ChemPubSoc Europe

DOI: 10.1002/ejoc.201600423

EurJOC European Journal of Organic Chemistry

Full Paper

C–C Coupling

A Metal-Free Oxidative Cross-Dehydrogenative Coupling of *N*-Aryl Tetrahydroisoquinolines and 2-Methylazaarenes Using a Recyclable Oxoammonium Salt as Oxidant in Aqueous Media

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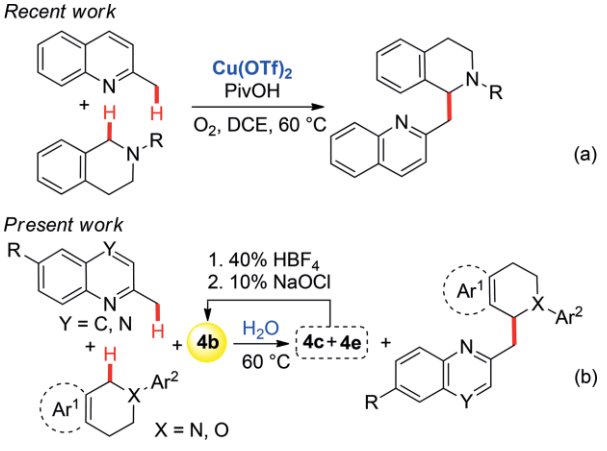
Abstract: A metal-free oxidative cross-dehydrogenative coupling of *N*-aryl tetrahydroisoquinolines and 2-methylazaarenes in water under mild conditions has been developed. 4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate was employed as a mild oxidant that can be recovered and reused directly. The reaction proceeds through formation of an iminium ion in situ followed by condensation with various nucleophiles, providing the desired products in moderate to good yields.

Introduction

From the viewpoint of academic and industrial research, development of an "ideal synthetic procedure" for the synthesis of structurally valued building blocks from simple starting materials through direct C–C bond formation is of paramount interest to chemists.[1] From this perspective, cross-dehydrogenative coupling (CDC) reaction, which represents the state-of-art in C–C bond-forming reactions, is becoming firmly established.[2] During the past decades, impressive progress has been achieved to efficiently construct a variety of functionalized molecules,[3] especially for the coupling of tetrahydroisoquinoline (THIQ) derivatives to various C–H nucleophiles, including nitroalkanes,[4a,4b] ketones,[4c] terminal acetylenes,[4d] coumarins,[4e] dialkyl malonates,[4f,4g] and phosphites.[4h] However, the use of 2-alkylazaarenes as coupling partners has rarely been explored, barring one report for such transformation.[5a]

The THIQ moiety is present in numerous natural products and biologically active materials.[6] For example, the THIQ framework containing Ecteinascidin 743 (also known as trabectidin or Yondelis) is an antitumor agent,[7] and methopholine is an opioid analgesic used for the treatment of postoperative pain.[8] Moreover, substituted quinolines are also important scaffolds occurring in many biologically active compounds.[9] For instance, substituted quinoline hydroxamic acid derivatives are histone deacetylase (HDAC) inhibitors,[10] and styrylquinolines are antagonists of Leukotriene D_4 receptor with high-affinity.[11] Therefore, developing protocols for cross-dehydrogenative coupling of structurally diverse THIQs with 2-alkylazaarenes will be of significant interest. So far, a method capable of coupling *N*-aryl-substituted THIQs and 2-alkylazaarenes using copper/Brønsted acid as dual-catalyst was reported by Yang and co-workers (Scheme 1, a).[5a] Other studies on the nucleophilic functionalization of 2-methylazaarenes via $FeCl_3$ combined with TBHP or $K_2S_2O_8$ have been reported.[5b–5d] Despite these breakthroughs, the use of metal catalyst and organic additives may limit their further application. Thus, the development of an economic and environmentally benign coupling method is still an attractive project to pursue.



Scheme 1. Methods of coupling *N*-aryl-substituted THIQs to 2-methylazaarenes.

More recently, oxoammonium salts (Figure 1) have emerged as efficient organic oxidants for activating C–H bonds, playing a pivotal role in the construction of C–C bonds.[12] By virtue of the advantages of oxoammonium salts as oxidants, namely that they are environmentally benign, recyclable and metal-free spe-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600423.

cies that can facilitate oxidation under mild reaction conditions, herein, we explore a 4-acetylamino-2,2,6,6-tetramethylpiperidine-*N*-oxoammonium tetrafluoroborate (Bobbitt's salt, **4b**) mediated cross-dehydrogenative coupling reaction between *N*-aryl THIQs and 2-methylazaarenes (Scheme 1, b). The structures of oxoammonium derivatives used in this investigation are presented in Figure 1.

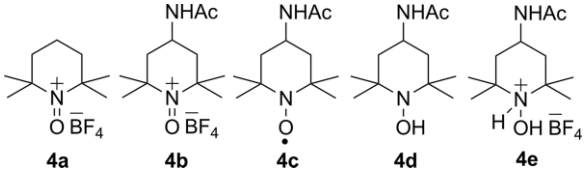


Figure 1. Oxoammonium salts as well as related species discussed in this paper.

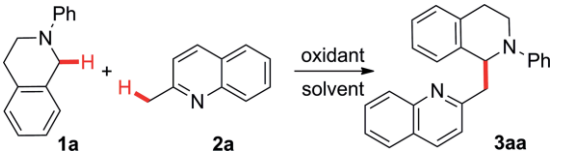
Results and Discussion

To explore the feasibility of this transformation, the coupling of *N*-phenyl THIQ (**1a**) and 2-methylquinoline (**2a**) was initially investigated as a model reaction (Table 1). An oxidant evaluation test in the presence of **1a** (1.0 equiv.), **2a** (2.0 equiv.), and oxidant (1.2 equiv.) in dichloromethane (DCM) was performed first. Compound **4b** was found to be superior to **4a** in the transformation, yielding the desired product **3aa** in 80 % yield (Table 1, entries 1, 2). However, only a trace amount of **3aa** was obtained when the radical oxidants 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl (**4c**) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) were used (entries 3, 4). For comparison, catalytic amounts of $Fe(NO_3)_3{\cdot}9H_2O$ and $FeCl_3{\cdot}6H_2O$ were added, respectively (entries 5, 6). Surprisingly, an undesired compound 2-[2-(phenylamino)ethyl]benzaldehyde (Figure 2, **3x**) was obtained in the presence of $Fe(NO_3)_3{\cdot}9H_2O$, whereas only trace amounts of **3aa** were detected with the addition of $FeCl_3{\cdot}6H_2O$.

Further screening of solvents showed DCM remained the optimal solvent (entries 7–14). Nevertheless, a promising yield (56 %) was obtained by using H_2O at 40 °C, which was of significant interest (Table 1, entry 14). The lower yield obtained in water might be attributed to the insufficient interplay between organic substrates and water-soluble oxidant. Therefore, we considered that a higher temperature might make this transformation proceed more smoothly. Gratifyingly, the reaction proceeded at a relatively mild temperature (60 °C) with 92 % yield (entry 15). Further increase of temperature to 80 °C resulted in decreased yield (70 %) (entry 16), which might be attributed to the further oxidation of **3aa**.[5a] The effect of the amount of **4b** on the reaction was then investigated. From the experimental results (entries 15, 17–20), 1.2 equiv. turned out to be the optimal choice; either reducing or increasing the load of **4b** led to a decrease in yield. Additionally, the use of O_2 instead of air atmosphere led to a lower yield of **3aa** (entry 21), which might be attributed to the further oxidation of **3aa**.[5a] Repeating the reaction under N_2 atmosphere, with a longer reaction time (48 h) was required to afford a good yield (entry 22).

