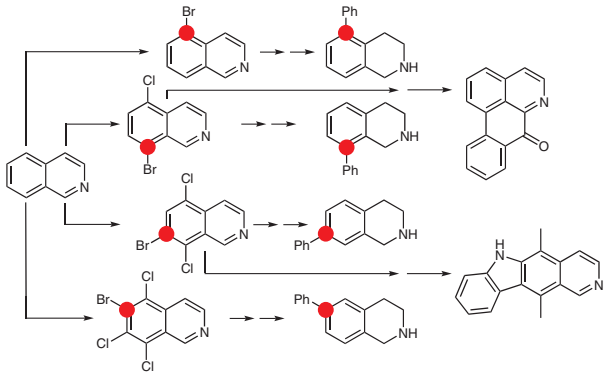
Synthesis D. V. Horváth et al. Paper

Regioexhaustive Functionalization of the Carbocyclic Core of Isoquinoline: Concise Synthesis of Oxoaporphine Core and Ellipticine

Dániel Vajk Horváth
Frigyes Domonyi
Roberta Palkó
Andrea Lomoschitz
Tibor Soós*

Institute of Organic Chemistry, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok körútja 2, 1117 Budapest, Hungary
soos.tibor@ttk.mta.hu



Received: 08.12.2017
Accepted: 15.12.2017
Published online: 07.03.2018
DOI: 10.1055/s-0037-1609153; Art ID: ss-2017-z0804-op

Abstract A general and versatile strategy has been developed for the functionalization of the carbocyclic core of the isoquinoline. This regioexhaustive approach employs electrophilic halogenation as a toolbox methodology and delivers highly decorated intermediates that can be further elaborated toward medicinally relevant building blocks or natural products.

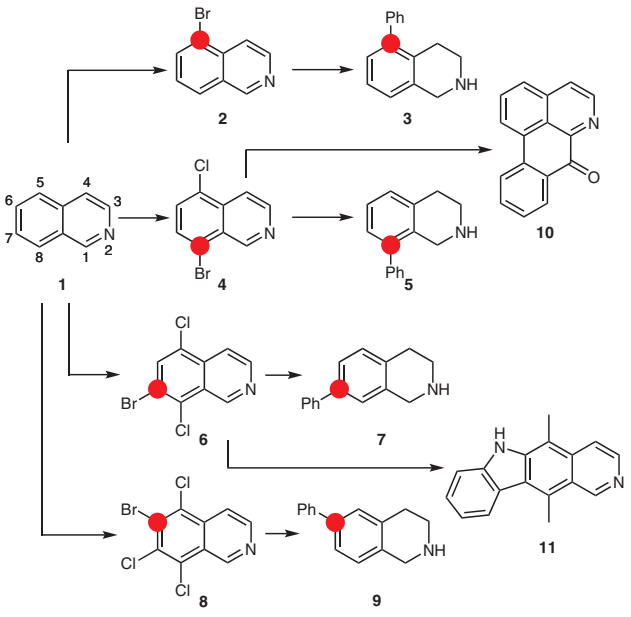
Key words isoquinoline, regioexhaustive, cross-coupling, heterocycles, fused-ring systems, ellipticine

Isoquinoline and 1,2,3,4-tetrahydroisoquinoline are widely present as key structural motifs in a large number of natural products, pharmaceuticals, and organic materials.[1] Owing to their importance, a myriad of synthetic methodologies have been developed towards the synthesis of this class of compounds. Of particular note are the traditional Pomeranz–Fritsch, Pictet–Spengler, and Bischler–Napieralski reactions, as they are still the fundamental gateways to isoquinoline skeletons.[2] Despite their utility, each of these approaches has well-known limitations; they work only well for arenes with electron-donating groups and the commonly required harsh acidic reaction conditions imply low functional group tolerance. Recently, various transition-metal-mediated methodologies have emerged as promising alternatives to construct isoquinolines.[3] Although reasonable scopes have been demonstrated, the limited commercial availability of the starting materials, together with the requisite pre-installation of necessary functionalities en route to isoquinolines impart certain limitations on these methodologies.

To achieve a more divergent strategy toward functionalized isoquinolines, we envisioned exploiting the regioexhaustive-functionalization concept, introduced by Schlosser.[4] This holistic strategy has been devised to generate structural diversity from a given aromatic or heteroaromatic core structure via iterative and selective 'site-silencing' transformations. The practical realization of this chemistry has relied on site-selective metalation as a toolbox methodology followed by introduction of protective Cl or TMS groups.

To demonstrate the utility of the regioexhaustive concept in the realm of isoquinolines, we set ourselves the goal to use the inexpensive isoquinoline (**1**) as a starting material and attach a phenyl group at any of the four possible vacant positions of its carbocyclic core. At the outset, owing to the reactivity of isoquinolines, it appeared worthwhile to use the aromatic electrophilic substitution reaction as a toolbox methodology instead of metalation chemistry.[5] Without an added catalyst, a halogenation at the C-4 position was reported.[6] The swamping catalyst effect, however, enables the change of the regioselectivity of the halogenation reaction from the C-4 position to the benzene ring.[7] In these reactions, however, $AlCl_3$ is used in more than one equivalent under forcing reaction conditions. As a result, these procedures are not easy to handle and not attractive even for laboratory-scale production. Not surprisingly, practicality and cost issues have spurred efforts to develop alternative procedures. Recently, it has been demonstrated that strong Brønsted acids can behave as a swamping catalyst in isoquinoline (**1**) halogenation. Thus, selective monobromination and dichlorination has been achieved at ambient temperature with *N*-bromosuccinimide (NBS)[8] and 1,3-dichloro-5,5-dimethylhydantoin (DCH).[9]

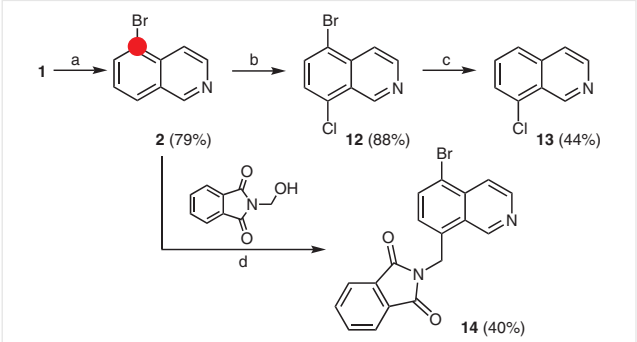
With this in mind, we questioned whether the swamping Brønsted catalysis-based isoquinoline halogenation could be expanded to a regioexhaustive toolbox which expediently and selectively produces various bromo- and chloro-substituted isoquinolines. Given the intrinsic order of reactivity of the carbocyclic core of isoquinoline (5 > 8 > 7 > 6.), we anticipated that gradually functionalizing isoquinoline by chlorine or bromine would be possible.[5] Thus, chlorine or bromine would function as an easily removable 'site-silencing' group which allows accesss to less reactive positions (Scheme 1).



Scheme 1 The regioexhaustive strategy for isoquinoline derivatization

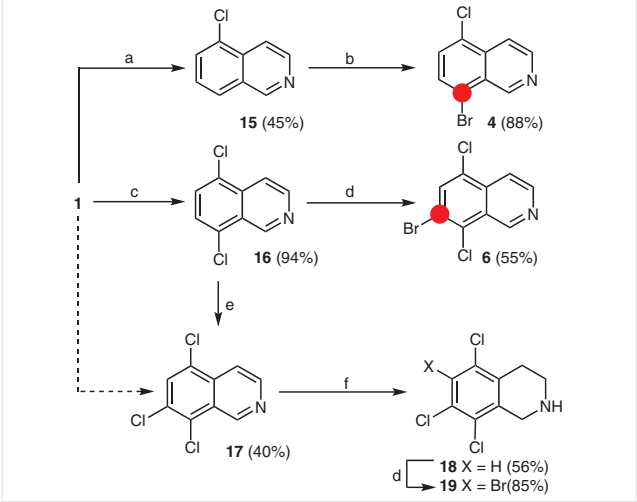
First, the most reactive position, C-5 of isoquinoline's carbocycle was blocked by selective bromination by using NBS/concd H_2SO_4.[8] Slight modification of a previously used workup procedure allowed us to isolate the desired product **2** in excellent yield in a scalable manner (Scheme 2).

