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β-Amino Alcohols from Anilines and Ethylene Glycol through Heterogeneous Borrowing Hydrogen Reaction

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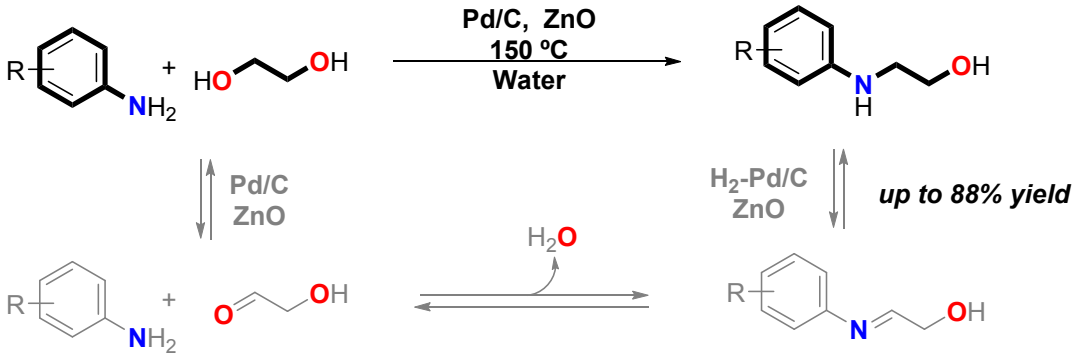
Abstract

Borrowing Hydrogen (BH), also called Hydrogen Autotransfer (HA), reaction with neat ethylene glycol represents a key step in the preparation of β-amino alcohols. However, due to the stability of ethylene glycol, mono-activation has rarely been achieved. Herein, a combination of Pd/C and ZnO is reported as heterogeneous catalyst for this BH/HA reaction. This system results in an extremely air and moisture stable, and economic catalyst able to mono-functionalize ethylene glycol in water, without further activation of the diol. In this work, different diols and aromatic amines have been explored affording a new approach towards amino alcohols. This study reveals how the combination of two solid species can afford interesting catalytic properties in heterogeneous phase. ZnO activates ethylene glycol while Pd/C is the responsible of the BH/HA cycle. This catalytic system has also been found useful to dehydrogenate indoles affording indolines that undergo in situ BH/HA cycle prior to re-aromatization, representing a tandem heterogeneous process.



Introduction

The development of green processes in organic synthesis represents a major goal nowadays.[1] From atom economy[2] to the use of environmentally friend reagents, many different strategies can be employed for the development of green reactions. Borrowing Hydrogen (BH) reactions[3,4] (also called Hydrogen Autotransfer (HA) reactions[5]) (Figure 1, top) represent a unique opportunity for the creation of molecular complexity with extremely high atom economy and, in many cases, under green principles. Important results concerning the preparation of secondary unsymmetrical amines, starting from primary amines and alcohols, are reported. Recently, Michlik and Kempe[6] employed this methodology for the preparation of pyrroles coupling two BH/HA processes with amino alcohols. The preparation of β-amino alcohols (vicinal or 1,2-amino alcohols) by means of BH/HA reactions under heterogeneous catalysis is a major goal due to the relevance of these compounds.[7,8] In addition, efficient preparation of β-amino alcohols derived from anilines is a key step in the preparation of important compounds like pyrroles.[6] Retrosynthetic analysis indicates that under controlled BH/HA conditions aniline and ethylene glycol may lead towards β-amino alcohols (Figure 1, bottom).

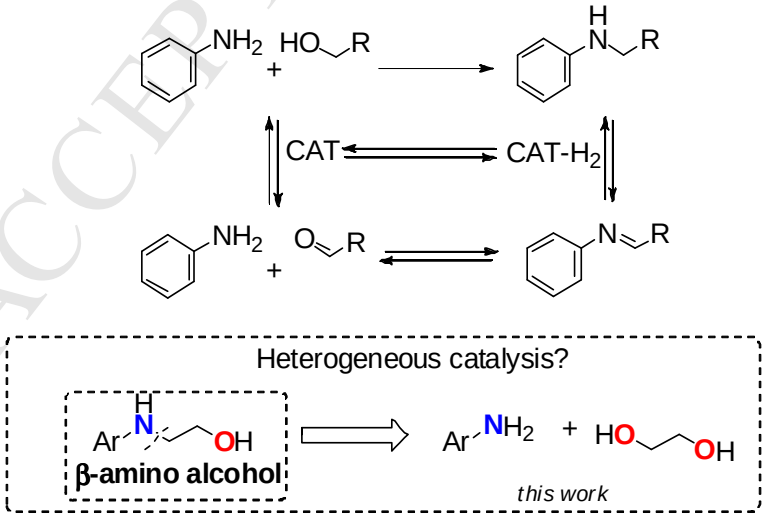


Figure 1. BH/HA strategy for the preparation of unsymmetrical amines (up) and retro synthetic approach to β-amino alcohols with ethylene glycol (down).

However, in the literature, Kempe has reported this reaction in 32% yield with transition metal complex as catalyst starting from anilines and in presence of an excess of ethylene glycol.[6a] Börner also reported on monoaminations with an homogeneous Iridium pincer catalyst in excellent yields.[6b] Another important reaction reported by Williams with a secondary amine (phenyl benzyl amine) yielded 70% under homogeneous Ru catalysis.[9] Watanabe also reported on the formation of indoles and cyclic compounds under similar conditions, the formation of cyclic compounds was also reported by Beller.[10] Those examples are by far the most efficient ones with ethylene glycol and any other alternative found in the literature requires 300ºC or transformation of ethylene glycol into a better reagent with diethyl carbonate.[11,12] Even more, diols are also used to generate typically cyclic compounds like pyrrolidines that came from functionalization of both alcohols.[9] In view of this, single functionalization of ethylene glycol is challenging and relevant. Herein, we report our recent advances on the use of BH/HA reactions to obtain β-amino alcohols, based on a heterogeneous catalysis. The catalytic system is formed by Pd/C and ZnO, and different aryl amines have been reacted with ethylene glycol, in order to test the scope of this heterogeneous catalysis, less common in BH/HA processes.[13]

The challenge in the use of ethylene glycol as reagent relies on its stability compared to benzylic alcohols that are normally used in BH/HA reactions. It is important to enhance that diols are rarely used because they trend to react twice, yielding dimers or cyclic compounds.[10] The choice of the catalyst represents the key of the process, because an extremely powerful catalyst may be able to di-oxidize the glycol or the final β-amino alcohol, leading to different products as Milstein reported.[14] Thus, preparing β-amino alcohols using ethylene glycol as reagent remains a challenge.

Results and Discussion

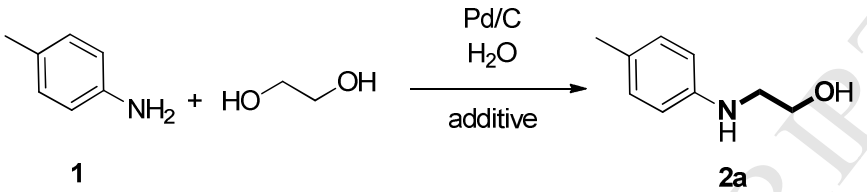
Recently, in our group, we developed a tandem process of hydrogenation and BH/HA in alcohol/water mixtures at high temperature with metallic Zn as reducing agent and under Pd/C catalysis.[15] Understanding that Pd/C could undergo BH/HA cycle, we firstly investigated these conditions. However, the presence of Zn(0) as electron donor represented non-green conditions, so we thought about ZnO as an activating agent for the glycol. Zinc oxide is an amphoteric material that can activate alcohols.[16-22] Indeed, under our previous studies, Zn(0) was transformed *in situ* into ZnO. There are a few reports in the literature indicating that ZnO nanoparticles can act as catalyst[23] it is almost stable over the catalysis, cheap and can be recovered with de Pd/C after reaction, being a greener reagent compared to metal Zn.

The first screening of conditions was performed at 200ºC and 64h, observing complete degradation of the starting aniline **1** and no traces of β-amino alcohol. Either with Zn or ZnO, 24 or 64 hours were extremely hard conditions and induced complete transformation of the product without any selectivity (Table 1, entries 1 to 3). Surprisingly, when we reduced the temperature to 150ºC, excellent conversion and selectivity was observed, and the corresponding β-amino alcohol **2a** was isolated in 88% yield (Table 1, entry 4 and Figure S1). Evaluating the kinetics of the reaction, 24 h was found to be efficient for high conversions and selectivity (Table 1, entries 4 to 8), moreover, no degradation of the product was observed at longer times. Reaction was clear yielding to product **2a** with small traces of dimeric compounds (Table S2). The 1:1 solvents ratio was also optimal, as long as any modification induced lower conversion (Table 1, entries 8 to 10).

In this reaction, ethylene glycol is employed also as solvent, however, the absence of water afforded no conversion (Table 1, entry 9). Any other modifications of these conditions afforded lower conversions. When comparing Pd/C with common commercial heterogeneous BH/HA catalysts Pt/Al_2O_3 or Ru/Al_2O_3[13] (Table 1, entries 17 and 18), moderate conversions

and selectivities were observed under the same conditions. As long as catalyst support may have significant influence, more specific Pt/C and Ru/C were also evaluated. However, the overall conversion and selectivity were smaller (See SI for complete details).

