Chemoselective Zinc/HCl Reduction of Halogenated β-Nitrostyrenes: Synthesis of Halogenated Dopamine Analogues

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Chemoselective Zinc/HCl Reduction of Halogenated β-Nitrostyrenes: Synthesis of Halogenated Dopamine Analogues

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Abstract: A detailed account regarding the synthesis of 2- and 5-halogenated dopamine is given. The key step is a chemoselective reduction of a nitrostyrene by Zn/HCl at 0 °C. These conditions represent a simple, low-cost alternative to reduction by water-sensitive hydride donors and two-step procedures. Under these conditions, aryl fluoride, chloride, and bromide groups are stable. However, iodine undergoes significant reductive dehalogenation.

Key words: reduction, nitroalkene, zinc, dopamine, dehalogenation

An objective of our research is to explore the capacity of preexisting biosynthetic pathways to transform analogues of dopamine (**1i**, X^1 = H, X^2 = H), a metabolic precursor to at least 2500 benzylisoquinoline alkaloids (BIA) produced by 20% of all flowering plants,[1] into novel alkaloids. We have chosen to prepare halogenated analogues of increasing size to potentially identify sterically restrictive bottlenecks in the active sites of biosynthetic enzymes. Halogens that are accepted by multistep biosynthetic pathways are demonstrated to effectively introduce a selective unnatural functional group into a natural product for postbiosynthetic reactions such as cross-coupling.[2] For example, a brominated analogue of the BIA berberine was prepared by total synthesis, and Suzuki coupling was used to generate a library of compounds with greater potency against multidrug resistant bacteria than natural berberine.[3] Potentially, brominated berberine could be prepared by biosynthesis from brominated dopamine.

Here we describe an account of our efforts to develop a general synthetic strategy for the low-cost production of 2- and 5-halogenated analogues of dopamine (**1a**–**h**, Table 1). A previous report has described the synthesis of **5c** and **5e** via halogenation, sodium borohydride reduction of the aldehyde, substitution of the alcohol for chlorine, substitution with nitrile using cyanide ion, followed by borane reduction.[4] We sought to develop a shorter, low-cost, general synthetic approach employing fewer steps for all 2- and 5-halogenated dopamine analogues. An account of optimization of each step is described. Gratifyingly, no steps in our scheme require column chromatography and most of the products are obtained in good yields (Table 1). Thus, dopamine analogues produced by this process are suitable for large-scale production.

In particular, we highlight the utility of using Zn/HCl to chemoselectively reduce the alkene and nitro groups of halogenated nitrostyrenes to primary amines with no side products in good yield and without the simultaneous reduction of aryl chloride or bromide groups.

Vanillin and isovanillin were selected as common starting compounds due to their low cost and well-established conditions for selective monohalogenation in good yields (see compounds **2c**–**f** and **2h** in Table 1 and the Supporting Information).[5] *m*-Fluoroanisole was easily converted into 5-fluorovanillin (**2b**) following a known procedure.[6] However, we found that the equivalent preparation of 2-fluoroisovanillin (**2a**)[6] in fact yields an inseparable 1:1 mixture of regioisomers with a melting point identical to the reported melting point of supposedly pure 2-fluoroisovanillin.[7] As a result, we found it more economical to prepare 2-fluorodopamine (**1a**) via an alternative scheme.[8]

We initially attempted to complete the synthesis of halogenated dopamine analogues **1a**–**h** without protection of the phenol functionalities. However, the high aqueous solubility of the corresponding phenolic phenethylamines after reduction (vide infra) prevented their isolation from the reaction mixture in good yield. Thus, phenols **2a**–**h** were protected as methyl ethers **3b**–**h** by reaction with methyl iodide in a two-phase system of CH_2Cl_2 and aqueous hydroxide with a quaternary ammonium phase-transfer catalyst (Table 1).[9] To reduce the cost of this convenient procedure, we developed a variation to recover the relatively expensive phase-transfer catalyst for recycling (see the Supporting Information).

All nitrostyrenes **3c**–**f** were easily prepared by nitroaldol condensation of the aromatic aldehydes with nitromethane with ammonium acetate catalyst and acetic acid.[10,11] Although we did not ultimately use the nitrostyrene products of phenolic aldehydes **2b**–**h** (vide supra), we wish to note that these compounds generate significant side products when heated with acetic acid. Two nitroaldol reaction conditions that minimize side-product formation with phenols, reflux without acetic acid and sonication at room temperature,[12] yielded 30–60% conversion (as monitored by HPLC). We eventually achieved high-yield, large-scale conversion of phenolic aldehydes by heating at 130–150 °C in sealed high-pressure glassware without acetic acid (see discussion and results in Supporting Informa-

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tion). This procedure appears to be generally useful for reaction of low reactivity aldehydes with sensitive phenol moieties.