With the optimized conditions in hand, the scope of the method was explored (Table 2). First, **1a** was treated with a

Table 1. Optimization of the benzylic CDC of azaarenes mediated by oxoammonium salt.[a]



Entry	Oxidant	Temp. [°C]	Solvent	Yield [%][b]
1	**4a**	30	DCM	63
2	**4b**	30	DCM	80
3	**4c**	30	DCM	trace
4	TEMPO	30	DCM	trace
5[c]	***4b***	***30***	***DCM***	***50***
6[d]	**4b**	30	DCM	trace
7	**4b**	30	DCE	52
8	**4b**	30	MeOH	35
9	**4b**	30	CH_3CN	42
10	**4b**	30	THF	49
11	**4b**	30	DMF	51
12	**4b**	30	PhMe	50
13	**4b**	30	PhCl	60
14	**4b**	40	H_2O	56
15	***4b***	***60***	***H_2O***	***92***
16	**4b**	80	H_2O	70
17[e]	**4b**	60	H_2O	38
18[f]	**4b**	60	H_2O	90
19[g]	**4b**	60	H_2O	81
20[h]	**4b**	60	H_2O	78
21[i]	**4b**	60	H_2O	34
22[j]	**4b**	60	H_2O	88

[a] Unless otherwise mentioned, the reactions were performed with **1a** (0.5 mmol), **2a** (1.0 mmol), oxidant (1.2 equiv.), solvent (2.0 mL) under air (1 atm) for 24 h. [b] Isolated yields based on **1a**. [c] **4b** (0.1 mmol) and $Fe(NO_3)_3{\cdot}9H_2O$ (0.4 mmol) were used to generate a different product **3x**. [d] **4b** (0.1 mmol) and $FeCl_3{\cdot}6H_2O$ (0.4 mmol) were used. [e] **4b** (0.5 equiv.) was used. [f] **4b** (1 equiv.) was used. [g] **4b** (1.5 equiv.) was used. [h] **4b** (2.0 equiv.) was used. [i] The reaction was performed under O_2 atmosphere. [j] The reaction was performed under N_2 atmosphere for 48 h.

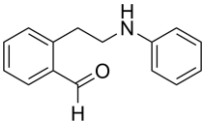
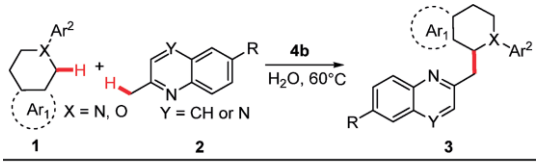


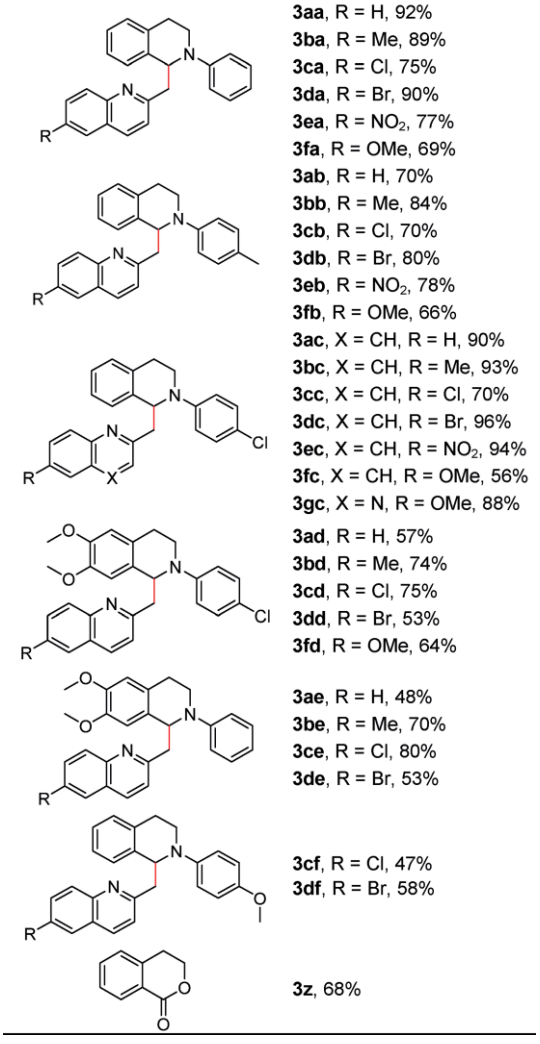
Figure 2. Structure of **3x**.

variety of 2-methylquinoline derivatives to furnish the corresponding coupled products. The 2-methyl-, 2,6-dimethyl-, 2-methyl-6-chloro-, 2-methyl-6-bromo-, and 2-methyl-6-nitro-substituted quinolines furnished the desired products **3aa**, **3ba**, **3ca**, **3da**, and **3ea**, respectively, in moderate to good yields (92, 89, 75, 90, and 77 %, respectively). On the other hand, product **3fa** was obtained in lower yield (69 %) with methoxyl substitution at the 6-position of 2-methylquinoline. These results indicated that both electron-donating groups and electron-withdrawing groups on 2-methylazaarenes had little effect on the outcome of the reaction, except where strong electron-donating groups were included. This was probably due to the strong positive mesomeric effect of the methoxyl group, which inhibits the delocalization of the negative charge at the 2-position of 2-methylazaarene, making it less stable. Additionally, 3-methyl-

quinoline **2h** was also tested but no reaction was detected, indicating that the substrate with a methyl group on the *meta*-position with respect to the nitrogen atom is less reactive.

Table 2. Investigation of the substrate scope.[a,b]





3aa, R = H, 92%
3ba, R = Me, 89%
3ca, R = Cl, 75%
3da, R = Br, 90%
3ea, R = NO_2, 77%
3fa, R = OMe, 69%
3ab, R = H, 70%
3bb, R = Me, 84%
3cb, R = Cl, 70%
3db, R = Br, 80%
3eb, R = NO_2, 78%
3fb, R = OMe, 66%
3ac, X = CH, R = H, 90%
3bc, X = CH, R = Me, 93%
3cc, X = CH, R = Cl, 70%
3dc, X = CH, R = Br, 96%
3ec, X = CH, R = NO_2, 94%
3fc, X = CH, R = OMe, 56%
3gc, X = N, R = OMe, 88%
3ad, R = H, 57%
3bd, R = Me, 74%
3cd, R = Cl, 75%
3dd, R = Br, 53%
3fd, R = OMe, 64%
3ae, R = H, 48%
3be, R = Me, 70%
3ce, R = Cl, 80%
3de, R = Br, 53%
3cf, R = Cl, 47%
3df, R = Br, 58%
3z, 68%

[a] All the reactions were performed with **1** (0.5 mmol), **2** (1.0 mmol), **4b** (0.6 mmol), and H_2O (2.0 mL) at 60 °C under air (1 atm) for 24 h. [b] Isolated yields based on **1**.

