# A Short Approach to N-Aryl-1,2,3,4-tetrahydroisoquinolines from N -(2-Bromobenzyl)anilines via a Reductive Amination/PalladiumCatalyzed Ethoxyvinylation/Reductive $N$-Alkylation Sequence 

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#### Abstract

N\)-Aryl-1,2,3,4-tetrahydroisoquinolines are obtained via a convenient and short protocol with a broad range of substituents on both aromatic rings and high functional group tolerance. Starting from readily available ortho-brominated aromatic aldehydes and primary aromatic amines, condensation of these building blocks under reductive conditions gives N -aryl 2 -bromobenzylamines. The $\mathrm{C}-3 / \mathrm{C}-4$-unit of the tetrahydroisoquinoline is introduced using commercially available 2ethoxyvinyl pinacolboronate under Suzuki conditions. Finally, the obtained crude ortho-ethoxyvinyl benzylamines are cyclized via an intramolecular reductive amination using the combination of triethylsilane/TFA to give the desired $N$-aryl-1,2,3,4-tetrahydroisoquinolines.


Key words $N$-aryl-1,2,3,4-tetrahydroisoquinolines, reductive cyclization, Pd-catalyzed ethoxyvinylation, reductive $N$-alkylation, cross-coupling

The isoquinoline ring system is an important structural motif in bioactive heterocycles. Due to its biosynthetic origin from amino acid derived arylethylamine precursors, 1substituted 1,2,3,4-tetrahydroisoquinolines (especially 1benzyl derivatives) are a dominant structural element in isoquinolines obtained from natural sources, and compounds of this chemotype show a wide spectrum of biological activity. ${ }^{1}$

In contrast, $N$-aryl-1,2,3,4-tetrahydroisoquinolines are rather underexplored. Diverse biological activities have been reported for this chemotype, mostly in patents, e.g., the inhibition of enzymes such as cathepsin B and calpain$2,{ }^{2 \mathrm{a}}$ tumor-relevant NADPH quinone oxidoreductase and $E$. coli nitroreductase, ${ }^{2 \mathrm{~b}}$ blocking of P-gp efflux pumps in tumor cells, ${ }^{2 c}$ and modulation of potassium and sodium channels leading to antiepileptic ${ }^{2 \mathrm{~d}}$ and analgesic effects, respec-
tively. ${ }^{2 e} \quad$ Further, $N$-aryl-1,2,3,4-tetrahydroisoquinolines have been described as ligands for estrogen receptors, ${ }^{3 a} \mathrm{G}$ protein coupled receptors, ${ }^{3 \mathrm{~b}}$ and serotonin transporters. ${ }^{3 \mathrm{c}}$

Whereas common 1 -substituted 1,2,3,4-tetrahydroisoquinolines are readily available starting from arylethylamines through established cyclization reactions (PictetSpengler, Bischler-Napieralski, followed by reduction) ${ }^{4}$ or through controlled reduction of fully aromatic isoquinolines, ${ }^{5}$ to date, there are only a limited number of published synthetic routes to $N$-aryl-1,2,3,4-tetrahydroisoquinolines. These include mainly $N$-arylations of 1,2,3,4-tetrahydroisoquinolines utilizing aryl bromides or iodides under palladium (Buchwald-Hartwig reaction) ${ }^{6 a, b}$ or copper catalysis (Ullmann reaction);6c alternatively, arylboronic acids or trifluoroborates were coupled under copper catalysis. ${ }^{6 d}$ Tran-sition-metal-free $N$-arylations can be achieved with reactive aryl halides ${ }^{2 b}$ or by using in situ prepared arynes ${ }^{6 e}$ (with associated regioselectivity issues). Other procedures involving the de novo construction of the 1,2,3,4-tetrahydroisoquinoline ring system via incorporation of primary aromatic amines are less convenient as they require either hazardous (ortho-halomethyl-arylethyl halides) ${ }^{7}$ or poorly accessible (benzo-anellated dihydropyrans) ${ }^{7 \mathrm{~b}, \mathrm{c}}$ starting materials (Figure 1). A Pomeranz-Fritsch-type cyclization of N -aryl- N -benzylaminoacetaldehyde acetals to 4-hy-droxy- $N$-aryl-1,2,3,4-tetrahydroisoquinolines is hampered by the strongly acidic conditions required and the formation of diverse side products. ${ }^{8}$

Consequently, the development of convenient approaches to $N$-aryl-1,2,3,4-tetrahydroisoquinolines is still a promising task. In continuation of our research on bioactive isoquinolines ${ }^{9}$ we were interested in the synthesis of $N$ -aryl-1,2,3,4-tetrahydroisoquinolines as rigid analogues of steroids ${ }^{3 a}$ and azobenzenes. ${ }^{10}$


Figure 1 Published approaches to N -aryl-1,2,3,4-tetrahydroisoquinolines and the retrosynthetic concept of the new approach reported herein

In order to achieve a short approach to the target N -aryl-1,2,3,4-tetrahydroisoquinolines and related ring systems with maximum variability in both aromatic rings, we have developed a novel modular method starting from or-tho-brominated aromatic aldehydes and primary aromatic amines (Figure 1). Both of these building blocks are readily available with a broad variety of additional substituents on the rings. Condensation of these building blocks under reductive conditions would give $N$-aryl 2-bromobenzylamines. The missing C-3/C-4-unit of the isoquinoline was to be introduced using commercially available 2-ethoxyvinyl pinacolboronate under Suzuki conditions. ${ }^{9 b, 11}$ Finally, the obtained ortho-ethoxyvinyl N -arylbenzylamine would undergo an intramolecular reductive amination using the combination of triethylsilane/trifluoroacetic acid (TFA) to give the desired $N$-aryl-1,2,3,4-tetrahydroisoquinolines. Similar N -arylethylations of aromatic amines using enol ethers have recently been performed in our group for the synthesis of arylethylated anilines and N -heterocycles. ${ }^{12}$ In a similar manner, benzodiazepines were obtained by intramolecular reductive amination with acetals, ${ }^{13}$ and intermolecular $N$-alkylations using silane/TFA reagents were accomplished with acetals ${ }^{14 \mathrm{a}}$ and free aldehydes. ${ }^{14 \mathrm{~b}}$

We performed our pilot experiment with 2-bromobenzaldehyde (1) and aniline (2) (Scheme 1; reactions are depicted with optimized conditions). For the first step, the intermolecular reductive amination, we employed standard conditions utilizing $\mathrm{NaCNBH}_{3}$ as the reducing agent and obtained $N$-phenyl 2-bromobenzylamine (3a) in quantitative yield. For the subsequent de novo construction of the $N$ -aryl-1,2,3,4-tetrahydroisoquinoline ring system, we investigated different conditions in order to optimize the yield and to reduce waste, purification efforts and workload (Table 1 and Scheme 1).

First, the Suzuki reaction was performed according to an established protocol from our previous work ${ }^{9 b, 11}$ using 2ethoxyvinyl pinacolboronate, tetrakis(triphenylphosphine)palladium(0) and cesium carbonate (Scheme 1). The formation of enol ether $\mathbf{4 a}$ could be monitored by TLC. We decided not to purify the intermediate ortho-ethoxyvinyl benzylamine 4a, but only isolated the crude organic material after aqueous work-up and then re-dissolved it in dichloromethane (DCM), an established solvent for silane/TFA reductions. For the reductive cyclization of crude $\mathbf{4 a}$ we examined procedures derived from similar $N$-arylethylation reactions, ${ }^{12,13}$ as shown in Table 1.

Table 1 The Reaction Conditions Explored for the Reductive Cyclization

| Entry | Conditions for the cyclization of crude enol ether 4a | Yield of 5a |
| :---: | :---: | :---: |
| $1^{12 \mathrm{a}}$ | $\mathrm{Et}_{3} \mathrm{SiH}$ (10 equiv), TFA (10 equiv), dry DCM, $0^{\circ} \mathrm{C}, 3.5 \mathrm{~h}$ | $30 \%$ over 2 steps |
| $2^{13}$ | $\mathrm{Et}_{3} \mathrm{SiH}$ (2.5 equiv), TFA (13 equiv), dry DCM, rt, 2.5 h | $34 \%$ over 2 steps |
| 3 | pure 4a, $\mathrm{Et}_{3} \mathrm{SiH}$ ( 2.5 equiv), TFA (13 equiv), dry DCM, rt, 2.5 h | $41 \%$ over 1 step ( $21 \%$ over 2 steps) |
| 4 | one-pot, $\mathrm{Et}_{3} \mathrm{SiH}$ (10 equiv), TFA (13 equiv), $0^{\circ} \mathrm{C}$ to rt, 72 h | $6 \%$ over 2 steps |
| $5^{9 b}$ | $\mathrm{Et}_{3} \mathrm{SiH}$ (0 equiv), TFA (13 equiv), dry DCM, $0^{\circ} \mathrm{C}, 3.5 \mathrm{~h}$ | 6\% over 2 steps |

We first followed the protocol of Vögerl et al. ${ }^{12 a}$ and used 10 equivalents of triethylsilane at $0{ }^{\circ} \mathrm{C}$ (Table 1, entry 1 ). The desired $N$-aryl-1,2,3,4-tetrahydroisoquinoline 5a


Scheme 1 A pilot experiment using 2-bromobenzaldehyde (1) and aniline (2) for the new synthetic approach to $N$-aryl-1,2,3,4-tetrahydroisoquinolines (illustrated with optimized conditions)
was formed within 3.5 hours in $30 \%$ yield, however, a laborious purification by repeated flash column chromatography (FCC) was required due to the necessity to remove excess triethylsilane. To minimize the purification efforts, we explored the conditions described by Popp et al. ${ }^{13}$ (Table 1, entry 2 ). Here, only 2.5 equivalents of triethylsilane were used, and the reaction was performed at room temperature. TLC monitoring indicated full consumption of the starting material after 2.5 hours, and product $5 \mathbf{a}$ was obtained in a slightly increased yield of $34 \%$ after only one round of FCC. To investigate a possible negative impact of residual reagents or impurities from the Suzuki reaction, we purified enol ether 4a by FCC ( $50 \%$ yield) and then performed the cyclization reaction (Table 1, entry 3) according to the conditions in entry 2 . In this case product $\mathbf{5 a}$ was obtained in $41 \%$ yield ( $21 \%$ over 2 steps), leading us to the conclusion that
purification of 4a was not necessary and rather causes a decrease in the overall yield of $\mathbf{5 a}$.

In another experiment we omitted the solvent change and directly added, in a one-pot procedure, the required reagents for the cyclization (triethylsilane/TFA) into the reaction mixture of the Suzuki coupling (Table 1, entry 4; following the conditions in entry 1 ). The reaction was stopped after 72 hours as formation of the cyclized product 5a was not clearly visible by TLC. Nevertheless, after FCC, product $\mathbf{5 a}$ was isolated in a very poor yield of $6 \%$.