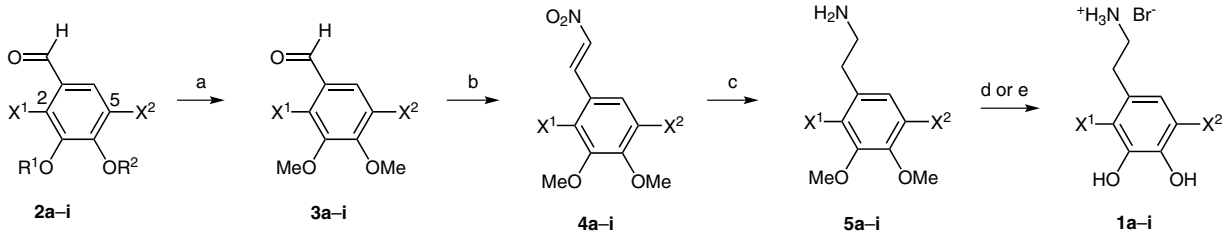
Although the alkene and nitro groups of nitrostyrenes may be reduced in separate steps, we sought a simple, high-yield, low-cost reaction that would selectively reduce both groups in a single step without reducing the C_{sp2}–halogen bond.

Hydride donors are commonly employed to reduce nitrostyrenes and nitroalkene groups in general. By far, the most commonly employed reagent is $LiAlH_4$ in dry THF or diethyl ether.[13] However, it is often observed that this reducing agent leads to partial or complete reduction of aryl halides.[14] To avoid this side reaction, a single equivalent of Lewis or Brønsted acid may be added to generate in situ aluminum hydride (AlH_3), a more electrophilic reducing agent.[15] This approach has been used previously in a synthesis of 2-chlorodopamine (**1c**).[11] Similarly, borohydride reducing agents avoid dehalogenation. Borane in dry THF has been reported to reduce nitrostyrenes with catalytic $NaBH_4$ or when generated in situ from $NaBH_4$ with $BF_3{\cdot}OEt_2$.[16] Additionally, $LiBH_4$–TMSCl in dry THF has also been reported to cleanly convert nitrostyrenes into amines. We chose to avoid hydride-donating reagents due to the costs associated with the reagents themselves and necessity for rigorously dry reaction conditions.

Catalytic hydrogenation with either 10% palladium[17] or platinum on carbon in the presence of HCl successfully reduced fluorinated nitrostyrene **4b**, but resulted in partial or complete dehalogenation of all other halogens (**4c**–**f**, and **4h**).[7] Moreover, significant poisoning of the expensive metal catalysts necessitated their use in high proportions and precluded catalyst recycling.

Metal reductions have also been applied to the one-step reduction of nitrovinyl groups. Conversion in poor to moderate yield has been reported with Fe/HCl (63–72%),[18] Sn/AcOH (59–60%),[19] $SmI_2/H_2O/i\text{-}PrNH_2$ (22–60%),[20] and Zn/AcOH (24%).[21] Recently, Zn/HCl reduction was utilized in the preparation of phenylethylamines, but scant experimental details and no yields were provided.[22] Additionally, amalgamated zinc with mercuric chloride in HCl has been reported to afford excellent yields (85–100%).[23] Based on this latter precedent, we explored zinc reduction for this transformation of compounds **4** into **5**.

Table 1 General Synthetic Scheme



Entry		R^1	R^2	X^1	X^2	Yield of **3** (%)[f]	Yield of **4** (%)[f]	Conv. to **5** (%)[g,h]	Conv. to **1** (%)[g,h]
1	**2a**	–	–	F	H	**3a** –[i]	**4a** –[i]	**5a** –[i]	**1a** >99 (90)[d]
2	**2b**	Me	H	H	F	**3b** 97	**4b** 98	**5b** >99 (83)	**1b** >99 (91)[d]
3	**2c**	H	Me	Cl	H	**3c** 92	**4c** 99	**5c** >99 (73)	**1c** >99 (88.2)[e]
4	**2d**	Me	H	H	Cl	**3d** 96	**4d** 92	**5d** >99 (87)	**1d** >99 (98.9)[e]
5	**2e**	H	Me	Br	H	**3e** 96	**4e** 99	**5e** >99 (77)	**1e** >99 (94.8)[e]
6	**2f**	Me	H	H	Br	**3f** 93	**4f** 93	**5f** >99 (83)	**1f** >99 (90.8)[e]
7	**2g**	H	Me	I	H	**3g** 90	**4g** –	**5g** –	**1g** >99 (99.5)[e]
8	**2h**	Me	H	H	I	**3h** 97	**4h** 83	**5h** 0[j]	**1h** >99 (98)[e]
9	**2i**	–	–	H	H	**3i** –	**4i** 98	**5i** >99 (85)	–