The effect of substituent on the phenyl group of THIQ moiety on the coupling reaction was then investigated (Table 2). The reaction was performed under the optimal conditions. As expected, 2-methyl-6-bromoquinoline (**2d**) reacted smoothly with the substrates containing methyl or chloro groups (**1b**, **1c**), affording the products **3db** and **3dc** in good yields of 80 and 96 %, respectively, whereas the reaction involving the substrates with methoxyl or dimethoxyl groups (**1f**, **1d**, **1e**) provided the products **3df**, **3dd**, **3de** in lower yields (58, 53, and 53 %, respectively). Furthermore, 2-methylquinoxaline (**2g**) underwent a smooth reaction with **1c** to furnish the product **3gc** in good yield (88 %). From the experimental results, we assume that the electron density delocalization of products was inhibited by the positive mesomeric effect of strongly electron-donating groups such as methoxyl.

The scope of this coupling reaction was further explored by employing a variety of N-substituted THIQs and 2-methylazaarene derivatives under the optimal reaction conditions. The desired products were obtained in moderate to good yields (Table 2) except for *N*-Boc-THIQ **1h** and *N*-(4-bromobenzoyl)-THIQ **1i**, which only afforded some complex, unknown byproducts. Notably, isochromane **1g** generated isochroman-1-one **3z** instead of the corresponding coupling product under the optimized conditions (Table 2).

To further improve this method, the ability to recycle the oxidant system was investigated. The recovery of the oxidant had been well-studied previously: the oxidation of **4c** to **4b** was performed in the presence of HBF_4, followed by the addition of bleach (NaClO), $NaBF_4$ was then added to precipitate **4b**.[13] However, the recovery and reuse of the oxidant directly in reaction solution without separation has rarely been explored. In the present study, the reacted mixture underwent the recycling procedure to afford an aqueous reaction system containing mainly **4b**, $NaBF_4$, NaCl, and water. Next, **1a** and **2a** were treated with this mixture directly, obtaining **3aa** in only 60 % yield, which was probably caused by the loss of **4b** during the phase separation procedure. The yield of **3aa** was found to increase to 90 % by adding additional 0.4 equiv. of **4b** to the reaction mixture. As shown in Figure 3, the yield of the 3rd recycle run decreased significantly, likely due to over-dilution of the reaction system. After evaporating half volume of water from the oxidant system, yield of the 4th recycle run increased to 90 %.

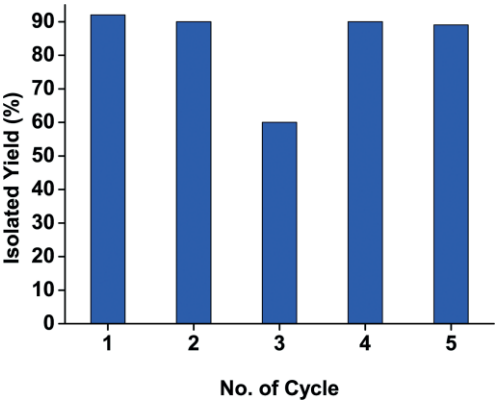
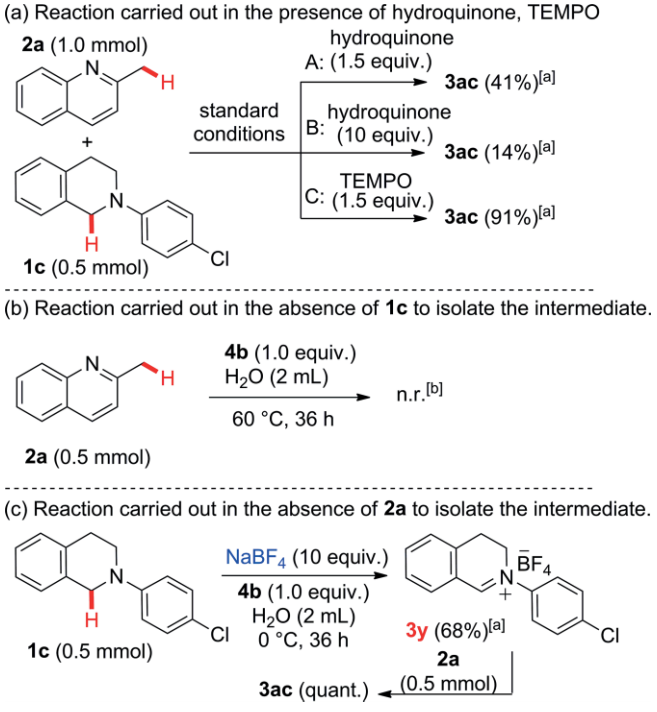


Figure 3. Recyclability chart (recyclability of the oxidant system was tested on the reaction with **1a** and **2a**).

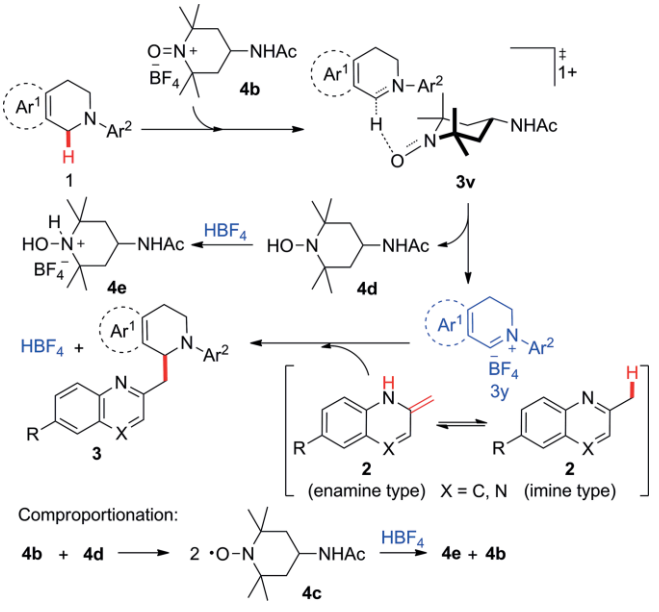
To elucidate the mechanism of this coupling reaction, control experiments were carried out. We faced a dilemma when the coupling of **2a** to **1c** was performed in the presence of some free-radical scavengers: the yield of the coupled product **3ac** decreased drastically in the presence of hydroquinone, whereas excellent yield was obtained with TEMPO (Scheme 2, a). Thus it was difficult to determine whether this reaction proceeded through a free-radical pathway. Inspired by the previous studies,[15] we hypothesized that the reaction was performed via an

iminium ion as the key immediate, which was attacked by 2-methylazaarene to give the coupled product. To validate our hypothesis, experiments were conducted to capture the key intermediate. No reaction was detected when the reaction was carried out with **2a** (0.5 mmol) and **4b** (0.5 mmol) in H_2O (2 mL) at 60 °C even for 36 h (Scheme 2, b), suggesting that the intermediate was not derived from **2a**. To our delight, in the presence of **1c** (0.5 mmol) and **4b** (0.5 mmol) under the same conditions, an intermediate was detected by HPLC analysis of the reaction mixture (see the Supporting Information for details), but it was converted into other unknown products during the chromatography procedure. Repeating the reaction with additional 10 equiv. $NaBF_4$ at 0 °C for 36 h, led to the observation of a common ion assisted precipitation. Reaction of **2a** with the precipitated solid **3y** at 60 °C afforded **3ac** quantitative within 5 minutes (Scheme 2, c), indicating that **3y** is an intermediate in the reaction. Based on a previous report,[14] the structure of **3y** was anticipated to be an iminium salt, which was supported by NMR and HRMS analyses (see the Supporting Information for details).