Table 1. Screening conditions for the preparation of β-amino alcohol **2a** by Heterogeneous BH/HA Reaction



1 **2a**

Entry	1	T	Time	EG	Water	Catalyst	Additive	Conversion[a]	Selectivity
1	1 mmol	200ºC	64h	6 mL	6 mL	Pd/C 7%	Zn 3eq.	99%	0%
2	1 mmol	200ºC	64h	6 mL	6 mL	Pd/C 7%	ZnO 3eq.	99%	0%
3	1 mmol	200ºC	24h	6 mL	6 mL	Pd/C 7%	ZnO 3eq.	99%	0%
4	**1 mmol**	**150ºC**	**24h**	**6 mL**	**6 ml**	**Pd/C 7%**	**ZnO 3eq.**	**92%**	**98% (88%)[b]**
5	1 mmol	150ºC	0,5h	6 ml	6 ml	Pd/C 7%	ZnO 3eq.	0%	0%
6	1 mmol	150ºC	6h	6 ml	6 ml	Pd/C 7%	ZnO 3eq.	67%	71%
7	1 mmol	150ºC	12h	6 ml	6 ml	Pd/C 7%	ZnO 3eq.	90%	82%
8	1 mmol	150ºC	64h	6 mL	6 ml	Pd/C 7%	ZnO 3eq.	99%	90%
9	1 mmol	150ºC	24h	12 mL	0 mL	Pd/C 7%	ZnO 3eq.	0%	0%
10	1 mmol	150ºC	64h	0,25 ml	6 ml	Pd/C 7%	ZnO 3eq.	<5%	99%
11	1 mmol	150ºC	24h	6 ml	6 ml	Pd/C 7%	no ZnO	<5%	99%
12	1 mmol	150ºC	24h	6 ml	6 ml	Pd/C 7%	ZnO 1eq.	50%	99%
13	1 mmol	150ºC	24h	6 ml	6 ml	Pd/C 7%	ZnO 2eq.	56%	80%
14	2 mmol	150ºC	24h	6 ml	6 ml	Pd/C 7%	ZnO 4eq.	99%	66%
15	1 mmol	150ºC	24h	6 ml	6 ml	Pd/C 3%	ZnO 3eq.	50%	75%
16	1mmol	150ºC	24h	6 ml	6 ml	Pt/Al_2O_3 7%	ZnO 3eq.	47%	80%
17	1 mmol	150ºC	24h	6 ml	6 ml	Ru/Al_2O_3 7%	ZnO 3eq.	21%	71%
18	1mmol	150ºC	24h	6 ml	6 ml	Pt/C 7%	ZnO 3eq.	81%	37%
19	1 mmol	150ºC	24h	6 ml	6 ml	Ru/C 7%	ZnO 3eq.	71%	65%

a. Conversion obtained by ^{1}H-NMR. Selectivity measured towards **2a**. b. Isolated yield after purification.

The stability of the catalytic system was evaluated by means of PXRD before and after the reaction observing no significant changes (Figure S2). Reuses without any cleaning of the catalyst, just removing by decantation the liquid phase and adding amine and solvents again, afforded 70% of conversion up to three rounds. ICP analysis indicated no significant Pd or Zn leaching after the reaction. However, small modification on the ZnO particle size was

detected that may explain this decrease in combination of the inevitable loss of catalyst during the decantation (see the SI for more details). Hot filtration test confirmed a complete heterogeneous process (Scheme S3).

Once optimized the reaction conditions for the preparation of β-amino alcohol **2a**, the scope of the reaction was studied (Figure 2). In view of the major challenge that represents diols in BH/HA processes different aromatic amines were selected as reagents in order to avoid any side reactions on the initial amine as Williams reported with some amino alcohols.[10] In general, all reagents afforded moderated to good conversion and selectivity.

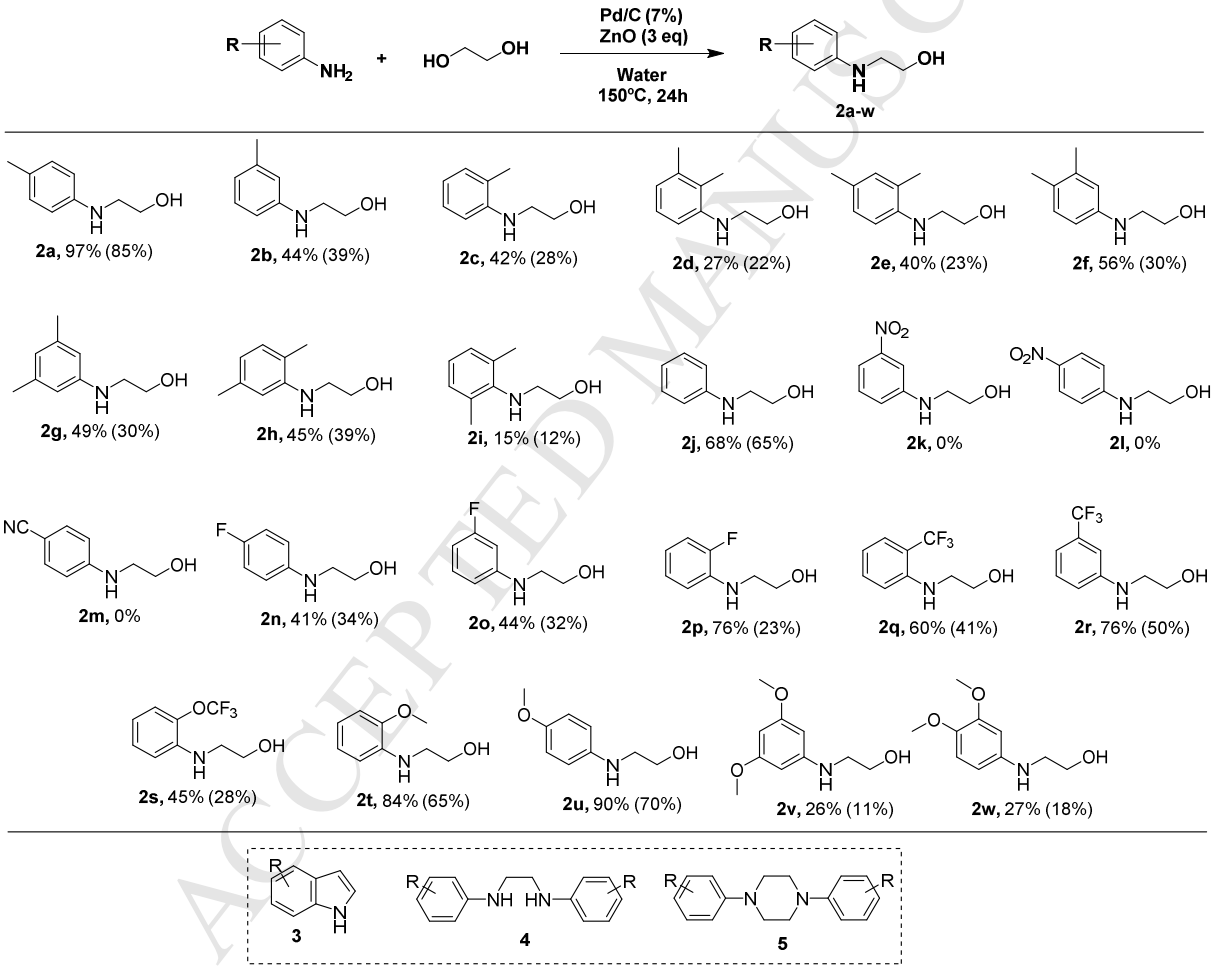


Figure 2. Scope of the catalysis using different aryl amines. Structure of side compounds (**3**-**5**). ^{1}H-NMR and isolated yields (brackets) are shown.

First, different mono-methyl anilines were submitted to the conditions, affording compounds **2a**-**2i**. Conversion decreased with steric hindrance at the ortho position, but in all cases β-amino alcohols were isolated in moderate yields. Compound **2j**, derived from aniline, was also obtained in 65%. When the substituents were strong electron withdrawing groups no conversion was observed (**2k**, **2l** and **2m**). However, moderate withdrawing groups like fluorine allowed the isolation of the desired amino alcohols **2n**, **2o** and **2p** (34%, 32% and 23% isolated yields). Trifluoromethyl and trifluoromethoxyl groups were also employed and afforded alcohols **2q**, **2r** and **2s** in moderate yields. Amino alcohols **2t**, **2u**, **2v** and **2w** contain methoxyl groups. In almost all cases, side products traces (indoles **3** and/or dimers **4** and **5**, Table S2) could be isolated. These compounds are known to appear when ethylene glycol and anilines are heated and are the main responsible of yield dicrease.[10]

We also wanted to explore to possibility of inducing strain in the amine by using 1,2,3,4-tetrahydroquinoline (**6**) as long as in our previous work we determine that this compound generates indole in a more efficient way.[15] When the reaction was performed with **6** the amount of indole increased (Figure 3) yielding to compounds **7a** in 45% yield and **7b** in 45%. With a methoxide derivative **8** similar behavior was observed, yielding **9a** in 18% and **9b** in 16 % (isolated yields).