With **2** in hand, a chlorine atom was inserted at position 8 by using trichloroisocyanuric acid (TCCA) (Scheme 2).[10] This 8-chloro-5-bromo compound **12** was then reduced to 8-chloroisoquinoline (**13**). It is worth mentioning that neither the classical Pomeranz–Fritsch method (only 9%) nor multistep deamination protocols (26%) could provide **13** with higher overall yields than this process.[11] Next, by using swamping Brønsted acid catalysis, an amidomethylene group was introduced at position 8. Although the yield of the Tscherniac–Einhorn reaction[12] was moderate, the simplicity of the isolation of **14** improved the utility of this transformation.



Scheme 2 Transformations of 5-bromoisoquinoline. *Reagents and conditions*: (a) NBS, H_2SO_4, –20 to –25 °C; (b) TCCA, H_2SO_4, 25 °C; (c) $NaBH_4$, Pd/C, 2-methyltetrahydrofuran/MeOH, 25 °C; (d) H_2SO_4, 70 °C.

As bromine has a more restricted area of application than chlorine for site-silencing, the more valuable 5-chloro compound was targeted. By using TCCA at 10 °C, **15** was produced in moderate yield, high purity, and a scalable manner (Scheme 3).



Scheme 3 Preparation of different chloro- and bromoisoquinoline derivatives. *Reagents and conditions*: (a) TCCA, H_2SO_4, 10 °C; (b) NBS, H_2SO_4, 25 °C; (c) TCCA, H_2SO_4, 25 °C; (d) DBDMH, H_2SO_4, 25 °C; (e) TCCA, H_2SO_4, 100 °C; (f) $BH_3{\cdot}SMe_2$, THF, 70 °C.

The monochlorination reaction proved to be less selective than the monobromination reaction, and thus formation of a mixture of **15**, 8-chloroisoquinoline (**13**), and 5,8-dichloroisoquinoline (**16**) was observed. Fortunately, the different basicities of the mono- and dichlorinated products made it possible to separate them by extractions at different pH, and the monochlorinated isoquinolines were subsequently purified by recrystallization. Then, **15** was converted into the 8-bromo derivative **4** (88% yield) by using NBS at ambient temperature (Scheme 3).

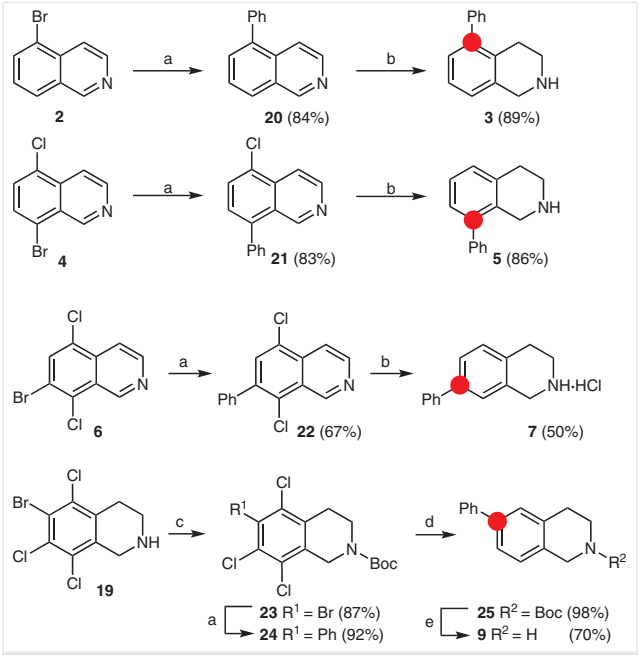
Next, the same key operations, subsequent chlorination–bromination, were employed to access C-7 brominated **6**. To this end, the synthesis of the 5,8-dichlorinated **16** had to be accomplished. While the reported method used a 1,3-dichloro-5,5-dimethylhydantoin reagent in concd H_2SO_4,[9] we employed an even more cost-effective agent, TCCA, with great success (Scheme 3). For the subsequent bromination reaction, NBS was replaced by the more active 1,3-dibromo-5,5-dimethylhydantoin (DBDMH). The reaction was conducted between 15 and 20 °C to minimize the decomposition[13] of the starting material, and **6** was obtained in 55% yield after precipitation of the crude product (Scheme 3).

The preparation of the remaining C-6 brominated derivative required a multistep synthesis. First, the more reactive 5-, 7-, and 8-positions were 'switched off' by chlorination. While the direct trichlorination from isoquinoline (**1**) in TCCA/H_2SO_4 provided only a trace amount of **17**, its synthesis became possible in a two-step process. Thus, **16** was chlorinated by TCCA at 100 °C (Scheme 3) and the reaction was stopped as soon as the conversion reached 50%. In this manner, the decomposition of the isoquinoline product was less extensive and a 40% isolated yield was realized. The unchanged starting material could be recovered and reused. In the next step, however, **17** failed to react with DBDMH owing to the presence of the large number of deactivating groups. Therefore, the pyridine ring of isoquinoline in **17** was saturated, forming **18**, by using the borane–dimethyl sulfide complex and then the bromo substituent could be attached with high yield in the last available position, giving **19**.

With all possible chloro- and bromo-substituted isoquinoline derivatives in hand, we embarked on their arylation by using phenylboronic acid in the Suzuki reaction. The appropriate phenylisoquinoline derivatives **20**, **21**, and **22** were isolated in moderate to excellent yields (Scheme 4). Thus, the reactivity difference between bromine and chlorine was sufficient in cross-coupling reactions to obtain the targeted molecules selectively.

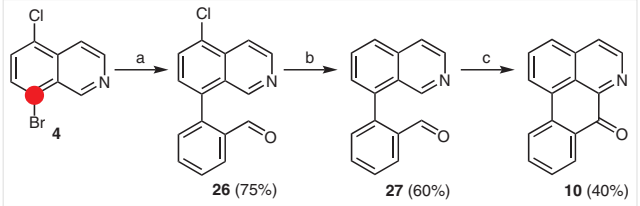
Then, phenylisoquinolines **20**–**22** were transformed into tetrahydroisoquinoline derivatives. In these reactions, 10% Pd/C was used as catalyst in methanol in the presence of acetic acid, and the corresponding tetrahydroisoquinoline derivatives **3**, **5**, and **7** were obtained moderate to good yields (Scheme 4).

6-Phenyl-1,2,3,4-tetrahydroisoquinoline (**25**) was synthesized in a similar fashion, except that the NH group had to be protected before the cross-coupling reaction (Scheme 4). Therefore, **19** was reacted with di-*tert*-butyl dicarbonate, which gave **23** in good yield (87%). Then **23** was effectively converted into **25** in high yield by using the above-mentioned sequence. Finally, **25** was deprotected by using a TFA/H_2O mixture under an inert atmosphere to avoid partial oxidation, which provided **9** in 70% isolated yield.



Scheme 4 Transformation of the brominated isoquinoline derivatives. *Reagents and conditions*: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 85 °C; (b) Pd/C, H_2 (10 bar), AcOH, MeOH, 25 °C; (c) Boc_2O, EtOAc, 50 °C; (d) Pd/C, H_2 (10 bar), Et_3N, MeOH, 25 °C; (e) TFA, H_2O, 25 °C.

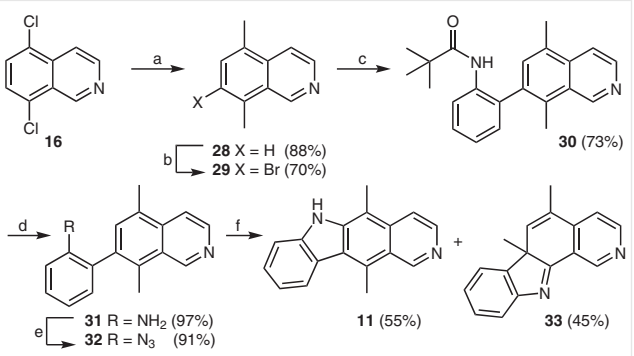
To demonstrate the synthetic value of these chloro- and bromo-substituted isoquinolines, short, concise routes to the core of oxoaporphine[14] **10** and ellipticine[15] (**11**) were developed (Scheme 5 and Scheme 6).



Scheme 5 Synthesis of the oxoaporphine core. *Reagents and conditions*: (a) 2-$OHCC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 85 °C; (b) Et_3N, Pd/alumina, H_2 (1 bar), MeOH, 25 °C; (c) TBHP, TFA, DCE, 60 °C.

First, 8-bromo-5-chloroisoquinoline (**4**) was used in a Suzuki reaction with 2-formylphenylboronic acid and **26** was isolated in good yield (Scheme 5). Next, the chlorine atom was removed from position 5 by hydrogen by using Pd on alumina as catalyst in methanol to provide **27** in 60% yield. Finally, the oxoaporphine framework **10** was formed in 40% yield in a Minisci-type reaction.