Scheme 2. Mechanistic studies.

Based on the results obtained in the preliminary study and on previous reports,[15a] a plausible mechanism was proposed (Scheme 3). A direct hydride abstraction from the N-protected THIQs **1** proceeded to form the iminium salt **3y** through an ionic pathway involving hydride transfer via **3v**. Simultaneously, *N*-(1-hydroxy-2,2,6,6-tetramethylpiperidin-4-yl)acetamide (**4d**) was produced from **4b**. Subsequently, an imine-enamine-type tautomerization between substrate **2** took place and the corresponding reactive enamine type acted as nucleophile in the coupling with the iminium salt **3y**, furnishing the desired CDC adduct **3**. Additionally, a radical compound **4c** was detected during the reaction process, which might be attributed to the reaction between **4b** and **4d**.[15b] Moreover, HBF_4 should be reformed but the reaction mixture was neutral.[12e] Thus we concluded that part of HBF_4 reacted with **4d** to produce 4-acetamido-1-hydroxy-2,2,6,6-tetramethylpiperidin-1-ium tetrafluoroborate (**4e**), while the rest of the HBF_4 reacted with **4c** to regenerate **4e** and **4b**;[15c] this process explains why the inclusion of an additional 1.5 equiv. TEMPO increased the yield (Scheme 2, a).



Scheme 3. Possible mechanism.

Conclusions

We have developed an efficient method for C(sp^3)–C(sp^3) bond formation by cross-dehydrogenative coupling of *N*-aryl THIQs and 2-methylazaarenes oxidized by 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate in water under mild conditions. The reaction is thought to proceed via a reactive intermediate iminium salt, followed by condensation with various nucleophiles. In addition, the easily-regenerated oxidant and aqueous reaction media mean that this process has significant advantages, for instance, low cost, safety, simplicity of work-up, and environmental compatibility.

Experimental Section

General Information: Unless otherwise noted, all commercially available reagents and solvents were used as provided without further purification. 1,2,3,4-Tetrahydroisoquinoline derivatives were prepared according to reported protocols.[16] TLC analysis was carried out using precoated glass plates. Silica gel for column chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. Flash column chromatography was performed using 200–300 mesh silica gel. ^1H and ^{13}C NMR spectra were respectively recorded at 400 MHz and 100 MHz. The following abbreviations (or combinations thereof) were used to report multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J* are reported in hertz (Hz). The reaction mechanism

was investigated by using high performance liquid chromatography (HPLC) with Aglient 1200 SB-C18 column and HPLC-MS with Agilent 1200 sunfire-C18 column. Melting points (m.p.) were determined with a Büchi B-540 and are uncorrected.

Synthesis of 2-[(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-methyl]quinoline (3aa); Typical Procedure: To a stirred solution of *N*-phenyl-tetrahydroisoquinoline (**1a**; 104.5 mg, 0.5 mmol, 1.0 equiv.) and 2-methylquinoline (**2a**; 143.2 mg, 1.0 mmol, 2.0 equiv.) in H_2O (2 mL) was added 4-acetylamino-2,2,6,6-tetramethyl-piperidine-1-oxoammonium tetrafluoroborate (**4b**; 180.6 mg, 0.6 mmol, 1.2 equiv.) in one portion, then the mixture was heated at 60 °C under air (1 atm). The progress of the reaction was monitored by TLC. Upon completion, ethyl acetate (2 mL) was added to extract organic products. After separation, the aqueous phase was collected to regenerate **4d** (see the procedure for oxidant recyclability); the organic phase was washed with warm water (2 × 1 mL) and dried with anhydrous Na_2SO_4, then transferred to silica gel column and eluted with hexanes and ethyl acetate (10:1) to give product **3aa** (161.1 mg, 92 % yield) as a white solid. m.p. 114–115 °C; CAS: 1608092-46-1.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.6 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.81–7.52 (m, 2 H), 7.48 (t, *J* = 7.2 Hz, 1 H), 7.20–7.08 (m, 4 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.98 (t, *J* = 6.8 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 5.6 Hz, 1 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 5.45 (t, *J* = 6.8 Hz, 1 H), 3.85–3.74 (m, 1 H), 3.74–3.55 (m, 2 H), 3.33 (dd, *J* = 11.6, 6.0 Hz, 1 H), 3.17–3.06 (m, 1 H), 2.90 (dt, *J* = 16.0, 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 149.1, 147.7, 138.0, 135.7, 134.6, 129.1, 128.9 (2 C), 128.8, 128.4, 127.3, 127.2, 126.7, 126.4, 125.7, 125.6, 122.6, 117.2, 113.9 (2 C), 59.9, 45.4, 41.8, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{22}N_2Na$ $[M + Na]^+$ 373.1675; found 373.1670.

Oxidant Recycling: The aqueous phase was treated by the slow dropwise addition of a 40 % aqueous solution of HBF_4 under vigorous stirring until **4c** was consumed (monitored by TLC), followed by the slow dropwise addition of a 10 % solution of NaClO (298 mg, 0.4 mmol). Upon complete addition, the solution was stirred for 16 h at room temperature to regenerate **4b**. The reaction mixture (mainly containing **4b**, H_2O, NaCl and $NaBF_4$) could be used to react with substrates **1** and **2** directly.

6-Methyl-2-[(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]quinoline (3ba): White solid; m.p. 122–124 °C, CAS: 1608092-47-2.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.8 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.60–7.40 (m, 2 H), 7.19–7.04 (m, 4 H), 7.03–6.93 (m, 2 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 7.2 Hz, 1 H), 6.63 (t, *J* = 7.2 Hz, 1 H), 5.42 (t, *J* = 6.8 Hz, 1 H), 3.81–3.71 (m, 1 H), 3.70–3.52 (m, 2 H), 3.31 (dd, *J* = 13.2, 6.8 Hz, 1 H), 3.15–3.03 (m, 1 H), 2.90 (dt, *J* = 16.0, 4.8 Hz, 1 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 148.6, 145.7, 137.6, 135.0, 134.7, 134.2, 131.0, 128.5 (2 C), 128.0, 126.8, 126.4, 126.0, 125.9, 125.2, 122.2, 116.9, 113.6 (3 C), 60.1, 45.5, 42.1, 27.7, 22.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}N_2Na$ $[M + Na]^+$ 387.1832; found 387.1831.

6-Chloro-2-[(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]quinoline (3ca): White solid; m.p. 130–131 °C, CAS: 1608092-50-7.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 2.8 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.21–7.08 (m, 4 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.99 (t, *J* = 5.2 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 3 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 5.42 (t, *J* = 6.8 Hz, 1 H), 3.81–3.72 (m, 1 H), 3.71–3.55 (m, 2 H), 3.42–3.24 (m, 1 H), 3.16–3.04 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 149.0, 146.2, 137.9, 134.6 (2 C), 131.3, 130.5, 130.0, 129.0 (2 C), 128.4, 127.3, 127.1, 126.5, 126.0, 125.6, 123.4, 117.3, 113.9 (2 C), 59.9, 45.4, 41.8, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}ClN_2Na$ $[M + Na]^+$ 407.1285; found 407.1287.

