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Palladium-Catalyzed Synthesis of 6-aryl Dopamine Derivatives

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Abstract: Dopamine is a key neurotransmitter involved in a series of biologically relevant processes and its derivatives have sparked significant interest as intriguing synthetic targets. This class of compounds is indeed not only considerable for the potential biological activities but is also promising for diverse applications in material science. In light of this, our research was focused on the synthesis of 6-aryldopamine derivatives starting from 4-(2-aminoethyl)phenol through a sequential protocol, whose main steps are hydroxylation, halogenation, and Suzuki cross-coupling. Our method demonstrated versatility, efficiency, and compatibility with various functional groups, including aldehydes, ketones, esters, ethers, and fluorine.

Keywords: dopamine; palladium-catalyzed synthesis; Suzuki reaction; dopamine derivatives; regioselective hydroxylation; catechol; regioselective aromatic chlorination

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1. Introduction

Dopamine is a biological monoamine included in the class of "catecholamines", a family of neurotransmitters to which norepinephrine and epinephrine also belong [1].

It is synthesized both in the central nervous system (CNS) and in the periphery, and works by activating G-coupled protein receptors, also known as dopamine receptors. Specifically, there are five different types of dopamine receptors, which include D1, D2, D3, D4, and D5. Each kind of receptor has a different function and is found in different locations, such as the CNS, blood vessels, kidneys, heart, retina, and adrenal glands [2,3].

Dopamine exhibits various biological functions. For instance, it has key roles in regulating motor neurons, spatial memory function, motivation, arousal, reward, and pleasure, as well as lactation, sexual, and maternal behaviors.

Dopamine applications in therapy include the correction of hemodynamic imbalances present in shock syndrome, Ref. [4] traumatic brain injury, Ref. [5] septic shock, Ref. [6] and open heart surgery Ref. [7].

Furthermore, due to the ability of the catechol moiety to scavenge free radicals, Ref. [8], it provides an antioxidant defense in the brain against oxidant agents and free radical-induced damage [9].

Because of these remarkable features, the synthesis and metabolism of dopamine derivatives have been of great interest to researchers in various fields, including neuroscience, pharmacology, and medicinal chemistry.

Particularly, 6-substituted dopamine analogs have garnered attention due to their potential applications in understanding enzyme mechanisms. In this regard, they have been used as substrates for enzymes like L-DOPA dioxygenase and sulfotransferase 1A3

to investigate these enzymes' catalytic mechanisms and structural features [10,11]. By studying the interactions between dopamine derivatives and enzymes, researchers investigated the biochemical pathways involved in dopamine metabolism, identifying new drug targets for the treatment of dopamine-related disorders, including Parkinson's disease, schizophrenia, and neuropsychiatric disorders.

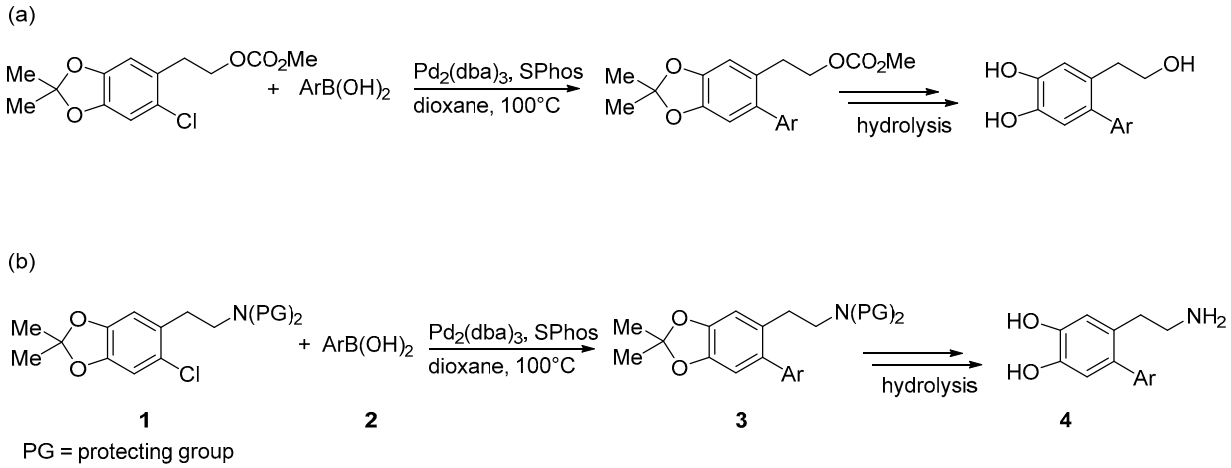
In addition to their role in enzyme studies, dopamine derivatives have shown promise as potential therapeutic agents. For instance, computational studies suggested that 6-substituted dopamine analogs may act as catechol-O-methyl transferase inhibitors, which could be useful in the treatment of conditions such as Parkinson's disease [12]. Particularly, it was demonstrated that by inhibiting the activity of catechol-O-methyl transferase, these compounds could regulate dopamine levels in the brain and alleviate symptoms associated with dopamine dysregulation.

Furthermore, dopamine derivatives have been explored for their potential applications in material science. For example, the ability of dopamine derivatives to coordinate metal ions makes them ideal candidates for sensing applications characterized by high selectivity and sensitivity. In this regard, catechol-based materials are known to be used for the detection of metal ions in solution, providing a simple and cost-effective way to monitor metal concentrations [13].

Because of the presence of the catechol ring, dopamine and its derivatives exhibit adhesive properties that have inspired the development of biomimetic materials for various applications. For example, DOPA/catechol-tethered polymers have been used as adhesive materials that mimic the adhesion mechanisms of marine organisms, such as mussels [14]. These materials showed excellent adhesion to a variety of surfaces, making them attractive for use in medical devices, tissue engineering, and other biomaterial applications [15].

Thus, the remarkable versatility of dopamine derivatives captured our interest, prompting us to embark on the development of a synthetic protocol for 6-substituted dopamine derivatives utilizing palladium catalysis.

Drawing upon our experience in palladium catalysis for the synthesis and functionalization of biologically significant derivatives [16–18], and based on our previous work on hydroxytyrosol derivative synthesis via Suzuki−Miyaura cross-coupling (Scheme 1a), Ref. [19], we were inspired to expand our research efforts to devise a methodology for producing 6-substituted dopamine analogs (Scheme 1b).

