^+$, 156 (100), 129 (22), 128 (15).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{11}H_{10}N$: 156.0808; found: 156.0806.

2-(4-Methylphenethyl)quinoline (3d)

A cross-coupling was performed according to the typical procedure between 2-chloro-4-methylquinoline (**1b**) (89 mg) and Grignard reagent **2a** (0.82 mL, 0.91 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3d** (101 mg, 82%) was obtained as a colorless oil.

IR (ATR): 3061, 3027, 2923, 1602, 1562, 1496, 1450, 754, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.34–7.15 (m, 5 H), 7.11 (s, 1 H), 3.24 (dd, *J* = 10.3, 5.8 Hz, 2 H), 3.14 (dd, *J* = 10.0, 5.5 Hz, 2 H), 2.67 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.7, 147.9, 144.4, 141.8, 129.5, 129.2, 128.6, 128.5, 127.0, 126.1, 125.7, 123.8, 122.4, 41.1, 36.1, 18.9.

MS (EI, 70 eV): *m*/*z* (%) = 247 (100) $[M]^+$, 87 (246), 232 (28), 231 (13), 170 (67), 143 (32), 116 (12), 115 (19), 91 (12).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{17}N$: 247.1361; found: 247.1356.

2-(2-Cyclohexylethyl)-4-methylquinoline (3e)

A cross-coupling was performed according to the typical procedure between 2-chloro-4-methylquinoline (**1b**) (89 mg) and Grignard reagent **2b** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3e** (100 mg, 79%) was obtained as a colorless oil.

IR (ATR): 2919, 2848, 2360, 1602, 1561, 1446, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 1 H), 7.90 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.64 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.46 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.11 (d, *J* = 1.1 Hz, 1 H), 2.98–2.85 (m, 2 H), 2.63 (d, *J* = 1.0 Hz, 3 H), 1.85–1.77 (m, 2 H), 1.76–1.58 (m, 5 H), 1.41–1.08 (m, 4 H), 1.03–0.83 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.2, 147.7, 144.2, 129.3, 129.0, 126.8, 125.4, 123.6, 122.1, 37.9, 37.8, 36.8, 33.3, 26.7, 26.4, 18.7.

MS (EI, 70 eV): *m*/*z* (%) = 253 (2) $[M]^+$, 170 (37), 158 (11), 157 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{23}N$: 253.1830; found: 253.1825.

2-Ethyl-4-methylquinoline (3f)

A cross-coupling was performed according to the typical procedure between 2-chloro-4-methylquinoline (**1b**) (89 mg) and Grignard reagent **2c** (0.65 mL, 1.15 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3f** (68 mg, 79%) was obtained as a colorless oil.

IR (ATR): 2969, 2933, 2873, 1604, 1562, 1507, 1448, 862, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 8.5, 0.7 Hz, 1 H), 7.91 (dd, *J* = 8.4, 0.8 Hz, 1 H), 7.65 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1 H), 7.47 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.12 (d, *J* = 1.0 Hz, 1 H), 2.94 (q, *J* = 7.6 Hz, 2 H), 2.64 (s, 3 H), 1.37 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7, 147.7, 144.4, 129.3, 129.1, 126.8, 125.4, 123.6, 121.6, 32.3, 18.8, 14.2.

MS (EI, 70 eV): *m*/*z* (%) = 171 (48) $[M]^+$, 170 (76), 70 (12), 61 (18), 45 (15), 43 (100).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{12}H_{12}N$: 170.0964; found: 170.0964.

2,4-Dimethylquinoline (3g)

A cross-coupling was performed according to the typical procedure between 2-chloro-4-methylquinoline (**1b**) (89 mg) and commercial MeMgCl (**2d**) (0.32 mL, 2.34 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3g** (44 mg, 56%) was obtained as a colorless oil.

IR (ATR): 2952, 2922, 1604, 1564, 1447, 859, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.95 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.67 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1 H), 7.50 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1 H), 7.14 (d, *J* = 1.2 Hz, 1 H), 2.70 (s, 3 H), 2.67 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 147.8, 144.3, 129.3, 129.3, 126.7, 125.6, 123.7, 122.9, 25.4, 18.8.

MS (EI, 70 eV): *m*/*z* (%) = 157 (100) $[M]^+$, 156 (19), 115 (13), 44 (12).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}N$: 157.0891; found: 157.0883.

2-(But-3-en-1-yl)-4-methylquinoline (3h)

A cross-coupling was performed according to the typical procedure between 2-chloro-4-methylquinoline (**1b**) (89 mg) and Grignard reagent **2e** (0.88 mL, 0.85 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 9:1), the title compound **3h** (63 mg, 69%) was obtained as a yellow oil.

