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Isoquinoline Derivatives via Stepwise Regioselective sp^2 and sp^3 C−H Bond Functionalizations

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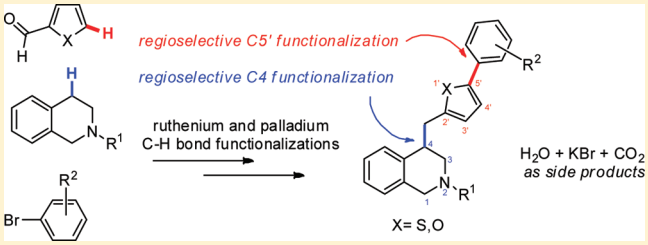
Supporting Information

ABSTRACT: Efficient and practically attractive stepwise ruthenium- and palladium-catalyzed regioselective C−H bond functionalizations were achieved to produce 4-substituted tetrahydroisoquinoline derivatives featuring various heteroaromatic substructures in moderate to good yields. Both ruthenium- and palladium-based catalytic processes generated nontoxic and easily separable side products.



Considering the importance of cyclic amines and alkaloids in industry as dyes and as pharmaceutical and agrochemical drugs, straightforward and environmentally benign approaches for the preparation of these compounds still represents a challenging task for chemists.[1,2] Among them, tetrahydroisoquinoline (THIQ) derivatives constitute an important class of compounds with numerous biological properties such as anti-HIV,[3] antitumor,[4] and antipsychotic[5] activities. They are actually produced by multistep methods, and new direct synthetic routes to access THIQ derivatives are highly desired and at the center of active research activities. Main THIQ derivatives arise from the functionalization at position 1 via cross dehydrogenative coupling (CDC)[6−8] or at position 3 with multistep syntheses.[4b,9] In contrast, functionalization at position 4 is scarce.[10] In recent years, C−H bond functionalization involving activation of inert C−H bonds to allow direct C−C coupling has attracted considerable attention since this type of reaction minimizes the reaction steps and therefore the number of purification processes and the production of wastes and fullfills the criteria of sustainability and green chemistry. In our laboratory, we have recently described, on one hand, the first ruthenium-catalyzed C(β)−H functionalization of various cyclic amines and highlighted the formation of reactive enamine intermediates via hydrogen autotransfer processes[11−13] (Figure 1) and, on the other hand, the regioselective palladium-catalyzed C(5) functionalization of five-membered heterocycles.[14,15]

In order to take advantage of these two catalytic transformations, we evaluated the reactivity of the THIQ core structure with unexplored formyl heterocycles. Herein, we report on environmentally attractive and selective transformations of the tetrahydroisoquinoline core providing access to diverse C(4)-substituted products containing functionalized heteroaromatic subunits via stepwise ruthenium and palladium C−H bond functionalizations.

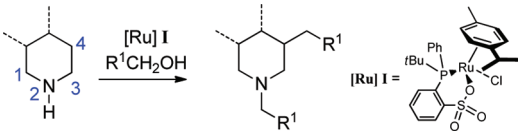


Figure 1. C(β)−H alkylation of cyclic amines via multi-hydrogen transfer processes.

We started our study by examining the feasibility of the C(4) alkylation of the tetrahydroisoquinoline **1a** with various heteroaromatic aldehydes **2**. Selective alkylation was carried out in toluene at 150 °C using 2.5 mol % of the ruthenium catalyst **I** (Figure 1) and formic acid as the final hydrogen donor to fully convert enamine and iminium intermediates (Table 1). After optimizing the amount of camphorsulfonic acid (CSA), it was found that the best reaction conditions were obtained using 8 mol % of CSA leading to 69% isolated yield of **3a** starting from 2-furaldehyde **2a** (Table 1, entry 1). Similar results were obtained with substituted furaldehyde **2g** reaching 62% yield (entry 7). Interestingly, reaction of 3-furaldehyde **2f** stabilized with BHT afforded 4-substituted THIQ **3f** in excellent yield (entry 6). 1-Methyl-2-carboxaldehyde pyrrole **2b** exhibited lower reactivity, affording the expected product **3b** in 30% yield along with noticeable amounts of byproducts resulting from the partial hydrogenation and hydrolysis of the pyrrole structure (entry 2). The influence of the position of the