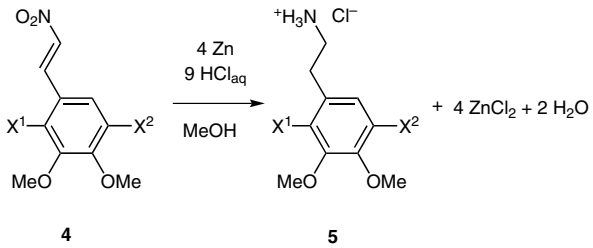
[a] Phenol protection: MeI, tetrabutylammonium hydrogensulfate, and NaOH in CH_2Cl_2 and H_2O for 4 h at 25 °C.
[b] Nitroaldol condensation: $MeNO_2$ and NH_4OAc in AcOH for 4 h at 90–100 °C.
[c] Reduction: Zn dust, HCl in MeOH for 4–6 h at 0 °C.
[d] Phenol deprotection method A: reflux in 37% HBr for 1 h.
[e] Phenol deprotection method B: BBr_3 in CH_2Cl_2 from 0–23 °C.
[f] Isolated yield.
[g] Estimated from relative HPLC peak area at 225 nm for the product and starting material peaks just before quench.
[h] Isolated yield in parentheses.
[i] It was more economical to prepare compound **5a** by the route of Ladd and Weinstock (1981).
[j] Dehalogenation was complete. Isolation of product was not attempted.

Due to the lack of prior literature precedent, it was not clear if zinc would afford a high yield of product without the addition of mercury or if it would be compatible with aryl halide moieties. When zinc dust, 37% HCl, and **4i** were stirred at room temperature in methanol, we observed multiple products by HPLC. Side-product formation was reduced by slow alternating addition of all three reagents with solid zinc in excess. Side-product formation was effectively eliminated when the temperature was maintained at ≤0 °C. In general, the disappearance of nitrostyrene was relatively rapid. The characteristic yellow color disappeared within 30 minutes of complete reactant addition after which one major intermediate dominated (Supporting Information, Figure S1 illustrates this intermediate in **4f** reduction). Reverse-phase HPLC indicated that the polarity of this intermediate was similar to the final product and was likely to be the hydroxylamine. Conversion of this intermediate into phenethylamine **5i** was the slowest step of this multistep reduction reaction, requiring three to four hours.

This multistep zinc reduction is somewhat sensitive to the concentrations of reactants and intermediates. However, we have found that this reaction is reliable when all reagents are added in slow alternating portions with adequate cooling. Besides controlling the reaction temperature, slow, continuous addition of zinc dust accelerated the disappearance of the nitrostyrenes and lower polarity intermediates (as monitored by HPLC) indicating that one or more critical steps require an unoxidized zinc surface. The reaction is also sensitive to high HCl concentration. Either short bursts of rapid HCl addition or inadequate stirring during HCl addition often led to the significant accumulation of an uncharacterized side product with an HPLC retention time similar to the nitrostyrene (see Supporting Information, Figure S2). Additionally, we found that substitution of HCl with glacial acetic acid resulted in three major and numerous minor side products, suggesting that this acid should be avoided.

Scheme 1 illustrates the expected stoichiometry for eight-electron Zn/HCl reduction of a nitrostyrene. Due to the additional loss of zinc and acid as volatile hydrogen gas, we found it necessary to at least double the equivalents of zinc and HCl.

Zinc is well-known as a selective reagent for the reductive dehalogenation of aryl halides in both acidic and basic conditions at or above 20 °C.[24] The relative rates for dehalogenation by zinc are reported as I > Br > Cl. Accordingly, at 10–15 °C, we observed <5% dechlorination for **4c** and **4d**, nearly 50% debromination for **4e** and **4f**, and complete deiodination for **4h** by HPLC. However, below 4 °C, aryl chloride and bromide moieties were stable under our conditions (see Supporting Information, Figure S1). We attempted to minimize the loss of the aryl iodide moiety by further lowering the temperature. At –10 °C, dehalogenation of iodine was still rapid enough that only dehalogenated species were observed by HPLC after 90 minutes (see Supporting Information, Figure S3). Moreover, this temperature also failed to generate phenethylamine products. Instead, the major species was a dehalogenated reduction intermediate (see Supporting Information, Figure S3). Thus, iodinated products **5g** and **5h** were not conveniently accessible by zinc reduction and were ultimately prepared following an alternative scheme[4] (see Supporting Information, Methods).