IR (ATR): 3063, 2975, 2921, 1602, 1561, 1508, 1446, 1411, 910, 860, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 1 H), 7.94 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.49 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1 H), 7.13 (d, *J* = 1.1 Hz, 1 H), 5.93 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 5.09 (dq, *J* = 17.1, 1.7 Hz, 1 H), 5.04–4.95 (m, 1 H), 3.06–2.97 (m, 2 H), 2.66 (d, *J* = 1.0 Hz, 3 H), 2.63–2.53 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.8, 147.8, 144.4, 137.9, 129.4, 129.2, 126.9, 125.6, 123.7, 122.2, 115.2, 38.6, 34.0, 18.8.

MS (EI, 70 eV): *m*/*z* (%) = 197 (58) $[M]^+$, 184 (100), 170 (62), 157 (72), 144 (92), 130 (15), 115 (32).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}N$: 197.1204; found: 197.1207.

6-Chloro-2-phenethylquinoline (3i)

A cross-coupling was performed according to the typical procedure between 2,6-dichloroquinoline (**1c**) (99 mg) and Grignard reagent **2a** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 19:1), the title compound **3i** (78 mg, 58%) was obtained as a colorless solid.

Mp 94.6–95.8 °C.

IR (ATR): 2949, 2924, 2856, 1594, 1558, 1488, 1452, 1308, 1073, 830, 820, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 9.0 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.72 (d, *J* = 2.4 Hz, 1 H), 7.61 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.33–7.16 (m, 6 H), 3.30–3.24 (m, 2 H), 3.20–3.11 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2, 146.4, 141.4, 135.3, 131.5, 130.6, 130.3, 128.6, 128.5, 127.4, 126.3, 126.1, 122.5, 41.0, 35.8.

MS (EI, 70 eV): *m*/*z* (%) = 266 (100) $[M - H]^+$, 192 (17), 190 (48), 163 (18), 91 (26).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{13}{}^{35}ClN$: 266.0731; found: 266.0726.

6-Chloro-2-(2-cyclohexylethyl)quinoline (3j)

A cross-coupling was performed according to the typical procedure between 2,6-dichloroquinoline (**1c**) (99 mg) and Grignard reagent **2b** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 19:1), the title compound **3j** (105 mg, 77%) was obtained as a colorless solid.

Mp 69.2–70.3 °C.

IR (ATR): 2919, 2849, 1599, 1557, 1489, 1447, 1072, 875, 829, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.6 Hz, 2 H), 7.74 (d, *J* = 2.4 Hz, 1 H), 7.60 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 3.02–2.91 (m, 2 H), 1.86–1.76 (m, 2 H), 1.75–1.61 (m, 4 H), 1.41–1.12 (m, 4 H), 1.03–0.90 (m, 2 H), 0.90–0.80 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.0, 146.4, 135.4, 131.3, 130.6, 130.3, 127.4, 126.3, 122.4, 37.9, 37.7, 36.9, 33.4, 26.8, 26.5.

MS (EI, 70 eV): *m*/*z* (%) = 273 (3) $[M]^+$, 192 (12), 190 (38), 176 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{20}{}^{35}ClN$: 273.1284; found: 273.1292.

6-Chloro-2-ethylquinoline (3k)

A cross-coupling was performed according to the typical procedure between 2,6-dichloroquinoline (**1c**) (99 mg) and Grignard reagent **2c** (0.65 mL, 1.15 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 29:1), the title compound **3k** (60 mg, 63%) was obtained as a yellow oil.

IR (ATR): 2970, 2934, 2874, 1598, 1490, 1302, 1188, 1074, 897, 876, 829 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.94 (m, 2 H), 7.76 (d, *J* = 2.4 Hz, 1 H), 7.61 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 2.99 (q, *J* = 7.7 Hz, 2 H), 1.39 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 146.4, 135.5, 131.4, 130.6, 130.3, 127.4, 126.3, 121.9, 32.4, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 190 (100) [M – H]$^+$, 164 (16), 143 (22), 128 (13).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{11}H_9{}^{35}ClN$: 190.0418; found: 190.0412.

6-Chloro-2-methylquinoline (3l)

A cross-coupling was performed according to the typical procedure between 2,6-dichloroquinoline (**1c**) (99 mg) and Grignard reagent **2d** (0.32 mL, 2.34 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 19:1), the title compound **3l** (74 mg, 83%) was obtained as a colorless solid.

Mp 95.2–96.0 °C.