The underlying mechanism of the cyclization reaction using triethylsilane/TFA involves $\beta$-protonation of the ethoxyvinyl moiety in 4a giving a carbenium-oxonium ion, a subsequent intramolecular cyclization leading to formation of a $\mathrm{C}-\mathrm{N}$ bond with the (necessarily unprotonated) amino group, and finally 0 -protonation, elimination of


Scheme 2 Scope and limitations of the newly developed synthetic approach towards $N$-aryl-1,2,3,4-tetrahydroisoquinolines
ethanol, and hydride transfer from triethylsilane to the resulting iminium ion. This prompted us to examine whether we would obtain the 3,4-dehydro analogue of $\mathbf{5 a}$, an $N$-aryl-1,2-dihydroisoquinoline, when only TFA, but no triethylsilane was used (Table 1, entry 5; following conditions published for the synthesis of 1-oxo-1,2-dihydroisoquinolines by Schütz et al. ${ }^{9 b}$ ). Thus crude enol ether 4a was treated with only TFA at $0{ }^{\circ} \mathrm{C}$, and after 3.5 hours, enol ether $4 \mathbf{a}$ was completely consumed. The only product we could isolate from the product mixture in pure form was, surprisingly, N -aryl-1,2,3,4-tetrahydroisoquinoline $\mathbf{5 a}$ in a poor yield of $6 \%$ over both steps.

With optimized cyclization conditions in hand, we next applied our newly developed approach for the synthesis of N -aryl-1,2,3,4-tetrahydroisoquinolines and related heterocycles starting from differently substituted ortho-brominated aromatic aldehydes and primary aromatic amines (Scheme 2).

Overall, this method enabled us to synthesize a variety of $N$-aryl-1,2,3,4-tetrahydroisoquinolines with yields ranging from $24-70 \%$ over two steps starting from the corresponding $N$-aryl 2-bromobenzylamines. As shown in Scheme 2 there was a noticeable difference in the yield of the final products depending on the substitution pattern of the starting material. It is important to note that during their investigation on the scope and limitations of the Suzu-
ki-Miyaura coupling, Buchwald et al. came to the conclusion that differently substituted aryl bromides did not affect the yield significantly when coupled with alkenyl boronic acids. ${ }^{15}$ Therefore, the herein observed differences supposedly occur mainly during the final cyclization step.

During this work, we observed an increase in the yield of the final products when anilines with electron-withdrawing substituents were used. Product $\mathbf{5 k}$, carrying an ester group, and halogenated product $\mathbf{5 m}$ were obtained in $70 \%$ and $69 \%$ yields over two steps, being twice as high compared to that of product $\mathbf{5 a}$ derived from unsubstituted aniline ( $34 \%$ yield over two steps). A similar trend was observed with products derived from 4-methoxyaniline ( $\mathbf{5 j}$, yield 55\%) and methoxylated benzaldehydes (5b, 5c, 5d, yields $48-55 \%$ ), compared to product $\mathbf{5 g}$ derived from a nitrobenzaldehyde (yield 63\%).

Using our approach even products $\mathbf{5 e}$ and $\mathbf{5 f}$ bearing a free phenolic group could be obtained. Tetrahydroisoquinoline $\mathbf{5 f}$ bearing the phenolic group at a remote position was isolated in a good yield of $56 \%$ over two steps. In contrast, phenolic product 5 e was only generated in $29 \%$ yield. In this case the intermediate enol ether probably underwent, in part, a competing reaction with the hydroxy group at the other ortho-position with cyclization to a benzofuran derivative. A comparable cyclization under acidic conditions has been published by Sakamoto et al. ${ }^{16}$






Scheme 3 Application of the method toward the rigidized azobenzene analogue $N$-aryl-1,2,3,4-tetrahydroisoquinoline 50

However, our newly developed method is not limited to bromobenzaldehydes and anilines as starting materials and was successfully applied utilizing heteroaromatic compounds. Intermediates $\mathbf{3 h}$ (derived from a brominated thiophenecarbaldehyde) and $\mathbf{3 n}$ (derived from 2-aminopyridine) gave the expected cyclization products $\mathbf{5 h}$ and $\mathbf{5 n}$ in $38 \%$ and $24 \%$ yields, respectively, over two steps. In contrast, 2-bromonicotinaldehyde-derived amine $\mathbf{3 i}$ underwent the Suzuki coupling, but did not result in the desired cyclized 6-phenyl-5,6,7,8-tetrahydro[1,6]naphthyridine (5i) using the standard conditions. The unsuccessful formation of the N aryltetrahydroisoquinoline derivative here, and the poor yield of $N$-pyridyl-1,2,3,4-tetrahydroisoquinoline (5n), might in part be due to counter-productive protonation of the pyridine-containing intermediates by TFA during the cyclization step.

In previous work in this field, ${ }^{12 a, 13,17}$ we found that $N$ arylethylations utilizing enol ethers and the triethylsilane/TFA reagent mixture were limited to nitrogen compounds of low to very low basicity, like anilines, carbazoles, indoles and phenothiazines. Aliphatic amines, however, are protonated by TFA and hence are prevented from nucleophilic attack at the protonated enol ether, leading to failure of the reaction. This finding was again confirmed in this work during examination of the intermolecular reductive amination with $N$-cyclohexyl-2-bromobenzylamine (31).

The successful Suzuki coupling could again be confirmed by TLC and mass spectrometry, but as expected, subsequent cyclization did not result in the desired N -cy-clohexyl-1,2,3,4-tetrahydroisoquinoline (51), and only unidentifiable side products were observed.

During these studies on the scope and limitations of our method, we observed that some of the compounds were air-sensitive and experienced oxidative degradation. Therefore, the final $N$-aryl-1,2,3,4-tetrahydroisoquinolines should be stored under inert gas after their preparation.

In the course of a project aimed at the synthesis of N -aryl-1,2,3,4-tetrahydroisoquinolines as rigidized analogues of bioactive azobenzenes, ${ }^{10}$ we applied our new approach to the synthesis of analogue 50, starting from known ace-tonide-protected 5-aminosalicylic acid $\mathbf{7}^{18}$ and amide-substituted 2-bromobenzaldehyde $\mathbf{6}$ (obtained from the corresponding carboxylic acid and $\beta$-alanine ethyl ester under standard amidation conditions), introducing two more functional groups for the analysis of the scope and limitations of the novel cyclization method (Scheme 3). The intermolecular reductive amination yielded $\mathbf{3 o}$ in $96 \%$ yield. The Suzuki reaction, cyclization and subsequent alkaline deprotection generated target compound $\mathbf{5 0}$ in $60 \%$ yield over 3 steps, once again confirming the beneficial effects of elec-tron-withdrawing substituents on the yield of the cyclization. Unfortunately, this product was not stable and had to be analyzed and, if desired, tested shortly after preparation.

In conclusion, we have developed a convenient and short protocol for the synthesis of $N$-aryl-1,2,3,4-tetrahydroisoquinolines and related heterocyclic ring systems possessing a wide range of substituents on both aromatic rings, whilst demonstrating high functional group tolerance. Starting from readily available ortho-brominated aromatic aldehydes and primary aromatic amines, the application of reductive conditions allows condensation of these building blocks to give $N$-aryl 2-bromobenzylamines. Commercially available 2-ethoxyvinyl pinacolboronate is then employed under Suzuki conditions to introduce the C-3/C-4-unit of the tetrahydroisoquinoline. Finally, the obtained orthoethoxyvinyl benzylamines undergo cyclization via an intramolecular reductive amination using triethylsilane/TFA to give the desired $N$-aryl-1,2,3,4-tetrahydroisoquinolines. Notwithstanding that the Suzuki reaction and final cyclization gave only moderate to good yields over two steps, this protocol is more effective than previous approaches to the target chemotype, due to the good availability of the building blocks and the very small number of steps.

Further, compared to previous methods, this protocol yields products of predictable structure; the formation of regioisomeric products is excluded due to the utilization of ortho-brominated aromatic aldehydes. In summary, this methodology opens a novel and straightforward access to N -aryl-1,2,3,4-tetrahydroisoquinolines and represents an attractive alternative to previous approaches.
(E)-2-Ethoxyvinylboronic acid pinacol ester was purchased from Sigma Aldrich. All solvents were purchased from commercial sources and used without further purification. Solvents were dried, if necessary, according to standard methods and stored over activated molecular sieves under a nitrogen atmosphere. Standard vacuum-line techniques were used and glassware was flame-dried prior to use. Organic solvents were dried during workup using phase separation paper. Reactions were monitored via thin-layer chromatography (TLC) using POLYGRAM SIL G/UV 254 polyester sheets coated with 0.2 mm silica gel (Macherey-Nagel). Plates were visualized using UV light ( 254 nm or 365 nm ) or by staining with $1 \%$ aq $\mathrm{KMnO}_{4}$ or CAM (ceric ammonium molybdate). Monitoring was also performed by mass spectrometry using an atmospheric pressure solids analysis probe (ASAP) with atmospheric pressure chemical ionization (APCI) on an expression LCMS device (Advion, Ithaca, USA). Products were purified by flash column chromatography (normal-phase silica gel chromatography) using $\mathrm{SiO}_{2} 60$ ( $0.040-0.063 \mathrm{~mm}, 230-400$ mesh ASTM) from Merck. Melting points were measured with a Büchi Schmelzpunktapparatur B-540 and are reported in ${ }^{\circ} \mathrm{C}$. Infrared spectra were recorded from 4000 to $650 \mathrm{~cm}^{-1}$ on a PERKIN ELMER Spectrum BX-59343 FT-IR instrument. A Smiths Detection DuraSamp IR II Diamond ATR sensor was used for detection. The absorption bands are reported in wavenumbers ( $\mathrm{cm}^{-1}$ ). NMR spectra ( ${ }^{1} \mathrm{H}$ NMR, ${ }^{13} \mathrm{C}$ NMR, DEPT, COSY, HSQC, HMBC) were recorded using Avance III HD 400 MHz Bruker BioSpin and Avance III HD 500 MHz Bruker BioSpin spectrometers ( ${ }^{1} \mathrm{H}$ NMR: 400 MHz and $500 \mathrm{MHz},{ }^{13} \mathrm{C}$ NMR: 101 MHz and 126 MHz ) and the deuterated solvent stated. Chemical shifts ( $\delta$ ) are quoted in parts per million ( ppm ) and are referenced to the residual solvent peak. Multiplicities are denoted as $s$ (singlet), $d$ (doublet), $t$ (triplet), $q$ (quartet)
and derivatives thereof. Coupling constants $J$ are given in Hz. Highresolution mass spectrometry (HRMS) was performed using a Jeol MStation 700 or JMS GCmate II Jeol instrument for electron impact ionization (EI). A Thermo Finnigan LTQ was used for electrospray ionization (ESI).

## Reductive Amination; General Procedure A

The appropriate 2-bromobenzaldehyde (1.2 equiv) and aniline (1.0 equiv) were dissolved in MeOH to a concentration of 0.15 M (with respect to the aniline). A catalytic amount of acetic acid was added, and the reaction mixture stirred at room temperature for 16 h . Sodium cyanoborohydride ( 3.0 equiv) was added in portions at room temperature. After stirring for an additional $2.5-3 \mathrm{~h}$ (TLC monitoring), water was added and the mixture extracted with ethyl acetate ( $\times 3$ ). The combined organic phase was dried using phase separation paper and the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography (FCC) using the indicated eluent.