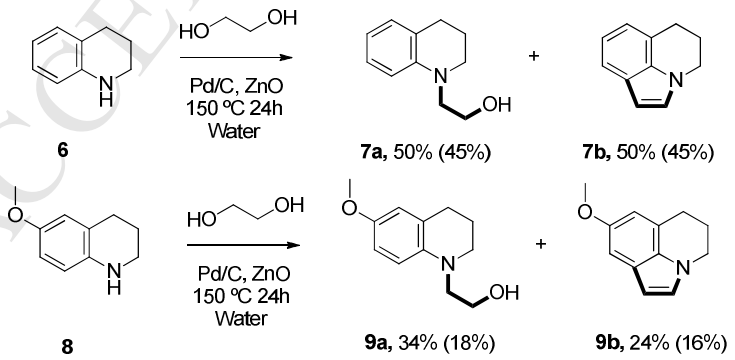


Figure 3. Heterogeneous BH/HA reactions with tetrahydroquinolines **6** and **8**. Yields obtained by ^{1}H-NMR and isolated yields.

In view of these results, a rational mechanism could be proposed for this reaction. The formation of amino alcohols follows a typical BH/HA pathway, being Pd/C the responsible for the hydrogenation/dehydrogenation process. In addition, as it has been shown in Table 1, ZnO is required to activate alcohol. Many examples reported in the literature with diols under homogeneous[4,24] or heterogeneous[13] catalysis afford the double functionalization.[25] This avoids the formation of amino alcohols yielding to diamines, either inter- or intra-molecular as it is the case when Pd/MgO is used as catalyst with ethylene glycol as reported by Corma.[26] Kempe and Williams methodologies[6,9] are the unique successful conditions for this challenging mono activation of ethylene glycol. These methodologies employed an excess of ethylene glycol (significantly smaller than in our conditions, 3 eq[6] or 5 eq[9]) and solvents. However, by using our systems, even having a large excess of glycol (it is indeed co-solvent with water), we are able to obtain the amino alcohols without anhydrous conditions.

In Figure 4, the rational mechanism is represented. Normal BH/HA pathway is employed for the formation of amino alcohol. Ethylene glycol is transformed into the corresponding mono-aldehyde by means of Pd/C in presence of ZnO as activating agent (conversion decreases when smaller amount of ZnO are employed, Table 1 entries 12 and 13). The relatively long reaction times required (24h) and also the absence of 2-hydroxyacetaldehyde in the crude may indicate that this first process is the rate limiting one. This hypothesis may be supported by the fact that this step must be mediated by both heterogeneous catalysts, while all the subsequent steps require just Pd/C. In addition, ZnO may be partially soluble under our conditions.[27] The interaction between both catalyst may be facilitated thanks to this solubility combined with the excess (300%) of ZnO. Then, the amine generates the corresponding imine that is reduced yielding to the β-amino alcohol closing BH/HA cycle. However, with ethylene glycol, a tautomeric equilibrium of this imine can yield to a different compound that may undergo indole formation or dimers. Williams[9] and Bruneau[24] reported on a similar tautomeric feature with amino alcohols under BH/HA reactions in homogeneous phase. When

imine is generated, the tautomeric pathway implicates a migration of the double bond. This migration is also well known in the literature and employed in the Voigth reaction for the preparation of β-amino ketones.[28] This takes place through the aliphatic chain yielding to an enol that is formally a hidden indole. In order to capture intermediates, 1,2-diamino benzene was employed to give alcohol **10**[29a] in excellent yield by means of condensation, suggesting once again that the imine is an intermediate, even if it has not been detected in any example.

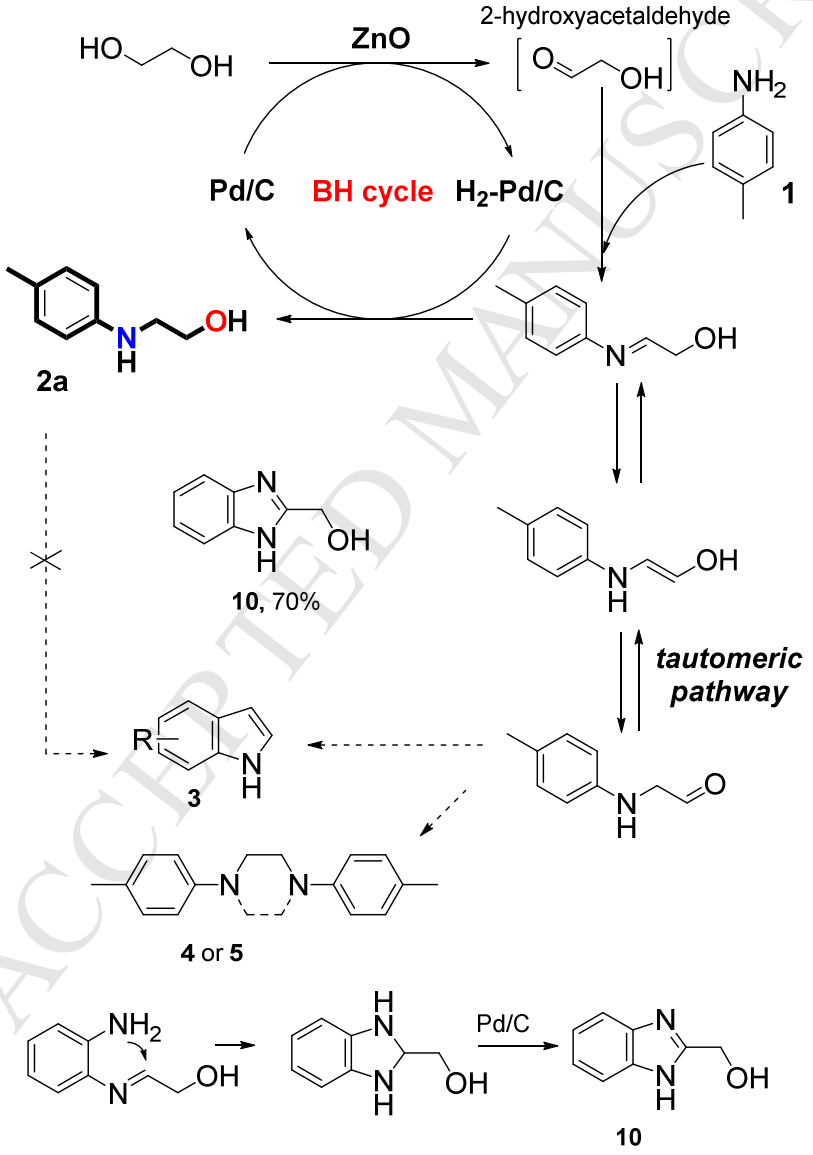


Figure 4. Rational mechanism and key intermediates

Indole formation has been found more efficient using **6** compared to anilines that requires activation of the aromatic ring (Figure 5). Rigidity in **6** induces an intermediate with the adequate geometry leading to a more efficient indole formation. In anilines, free rotation may difficult the achieving of this intermediate and is responsible of smaller yields. Even if the formation of the indole reduces the yield of the amino alcohol, a straight synthesis of indoles also represents a major advancement in catalysis. However, the formation of indole cannot be produced by over reaction of the corresponding β-amino alcohol. When compound **7a** was submitted to the reaction conditions, no conversion was observed (Scheme S4).

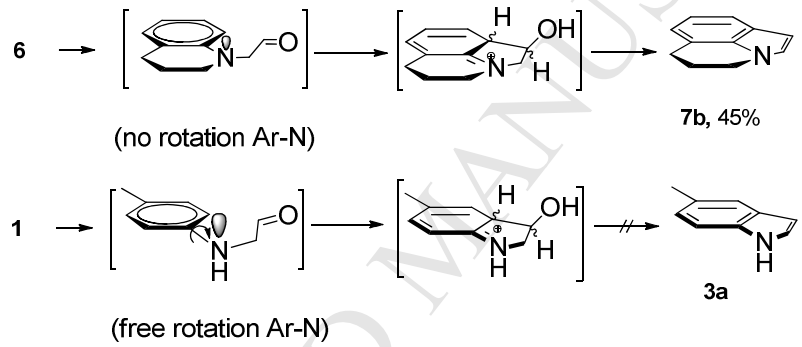
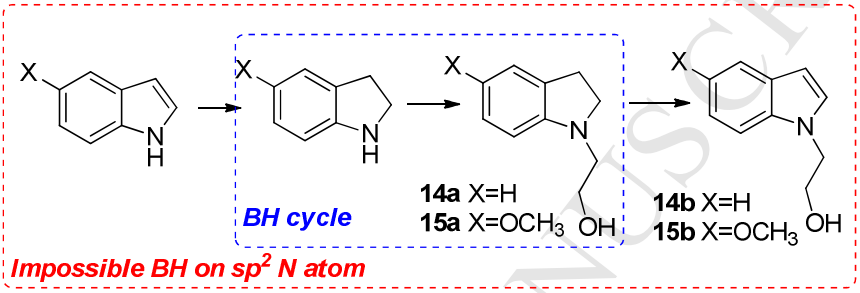


Figure 5. Structural differences in indole formation between 1,2,3,4-tetrahydroquinoline (**6**) and *p*-toluidine (**1**) intermediates.