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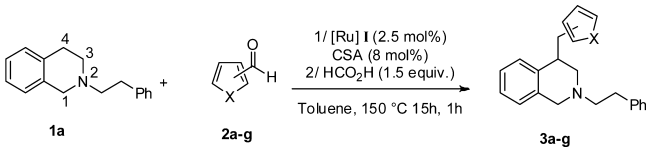
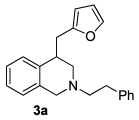
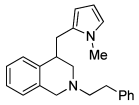
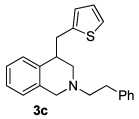
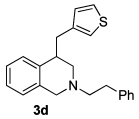
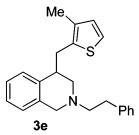
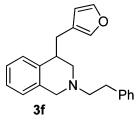
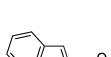
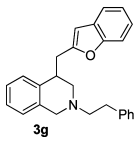
Table 1. Ruthenium-Catalyzed C(4) Alkylation of 1a[a]



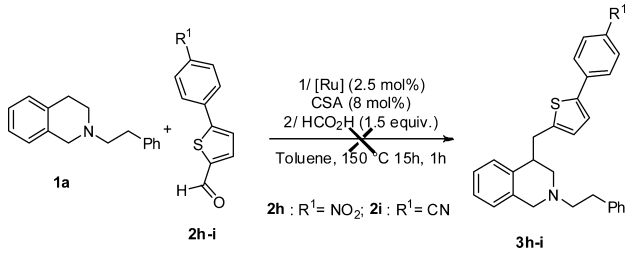
Entry	2	product 3	Yield[b]
1			69
2			30
3			71
4			83
5			95
6			90
7			62

[a]All reactions were carried out at 0.2 M concentration in toluene at 150 °C for 15 h under an inert atmosphere with **2**/**1a**/[Ru]/CSA in 1/1/0.025/0.08 molar ratio. [b]Isolated yield.

carboxaldehyde substituent on the starting thiophene ring was next investigated. After purification, the 2-formylthiophenes **2c** and **2e** afforded the expected C(4)-alkylated compounds **3c** and **3e** in 71 and 95% yield, respectively (Table 1, entries 3 and 5). The same reactivity was observed with 3-thiophenecarboxaldehyde **2d**, and **3d** was isolated in 83% yield (Table 1, entry 4).

C(4) Alkylation of **1a** with heterocycles **2h** and **2i** containing electron-withdrawing groups such as cyano and nitro groups led to the formation of the expected compounds in only little amounts, and byproducts featuring amino groups resulting from the reduction of these hydrogen acceptors under our reaction conditions were detected (Scheme 1). In order to gain access to highly functionalized C(4)-alkylated tetrahydroisoquinolines, we investigated a sequential selective sp^2 C−H functionalization of the heteroaromatic moieties with a range of aryl bromides via palladium-catalyzed regioselective arylation (Table 2). Thus, tetrahydroisoquinolines **3a** and **3c** (1.5 equiv)