## Suzuki-Miyaura Coupling and Subsequent Cyclization; General Procedure B

The appropriate $N$-(2-bromobenzyl)aniline (1.0 equiv), $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(0.1$ equiv) and ( $E$-2-ethoxyvinylboronic acid pinacol ester ( 2.0 equiv) were dissolved in degassed 1,4-dioxane to a concentration of 0.15 M (with respect to the aniline) under a nitrogen atmosphere. The resulting mixture was then stirred for 10 min at room temperature. Cesium carbonate ( 5.0 equiv) was dissolved in degassed water to a concentration of 0.5 M (with respect to the aniline) under a nitrogen atmosphere and added to the reaction mixture. Stirring was continued at $75^{\circ} \mathrm{C}$ for $16-19 \mathrm{~h}$, after which the reaction mixture was allowed to cool to room temperature and sat. aq ammonium chloride solution was added. The organic material was extracted with EtOAc $(\times 3)$ and the combined organic phases were dried using phase separation paper. The solvent was removed in vacuo. The crude product was dissolved in dry DCM to a concentration of 0.33 M (with respect to the aniline) under a nitrogen atmosphere. Trifluoroacetic acid (13 equiv) and triethylsilane ( 2.5 equiv) were added under a nitrogen atmosphere at room temperature in rapid succession. After completion of the reaction (2.5-4.5 h; TLC monitoring), 2 M NaOH was added and the mixture was extracted with $\mathrm{DCM}(\times 3)$. The combined organic extracts were dried using phase separation paper. The solvent was removed in vacuo and the crude product purified by FCC using the indicated eluent.

## N -(2-Bromobenzyl)aniline (3a)

Prepared according to General Procedure A but with 2.0 equivalents of 2-bromobenzaldehyde (1) ( $1.85 \mathrm{~g}, 10.0 \mathrm{mmol}$ ) and aniline (2) (456 $\mu \mathrm{L}, 5.00 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtO$\mathrm{Ac}, 95: 5$ ) to give product $\mathbf{3 a}(1.31 \mathrm{~g}, 5.00 \mathrm{mmol}$, quant.) as a white solid.
$R_{f}=0.25$ (hexanes/EtOAc, 95:5); mp 40-42 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3381, 3049, 2837, 1601, 1504, 1464, 1433, 1319, 1253, 1178, 1100, 1067, 1043, 1023, 991, 748, 691, $658 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=7.56\left(\mathrm{dd}, \mathrm{J}=7.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 3{ }^{\prime}-\mathrm{H}\right), 7.47$ (dd, J = 7.7, 1.7 Hz, $1 \mathrm{H}, 6^{\prime}-\mathrm{H}$ ), 7.29-7.23 (m, $\left.1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 7.22-7.16$ (m, 2 $\mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 7.13\left(\mathrm{td}, J=7.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.82-6.76(\mathrm{~m}, 1 \mathrm{H}$, 4-H), 6.73-6.67 (m, $2 \mathrm{H}, 3-\mathrm{H}$ and 5-H), $4.43\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=146.4$ (C-1), 137.4 (C-1'), 133.0 (C-3'), 129.7 (C-6'), 129.5 (C-2 and C-6), 129.1 (C-4'), 127.7 (C-5'), 123.7 (C$2^{\prime}$ ), 119.1 (C-4), 114.3 ( $\mathrm{C}-3$ and $\mathrm{C}-5$ ), $49.2\left(1^{\prime}-\mathrm{CH}_{2}\right)$.

HRMS (ESI): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{13} \mathrm{H}_{13} \mathrm{BrN}^{+}$: 262.0226; found: 262.0227.

The analytical data are in accordance with those published in the literature. ${ }^{19}$

## (E)-N-[2-(2-Ethoxyvinyl)benzyl]aniline (4a)

Under a nitrogen atmosphere, compound 3a ( $131 \mathrm{mg}, 0.500 \mathrm{mmol}$ ), $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(57.8 \mathrm{mg}, 0.0500 \mathrm{mmol}, 10 \mathrm{~mol} \%)$ and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester ( $212 \mu \mathrm{~L}, 1.00 \mathrm{mmol}$ ) were dissolved in degassed 1,4-dioxane ( 3.0 mL ) and stirred for 10 min at rt. Under a nitrogen atmosphere, cesium carbonate ( $815 \mathrm{mg}, 2.50 \mathrm{mmol}$ ) was dissolved in degassed water ( 1.0 mL ) and added to the reaction mixture. Stirring was then continued at $75{ }^{\circ} \mathrm{C}$ for 19 h . The reaction mixture was allowed to cool to room temperature and sat. aq ammonium chloride solution ( 10.0 mL ) was added. The organic material was extracted with EtOAc ( $3 \times 15.0 \mathrm{~mL}$ ) and the combined organic phases were dried using phase separation paper. The solvent was removed in vacuo and the crude product was purified by FCC (hexanes/EtOAc, $95: 5)$ to give product $\mathbf{4 a}(63.4 \mathrm{mg}, 0.250 \mathrm{mmol}, 50 \%)$ as a yellow oil.
$R_{f}=0.48$ (hexanes/EtOAc, 95:5).
IR (ATR): 3430, 3061, 2976, 1631, 1599, 1507, 1327, 1158, 930, 747, $691 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=7.34$ (ddd, $J=9.3,7.6,1.4 \mathrm{~Hz}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 7.25-7.21\left(\mathrm{~m}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 7.22-7.18(\mathrm{~m}, 2 \mathrm{H}, 3-\mathrm{H}$ and 5-H), 7.16 (td, $\left.J=7.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 6.89$ (d, J = $\left.12.8 \mathrm{~Hz}, 1 \mathrm{H}, 2^{\prime \prime}-\mathrm{H}\right), 6.73$ ( $\mathrm{tt}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H}$ ), 6.67-6.63 (m, $2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 6.05(\mathrm{~d}$, $\left.J=12.8 \mathrm{~Hz}, 1 \mathrm{H}, 1^{\prime \prime}-\mathrm{H}\right), 4.28\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right), 3.85(\mathrm{q}, J=7.0 \mathrm{~Hz}, 2 \mathrm{H}$, $\left.\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 1.31\left(\mathrm{t}, \mathrm{J}=7.0 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=149.4$ (C-2"), 148.4 (C-1), 135.6 (C-2'), 135.3 (C-1'), 129.4 (C-3 and C-5), 129.2 (C-6'), 127.9 (C-4'), 126.3 (C5'), 125.5 (C-3'), 117.6 (C-4), 112.9 (C-2 and C-6), 103.0 (C-1"), 65.8 $\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 46.9\left(1^{\prime}-\mathrm{CH}_{2}\right), 14.9\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right)$.
HRMS (ESI): $m / z[M+H]^{+}$calcd for $\mathrm{C}_{17} \mathrm{H}_{20} \mathrm{NO}^{+}$: 254.1539; found: 254.1536.

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

Prepared according to General Procedure B from N -(2-bromobenzyl)aniline ( $\mathbf{3 a}$ ) ( $131 \mathrm{mg}, 0.500 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester $(212 \mu \mathrm{~L}, 1.00 \mathrm{mmol})$. The crude product was purified by FCC (hexanes/EtOAc, 95:5) to give product 5a ( $35.6 \mathrm{mg}, 0.169$ $\mathrm{mmol}, 34 \%$ ) as a dark yellow-orange oily solid.
$R_{f}=0.38$ (hexanes/EtOAc, 95:5).
IR (ATR): 3023, 2922, 2821, 1661, 1598, 1498, 1460, 1387, 1293, 1212, 1151, 1112, 1034, 989, 935, 741, $690 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.32-7.27$ (m, $2 \mathrm{H}, 3^{\prime}-\mathrm{H}$ and $5^{\prime}-\mathrm{H}$ ), 7.21-7.15 (m, $4 \mathrm{H}, 5-\mathrm{H}, 6-\mathrm{H}, 7-\mathrm{H}$ and $8-\mathrm{H}$ ), $7.01-6.97$ (m, $2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 6.84\left(\mathrm{tt}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 4.42(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.57(\mathrm{t}$, $J=5.8 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 3.00(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=150.7$ (C-1'), 135.0 (C-4a or C-8a), 134.6 (C-4a or C-8a), 129.3 (C-3' and C-5'), 128.7 (C-5), 126.7 (C-8), 126.5 (C-6 or C-7), 126.2 (C-6 or C-7), 118.8 (C-4'), 115.3 (C-2' and C6'), 50.9 (C-1), 46.7 (C-3), 29.3 (C-4).
HRMS (ESI): $m / z[\mathrm{M}-\mathrm{H}]^{-}$calcd for $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~N}^{-}$: 208.1126; found: 208.1120.

The analytical data are in accordance with those published in the literature. ${ }^{6 c}$

## $N$-(2-Bromo-4-methoxybenzyl)aniline (3b)

Prepared according to General Procedure A from 2-bromo-4-methoxybenzaldehyde ( $129 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}$, 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $95: 5$ ) to give product $\mathbf{3 b}(123 \mathrm{mg}, 0.422 \mathrm{mmol}, 85 \%)$ as a pale yellow solid.
$R_{f}=0.25$ (hexanes/EtOAc, 95:5); mp 69-73 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3439, 3062, 2937, 2832, 1601, 1567, 1507, 1486, 1456, 1435, $1319,1270,1229,1176,1028,988,879,809,749,688 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.37(\mathrm{~d}, \mathrm{~J}=8.5 \mathrm{~Hz}, 1 \mathrm{H}, 6$ '-H), 7.22-7.15 ( $\mathrm{m}, 2 \mathrm{H}, 3-\mathrm{H}$ and $5-\mathrm{H}$ ), $7.11\left(\mathrm{~d}, J=2.6 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 6.83-6.77(\mathrm{~m}, 2 \mathrm{H}$, $4-\mathrm{H}$ and $\left.5^{\prime}-\mathrm{H}\right), 6.72(\mathrm{~d}, \mathrm{~J}=7.7 \mathrm{~Hz}, 2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.37$ (s, $2 \mathrm{H}, 1^{\prime}-$ $\mathrm{CH}_{2}$ ), $3.78\left(\mathrm{~s}, 3 \mathrm{H}, 4^{\prime}-\mathrm{OCH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=159.6\left(\mathrm{C}-4{ }^{\prime}\right), 146.2(\mathrm{C}-1), 130.6\left(\mathrm{C}-6{ }^{\prime}\right)$, 129.5 (C-3 and C-5), 129.1 (C-1'), 124.1 (C-2'), 119.4 (C-4 and C-5'), 118.3 (C-3'), 114.6 (C-2 or C-6), 113.7 (C-2 or C-6), $55.7\left(4^{\prime}-\mathrm{OCH}_{3}\right)$, 48.8 ( $1^{\prime}-\mathrm{CH}_{2}$ ).

HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{BrNO}^{++}$: 291.0253; found: 291.0253.