The synthesis of ellipticine (**11**), based on an approach by Miller,[15b] was envisioned to proceed via 7-bromo-5,8-dimethylisoquinoline (**29**) that could be easily accessed from **16** (Scheme 6). Accordingly, 5,8-dichloroisoquinoline (**16**)



Scheme 6 Concise total synthesis of ellipticine (**11**). *Reagents and conditions*: (a) $AlMe_3$, $Pd(PPh_3)_4$, THF, 85 °C; (b) NBS, H_2SO_4, 25 °C; (c) 2-PivNHC$_6$H$_4$B(OH)$_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 85 °C; (d) 20% aq H_2SO_4, 120 °C; (e) $NaNO_2$, NaOAc, NaN_3, HCl, 0–5 °C; (f) 1,2-dichlorobenzene, 190 °C.

was transformed into 5,8-dimethylisoquinoline (**28**) by using trimethylaluminum in a cross-coupling reaction in a good yield (88%). Then **28** was brominated with NBS to afford **29** in a selective manner. It is worth mentioning that **28** and its brominated derivative **29** were previously reported, but their synthesis required a multistep, tedious process starting from *p*-xylene or its halogenated derivative.[15c–e] Next, the cross-coupling reaction of **29** and the subsequent deprotection of the amine group was realized to afford **31**. The amino group was then smoothly converted into an azido group in **32** in excellent yield. The final ring closure of **32** in 1,2-dichlorobenzene was carried out in a microwave at 190 °C, and ellipticine (**11**) was isolated in 55% yield.

In summary, we have demonstrated the utility of an exhaustive strategy to deliver valuable isoquinoline and tetrahydroisoquinoline derivatives, many of which are difficult to access by other methods. Owing to the operational simplicity of this approach, one can easily access these derivatives on a multigram scale. We also showed that these isoquinoline derivatives are valuable starting materials for generating structural diversity among isoquinolines and they can be utilized for a concise synthesis of natural products. Further extension of our regioexhaustive method toward new isoquinolines bearing other substituent patterns and their application in total synthesis is underway.

TLC was performed on Merck Silica gel 60 F_{254} precoated TLC plates (0.25 mm thickness) and visualization was carried out with short-wavelength UV light (254 nm). Flash chromatography was carried out by using Teledyne ISCO CombiFlash Rf200 UV/VIS and Merck Silica gel 60 H. Melting points were recorded on an automatic melting point apparatus (Jasco SRS Optimelt) and are uncorrected. IR spectra were recorded on a Varian 2000 ATR-FTIR spectrophotometer. NMR spectra were measured on 400 MHz or 500 MHz instruments at r.t. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (^{1}H, $CHCl_3$: δ = 7.26, DMSO: δ = 2.50; ^{13}C: $CHCl_3$: δ = 77.16, DMSO: δ = 39.52). HRMS was carried out on a Q-TOF Premier (Waters Corporation) spectrometer. GC-MS analysis was conducted on a Shimadzu GC-2010 Plus Ultra instrument. LC-MS analysis was conducted on a Shimadzu LCMS2020. Isoquinoline (**1**) was redistilled and NBS was recrystallized from H_2O prior to use. The 2-(pivaloylamino)phenylboronic acid was prepared as described in the literature.[16] THF and toluene were freshly distilled from sodium/benzophenone. All other chemicals were purchased from commercial sources and used as received.

5-Bromoisoquinoline (2)[8]

To mechanically stirred concd H_2SO_4 (170 mL), isoquinoline (**1**; 21.8 g, 169.2 mmol, 1.0 equiv) was slowly added at 0 °C. The mixture was cooled to –25 °C and NBS (39.3 g, 220.5 mmol, 1.3 equiv) was added at such a rate that the reaction temperature was kept between at –25 and –22 °C. The mixture was stirred between –25 and –20 °C for 2 h and at –18 °C for 2 h. It was then poured onto crushed ice (600 g) and made alkaline (pH 8–9) by using concd aq NH_3 solution with intensive cooling. The alkaline slurry was extracted with Et_2O (3 × 300 mL). The combined organic layer was washed with 1.0 M aq NaOH (2 × 300 mL) and H_2O (300 mL), dried over anhyd Na_2SO_4, filtered, and evaporated to give a brown oil. The crude product was purified by vacuum distillation (128–130 °C/2 Torr) to give **2** as a white powder.

Yield: 27.8 g (79%); mp 82–83 °C.

IR (ATR): 1580, 1485, 1368, 1263, 1199, 1136, 962, 817, 750, 673, 627, 525 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.64 (d, *J* = 6.0 Hz, 1 H), 7.99–7.94 (m, 3 H), 7.48 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 144.5, 135.2, 134.2, 129.8, 127.9, 127.6, 121.7, 119.6.

5-Bromo-8-chloroisoquinoline (12)

5-Bromoisoquinoline (**2**; 5.2 g, 25 mmol, 1.0 equiv) was dissolved in concd H_2SO_4 (55 mL) at 0 °C, and addition of TCCA (2.32 g, 10 mmol, 1.2 equiv) followed in small portions. The mixture was allowed to warm to 25 °C and stirred overnight. Then the mixture was poured onto crushed ice (ca. 100 g). The precipitate was filtered and the filtrate was cooled and made alkaline by careful addition of cold concd aq NH_3 solution. The slurry was extracted with EtOAc (3 × 60 mL). The combined organic layer was washed with 1.0 M NaOH (3 × 50 mL), H_2O (3 × 50 mL), and brine (3 × 50 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 treated with Tonsil® to remove the contaminants. Removal of the solvent under reduced pressure gave **12** as a white powder.

Yield: 5.31 g (88%); mp 111–114 °C.

IR (ATR): 1886, 1606, 1568, 1479, 1423, 1359, 1256, 1209, 1182, 1045, 979, 831, 815, 792, 694, 630, 565 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 8.7 (d, *J* = 5.9 Hz, 1 H), 7.99 (d, *J* = 5.9 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 145.4, 136.3, 134.0, 132.5, 128.1, 126.7, 120.4, 119.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_9H_6ClBrN: 241.9372; found: 241.9380.

8-Chloroisoquinoline (13)[11a]

A one-necked glass flask was charged with **12** (1.20 g, 4.95 mmol, 1.0 equiv), 2-methyltetrahydrofuran (10 mL), and MeOH (10 mL), and then N_2 gas was bubbled through the mixture. Under an inert atmosphere, 10% Pd/C (530 mg, 0.5 mmol, 0.1 equiv) was added followed

by careful addition of $NaBH_4$ (206 mg, 5.45 mmol, 1.1 equiv). The flask was closed by a gas bubbler filled with silicon oil. The mixture was stirred for 70 min at 25 °C (longer reaction times resulted in an extensive formation of over-reduced products such as 1,2,3,4-tetrahydroisoquinoline and 8-chloro-1,2,3,4-tetrahydroisoquinoline), and then quenched with glacial AcOH (500 µL, 8.74 mmol, 1.75 equiv). The mixture was then stirred for another 10 min, followed by filtration through Celite. The cake was washed with MeOH and CH_2Cl_2. The filtrate was evaporated and the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 93:7), which afforded off-white crystals.

Yield: 360 mg (44%); mp 50–55 °C.

IR (ATR): 1620, 1553, 1429, 1379, 1300, 1204, 1038, 970, 827, 748, 686, 634, 534 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 8.60 (d, *J* = 5.7 Hz, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 7.69–7.56 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 143.8, 137.1, 132.5, 130.3, 127.5, 125.6, 125.7, 120.1.

5-Chloroisoquinoline (15)[11b]

To mechanically stirred concd H_2SO_4 (100 mL), isoquinoline (**1**; 12.9 g, 0.1 mol, 1.0 equiv) was slowly added at 0 °C. During intensive stirring TCCA (12.8 g, 55 mmol, 1.65 equiv) was then added in 4 portions while the reaction temperature was kept at 10 °C. The mixture was then stirred at 10 °C and followed by GC-MS. After 24 h the reaction mixture was poured onto crushed ice (ca. 200 g) and the precipitate was filtered. The pH of the filtrate was adjusted to 2 with concd aq NH_3 solution with extensive cooling. The slurry was then filtered. The filtrate was extracted with toluene (6 × 75 mL) to remove the side product, 5,8-dichloroisoquinoline (**16**). The aqueous phase was further basified with concd aq NH_3 solution until pH 6 was reached. At this point the precipitate was filtered, washed with H_2O, and dried in air. Finally, the filtrate was recrystallized from methylcyclohexane to afford **15**.