In order to verify this mechanism some tests were performed (See the SI for more details). To add evidences of imine tautomerism, deuteration essays in **6** reactions were carried out. The D/H ratios agree with this double bond migration (Scheme S1). Alcohol **7a** was also oxidized under Swern conditions yielding to an aldehyde that evolved spontaneously to **7b** proving that this aldehyde is extremely reactive under our reaction conditions (Scheme S2). However, imine intermediates were not isolated, compared with Corma results.[27] This is also in agreement with the inability of the catalyst to dehydrogenate β-amino alcohols (Scheme S4). Diols and anilines can be transformed into indoles with homogenous catalysis, but normally diols have methyl substituents.[29b,29c]

Finally, tandem reactions were tested. In view of the difficulty that requires activation of ethylene glycol, we considered that under these conditions we may be able to hydrogenate indoles (Figure 6). Under heterogeneous conditions, this kind of reaction is proposed without this hydrogenation step.[30] However, Williams and Beller[31] reported on the pre-formation of indolines as a part of a more functional BH/HA cycle and end up by re-aromatization towards and alkylated indole.



Starting Reagent	Conversion	Combined selectivity
Indole (**11**) (X=H)	72%	65% (**14a**+144**b**)
Indoline (**12**) (X=H)	>95%	75% (**14a**+**14b**)
5-Methoxy indole (**13**) ($X=OCH_3$)	52%	>95%(**15a**+**15b**)

Figure 6. Tandem functional BH/HA cycles.

To check this, we performed reactions with indole (**11**), indoline (**12**) and 5-methoxy indole (**13**). In all cases amino alcohols were isolated, proving that our catalyst was able to hydrogenate the five-member ring generating an amine that could undergo BH/HA cycle. The combined selectivity of **14a-b** or **15a-b** proves that Pd/C, ZnO combination is a powerful catalyst that is not only able to activate ethylene glycol but also dehydrogenate/hydrogenate indoles.

Conclusion

The combination of Pd/C and ZnO has been proved to be an adequate heterogeneous catalyst for the single-alcohol activation of ethylene glycol in presence of aromatic amines under BH/HA cycles in water/ethylene glycol mixture. We have prepared a large family of β-amino alcohols by a new protocol. In addition, major secondary products of this reaction are indoles, and even their low yield, it represents also a major input on a straight synthesis of these heterocycles. The present methodology reveals to be useful as long as it is air and moisture stable. Furthermore, we have proved that Pd/C, ZnO is also able to hydrogenate indoles to indolines inducing tandem BH/HA reactions all of them driven by a heterogeneous catalyst. All these reactions are possible by a mono-activation of ethylene glycol that takes place thanks to the combination of Pd/C and ZnO and an excess of glycol. This is the unique heterogeneous approach towards β-amino alcohols with high atom efficiency (due to the BH/HA process), and without derivatization of glycol. The complementarity between BH/HA common economical catalyst (Pd/C) with and alcohol activation agents (ZnO) represents a different approach towards extremely stable poly alcohols. Further studies are undergoing with the aim reducing the amount of ethylene glycol as well as the use of different diols.

Experimental Methods

General procedure:

1 mmol of amine, 0.07 mmol of Pd/C, 3 mmol of ZnO, 6 mL of distilled water and 6 mL of ethylene glycol were mixed manually inside a 20mL Teflon flask. Then it was sealed into a steel autoclave and introduced in a preheated oven at 150ºC for 24h. The reaction mixture was cooled to room temperature, 25mL of distilled water were added and the crude was filtered through a 0.2µm Teflon filter. The reaction mixture was extracted with ethyl acetate 3x15ml and organic layers were combined, dried with Na_2SO_4, filtered and concentrated affording the reaction crude that was cheeked by NMR. Crude reaction was purified by chromatotron (1

mm, silica, from hexane to hexane/AcOEt 1:3) affording pure β-amino alcohols. Similar conditions were employed with tetrahydroquinolines **6** and **8**. Tandem reactions were performed under the same conditions employing indoles or indoline instead of aniline. For all isolated compounds in this work that are new: name, structure, isolated yield, physical aspect and characterization by ^{1}H-NMR, ^{13}C-NMR, HRMS and IR are shown. For those products that are already described in the literature: name, structure, isolated yield, physical aspect, and characterization by ^{1}H-NMR and ^{13}C-NMR are shown. An isolated yield defined as "traces" is referred to an amount of isolated product between 1 and 5 mg, considering this range of values not enough to give a representative yield.

2-(4-Methylphenylamino)ethanol (**2a**)[32] Isolated yield: 130 mg (88%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (d, J=8.6 Hz, 2H), 6.60 (d, J=8.5 Hz, 2H), 3.82 (t, J= 5.2 Hz, 2H), 3.28 (t, J= 5.2 Hz, 2H), 2.85 (bs, 1H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.8(1C, C), 129.9 (2C, CH), 127.5 (1C, C), 113.7 (2C, CH), 61.4 (1C, CH_2), 46.8 (1C, CH_2), 20.5 (1C, CH_3).

2-(3-Methylphenylamino)ethanol (**2b**)[33] Isolated yield: 60 mg (39%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (dd, J=11.0; 5.1 Hz, 1H), 6.44 (m, 3H), 3.71 (t, J=5.2 Hz, 2H), 3.19 (t, J=5.2 Hz, 2H), 2.82 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4 (1C, C), 139.5 (1C, C), 129.6(1C, CH), 119.4 (1C, CH), 114.4 (1C, CH), 110.9 (1C, CH), 61.7 (1C, CH_2), 46.7 (1C, CH_2), 22.0 (1C, CH_3).

2-(2-Methylphenylamino)ethanol (**2c**)[34] Isolated yield: 44 mg (28%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12 (m, 2H), 6.69 (m, 2H), 3.87 (t, J= 5.1 Hz, 2H), 3.35 (t, J= 5.1 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.1 (1C, C), 130.4 (1C, CH), 127.2(1C, CH), 122.7 (1C, C), 117.6(1C, CH), 110.2 (1C, CH), 61.3 (1C, CH_2), 46.1 (1C, CH_2), 17.6 (1C, CH_3).

2-(2,3-Dimethylphenylamino)ethanol (**2d**) Isolated yield: 30 mg (22%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04 (t, J = 7.8 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H),

3.87 (t, J = 5.2, 2H), 3.34 (t, J = 5.2, 2H), 2.30 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.1 (1C, C), 136.9 (1C, C), 126.3(1C, CH), 121.2 (1C, C), 120.0(1C, CH), 108.6 (1C, CH), 61.4 (1C, CH_2), 46.5 (1C, CH_2), 20.8 (1C, CH_2), 12.7 (1C, CH_3). HRMS for $C_{10}H_{15}NO$ [M+H$^+$]: calculated: 166.1220; found: 166.1219. IR (ATR): 3409, 2943, 2878, 1589, 1506, 1476, 1458, 1317, 1283, 1141, 1060, 765, 713.

2-(2,4-Dimethylphenylamino)ethanol (**2e**) Isolated yield: 30 mg (23%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.58 (d, J = 8.0 Hz, 1H), 3.86 (t, J = 5.2, 2H), 3.33(t, J = 5.2, 2H), 2.24 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.8 (1C, C), 131.3 (1C, CH), 127.5 (1C, CH), 127.0 (1C, C), 123.0 (1C, C), 110.6 (1C, CH), 61.4 (1C, CH_2), 46.5 (1C, CH_2), 20.7 (1C, CH_3), 17.6 (1C, CH3). HRMS for $C_{10}H_{15}NO$ [M+H$^+$]: calculated: 166.1226; found: 166.1217. IR (ATR): 3403, 2918, 1618, 1514, 1457, 1378, 1314, 1269, 1219, 1144, 1061, 875, 804, 772, 607.

2-(3,4-Dimethylphenylamino)ethanol (**2f**) Isolated yield: 43 mg (30%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.96 (d, J=8.0 Hz, 1H), 6.50 (d, J=2.4 Hz, 1H), 6.44 (dd, J=8.0;2.5, 1H), 3.81 (t, J=5.4 Hz, 2H), 3.28 (t, J=5.3 Hz, 2H), 2.72 (s, 1H), 2.21 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.3 (1C, C), 137.5 (1C, C), 130.5 (1C, CH), 126.2 (1C, C), 115.4 (1C, CH), 110.9 (1C, CH), 61.4 (1C, CH_2), 46.7 (1C, CH_2), 20.1 (1C, CH_3), 18.8 (1C, CH_3). HRMS for $C_{10}H_{15}NO$ [M+H$^+$]: calculated: 166.1226; found: 166.1225. IR (ATR): 3354, 2917, 2861, 1616, 1507, 1448, 1319, 1262, 1217, 1059, 1021, 852, 803, 703.