Scheme 1. Incompatible Substrates for C(4) Alkylation of 1a



and aryl bromides **4** (1 equiv) were reacted in the presence of $Pd(OAc)_2$ using dimethylacetamide as the solvent in the presence of potassium acetate acting as base to assist the deprotonation of the heteroaromatic substrates **3**. Examination of the $Pd(OAc)_2$ loading showed that 0.5 mol % was the best condition affording the expected arylated THIQ **5**, whereas higher catalyst loading inhibited the reaction.[16] For the substrate **3a** featuring a furan heterocycle, reactions proceeded smoothly, affording exclusively the C′(5)-arylated products **5a**−**e** in 64−95% isolated yields along with only trace amounts of the undesired Ullmann-type aryl bromide homocoupling byproducts (Table 2, entries 1−5). With *para*-substituted electron-deficient aryl bromides, moderate yields were obtained with **4a** and **4b** (Table 2, entries 1 and 2). The highly electron-deficient 4-bromonitrobenzene **4e** gave the best result, yielding **5e** in 95% isolated yield (Table 2, entry 5). The *meta*-substituted bromobenzonitrile **4c** exhibited a reactivity similar to that of **4b** (Table 2, entry 3). In addition, to further explore the scope of the arylation postfunctionalization, we selected the substrate **3c** containing a 2′-substituted thiophene structure to test the arylation reaction. Good reactivities and high regioselectivities with formation of the carbon−carbon bond at C′(5) were obtained in all cases, and products **5f**−**i** were isolated in 54−73% yields (Table 2, entries 6−9). Again 4-bromonitrobenzene **4e** gave the best result, yielding **5j** in 96% yield (Table 2, entry 10). In contrast, reactions of 3′-substituted thiophene **3d** were more sluggish. The major formation of homocoupling byproducts was observed, together with the formation of two arylated compounds in almost equimolar ratio resulting from the C′(2) and C′(5) functionalization of **3d** in low yields[17] (not presented in Table 2). A crucial advantage of the sequential procedure is illustrated by the formation of the aldehydes **5a** and **5f** in good yields, whereas the direct ruthenium-catalyzed reaction starting from a dialdehyde substrate and **1a** would have led to a mixture of products resulting from the two different possible C−C bond formations.

In summary, a sequence involving two consecutive and highly regioselective metal-catalyzed functionalizations of THIQ and heteroaromatics is reported. The reactions occur through sp^3 C−H and sp^2 C−H bond functionalization and generate KBr, carbon dioxide, and water as the major side products. The overall sequential procedure also represents a double functionalization of aromatic heterocycles. It is noteworthy that the two-step procedure makes possible the preparation of products **5g** and **5j**, which was not possible from the direct ruthenium-catalyzed reaction (**3h** and **3i** in Scheme 1), pointing out the complementarity of the two catalytic transformations. These achievements also demonstrate the potential of C−H functionalization as a viable and eco-friendly tool toward the access to various alkaloids.

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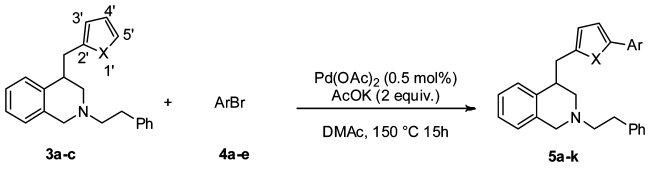
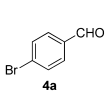
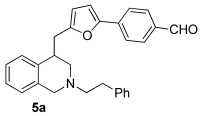
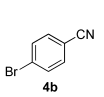
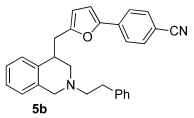
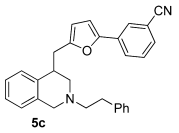
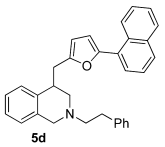
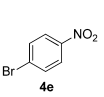
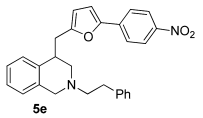
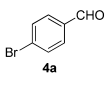
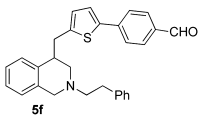
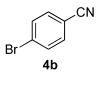
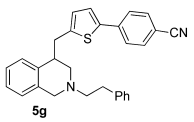
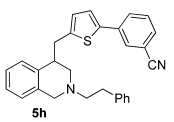
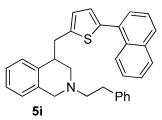
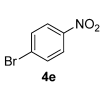
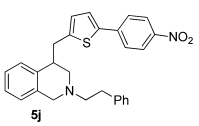
Table 2. Palladium-Catalyzed C′(5) Arylation of 3[a]



Entry	3	4	product 5	Yield[b]
1	3a			64
2	3a			67
3	3a			67
4	3a			67
5	3a			95
6	3c			61
7	3c			54
8	3c			69
9	3c			73
10	3c			96

[a]All reactions were carried out at 0.04 M concentration in DMAc at 150 °C for 15 h under an inert atmosphere with **3**/**4**/AcOK/$Pd(OAc)_2$ in 1.5/1/2/0.005 molar ratio. [b]Isolated yield.