Scheme 1

Although Zn/HCl reduction cleanly generated halogenated phenethylamines, care was required for product isolation without subsequent decomposition. Even after filtration to remove solid zinc, compounds **5c**–**f** were still prone to decomposition if the soluble zinc salts were not completely removed. When the reaction was made basic by slow addition of base (either saturated aqueous NaOH or NH_4OH), extracted into organic solvent (either CH_2Cl_2, $CHCl_3$, or Et_2O), and the residual water removed with drying agents ($MgSO_4$, $NaSO_4$, or K_2CO_3), significant amounts of inorganic solids were still recovered after solvent evaporation. The presence of these salts led to dehalogenation and decomposition of **5c**–**f** within hours, even when stored at –80 °C. Moreover, elution of these organic extracts through either Celite, silica gel, or alumina lead to rapid decomposition of **5c**–**f** into numerous unidentified products and should be avoided. To minimize the extraction of salts, we avoided the formation of an aqueous phase by precipitating zinc hydroxide with saturated methanolic NaOH and washed the product amines from the zinc hydroxide solids with $CHCl_3$. Stable phenethylamine products were recovered from this organic extract in good yields (Table 1).

After reduction to phenethylamines, electrophilic demethylation by BBr_3 in dichloromethane at room temperature produced the target halogenated dopamine analogues as solids in good yield (Table 1).

In summary, we have described a short route to the synthesis of a variety of halogenated analogues of dopamine with relatively low-cost reagents and high-yield steps that do not require column chromatography. The electronic properties of low-cost vanillin and isovanillin direct halogenation to the 5- and 2-positions, respectively. High-yield methylation facilitates purification of the reduced amines by simple extraction and avoids costly chromatographic purification.

After nitroaldol condensation, fluorinated, chlorinated, and brominated nitrostyrenes were cleanly converted into

phenethylamines by Zn/HCl reduction at 0 °C without reduction of the aryl halide bond. The stability of aryl bromide moieties via kinetic control at temperatures below 0 °C may extend to other zinc reduction reactions. Single-step zinc reduction of nitrostyrenes has rarely been used in the literature and with variable results. The reaction is significantly lower cost, simpler than common alternative reduction procedures, and generates no side products. Losses during isolation are the only limit on the yield. It is our experience that this reaction is sensitive to the reaction conditions, but we have described a reliable procedure that should be widely applicable to related compounds.

General Procedure for Zn/HCl Reduction of Nitrostyrenes

For every 1.0 mmol of nitrostyrene, 2 mL of MeOH, 800 mg of zinc dust (12 mmol), and 2 mL of 37% HCl (24 mmol) were used. MeOH was vigorously stirred in an ice bath maintained <0 °C (ice/NaCl or freezer-chilled commercial antifreeze). HCl, zinc dust, and nitrostyrene were slowly added over the course of 30 min in alternating small portions taking care that the temperature did not rise above 0 °C. For large-scale reactions (>25 mmol), HCl was added continuously by syringe pump. The reaction is typically complete 4–6 h after the yellow color has disappeared. The reaction may stir for as long as 16 h in a 4 °C refrigerator without significant formation of side products. Once complete, the excess solid zinc was removed by filtration. The solution was made basic by dropwise addition of sat. NaOH in MeOH, while maintaining the temperature below 5 °C, until the pH was greater than 11 by pH paper. Next, 10 mL of $CHCl_3$ was added (per mmol of reactant). Solid anhydrous $MgSO_4$ was added to dry the organic layer. The organic extract was decanted. The paste was extracted and decanted two more times with $CHCl_3$ and filtered through filter paper. Solvent was removed by evaporation in vacuo to yield phenethylamine as an amber oil. In cases when an oil was not obtained, the product was dissolved in minimal $CHCl_3$ and the remaining inorganic salts were precipitated by addition of Et_2O. An oil was obtained after filtration and evaporation.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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SUPPORTING INFORMATION