2-(3,5-Dimethylphenylamino)ethanol (**2g**) Isolated yield: 41 mg (30%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.43 (s, 1H), 6.31 (s, 2H), 3.80 (t, J=5.2 Hz, 2H), 3.28 (t, J=5.2 Hz, 2H), 2.27 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.3 (1C, C), 139.1 (2C, C), 120.1(1C, CH), 111.4 (2C, CH), 61.4 (1C, CH_2), 46.3 (1C, CH_2), 21.6 (2C, CH_3). HRMS for $C_{10}H_{15}NO$ [M+H$^+$]: calculated: 166.1226; found: 166.1219. IR (ATR): 3381, 2927, 2842, 1601, 1574, 1504, 1456, 1373, 1346, 1329, 1302, 1241, 1212, 1194, 1131, 1095, 1058, 1011, 938, 872, 831, 800, 743, 718.

2-*(2,5-Dimethylphenylamino)ethanol* (**2h**) Isolated yield: 53 mg (39%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.87 (d, J=7.4 Hz, 1H), 6.44 (d, J=7.5 Hz, 1H), 6.40 (s, 1H), 3.78 (t, J=5.3 Hz, 2H), 3.26 (t, J=5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.2 (1C, C), 137.6 (1C, C), 130.5(1C, CH), 120.1 (1C, C), 118.6(1C, CH), 111.5 (1C, CH), 61.7 (1C, CH_2), 46.3 (1C, CH_2), 21.9 (1C, CH_3), 17.4 (1C, CH_3). HRMS for $C_{10}H_{15}NO$ [M+H$^+$]: calculated: 166.1226; found: 166.1220. IR (ATR): 3405, 3014, 2919, 1614, 1581, 1519, 1456, 1422, 1376, 1297, 1272, 1206, 1167, 1139, 1058, 1000, 877, 842, 793.

2-(2,6-Dimethylphenylamino)ethanol (**2i**)[34] Isolated yield: 20 mg (12%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (d, J= 7.4 Hz, 2H), 6.86 (dd, J= 7.9; 7.0 Hz, 1H), 3.80 (t, J= 5.0 Hz, 2H), 3.15 (t, J= 5.0 Hz, 2H), 2.73 (bs, 1H), 2.33 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.1 (1C, C), 130.2 (1C, C), 129.1 (2C, CH), 122.8 (1C, CH), 62.3 (1C, CH_2), 50.6 (1C, CH_2), 18.5 (2C, CH_3).

2-Phenylaminoethanol (**2j**)[35] Isolated yield: 89 mg (65%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14-7.06 (m, 2H), 6.69-6.62 (m, 1H), 6.60 (dd, J= 8.6; 1.0 Hz, 2H), 3.71 (t, J= 5.3 Hz, 2H), 3.19 (t, J= 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.2 (1C, C), 129.4 (2C, CH), 118.0 (1C, CH), 113.4 (2C, CH), 61.3 (1C, CH_2), 46.2 (1C, CH_2).

2-(4-Fluorophenylamino)ethanol (**2n**)[36] Isolated yield: 52 mg (34%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90-6.85 (m, 2H), 6.60-6.55 (m, 2H), 3.82 (m, 2H), 3.24 (t, J= 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.0 (1C, C), 160.1 (1C, C), 114.6 (1C, C), 114.4 (1C, C), 115.8 (1C, C), 115.4 (1C, C), 61.4 (1C, CH_2), 46.2 (1C, CH_2).

2-(3-Fluorophenylamino)ethanol (**2o**) Isolated yield: 50 mg (32%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (td, J=8.1; 6.7 Hz, 1C), 6.34 (m, 2H), 6.26 (dt, J=11.5; 2.3 Hz, 1C), 3.76 (t, J=5.2 Hz, 2H), 3.21 (t, J=5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.5 (1C, C), 149.8(1C, C), 130.4 (1C, CH), 109.1(1C, CH), 104.4 (1C, CH), 99.9 (1C, CH), 61.1 (1C, CH_2), 45.94 (1C, CH_2). HRMS for $C_8H_{10}FNO$ [M+H$^+$]: calculated: 156.0819; found:

156.0807. IR (ATR): 3351, 2929, 1617, 1588, 1510, 1495, 1459, 1334, 1286, 1175, 1149, 1054, 997, 963, 828, 756, 681.

2-(2-Fluorophenylamino)ethanol (**2p**) Isolated yield: 35 mg (23%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00 (m, 2H), 6.76 (td, J=8.4; 1.5 Hz, 1H), 6.66 (m, 1H), 3.86 (t, J=5.2 Hz, 2H), 3.35 (t, J=5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.6 (1C, C), 150.4(1C, C), 124.8 (1C, CH), 117.6 (1C, CH), 114.9(1C, CH), 112.9 (1C, CH), 61.4 (1C, CH_2), 46.0 (1H, CH_2). HRMS for $C_8H_{11}FNO$ [M+H$^+$]: calculated: 156.0825; found: 156.0811. IR (ATR): 3402, 1620, 1514, 1544, 1336, 1297, 1252, 1188, 1061, 1033, 741.

2-(2-Trifluoromethylphenylamino)ethanol (**2q**) Isolated yield: 84 mg (41%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (ddd, J= 7.9; 1.6; 0.6 Hz, 1H), 7.26 (m, 1H), 6.64 (m, 2H), 2.11 (t, J= 4.6 Hz, 2H), 3.92 (t, J= 4.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)δ: 168.5 (1C, C), 150.7(1C, C), 134.5 (1C, CH), 131.6 (1C, CH), 116.9 (1C, CH), 116.4 (1C, CH), 110.5 (1C, C), 66.2 (1C, CH_2), 61.6 (1C, CH_2). HRMS for $C_9H_{10}F_3NO$ [M-2H$^+$]: calculated: 204.0631; found: 204.0625. IR (ATR): 3473, 3368, 1682, 1614, 1587, 1561, 1487, 1455, 1291, 1240, 1161, 1131, 1065, 751, 702, 665.

2-(3-Trifluoromethylphenylamino)ethanol (**2r**)[37] Isolated yield: 101 mg (50%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10 (t, J= 7.9 Hz, 1H), 6.82-6.77 (m, 1H), 6.67 (s, 1H), 6.61 (dd, J= 8.2; 2.3Hz, 1H), 3.67 (t, J= 5.2 Hz, 2H), 3.15 (t, J= 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.5 (1C, CF_3), 129.8(1C, CH), 126.2 (1C, C), 122.6 (1C, C), 116.3 (1C, CH), 114.3 (1C, CH), 109.3 (1C, CH), 61.1 (1C, CH_2), 45.8 (1C, CH_2).

2-(2-Trifluoromethoxyphenylamino)ethanol (**2s**) Isolated yield: 59 mg (28%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (m, 2H), 6.70 (dd, J= 8.5; 1.5 Hz, 1H), 6.62 (m, 1H), 3.78 (t, J= 5.2 Hz, 2H), 3.28 (t, J= 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.9 (1C, C), 134.9 (1C, C), 128.1 (1C, CH), 121.4 (1C, CH), 117.4 (1C, CH), 112.8 (1C, CH), 61.5 (1C, CH_2), 46.0 (1C, CH_2). HRMS for $C_9H_{10}F_3NO_2$ [M+H$^+$]: calculated: 222.0736; found: 222.0729. IR

(ATR): 3420, 2930, 2360, 1614, 1515, 1457, 1330, 1246, 1215, 1166, 1042, 923, 745, 669, 630, 604.

2-(2-Methoxyphenylamino)ethanol (**2t**)[38] Isolated yield: 108 mg (65%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.88 (td, J= 7.6; 1.6 Hz, 1H), 6.79 (dd, J= 7.9; 1.5 Hz, 1H), 6.72 (dd, J= 7.5; 1.6 Hz, 1H), 6.66 (dd, J= 7.8; 1.5 Hz, 1H), 3.75 (s, 3H), 3.74 (t, J= 5.3 Hz, 2H), 3.32 (t, J= 5.3 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.3 (1C, C), 138.1 (1C, C), 121.3 (1C, CH), 117.1 (1C, CH), 110.4(1C, CH), 109.7 (1C, CH), 61.4 (1C, CH_3), 55.5 (1C, CH_2), 46.0 (1C, CH_2).

2-(4-Methoxyphenylamino)ethanol (**2u**)[35] Isolated yield: 115 mg (70%). Oil.^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.76 (d, J= 9.2 Hz, 2H), 6.58 (d, J= 8.8 Hz, 2H), 3.74 (t, J= 5.2 Hz, 2H), 3.73 (s, 3H), 3.25 (t, J= 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.8 (1C, C), 142.5 (1C, C), 115.1 (2C, CH), 114.9 (1C, CH), 61.3 (1C, CH_3),55.8 (1C, CH_2), 47.1 (1C, CH_2).