EXPERIMENTAL SECTION

General Information: All reactions were carried out under argon atmosphere in dried glassware with magnetic stirring. Toluene was distilled under conventional methods and stored under argon atmosphere. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. Proton magnetic resonance (^{1}H NMR) spectra were recorded on 400, 300, and 500 MHz spectrometers, and carbon magnetic resonance (^{13}C NMR) spectra were performed at 100 and 75 MHz. $CDCl_3$ was the solvent used for the NMR analysis. Chemical shifts were reported in parts per million downfield from internal Me_4Si. HRMS were recorded on a Q-TOF2 mass spectrometer with an ESI source.

General Procedure I for the C4 Alkylation of 1a: To a stirred solution of tetrahydroisoquinoline **1a** (0.840 mmol, 1 equiv) and aldehyde **2** (1 mmol, 1.2 equiv) in 4 mL of toluene were added sequentially catalyst **I** (2.5 mol %) and camphorsulfonic acid (8 mol %). Then the reaction mixture was stirred at 150 °C for 15 h. After cooling the reaction mixture, formic acid (1.5 equiv) was added and the resulting mixture was stirred at 150 °C for an additional hour. After concentration, the residue was directly purified by column chromatography (Et_2O/PE (petroleum ether)) to afford the C4-alkylated amines **3**.

4-(Furan-2-ylmethyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 3a: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 69% yield (184 mg) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 1.2 Hz, 1H), 7.42−7.30 (m, 5H), 7.30−7.23 (m, 3H), 7.20−7.15 (m, 1H), 6.41 (dd, J = 1.8, 3.0 Hz, 1H), 6.07 (d, J = 3.0 Hz, 1H), 4.02 (d, J = 14.6 Hz, 1H), 3.62 (d, J = 14.6 Hz, 1H), 3.38−3.27 (m, 1H), 3.21−3.11 (m, 2H), 3.07−2.76 (m, 5H), 2.63 (dd, J = 3.2, 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 140.9, 140.5, 137.8, 134.9, 128.7, 128.4, 128.2, 126.4, 126.1, 125.9, 125.8, 110.1, 106.5, 60.0, 56.6, 54.0, 38.2, 34.7, 33.7; HRMS calcd for $C_{22}H_{24}NO$ $[M + H]^+$ 318.18579, found $[M + H]^+$ 318.1859.

4-((1-Methyl-1*H*-pyrrol-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 3b: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 30% yield (82 mg) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 7.23−7.17 (m, 2H), 7.16−7.10 (m, 2H), 6.58 (br s, 1H), 6.14 (br s, 1H), 6.00 (br s, 1H), 4.01 (d, J = 15.0 Hz, 1H), 3.52 (d, J = 15.0 Hz, 1H), 3.48 (s, 3H), 3.10−3.02 (m, 1H), 3.00−2.86 (m, 3H), 2.83−2.75 (m, 2H), 2.57 (dd, J = 3.0, 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 138.1, 134.9, 131.9, 128.7, 128.3, 128.2, 126.4, 126.1, 125.9, 125.8, 120.9, 106.9, 106.5, 60.2, 56.4, 54.2, 39.4, 33.6, 33.5, 32.9; HRMS calcd for $C_{23}H_{27}N_2$ $[M + H]^+$ 331.21742, found $[M + H]^+$ 331.2168.