6-Bromo-2-[(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]quinoline (3da): White solid; m.p. 132–133 °C, CAS: 1608092-51-8.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 1.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.76 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.21–7.08 (m, 4 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.99 (t, *J* = 6.0 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 4.8 Hz, 1 H), 6.65 (t, *J* = 7.2 Hz, 1 H), 5.42 (t, *J* = 6.8 Hz, 1 H), 3.81–3.72 (m, 1 H), 3.71–3.56 (m, 2 H), 3.31 (dd, *J* = 11.6, 6.4 Hz, 1 H), 3.15–3.06 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 149.0, 146.4, 137.9, 134.7, 134.5, 132.5, 130.7, 129.4, 129.0 (2 C), 128.4, 127.8, 127.1, 126.5, 125.6, 123.4, 119.4, 117.4, 113.9 (2 C), 59.9, 45.5, 41.8, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}BrN_2Na$ $[M + Na]^+$ 451.0780; found 451.0786.

6-Nitro-2-[(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-methyl]quinoline (3ea): Yellow solid; m.p. 135–137 °C. CAS: 1608092-55-2.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 2.4 Hz, 1 H), 8.46 (dd, *J* = 9.2, 2.8 Hz, 1 H), 8.22 (d, *J* = 9.2 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.22–7.06 (m, 5 H), 7.04–6.98 (m, 1 H), 6.93–6.81 (m, 3 H), 6.65 (t, *J* = 7.2 Hz, 1 H), 5.46 (t, *J* = 6.8 Hz, 1 H), 3.81–3.73 (m, 1 H), 3.73–3.63 (m, 2 H), 3.37 (dd, *J* = 13.2, 6.8 Hz, 1 H), 3.16–3.07 (m, 1 H), 2.92 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 149.9, 148.8, 144.9, 137.6, 137.1, 134.7, 130.6, 129.0 (2 C), 128.6, 126.9, 126.7, 125.7, 125.4, 124.5, 124.2, 122.7, 117.6, 114.1 (2 C), 59.8, 45.8, 41.8, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{21}N_3NaO_2$ $[M + Na]^+$ 418.1526; found 418.1529.

6-Methoxy-2-[(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]quinoline (3fa): White solid; m.p. 51–53 °C. CAS: 1608092-48-3.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.2 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.35 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.20–7.03 (m, 4 H), 7.03–6.92 (m, 3 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 5.39 (t, *J* = 7.2 Hz, 1 H), 3.91 (s, 3 H), 3.81–3.73 (m, 1 H), 3.70–3.56 (m, 2 H), 3.28 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.15–3.06 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 156.4, 148.6, 143.5, 137.7, 134.3, 134.0, 130.0, 128.6 (2 C), 128.0, 127.2, 126.8, 126.1, 125.2, 122.5, 121.4, 116.8, 113.6 (2 C), 104.9, 60.1, 55.6, 45.5, 42.0, 27.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}N_2NaO$ $[M + Na]^+$ 403.1781; found 403.1797.

2-{[2-(4-Tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3ab): White solid; m.p. 106–108 °C. CAS: 1608092-58-5,[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 6.8 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.79–7.62 (m, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.16–7.03 (m, 3 H), 7.02–6.95 (m, 1 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 5.38 (t, *J* = 7.2 Hz, 1 H), 3.80–3.70 (m, 1 H), 3.70–3.56 (m, 2 H), 3.33 (dd, *J* = 12.4, 5.6 Hz, 1 H), 3.14–3.03 (m, 1 H), 2.85 (dt, *J* = 16.0, 4.4 Hz, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 147.8, 147.1, 138.1, 135.5, 134.6, 129.4 (3 C), 129.0, 128.9, 128.5, 127.3, 127.2, 126.7, 126.3, 125.6, 125.5, 122.6, 114.7 (2 C), 60.2, 45.5, 41.8, 27.1, 20.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}N_2Na$ $[M + Na]^+$ 387.1832; found 387.1814.

6-Methyl-2-{[2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3bb): White solid; m.p. 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.58–7.44 (m, 2 H), 7.16–7.06 (m, 2 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 5.35 (t, *J* = 6.8 Hz, 1 H), 3.78–3.70 (m, 1 H), 3.69–3.55 (m, 2 H), 3.30 (dd, *J* = 13.2, 6.4 Hz, 1 H), 3.13–3.05 (m, 1 H), 2.85 (dt, *J* = 16.0, 4.4 Hz, 1 H), 2.52 (s, 3 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 147.2, 146.4, 138.2, 135.3, 134.9, 134.6, 131.3, 129.4 (2 C), 128.6, 128.5, 127.2, 126.7, 126.6, 126.3, 126.2, 125.5, 122.6, 114.6 (2 C), 60.3, 45.3, 41.9, 27.2,

21.6, 20.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{26}N_2Na$ [M + Na]$^+$ 401.1988; found 401.1975.

6-Chloro-2-{[2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3cb): White solid; m.p. 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 2.4 Hz, 1 H), 7.62 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.15–7.04 (m, 3 H), 7.02–6.96 (m, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 6.8 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.35 (t, *J* = 6.8 Hz, 1 H), 3.77–3.70 (m, 1 H), 3.68–3.56 (m, 2 H), 3.31 (dd, *J* = 12.8, 5.6 Hz, 1 H), 3.13–3.05 (m, 1 H), 2.84 (dt, *J* = 16.0, 4.4 Hz, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 147.0, 146.1, 137.9, 134.6, 134.5, 131.2, 130.5, 129.9, 129.4 (2 C), 128.5, 127.2, 127.1, 126.8, 126.4, 126.0, 125.5, 123.4, 114.6 (2 C), 60.2, 45.4, 41.8, 27.1, 20.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}ClN_2Na$ [M + Na]$^+$ 421.1442; found 421.1451.

6-Bromo-2-{[2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3db): White solid; m.p. 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.8 Hz, 1 H), 7.87 (d, *J* = 2.4 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.73 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.11 (d, *J* = 4.0 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 7.03–6.95 (m, 1 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.34 (t, *J* = 6.8 Hz, 1 H), 3.77–3.68 (m, 1 H), 3.68–3.53 (m, 2 H), 3.29 (dd, *J* = 13.2, 6.4 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.83 (dt, *J* = 16.0, 4.8 Hz, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 147.1, 146.4, 137.9, 134.6, 134.5, 132.5, 130.7, 129.5 (2 C), 129.4, 128.5, 127.8, 127.1, 126.9, 126.4, 125.5, 123.4, 119.3, 114.7 (2 C), 60.2, 45.4, 41.8, 27.1, 20.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}BrN_2Na$ [M + Na]$^+$ 465.0937; found 465.0929.

6-Nitro-2-{[2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3eb): Yellow solid; m.p. 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 2.4 Hz, 1 H), 8.44 (dd, *J* = 9.2, 2.4 Hz, 1 H), 8.19 (d, *J* = 9.2 Hz, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 4.4 Hz, 2 H), 7.04–6.99 (m, 1 H), 6.94–6.85 (m, 3 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 5.39 (t, *J* = 6.8 Hz, 1 H), 3.78–3.70 (m, 1 H), 3.69–3.61 (m, 2 H), 3.36 (dd, *J* = 13.6, 6.4 Hz, 1 H), 3.13–3.04 (m, 1 H), 2.85 (dt, *J* = 16.0, 4.4 Hz, 1 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 149.8, 147.0, 144.8, 137.7, 137.0, 134.6, 130.6, 129.5 (2 C), 128.7, 127.1, 126.9, 126.6, 125.6, 125.3, 124.5, 124.2, 122.6, 114.9 (2 C), 60.1, 45.7, 41.9, 27.0, 20.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}N_3NaO_2$ [M + Na]$^+$ 432.1682; found 432.1687.