Yield: 7.60 g (45%); mp 70–72 °C.

IR (ATR): 1580, 1489, 1371, 1267, 1204, 1140, 1065, 984, 822, 750, 687, 628, 536 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 8.64 (d, *J* = 6.0 Hz, 1 H), 8.02 (d, *J* = 6.0 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 143.9, 133.7, 131.0, 130.3, 129.4, 127.3, 126.7, 116.9.

8-Bromo-5-chloroisoquinoline (4)

5-Chloroisoquinoline (**15**; 1.64 g, 10 mmol, 1.0 equiv) was dissolved at 0 °C in concd H_2SO_4 (30 mL); then NBS (2.67 g, 15 mmol, 1.5 equiv) was added. The mixture was stirred at ambient temperature overnight. After that the mixture was poured onto crushed ice (ca. 50 g). The precipitate was filtered and the filtrate was made alkaline (pH 8–9) by careful addition of cold concd aq NH_3 solution with intensive cooling. The slurry was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with 1.0 M aq NaOH (3 × 50 mL), H_2O (3 × 50 mL), and brine (3 × 50 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 treated with Tonsil® to remove the contaminants, and then filtered. Removal of the solvent under reduced pressure gave **4** as a white powder.

Yield: 2.06 g (88%); mp 129–132 °C.

IR (ATR) 1608, 1574, 1483, 1425, 1369, 1258, 1213, 1184, 1099, 1045, 979, 835, 815, 813, 694, 629, 573, 534 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.63 (s, 1 H), 8.74 (d, *J* = 5.8 Hz, 1 H), 8.01 (d, *J* = 5.8 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.5, 145.3, 135.4, 131.3, 131.2, 130.8, 127.7, 121.5, 117.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_9H_6BrClN: 241.9372; found: 241.9375.

5,8-Dichloroisoquinoline (16)[9]

Isoquinoline (**1**; 24.7 g, 191.3 mmol, 1.0 equiv) was dissolved in concd H_2SO_4 (200 mL) at 0 °C, and then TCCA (35.6 g, 153.0 mmol, 2.4 equiv) was added in small portions to the solution at the same temperature. The reaction mixture was allowed to warm to r.t. and stirred overnight. It was then poured onto crushed ice and the precipitate was filtered. The filtrate was made alkaline (pH 8–9) by addition of concd aq NH_3 solution with intensive cooling and extracted with Et_2O (3 × 400 mL). The combined organic layer was washed with 1.0 M NaOH (3 × 200 mL), H_2O (3 × 200 mL), and brine (1 × 200 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The crude product was recrystallized from CH_2Cl_2–methylcyclohexane to give **16** as a white powder.

Yield: 35.6 g (94%); mp 115–117 °C.

IR (ATR): 1610, 1572, 1483, 1363, 1257, 1186, 1045, 989, 817, 700, 633, 594 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 8.73 (d, *J* = 5.9 Hz, 1 H), 8.03 (d, *J* = 5.9 Hz, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 144.9, 135.0, 131.6, 130.4, 130.2, 127.7, 126.4, 117.0.

7-Bromo-5,8-dichloroisoquinoline (6)

5,8-Dichloroisoquinoline (**16**; 15.0 g, 0.759 mol, 1.0 equiv) was dissolved at 0 °C in concd H_2SO_4 (100 mL). The reaction mixture was allowed to warm to 10 °C and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH; 35.60 g, 0.124 mol, 1.6 equiv) was added at such a rate that the reaction temperature was kept between 15 and 20 °C. The reaction was followed by GC-MS. When the reaction was completed, the mixture was poured onto crushed ice (200 g) and the pH was adjusted to 2 by addition of concd aq NH_3 solution with extensive cooling. The slurry was stirred for 15 min then filtered. The cake was washed with 10% aq NaOH (2 × 100 mL) and H_2O (2 × 100 mL) and first dried in air and then over P_2O_5. Compound **6** was obtained as a white solid.

Yield: 11.7 g (55%); mp 190–191 °C.

IR (ATR): 1600, 1564, 1342, 1217, 1140, 1051, 920, 824, 714, 654, 568 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 8.76 (br s, *J* = 5.2 Hz, 1 H), 8.00 (d, *J* = 5.8 Hz, 1 H), 7.98 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 144.9, 134.2, 134.2, 134.0, 131.7, 130.6, 121.4, 117.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_5Cl_2BrN$: 275.8982; found: 275.8983.

5,7,8-Trichloroisoquinoline (17)[7]

To mechanically stirred concd H_2SO_4 (50 mL), 5,8-dichloroisoquinoline (**16**; 10.0 g, 50.4 mmol 1.0 equiv) was slowly added at 0 °C. Then TCCA (11.7 g 50.4 mmol, 3 equiv) was added at 0 °C. The mixture was then rapidly heated to 100–104 °C. The reaction was followed by GC-MS. When the reaction reached 50% conversion, the mixture was cooled to r.t. and poured onto crushed ice. (The conversion cannot be increased further without extensive decomposition of the product). The precipitate was filtered off and washed with H_2O. The filtrate was

made alkaline (pH 8–9) by careful addition of cold concd aq NH_3 solution with intensive cooling and the alkaline slurry was filtered. The precipitate was dissolved in hot EtOAc and treated with Tonsil®, after which it was filtered. The filtrate was allowed to cool to r.t. and was left to stand overnight; a white precipitate formed. Filtration of the precipitate gave **17** as white crystals.

Yield: 4.60 g (40%); mp 180–182 °C.

IR (ATR): 1566, 1342, 1252, 1147, 1053, 918, 823, 725, 671, 571, 503 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1 H), 8.74 (d, *J* = 5.9 Hz, 1 H), 8.00 (d, *J* = 5.9 Hz, 1 H), 7.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 145.0, 133.6, 131.5, 131.4, 130.6, 129.4, 126.9, 116.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_5Cl_3N$: 231.9488; found: 231.9497.

5,7,8-Trichloro-1,2,3,4-tetrahydroisoquinoline (18)

$BH_3{\cdot}SMe_2$ (11.4 mL, 120 mmol, 6 equiv) was added to a solution of **17** (4.65 g, 20.0 mmol, 1.0 equiv) in anhyd THF (80 mL) under a N_2 atmosphere. The mixture was heated at reflux overnight. After that the reaction mixture was cooled to 0 °C and then carefully quenched with MeOH (ca. 30 mL), after which the solvent was evaporated. A H_2O/H_2SO_4 solution (1:1; 80 mL) was added to the residue and the mixture was heated at reflux for 24 h. Then the mixture was cooled to 0 °C, made alkaline (pH 8–9) by using cold concd aq NH_3 solution, and extracted with EtOAc (4 × 50 mL). The combined organic layer was washed with brine, dried over anhyd Na_2SO_4, and evaporated. The crude product was recrystallized from cyclohexane to give white crystals.

Yield: 2.65 g (56%); mp 114–116 °C.

IR (ATR): 1572, 1419, 1321, 1188, 1159, 1126, 1095, 979, 945, 878, 804, 727, 532 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 1 H), 4.00 (s, 2 H), 3.11 (t, *J* = 6.0 Hz, 2 H), 2.72 (t, *J* = 6.0 Hz, 2 H), 1.77 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 133.8, 133.3, 130.5, 129.1, 127.9, 47.7, 42.8, 27.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_9Cl_3N$: 235.9801; found: 235.9807.

6-Bromo-5,7,8-trichloro-1,2,3,4-tetrahydroisoquinoline (19)

Compound **18** (5.30 g, 22.4 mmol, 1.0 equiv) was slowly added to mechanically stirred concd H_2SO_4 (51 mL) at 0 °C. Over 20 min, DBDMH (3.84 g, 13.44 mmol, 1.2 equiv) was added slowly; then the reaction mixture was allowed to warm to r.t. and stirred for 2 h. The solution was made alkaline (pH 8–9) by using cold concd aq NH_3 solution with intensive cooling. The alkaline slurry was extracted with EtOAc (4 × 40 mL). The combined organic layer was washed with 1.0 M aq NaOH (3 × 25 mL) and H_2O (25 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The crude product was recrystallized from cyclohexane to give white crystals.

Yield: 6.00 g (85%); mp 156–158 °C.

IR (ATR): 1421, 1358, 1304, 1206, 1132, 981, 883, 777, 731, 698, 636, 517 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 2 H), 3.11 (t, *J* = 6.0 Hz, 2 H), 2.78 (t, *J* = 6.0 Hz, 2 H), 1.67 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3, 135.0, 134.8, 132.1, 130.1, 122.3, 47.8, 43.0, 29.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_8Cl_3BrN$: 313.8906; found: 313.8908.