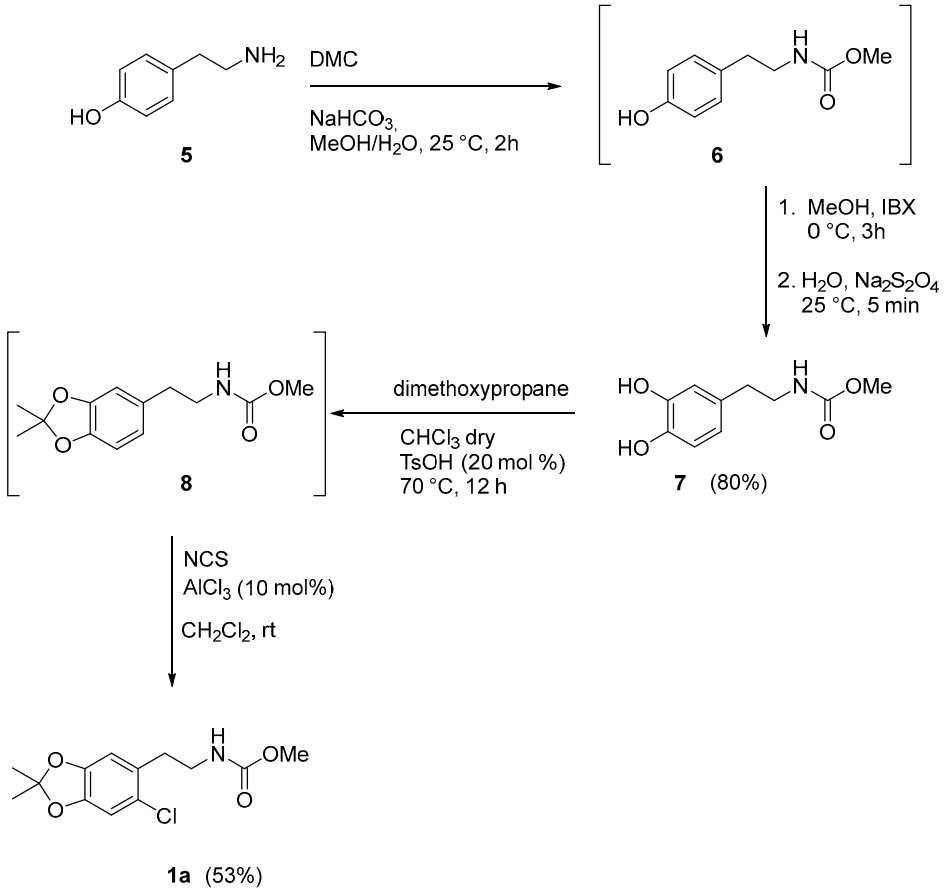


Scheme 1. (**a**) Our previous work. (**b**) This work.

This approach is based on the palladium-catalyzed Suzuki coupling of the derivatives 1, in turn, synthesized according to a protocol properly designed and developed. Outlined below are the findings from our investigations.

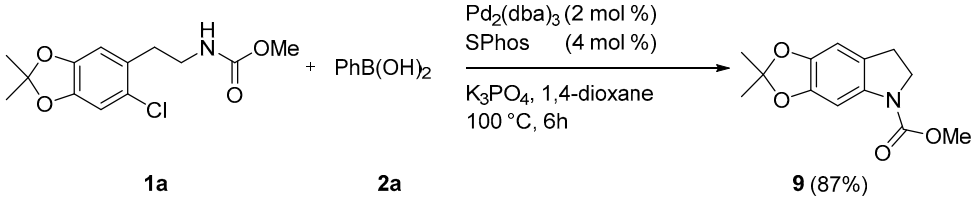
2. Results and Discussion

The synthesis of compound 1, employed in our investigation, was achieved through a suitably optimized multistep protocol, starting from the commercially available 4-(2-aminoethyl)phenol **5**. To avoid the occurrence of the Pictet–Spengler reaction during the acetonide formation, the first proposed step was the amino group protection. Thus, as carbamates are recognized as useful in protecting groups for amines, we decided to convert the 4-(2-aminoethyl)phenol **5** into the corresponding carbamate derivative **6** using dimethyl carbonate (DMC) in the presence of $NaHCO_3$ in $MeOH/H_2O$, at 25 °C (Scheme 2, step 1). The catechol derivative **7** was synthesized from **6** via the regioselective hydroxylation at the C2 position (Scheme 2, step 2) by treatment with iodoxybenzoic acid (IBX) followed by reductive conditions. Before proceeding with the subsequent steps, the catechol protection as acetonide (Scheme 2, step 3) was performed, affording compound **8**. Finally, the selective chlorination of C5 with N-chlorosuccinimide (NCS) in DCM at 25 °C led to the formation of compound **1a** in a satisfactory yield.



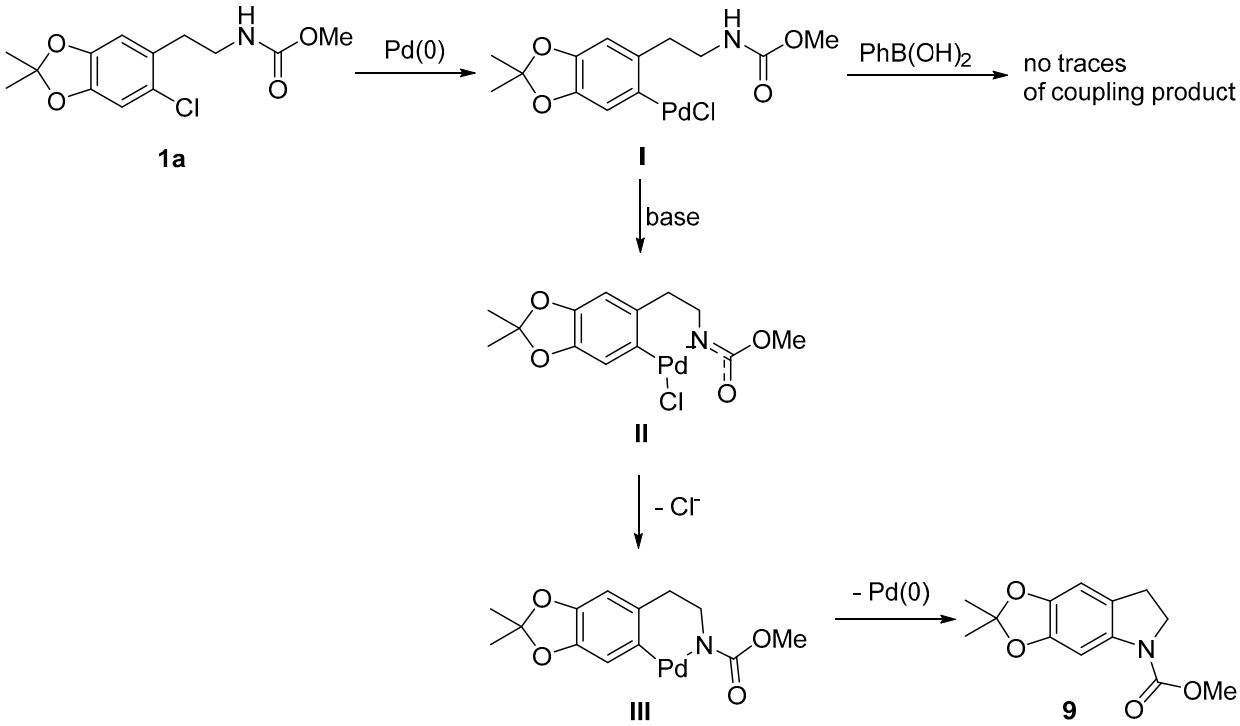
Scheme 2. Synthesis of the starting material **1a**.

The proposed method appeared to be simple overall, with good yields, and generally employes mild reaction conditions. Thus, with this procedure in our hands, we decided to proceed with evaluating the feasibility of the next Suzuki reaction. As a first attempt, we carried out the reaction of **1a**, with the phenylboronic acid **2a** in the presence of Pd_2dba_3/Sphos as the catalytic system, and K_3PO_4 as the base, in 1,4-dioxane at 100 °C (Scheme 3). Surprisingly, we did not observe the formation of the expected cross-coupling product in these conditions, and a significant amount of the methyl indoline-1-carboxylate derivative **9** was isolated.