6-Methoxy-2-{[2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3fb): White solid; m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 9.2 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.10 (d, *J* = 3.2 Hz, 2 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 6.99–6.87 (m, 4 H), 6.84 (d, *J* = 7.2 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 5.33 (t, *J* = 6.8 Hz, 1 H), 3.89 (s, 3 H), 3.76–3.69 (m, 1 H), 3.68–3.51 (m, 2 H), 3.27 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.83 (dt, *J* = 16.4, 4.8 Hz, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 157.3, 147.4, 144.1, 138.4, 134.9, 134.7, 130.5, 129.7 (2 C), 128.7, 127.8, 127.5, 126.9, 126.6, 125.7, 123.1, 121.9, 114.8 (2 C), 105.3, 60.6, 55.8, 45.4, 42.1, 27.4, 20.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{26}N_2NaO$ [M + Na]$^+$ 417.1937; found 417.1923.

2-{[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}quinoline (3ac): White solid; m.p. 146–147 °C. CAS: 1608092-61-0.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.67 (dd, *J* = 17.6, 8.4 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 1 H), 7.15–7.04 (m, 2 H), 7.03–6.85 (m, 4 H), 6.85–6.56 (m, 3 H), 5.38 (t, *J* = 7.2 Hz, 1 H), 3.77–3.68 (m, 1 H), 3.65–3.49 (m, 2 H), 3.29 (dd, *J* = 12.8, 6.8 Hz, 1 H), 3.12–3.02 (m, 1 H), 2.91 (dt, *J* = 15.6, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 147.8, 147.6, 137.8, 135.7, 134.4, 129.2, 128.8, 128.7 (2 C), 128.4, 127.4, 127.1, 126.7, 126.6, 125.7 (2 C), 122.5, 121.8, 114.9 (2 C), 60.0, 45.5, 41.9, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{22}ClN_2$ [M + H]$^+$ 385.1466; found 385.1474.

2-{[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}-6-methylquinoline (3bc): White solid; m.p. 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.58–7.43 (m, 2 H), 7.17–7.08 (m, 2 H), 7.06–6.89 (m, 4 H), 6.87–6.75 (m, 3 H), 5.37 (t, *J* = 6.8 Hz, 1 H), 3.77–3.69 (m, 1 H), 3.64–3.53 (m, 2 H), 3.28 (dd, *J* = 13.2, 6.8 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 147.6, 146.4, 137.8, 135.4, 135.0, 134.4, 131.4, 128.6 (2 C), 128.5, 128.3, 127.1, 126.7, 126.5, 126.2, 125.7, 122.5, 121.7, 114.8 (2 C), 60.0, 45.4, 41.9, 27.3, 21.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}ClN_2$ [M + H]$^+$ 399.1623; found 399.1616.

6-Chloro-2-{[2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]m-ethyl}quinoline (3cc): White solid; m.p. 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 2.4 Hz, 1 H), 7.63 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.22–7.08 (m, 2 H), 7.08–6.88 (m, 4 H), 6.87–6.73 (m, 3 H), 5.36 (t, *J* = 6.8 Hz, 1 H), 3.77–3.65 (m, 1 H), 3.64–3.50 (m, 2 H), 3.29 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.6, 146.2, 137.6, 134.7, 134.4, 131.4, 130.5, 130.1, 128.7 (2 C), 128.5, 127.3, 127.0, 126.7, 126.1, 125.7, 123.4, 122.0, 115.0 (2 C), 59.9, 45.4, 42.0, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{20}Cl_2N_2Na$ [M + Na]$^+$ 441.0896; found 441.0905.

6-Bromo-2-{[2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]m-ethyl}quinoline (3dc): White solid; m.p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 9.2 Hz, 1 H), 7.89 (d, *J* = 1.6 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.76 (dd, *J* = 9.2, 2.0 Hz, 1 H), 7.19–7.09 (m, 2 H), 7.09–6.92 (m, 4 H), 6.88–6.72 (m, 3 H), 5.37 (t, *J* = 6.8 Hz, 1 H), 3.77–3.67 (m, 1 H), 3.64–3.51 (m, 2 H), 3.28 (dd, *J* = 13.2, 6.8 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.91 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 147.6, 146.4, 137.6, 134.6, 134.4, 132.6, 130.6, 129.4, 128.7 (2 C), 128.4, 127.8, 127.0, 126.7, 125.7, 123.3, 122.0, 119.5, 115.0 (2 C), 59.9, 45.4, 42.0, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{20}BrClN_2Na$ [M + Na]$^+$ 485.0391; found 485.0388.

2-{[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}-6-nitroquinoline (3ec): Yellow solid; m.p. 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 2.8 Hz, 1 H), 8.47 (dd, *J* = 9.2, 2.8 Hz, 1 H), 8.21 (d, *J* = 9.2 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.20–7.09 (m, 3 H), 7.09–6.95 (m, 3 H), 6.89–6.76 (m, 3 H), 5.42 (t, *J* = 7.2 Hz, 1 H), 3.77–3.70 (m, 1 H), 3.68–3.57 (m, 2 H), 3.35 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.13–3.05 (m, 1 H), 2.93 (dt, *J* = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 150.1, 147.8, 145.2, 137.6, 137.5, 134.7, 130.8, 129.0 (2 C), 128.9, 127.1 (2 C), 126.1, 125.7, 124.7, 124.5, 123.0, 122.5, 115.4 (2 C), 60.1, 46.0, 42.3, 27.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{20}ClN_3NaO_2$ [M + Na]$^+$ 452.1136; found 452.1148.

2-{[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}-6-methoxyquinoline (3fc): White solid; m.p. 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.17–7.09 (m, 2 H), 7.08–6.90 (m, 5 H), 6.86 (d, *J* = 6.4 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.36 (t, *J* = 6.8 Hz, 1 H), 3.92 (s, 3 H), 3.78–3.70 (m, 1 H), 3.65–3.52 (m, 2 H), 3.28 (dd, *J* = 12.8, 5.6 Hz, 1 H), 3.13–3.05 (m, 1 H), 2.92 (dt, *J* = 16.0, 5.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 156.6, 147.6, 143.9, 137.8, 134.5, 134.4, 130.3, 128.6 (2 C),

128.4, 127.6, 127.1, 126.5, 125.7, 122.7, 121.8, 121.7, 114.8 (2 C), 105.1, 60.0, 55.5, 45.2, 41.9, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}ClN_2O$ $[M + H]^+$ 415.1572; found 415.1569.

2-{[2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-methyl}qui-noxaline (3gc): White solid; m.p. 95–96 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 8.09 (d, J = 8.0 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.79–6.68 (m, 2 H), 7.16 (d, J = 4.0 Hz, 2 H), 7.11–6.98 (m, 3 H), 6.87 (d, J = 7.6 Hz, 1 H), 6.80 (d, J = 9.2 Hz, 2 H), 5.35 (t, J = 7.2 Hz, 1 H), 3.80–3.72 (m, 1 H), 3.68–3.57 (m, 2 H), 3.36 (dd, J = 14.0, 6.8 Hz, 1 H), 3.12–3.03 (m, 1 H), 2.92 (dt, J = 16.0, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 147.4, 146.1 (2 C), 142.0, 141.1, 137.0, 134.4, 129.8 (2 C), 129.1, 129.0, 128.7, 128.6, 126.9, 126.8, 126.0, 122.5, 115.3 (2 C), 59.8, 42.8, 42.2, 27.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{24}H_{20}ClN_3Na$ $[M + Na]^+$ 408.1238; found 408.1248.