6-Bromo-2-*tert*-butoxycarbonyl-5,7,8-trichloro-1,2,3,4-tetrahydroisoquinoline (23)

Tetrahydroisoquinoline **19** (1.05 g, 3.0 mmol, 1.0 equiv) was suspended in EtOAc (20 mL) and the mixture was warmed to 50 °C. When the starting material had dissolved, Boc_2O (786 mg, 3.6 mmol, 1.2 equiv) was added and the mixture was stirred overnight. The reaction was followed by TLC (hexane–EtOAc, 3:1). When the reaction was completed, the solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 98:2); this gave **23** as a white solid.

Yield: 1.09 g (87%); mp 148–150 °C.

IR (ATR): 1676, 1417, 1364, 1317, 1242, 1157, 1105, 966, 928, 864, 766, 743, 706, 625, 503 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.55 (s, 2 H), 3.65 (t, *J* = 5.9 Hz, 2 H), 2.88 (t, *J* = 5.9 Hz, 2 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 146.2, 134.6, 134.5, 132.7, 126.1, 122.8, 80.8, 45.3, 45.1, 28.6, 28.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}BrCl_3NO_2Na$: 435.9249; found: 435.9264.

Arylisoquinolines 20–22; General Procedure

Into a Schlenk bomb, the appropriate haloisoquinoline (2.40 mmol, 1.0 equiv), $PhB(OH)_2$ (352 mg, 2.9 mmol, 1.2 equiv), Na_2CO_3 (510 mg, 4.81 mmol, 2 equiv), DME (10 mL), and distilled H_2O (5 mL) were placed under an inert atmosphere. N_2 gas was bubbled through the stirred mixture for 10 min. Then $Pd(PPh_3)_4$ (167 mg, 0.144 mmol, 0.06 equiv) was added. The reaction mixture was heated to 85 °C and kept at this temperature. The progress of the reaction was monitored by TLC. After completion, the mixture was cooled to r.t. and diluted with H_2O (16 mL) and EtOAc (27 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc) to give the corresponding phenylisoquinoline derivative.

5-Phenylisoquinoline (20)[17]

According to the general procedure, starting from 5-bromoisoquinoline (**2**; 500 mg, 2.40 mmol, 1.0 equiv), the product was obtained after chromatography (silica gel, hexane–EtOAc, 91:9) as a pale yellow oil.

Yield: 415 mg (84%).

IR (ATR): 1616, 1584, 1485, 1443, 1379, 1029, 829, 754, 700, 629, 532 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 8.49 (d, *J* = 6.0 Hz, 1 H), 8.02–7.99 (q, 1 H), 7.75 (d, *J* = 6.0 Hz, 1 H), 7.68 (s, 1 H), 7.67 (d, *J* = 1.2 Hz, 1 H), 7.53–7.47 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.7, 143.0, 139.5, 139.1, 134.4, 131.3, 130.0, 129.1, 128.7, 128.0, 127.4, 127.1, 118.9.

5-Chloro-8-phenylisoquinoline (21)

According to the general procedure, starting from **4** (581 mg, 2.40 mmol), the product was obtained after chromatography (silica gel, hexane–EtOAc, 98:2) as an off-white solid.

Yield: 477 mg (83%); mp 75–78 °C.

IR (ATR): 1601, 1558, 1483, 1447, 1369, 1263, 1213, 1171, 1078, 1047, 978, 901, 854, 833, 791, 758, 702, 653, 568, 542, 526 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 8.57 (d, *J* = 6.0 Hz, 1 H), 7.72–7.69 (m, 2 H), 7.56 (d, *J* = 7.7 Hz, 1 H), 7.57–7.43 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 143.9, 138.8, 138.3, 135.8, 132.0, 131.0 (2 C), 130.0 (2 C), 128.8, 128.2, 127.3, 126.0, 118.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ClN$: 240.0580; found: 240.0577.

5,8-Dichloro-7-phenylisoquinoline (22)

According to the general procedure, starting from **6** (666 mg, 2.40 mmol), the product was obtained after chromatography (silica gel, hexane–EtOAc, 97:3) as a white solid.

Yield: 441 mg (67%); mp 147–151 °C.

IR (ATR): 1577, 1483, 1346, 1269, 1215, 1172, 1047, 991, 912, 822, 762, 694, 594, 553 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 8.75 (d, *J* = 5.9 Hz, 1 H), 8.07 (d, *J* = 5.9 Hz, 1 H), 7.80 (s, 1 H), 7.51–7.45 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 144.5, 139.8, 138.0, 134.2, 132.9, 129.9, 129.7, 129.2, 128.6, 128.5, 127.0, 116.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}Cl_2N$: 274.0190; found: 274.0188.

2-*tert*-Butoxycarbonyl-5,7,8-trichloro-6-phenyl-1,2,3,4-tetrahydroisoquinoline (24)

Into a Schlenk bomb, **23** (1.33 g, 3.20 mmol, 1.0 equiv), $PhB(OH)_2$ (780 mg, 6.40 mmol, 2.0 equiv), Cs_2CO_3 (2.09 g, 6.410 mmol, 2 equiv), and DME (22 mL) were placed under an inert atmosphere. N_2 gas was bubbled through the stirred mixture for 10 min, and then $Pd(PPh_3)_4$ (167 mg, 0.144 mmol, 0.06 equiv) was added. The reaction mixture was heated to 85 °C and kept at this temperature for 3 h. The mixture was cooled to r.t., the base Cs_2CO_3 was collected by filtration and washed with DME, and the filtrate was evaporated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 98:2). The crude product was recrystallized from hexane to give **24** as a white solid.

Yield: 1.22 g (92%); mp 108–110 °C.

IR (ATR): 1690, 1402, 1366, 1315, 1238, 1157, 1107, 972, 932, 868, 746, 725, 702, 683, 642, 619, 606, 550, 507 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 3 H), 7.19 (d, *J* = 6.8 Hz, 2 H), 4.66 (s, 2 H), 3.70 (t, *J* = 5.2 Hz, 2 H), 2.89 (t, *J* = 5.2 Hz, 2 H), 1.52 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 139.3, 137.9, 134.3, 133.5, 133.4, 131.4, 129.2, 128.5, 128.3, 80.6, 45.5, 40.9, 39.8, 28.6, 27.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}Cl_3NO_2Na$: 434.0457; found: 434.0448.

5-Phenyl-1,2,3,4-tetrahydroisoquinoline (3)

5-Phenylisoquinoline (**20**; 400 mg, 1.95 mmol, 1.0 equiv) and glacial AcOH (115 µL, 1.95 mmol, 1.0 equiv) were dissolved in MeOH (10 mL) in an autoclave. Under an inert atmosphere, 10% Pd/C (213 mg, 0.20 mmol, 0.1 equiv) was then added to the reaction mixture in one portion. The suspension was stirred under H_2 (10 bar) overnight at ambient temperature. The reaction was followed by LC-MS. The catalyst was removed by filtration on Celite and washed with MeOH and CH_2Cl_2. The filtrate was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with 10% aq NaOH (2 × 10 mL) and H_2O (2 × 10 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. Isoquinoline **3** was obtained as a white, amorphous solid.

Yield: 334 mg (89%); mp 95–99 °C.

IR (ATR): 2452, 2325, 1571, 1458, 1422, 1338, 1294, 1253, 1176, 1072, 1029, 948, 781, 762, 729, 704, 648, 599, 568, 546 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (t, *J* = 7.3 Hz, 2 H), 7.37–7.27 (m, 3 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 7.4 Hz, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 4.14 (s, 2 H), 3.09 (t, *J* = 5.9 Hz, 2 H), 2.68 (t, *J* = 5.9 Hz, 2 H), 2.64 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.5, 141.4, 135.3, 132.3, 129.3 (2 C), 128.3 (2 C), 127.9, 127.1, 125.9, 125.7, 48.4, 44.0, 28.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N$: 210.1283; found: 210.1280.

8-Phenyl-1,2,3,4-tetrahydroisoquinoline (5)

5-Chloro-8-phenylisoquinoline (**21**; 168 mg, 0.70 mmol) and glacial AcOH (41 µL, 0.70 mmol, 1.0 equiv) were dissolved in MeOH (10 mL) in an autoclave. Under an inert atmosphere, 10% Pd/C (75 mg, 0.07 mmol, 0.1 equiv) was then added to the reaction mixture in one portion. The suspension was stirred under H_2 (10 bar) overnight at ambient temperature. The reaction was followed by LC-MS. The catalyst was removed by filtration on Celite and washed with MeOH and CH_2Cl_2. The filtrate was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with 10% aq NaOH (2 × 10 mL) and H_2O (2 × 10 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The product was obtained as a colorless, viscous oil.