Scheme 3. Reaction of compound **1a** in the Suzuki coupling conditions.

It is very likely, in these reaction conditions, that the intramolecular palladium-catalyzed *N*-arylation occurred faster than the transmetallation of the σ complex **I** with the boronic acid (Scheme 4).

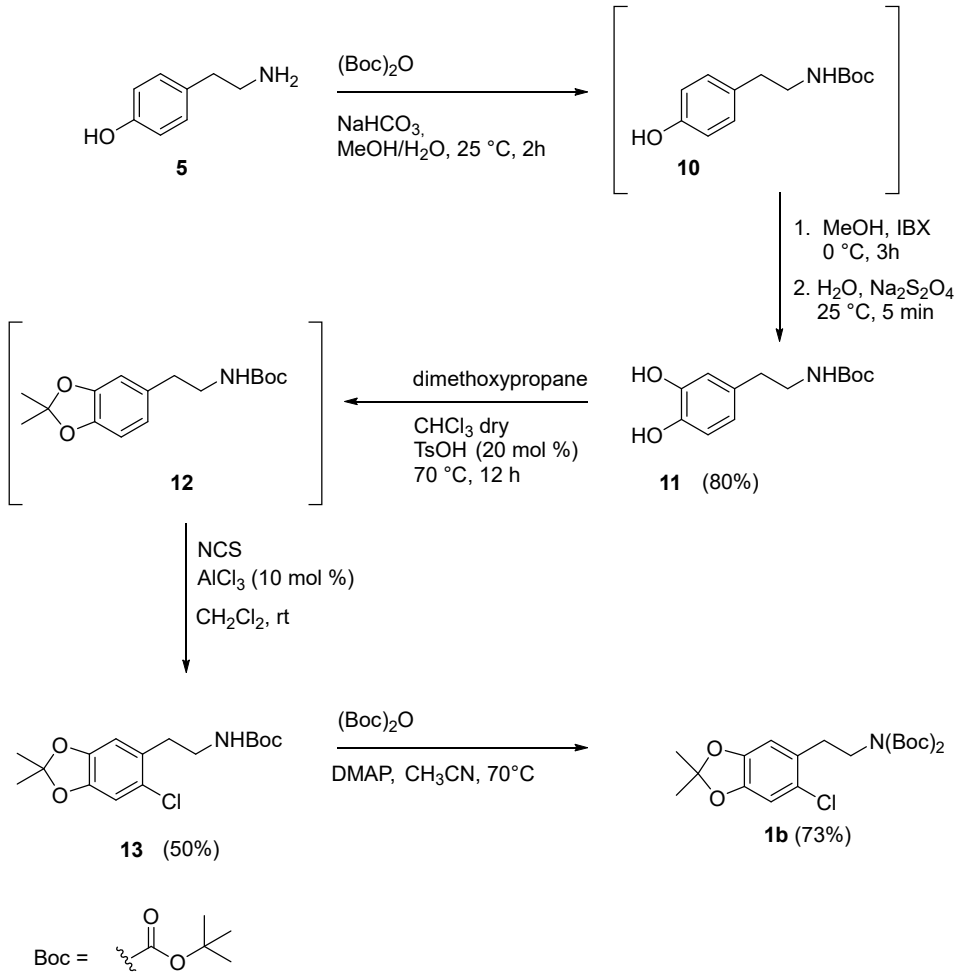


Scheme 4. Intramolecular palladium-catalyzed *N*-arylation of derivative **1a**.

Indeed, as reported in Scheme 4, in the basic reaction conditions, the σ-complex **I**, formed via oxidative addition of Pd(0) to **1a**, was deprotonated into the anionic form **II** and could rapidly give the six-membered palladacycle **III**. After a reductive elimination step, the catalytic active specie Pd(0) was regenerated and the final methyl indoline-1-carboxylate derivative **9** was provided.

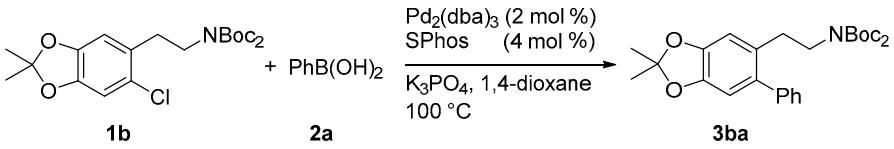
Therefore, we decided to start over by modifying the structure of the starting material **1.** We opted to introduce two protecting groups on the nitrogen atom, so that it would prevent the subsequent cyclization reaction with the σ-palladium complex and, according to the procedure outlined as follows in Scheme 5, we were able to synthesize the derivative **1b**.

We started with the amino group protection as carbamate, obtaining the derivative **10** from **5** using di-*tert*-butyl dicarbonate in MeOH/H_2O, in the presence of $NaHCO_3$ as the base. Then, the selective C3-hydroxylation with IBX was performed to achieve the *tert*-butyl (3,4-dihydroxyphenethyl)carbamate **11**, which was subjected to protection as acetonide, giving compound **12**. In the subsequent step, the regioselective chlorination was achieved to afford *tert*-butyl (2-(6-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate **13,** which was finally subjected to the last step for the further nitrogen protection for obtaining compound **1b**.



Scheme 5. Synthetic protocol for the synthesis of compound **1b**.

Once isolated, derivative **1b** underwent the Suzuki reaction in the same condition used for the previous attempt, and pleasingly we observed the formation of the desired cross-coupling product **3ba** in good yields (90%) (Scheme 6).



Scheme 6. Reaction of compound **1b** with phenylboronic acid in the Suzuki conditions.

Based on this encouraging result, the reaction was then extended to various aryl boronic acids **2**, to obtain a collection of new 6-arylated dopamine derivatives (Table 1).

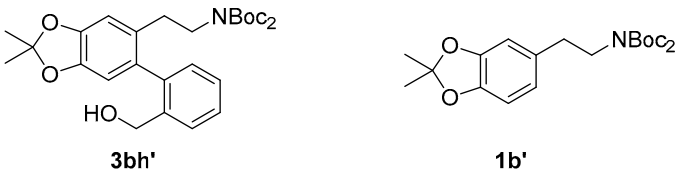
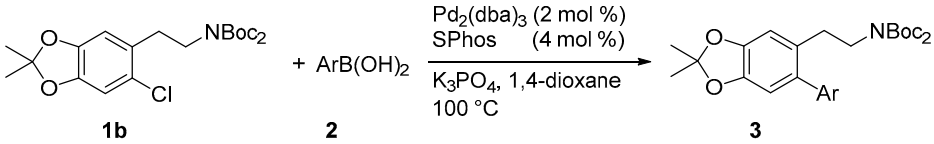


Figure 1. Structure of compounds **3bh'**, obtained through the Cannizzaro-type reaction on the (2-formylphenyl)boronic acid in the reaction conditions, and **1b'**, obtained via reduction of the starting material.

Table 1. Synthesis of 6-arylated dopamine derivatives via Suzuki cross-coupling [a].