2-{[2-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinolin-1-yl]methyl}quinoline (3ad): White solid; m.p. 134–135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 6.4 Hz, 1 H), 7.95 (d, J = 7.6 Hz, 1 H), 7.78–7.66 (m, 2 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.05 (d, J = 8.4 Hz, 3 H), 6.82 (d, J = 8.8 Hz, 2 H), 6.61 (s, 1 H), 6.27 (s, 1 H), 5.31 (t, J = 6.8 Hz, 1 H), 3.83 (s, 3 H), 3.76–3.69 (m, 1 H), 3.67–3.56 (m, 2 H), 3.45 (s, 3 H), 3.31 (dd, J = 14.8, 12.0 Hz, 1 H), 3.06–2.98 (m, 1 H), 2.81 (dt, J = 16.0, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 147.2, 147.0, 146.2 (2 C), 135.3 (2 C), 129.2, 128.9, 128.3 (2 C), 127.0, 126.3, 125.8, 125.4, 122.4, 121.7, 115.0 (2 C), 111.0, 110.0, 59.7, 56.0, 55.7, 45.2, 42.0, 27.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{25}ClN_2NaO_2$ $[M + Na]^+$ 467.1497; found 467.1505.

2-{[2-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinolin-1-yl]methyl}-6-methylquinoline (3bd): White solid; m.p. 137–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.4 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.58–7.44 (m, 2 H), 7.05 (d, J = 8.8 Hz, 2 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 2 H), 6.61 (s, 1 H), 6.27 (s, 1 H), 5.28 (t, J = 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.76–3.69 (m, 1 H), 3.67–3.53 (m, 2 H), 3.46 (s, 3 H), 3.27 (dd, J = 12.4, 6.8 Hz, 1 H), 3.06–2.97 (m, 1 H), 2.80 (dt, J = 16.0, 4.4 Hz, 1 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 147.2, 147.0, 146.2, 145.8, 135.1, 134.6, 131.1, 129.2, 128.3 (2 C), 127.9, 126.3, 125.8 (2 C), 122.3, 121.6, 114.9 (2 C), 110.9, 110.0, 59.7, 55.9, 55.7, 45.1, 41.9, 27.1, 21.9 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}ClN_2O_2$ $[M + H]^+$ 459.1834; found 459.1816.

6-Chloro-2-{[2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetra-hydroiso-quinolin-1-yl]methyl}quinoline (3cd): White solid; m.p. 145–146 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.8 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.72 (s, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.05 (d, J = 8.8 Hz, 3 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.62 (s, 1 H), 6.28 (s, 1 H), 5.28 (t, J = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.74–3.67 (m, 1 H), 3.66–3.54 (m, 2 H), 3.49 (s, 3 H), 3.28 (dd, J = 12.8, 6.4 Hz, 1 H), 3.05–2.97 (m, 1 H), 2.80 (dt, J = 15.6, 4.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 147.7, 147.6, 146.7, 146.1, 134.7, 131.4, 130.3, 130.2, 129.4, 128.7 (2 C), 127.2, 126.2, 126.0, 123.6, 122.1, 115.3 (2 C), 111.3, 110.1, 59.6, 55.9, 55.7, 45.1, 41.8, 26.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{24}Cl_2N_2NaO_2$ $[M + Na]^+$ 501.1107; found 501.1098.

6-Bromo-2-{[2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetra-hydroisoquinolin-1-yl]methyl}quinoline (3dd): White solid; m.p. 146–147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.8 Hz, 1 H), 7.89 (d, J = 2.0 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.76 (dd, J = 8.8, 2.0 Hz, 1 H), 7.05 (d, J = 9.2 Hz, 3 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.62 (s, 1 H), 6.28 (s, 1 H), 5.27 (t, J = 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.74–3.67 (m, 1 H), 3.66–3.53 (m, 2 H), 3.50 (s, 3 H), 3.28 (dd, J = 13.2, 6.4 Hz, 1 H), 3.05–2.97 (m, 1 H), 2.80 (dt, J = 16.0, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 147.6, 147.5, 146.7, 146.2, 134.6, 132.6, 130.4, 129.3 (2 C), 128.7 (2 C), 127.7, 126.2, 123.5, 122.1, 119.5, 115.2 (2 C), 111.2, 110.1, 59.5, 55.8, 55.6, 45.1, 41.8, 26.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{24}BrClN_2NaO_2$ $[M + Na]^+$ 545.0602; found 545.0591.

2-{[2-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinolin-1-yl]methyl}-6-methoxyquinoline (3fd): White solid; m.p. 146–147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 9.6 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.36 (dd, J = 8.8, 1.2 Hz, 1 H), 7.05 (d, J = 8.8 Hz, 2 H), 7.02–6.94 (m, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.61 (s, 1 H), 6.26 (s, 1 H), 5.26 (t, J = 7.2 Hz, 1 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.75–3.60 (m, 2 H), 3.58–3.51 (m, 1 H), 3.46 (s, 3 H), 3.25 (dd, J = 11.6, 5.2 Hz, 1 H), 3.06–2.97 (m, 1 H), 2.81 (dt, J = 16.0, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 156.4, 147.3, 147.0, 146.2, 143.4, 134.1, 129.8, 129.3, 128.3 (2 C), 127.2, 125.9, 122.7 (2 C), 121.6, 115.0 (2 C), 111.0, 110.1, 104.9, 59.8, 56.0, 55.8, 55.7, 45.1, 42.0, 27.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}ClN_2O_3$ $[M + H]^+$ 475.1783; found 475.1770.

2-[(6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]quinoline (3ae): White solid; m.p. 118–119 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 7.6 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.71 (dd, J = 18.8, 8.4 Hz, 2 H), 7.48 (t, J = 7.2 Hz, 1 H), 7.14 (t, J = 8.0 Hz, 2 H), 7.08 (d, J = 8.0 Hz, 1 H), 6.91 (d, J = 8.0 Hz, 2 H), 6.66 (t, J = 7.2 Hz, 1 H), 6.61 (s, 1 H), 6.24 (s, 1 H), 5.34 (t, J = 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.79–3.69 (m, 2 H), 3.66–3.59 (m, 1 H), 3.42 (s, 3 H), 3.31 (dd, J = 13.2, 8.0 Hz, 1 H), 3.08–2.99 (m, 1 H), 2.81 (dt, J = 16.8, 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 148.7, 147.3, 146.9, 146.1, 135.2, 129.5, 128.8, 128.6 (2 C), 128.4, 127.0, 126.3, 126.1, 125.4, 122.5, 117.1, 114.0 (2 C), 111.0, 110.1, 59.7, 56.0, 55.7, 45.3, 41.9, 27.2 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{26}N_2NaO_2$ $[M + Na]^+$ 433.1886; found 433.1890.