IR (ATR): 2951, 2916, 1597, 1557, 1489, 1369, 1066, 885, 833, 805 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 2.3 Hz, 1 H), 7.93 (d, *J* = 3.2 Hz, 1 H), 7.74 (d, *J* = 2.4 Hz, 1 H), 7.60 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 2.73 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 146.4, 135.3, 131.4, 130.4, 127.2, 126.3, 123.0, 25.5.

MS (EI, 70 eV): *m*/*z* (%) = 177 (100) [M]$^+$, 162 (11), 142 (26), 140 (11), 115 (21), 43 (29).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_8{}^{35}ClN$: 177.0345; found: 177.0343.

2-(But-3-en-1-yl)-6-chloroquinoline (3m)

A cross-coupling was performed according to the typical procedure between 2,6-dichloroquinoline (**1c**) (99 mg) and Grignard reagent **2e** (0.88 mL, 0.85 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 39:1), the title compound **3m** (90 mg, 84%) was obtained as a colorless oil.

IR (ATR): 3076, 2920, 1640, 1598, 1556, 1488, 1072, 909, 875, 829, 811 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.90 (m, 2 H), 7.71 (d, *J* = 2.3 Hz, 1 H), 7.58 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 5.90 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.06 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.98 (dd, *J* = 10.3, 1.6 Hz, 1 H), 3.12–2.97 (m, 2 H), 2.70–2.47 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.4, 146.3, 137.6, 135.3, 131.4, 130.5, 130.3, 127.4, 126.2, 122.4, 115.5, 38.5, 33.7.

MS (EI, 70 eV): *m*/*z* (%) = 216 (100) [M – H]$^+$, 204 (15), 190 (38), 177 (31), 163 (18), 140 (27).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{13}H_{11}{}^{35}ClN$: 216.0575; found: 216.0568.

Ethyl 2-Phenethylquinoline-4-carboxylate (3n)

A cross-coupling was performed according to the typical procedure between ethyl 2-bromoquinoline-4-carboxylate (**1d**) (140 mg) and Grignard reagent **2a** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 19:1), the title compound **3n** (76 mg, 50%) was obtained as a yellow oil.

IR (ATR): 3063, 3027, 2981, 1721, 1594, 1507, 1371, 1268, 1242, 1200, 1147, 1026, 797, 776, 750, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (dd, *J* = 8.5, 1.4 Hz, 1 H), 8.12 (dt, *J* = 8.4, 1.0 Hz, 1 H), 7.76–7.69 (m, 2 H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H), 7.32–7.22 (m, 4 H), 7.22–7.14 (m, 1 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 3.38–3.27 (m, 2 H), 3.23–3.09 (m, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 161.3, 149.0, 141.3, 135.5, 129.7, 129.5, 128.6, 128.5, 127.4, 126.2, 125.5, 123.7, 122.8, 61.9, 40.9, 35.7, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 305 (100) [M]$^+$, 274 (46), 231 (28), 199 (16), 91 (21), 71 (43), 57 (63), 43 (93).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{19}O_2N$: 305.1416; found: 305.1408.

1-Phenethylisoquinoline (3o)

A cross-coupling was performed according to the typical procedure between 1-iodoisoquinoline (**1e**) (128 mg) and Grignard reagent **2a** (0.87 mL, 0.86 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 19:1), the title compound **3o** (58 mg, 50%) was obtained as a yellow oil.

IR (ATR): 3052, 3026, 2929, 1622, 1586, 1562, 1496, 1453, 1388, 1358, 823, 744, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5.7 Hz, 1 H), 8.11–8.05 (m, 1 H), 7.75 (d, *J* = 8.2 Hz, 1 H), 7.60 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.51 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1 H), 7.47 (dd, *J* = 5.8, 0.9 Hz, 1 H), 7.28–7.23 (m, 4 H), 7.20–7.12 (m, 1 H), 3.58–3.51 (m, 2 H), 3.18–3.10 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.1, 142.0, 142.0, 136.3, 129.9, 128.6, 128.6, 127.5, 127.2, 127.0, 126.2, 125.2, 119.5, 37.4, 35.6.

MS (EI, 70 eV): *m*/*z* (%) = 232 (100) [M – H]$^+$, 217 (17), 156 (41), 129 (35), 115 (19), 91 (17), 43 (12).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{17}H_{14}N$: 232.1121; found: 232.1117.

(2-Phenethylphenyl)(phenyl)methanone (5a)

A cross-coupling was performed according to the typical procedure between 2-chlorobenzophenone (**4a**) (434 mg, 2.0 mmol) and Grignard reagent **2a** (3.49 mL, 0.86 M) with $CrCl_3$·3THF (0.6 mL, 0.06 mmol). After purification by flash column chromatography (*i*-hexane–EtOAc, 29:1), the title compound **5a** (400 mg, 70%) was obtained as a colorless oil.