1b **2** **3**

Entry	2	Ar	Time (h)	3	Yield (%) [b]
1	**2a**	Ph	3	**3ba**	90
2	**2b**	4-COMe-C_6H_4	9	**3bb**	68
3	**2c**	4-MeO-C_6H_4	1	**3bc**	87
4	**2d**	2-Me-C_6H_4	5	**3bd**	85
5	**2e**	4-F-3-Me-C_6H_3	4.5	**3be**	52
6	**2f**	4-Me-C_6H_4	21	**3bf**	67
7	**2g**	2,6-$(MeO)_2$-C_6H_3	7	**3bg**	-
8	**2h**	2-CHO-C_6H_4	7	**3bh**	10 [c]
9	**2i**	3-CHO-C_6H_4	7	**3bi**	67 [d]
10	**2j**	4-CHO-C_6H_4	24	**3bj**	40 [e]
11	**2k**	3-thiophene	7	**3bk**	-
12	**2l**	3-MeO_2C-C_6H_4	7	**3bl**	90
13	**2m**	4-MeO_2C-C_6H_4	31	**3bm**	60 [f]
14	**2n**	4-(C_6H_5)-C_6H_4	2.5	**3bn**	70
15	**2o**	1-naphthalene	4.5	**3bo**	60
16	**2p**	4-Cl-C_6H_4	9.5	**3bp**	traces

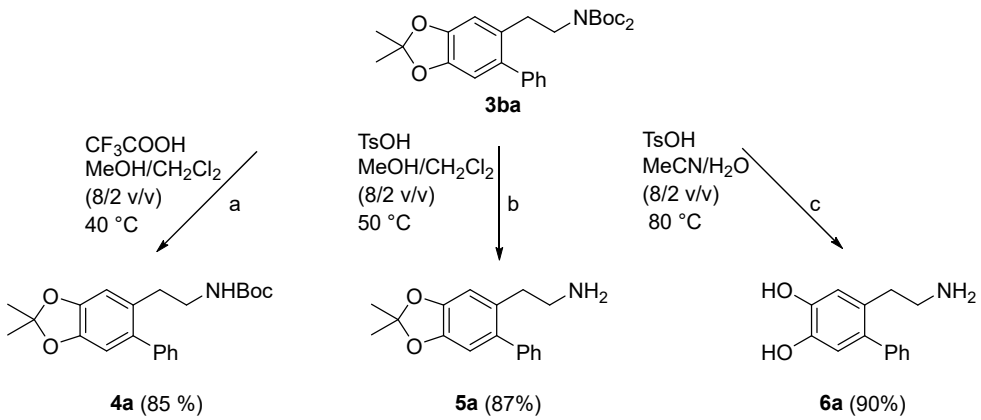
[a] Reactions were carried out on a 0.30 mmol scale using 1.5 equiv. of boronic acid **2**, 0.02 equiv. of Pd_2dba_3, 0.04 equiv. of Sphos, and 3.0 equiv. of anhydrous K_3PO_4 in 2.5 mL of 1,4 dioxane at 100 °C under nitrogen. [b] Yields are given for isolated compounds. [c] Compound **3bh'** (see Figure 1) was isolated in 51% yield. [d] 16% of **1b** recovered. [e] 11% of **1b** was recovered along with 21% of the corresponding reduction product **1b'** (see Figure 1). [f] 20% of **1b** recovered.

The preparative results showed that the aryl derivatives **3** could be easily obtained in good yield under the reported reaction conditions, resulting in them being compatible with the use of boronic acids bearing different functional groups, including aldehyde, ketone, esters, ethers, and fluorine (entries 1–6, 9–10, 12–15).

Steric hindrance at the *ortho* position of the boronic acid was tolerated to some extent. To this regard, it is worth noting that, while the reaction of **1b** with the *o*-tolyl boronic acid proceeded smoothly with good yield (entry 4), in the presence of the more hindered 2,6-dimethoxyphenylboronic acid, the formation of the final compound **3bg** was not observed in traces either, and the starting material **1b** was recovered in the almost quantitative yield (entry 7). On the other hand, the low yield observed using the 2-formylphenylboronic acid (entry 8) could be determined by the occurrence of a Cannizzaro-type reaction, helped by the *ortho* borate group that converts the 2-formylphenylboronic acid (**2h**) into 2-hydroxymethylphenylboronic acid. Indeed, in this case, along with the 10% of compound **3bh**, 51% of **3bh'** was isolated (Table 1 entry 8 and Figure 1) with a cross-coupling overall yield of 61%.

Only traces of **3bp** were obtained using the 4-chlorophenyl boronic acid **2p** (entry 15). This result was explained by the low selectivity of the cross-coupling reaction in the presence of the chlorinated boronic acid **2p**, which is consumed during the reaction, giving dimeric species as side products.

Afterward, having investigated the generality and the scope of the reaction, we turned our attention to the protecting groups' removal. As reported in Scheme 7, our studies demonstrated the possibility of selectively deprotecting the amino group and/or the catechol moiety, with the results of producing three kinds of dopamine derivatives **4a**, **5a**, and **6a**.



Scheme 7. Conditions for the selective protecting groups' removal.

Each protocol appeared simple and allowed for the isolation in a good yield of compounds of interest, both for their potential biological activity and for further functionalization reactions.

3. Materials and Methods

3.1. General Information

All the commercially available reagents, catalysts, bases, and solvents were used as purchased, without further purification. $Pd_2(dba)_3$ 97% (CAS: 51364-51-3) was obtained from Merck Science Life s.r.l. (Milan, Italy) Starting materials were purified on axially compressed columns, packed with SiO_2 (25–40 μm), connected to a solvent-delivery system and a refractive-index detector, eluting with *n*-hexane/EtOAc mixtures. Compounds **3ba-bo** were purified by flash chromatography, using SiO_2 as the stationary phase and eluting with an *n*-hexane/ethyl acetate mixture. When necessary, to obtain suitable NMR spectra, compounds **3** were further purified using a semi-preparative HPLC system (column: Nucleosil 100-7 Macherey Nagel, (Dueren, Germany) and eluted with an *n*-hexane/ethyl acetate mixture. ^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.6 MHz), were recorded with a Bruker Avance 400 spectrometer (Bruker Italia Srl, Milan, Italy). Splitting patterns are designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Copies of the NMR spectra are included in Supplementary Materials. HRMS were recorded in positive ion mode on a Thermo Fisher Orbitrap Exactive Mass Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Melting points were determined with a Büchi B-545 apparatus and are uncorrected.

3.2. Synthetic Procedures

3.2.1. Procedure for the Preparation of **7** or **11**

Step 1. To a solution of 4-(2-aminoethyl)phenol **5** (5.0 mmol, 0.885 g, 1.0 equiv) in methanol 5.0 mL and water 2.5 mL, NaHCO3 (5.0 mmol, 0.420 g, 1.0 equiv) was added. The resulting mixture was stirred at room temperature for 10 min before adding dimethyl carbonate (6.0 mmol, 0.541 g, 1.2 equiv.) or di-*tert*-butyl dicarbonate (6.0 mmol, 1.31 g, 1.2 equiv). The reaction was stirred for 2 h, monitoring the disappearance of the starting material by TLC. After this time, the reaction mixture was diluted with Et_2O, and washed with water and brine. Then, the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (4-hydroxyphenethyl)carbamate **6** or *tert*-butyl (4-hydroxyphenethyl)carbamate **10**, which were used without further purification in the next step.