2-(3,5-Dimethoxylphenylamino)ethanol (**2v**) Isolated yield: 22 mg (11%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92 (t, J=2.1 Hz, 1H), 5.87 (s, 1H), 5.86 (s, 1H), 3.82 (t, J=5.2 Hz, 2H), 3.75 (s, 6H), 3.27 (t, J=5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.9 (2C, C), 149.9 (1C, C), 92.5 (2C, CH), 90.6 (1C, CH), 61.3 (1C, CH_3), 55.3 (2C, CH_2), 46.5 (1C, CH_2). HRMS for $C_{10}H_{15}NO_3$ [M+H$^+$]: calculated: 198.1125; found: 198.1113. IR (ATR): 3384, 2938, 2839, 1613, 1507, 1456, 1235, 1203, 1176, 1151, 1127, 1059, 808.

2-(3,4-Dimethoxylphenylamino)ethanol (**2w**) Isolated yield: 35 mg (18%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.74 (d, J= 8.5 Hz, 1H), 6.30 (d, J= 2.6 Hz, 1H), 6.20 (dd, J= 8.5; 2.6 Hz, 1H), 3.84-3.81 (m, 5H), 3.80 (s, 3H), 3.26 (t, J= 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.1 (1C, C), 142.9 (1C, C), 142.2(1C, C), 113.3 (1C, CH), 104.4 (1C, CH), 99.8 (1C, CH), 61.4 (1C, CH_2), 56.8 (1C, CH_3), 55.9 (1C, CH_3), 47.3 (1C, CH_2). HRMS for $C_{10}H_{15}NO_3$ [M+H$^+$]: calculated: 198.1125; found: 198.1125. IR (ATR): 3383, 2940, 2832, 1616, 1515, 1463, 1232, 1210, 1168, 1139, 1024, 797, 611.

5-Methylindole (**3a**)[39] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (m, 2H), 7.26 (d, J= 8.5 Hz, 1H), 7.12 (d, J= 3.0 Hz, 1H), 6.44 (d, J= 3.0 Hz, 1H), 2.39 (s, 3H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 148.0 (1C, C), 138.6 (1C, C), 134.0 (1C, C), 130.2 (1C, CH), 121.2 (2C, CH), 119.4 (1C, CH), 94.8 (1C, CH), 20.9 (1C, CH_3).

6-Methylindole (**3b**) and *4-Methylindole* (**3b'**)[40] Isolated yield: 23 mg (17%, mixture). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (bs, 1H), 8.01 (bs, 1H), 7.54 (d, J= 8.1 Hz, 1H'), 7.16 (m, 5H), 6.97 (d, J= 8.3 Hz, 1H'), 6.93 (d, J= 7.2 Hz, 1H), 6.58 (s, 1H), 6.51 (s, 1H'), 2.58 (s, 3H), 2.48 (s, 3H'). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.4 (1C', C), 135.6 (1C, C), 131.9 (1C, C), 130.4 (1C', C), 127.9(1C', C), 125.7 (1C, C), 123.6 (1C, CH), 122.2 (1C, CH), 121.7 (1C', CH), 120.4 (1C', CH), 120.0 (1C, CH), 111.1 (1C, CH), 108.7 (1C, CH), 102.5 (1C', CH), 101.2 (1C, CH), 21.8 (1C, CH_3), 18.9 (1C', CH_3).

7-Methylindole (**3c**)[41] Isolated yield: 27 mg (20%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (bs, 1H), 7.51 (d, J= 7.5 Hz, 1H), 7.22 (s, 1H), 7.09-6.97 (m, 2H), 6.57 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 131.2 (1C, C), 123.9 (2C, CH and C), 122.63 (2C, CH), 120.2 (1C, CH), 118.6(1C, CH), 103.3 (1C, CH), 16.8 (1C, CH_3).

6,7-Dimethylindole (**3d**)[42] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, J=8.0 Hz, 1H), 7.16 (m, 1H), 6.96 (d, J=8.1, 1H), 6.51 (dd, J=3.2; 2.1, 1H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 129.4 (2C, C), 123.5 (1C, CH), 122.80 (1C, CH), 117.85 (1C, CH), 103.2 (1C, CH), 19.4 (1C, CH_3), 13.3 (1C, CH_3).

5,7-Dimethylindole (**3e**)[43] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (bs, 1H), 7.18 (m, 1H), 6.84 (bs, 1H), 6.48 (dd, J=3.1; 2.1, 1H), 2.47 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.3(1C, C), 131.3 (1C, C), 127.4 (1C, C), 124.42 (1C, CH), 124.0 (1C, CH), 119.9 (1C, C), 102.8 (1C, CH), 21.5 (1C, CH_3), 16.8 (1C, CH_3).

5,6-Dimethylindole (**3f**)[44] *and 4,5-Dimethylindole* (**3f'**)[45] Isolated yield: traces (mixture). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (bs, 1H), 7.96 (bs, 1H'), 7.40 (s, 1H'), 7.16 (m, 3H), 7.10 (t, J= 2.8 Hz, 1H'), 7.01 (d, J= 8.2 Hz, 1H), 6.54 (ddd, J= 3.1; 2.1; 0.9 Hz, 1H), 6.44 (ddd, J= 3.0; 2.0; 0.9 Hz, 1H'), 2.47 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H'), 2.35 (s, 3H'). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.4 (2C, C), 128.6 (2C, C), 127.7 (2C, C), 126.6 (2C, C), 124.8 (1C, CH),

123.8 (1C, CH), 123.4 (1C', CH), 120.8 (1C', CH), 111.5 (1C', CH), 108.2 (1C, CH), 102.0 (1C', CH), 101.1 (1C, CH), 20.6 (1C', CH_3), 19.6 (1C', CH_3), 19.4 (1C, CH_3), 15.6 (1C, CH_3).

4,6-Dimethylindole(**3g**)[46] Isolated yield: 38 mg (32%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (bs, 1H), 7.13 (m, 1H), 7.04 (s, 1H), 6.78 (s, 1H), 6.52 (ddd, J= 3.1; 2.1; 0.9 Hz, 1H), 2.54 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.1 (1C, C), 132.0 (1C, C), 129.9 (1C, C), 125.7 (1C, C), 122.9 (1C, CH), 122.0 (1C, CH), 108.6(1C, CH), 101.1 (1C, CH), 21.8 (1C, CH_3), 18.8 (1C, CH_3).

4,7-Dimethylindole (**3h**)[42] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 7.22 (m, 1H), 6.93 (d, J=7.2 Hz, 1H), 6.86 (d, J=7.1 Hz, 1H), 6.60 (m, 1H), 2.56 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.1 (1C, C), 127.9 (1C, C), 127.4(1C, C), 123.3 (1C, CH), 122.6 (1C, CH), 120.1 (1C, CH), 117.7 (1C, C), 101.79 (1C, CH), 18.7 (1C, CH_3), 16.6 (1C, CH_3).

4,6-Dimethoxyindole (**3v**)[47] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (bs, 1H), 6.99 (dd, J=3.2; 2.3 Hz, 1H), 6.57 (ddd, J= 3.1; 2.2; 0.8 Hz, 1H), 6.50 (dd, J= 1.8; 0.8 Hz, 1H), 6.24 (d, J= 1.9 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.7 (1C, C), 153.8 (1C, C), 137.3 (1C, C), 121.3 (1C, CH), 113.2 (1C, C), 99.9 (1C, CH), 91.8 (1C, CH), 86.9 (1C, CH), 55.8 (1C, CH_3), 55.5 (1C, CH_3).

5,6-Dimethoxyindole (**3w**)[48] Isolated yield: 36 mg (20%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (bs, 1H), 7.10 (s, 1H), 7.08 (dd, J= 3.1; 2.4 Hz, 1H), 6.89 (s, 1H), 6.45 (ddd, J= 3.0; 2.1; 0.9 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.2 (1C, C), 145.3 (1C, C), 130.3 (1C, C), 122.8(1C, CH), 120.7 (1C, C), 102.4 (2C, CH), 94.6 (1C, CH), 56.4 (1C, CH_3), 56.3 (1C, CH_3).

N,N'-Bis(4-methylphenyl)-1,2-ethanediamine (**4a**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01 (d, J= 8.0 Hz, 4H), 6.64 (d, J= 8.4 Hz, 4H), 3.39 (s, 4H), 2.25 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.1(2C, C), 130.0 (4C, CH), 128.0 (2C, C), 114.0 (4C, CH),

44.2 (2C, CH_2), 20.5 (2C, CH_3). HRMS for $C_{16}H_{20}N_2$ [M+H^+]: calculated: 241.1699; found: 241.1688. IR (ATR): 2918, 2858, 1616, 1517, 1464, 1317, 1296, 1256, 1182, 1127, 806.

N,N'-Bis(2-methylphenyl)-1,2-ethanediamine (**4c**)[49] Isolated yield: 13 mg (24%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.15 (t, J=7.6 Hz, 2H), 7.08 (d, J=7.2 Hz, 2H), 6.70 (m, 4H), 3.50 (s, 4H), 2.13 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 130.4 (2C, CH), 127.3 (2C, CH), 122.7 (4C, C), 117.8(2C, CH), 110.2 (2C, CH), 43.4 (2C, CH_2), 17.7 (2C, CH_3)

N,N'-Bis(2,4-dimethylphenyl)-1,2-ethanediamine (**4e**)[49] Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.87 (d, J=8.1 Hz, 2H), 6.83 (s, 2H), 6.53 (d, J=8.0 Hz, 2H), 3.38 (s, 4H), 2.16 (s, 6H), 2.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.7 (2C, C), 131.3 (2C, CH), 127.5 (2C, CH), 126.9 (2C, C), 110.5 (2C, CH), 43.7 (2C, CH_2), 20.5 (2C, CH_3), 17.6 (2C, CH3).