## 6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5b)

Prepared according to General Procedure B from N-(2-bromo-4-methoxybenzyl)aniline (3b) ( $73.0 \mathrm{mg}, 0.250 \mathrm{mmol}$ ) and (E)-2-ethoxyvinylboronic acid pinacol ester ( $106 \mu \mathrm{~L}, 0.500 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 92:8) to give product 5b ( $28.6 \mathrm{mg}, 0.120 \mathrm{mmol}, 48 \%$ ) as a yellow solid.
$R_{f}=0.32$ (hexanes/EtOAc, 92:8); mp 39-44 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3060, 2933, 2833, 1731, 1597, 1504, 1460, 1388, 1331, 1275, 1227, 1194, 1152, 1032, 913, 849, 805, 751, $690 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.32-7.27\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.08 $(\mathrm{d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}, 8-\mathrm{H}), 7.01\left(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}\right.$ and $\left.6^{\prime}-\mathrm{H}\right), 6.85(\mathrm{t}$, $\left.J=6.9 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.77(\mathrm{dd}, J=8.4,2.7 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}), 6.70(\mathrm{~d}, J=2.6$ $\mathrm{Hz}, 1 \mathrm{H}, 5-\mathrm{H}), 4.37$ (s, $2 \mathrm{H}, 1-\mathrm{H}), 3.80\left(\mathrm{~s}, 3 \mathrm{H}, 6-\mathrm{OCH}_{3}\right), 3.56(\mathrm{t}, \mathrm{J}=5.9$ $\mathrm{Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.97(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=158.2$ (C-6), 150.7 (C-1'), 136.2 (C-4a), 129.3 (C-3' and C-5'), 127.6 (C-8), 126.8 (C-8a), 118.8 (C-4'), 115.3 (C$2^{\prime}$ and $\left.\mathrm{C}-6^{\prime}\right), 113.3$ (C-5), 112.5 (C-7), $55.4\left(6-\mathrm{OCH}_{3}\right), 50.4$ (C-1), 46.6 (C-3), 29.5 (C-4).
HRMS (EI): $m / z[M-H]^{\cdot}$ calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{NO}:$ 238.1232; found: 238.1227.

## N -(2-Bromo-5-methoxybenzyl)aniline (3c)

Prepared according to General Procedure A from 2-bromo-5-methoxybenzaldehyde ( $129 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}$, 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $95: 5$ ) to give product $\mathbf{3 c}(108 \mathrm{mg}, 0.370 \mathrm{mmol}, 74 \%$ ) as a yellow oil.
$R_{f}=0.33$ (hexanes/EtOAc, 95:5).
IR (ATR): 3418, 3048, 3003, 2932, 2836, 1600, 1504, 1466, 1432, 1294, $1265,1240,1159,1053,1015,868,803,747,691,600 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.43\left(\mathrm{~d}, \mathrm{~J}=8.8 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 7.22-7.16$ ( m, 2 H, 3-H and 5-H), 7.05 (d, J = $\left.2.9 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 6.78(\mathrm{t}, J=7.4 \mathrm{~Hz}$, $1 \mathrm{H}, 4-\mathrm{H}), 6.73-6.66\left(\mathrm{~m}, 3 \mathrm{H}, 2-\mathrm{H}, 6-\mathrm{H}\right.$ and $\left.4^{\prime}-\mathrm{H}\right), 4.38\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right)$, 3.74 ( $\mathrm{s}, 3 \mathrm{H}, 5^{\prime}-\mathrm{OCH}_{3}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=159.4$ (C-5'), 146.6 (C-1), 138.6 (C-1'), 133.5 (C-3'), 129.5 (C-3 and C-5), 119.1 (C-4), 115.3 (C-6'), 114.7 (C$\left.4^{\prime}\right), 114.2$ (C-2 and C-6), $113.8\left(\mathrm{C}-2^{\prime}\right), 55.6\left(5^{\prime}-\mathrm{OCH}_{3}\right), 49.3\left(1^{\prime}-\mathrm{CH}_{2}\right)$.

HRMS (EI): m/z [M] ${ }^{+}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{BrNO}^{++}$: 291.0253; found: 291.0253.

## 7-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5c)

Prepared according to General Procedure B from N-(2-bromo-5-methoxybenzyl)aniline (3c) ( $73.0 \mathrm{mg}, 0.250 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester ( $106 \mu \mathrm{~L}, 0.500 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 95:5) to give product 5c (29.0 $\mathrm{mg}, 0.121 \mathrm{mmol}, 49 \%$ ) as a colorless oil.
$R_{f}=0.27$ (hexanes/EtOAc, 95:5).
IR (ATR): 3023, 2907, 2832, 1598, 1501, 1461, 1382, 1319, 1253, 1234, $1147,1119,1038,932,813,748,691 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.33-7.27\left(\mathrm{~m}, 2 \mathrm{H}, 3{ }^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.08 (d, $J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, 5-\mathrm{H}), 6.99\left(\mathrm{dd}, J=8.8,1.1 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}\right.$ and $\left.6^{\prime}-\mathrm{H}\right)$, $6.87-6.81\left(\mathrm{~m}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.76(\mathrm{dd}, J=8.4,2.7 \mathrm{~Hz}, 1 \mathrm{H}, 6-\mathrm{H}), 6.71(\mathrm{~d}, J=$ $2.7 \mathrm{~Hz}, 1 \mathrm{H}, 8-\mathrm{H}), 4.39(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.81\left(\mathrm{~s}, 3 \mathrm{H}, 7-\mathrm{OCH}_{3}\right), 3.56(\mathrm{t}, \mathrm{J}=$ $5.8 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.92(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=158.0$ (C-7), 150.7 (C-1'), 135.7 (C-8a), 129.6 (C-5), 129.3 (C-3' and C-5'), 127.1 (C-4a), 118.8 (C-4'), 115.4 (C$2^{\prime}$ and $\left.\mathrm{C}-6^{\prime}\right), 112.7(\mathrm{C}-6), 111.4(\mathrm{C}-8), 55.5\left(7-\mathrm{OCH}_{3}\right), 51.1(\mathrm{C}-1), 47.0$ (C-3), 28.3 (C-4).
HRMS (EI): $m / z[M-H]^{\cdot}$ calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{NO}:$ 238.1232; found: 238.1226.

The analytical data are in accordance with those published in the literature. ${ }^{20}$

## N -(2-Bromo-4,5-dimethoxybenzyl)aniline (3d)

Prepared according to General Procedure A from 2-bromo-4,5-dimethoxybenzaldehyde ( $147 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}$, 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $80: 20$ ) to give product $\mathbf{3 d}$ ( $126 \mathrm{mg}, 0.392 \mathrm{mmol}, 78 \%$ ) as a yellow solid.
$R_{f}=0.36$ (hexanes/EtOAc, 80:20); mp 81-83 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3378, 2929, 2837, 1600, 1499, 1434, 1388, 1312, 1255, 1223, $1164,1099,1027,958,851,797,754,694 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.21-7.16(\mathrm{~m}, 2 \mathrm{H}, 3-\mathrm{H}$ and $5-\mathrm{H}$ ), 7.04 ( $\mathrm{s}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}$ ), 6.97 ( $\left.\mathrm{s}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 6.78-6.73(\mathrm{~m}, 1 \mathrm{H}, 4-\mathrm{H}), 6.68-6.63$ (m, $2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.33\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, 4^{\prime}-\mathrm{OCH}_{3}\right.$ or $5^{\prime}-$ $\left.\mathrm{OCH}_{3}\right), 3.79\left(\mathrm{~s}, 3 \mathrm{H}, 4^{\prime}-\mathrm{OCH}_{3}\right.$ or $\left.5^{\prime}-\mathrm{OCH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=148.8$ (C-4' or C-5'), 148.7 (C-4' or C5'), 147.7 (C-1), 130.2 (C-1'), 129.4 (C-3 and C-5), 118.4 (C-4), 115.7 ( $\mathrm{C}-3^{\prime}$ ), 113.5 ( $\mathrm{C}-2$ and $\mathrm{C}-6$ ), 113.3 (C-2'), $112.4\left(\mathrm{C}-6^{\prime}\right), 56.4\left(4^{\prime}-\mathrm{OCH}_{3}\right.$ or $\left.5^{\prime}-\mathrm{OCH}_{3}\right), 56.2\left(4^{\prime}-\mathrm{OCH}_{3}\right.$ or $\left.5^{\prime}-\mathrm{OCH}_{3}\right), 48.7\left(1^{\prime}-\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{15} \mathrm{H}_{16} \mathrm{BrNO}_{2}{ }^{++}$: 321.0359; found: 321.0358.

The analytical data are in accordance with those published in the literature. ${ }^{21}$

## 6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5d)

Prepared according to General Procedure B from $N$-(2-bromo-4,5-dimethoxybenzyl)aniline (3d) ( $80.6 \mathrm{mg}, 0.250 \mathrm{mmol}$ ) and (E)-2ethoxyvinylboronic acid pinacol ester ( $106 \mu \mathrm{~L}, 0.500 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 75:25) to give product $\mathbf{5 d}$ ( $36.7 \mathrm{mg}, 0.136 \mathrm{mmol}, 55 \%$ ) as a yellow solid.
$R_{f}=0.45$ (hexanes/EtOAc, 75:25); mp 86-90 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 2920, 2805, 2684, 1599, 1516, 1462, 1450, 1377, 1252, 1209, $1114,1025,979,932,855,825,750,731,693 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.33-7.27\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.03 (d, $J=7.9 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ), $6.87\left(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.65(\mathrm{~s}$, $1 \mathrm{H}, 5-\mathrm{H}$ or $8-\mathrm{H}), 6.65(\mathrm{~s}, 1 \mathrm{H}, 5-\mathrm{H}$ or $8-\mathrm{H}), 4.35(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.88(\mathrm{~s}, 3$ $\mathrm{H}, 6-\mathrm{OCH}_{3}$ or $\left.7-\mathrm{OCH}_{3}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, 6-\mathrm{OCH}_{3}\right.$ or $\left.7-\mathrm{OCH}_{3}\right), 3.56(\mathrm{t}, \mathrm{J}=5.8$ $\mathrm{Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.91(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=149.6$ (C-1'), 147.9 (C-6 or C-7), 147.8 (C-6 or C-7), 129.4 (C-3' and C-5'), 126.5 (C-4a and C-8a), 122.2 (C-4'), 115.9 (C-2' and C-6'), 111.5 (C-5), $109.5(\mathrm{C}-8), 56.13\left(6-\mathrm{OCH}_{3}\right.$ or $7-$ $\left.\mathrm{OCH}_{3}\right), 56.08\left(6-\mathrm{OCH}_{3}\right.$ or $\left.7-\mathrm{OCH}_{3}\right), 51.0(\mathrm{C}-1), 47.3(\mathrm{C}-3), 28.3(\mathrm{C}-4)$.
HRMS (EI): $m / z[M-H]$ calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{NO}_{2}{ }^{\bullet}: 268.1338$; found: 268.1332.

The analytical data are in accordance with those published in the literature. ${ }^{22}$

## 2-Bromo-6-methoxy-3-[(phenylamino)methyl]phenol (3e)

Prepared according to General Procedure A from 2-bromo-3-hydroxy-4-methoxybenzaldehyde ( $139 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) (45.6 $\mu \mathrm{L}, 0.500 \mathrm{mmol})$. The crude product was purified by FCC (DCM/hexanes, $0: 100$ to $65: 35$ ) to give product $\mathbf{3 e}(137 \mathrm{mg}, 0.445 \mathrm{mmol}, 89 \%)$ as a beige solid.
$R_{f}=0.23$ (DCM/hexanes, 65:35); mp 86-88 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3424, 2840, 1599, 1487, 1435, 1332, 1276, 1232, 1193, 1139, 1030, 987, 947, 810, 741, $689 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.21-7.15\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $\left.5^{\prime}-\mathrm{H}\right), 6.98$ $(\mathrm{d}, J=8.4 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H}), 6.79-6.74\left(\mathrm{~m}, 2 \mathrm{H}, 4^{\prime}-\mathrm{H}\right.$ and $\left.5-\mathrm{H}\right), 6.68(\mathrm{~d}, J=$ $7.8 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ), $4.38\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 3.88\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=146.8$ (C-1'), 146.5 (C-6), 143.4 (C-1), 130.4 (C-3), 129.4 (C-3' and C-5'), 120.3 (C-4), 118.8 (C-4'), 114.0 (C-2 and C-6), $109.8(\mathrm{C}-2), 109.6(\mathrm{C}-5), 56.5\left(\mathrm{OCH}_{3}\right), 48.8\left(\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{BrNO}_{2}{ }^{++}$: 307.0202; found: 307.0201.