2-Phenethyl-4-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline 3c: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 71% yield (198 mg) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.15 (m, 9H), 7.08−7.06 (m, 1H), 6.93 (dd, J = 3.3, 5.2 Hz, 1H), 6.73 (d, J = 3.3 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.51 (d, J = 14.8 Hz, 1H), 3.29 (dd, J = 10.8, 14.3 Hz, 1H), 3.17−3.07 (m, 2H), 2.91−2.75 (m, 3H), 2.72−2.65 (m, 1H), 2.50 (dd, J = 3.6, 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 140.5, 137.8, 134.8, 128.7, 128.4, 128.3, 126.7, 126.5, 126.3, 126.0, 125.9, 125.6, 123.5, 60.0, 56.5, 53.6, 41.4, 36.3, 33.7, HRMS calcd for $C_{22}H_{24}NS$ $[M + H]^+$ 334.16295, found $[M + H]^+$ 334.1631.

2-Phenethyl-4-(thiophen-3-ylmethyl)-1,2,3,4-tetrahydroisoquinoline 3d: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 83% yield (232 mg) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 5H), 7.21−7.15 (m, 4H), 7.09−7.08 (m, 1H), 6.95 (d, J = 4.7 Hz, 1H), 6.86 (s, 1H), 3.92 (d, J = 14.8 Hz, 1H), 3.53 (d, J = 14.8 Hz, 1H), 3.10−2.98 (m, 3H), 2.89−2.63 (m, 5H), 2.50 (dd, J = 3.1, 11.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 140.5, 138.2, 134.8, 128.8, 128.5, 128.4, 128.3, 126.5, 126.2, 125.9, 125.8, 125.3, 121.5, 60.1, 56.5, 54.0, 40.1, 36.7, 33.7; HRMS calcd for $C_{22}H_{23}NNaS$ $[M + Na]^+$ 356.14489, found $[M + Na]^+$ 356.1451.

4-((3-Methylthiophen-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 3e: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 95% yield (278 mg) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.13 (m, 9H), 7.08−7.06 (m, 1H), 6.57 (dq, J = 2.9, 1.5 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 3.90 (d, J = 15.0 Hz, 1H), 3.51 (d, J =

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15.0 Hz, 1H), 3.20 (dd, J = 10.9, 14.8 Hz, 1H), 3.10−3.02 (m, 2H), 2.93−2.64 (m, 5H), 2.51 (dd, J = 3.8, 11.7 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 140.6, 138.0, 137.8, 134.9, 128.7, 128.6, 128.5, 128.3, 126.5, 126.2, 125.9, 125.3, 124.7, 60.1, 56.6, 53.6, 41.3, 36.6, 33.8, 15.3; HRMS calcd for $C_{23}H_{26}NS$ $[M + H]^+$ 348.1786, found $[M + H]^+$ 348.1782.

4-(Furan-3-ylmethyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 3f: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 90% yield (238 mg) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.20−7.06 (m, 8H), 7.02 (s, 1H), 6.98−6.97 (m, 1H), 6.19 (s, 1H), 3.78 (d, J = 14.8 Hz, 1H), 3.44 (d, J = 14.8 Hz, 1H), 2.94−2.88 (m, 1H), 2.80−2.57 (m, 7H), 2.44 (dd, J = 11.6, 3.2 Hz, 1H ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 140.5, 139.9, 138.3, 134.9, 128.7, 128.3, 128.2, 126.4, 126.1, 125.9, 125.8, 123.3, 111.1, 60.1, 56.6, 54.0, 39.4, 33.7, 31.1; HRMS calcd for $C_{22}H_{24}NO$ $[M + H]^+$ 318.18579, found $[M + H]^+$ 318.1856.