N,N'-Bis(3,5-dimethylphenyl)-1,2-ethanediamine (**4g**) Isolated yield: traces. Oil. 1H NMR (300 MHz, CDCl3) δ: 6.40 (s, 2H), 6.29 (s, 4H), 3.36 (s, 4H), 2.24 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.1 (2C, C), 138.2 (4C, C), 120.1(2C, CH), 111.3 (4C, CH), 43.7 (2C, CH_2), 21.6 (4C, CH_3). HRMS for $C_{18}H_{24}N_2$ [M+H^+]: calculated: 269.2012; found: 269.2016. IR (ATR): 2916., 2358, 2342, 1652, 1601, 1558, 1540, 1520, 1506, 1489, 1472, 1456, 1338, 1186, 819, 772.

N,N'-Bis(3-fluorophenyl)-1,2-ethanediamine (**4o**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14-7.09 (m, 2H), 6.48-6.28 (m, 6H), 3.39 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.2 (d, *J* = 243.4 Hz, 2C, C), 149.0 (d, *J* = 10.6 Hz, 2C, C), 130.6 (d, *J* = 10.2 Hz, 2C, CH), 109.2 (d, *J* = 2.5 Hz, 2C, CH), 104.8 (d, *J* = 21.5 Hz, 2C, CH), 100.1 (d, *J* = 25.3 Hz, 2C, CH), 43.3 (2C, CH_2). HRMS for $C_{14}H_{14}F_2N_2$ [M+H^+]: calculated: 249.1198; found: 249.1202. IR (ATR): 1616, 1589, 1507, 1496, 1175, 1150, 830, 757, 682.

N,N'-Bis(2-trifluoromethoxyphenyl)-1,2-ethanediamine (**4s**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19-7.12 (m, 4H), 6.77 (dd, J=8.5; 1.5 Hz, 2H), 6.73-6.66 (m, 2H), 3.46 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)δ: 140.4 (2C, C), 136.6 (2C, C), 127.9 (2C,

CH), 122.7(2C, C), 121.3 (2C, CH), 117.1(2C, CH), 112.1 (2C, CH), 42.7 (2C, CH_2). HRMS for $C_{16}H_{14}F_6N_2O_2$ [M+H^+]: calculated: 381.1032; found: 381.1012. IR: 3454, 2928, 1612, 1558, 1514, 1472, 1328, 1248, 1217, 1166, 1043, 920, 772, 746, 674, 630, 606.

1,4-Bis(4-methylphenyl)-piperazine (**5a**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (d, J= 8.6 Hz, 4H), 6.91 (d, J= 8.5 Hz, 4H), 3.30 (s, 8H), 2.29 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.3 (2C, C), 129.8 (6C, C and CH), 116.9 (4C, CH), 50.2 (4C, CH_2), 20.6 (2C, CH_3). HRMS for $C_{18}H_{22}N_2$ [M+H^+]: calculated: 267.1856; found: 267.1844. IR (ATR): 2953, 2919, 2855, 2820, 2360, 2343, 1743, 1615, 1515, 1489, 1452, 1384, 1317, 1293, 1265, 1229, 1211, 1180, 1150, 1041, 939, 823, 813, 771.

1,4-Bis(3-methylphenyl)-piperazine (**5b**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19 (t, J= 7.9 Hz, 2H), 6.81 (m, 4H), 6.73 (d, J=7.3 Hz, 2H), 3.33 (s, 8H), 2.35 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5 (2C, C), 139.0 (2C, C), 129.2 (2C, CH), 121.1 (2C, CH), 117.35 (2C, CH), 113.6 (2C, CH), 49.7 (4C, CH_2), 21.9 (2C, CH_3). HRMS for $C_{18}H_{22}N_2$ [M+H^+]: calculated: 267.1856; found: 267.1844. IR (ATR): 2826, 1604, 1583, 1494, 1448, 1242, 995, 955, 690, 609.

1,4-Bis(2-methylphenyl)-piperazine (**5c**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (m, 4H), 7.11, (d, J=7.90 Hz, 2H), 7.01 (t, J=7.2 Hz, 2H), 3.08 (s, 8H), 2.37 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8 (2C, C), 132.8 (2C, C), 131.3 (2C, CH), 126.7 (2C, CH), 123.3(2C, CH), 119.3 (2C, CH), 52.4 (4C, CH_2), 18.1 (2C, CH_3). HRMS for $C_{18}H_{22}N_2$ [M+H^+]: calculated: 267.1856; found: 267.1854. IR (ATR): 2946, 2823, 1596, 1490, 1442, 1372, 1253, 1222, 1142, 1112, 1039, 945, 767, 722.

1,4-Bis(2,3-dimethylphenyl)-piperazine (**5d**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (t, J=7.7 Hz, 2H), 7.00 (d, J=7.6 Hz, 2H), 6.92 (d, J=7.4 Hz, 2H), 3.05 (s, 8H), 2.29 (s, 6H), 2.28 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.9 (2C, C), 138.1 (2C, C), 131.5(2C, C), 125.9 (2C, CH), 125.1(2C, CH), 116.9 (2C, CH), 52.9 (2C, CH_2), 20.8 (2C, CH_3), 14.2 (2C, CH_3). HRMS for $C_{20}H_{26}N_2$ [M+H^+]: calculated: 295.2169; found: 295.2163.

IR (ATR): 2949, 2814, 2744, 1580, 1507, 1475, 1449, 1373, 1315, 1272, 1233, 1219, 1140, 1085, 1028, 994, 944, 775, 717.

1,4-Bis(2,4-dimethylphenyl)-piperazine (**5e**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (m, 6H), 3.04 (s, 8H), 2.33 (s, 6H), 2.30 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4 (2C, C), 132.8 (4C, C), 127.2(2C, CH), 119.2 (2C, CH), 52.7 (4C, CH_2), 20.8 (2C, CH_3), 17.9 (2C, CH_3). HRMS for $C_{20}H_{26}N_2$ [M+H$^+$]: calculated: 295.2169; found: 295.2175. IR (ATR): 2943, 2813, 2359, 2343, 1504, 1447, 1370, 1353, 1311, 1293, 1257, 1234, 1220, 1163, 1143, 1125, 1044, 961, 947, 913, 888, 812, 755, 720, 668.

1,4-Bis(3,4-dimethylphenyl)-piperazine (**5f**) Isolated yield: 23 mg (20%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06 (d, J= 8.2 Hz, 2H), 6.82 (d, J=2.4 Hz, 2H), 6.75 (dd, J=8.2, 2.6 Hz, 2H), 3.29 (s, 8H), 2.26 (s, 6H), 2.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.8 (2C, C), 137.3(2C, C), 130.4 (2C, CH), 128.5(2C, C), 118.5 (2C, CH), 114.2 (2C, CH), 50.3 (4C, CH^2), 20.4 (2C, CH_3), 18.9 (2C, CH_3). HRMS for $C_{20}H_{26}N_2$ [M+H$^+$]: calculated: 295.2169; found: 295.2170. IR (ATR): 2963, 2919, 2822, 1616, 1504, 1447, 1336, 1235, 1178, 1156, 1127, 1023, 1000, 961, 872, 850, 807, 703.

1,4-Bis(3,5-dimethylphenyl)-piperazine (**5g**) Isolated yield: 33 mg (27%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.64 (s, 4H), 6.58, (s, 2H), 3.33 (s, 8H), 2.32 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5(2C, C), 138.4 (2C, CH), 122.5 (4C, C), 114.5 (4C, CH), 49.9 (8C, CH_2), 21.8 (4C, CH_3). HRMS for $C_{20}H_{26}N_2$ [M+H$^+$]: calculated: 295.2169; found: 295.2168. IR (ATR): 2978, 2830, 2802, 1596, 1451, 1438, 1384, 1343, 1257, 1198, 1153, 1011, 827, 696, 685.

1,4-Bis(2,5-dimethylphenyl)-piperazine (**5h**) Isolated yield: 25 mg (20%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (d, J=7.5 Hz, 2H), 6.92 (s, 2H), 6.83 (d, J=7.5 Hz, 2H), 3.07 (s, 8H), 2.33 (s, 6H), 2.32 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.7 (2C, C), 136.2 (2C, C), 131.1 (2C CH), 129.5 (2C, C), 123.9 (2C, CH), 120.1(2C, CH), 52.4 (4C, CH2), 21.4 (2C, CH_3), 17.7 (2C, CH_3).HRMS for $C_{20}H_{26}N_2$ [M+H$^+$]: calculated: 295.2159, found: 295.2167. IR: 2946, 2920, 2812, 1504, 1448, 1370, 1238, 1219, 1145, 1126, 992, 804, 772.