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Supporting Material

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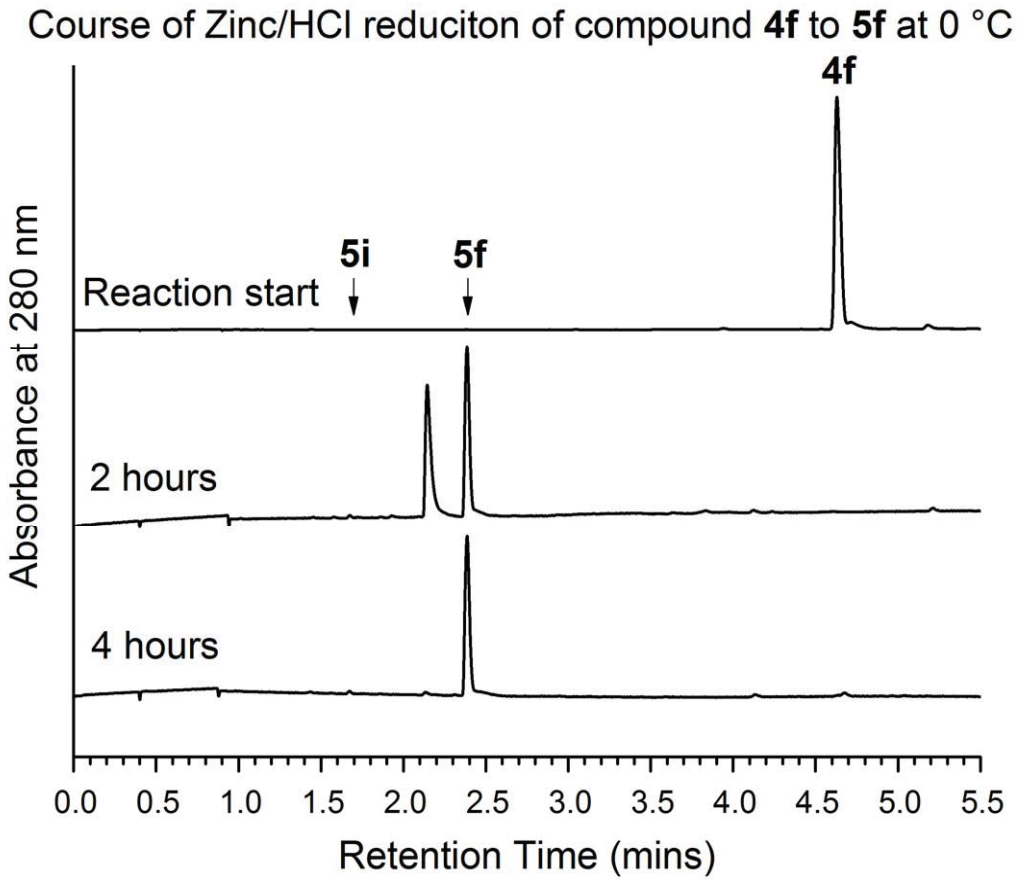


Figure S1. Zn/HCl reduction of a halogenated nitrostyrene **4f** proceeds cleanly to phenethylamine **5f** as monitored by HPLC-UV. Of the chlorinated and brominated nitrostyrene compounds **4c – 4f**, the 5-brominated compound **4f** was the most prone to dehalogenation above 4 °C. However, below this temperature, less than 1% reduction of the C_{sp2}-Br bond was observed (compound **5i**). The retention time of **5i** was assigned based on an authentic standard. HPLC conditions are described in the General Information section of the Supporting Information.