4-(Benzofuran-2-ylmethyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 3g: Prepared according to general procedure I after purification through column chromatography (Et_2O/PE 2:8) in 62% yield (190 mg) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (t, J = 8.0 Hz, 2H), 7.37−7.20 (m, 10 H), 7.13−7.11 (m, 1H), 6.33 (s, 1H), 3.98 (d, J = 15.0 Hz, 1 h), 3.55 (d, J = 15.0 Hz, 1H), 3.44−3.36 (m, 1H), 3.27 (dd, J = 10.0, 14.0 Hz, 1H), 3.13 (dd, J = 3.8, 14.3 Hz, 1H), 2.96−2.81 (m, 4H), 2.77−2.68 (m, 1H), 2.57 (dd, J = 3.4, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 154.7, 140.5, 137.7, 134.9, 128.8, 128.7, 128.5, 128.3, 126.5, 126.2, 126.0, 125.9, 123.2, 122.4, 120.3, 110.7, 103.6, 59.9, 56.5, 54.0, 37.9, 35.3, 33.7; HRMS calcd for $C_{26}H_{26}NO$ $[M + H]^+$ 368.20144, found $[M + H]^+$ 368.2015.

General Procedure II for the C′5 Arylation of Amines 3: To a stirred solution of amine **3** (30 mg, 1.5 equiv) and arylbromides **4** (1 equiv) in 2 mL of *N*,*N*-dimethylacetamide were added sequentially potassium acetate (2 equiv) and $PdOAc_2$ (0.5 mol %), and the resulting mixture was stirred at 150 °C for 15 h. After evaporation of the solvent, the crude mixture was suspended on silica and purified by column chromatography to afford the C′5-arylated compounds **5**.

4-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)furan-2-yl)benzaldehyde 5a: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 3:7) in 64% yield (17.1 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.33−7.05 (m, 9H), 6.77 (d, J = 3.1 Hz, 1H), 6.08 (d, J = 3.1 Hz, 1H), 3.93 (d, J = 15.0 Hz, 1H), 3.52 (d, J = 15.à Hz, 1H), 3.31−3.22 (m, 1H), 3.15−2.98 (m, 2H), 2.94−2.68 (m, 5H), 2.58 (dd, J = 3.6, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 156.5, 142.3, 140.4, 138.9, 137.5, 136.3, 134.4, 130.3, 128.7, 128.4, 128.3, 126.5, 126.2, 126.0, 126.0, 123.4, 109.6, 109.2, 60.0, 56.5, 54.2, 38.4, 35.0, 33.7, HRMS calcd for $C_{29}H_{28}NO_2$ $[M + H]^+$ 422.21200, found $[M + H]^+$ 422.2117.

4-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)furan-2-yl)benzonitrile 5b: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 3:7) in 67% yield (17.9 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 7.33−7.09 (m, 9H), 6.72 (d, J = 3.3 Hz, 1H), 6.07 (d, J = 3.3 Hz, 1H), 3.92 (d, J = 15.0 Hz, 1H), 3.51 (d, J = 15.0 Hz, 1H), 3.28−3.06 (m, 3H), 2.98−2.64 (m, 5H), 2.56 (dd, J = 2.9, 13.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 151.0, 140.8, 137.9, 135.4, 135.2, 132.9, 129.1, 128.8, 128.7, 126.9, 126.7, 126.5, 126.5, 123.8, 119.5, 110.0, 109.6, 60.4, 56.9, 54.6, 38.8, 35.4, 34.2; HRMS calcd for $C_{29}H_{27}N_2O$ $[M + H]^+$ 419.21234, found $[M + H]^+$ 419.2124.

3-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)furan-2-yl)benzonitrile 5c: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 3:7) in 67% yield (17.8 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.42−7.16 (m, 10H), 7.14−7.06 (m, 1H), 6.11 (d, J = 3.0 Hz, 1H), 3.96 (d, J = 15.0 Hz, 1H), 3.54 (d, J = 15.0 Hz, 1H), 3.39−3.26 (m, 1H), 3.18−3.06 (m, 2H), 3.06−2.70 (m, 5H), 2.60 (dd, J = 3.6, 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 148.4, 141.0, 140.5, 137.6, 134.9, 134.1, 133.5, 132.8, 128.7, 128.5, 128.3, 126.5, 126.2, 126.0, 125.9, 125.5, 119.1, 111.4, 109.6, 106.3, 59.9, 56.5, 54.2, 38.3, 34.9, 33.7; HRMS calcd for $C_{29}H_{27}N_2O$ $[M + H]^+$ 419.21234, found $[M + H]^+$ 419.2122.