IR (ATR): 3061, 3025, 2925, 2860, 1662, 1597, 1494, 1448, 1314, 1267, 927, 757, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.68 (m, 2 H), 7.56–7.47 (m, 1 H), 7.42–7.31 (m, 3 H), 7.24 (dd, *J* = 7.6, 1.5 Hz, 2 H), 7.20 (dd, *J* = 7.3, 1.3 Hz, 1 H), 7.18–7.10 (m, 2 H), 7.10–6.99 (m, 3 H), 2.99–2.88 (m, 2 H), 2.85–2.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.6, 141.6, 140.8, 138.5, 137.9, 133.2, 130.4, 130.3, 130.2, 128.8, 128.5, 128.5, 128.3, 126.0, 125.5, 38.2, 35.6.

MS (EI, 70 eV): *m*/*z* (%) = 286 (2) [M]$^+$, 195 (100), 177 (13), 165 (20), 91 (22).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{18}O$: 286.1358; found: 286.1353.

Phenyl{2-[(trimethylsilyl)methyl]phenyl}methanone (5b)

A cross-coupling was performed according to the typical procedure between 2-chlorobenzophenone (**4a**) (108 mg) and Grignard reagent **2f** (1.03 mL, 0.73 M). After purification by flash column chromatography (*i*-hexane–EtOAc, 39:1), the title compound **5b** (118 mg, 88%) was obtained as a colorless oil.

IR (ATR): 3061, 2953, 2897, 1659, 1597, 1447, 1262, 1246, 1152, 927, 837, 760, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.18–7.09 (m, 2 H), 2.35 (s, 2 H), –0.05 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.6, 141.2, 138.4, 136.4, 132.9, 130.4, 130.3, 130.3, 130.1, 128.4, 123.4, 24.3, –1.3.

MS (EI, 70 eV): *m*/*z* (%) = 267 (100) $[M - H]^+$, 253 (24), 178 (14), 165 (23), 149 (18), 111 (12), 73 (47), 69 (18), 57 (12), 43 (24).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{19}O^{28}Si$: 267.1200; found: 267.1184.

2-Phenethylbenzaldehyde (5c)

A cross-coupling was performed according to the typical procedure between 1-(2-chlorophenyl)-*N*-phenylmethanimine (**4b**) (108 mg) and Grignard reagent **2a** (0.87 mL, 0.86 M). The reaction mixture was stirred with 2 M HCl (2 mL) for 1 h before work-up. After purification by flash column chromatography (*i*-hexane–EtOAc, 39:1), the title compound **5c** (75 mg, 71%) was obtained as a yellow oil.

IR (ATR): 3062, 3026, 2924, 2859, 1691, 1599, 1573, 1495, 1452, 1191, 755, 724, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, 1 H), 7.82 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.38 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.32–7.25 (m, 2 H), 7.24–7.16 (m, 4 H), 3.37–3.29 (m, 2 H), 2.94–2.87 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.4, 144.4, 141.3, 133.9, 133.8, 132.5, 131.3, 128.7, 128.5, 126.8, 126.2, 38.4, 35.0.

MS (EI, 70 eV): *m*/*z* (%) = 210 (16) $[M]^+$, 192 (10), 132 (12), 91 (100), 65 (29), 61 (11), 43 (48).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{14}O$: 210.1045; found: 210.1028.

2-Cyclopropylbenzaldehyde (5d)

A cross-coupling was performed according to the typical procedure between 1-(2-chlorophenyl)-*N*-phenylmethanimine (**4b**) (108 mg) and Grignard reagent **2g** (0.86 mL, 0.87 M). The reaction mixture was stirred with 2 M HCl (2 mL) for 1 h before work-up. After purification by flash column chromatography (*i*-hexane–EtOAc, 39:1), the title compound **5d** (54 mg, 74%) was obtained as a colorless oil.

IR (ATR): 3005, 2854, 2758, 1689, 1599, 1489, 1288, 1224, 1191, 1030, 823, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.60 (s, 1 H), 7.82 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.36–7.27 (m, 1 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 2.63 (tt, *J* = 8.5, 5.3 Hz, 1 H), 1.14–1.04 (m, 2 H), 0.82–0.76 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.9, 146.2, 135.0, 134.1, 130.2, 126.7, 126.2, 11.9, 8.6.

MS (EI, 70 eV): *m*/*z* (%) = 145 (22) $[M - H]^+$, 131 (69), 128 (21), 115 (100), 103 (44), 90 (49), 77 (32), 63 (29), 51 (23).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{10}H_9O$: 145.0648; found: 145.0651.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561615.

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