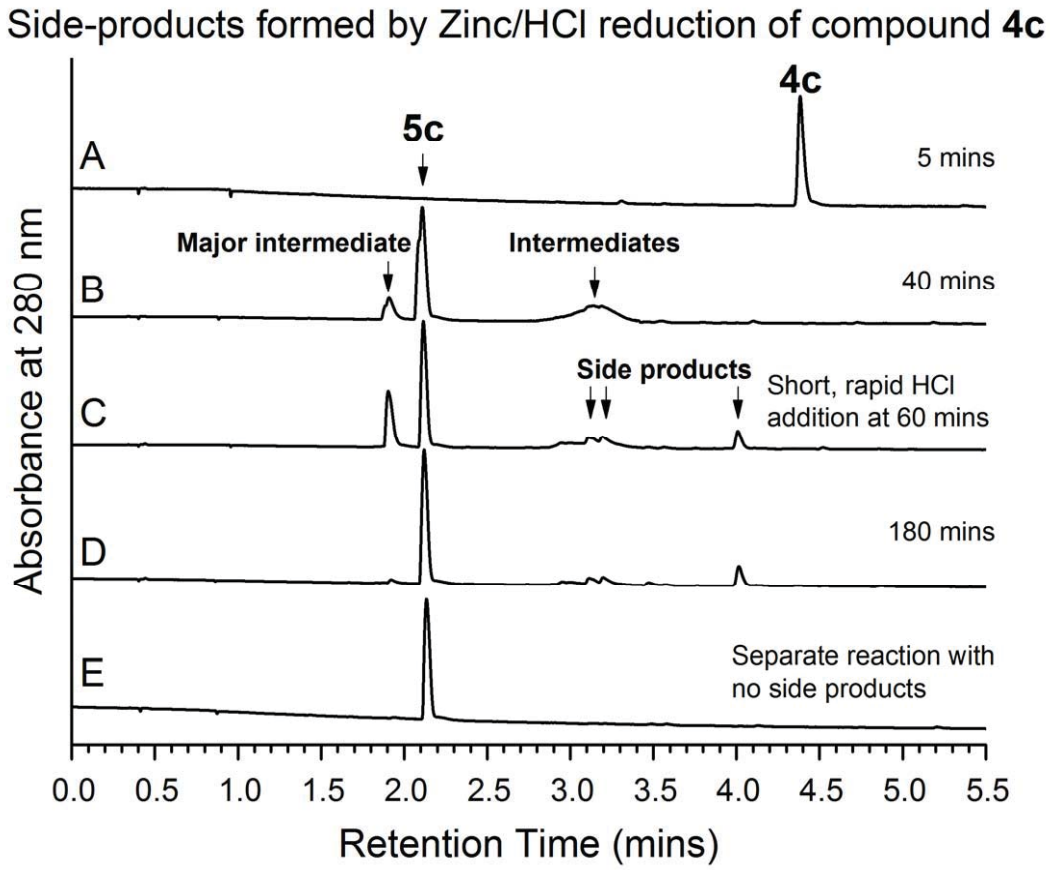


Figure S2. Reverse-phase HPLC chromatograms illustrating typical side-products generated by Zn/HCl reduction. Reaction conditions: 25 mmol (6 g) of nitrostyrene **4c**, 20 g of zinc dust, and 50 mL of 37% HCl at -5 to 0 °C. Solid reagents were added in alternating portions over one hour while HCl was added continuously by syringe pump over the same period**.** (A) Five minutes after the initial addition of **4c** and zinc dust. (B) At 40 minutes, approximately one half of the solid reagents and HCl had been added. (C) At 60 minutes, a short burst of 1-2 mL of cold concentrated HCl was added after the last addition of solid reagents. HPLC chromatography revealed that one major and several minor side products had formed immediately after the HCl addition. (D) Once the reaction had completed, the side products persisted and were present after extraction. (E) A separate reduction of **4c** with full adherence to the procedure. HPLC conditions are described in the General Information section of the Supporting Information.