4-((5-(Naphthalen-1-yl)furan-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 5d: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 2:8) in 67% yield (18,7 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47−8.43 (m, 1H), 7.91−7.73 (m, 3H), 7.54−7.46 (m, 3H), 7.33−7.06 (m, 9H), 6.65 (d, J = 3.2 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 3.95 (d, J = 15.0 Hz, 1H), 3.54 (d, J = 15.0 Hz, 1H), 3.38−3.27 (m, 1H), 3.20−3.05 (m, 2H), 2.99−2.69 (m, 5H), 2.61 (dd, J = 3.3, 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 151.9, 140.4, 137.7, 134.9, 133.9, 130.1, 128.7, 128.4, 128.3, 128.1, 126.5, 126.4, 126.2, 125.9, 125.9, 125.8, 125.6, 125.5, 125.3, 125.3, 110.0, 108.6, 60.0, 56.6, 54.3, 38.4, 34.9, 33.7; HRMS calcd for $C_{32}H_{30}NO$ $[M + H]^+$ 444.23274, found $[M + H]^+$ 444.2329.

4-((5-(4-Nitrophenyl)furan-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 5e: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 2:8) in 95% yield (26 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.35−7.18 (m, 9H), 7.12−7.10 (m, 1H), 6.82 (d, J = 3.0 Hz, 1H), 6.11 (d, J = 3.0 Hz, 1H), 3.95 (d, J = 15.0 Hz, 1H), 3.54 (d, J = 15.0 Hz, 1H), 3.33−3.26 (m, 1H), 3.24−3.17 (m, 1H), 3.06 (dd, J = 4.0, 14.0 Hz, 1H), 2.97−2.68 (m, 5 H), 2.60 (dd, J = 3.3, 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 150.3, 145.9, 140.5, 137.5, 136.6, 135.0, 128.7, 128.4, 128.3, 126.5, 126.2, 126.1, 126.0, 124.3, 123.3, 110.0, 109.8, 59.9, 56.4, 54.2, 38.4, 34.9, 33.7; HRMS calcd for $C_{28}H_{27}N_2O_3$ $[M + H]^+$ 439.20217, found $[M + H]^+$ 439.2022.

4-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)thiophen-2-yl)benzaldehyde 5f: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 1:9) in 61% yield (16 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.2 Hz, 1H), 7.30−7.17 (m, 10H), 7.10−7.07 (m, 1H), 6.71 (d, J = 3.3 Hz, 1H), 3.94 (d, J = 15.0 Hz, 1H), 3.51 (d, J = 15.0 Hz, 1H), 3.30 (dd, J = 11.6, 15.4 Hz, 1H), 3.17−3.09 (m, 2H), 2.92−2.65 (m, 5H), 2.54 (dd, J = 3.7, 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 145.9, 140.6, 140.5, 140.3, 137.6, 135.0, 134.7, 130.4, 128.8, 128.4, 128.3, 127.2, 126.6, 126.3, 126.1, 126.0, 125.5, 124.9, 60.1, 56.4, 53.7, 41.4, 36.8, 33.8; HRMS calcd for $C_{29}H_{28}NOS$ $[M + H]^+$ 438.18916, found $[M + H]^+$ 438.1893.

4-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)thiophen-2-yl)benzonitrile 5g: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 1:9) in 54% yield (14.1 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.36−7.16 (m, 10H), 6.70 (d, J = 3.3 Hz, 1H), 3.92 (d, J = 15.0 Hz, 1H), 3.50 (d, J = 15.0 Hz, 1H), 3.30 (dd, J= 11.0, 14.6 Hz, 1H), 3.20−3.03 (m, 2H), 2.88−2.67 (m, 5H), 2.53 (dd, J = 2.5, 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 140.5, 139.9, 138.8, 137.5, 134.9, 132.6, 128.8, 128.4, 128.3, 127.2, 126.6, 126.2, 126.1, 126.0, 125.5, 124.9, 118.9, 110.0, 60.0, 56.4, 53.6, 41.4, 36.8, 33.7; HRMS calcd for $C_{29}H_{27}N_2S$ $[M + H]^+$ 435.1895, found $[M + H]^+$ 435.1891.