Yield: 126 mg (86%).

IR (ATR): 1460, 1431, 839, 783, 756, 723, 700, 675, 665, 637, 611, 596, 571, 540 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (dd, J_1 = 7.9, J_2 = 6.6 Hz, 2 H), 7.35–7.32 (m, 1 H), 7.28–7.26 (m, 2 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 1 H), 3.87 (s, 2 H), 3.16 (t, *J* = 6.1 Hz, 2 H), 2.92 (t, *J* = 6.1 Hz, 2 H), 2.56 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.5, 141.4, 135.3, 132.3, 129.3 (2 C), 128.3 (2 C), 127.9, 127.1, 125.9, 125.7, 48.4, 44.0, 28.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N$: 210.1283; found: 210.1275.

7-Phenyl-1,2,3,4-tetrahydroisoquinoline (7)

5,8-Dichloro-7-phenylisoquinoline hydrochloride (**22**·HCl; 168 mg, 0,54 mmol) was dissolved in MeOH (10 mL) in an autoclave. Under an inert atmosphere, 10% Pd/C (58 mg, 0.05 mmol, 0.1 equiv) was then added to the reaction mixture in one portion. The suspension was stirred under H_2 (10 bar) for 3 h at 70 °C. The reaction was followed by LC-MS. The catalyst was removed by filtration on Celite and washed with MeOH and CH_2Cl_2. The filtrate was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with sat. aq Na_2CO_3 (2 × 10 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The product (colorless oil, 170 mg) was stored and characterized as a hydrochloride salt, therefore it was dissolved in anhyd Et_2O and precipitated with HCl in anhyd Et_2O. Recrystallization of the salt in MeOH gave 7-phenyl-1,2,3,4-tetrahydroisoquinolinium chloride (**7**·HCl) as an off-white powder.

Yield: 67 mg (50%); mp >220 °C (decomp).

IR (ATR): 1589, 1487, 1454, 1383, 1352, 1178, 1070, 964, 883, 760, 736, 690 cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ = 9.80 (br s, 2 H), 7.64–7.29 (m, 8 H), 4.29 (s, 2 H), 3.34 (s, 2 H), 3.05 (s, 2 H).

^{13}C NMR (125 MHz, DMSO): δ = 139.3, 138.2, 131.1, 129.4, 129.2, 128.8, 127.3, 126.3, 125.4, 124.8, 43.4, 40.3, 24.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N$: 210.1283; found: 210.1281.

2-*tert*-Butoxycarbonyl-6-phenyl-1,2,3,4-tetrahydroisoquinoline (25)

Tetrahydroisoquinoline **24** (227 mg, 0.55 mmol, 1.0 equiv) and Et_3N (232 µL, 1.65 mmol, 3.0 equiv) were dissolved in MeOH (12 mL) in an autoclave. Under an inert atmosphere, 10% Pd/C (59 mg, 0.06 mmol, 0.1 equiv) was then added to the reaction mixture in one portion. The suspension was stirred under H_2 (10 bar) for 3 h at 70 °C. The catalyst was removed by filtration on Celite and washed with MeOH and CH_2Cl_2. The filtrate was evaporated under vacuum. The residue was dissolved in EtOAc (20 mL) and H_2O (20 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over anhyd Na_2SO_4, filtered, and evaporated; this gave **25** as a colorless oil.

Yield: 167 mg (98%).

IR (ATR): 1691, 1483, 1418, 1366, 1331, 1238, 1159, 1103, 1045, 986, 935, 906, 860, 760, 729, 696, 646, 534 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 3 H), 7.37–7.31 (m, 2 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 4.62 (s, 2 H), 3.69 (t, *J* = 6.6 Hz, 2 H), 2.90 (t, *J* = 6.2 Hz, 2 H), 1.51 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 141.0, 139.6, 135.3, 133.0, 128.9, 127.5, 127.4, 127.2, 126.9, 125.2, 80.0, 45.7, 41.4, 29.3, 28.7.

6-Phenyl-1,2,3,4-tetrahydroisoquinoline (9)

Tetrahydroisoquinoline **25** (60 mg, 0.193 mmol, 1.0 equiv) was dissolved in H_2O (1 mL) and TFA (4 mL) under a N_2 atmosphere. The reaction mixture was stirred for 3 h at r.t. Then the reaction mixture was diluted with CH_2Cl_2 and extracted with sat. aq $NaHCO_3$. After that, the aqueous phase was washed with CH_2Cl_2. The combined organic layer was washed with sat. aq $NaHCO_3$ and dried over anhyd Na_2SO_4, filtered, and evaporated; this gave **9** as white crystals.

Yield: 28 mg (70%); mp 91–94 °C.

IR (ATR): 1589, 1487, 1454, 1383, 1352, 1178, 1070, 964, 883, 760, 736, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.2 Hz, 2 H), 7.42 (t, *J* = 7.60 Hz, 2 H), 7.37–7.32 (m, 3 H), 7.09 (d, *J* = 7.60 Hz, 1 H), 4.06 (s, 2 H), 3.18 (t, *J* = 6.5 Hz, 2 H), 2.87 (t, *J* = 6.5 Hz, 2 H), 2.10 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.2, 139.2, 135.2, 135.0, 128.6, 128.1, 127.1, 127.1, 126.8, 124.7, 48.1, 44.0, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N$: 210.1283; found: 210.1264.

2-[(5-Bromoisoquinolin-8-yl)methyl]isoindoline-1,3-dione (14)

5-Bromoisoquinoline (**2**; 1.0 g, 4.8 mmol, 1.0 equiv) and *N*-(hydroxymethyl)phthalimide (1.7 g, 9.6 mmol, 2.0 equiv) was dissolved at 0 °C in concd H_2SO_4 (10 mL). The mixture was stirred for 1 week at 70 °C. Then the reaction mixture was poured onto crushed ice and filtered. Recrystallization from EtOAc gave **14** as a white solid.

Yield: 705 mg (40%); mp 212–214 °C.

IR (ATR): 1768, 1713, 1419, 1392, 1373, 1333, 1262, 1111, 748, 714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.8 (s, 1 H), 8.7 (d, *J* = 5.9 Hz, 1 H), 8.0 (d, *J* = 5.9 Hz, 1 H), 7.9 (d, *J* = 7.7 Hz, 1 H), 7.88–7.82 (m, 2 H), 7.76–7.69 (m, 2 H), 7.53 (d, *J* = 7.7 Hz, 1 H), 5.38 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 149.1, 144.7, 135.4, 134.3, 133.6, 132.6, 132.0, 129.0, 127.3, 123.6, 122.1, 119.9, 38.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{12}BrN_2O_2$: 367.0082; found: 367.0073.

2-(5-Chloroisoquinolin-8-yl)benzaldehyde (26)

8-Bromo-5-chloroisoquinoline **4** (10.0 mmol, 2.43 g, 1.0 equiv), 2-$OHCC_6H_4B(OH)_2$ (1.80 g, 12.0 mmol, 1.2 equiv), Na_2CO_3 (2.12 g, 20.0 mmol, 2 equiv), DME (30 mL), and distilled H_2O (15 mL) were placed in a Schlenk bomb under an inert atmosphere. N_2 gas was bubbled through the stirred mixture for 10 min. Then $Pd(PPh_3)_4$ (696 mg, 0.6 mmol, 0.06 equiv) was added. The reaction mixture was heated to 85 °C and kept at this temperature. The progress of the reaction was monitored by TLC (hexane–EtOAc, 2:1). After completion, the mixture was cooled to r.t. and diluted with H_2O (45 mL) and EtOAc (90 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhyd Na_2SO_4, and then filtered and evaporated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 80:20) to give **26** as a yellow solid.

Yield: 2.0 g (75%); mp 97–101 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (s, 1 H), 8.93 (s, 1 H), 8.69 (d, *J* = 5.8 Hz, 1 H), 8.17–8.06 (m, 2 H), 7.84 (d, *J* = 7.5 Hz, 1 H), 7.73 (t, *J* = 6.9 Hz, 1 H), 7.66 (t, *J* = 7.3 Hz, 1 H), 7.48–7.35 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 151.2, 144.7, 140.8, 135.9, 135.1, 133.9, 133.8, 132.0, 131.6, 129.5, 129.27, 129.26, 128.8, 128.6, 117.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}ClNO$: 268.0529; found: 268.0524.