Step 2. A round bottom balloon equipped with a magnetic stirring bar was charged with methyl (4-hydroxyphenethyl)carbamate **6** or *tert*-butyl (4-hydroxyphenethyl)carbamate **10** (4.2 mmol, 1.0 g) and MeOH (100 mL). The mixture was cooled at 0 °C before adding IBX (5.02 mmol, 1.4 g), and stirred for 3 h. After this time the reaction was allowed to warm at room temperature, a solution of $Na_2S_2O_4$ (5.02 mmol, 0.87 g in 50 mL of water) was

added, and the mixture was stirred for 5 min. Then, the mixture was concentrated under reduced pressure, the residue solubilized with AcOEt, and washed with a saturated solution of $NaHCO_3$ and with brine. Then, the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 75/25 (*v*/*v*) *n*-hexane/AcOEt mixture (R_f = 0.24) to afford 0.435 g of **7** (49% yield, over two steps from compound **5**) or 0.904 g of *tert*-butyl (3,4-dihydroxyphenethyl)carbamate **11** (85% yield). The spectral data for compound **7** were identical to those reported in the literature [20]. Compound **11** was used without further purification in the subsequent step.

3.2.2. Typical Procedure for the Preparation of **1a**

Step 1. Under a nitrogen atmosphere, a two-necked round bottom balloon equipped with a magnetic stirring bar was charged with methyl (3,4-dihydroxyphenethyl)carbamate **7** (3.5 mmol, 0.739 g), 2,2-dimethoxypropane (31.5 mmol, 3.3 g), TsOH (0.7 mmol, 0.120 g), and dry $CHCl_3$ (30 mL). The resulting mixture was warmed at 70 °C and stirred overnight at 70 °C. Then, the reaction mixture was cooled at room temperature, neutralized with a saturated solution of $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product methyl (2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**8**) was used without further purification in the subsequent step.

Step 2. To a solution of the crude **8** in dichloromethane 7.0 mL, *N*-chlorosuccinimide (3.5 mmol, 465.5 mg) and aluminum trichloride (0.35 mmol, 46.7 mg) were added. The resulting mixture was stirred at room temperature, monitoring by HPLC (Jasco Europe s.r.l., Cremella, Italy) (Column details: NUCLEODUR Sphinx RP (Macherey Nagel, Dueren, Germany; flow: 1 mL/min; mobile phase: CH_3CN/H_2O 9:1 *v*/*v*, Merck Science Life s.r.l., Milan, Italy). After 1 hour the disappearance of the starting material was detected, and the reaction mixture was concentrated at reduced pressure, diluted with Et_2O, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 90/10 (*v*/*v*) *n*-hexane/AcOEt mixture (R_f = 0.21) to obtain 214 mg (50% yield) of **1a**.

Compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.57 (s, 1H), 3.66 (s, 3H), 3.43–3.34 (m, 2H), 2.82 (t, *J* = 7.0 Hz, 2H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 147.0, 146.7, 128.7, 125.0, 119.2, 110.2, 109.8, 52.2, 41.1, 33.9, 25.9. HRMS (ESI Orbitrap) *m*/*z* 286.0843 $[M + H]^+$ (calcd for $C_{13}H_{15}ClNO_4^+$, 286.0841), 308.0659 $[M + Na]^+$ (calcd for $C_{13}H_{16}ClNNaO_4^+$, 308.0660).

3.2.3. Typical Procedure for the Preparation of **13**

Step 1. Under a nitrogen atmosphere, a two-necked round bottom balloon equipped with a magnetic stirring bar was charged with *tert*-butyl (3,4-dihydroxyphenethyl)carbamate **11** (3.5 mmol, 0.886 g), 2,2dimethoxypropane (31.5 mmol, 3.3 g), TsOH (0.7 mmol, 0.120 g), and dry $CHCl_3$ (30 mL). The resulting mixture was warmed at 70 °C and stirred overnight at 70 °C. Then, the reaction mixture was cooled at room temperature, neutralized with a saturated solution of $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain crude *tert*-butyl (2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate **12**, which was used without further purification in the subsequent step.

Step 2. To a solution of crude *tert*-butyl (2-(2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl) carbamate **12** in dichloromethane 7.0 mL, *N*-chlorosuccinimide (3.5 mmol, 465.5 mg) and aluminum trichloride (0.15 mmol, 20.0 mg) were added. The resulting mixture was stirred at room temperature, monitoring by HPLC (NUCLEODUR Sphinx RP columns, 5 mL, mobile phase CH_3CN/H_2O 9:1 *v*/*v*). After 1 hour the disappearance of the starting material was detected, and the reaction mixture was concentrated at reduced pressure, diluted with Et_2O, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered,

and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 90/10 (*v*/*v*) *n*-hexane/AcOEt mixture (R_f = 0.22) to obtain 443.1 mg (90% yield) of **13**.

tert-butyl (2-(6-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (**13**): yellow solid; m.p. 115–116 °C; R_f = 0.21 (*n*-hexane-EtOAc, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.58 (s, 1H), 3.35–3.29 (m, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.65 (s, 6H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 146.9, 146.6, 128.9, 125.2, 119.1, 110.5, 109.6, 82.3, 46.2, 33.2, 28.2, 25.9. HRMS (ESI Orbitrap) *m*/*z* 328.1313 $[M + H]^+$ (calcd for $C_{16}H_{23}ClNO_4^+$, 328.1310), 350.1132 $[M + Na]^+$ (calcd for $C_{16}H_{22}ClNNaO_4^+$, 350.1130).

3.2.4. Typical Procedure for the Preparation of **1b**

To a solution of *tert*-butyl (2-(6-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl) carbamate **13** (1.2 mmol, 400.0 mg) in CH_3CN 12.0 mL, DMAP (1.2 mmol, 146.6 mg) and di-*tert*-butyl dicarbonate (1.8 mmol, 392.7 mg) were added. The resulting mixture was stirred at room temperature for 5 min and then heated at 70 °C. The reaction was stirred for 4 hours, monitoring the disappearance of the starting material by TLC. After this time, the reaction mixture was cooled at room temperature, diluted with AcOEt, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 90/10 (*v*/*v*) *n*-hexane/AcOEt mixture (R_f = 0.24) to afford 374.5 mg (73% yield) of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate **1b**.

tert-butyl (*tert*-butoxycarbonyl)(2-(6-chloro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethyl) carbamate **1b**: m.p. 74.7–74.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.58 (s, 1H), 3.77 (t, *J* = 8.0 Hz, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 1.64 (s, 6H), 1.18 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 146.9, 146.6, 128.9, 125.2, 119.1, 110.5, 109.6, 82.3, 46.2, 33.2, 28.2, 25.9. HRMS (ESI Orbitrap) *m*/*z* 428.1833 $[M + H]^+$ (calcd for $C_{21}H_{31}ClNO_6^+$, 428.1834), 450.1656 $[M + Na]^+$ (calcd for $C_{21}H_{31}NNaO_6^+$, 450.1654).