2-[(6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-6-methylquinoline (3be): White solid; m.p. 119–120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.6 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.56–7.46 (m, 2 H), 7.14 (t, J = 7.6 Hz, 2 H), 7.04 (d, J = 7.2 Hz, 1 H), 6.90 (d, J = 8.0 Hz, 2 H), 6.65 (t, J = 6.8 Hz, 1 H), 6.60 (s, 1 H), 6.24 (s, 1 H), 5.32 (t, J = 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.78–3.68 (m, 2 H), 3.64–3.57 (m, 1 H), 3.43 (s, 3 H), 3.28 (dd, J = 11.6, 6.0 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.80 (dt, J = 15.6, 5.2 Hz, 1 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 149.2, 147.3, 146.5, 146.2, 135.4, 135.0, 131.4, 129.9, 128.9 (2 C), 128.3, 126.6, 126.4, 126.1, 122.7, 117.3, 114.2 (2 C), 111.1, 110.3, 59.6, 55.8, 55.5, 45.0, 41.6, 26.8, 21.5 ppm. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}N_2NaO_2$ $[M + Na]^+$ 447.2043; found 447.2026.

6-Chloro-2-[(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroiso-quinolin-1-yl)methyl]quinoline (3ce): White solid; m.p. 143–144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.63 (dd, J = 8.8, 2.0 Hz, 1 H), 7.18–7.05 (m, 3 H), 6.87 (d, J = 8.0 Hz, 2 H), 6.66 (t, J = 7.2 Hz, 1 H), 6.61 (s, 1 H), 6.29 (s, 1 H), 5.31 (t, J = 7.2 Hz, 1 H), 3.83 (s, 3 H), 3.77–3.67 (m, 2 H), 3.64–3.57 (m, 1 H), 3.49 (s, 3 H), 3.31 (dd, J = 12.8, 6.4 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.79 (dt, J = 16.0, 4.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 149.1, 147.5, 146.7, 146.3, 134.5, 132.6, 130.5, 129.7, 129.3, 128.9 (2 C), 127.7, 126.5, 123.6, 119.4, 117.5, 114.3 (2 C), 111.3, 110.2, 59.5, 55.8, 55.6, 45.1, 41.6, 26.8 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{25}ClN_2NaO_2$ $[M + Na]^+$ 467.1497; found 467.1497.

6-Bromo-2-[(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroiso-quinolin-1-yl)methyl]quinoline (3de): White solid; m.p. 153–154 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 2.0 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 7.74 (dd, J = 9.2, 2.0 Hz,

1 H), 7.18–7.04 (m, 3 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 6.61 (s, 1 H), 6.28 (s, 1 H), 5.31 (t, *J* = 6.8 Hz, 1 H), 3.83 (s, 3 H), 3.76–3.66 (m, 2 H), 3.62–3.56 (m, 1 H), 3.48 (s, 3 H), 3.29 (dd, *J* = 13.6, 6.8 Hz, 1 H), 3.07–2.99 (m, 1 H), 2.79 (dt, *J* = 15.6, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 149.2, 147.5, 146.7, 146.1, 134.7, 131.4, 130.4, 130.1, 129.8, 129.0 (2 C), 127.2, 126.5, 126.0, 123.7, 117.6, 114.3 (2 C), 111.3, 110.3, 59.6, 55.9, 55.7, 45.2, 41.7, 26.8 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{25}BrN_2NaO_2$ [M + Na]$^+$ 511.0992; found 511.0979.

6-Chloro-2-{[2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-methyl}quinoline (3cf): White solid; m.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 5.2 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.62 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.12 (d, *J* = 4.0 Hz, 3 H), 7.05–6.99 (m, 1 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 5.28 (t, *J* = 7.2 Hz, 1 H), 3.78–3.68 (m, 1 H), 3.68 (s, 3 H), 3.64–3.54 (m, 2 H), 3.32 (dd, *J* = 13.6, 7.6 Hz, 1 H), 3.11–3.00 (m, 1 H), 2.83 (dt, *J* = 16.0, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 151.8, 145.6, 143.4, 137.6, 134.1 (2 C), 130.8, 130.1, 129.5, 128.3, 126.8, 126.7, 126.0, 125.6, 125.2, 123.1, 116.7 (2 C), 114.1 (2 C), 60.7, 55.7, 45.4, 42.7, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}ClN_2NaO$ [M + Na]$^+$ 437.1391; found 437.1388.

6-Bromo-2-{[2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-methyl}quinoline (3df): White solid; m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 2.0 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.74 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.16–7.04 (m, 3 H), 7.04–6.97 (m, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 6.84–6.78 (m, 2 H), 6.72–6.62 (m, 2 H), 5.26 (t, *J* = 6.4 Hz, 1 H), 3.78–3.69 (m, 1 H), 3.68 (s, 3 H), 3.63–3.50 (m, 2 H), 3.29 (dd, *J* = 13.6, 6.4 Hz, 1 H), 3.11–3.01 (m, 1 H), 2.82 (dt, *J* = 16.0, 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 156.6, 147.7, 143.7, 137.8, 134.6, 134.4, 130.1, 128.6 (2 C), 128.4, 127.6, 127.1, 126.6, 125.7, 122.8, 121.9, 121.8, 114.9 (2 C), 105.1, 60.1, 55.5, 45.1, 41.9, 27.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{26}H_{23}BrN_2NaO$ [M + Na]$^+$ 481.0886; found 481.0900.

2-[2-(Phenylamino)ethyl]benzaldehyde (3x): White solid; m.p. 85–86 °C. CAS: 65459-29-2.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1 H), 7.76 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 2 H), 7.52 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.49–7.39 (m, 3 H), 7.32 (dd, *J* = 12.8, 7.2 Hz, 2 H), 4.26 (t, *J* = 7.6 Hz, 2 H), 3.28 (t, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 141.1, 138.9, 134.2, 133.6, 133.4, 131.6, 128.9 (2 C), 127.1, 126.7, 119.0 (2 C), 45.1, 30.5 ppm. MS-ESI: *m/z* = 225.1 [M$^+$].

2-(4-Chlorophenyl)-3,4-dihydroisoquinolinium Tetrafluoroborate (3y): White solid; m.p. 200 °C (decomp.). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.60 (s, 1 H), 7.99 (d, *J* = 7.2 Hz, 1 H), 7.91–7.86 (m, 3 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 7.64–7.57 (m, 2 H), 4.56 (t, *J* = 7.9 Hz, 2 H), 3.40 (t, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO and D_2O): δ = 170.7, 145.3, 139.3, 136.2, 134.8, 130.9, 128.6 (2 C), 127.7, 126.0, 124.2, 112.0 (2 C), 52.0, 26.8 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{13}ClN$ [M$^+$] 242.0731; found 242.0738 [M – BF_4^-].

Isochroman-1-one (3z): White solid; m.p. 37–39 °C. CAS: 4702-34-5.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.6 Hz, 1 H), 7.52 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 4.52 (t, *J* = 6.0 Hz, 2 H), 3.05 (t, *J* = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 139.2, 133.2, 129.8, 127.2, 126.9, 124.9, 67.1, 27.6 ppm. MS-ESI: *m/z* = 149.1 [M + H] $^+$.

Acknowledgments

Support from the National Natural Science Foundation of China (NSFC) (grant numbers 21376221, 21576239 and 21506190) is gratefully acknowledged. Cooperation from the colleagues analytical research and development is highly appreciated.

Keywords: Cross-coupling · Oxidation · C–C coupling · Green chemistry

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Received: April 5, 2016
Published Online: July 4, 2016