2-(Isoquinolin-8-yl)benzaldehyde (27)

Benzaldehyde **26** (590 mg, 2.2 mmol, 1.0 equiv) and Et_3N (5.52 mL, 39.6 mmol, 18.0 equiv) were dissolved in MeOH (10 mL). Under an inert atmosphere 5% Pd on alumina (47 mg, 0.02 mmol, 0.01 equiv) was then added to the reaction mixture in one portion. The suspension was stirred under H_2 (atmospheric pressure) for 4.5 h. The reaction was followed by GC-MS. The catalyst was removed by filtration on Celite and washed with MeOH and CH_2Cl_2. The filtrate was evaporated under vacuum. The residue was dissolved in Et_2O (30 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 1:1) to give **27** as a yellow oil.

Yield: 307 mg (60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 8.95 (s, 1 H), 8.58 (d, *J* = 5.3 Hz, 1 H),), 8.13 (d, *J* = 5.3 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 1 H), 7.84–7.69 (m, 3 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.52–7.43 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.3, 150.9, 143.5, 141.9, 136.5, 136.1, 135.1, 133.7, 131.9, 129.6, 129.0, 128.2, 127.9, 127.2, 120.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}NO$: 234.0919; found: 234.0911.

7*H*-Dibenzo[*de*,*g*]quinolin-7-one (10)[18]

In a Schlenk bomb, **27** (205 mg, 0.88 mmol, 1.0 equiv) was dissolved in DCE (4 mL), and then TFA (80 µL, 0.96 mmol, 1.1 equiv) and 5 M TBHP in nonane (1.4 mL, 1.76 mmol, 8.0 equiv) were added. The mixture was deoxygenated by using the freeze–pump–thaw method, and then heated to 60 °C and kept at this temperature for 24 h. The reaction was monitored by LC-MS, and when it was complete, sat. aq $NaHCO_3$ (30 mL) was added to the mixture, which was then extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with sat.

aq $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 1:1, then EtOAc) to give **10** as a yellow solid.

Yield: 81 mg (40%); mp 210–214 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.05 (d, *J* = 5.1 Hz, 1 H), 8.53 (d, *J* = 7.7 Hz, 1 H), 8.41 (d, *J* = 7.3 Hz, 1 H), 8.26 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 7.3 Hz, 2 H), 7.84 (t, *J* = 7.8 Hz, 1 H), 7.76 (t, *J* = 7.3 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.7, 146.9, 145.6, 137.0, 135.0, 134.0, 131.8, 131.1, 129.3, 129.2, 128.8, 128.6, 125.1, 124.75, 124.67, 123.2.

5,8-Dimethylisoquinoline (28)[15d]

In a flame-dried Schlenk bomb, **16** (7.12 g, 36.0 mmol, 1.0 equiv) was dissolved in anhyd THF (80 mL). N_2 was bubbled through the stirred mixture for 10 min. Then $Pd(PPh_3)_4$ (1.8 g, 1.8 mmol, 0.05 equiv) was added. After that, 2.0 M $AlMe_3$ in toluene (66 mL, 72 mmol, 4 equiv) was added slowly to the cooled reaction mixture. The resulting brown mixture was then stirred overnight at 85 °C. Then the reaction mixture was cooled to r.t., poured onto crushed ice (ca. 200 g), and made alkaline (pH 8–9) with 10% aq NaOH. The slurry was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated. The residue (36.8 g, brown oil) was purified by Kugelrohr distillation under reduced pressure at 160 °C to give a colorless oil. The product was stored under an inert atmosphere in a freezer, otherwise it easily became brown.

Yield: 5.0 g (88%).

IR (ATR): 1612, 1591, 1580, 1491, 1462, 1441, 1425, 1385, 1279, 1219, 1066, 1029, 831, 804, 719, 640, 549, 542 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.43 (s, 1 H), 8.57 (d, *J* = 5.8 Hz, 1 H), 7.74 (d, *J* = 5.8 Hz, 1 H), 7.38 (d, *J* = 6.7 Hz, 1 H), 7.27 (d, *J* = 6.7 Hz, 1 H), 2.73 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.6, 142.5, 135.7, 133.3, 131.6, 130.6, 127.8, 127.7, 117.5, 18.5, 18.4.

7-Bromo-5,8-dimethylisoquinoline (29)[15d]

At 0 °C, **28** (1.80 g, 11.5 mmol, 1.0 equiv) was slowly added to intensively stirred concd H_2SO_4 (18.0 mL); addition of NBS (2.45 g, 13.8 mmol, 1.2 equiv) followed and the mixture was stirred at ambient temperature for 6 h. The mixture was poured onto crushed ice (40 g) and made alkaline (pH 8–9) by using concd aq NH_3 with intensive cooling. The alkaline slurry was extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with H_2O (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and evaporated to give a brown solid.

Yield: 1.90 g (70%); mp 98–100 °C.

IR (ATR): 1589, 1562, 1491, 1435, 1379, 1354, 1273, 1213, 1072, 1034, 961, 867, 816, 756, 719, 640, 596, 575, 540, 498 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 8.59 (d, *J* = 5.8 Hz, 1 H), 7.72 (d, *J* = 5.8 Hz, 1 H), 7.66 (s, 1 H), 2.83 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.4, 142.6, 135.04, 135.02, 133.3, 132.5, 128.5, 123.6, 117.6, 18.2, 17.8.

N-[2-(5,8-Dimethylisoquinolin-7-yl)phenyl]pivalamide (30)

Isoquinoline **29** (1.35 g, 5.70 mmol, 1.0 equiv), 2-$PivNHC_6H_4B(OH)_2$ (1.89 g, 8.55 mmol, 1.5 equiv), Na_2CO_3 (1.20 g, 11.4 mmol, 2 equiv), DME (18 mL), and distilled H_2O (9 mL) were placed in a Schlenk bomb under an inert atmosphere. N_2 gas was bubbled through the stirred mixture for 10 min, and then $Pd(PPh_3)_4$ (223 mg, 0.19 mmol, 0.06 equiv) was added. The reaction mixture was heated to 85 °C and stirred at this temperature overnight. The reaction was followed by TLC (hexane–EtOAc, 3:1). After completion, the mixture was cooled to r.t. and diluted with H_2O (30 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 3:2) to give **30** as a white amorphous solid.

Yield: 1.38 g (73%); mp 136–138 °C.

IR (ATR): 1678, 1584, 1518, 1445, 1389, 1306, 1229, 1153, 1083, 922, 885, 853, 822, 752, 598, 565, 542 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 8.67 (d, *J* = 5.9 Hz, 1 H), 8.37 (d, *J* = 8.2 Hz, 1 H), 7.92–7.86 (m, 1 H), 7.43–7.38 (m, 2 H), 7.20 (s, 2 H), 7.08 (s, 1 H), 2.68 (s, 3 H), 2.53 (s, 3 H), 0.94 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3, 149.4, 142.4, 135.9, 135.8, 135.7, 133.3, 132.5, 132.0, 131.1, 129.8, 128.8, 124.1, 121.1, 117.9, 39.8, 27.4, 18.4, 15.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}N_2O$: 333.1967; found: 333.1955.

2-(5,8-Dimethylisoquinolin-7-yl)aniline (31)

Pivalamide **30** (1.16 g, 3.5 mmol) was dissolved in 20% aq H_2SO_4 (22 mL) and EtOH (6 mL). The reaction was refluxed for 24 h. The mixture was cooled and made alkaline by using concd aq NH_3 during extensive cooling while a white precipitate formed. The slurry was filtered and the cake was washed with H_2O and dried on air to give **31** as a white powder.

Yield: 840 mg (97%); mp 168–170 °C.

IR (ATR): 1627, 1599, 1499, 1450, 1381, 1304, 1146, 1036, 959, 889, 854, 816, 743, 664, 594, 532 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.52 (s, 1 H), 8.58 (d, *J* = 5.6 Hz, 1 H), 7.78 (d, *J* = 5.6 Hz, 1 H), 7.42 (s, 1 H), 7.21 (d, J_1 = 7.5 Hz, 1 H), 7.05 (d, J_1 = 7.4 Hz), 6.86–6.80 (m, 2 H), 3.81 (br s, 2 H), 2.65 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 143.9, 142.3, 137.0, 135.4, 133.6, 131.8, 131.7, 130.4, 128.9, 128.1, 126.8, 118.5, 117.5, 115.3, 18.5, 14.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2$: 249.1392; found: 249.1382.