1,4-Bis(2,3-dimethoxyphenyl)-piperazine (**5w**) Isolated yield: traces. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.82 (d, J= 8.7 Hz, 2H), 6.66 (bs, 2H), 6.53 (dd, J= 8.6; 2.6 Hz, 2H), 3.89 (s, 6H), 3.85 (s, 6H), 3.28 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.7 (4C, C), 112.2 (2C, CH), 108.5 (4C, C), 103.4 (2C, CH), 56.4 (2C, CH_3), 56.0 (2C, CH_3), 51.3 (4C, CH_2). HRMS for $C_{20}H_{26}N_2O_4$ [M+H$^+$]: calculated: 359.1965; found: 359.1963. IR (ATR): 2943, 2836, 2803.

N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroquinoline (**7a**)[49] Isolated yield: 79 mg (45%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26-6.36 (m, 4H), 3.70-3.10 (m, 6H), 2.75 (t, J= 6 Hz, 2H), 1.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.0(1C, C), 129.5 (1C, CH), 127.2 (1C, CH), 123.02 (1C, C), 116.6(1C, CH), 111.5 (1C, CH), 60.1 (1C, CH_2), 54.3 (1C, CH_2), 50.5 (1C, CH_2), 28.2 (1C, CH_2), 23.03 (1C, CH_2).

5,6-Dihydro-4H-pyrrolo-[3,2,1-ij]-quinoline (**7b**)[50] Isolated yield: 70 mg (45%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (dd, J= 7.9; 0.8 Hz, 1H), 7.00 (d, J= 3.0 Hz, 1H), 6.94 (dd, J= 7.9; 7.1 Hz, 1H), 6.84 (dd, J= 7.1; 0.9 Hz, 1H), 6.37 (d, J= 3.0 Hz, 1H), 4.09 (t, J= 5.7 Hz, 2H), 2.93 (t, J= 6.1 Hz, 2H), 2.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.3 (1C, CH), 126.1(1C, CH), 126.0 (1C, C), 122.0 (1C, C), 119.8 (1C, CH), 118.7 (1C, CH), 118.3(1C, CH), 100.5 (1C, CH), 44.3 (1C, CH_2), 24.9 (1C, CH_2), 23.1 (1C, CH_2).

3,4-Dihydro-6-methoxy-1(2H)-quinolinethanol (**9a**) Isolated yield: 39 mg (18%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.66 (m, 2H), 6.59 (m, 1H), 3.79 (t, J= 5.7 Hz, 2H), 3.73 (s, 3H), 3.37 (t, J= 5.7 Hz, 2H), 3.25-3.20 (m, 2H), 2.77 (t, J= 6.5 Hz, 2H), 2.01-1.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.7 (1C, C), 140.7 (1C, C), 125.0 (1C, C), 115.3 (1C, CH), 113.7(1C, CH), 112.7 (1C, CH), 59.9 (1C, CH_3), 55.9 (1C, CH_2), 55.5 (1C, CH_2), 50.3 (1C, CH_2), 28.3 (1C, CH_2), 22.2 (1C, CH_2). HRMS for $C_{12}H_{17}NO_2$ [M+H+]: calculated: 208.1332; found: 208.1326. IR (ATR): 3355, 2929, 1502, 1464, 1429, 1334, 1296, 1265, 1238, 1201, 1151, 1036, 1004, 922, 879, 843, 796, 721, 670, 631.

5,6-Dihydro-8-methoxy-4H-pyrrolo[3,2,1-ij]quinoline (**9b**) Isolated yield: 30 mg (16%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.05 (d, J= 2.9 Hz, 1H), 6.91 (d, J= 2.2 Hz, 1H), 6.62 (dd, J=

1.5; 0.6 Hz, 1H), 6.36 (d, J= 2.9 Hz, 1H), 4.13 (t, J= 5.7 Hz, 2H), 3.84 (s, 3H), 2.96 (dd, J= 8.9; 3.4 Hz, 2H), 2.28-2.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.84 (1C, C), 126.34 (1C, CH), 125.8 (1C, C), 122.7(2C, C), 109.4 (1C, CH), 100.1 (1C, CH), 99.9 (1C, CH), 56.2 (1C, CH_3), 44.2 (1C, CH_2), 25.0 (1C, CH_2), 23.2 (1C, CH_2). HRMS for $C_{12}H_{13}NO$ [M+H$^+$]: calculated: 188.1070; found: 188.1066. IR (ATR): 2938, 1618, 1601, 1495, 1436, 1394, 1342, 1298, 1261, 1234, 1218, 1140, 1047, 1031, 830, 799, 716.

1H-Benzimidazole-2-methanol (**10**)[28,51] Isolated yield: 103 mg (70%). Yellow powder, m.p.= 169.5-170.5 ºC. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.60-7.48 (m, 2H), 7.27-7.15 (m, 2H), 4.85 (s, 2H).^{13}C NMR (75 MHz, CD_3OD) δ: 157.6 (1C, C), 139.9 (2C, C), 122.6 (2C, CH), 117.6 (2C, CH), 58.7 (1C, CH_2).

2,3-Dihydro-1H-indole-1-ethanol (**14a**) *& 2-Indol-1-yl-ethanol* (**14b**)[52] Isolated yield: 43 mg (26%, mixture). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67-7.63 (m, 1H-b), 7.38 (dd, J= 8.2; 0.8 Hz, 1H-b), 7.26-7.19 (m, 1H-a), 7.16 (d, J= 3.2 Hz, 1H-a), 7.15-7.06 (m, 3H-a,b), 6.72 (td, J=7.5; 0.9 Hz, 1H-a), 6.57 (d, J= 7.8 Hz, 1H-a, 6.53 (dd, J= 3.1; 0.8 Hz, 1H-a), 4.27 (t, J= 5.3 Hz, 2H-b), 3.93 (t, J= 5.3 Hz, 2H-b), 3.80 (t, J= 5.4 Hz, 2H-a), 3.39 (t, J= 8.3 Hz, 2H-a), 3.23 (t, J= 5.3 Hz, 2H-a), 3.00 (t, J= 8.3 Hz, 2H-a). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.8 (1C, C), 136.2 (1C, C), 130.2 (1C, C), 128.8 (1C, C), 128.5 (1C, CH-a), 127.5 (1C, CH-a,b), 124.7 (1C, CH-a,b), 121.8 (1C, CH-a), 121.2 (1C, CH-b), 119.7 (1C, CH-a,b), 118.6 (1C, CH-a), 109.4 (1C, CH-b), 107.6 (1C, CH-a), 101.6 (1C, CH-b), 62.0 (1C, CH_2-b), 60.3 (1C, CH_2-a), 54.0 (1C, CH_2-a), 52.8 (1C, CH_2-a), 48.9 (1C, CH_2-b), 28.8 (1C, CH_2-a).

2-(5-Methoxyindolin-1-yl)ethanol (**15a**) Isolated yield: 22 mg (11%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78-6.75 (m, 1H), 6.66 (dd, J= 8.5; 2.6 Hz, 1H), 6.53 (d, J=8.5 Hz, 1H), 3.81 (t, J= 5.4 Hz, 2H), 3.75 (s, 3H), 3.35 (t, J= 8.1 Hz, 2H), 3.18 (t, J= 5.4 Hz, 2H), 2.97 (t, J= 8.1 Hz, 2H), 2.24 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.8(1C, C), 132.0 (2C, C), 112.1(2C, CH), 108.5 (1C, CH), 60.2 (1C, CH_2), 56.2 (1C, CH_2), 54.8 (1C, CH_3), 54.1 (1C, CH_2), 29.1 (1C, CH_2). HRMS for $C_{11}H_{15}NO_2$ [M+H$^+$]: calculated: 194.1176; found:

194.1171. IR (ATR): 3361, 2934, 2830, 1620, 1594, 1576, 1488, 1449, 1435, 1397, 1360, 1236, 1190, 1150, 1051, 1030, 939, 864, 833, 798, 753, 724.

2-(5-Methoxy-1H-indol-1-yl)ethanol (**15b**) Isolated yield: 20 mg (10%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, J= 8.9 Hz, 1H), 7.12 (d, J= 3.1 Hz, 1H), 7.10 (d, J= 2.4 Hz, 1H), 6.88 (dd, J= 8.9; 2.5 Hz, 1H), 6.44 (dd, J= 3.1; 0.8 Hz, 1H), 4.23 (t, J= 5.3 Hz, 2H), 3.91 (t, J= 5.3 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.3 (1C, C), 131.6 (1C, C), 129.2(1C, C), 129.0 (1C, CH), 112.2 (1C, CH), 110.2 (1C, CH), 102.8(1C, CH), 101.3 (1C, CH), 62.2 (1C, CH_2), 56.0 (1C, CH_2), 49.0 (1C, CH_3). HRMS for $C_{11}H_{13}NO_2$ [M+H^+]: calculated: 192.1019; found: 192.1013. IR (ATR): 3409, 2940, 2831, 1621, 1487, 1449, 1237, 1190, 1150, 1063, 1030, 799, 721.

Associated Content

Supporting Information.

Additional information, complete table of Figure 2, additional mechanistic experiments, ^{1}H- and ^{13}C-NMR spectra of all compounds (PDF).

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Notes

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