3-(5-((2-Phenethyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-methyl)thiophen-2-yl)benzonitrile 5h: Prepared according to general procedure II after purification through column chromatography (Et_2O/PE 1:9) in 69% yield (18 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.53−7.42 (m, 2H), 7.33−7.08 (m, 10H), 6.70 (d, J = 2.9 Hz, 1H), 3.95 (d, J = 14.8 Hz, 1H), 3.53 (d, J = 14.8 Hz, 1H), 3.30 (dd, J = 11.3, 15.4 Hz, 1H), 3.17−3.09 (m, 2H), 2.93−2.67 (m, 5H), 2.57 (dd, J = 2.6, 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 139.4, 138.5, 136.5, 134.8, 133.9, 129.1, 128.6, 128.4, 127.8, 127.6, 127.4, 127.3, 126.0, 125.6, 125.3, 125.1, 125.0, 123.1, 112.0, 59.1, 55.3, 52.6, 40.3, 35.7, 32.7; HRMS calcd for $C_{29}H_{27}N_2S$ $[M + H]^+$ 435.1895, found $[M + H]^+$ 435.1893.

4-((5-(Naphthalen-1-yl)thiophen-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 5i: Prepared according to general

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procedure II after purification through column chromatography (Et_2O/PE 3:7) in 73% yield (20.3 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31−8.29 (m, 1H), 7.91−7.83 (m, 2H), 7.58−7.56 (m, 1H), 7.51−7.47 (m, 3H), 7.32−7.22 (m, 4H), 7.21−7.16 (m, 5H), 7.08 (s,1H), 6.80 (s, 1H), 3.93 (d, J = 14.8 Hz, 1H), 3.52 (d, J = 14.8 Hz, 1H), 3.35−3.30 (m, 1H), 3.23−3.17 (m, 2H), 2.96−2.73 (m, 5H), 2.61−2.53 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 140.5, 139.8, 137.9, 135.0, 133.8, 132.7, 131.7, 128.8, 128.5, 128.3, 128.3, 128.1, 127.9, 127.0, 126.5, 126.3, 126.2, 126.0, 125.9, 125.9, 125.7, 125.2, 123.4, 59.2, 55.5, 52.7, 40.5, 35.7, 32.8; GC−MS m/z (%) 459 (M+, 3%), 398 (12%), 357 (21%), 333 (60%).

4-((5-(4-Nitrophenyl)thiophen-2-yl)methyl)-2-phenethyl-1,2,3,4-tetrahydroisoquinoline 5j: Prepared according to general procedure II after purification through column chromatography (Et_2O/EP 1:9) in 96% yield (26.1 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.62−7.06 (m, 9H), 7.05−7.04 (m, 1H), 6.68 (d, J = 3.0 Hz, 1H), 3.91 (d, J = 15.0 Hz, 1H), 3.46 (d, J = 15.0 Hz, 1H), 3.25 (dd, J = 11.0, 14.0 Hz, 1H), 3.13−3.05 (m, 2H), 2.85−2.63 (m, 5H), 2.50 (dd, J = 3.0, 11.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 145.2, 139.8, 139.5, 138.5, 136.5, 133.9, 127.7, 127.4, 127.3, 126.4, 125.6, 125.3, 125.2, 125.0, 124.6, 124.4, 123.3, 59.1, 55.4, 52.6, 40.4, 35.8, 32.7; HRMS calcd for $C_{28}H_{27}N_2O_2S$ $[M + H]^+$ 455.17933, found $[M + H]^+$ 455.1795.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all new compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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