## 6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-5-ol (5e)

Prepared according to General Procedure B from 2-bromo-6-me-thoxy-3-[(phenylamino)methyl]phenol (3e) ( $116 \mathrm{mg}, 0.376 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester (159 $\mu \mathrm{L}, 0.753$ mmol ). The crude product was purified by FCC (DCM/hexanes, 0:100 to $70: 30$ ) to give product $\mathbf{5 e}(28.0 \mathrm{mg}, 0.110 \mathrm{mmol}, 29 \%)$ as a yellow solid.
$R_{f}=0.26$ (DCM/hexanes, 70:30); mp 84-86 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3457, 2923, 2839, 1598, 1500, 1445, 1392, 1342, 1281, 1228, 1196, 1090, 1043, 1006, 875, 793, 747, $689 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.32-7.27\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.03 (d, $J=8.1 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 6.86\left(\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.75(\mathrm{~d}$, $J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, 7-\mathrm{H}), 6.68(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}, 8-\mathrm{H}), 5.70(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 4.36$ (s, $2 \mathrm{H}, 9-\mathrm{H}), 3.88\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.57(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.95(\mathrm{t}, \mathrm{J}=$ 6.0 Hz, $2 \mathrm{H}, 4-\mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=144.6$ (C-6), 143.0 (C-5), 129.3 (C-3' and C-5'), 127.9 (C-8a), 121.5 (C-4a), 119.4 (C-4'), 117.3 (C-8), 116.1 ( $\mathrm{C}-2^{\prime}$ and $\mathrm{C}-6^{\prime}$ ), $108.8(\mathrm{C}-7), 56.3\left(\mathrm{C}-\mathrm{OCH}_{3}\right), 50.9(\mathrm{C}-9), 47.0(\mathrm{C}-3), 22.9$ (C-4); [C-1' not visible].
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{16} \mathrm{H}_{17} \mathrm{NO}_{2}{ }^{\bullet+}$ : 255.1254; found: 255.1260.

## 4-Bromo-2-methoxy-5-[(phenylamino)methyl]phenol (3f)

Prepared according to General Procedure A from 2-bromo-5-hydroxy-4-methoxybenzaldehyde ( $139 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) (45.6 $\mu \mathrm{L}, 0.500 \mathrm{mmol}$ ). The crude product was purified by FCC (DCM/hexanes, 0:100 to $70: 30$ ) to give product $\mathbf{3 f}(141 \mathrm{mg}, 0.458 \mathrm{mmol}, 92 \%$ ) as a brownish solid.
$R_{f}=0.20$ (DCM/hexanes, 70:30); mp 62-63 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3475, 2922, 1602, 1497, 1434, 1328, 1269, 1197, 1146, 1034, $861,822,797,745,692 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.21-7.15\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $\left.5^{\prime}-\mathrm{H}\right), 7.05$ (s, $1 \mathrm{H}, 6-\mathrm{H}), 7.02(\mathrm{~s}, 1 \mathrm{H}, 3-\mathrm{H}), 6.77\left(\mathrm{tt}, J=7.2,0.8 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.71-$ $6.66\left(\mathrm{~m}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}\right.$ and $\left.6^{\prime}-\mathrm{H}\right), 4.31\left(\mathrm{~s}, 2 \mathrm{H}, \mathrm{CH}_{2}\right), 3.87\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{OCH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=146.62$ (C-2), 146.56 (C-1'), 145.3 (C1), 130.4 (C-5), 129.4 (C-3' and C-5'), 118.9 (C-4'), 115.7 (C-6), 115.2 (C-3), 114.1 (C-2' and C-6'), $112.5(\mathrm{C}-4), 56.4\left(\mathrm{OCH}_{3}\right), 48.7\left(\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{BrNO}_{2}{ }^{-+}$: 307.0202; found: 307.0200.

## 6-Methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-7-ol (5f)

Prepared according to General Procedure B from 4-bromo-2-me-thoxy-5-[(phenylamino)methyl]phenol (3f) ( $77.0 \mathrm{mg}, 0.376 \mathrm{mmol}$ ) and (E)-2-ethoxyvinylboronic acid pinacol ester (106 $\mu \mathrm{L}, 0.500$ mmol). The crude product was purified by FCC (DCM/hexanes, 0:100 to $70: 30$ ) to give product $\mathbf{5 f}(36.0 \mathrm{mg}, 0.141 \mathrm{mmol}, 56 \%)$ as a brownish solid.
$R_{f}=0.26$ (DCM/hexanes, 70:30); mp 96-97 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3231, 2942, 2825, 1595, 1529, 1501, 1458, 1376, 1274, 1219, 1203, 1110, 1025, 924, 857, 828, 758, $684 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.32-7.27\left(\mathrm{~m}, 2 \mathrm{H}, 3{ }^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.02 ( $\mathrm{d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $6^{\prime}-\mathrm{H}$ ), $6.86\left(\mathrm{t}, J=6.8 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.72$ (s, $1 \mathrm{H}, 8-\mathrm{H}), 6.62(\mathrm{~s}, 1 \mathrm{H}, 5-\mathrm{H}), 5.54(\mathrm{~s}, 1 \mathrm{H}, \mathrm{OH}), 4.32(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.87(\mathrm{~s}$, $\left.3 \mathrm{H}, \mathrm{OCH}_{3}\right), 3.55(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.90(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=150.5$ (C-1'), 145.2 (C-6), 144.0 (C-7), 129.2 (C-3' and C-5'), 127.0 (C-4a or C-8a), 126.1 (C-4a or C-8a), 118.8 ( $\mathrm{C}-4^{\prime}$ ), 115.4 ( $\mathrm{C}-2^{\prime}$ and $\left.\mathrm{C}-6^{\prime}\right), 112.2(\mathrm{C}-8), 110.6(\mathrm{C}-5), 56.0\left(\mathrm{OCH}_{3}\right), 50.4$ (C-1), 46.9 (C-3), 28.6 (C-4).
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{16} \mathrm{H}_{17} \mathrm{NO}_{2}{ }^{++}$: 255.1254; found: 255.1248.

## N -(2-Bromo-5-nitrobenzyl)aniline (3g)

Prepared according to General Procedure A from 2-bromo-5-nitrobenzaldehyde ( $138 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}, 0.500$ mmol ). The crude product was purified by FCC (hexanes/EtOAc, $80: 20)$ to give product $\mathbf{3 g}(135 \mathrm{mg}, 0.440 \mathrm{mmol}, 88 \%)$ as a yellow solid.
$R_{f}=0.50$ (hexanes/EtOAc, 80:20); mp 123-128 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3398, 3089, 2929, 2857, 1602, 1573, 1525, 1493, 1340, 1270, 1239, 1108, 1027, 987, 917, 872, 806, 749, 737, $692 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.28\left(\mathrm{~d}, \mathrm{~J}=2.8 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 7.99$ (dd, $\left.J=8.7,2.8 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 7.76$ (d, $\left.J=8.6 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 7.22-7.14(\mathrm{~m}, 2$ H, 3-H and 5-H), 6.80-6.73 (m, $1 \mathrm{H}, 4-\mathrm{H}), 6.61-6.56$ (m, $2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.48\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=147.8$ (C-5'), $147.0(\mathrm{C}-1), 141.0\left(\mathrm{C}-1^{\prime}\right)$, 133.9 (C-3'), 130.1 (C-2'), 129.6 (C-3 and C-5), 123.7 (C-6'), 123.4 (C$4^{\prime}$ ), 118.7 (C-4), 113.1 (C-2 and C-6), 48.5 ( $1^{\prime}-\mathrm{CH}_{2}$ ).

HRMS (EI): $m / z[M]^{++}$calcd for $\mathrm{C}_{13} \mathrm{H}_{11} \mathrm{BrN}_{2} \mathrm{O}_{2}{ }^{++}$: 305.9998; found: 305.9999.

## 7-Nitro-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5g)

Prepared according to General Procedure B from N-(2-bromo-5-nitrobenzyl)aniline ( $\mathbf{3 g}$ ) ( $76.8 \mathrm{mg}, 0.250 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester $(106 \mu \mathrm{~L}, 0.500 \mathrm{mmol})$. The crude product was purified by FCC (hexanes/EtOAc, 85:15) to give product $\mathbf{5 g}(39.9 \mathrm{mg}$, $0.157 \mathrm{mmol}, 63 \%$ ) as an orange solid.
$R_{f}=0.50$ (hexanes/EtOAc, 85:15); mp 66-70 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 2920, 2846, 2774, 1599, 1514, 1493, 1460, 1378, 1340, 1262, 1194, 1086, 931, 891, 813, 756, 733, $695 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.07-8.02$ ( $\mathrm{m}, 2 \mathrm{H}, 6-\mathrm{H}$ and $8-\mathrm{H}$ ), 7.34$7.28\left(\mathrm{~m}, 3 \mathrm{H}, 3^{\prime}-\mathrm{H}, 5^{\prime}-\mathrm{H}\right.$ and $\left.5-\mathrm{H}\right), 7.02-6.98\left(\mathrm{~m}, 2 \mathrm{H}, 2^{\prime}-\mathrm{H}\right.$ and $\left.6^{\prime}-\mathrm{H}\right)$, $6.89\left(\mathrm{tt}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 4.48(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.61(\mathrm{t}, J=5.8 \mathrm{~Hz}$, $2 \mathrm{H}, 3-\mathrm{H}), 3.08(\mathrm{t}, \mathrm{J}=5.8 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=150.1$ (C-1'), 146.5 (C-7), 142.8 (C-4a), 136.2 (C-8a), 129.8 (C-5), 129.5 (C-3' and C-5'), 121.9 (C-6 or C-8), 121.5 (C-6 or C-8), 119.8 (C-4'), 115.9 (C-2' and C-6'), 51.0 (C-1), 46.6 (C-3), 29.3 (C-4).
HRMS (EI): $m / z[M-H]^{\bullet}$ calcd for $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{NO}_{2}{ }^{\bullet}: 253.0977$; found: 253.0971.

The analytical data are in accordance with those published in the literature. ${ }^{23}$

## $N$-[(3-Bromothiophen-2-yl)methyl]aniline (3h)

Prepared according to General Procedure A from 3-bromothiophene-2-carboxaldehyde ( $115 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}$, 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $95: 5)$ to give product $\mathbf{3 h}(117 \mathrm{mg}, 0.438 \mathrm{mmol}, 88 \%)$ as a yellow liquid.
$R_{f}=0.47$ (hexanes/EtOAc, 95:5).
IR (ATR): 3410, 1600, 1501, 1312, 1259, 1180, 1152, 1095, 1067, 923, $869,748,690 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.22-7.17$ ( $\mathrm{m}, 3 \mathrm{H}, 3-\mathrm{H}, 5-\mathrm{H}$ and $5^{\prime}-\mathrm{H}$ ), $6.96\left(\mathrm{~d}, J=5.3 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.76(\mathrm{tt}, J=7.4,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H}), 6.70-$ $6.66(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.48\left(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 2 \mathrm{H}, 2^{\prime}-\mathrm{CH}_{2}\right), 4.14(\mathrm{~s}, 1 \mathrm{H}$, NH).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=147.4$ (C-1), 138.0 (C-2'), 130.2 (C-4'), 129.4 (C-3 and C-5), 124.8 (C-5'), 118.6 (C-4), 113.5 (C-2 and C-6), 108.6 (C-3'), $43.1\left(2^{\prime}-\mathrm{CH}_{2}\right)$.

HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{11} \mathrm{H}_{10} \mathrm{BrNS}^{+}$: 266.9712; found: 266.9712.

## 6-Phenyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (5h)

Prepared according to General Procedure B from N -[(3-bromothio-phen-2-yl)methyl]aniline ( $\mathbf{3 h}$ ) ( $53.6 \mathrm{mg}, 0.200 \mathrm{mmol}$ ) and (E)-2ethoxyvinylboronic acid pinacol ester ( $84.7 \mu \mathrm{~L}, 0.400 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 95:5) to give product $5 \mathbf{h}(16.4 \mathrm{mg}, 0.0762 \mathrm{mmol}, 38 \%)$ as a yellow oil.
$R_{f}=0.26$ (DCM/hexanes, 25:75).
IR (ATR): 3318, 2920, 1598, 1497, 1381, 1317, 1244, 1228, 1183, 1127, 994, 886, 750, $690 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.30-7.25\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.14 (dt, J = 5.0, 0.8 Hz, 1 H, 2-H), 7.02-6.98 (m, $2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 6.86$ (tt, $\left.J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.81(\mathrm{~d}, J=5.0 \mathrm{~Hz}, 1 \mathrm{H}, 3-\mathrm{H}), 4.47-4.45$ (m, 2 H, 7-H), $3.62(\mathrm{t}, J=5.7 \mathrm{~Hz}, 2 \mathrm{H}, 5-\mathrm{H}), 2.82(\mathrm{tt}, J=5.8,1.7 \mathrm{~Hz}, 2 \mathrm{H}$, 4-H).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=150.6$ (C-1'), 134.3 (C-3a), 132.9 (C7a), 129.4 (C-3' and C-5'), 127.2 (C-3), 122.7 (C-2), 119.6 (C-4'), 116.4 (C-2' and C-6'), 48.3 (C-7), 47.6 (C-5), 25.5 (C-4).
HRMS (EI): $m / z[M]^{++}$calcd for $\mathrm{C}_{13} \mathrm{H}_{13} \mathrm{NS}^{++}$: 215.0763; found: 215.0763.

## $N$-[(2-Bromopyridin-3-yl)methyl]aniline (3i)

Prepared according to General Procedure A from 2-bromo-3-pyridinecarboxaldehyde ( $112 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and aniline (2) ( $45.6 \mu \mathrm{~L}$, 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $85: 15$ ) to give product $\mathbf{3 i}(121 \mathrm{mg}, 0.460 \mathrm{mmol}, 92 \%)$ as a beige solid. $R_{f}=0.26$ (hexanes/EtOAc, 85:15); mp 107-109 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3295, 2921, 1600, 1560, 1531, 1496, 1398, 1324, 1276, 1254, $1178,1051,987,860,800,745,689 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.27\left(\mathrm{dt}, J=4.7,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 6{ }^{\prime}-\mathrm{H}\right.$ ), 7.69 (ddt, $\left.J=7.6,1.9,0.9 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 7.22$ (dd, $J=7.6,4.7 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}$ ), 7.20-7.15 (m, $2 \mathrm{H}, 3-\mathrm{H}$ and $5-\mathrm{H}$ ), $6.75(\mathrm{tt}, J=7.3,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H})$, $6.59-6.55(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.41\left(\mathrm{~d}, \mathrm{~J}=4.6 \mathrm{~Hz}, 2 \mathrm{H}, 3^{\prime}-\mathrm{CH}_{2}\right), 4.29$ ( $\mathrm{s}, 1 \mathrm{H}, \mathrm{NH}$ ).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=148.7$ (C-6'), 147.2 (C-1), 142.8 (C-2'), 137.2 (C-4'), 135.8 (C-3'), 129.6 (C-3 and C-5), 123.2 (C-5'), 118.4 (C4), 113.1 ( $\mathrm{C}-2$ and $\mathrm{C}-6$ ), $47.5\left(3^{\prime}-\mathrm{CH}_{2}\right)$.

HRMS (EI): m/z [M] ${ }^{+}$calcd for $\mathrm{C}_{12} \mathrm{H}_{11} \mathrm{BrN}_{2}{ }^{++}$: 262.0100; found: 262.0101.

The analytical data are in accordance with those published in the literature. ${ }^{24}$

## N -(2-Bromobenzyl)-4-methoxyaniline (3j)

Prepared according to General Procedure A from 2-bromobenzaldehyde (1) ( $111 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and $p$-anisidine ( $62.2 \mathrm{mg}, 0.500$ mmol ). The crude product was purified by FCC (hexanes/EtOAc, $90: 10$ ) to give product $\mathbf{3 j}$ ( $108 \mathrm{mg}, 0.369 \mathrm{mmol}, 74 \%$ ) as a dark yellow liquid.
$R_{f}=0.39$ (hexanes/EtOAc, 90:10).
IR (ATR): 3419, 3059, 2995, 2931, 2831, 1618, 1568, 1509, 1464, 1440, $1357,1232,1178,1123,1082,1025,818,749,660 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.56\left(\mathrm{dd}, J=8.0,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right)$, 7.46-7.42 (m, $\left.1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 7.29-7.23$ (m, $\left.1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 7.15-7.10(\mathrm{~m}, 1 \mathrm{H}$, $\left.4^{\prime}-\mathrm{H}\right), 6.80-6.60(\mathrm{~m}, 4 \mathrm{H}, 2-\mathrm{H}, 3-\mathrm{H}, 5-\mathrm{H}$ and $6-\mathrm{H}), 4.38\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right)$, 3.74 (s, $3 \mathrm{H}, 4-\mathrm{OCH}_{3}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=153.0$ (C-4), 141.1 (C-1), 138.0 (C-1'), 132.9 (C-3'), 129.7 (C-6'), 128.9 (C-4'), 127.7 (C-5'), 123.6 (C-2'), 115.1 ( $\mathrm{C}-2$ and $\mathrm{C}-6$ or $\mathrm{C}-3$ and $\mathrm{C}-5$ ), 115.0 ( $\mathrm{C}-2$ and $\mathrm{C}-6$ or $\mathrm{C}-3$ and $\mathrm{C}-5$ ), 55.9 $\left(4-\mathrm{OCH}_{3}\right), 49.8\left(1^{\prime}-\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{+}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{BrNO}^{++}$: 291.0253; found: 291.0253.

The analytical data are in accordance with those published in the literature. ${ }^{25}$

## 2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5j)

Prepared according to General Procedure B from $N$-(2-bromobenzyl)-4-methoxyaniline ( $\mathbf{3 j}$ ) ( $51.0 \mathrm{mg}, 0.175 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester ( $74.2 \mu \mathrm{~L}, 0.350 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 85:15) to give product $\mathbf{5 j}$ (22.9 $\mathrm{mg}, 95.7 \mu \mathrm{~mol}, 55 \%$ ) as a brown solid.
$R_{f}=0.58$ (hexanes/EtOAc, 85:15); mp 80-84 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 2920, 2808, 1509, 1459, 1442, 1385, 1272, 1240, 1206, 1188, $1151,1111,1035,930,822,800,754,720,701 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.21-7.11$ (m, $4 \mathrm{H}, 5-\mathrm{H}, 6-\mathrm{H}, 7-\mathrm{H}$ and $8-$ H), 7.05-6.98 (m, $2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 6.90-6.85\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-$ H), $4.31(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.78\left(\mathrm{~s}, 3 \mathrm{H}, 4^{\prime}-\mathrm{OCH}_{3}\right), 3.46(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 3-$ H), $3.00(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=153.6$ (C-4'), 145.5 (C-1'), 134.8 (C-4a or C-8a), 134.7 (C-4a or C-8a), 128.8 (C-5), 126.7 (C-6 or C-7 or C-8), 126.4 (C-6 or C-7 or C-8), 126.0 (C-6 or C-7 or C-8), 118.2 (C-2' and C$6^{\prime}$ ), 114.7 (C-3' and C-5'), $55.8\left(4^{\prime}-\mathrm{OCH}_{3}\right), 52.8$ (C-1), 48.6 (C-3), 29.2 (C-4).
HRMS (EI): $m / z[M-H]^{\cdot}$ calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{NO}^{*}: 238.1232$; found: 238.1226.

The analytical data are in accordance with those published in the literature. ${ }^{6 c}$

## Ethyl 4-[(2-Bromobenzyl)amino]benzoate (3k)

Prepared according to General Procedure A from 2-bromobenzaldehyde (1) ( $111 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and ethyl-4-aminobenzoate ( 82.6 mg , 0.500 mmol ). The crude product was purified by FCC (hexanes/EtOAc, $75: 25)$ to give product $\mathbf{3 k}(108 \mathrm{mg}, 0.323 \mathrm{mmol}, 65 \%)$ as a white solid.
$R_{f}=0.47$ (hexanes/EtOAc, $75: 25$ ); mp 117-120 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3374, 2928, 1722, 1672, 1598, 1530, 1439, 1336, 1268, 1173, $1106,1023,839,770,752,700 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.91-7.85(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 7.57$ (dd, $\left.J=7.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 7.41\left(\mathrm{~d}, J=7.5 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 7.29-7.23$ (m, $1 \mathrm{H}, 5^{\prime}-\mathrm{H}$ ), 7.15 (td, $\left.J=7.6,1.7 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 6.67(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2$ $\mathrm{H}, 3-\mathrm{H}$ and $5-\mathrm{H}), 4.49\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right), 4.31(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}, 7-\mathrm{H}), 1.35$ (t, J=7.1 Hz, $3 \mathrm{H}, 8-\mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=166.8$ (1-COOEt), 150.6 (C-4), 136.9 ( $\mathrm{C}-1^{\prime}$ ), 133.1 ( $\mathrm{C}-3^{\prime}$ ), 131.6 ( $\mathrm{C}-2$ and $\mathrm{C}-6$ ), 129.4 ( $\mathrm{C}-6^{\prime}$ ), 129.3 ( $\left.\mathrm{C}-4^{\prime}\right)$, 127.8 (C-5'), 123.6 (C-2'), 120.3 (C-1), 112.7 (C-3 and C-5), 60.5 (C-7), $48.4\left(1^{\prime}-\mathrm{CH}_{2}\right), 14.6(\mathrm{C}-8)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{BrNO}_{2}{ }^{++}$: 333.0359; found: 333.0358.