3.2.5. Typical Procedure for the Preparation of **3ba**

A carousel reaction tube (Radleys Discovery, Radleys, Shire Hill, United Kingdom), equipped with a magnetic stirrer, was charged with Pd_2dba_3 (0.006 mmol, 5.5 mg,), Sphos (0.012 mmol, 4.9 mg) and 1,4-dioxane (2.0 mL). The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 10 min before adding **1b** (0.3 mmol, 128.4 mg, 1.0 equiv) phenyl boronic acid **2a** (0.45 mmol, 54.8 mg, 1.5 equiv), and anhydrous potassium triphosphate (191.0 mg, 0.9 mmoli, 3 equiv). The mixture was warmed at 100 °C and stirred under nitrogen until the disappearance of starting material. Then, the mixture was cooled at room temperature, diluted with AcOEt, and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (25–40 μm), eluting with a 95/5 (*v*/*v*) *n*-hexane/AcOEt mixture (R_f = 0.24) to obtain 126.7 mg (90% yield) of **3ba**.

tert-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl) ethyl)carbamate (**3ba**): m.p. 98.0–98.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 6.67 (s, 1H), 6.56 (s, 1H), 3.64 (t, *J* = 8.0 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H), 1.65 (s, 6H), 1.37 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 146.9, 145.8, 141.8, 135.2, 129.7, 129.1, 128.2, 126.7, 118.0, 110.1, 109.4, 82.1, 47.7, 32.2, 28.1, 26.0. HRMS (ESI Orbitrap) *m*/*z* 470.2535 $[M + H]^+$ (calcd for $C_{27}H_{36}NO_6^+$, 470.2537), 492.2353 $[M + Na]^+$ (calcd for $C_{27}H_{35}NNaO_6^+$, 492.2357).

3.2.6. Preparation of *tert*-butyl (2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**4a**)

tert-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl) ethyl)carbamate (**3ba**) (0.21 mmol, 100 mg) was dissolved in 5 mL of a solution of methanol/dichloromethane 8/2 *v*/*v*, and trifluoroacetic acid (0.42 mmol, 48 mg) was added. The reaction mixture was stirred at 40 °C for 12 h, monitoring the reaction by TLC, (Macherey

Nagel, Dueren, Germany) until the disappearance of starting material. The solvent was then evaporated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22) to obtain 66.0 mg (85% yield) of **4a**.

tert-butyl (2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**4a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.12 (m, 5H), 6.60 (s, 1H), 6.52 (s, 1H), 3.13–3.04 (m, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.62 (s, 6H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 147.0, 145.9, 141.8, 135.2, 129.6, 128.3, 126.9, 118.1, 110.2, 109.3, 79.2, 41.7, 33.2, 28.5, 26.1. HRMS (ESI Orbitrap) *m*/*z* 370.2015 $[M + H]^+$ (calcd for $C_{22}H_{28}NO_4^+$, 370.2013), 392.1833 $[M + Na]^+$ (calcd for $C_{22}H_{27}NNaO_4^+$, 392.1832).

3.2.7. Preparation of 2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethanamine (**5a**)

tert-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl) ethyl)carbamate (**3ba**) (0.21 mmol, 100 mg) was dissolved in 5 mL of a solution of methanol/dichloromethane 8/2 *v*/*v*, and *p*-toluenesulfonic acid monohydrate was added (0.42 mmol, 80 mg) was added. The reaction mixture was stirred at 50 °C for 24 h, monitoring the reaction by TLC, until the disappearance of starting material. The solvent was then evaporated under reduced pressure. The crude was diluted with ethyl acetate, and the organic layer was washed with sodium bicarbonate saturated solution and then with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was filtered on a pad of SiO_2 (25–40 μm), eluting with dichloromethane to obtain 49.2 mg (87% yield) of **5a**.

2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethanamine (**5a**). Waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 5H), 6.60 (s, 1H), 6.53 (s, 1H), 2.74–2.64 (m, 2H), 2.58 (t, *J* = 6.3 Hz, 2H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 145.7, 142.0, 135.2, 129.8, 129.6, 128.3, 126.8, 118.1, 110.2, 109.2, 43.5, 36.9, 26.0. HRMS (ESI Orbitrap) *m*/*z* 270.1491 $[M + H]^+$ (calcd for $C_{17}H_{20}NO_2^+$, 270.1489), 292.1309 $[M + Na]^+$ (calcd for $C_{17}H_{19}NNaO_2^+$, 292.1308).

3.2.8. Preparation of 6-(2-aminoethyl)-[1,1′-biphenyl]-3,4-diol (**6a**)

tert-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[*d*][1,3]dioxol-5-yl) ethyl)carbamate (**3ba**) (0.21 mmol, 100 mg) was dissolved in 5 mL of a solution of acetonitrile/water 8/2 *v*/*v*, and *p*-toluenesulfonic acid monohydrate was added (0.42 mmol, 80 mg) was added. The reaction mixture was stirred at 80 °C for 48 h, monitoring the reaction by TLC, until the disappearance of starting material. The solvent was then evaporated under reduced pressure. The crude was diluted with ethyl acetate, and the organic layer was washed with sodium bicarbonate saturated solution and then with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was filtered on a pad of celite (25–40 μm), eluting with dichloromethane to obtain 43.3 mg (90% yield) of **6a**.

6-(2-aminoethyl)-[1,1′-biphenyl]-3,4-diol (**6a**). Waxy solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.41–7.19 (m, 5H), 6.67 (s, 1H), 6.54 (s, 1H), 2.61 (t, *J* = 6.9 Hz, 2H), 2.50 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 144.6, 143.3, 141.6, 132.5, 129.2, 129.1, 128.1, 126.3, 117.2, 116.6, 42.6, 34.6. HRMS (ESI Orbitrap) *m*/*z* 230.1178 $[M + H]^+$ (calcd for $C_{14}H_{16}NO_2^+$, 230.1176), 252.0996 $[M + Na]^+$ (calcd for $C_{14}H_{15}NNaO_2^+$, 252.0995).

3.3. Characterization Data

Characterization Data of Compounds **9**, **1b′** and **3bb**–**bo**

Compound **9**. 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.54 (s, 1H), 4.12–3.67 (m, 5H), 3.00 (t, *J* = 8.6 Hz, 2H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 146.7, 143.1, 136.5, 122.1, 118.2, 105.0, 98.0, 52.5, 48.1, 27.7, 25.8. HRMS (ESI Orbitrap) *m*/*z* 250.1072 $[M + H]^+$ (calcd for $C_{13}H_{16}NO_4^+$, 250.1074), 272.0892 $[M + Na]^+$ (calcd for $C_{13}H_{15}NNaO_4^+$, 272.0893).