7-(2-Azidophenyl)-5,8-dimethylisoquinoline (32)[15b]

Aniline **31** (695 mg, 2.8 mmol, 1.0 equiv) was dissolved in concd HCl (16.5 mL). The mixture was cooled to 0 °C. Then a solution of $NaNO_2$ (445 mg, 6.44 mmol, 2.3 equiv) in H_2O (14 mL) was carefully added at such a rate that the temperature was kept under 5 °C. (During addition the colorless solution became yellow.) After the mixture had stirred for 2 h at 0 °C, a solution of NaOAc (5.84 g, 42.7 mmol, 13.3 equiv) and NaN_3 (419 mg, 6.44 mmol, 2.3 equiv) in H_2O (14 mL) was added while the temperature was maintained under 5 °C; then the mixture was stirred for another hour. The reaction progress was followed by TLC (hexane–EtOAc, 3:1). When the reaction was complete, it was quenched and the pH was adjusted to 7 with sat. aq Na_2CO_3. The mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layer was washed with H_2O, dried over anhyd Na_2SO_4, and evaporated to give a brown oil.

Yield: 700 mg (91%).

IR (ATR): 2122, 2099, 1598, 1576, 1487, 1443, 1384, 1283, 1096, 1038, 962, 891, 820, 748, 691, 644, 594, 532 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 8.62 (d, *J* = 5.7 Hz, 1 H), 7.80 (d, *J* = 5.7 Hz, 1 H), 7.48–7.45 (m, 1 H), 7.33 (s, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 7.27–7.24 (m, 2 H), 2.66 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.0, 142.6, 138.3, 136.3, 135.5, 133.3, 133.1, 131.6, 131.3, 131.1, 129.3, 127.9, 124.9, 118.6, 117.5, 18.5, 15.2.

Ellipticine (11)[15] and 5,6a-Dimethyl-6a*H*-pyrido[3,4-*a*]carbazole (33)

Azide **32** (36 mg, 0.13 mmol) was dissolved in 1,2-dichlorobenzene (2 mL). The mixture was heated in a microwave reactor at 190 °C for 1 h. Two products formed according to TLC. The mixture was concentrated under reduced pressure and purified by flash chromatography (hexane–EtOAc, 1:1, then hexane–EtOAc, 1:4) to give **11** (55%) as a yellow powder and **33** (45%) as an orange powder.

Ellipticine (11)

Yield: 18 mg (55%); mp 306–308 °C.

^1H NMR (50 MHz, DMSO): δ = 11.36 (s, 1 H), 9.70 (s, 1 H), 8.47–8.31 (m, 2 H), 7.92 (d, *J* = 5.6 Hz, 1 H), 7.61–7.49 (m, 2 H), 7.26 (t, *J* = 7.0 Hz, 1 H), 3.27 (s, 3 H), 2.80 (s, 3 H).

^{13}C NMR (125 MHz, DMSO): δ = 149.6, 142.6, 140.51, 140.45, 132.4, 128.0, 127.0, 123.7, 123.4, 123.1, 121.9, 119.1, 115.8, 110.6, 108.0, 14.3, 11.8.

5,6a-Dimethyl-6a*H*-pyrido[3,4-*a*]carbazole (33)

Yield: 13 mg (45%); mp 117–122 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 8.72 (d, *J* = 5.22 Hz, 1 H), 7.71 (d, *J* = 8.67 Hz, 1 H), 7.44 (d, *J* = 7.17 Hz, 1 H), 7.38 (t, *J* = 8.36 Hz, 1 H), 7.27 (t, *J* = 8.16 Hz, 1 H), 7.21 (d, *J* = 5.03 Hz, 1 H), 6.55 (br s, 1 H), 2.08 (br s, 3 H), 1.41 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.4, 154.6, 153.0, 146.4, 144.5, 141.7, 135.4, 130.2, 128.5, 126.2, 124.2, 121.9, 121.7, 118.6, 57.2, 27.6, 19.0.

Funding Information

We gratefully acknowledge the financial support from the National Research, Development and Innovation Office (K-116150). We are also grateful for the financial support from Soneas Research Ltd.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609153.

References

(1) (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers: Amsterdam, **1998**. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, **2003**. (c) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (d) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Wiley-Blackwell: West Sussex, **2010**, 5th ed.. (e) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (f) Iranshahy, M.; Quinn, R. J.; Iranshahi, M. *RSC Adv.* **2014**, *4*, 15900. (g) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. *Chem. Rev.* **2016**, *116*, 12369.

(2) (a) Pomeranz, C. *Monatsh. Chem.* **1893**, *14*, 116. (b) Fritsch, P. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 419. (c) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (d) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. (e) For a recent diversity-oriented approach, see: Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627.

(3) For pioneering work, see: (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (c) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572. (d) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. For recent examples, see: (e) Jiang, H.; Yang, J.; Tang, X.; Wu, W. *J. Org. Chem.* **2016**, *81*, 2053. (f) Chu, H.; Xue, P.; Yu, J.-T.; Cheng, J. *J. Org. Chem.* **2016**, *81*, 8009. (g) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. *Org. Lett.* **2017**, *19*, 2102.

(4) (a) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376. (b) Schlosser, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5432.

(5) Grethe, G. *The Chemistry of Heterocyclic Compounds, Isoquinolines*; John Wiley & Sons: New York, **1981**.

(6) Fortner, P. *Monatsh. Chem.* **1893**, *14*, 146.

(7) Gordon, M.; Pearson, D. E. *J. Org. Chem.* **1964**, *29*, 329.

(8) Brown, W. D.; Gouliaev, A. H. *Synthesis* **2002**, 83.

(9) Walker, M. D.; Andrews, B. I.; Burton, A. J.; Humphreys, L. D.; Kelly, G.; Schilling, M. B.; Scott, P. W. *Org. Process Res. Dev.* **2010**, *14*, 108.

(10) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.

(11) (a) Keilin, B.; Cass, W. E. *J. Am. Chem. Soc.* **1942**, *64*, 2442. (b) Graulich, A.; Scuvée-Moreau, J.; Seutin, V.; Liégeois, J.-F. *J. Med. Chem.* **2005**, *48*, 4972.

(12) (a) Tscherniac, J. German Patent 134979, **1901**. (b) Einhorn, A.; Bischkopff, E.; Szelinski, B.; Schupp, G.; Spröngerts, E.; Ladisch, C.; Mauermayer, T. *Liebigs Ann. Chem.* **1905**, *343*, 207.

(13) According to the literature,[9] the benzene ring of 5,8-dichloroisoquinoline can be oxidized to give the appropriate pyridine-3,4-dicarboxylic acid.

(14) (a) Rossini, A. F. C.; Muraca, A. C. A.; Casagrande, G. A.; Raminelli, C. *J. Org. Chem.* **2015**, *80*, 10033. (b) Ku, A. F.; Cuny, G. D. *Org. Lett.* **2015**, *17*, 1134. (c) Chen, J.; Wan, M.; Hua, J.; Sun, Y.; Lv, Z.; Li, W.; Liu, L. *Org. Biomol. Chem.* **2015**, *13*, 11561.

(15) (a) Miller, R. B.; Moock, T. *Tetrahedron Lett.* **1980**, *21*, 3319. (b) Miller, R. B.; Dugar, S.; Epperson, J. R. *Heterocycles* **1987**, *25*, 217. (c) Nagao, Y.; Endo, R.; Tokumaru, M.; Arimitsu, K. *Heterocycles* **2009**, *77*, 1403. (d) Nagao, Y.; Hirota, K.; Tokumaru, M.; Kozawa, K. *Heterocycles* **2007**, *73*, 593. (e) Liu, C.-Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106.

(16) Godard, A.; Rocca, P.; Pomel, V.; Thomas-dit-Dumont, L.; Rovera, J. C.; Thaburet, J. F.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1996**, *517*, 25.

(17) (a) Sam, J.; Shafik, R. M.; Aparajithan, K. *J. Pharm. Sci.* **1970**, *59*, 59. (b) Wieting, M. J.; Fisher, J. T.; Schafer, G. A.; Visco, D. M.; Gallucci, C. J.; Mattson, E. A. *Eur. J. Org. Chem.* **2015**, 525.

(18) (a) Cannon, G. J.; Kim, C. J.; Aleem, A. M. *J. Heterocycl. Chem.* **1972**, 731. (b) Tang, H.; Wei, Y.-B.; Zhang, C.; Ning, F.-X.; Qiao, W.; Huang, S.-L.; Ma, L.; Huang, Z.-S.; Gu, L.-Q. *Eur. J. Med. Chem.* **2009**, *44*, 2523. (c) Chuang, T.-H.; Li, C.-F.; Lee, H.-Z.; Wei, Y.-C. *J. Org. Chem.* **2013**, *78*, 4974.