The analytical data are in accordance with those published in the literature. ${ }^{26}$

## Ethyl 4-[3,4-Dihydroisoquinolin-2(1H)-yl]benzoate (5k)

Prepared according to General Procedure B from ethyl 4-[(2-bromobenzyl)amino]benzoate ( $\mathbf{3 k}$ ) ( $83.6 \mathrm{mg}, 0.250 \mathrm{mmol}$ ) and ( $E$ )-2ethoxyvinylboronic acid pinacol ester ( $106 \mu \mathrm{~L}, 0.500 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 85:15) to give product $5 \mathbf{k}$ ( $49.1 \mathrm{mg}, 0.175 \mathrm{mmol}, 70 \%$ ) as an off-white solid.
$R_{f}=0.32$ (hexanes/EtOAc, 95:5); mp 49-51 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 2977, 2850, 1695, 1604, 1519, 1390, 1362, 1277, 1228, 1181, 1102, 1024, 926, 827, 767, 741, $698 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.98-7.94(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 7.24-$ 7.16 (m, $4 \mathrm{H}, 5^{\prime}-\mathrm{H}, 6^{\prime}-\mathrm{H}, 7^{\prime}-\mathrm{H}$ and $\left.8^{\prime}-\mathrm{H}\right), 6.91-6.85$ (m, $2 \mathrm{H}, 3-\mathrm{H}$ and 5H), $4.52\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{H}\right), 4.33(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}, 7-\mathrm{H}), 3.66(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2$ $\left.\mathrm{H}, 3^{\prime}-\mathrm{H}\right), 3.00\left(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 1.38(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}, 8-\mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=167.0$ (1-COOEt), 153.1 (C-4), 135.2 (C$8^{\prime} \mathrm{a}$ ), 134.0 (C-4'a), 131.4 (C-2 and C-6), 128.4 (C-5'), 126.9 (C-6' or C$7^{\prime}$ or $\mathrm{C}-8^{\prime}$ ), 126.7 ( $\mathrm{C}-6^{\prime}$ or $\mathrm{C}-7^{\prime}$ or $\mathrm{C}-8^{\prime}$ ), 126.5 ( $\mathrm{C}-6^{\prime}$ or $\mathrm{C}-7^{\prime}$ or $\mathrm{C}-8^{\prime}$ ), 118.9 (C-1), 112.3 (C-3 and C-5), 60.4 (C-7), 49.3 (C-1'), 45.0 (C-3'), 29.2 (C-4'), 14.6 (C-8).

HRMS (EI): $m / z[M-H]^{\cdot}$ calcd for $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{NO}_{2}{ }^{\bullet}: 280.1338$; found: 280.1332.

The analytical data are in accordance with those published in the literature. ${ }^{27}$

## N -(2-Bromobenzyl)cyclohexanamine (31)

Prepared according to General Procedure A from 2-bromobenzaldehyde (1) ( $111 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and cyclohexylamine ( $57.8 \mu \mathrm{~L}, 0.500$ mmol ). The crude product was purified by FCC (hexanes/EtOAc + $\left.\mathrm{Et}_{3} \mathrm{~N}, 90: 10+1\right)$ to give product $31(64.0 \mathrm{mg}, 0.239 \mathrm{mmol}, 48 \%)$ as a colorless oil.
$R_{f}=0.30$ (hexanes/EtOAc, $90: 10+\mathrm{Et}_{3} \mathrm{~N}$ ).
IR (ATR): 2923, 2851, 1462, 1440, 1347, 1259, 1124, 1024, 888, 746, $656 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.53$ (dd, $J=7.9,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 3{ }^{\prime}-\mathrm{H}$ ), 7.40 (dd, $\left.J=7.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 7.27\left(\mathrm{td}, J=7.5,1.1 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 7.11$ (td, $\left.J=7.7,1.8 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 3.88\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right), 2.46(\mathrm{tt}, J=10.3,3.7$ $\mathrm{Hz}, 1 \mathrm{H}, 1-\mathrm{H}), 1.96-1.90(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and/or 6-H$), 1.77-1.71$ (m, 2 H , 3-H and/or $5-\mathrm{H}$ ), 1.64-1.58 (m, $1 \mathrm{H}, 4-\mathrm{H}), 1.31-1.20(\mathrm{~m}, 2 \mathrm{H}, 2-\mathrm{H}$ and/or 6-H), 1.20-1.10 (m, $3 \mathrm{H}, 4-\mathrm{H}$ and 3-H and/or 5-H).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=140.0\left(\mathrm{C}-1^{\prime}\right), 132.9$ (C-3'), 130.5 (C-6'), 128.6 (C-4'), 127.6 (C-5'), 124.1 (C-2'), 56.2 (C-1), 51.1 ( $\left.1^{\prime}-\mathrm{CH}_{2}\right), 33.7$ (C-2 and C-6), 26.3 (C-4), 25.2 (C-3 and C-5).
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{BrN}^{+}$: 267.0617; found: 267.0617.

The analytical data are in accordance with those published in the literature. ${ }^{28}$

## $\mathbf{N}$-(2-Bromobenzyl)-4-chloroaniline (3m)

Prepared according to General Procedure A from 2-bromobenzaldehyde (1) ( $111 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and 4-chloroaniline ( $65.1 \mathrm{mg}, 0.500$ mmol). The crude product was purified by FCC (hexanes/EtOAc, 95:5) to give product $\mathbf{3 m}(112 \mathrm{mg}, 0.379 \mathrm{mmol}, 76 \%)$ as a pale yellow oil.
$R_{f}=0.33$ (hexanes/EtOAc, 95:5).
IR (ATR): 3430, 2923, 2852, 1599, 1497, 1464, 1440, 1319, 1264, 1177, $1095,1024,812,747 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.57$ (dd, $\left.J=7.9,1.2 \mathrm{~Hz}, 1 \mathrm{H}, 3{ }^{\prime}-\mathrm{H}\right), 7.36$ (dq, $J=7.7,0.8 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}$ ), $7.26\left(\mathrm{td}, J=7.5,1.3 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right.$ ), $7.18-$ $7.13\left(\mathrm{~m}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 7.13-7.09(\mathrm{~m}, 2 \mathrm{H}, 3-\mathrm{H}$ and $5-\mathrm{H}), 6.55-6.51(\mathrm{~m}, 2$ $\mathrm{H}, 2-\mathrm{H}$ and $6-\mathrm{H}), 4.38\left(\mathrm{~d}, \mathrm{~J}=5.7 \mathrm{~Hz}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right), 4.22(\mathrm{t}, \mathrm{J}=5.0 \mathrm{~Hz}, 1 \mathrm{H}$, NH).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=146.4$ (C-1), 137.8 (C-1'), 133.1 (C-3'), 129.3 (C-3 and C-5), 129.2 (C-6'), 129.0 (C-4'), 127.7 (C-5'), 123.4 (C$\left.2^{\prime}\right), 122.5(\mathrm{C}-4), 114.2$ ( $\mathrm{C}-2$ and $\mathrm{C}-6$ ), $48.6\left(1^{\prime}-\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{13} \mathrm{H}_{11} \mathrm{BrClN}^{+}$: 294.9758; found: 294.9758.

## 2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (5m)

Prepared according to General Procedure B from N-(2-bromobenzyl)-4-chloroaniline ( $\mathbf{3 m}$ ) ( $59.3 \mathrm{mg}, 0.200 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester ( $84.7 \mu \mathrm{~L}, 0.400 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc, 98:2) to give product 5 m (33.6 $\mathrm{mg}, 0.138 \mathrm{mmol}, 69 \%$ ) as a beige solid.
$R_{f}=0.36$ (hexanes/EtOAc, 98:2); mp 59-62 ${ }^{\circ} \mathrm{C}$.
IR (ATR): 3316, 2915, 2842, 1595, 1494, 1459, 1430, 1384, 1341, 1300, $1224,1156,1093,928,806,738,720 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=7.24-7.21\left(\mathrm{~m}, 2 \mathrm{H}, 3^{\prime}-\mathrm{H}\right.$ and $5^{\prime}-\mathrm{H}$ ), 7.21-7.14 (m, $4 \mathrm{H}, 5-\mathrm{H}, 6-\mathrm{H}, 7-\mathrm{H}$ and 8-H), 6.90-6.87 (m, $2 \mathrm{H}, 2^{\prime}-\mathrm{H}$ and $\left.6^{\prime}-\mathrm{H}\right), 4.38(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.53(\mathrm{t}, \mathrm{J}=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.98(\mathrm{t}, J=5.9$ Hz, 2 H, 4-H).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=149.2$ (C-1'), 134.8 (C-4a), 134.2 (C8a), 129.2 (C-3' and C-5'), 128.7 (C-5), 126.7 (C-6 or C-7 or C-8), 126.6 (C-6 or C-7 or C-8), 126.3 (C-6 or C-7 or C-8), 123.5 (C-4'), 116.3 (C-2' and C-6'), 50.8 (C-1), 46.7 (C-3), 29.1 (C-4).
HRMS (EI): $m / z[M-H]^{\circ}$ calcd for $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{ClN}^{*}$ : 242.0737; found: 242.0730.

The analytical data are in accordance with those published in the literature. ${ }^{29}$

## N -(2-Bromobenzyl)pyridin-2-amine (3n)

Prepared according to General Procedure A from 2-bromobenzaldehyde (1) ( $111 \mathrm{mg}, 0.600 \mathrm{mmol}$ ) and 2-aminopyridine ( $47.1 \mathrm{mg}, 0.500$ mmol ). The crude product was purified by FCC (hexanes/EtOAc + $\left.\mathrm{Et}_{3} \mathrm{~N}, 90: 10+1\right)$ to give product $\mathbf{3 n}(62.0 \mathrm{mg}, 0.236 \mathrm{mmol}, 47 \%)$ as a yellow solid.
$R_{f}=0.25$ (hexanes/EtOAc $+\mathrm{Et}_{3} \mathrm{~N}, 90: 10+1$ ); mp 109-112 ${ }^{\circ} \mathrm{C}$.
IR (ATR): $3235,3020,1600,1580,1537,1448,1425,1331,1277,1152$, 1023, 767, $750 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.11$ (ddd, $J=5.1,1.9,0.9 \mathrm{~Hz}, 1 \mathrm{H}, 6-\mathrm{H}$ ), 7.56 (dd, $J=7.9,1.2 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}$ ), $7.45-7.39$ (m, $1 \mathrm{H}, 6^{\prime}-\mathrm{H}$ ), 7.40 (ddd, $J=8.7,7.1,1.9 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H}), 7.28-7.24$ (m, $\left.1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 7.15-7.10(\mathrm{~m}, 1$ H, 4'-H), 6.60 (ddd, $J=7.1,5.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}, 5-\mathrm{H}), 6.36$ (dt, $J=8.3,0.9$ Hz, $1 \mathrm{H}, 3-\mathrm{H}), 5.06-5.00(\mathrm{~m}, 1 \mathrm{H}, \mathrm{NH}), 4.59\left(\mathrm{~d}, \mathrm{~J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}, 1^{\prime}-\mathrm{CH}_{2}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=158.5$ (C-2), 148.3 (C-6), 138.2 (C-1'), 137.7 (C-4), 132.9 (C-3'), 129.4 (C-6'), 128.9 (C-4'), 127.7 (C-5'), 123.6 (C-2'), 113.5 (C-5), 107.0 (C-3), $46.6\left(1^{\prime}-\mathrm{CH}_{2}\right)$.
HRMS (EI): m/z [M] ${ }^{++}$calcd for $\mathrm{C}_{12} \mathrm{H}_{11} \mathrm{BrN}_{2}{ }^{++}$: 262.0100; found: 262.0100.