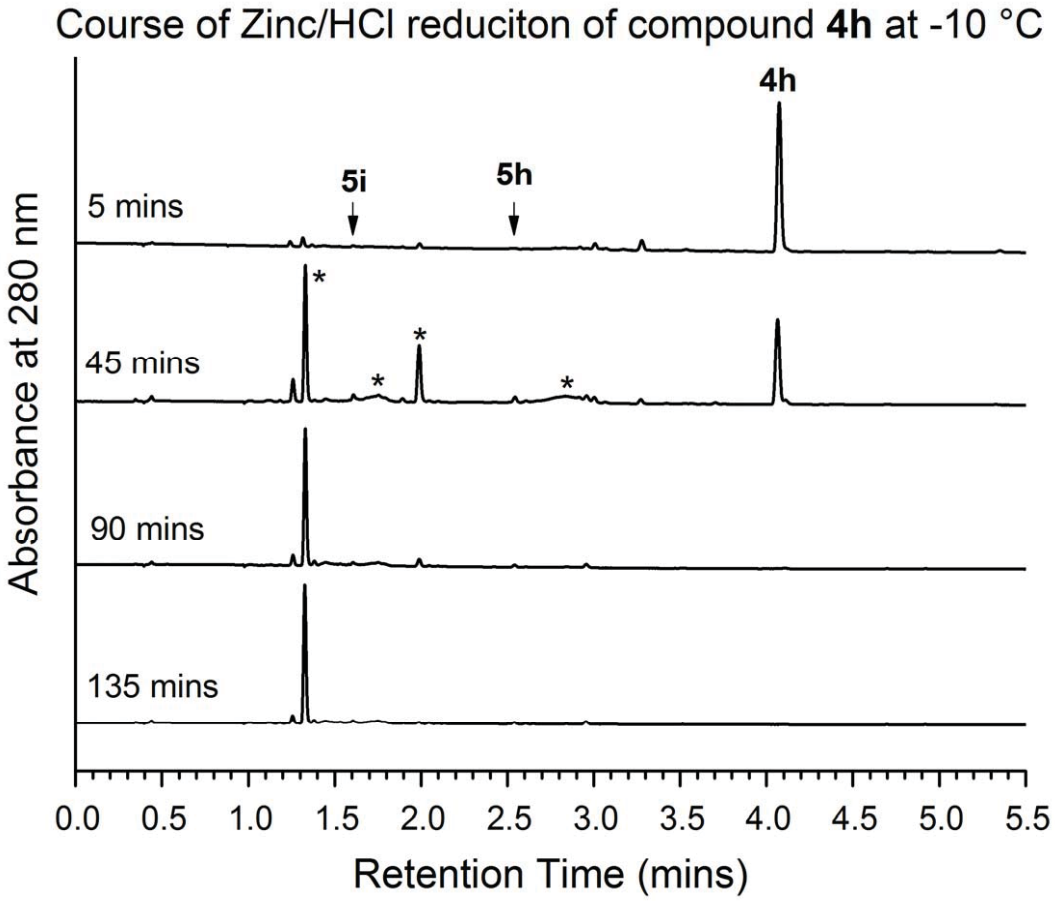


Figure S3. At -10 °C, Zn/HCl reduction of iodinated nitrostyrene **4h** proceeds with complete dehalogenation as monitored by HPLC-UV. The rate of iodine reduction was relatively rapid. Neither phenethylamine products **5h** or **5i** were observed. Instead, a dehalogenated intermediate of **5i**, was the exclusive product (retention time of 1.3 minutes). The retention times of **5h** and **5i** were assigned from authentic standards. Reduction intermediates that we have been previously observed in Zn/HCl reduction are indicated with an asterisk (*). HPLC conditions are described in the General Information section of the Supporting Information.

General information

All reagents were purchased from commercial suppliers at the highest available purity and used without further purification. Milli-Q water refers to water purified to resistivity of 18.2 MΩ·cm (25 °C) using an EMD Millipore Ultrapure Milli-Q reverse osmosis water purification system outfitted with ion exchange and organic removal cartridge filters.

All reactions involving air- or water-sensitive reagents were performed using flame dried glassware under an inert atmosphere of nitrogen using standard Schlenk line techniques.

Reactions were monitored using high pressure liquid chromatography (HPLC) on a Waters Acquity Ultra Performance Liquid Chromatography instrument with a photodiode array detector. The solvent and gradient conditions used for HPLC analysis were as follows: Acquity UPLC BEH C18 column (1.7 µm, 2.1x50 mm); 0.4 mL/min; 0-70% acetonitrile in 0.1 % TFA over 4.75 minutes, holding at 70% acetonitrile for 0.25 minutes. Percent conversion of reactions by HPLC was estimated from the HPLC peak areas measured at 225 nm.

All details of UV spectra are listed from most to least intense wavelength maximum.

Gas Chromatography Mass Spectroscopy (GC-MS) analysis of products was performed using a Hewlett Packard HP6890 Gas Chromatography System with an Agilent Technologies 5975 inert mass selective detector.

High resolution mass data (HRMS) were obtained on a Waters SYNAPT G1 High Definition Mass Spectrometer using an ESI ionization source and

^{1}H-, ^{19}F-, ^{13}C[^{1}H]- NMR spectroscopy were performed using a Bruker Avance 300 MHz NMR spectrometer at 300 MHz, 282, and 75 MHz respectively. All ^{1}H-NMR chemical shifts were referenced to a tetramethylsilane (TMS) internal standard set to 0.00 ppm. All ^{19}F{^{1}H}-NMR spectra were externally referenced to a sample of α,α,α-trifluorotoluene 0.05% in benzene-d_6 (Isotec distributed by Aldrich) with the ^{19}F singlet set to -63.72 ppm. For ^{13}C-NMR, the residual solvent peaks were used to reference the spectra as follows: in methanol-d_4 was referenced as 49.00 ppm and DMSO-d_6 was referenced as 39.52 ppm. Processing and spectra handling was performed using Topspin 1.3 program suite (Bruker Biospin GmbH, Rheinstetten, Germany).

Estimation of purity of halogenated dopamine analogs

To ensure accurate concentration estimates of halogenated dopamine analogs in subsequent enzyme assays and for isolated yields, the purity of each compound was estimated by quantitative ^{1}H-NMR as follows.

Certified quantitative NMR grade maleic acid (Fluka cat no. 92816) was used as an internal reference. The certified fractional purity was used as P_{std} in the analysis below.