tert-butyl (2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**1b′**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60–6.49 (m, 3H), 3.69–3.61 (m, 2H), 2.73–2.65 (m, 2H), 1.58 (s, 6H), 1.43 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 147.6, 146.1, 132.1, 121.4, 117.8, 109.3, 108.2, 82.3, 48.3, 35.4, 28.2, 26.0. HRMS (ESI Orbitrap) *m*/*z* 252.1230 $[M + H]^+$ (calcd for $C_{13}H_{18}NO_4^+$, 252.1230), 274,1051 $[M + Na]^+$ (calcd for $C_{13}H_{17}NNaO_4^+$, 274.1050).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(4-acetylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bb**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.21); m.p. 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.94 (m, 2H), 7.43–7.35 (m, 2H), 6.70 (s, 1H), 6.57 (s, 1H), 3.66 (t, *J* = 8.0, 2H), 2.73 (t, *J* = 8.0, 2H), 2.61 (s, 3H), 1.68 (s, 6H), 1.39 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 152.4, 147.4, 146.9, 146.1, 135.6, 134.0, 130.0, 129.2, 128.4, 118.3, 109.7, 109.7, 82.2, 47.6, 32.2, 28.0, 26.7, 26.1. HRMS (ESI Orbitrap) *m*/*z* 512.2644 $[M + H]^+$ (calcd for $C_{29}H_{38}NO_7^+$, 512.2643), 534.2465 $[M + Na]^+$ (calcd for $C_{29}H_{37}NNaO_7^+$, 534.2462).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methoxyphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bc**). 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.21); m.p. 99.0–99.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.16 (m, 2H), 6.95–6.88 (m, 2H), 6.67 (s, 1H), 6.58 (s, 1H), 3.82 (s, 3H), 3.70–3.62 (m, 2H), 2.78–2.70 (m, 2H), 1.68 (s, 6H), 1.41 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 152.4, 146.7, 145.8, 134.8, 134.2, 130.7, 129.2, 117.9, 113.6, 110.2, 109.4, 82.0, 55.3, 47.7, 32.2, 28.1, 26.0. HRMS (ESI Orbitrap) *m*/*z* 500.2641 $[M + H]^+$ (calcd for $C_{28}H_{38}NO_7^+$, 500.2643), 522.2461 $[M + Na]^+$ (calcd for $C_{28}H_{37}NNaO_7^+$, 522.2462).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(2-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bd**). 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22); m.p. 78.6–79.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 4H), 6.68 (s, 1H), 6.58 (s, 1H), 3.66 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 1.68 (s, 6H), 1.40 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 146.8, 145.8, 138.9, 136.3, 135.2, 129.6, 129.2, 129.0, 117.9, 110.1, 109.4, 82.1, 47.8, 32.3, 28.1, 26.1, 21.20. HRMS (ESI Orbitrap) *m*/*z* 484.2696 $[M + H]^+$ (calcd for $C_{28}H_{38}NO_6^+$, 484.2694), 506.2514 $[M + Na]^+$ (calcd for $C_{28}H_{37}NNaO_6^+$, 506.2513).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(4-fluoro-3-methylphenyl)-2,2-dimethylbenzo[d]dioxol-5-yl)ethyl)carbamate (**3be**) 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.24); m.p. 108.0–109.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.07 (m, 1H), 7.05 (ddd, *J* = 7.6, 5.1, 2.1 Hz, 1H), 7.03–6.94 (m, 1H), 6.68 (s, 1H), 6.55 (s, 1H), 3.69–3.61 (m, 2H), 2.76–2.68 (m, 2H), 2.30 (d, *J* = 1.9 Hz, 3H), 1.68 (s, 6H), 1.41 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 152.5, 147.0, 145.9, 137.5, 134.4, 132.8, 129.2, 128.5, 124.6, 124.4, 118.1, 114.8, 114.6, 110.1, 109.5, 82.1, 47.8, 32.3, 28.1, 26.1, 14.7. HRMS (ESI Orbitrap) *m*/*z* 502.2601 $[M + H]^+$ (calcd for $C_{28}H_{37}FNO_6^+$, 502.2599), 506.2514 $[M + Na]^+$ (calcd for $C_{28}H_{36}FNNaO_6^+$, 524.2419).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bf**). 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.24); m.p. 83.2–84.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 4H), 6.68 (s, 1H), 6.58 (s, 1H), 3.65 (t, *J* = 8.0, 2H), 2.75 (t, *J* = 8.0, 2H), 2.37 (s, 3H), 1.68 (s, 6H), 1.40 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 146.8, 145.8, 138.9, 136.3, 135.2, 129.6, 129.2, 128.9, 118.0, 110.1, 109.4, 82.1, 47.8, 32.2, 28.1, 26.1, 21.2. HRMS (ESI Orbitrap) *m*/*z* 484.2694 $[M + H]^+$ (calcd for $C_{28}H_{38}NO_6^+$, 484.2694), 506.2512 $[M + Na]^+$ (calcd for $C_{28}H_{37}NNaO_6^+$, 506.2513).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(2-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bh**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.21); Waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 6.53 (s, 1H), 3.68–3.51 (m, 2H), 2.64 (dt, *J* = 14.3, 7.3 Hz, 1H), 2.52 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.70 (s, 6H), 1.38 (s, 18H). HRMS (ESI Orbitrap) *m*/*z* 498.2485 $[M + H]^+$ (calcd for $C_{28}H_{36}NO_7^+$, 498.2486), 520.2304 $[M + Na]^+$ (calcd for $C_{28}H_{35}NNaO_7^+$, 520.2306).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(2-hydroxymethylphenyl)-2,2-dimethylbenzo[d]d ioxol-5-yl)ethyl)carbamate (**3bh′**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.18); Waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.36 (dt, *J* = 7.2 Hz, *J* = 3.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.11 (dd, *J* = 7.2 Hz, *J* = 3.2 Hz, 1H), 6.71 (s, 1H), 6.47 (s, 1H), 4.50–4.42 (m, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.61–2.54 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H), 1.40 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 146.6, 145.5, 140.6, 139.1, 133.1, 129.9, 129.4, 127.5, 127.2, 126.7, 118.4, 109.5, 109.3, 81.8, 61.0, 55.3, 47.1, 32.1, 27.9, 26.1. HRMS (ESI Orbitrap) *m*/*z* 500.2645 $[M + H]^+$ (calcd for $C_{28}H_{38}NO_7^+$, 500.2643), 522.2466 $[M + Na]^+$ (calcd for $C_{28}H_{37}NNaO_7^+$, 522.2462).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(3-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bi**) 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22);. m.p. 132.7–133.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.90–7.83 (m, 2H), 7.64–7.53 (m, 2H), 6.74 (s, 1H), 6.62 (s, 1H), 3.74–3.66 (m, 2H), 2.78–2.70 (m, 2H), 1.72 (s, 6H), 1.42 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 152.5, 147.4, 146.2, 142.8, 136.6, 135.8, 133.7, 131.8, 129.3, 129.0, 127.5, 118.4, 109.9, 109.7, 82.2, 47.7, 32.2, 28.2, 26.1. HRMS (ESI Orbitrap) *m*/*z* 498.2487 $[M + H]^+$ (calcd for $C_{28}H_{36}NO_7^+$, 498.2486), 520.2306 $[M + Na]^+$ (calcd for $C_{28}H_{35}NNaO_7^+$, 520.2306).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(4-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bj**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22); m.p. 121.0–122.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 6.74 (s, 1H), 6.60 (s, 1H), 3.69 (t, *J* = 7.4 Hz, 2H), 2.76 (t, *J* = 7.4 Hz, 2H), 1.72 (s, 6H), 1.42 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0, 152.4, 148.4, 147.6, 146.1, 135.0, 133.8, 130.5, 129.7, 129.2, 118.4, 109.8, 109.6, 82.2, 47.6, 32.2, 28.1, 26.1. HRMS (ESI Orbitrap) *m*/*z* 498.2485 $[M + H]^+$ (calcd for $C_{28}H_{36}NO_7^+$, 498.2486), 520.2305 $[M + Na]^+$ (calcd for $C_{28}H_{35}NNaO_7^+$, 520.2306).