## 2-(Pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (5n)

Prepared according to General Procedure B from N -(2-bromoben-zyl)pyridin-2-amine ( $\mathbf{3 n}$ ) ( $52.6 \mathrm{mg}, 0.200 \mathrm{mmol}$ ) and ( $E$ )-2-ethoxyvinylboronic acid pinacol ester ( $84.7 \mu \mathrm{~L}, 0.400 \mathrm{mmol}$ ). The crude product was purified by FCC (hexanes/EtOAc $+\mathrm{Et}_{3} \mathrm{~N}, 90: 10+1$ ) to give product 5 n ( $10.1 \mathrm{mg}, 0.0480 \mathrm{mmol}, 24 \%$ ) as an off-white oily solid.
$R_{f}=0.40$ (hexanes/EtOAc $+\mathrm{Et}_{3} \mathrm{~N}, 95: 5+1$ ).
IR (ATR): 3006, 2922, 2837, 1666, 1592, 1562, 1480, 1435, 1387, 1312, 1299, 1228, 1157, 978, 937, 764, $741 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.22$ (ddd, $J=5.0,2.0,0.9 \mathrm{~Hz}, 1 \mathrm{H}, 6{ }^{\prime}-\mathrm{H}$ ), 7.50 (ddd, $J=8.9,7.1,2.0 \mathrm{~Hz}, 1 \mathrm{H}, 4^{\prime}-\mathrm{H}$ ), $7.22-7.19$ ( $\mathrm{m}, 2 \mathrm{H}, 6-\mathrm{H}$ and/or 7-H and/or 8-H), 7.19-7.17 (m, $2 \mathrm{H}, 5-\mathrm{H}$ and $6-\mathrm{H}$ or $7-\mathrm{H}$ or $8-\mathrm{H}$ ), 6.68 (dt, $\left.J=8.6,1.0 \mathrm{~Hz}, 1 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 6.60$ (ddd, $J=7.1,5.0,0.9 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}$ ), $4.71(\mathrm{~s}, 2 \mathrm{H}, 1-\mathrm{H}), 3.85(\mathrm{t}, \mathrm{J}=6.0 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.98(\mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, 4-$ H).
${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=158.9$ (C-2'), 148.1 (C-6'), 137.6 (C-4'), 135.6 (C-4a), 134.5 (C-8a), 128.5 (C-5), 126.7 (C-8), 126.5 (C-6 or C-7), 126.3 (C-6 or C-7), 112.6 (C-5'), 106.8 (C-3'), 47.3 (C-1), 42.7 (C-3), 29.2 (C-4).

HRMS (EI): $m / z[M]^{++}$calcd for $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{~N}_{2}{ }^{++}: 210.1151$; found: 210.1150 . The analytical data are in accordance with those published in the literature. ${ }^{30}$

Ethyl 3-(3-Bromo-4-\{[(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]diox-in-6-yl)amino]methyl\}benzamido)propanoate (30)
Prepared according to General Procedure A (but with 1.5 equivalents of the aldehyde) from ethyl 3-(3-bromo-4-formylbenzamido)propanoate (6) ( $200 \mathrm{mg}, 0.609 \mathrm{mmol}$ ) and 6-amino-2,2-dimethyl-4H-ben-zo[d][1,3]dioxin-4-one (7) ( $78.5 \mathrm{mg}, 0.406 \mathrm{mmol}$ ). The product 30 ( $196 \mathrm{mg}, 0.389 \mathrm{mmol}, 96 \%$ ) was obtained without further purification as a yellow oily solid.
$R_{f}=0.34$ (hexanes/EtOAc, 50:50).
IR (ATR): 3369, 2989, 2938, 2322, 2178, 1715, 1648, 1536, 1495, 1378, $1295,1278,1196,1126,1051,1035,980,934,826 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ): $\delta=8.64(\mathrm{t}, \mathrm{J}=5.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CONH}$ ), 8.06 (d, $\left.J=1.7 \mathrm{~Hz}, 1 \mathrm{H}, 2^{\prime}-\mathrm{H}\right), 7.78$ (dd, $\left.J=8.0,1.7 \mathrm{~Hz}, 1 \mathrm{H}, 6^{\prime}-\mathrm{H}\right), 7.45(\mathrm{~d}, J=$ $\left.8.0 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right), 6.93$ (dd, $\left.J=8.9,2.8 \mathrm{~Hz}, 1 \mathrm{H}, 7{ }^{\prime \prime}-\mathrm{H}\right), 6.89$ (d, $J=8.7$ $\left.\mathrm{Hz}, 1 \mathrm{H}, 8^{\prime \prime}-\mathrm{H}\right), 6.86\left(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}, 5^{\prime \prime}-\mathrm{H}\right), 6.53(\mathrm{t}, J=6.0 \mathrm{~Hz}, 1 \mathrm{H}$, $\left.\mathrm{CH}_{2} \mathrm{NH}\right), 4.33\left(\mathrm{~d}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{NH}\right), 4.06(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}$, $\left.\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 3.47(\mathrm{td}, \mathrm{J}=6.7,5.4 \mathrm{~Hz}, 2 \mathrm{H}, 3-\mathrm{H}), 2.56(\mathrm{t}, \mathrm{J}=6.9 \mathrm{~Hz}, 2 \mathrm{H}, 2-\mathrm{H})$, $1.62\left[\mathrm{~s}, 6 \mathrm{H}, \mathrm{C}\left(\mathrm{CH}_{3}\right)_{2}\right], 1.17\left(\mathrm{t}, \mathrm{J}=7.1 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{3}\right)$.
${ }^{13} \mathrm{C}$ NMR (126 MHz, DMSO- $d_{6}$ ): $\delta=171.2(\mathrm{C}-1), 164.6$ (CONH), 160.7 (C-4"), 146.7 (C-8a"), 143.9 (C-6"), 141.2 (C-4'), 134.8 (C-1'), 131.1 (C2'), 128.6 (C-5'), 126.6 (C-6'), 122.4 (C-3'), 121.8 (C-7"), 117.9 (C-8"), 113.5 (C-4a"), 109.3 (C-5"), 105.9 (C-2"), $59.9\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right), 47.1$ $\left(\mathrm{CH}_{2} \mathrm{NH}\right), 35.6(\mathrm{C}-3), 33.6(\mathrm{C}-2), 25.2\left[\mathrm{C}\left(\mathrm{CH}_{3}\right)_{2}\right], 14.1\left(\mathrm{CH}_{2} \mathrm{CH}_{3}\right)$.
HRMS (ESI): $m / z[M-H]^{-}$calcd for $\mathrm{C}_{23} \mathrm{H}_{24} \mathrm{BrN}_{2} \mathrm{O}_{6}-: 503.0823$; found: 503.0827.

## 5-\{6-[(2-Carboxyethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl\}-2-hydroxybenzoic Acid (5o)

Prepared according to General Procedure B from ethyl 3-(3-bromo-4-\{[(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)amino]methyl\}benzamido)propanoate (30) ( $150 \mathrm{mg}, 0.208 \mathrm{mmol}$ ) and (E)-2ethoxyvinylboronic acid pinacol ester ( $88.0 \mu \mathrm{~L}, 0.416 \mathrm{mmol}$ ).
Without purification, the crude cyclized product ( 0.208 mmol ) was then dissolved in THF ( 1.4 mL ) followed by the addition of a solution of $\mathrm{KOH}(58.3 \mathrm{mg}, 1.04 \mathrm{mmol})$ in water $(1.4 \mathrm{~mL})$. The reaction mixture was stirred at room temperature for 1.5 h . Then water ( 10 mL ) was added and the mixture acidified to pH 1 using 2 N aq HCl . The organic material was extracted with EtOAc ( $3 \times 15 \mathrm{~mL}$ ). The combined organic layers were extracted with 0.5 M aq $\mathrm{NaOH}(3 \times 15 \mathrm{~mL})$. The aqueous phase was then again acidified to pH 1 using 2 M aq HCl and extracted with EtOAc ( $3 \times 15 \mathrm{~mL}$ ). The combined organic layers were dried using phase separating paper and the solvents were removed in vacuo. The crude product was purified by FCC ( $\mathrm{MeOH} / \mathrm{DCM}+\mathrm{AcOH}, 5: 95$ $+1)$ and dried under high vacuum to give $\mathbf{5 o}(47.9 \mathrm{mg}, 0.125 \mathrm{mmol}$, $60 \%$ over 3 steps) as a yellow-brown oily solid.
$R_{f}=0.14(\mathrm{MeOH} / \mathrm{DCM}+\mathrm{AcOH}, 5: 95+1)$.
IR (ATR): 3333, 2922, 2586, 1709, 1632, 1547, 1488, 1434, 1372, 1229, 1009, 828, $750 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( 500 MHz, DMSO- $d_{6}$ ): $\delta$ (contains residual AcOH$)=12.22(\mathrm{~s}, 2$ $\mathrm{H}, 1-\mathrm{COOH}$ and $\left.2^{\prime \prime}-\mathrm{COOH}\right), 8.46(\mathrm{t}, \mathrm{J}=5.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CONH}), 7.64(\mathrm{~s}, 1 \mathrm{H}$, $5^{\prime}-\mathrm{H}$ or $\left.7^{\prime}-\mathrm{H}\right), 7.64-7.61\left(\mathrm{~m}, 1 \mathrm{H}, 5^{\prime}-\mathrm{H}\right.$ or $\left.7^{\prime}-\mathrm{H}\right), 7.40(\mathrm{~s}, 1 \mathrm{H}, 6-\mathrm{H}), 7.28$ (d, $\left.J=7.9 \mathrm{~Hz}, 1 \mathrm{H}, 8^{\prime}-\mathrm{H}\right), 7.10$ (dd, $\left.J=9.2,2.7 \mathrm{~Hz}, 1 \mathrm{H}, 4-\mathrm{H}\right), 6.69(\mathrm{~d}, J=$ $8.7 \mathrm{~Hz}, 1 \mathrm{H}, 3-\mathrm{H}), 4.23\left(\mathrm{~s}, 2 \mathrm{H}, 1^{\prime}-\mathrm{H}\right), 3.45\left(\mathrm{q}, J=6.7 \mathrm{~Hz}, 2 \mathrm{H}, 1^{\prime \prime}-\mathrm{H}\right), 3.36$ $\left(\mathrm{t}, J=5.8 \mathrm{~Hz}, 3 \mathrm{H}, 3^{\prime}-\mathrm{H}\right), 2.95\left(\mathrm{t}, J=5.8 \mathrm{~Hz}, 2 \mathrm{H}, 4^{\prime}-\mathrm{H}\right), 2.53[\mathrm{~d}, J=1.6 \mathrm{~Hz}$, 2 H, 2"-H (collapses with DMSO)].
${ }^{13} \mathrm{C}$ NMR ( 126 MHz , DMSO- $d_{6}$ ): $\delta$ (contains residual AcOH$)=172.9(\mathrm{C}-$ $\left.3^{\prime \prime}\right), 171.8$ (1-COOH), 166.2 (CONH), 156.2 (C-2), 141.8 (C-5), 138.1 (C$\left.8 a^{\prime}\right), 134.3$ (C-4a'), 132.3 (C-6'), 127.4 (C-5'), 126.5 (C-8'), 124.5 (C-7'),
122.8 (C-4), 117.6 (C-6), 116.4 (C-3), 52.3 (C-1'), 48.2 (C-3'), 35.6 (C1"), 33.8 (C-2"), 28.6 (C-4"); [C-1' not clearly visible].
HRMS (ESI): $m / z[M-H]^{-}$calcd for $\mathrm{C}_{20} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{6}{ }^{-}: 383.1249$; found: 383.1249.

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## Supporting Information

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