methyl 3-(6-(2-(bis(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bl**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.24); m.p. 148.8–150.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.93 (m, 2H), 7.54–7.38 (m, 2H), 6.70 (s, 1H), 6.58 (s, 1H), 3.91 (s, 3H), 3.64 (t, J = 8.0, 2H), 2.72 (t, J = 8.0, 2H), 1.69 (s, 6H), 1.38 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 152.4, 147.3, 146.0, 142.1, 134.3, 134.1, 130.8, 130.3, 129.3, 128.4, 128.1, 118.2, 110.02, 110.01, 109.62, 109.61, 82.1, 52.2, 47.7, 32.2, 28.1, 26.1. HRMS (ESI Orbitrap) *m*/*z* 528.2594 $[M + H]^+$ (calcd for $C_{29}H_{38}NO_8^+$, 528.2592), 550.2414 $[M + Na]^+$ (calcd for $C_{29}H_{37}NNaO_8^+$, 550.2411).

methyl 4-(6-(2-(bis(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bm**). 90/10 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.23); m.p. 140.0–141.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 6.56 (s, 1H), 3.92 (s, 3H), 3.65 (t, *J* = 7.4 Hz, 2H), 2.77–2.69 (m, 2H), 1.68 (s, 6H), 1.39 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 152.4, 147.4, 146.7, 146.0, 134.1, 129.8, 129.6, 129.2, 128.6, 118.3, 109.7, 109.7, 82.2, 52.2, 47.6, 32.2, 28.1, 26.0. HRMS (ESI Orbitrap) *m*/*z* 528.2593 $[M + H]^+$ (calcd for $C_{29}H_{38}NO_8^+$, 528.2592), 550.2412 $[M + Na]^+$ (calcd for $C_{29}H_{37}NNaO_8^+$, 550.2411).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-([1,1′-biphenyl]-4-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bn**). 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.22); m.p. 136.1–137.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.58 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.73 (s, 1H), 6.64 (s, 1H), 3.69 (t, *J* = 7.5 Hz, 1H), 2.82 (t, *J* = 6.4 Hz, 1H), 1.70 (s, 4H), 1.40 (s, 13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 147.0, 146.0, 141.1, 140.8, 139.7, 134.8, 130.2, 129.2, 128.9, 127.3, 127.2, 127.0, 118.1, 110.1, 109.5, 82.1, 47.9, 32.3, 28.1, 26.1. HRMS (ESI Orbitrap) *m*/*z* 546.2849 $[M + H]^+$ (calcd for $C_{33}H_{40}NO_6^+$, 546.2850), 568.2671 $[M + Na]^+$ (calcd for $C_{33}H_{39}NNaO_6^+$, 568.2670).

tert-butyl (*tert*-butoxycarbonyl)(2-(6-(naphtalen-1-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bo**). 95/5 (*v*/*v*) *n*-hexane/AcOEt (R_f = 0.21); m.p. 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 15.0, 8.1 Hz, 2H), 7.58–7.31 (m, 5H), 6.79 (s, 1H), 6.60 (s, 1H), 3.65–3.48 (m, 2H), 2.66–2.34 (m, 2H), 1.73 (d, *J* = 11.4 Hz, 6H), 1.30 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 147.2, 145.8, 139.3, 133.8, 132.8, 132.8, 130.5, 128.2, 127.6, 126.3, 126.1, 125.8, 125.5, 118.0, 110.7, 109.3, 82.0, 47.7, 32.7, 28.0, 26.1. HRMS (ESI Orbitrap) *m*/*z* 520.2696 $[M + H]^+$ (calcd for $C_{31}H_{38}NO_6^+$, 520.2694), 542.2512 $[M + Na]^+$ (calcd for $C_{31}H_{37}NNaO_6^+$, 542.2513).

4. Conclusions

A new protocol for the synthesis of 6-aryldopamine derivatives from the commercially available 4-(2-aminoethyl)phenol has been developed. The method employed is simple,

compatible with a variety of functional groups, and allows for the isolation of various dopamine derivatives protected both at the catechol and amino moieties. The selective protecting group removal has also been achieved: three different protocols have been developed for the deprotection of each function to obtain different derivatives with specific properties for further derivatization reactions.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal14070401/s1, Figure S1;^{1}H NMR of Methyl (2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate; Figure S2: ^{13}C NMR of Methyl (2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate; Figure S3: ^{1}H NMR of Methyl 2,2-dimethyl-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole-5-carboxylate (**9**); Figure S4: ^{13}C NMR of Methyl 2,2-dimethyl-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole-5-carboxylate (**9**); Figure S5: DEPT 135 NMR of methyl 2,2-dimethyl-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]indole-5-carboxylate (**9**); Figure S6: ^{1}H NMR of *tert*-butyl (2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**13**); Figure S7: ^{13}C NMR of *tert*-butyl (2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**13**); Figure S8: ^{1}H NMR of (*tert*-butoxycarbonyl)(2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**1b**); Figure S9: ^{13}C NMR of (*tert*-butoxycarbonyl)(2-(6-chloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**1b**); Figure S10: ^{1}H NMR of *tert*-butyl (2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**1b'**); Figure S11: 13C NMR of *tert*-butyl (2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**1b'**); Figure S12: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3ba**); Figure S13: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3ba**); Figure S14: ^{1} H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-acetylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bb**); Figure S15: ^{13} C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-acetylphenyl)-2,2-dimethylbenzo[d][1,3] dioxol-5-yl)ethyl)carbamate (**3bb**); Figure S16: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methoxyphenyl)-2,2-dimethylbenzo[d][1,3] dioxol-5-yl)ethyl)carbamate (**3bc**); Figure S17: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methoxyphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl) carbamate (**3bc**); Figure S18: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(2-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bd**); Figure S19: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(2-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bd**); Figure S20: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-fluoro-3-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3be**); Figure S21: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-fluoro-3-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3be**); Figure S22: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bf**); Figure S23: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-methylphenyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bf**); Figure S24: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(2-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bh**); Figure S25: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(2-hydroxymethylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bh'**); Figure S26: 13C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(2-hydroxymethylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bh'**); Figure S27: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(3-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bi**); Figure S28: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(3-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bi**); Figure S29: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bj**); Figure S30: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(4-formylphenyl)-2,2-dimethylbenzo[d][1,3]d ioxol-5-yl)ethyl)carbamate (**3bj**); Figure S31: ^{1}H NMR of methyl 3-(6-(2-(bis(*tert*-butoxycarbonyl)amino) ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bl**); Figure S32: ^{13}C NMR of methyl 3-(6-(2-(bis(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bl**); Figure S33: ^{1}H NMR of methyl 4-(6-(2-(bis(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bm**); Figure S34: ^{13}C NMR of methyl 4-(6-(2-(bis(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)benzoate (**3bm**); Figure S35: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-([1,1′-biphenyl]-4-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bn**); Figure S36: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-([1,1′-biphenyl]-4-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bn**); Figure S37: ^{1}H NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(naphtalen-1-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bo**); Figure S38: ^{13}C NMR of *tert*-butyl (*tert*-butoxycarbonyl)(2-(6-(naphtalen-1-yl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**3bo**); Figure S39: ^{1}H NMR of *tert*-butyl (2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**4a**);

Figure S40: ^{13}C NMR of *tert*-butyl (2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethyl)carbamate (**4a**); Figure S41: ^{1}H NMR of 2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethanamine (**5a**); Figure S42: ^{13}C NMR of 2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-yl)ethanamine (**5a**); Figure S43: ^{1}H NMR of 6-(2-aminoethyl)-[1,1′-biphenyl]-3,4-diol (6a); Figure S44: ^{13}C NMR of 6-(2-aminoethyl)-[1,1′-biphenyl]-3,4-diol (**6a**).

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