To optimize the relaxation delay, T_1 relaxation time was measured using the inversion recovery method,[1] employing 16 different tau delays ranging from 0.01 to 30 sec, a repetition delay of 60 sec, 8 scans, 16K complex acquisition data points, 8K processing data points, and 1.0 Hz line broadening factor. Peak areas were fit to a three-parameter non-linear equation[2] using Origin 9.0 (OriginLab Corp.). At approximately 0.3 M in DMSO-d_6, the observed T_1 relaxation times for protons in dopamine HCl were 0.9 – 1.1 sec for aromatic protons and 0.3 sec for methylene protons. The T_1 relaxation for maleic acid in DMSO-d_6 was 2.4 sec. This value matched reported literature[3].

Each sample was prepared using an exact mass of dopamine analog (20 – 30 mg) and maleic acid (5 – 10 mg). The masses were taken as the mean of triplicate measurements. The mixture was dissolved in approximately 500 µL of DMSO-d_6, mixed by vortex, sonicated, and transferred into an NMR tube for analysis.

Following recommended guidelines for quantitative NMR analysis[4], ^{1}H-NMR spectra were collected with a calibrated 90° pulse and 30 sec relaxation delay, 12.5 times the longest T_1 (the maleic acid proton at 6.03 ppm).

The area of the signals in a ^{1}H-NMR spectrum acquired under these conditions is directly proportional to the number of protons present in the active volume of the sample[4]. Thus, the equation below is used to calculate the fractional purity.

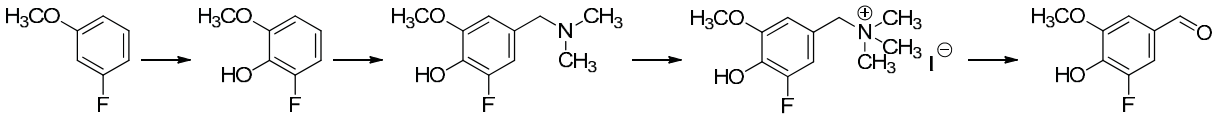
$$P_x = P_{std} \times \frac{n_{std}}{n_x} \times \frac{MW_x}{MW_{std}} \times \frac{M_{std}}{M_x} \times \frac{A_x}{A_{std}}$$

The subscript *std* represents data from the maleic acid standard and the subscript *x* represents data from the sample. The remaining terms are defined as follows: P is the fractional purity (mass/mass), n is the number of degenerate protons in the selected signal (n = 2 for maleic acid protons at 6.03 ppm and n = 1 for aromatic protons from the sample), MW is the molecular weight in g/mol, M is the recorded mass added to the sample, and A is the peak area.

Synthetic Procedures

Preparation of halogenated vanillin and isovanillin

***3-Methoxy-4-hydroxy-5-fluorobenzaldehyde*.**



(3b)

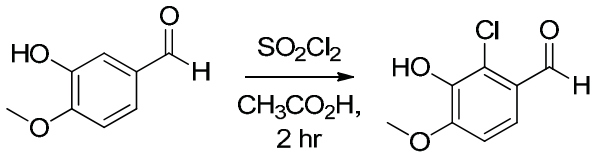
Following the procedure of Ladd and Weinstock,[5] 4.0 mL (9.4 mmol) of 2.36 M n-butyl lithium was added dropwise over 1 hr to a solution of 1.28 g (10 mmol) fluoroanisole (**1**) in 10.0 mL dry THF kept below -65 ^{o}C by a dry ice/acetone bath. The solution was stirred for 2 hrs at -78 ^{o}C under nitrogen. 1.17 g (11 mmol) of trimethoxyborane in 2.00 mL dry THF was added dropwise over 1 hr at -78 ^{o}C and the solution was stirred for an additional 30 mins at -78 °C. The solution was warmed to 0 ^{o}C and 0.88 mL (15 mmol) of glacial acetic acid was added followed by the dropwise addition of 1 mL (10 mmol) of 30% H_2O_2. The solution was stirred overnight at 25 °C. The solution was diluted with H_2O (10 mL) and extracted with THF (2 X 10 mL). The combined ether extracts were washed with H_2O (2 X 7 mL) and 10% Mohrs salt (2 X 3 mL). The ether phase was dried with $MgSO_4$ and evaporated under reduced pressure to yield 1.16 g of (80%) 2-fluoro-6-methoxyphenol. Yields for successive repetitions: 174 mmol gave 15.5 g (63%); 261 mmol gave 29.7 g (80%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 6.82 – 6.63 (m, 1H), 5.51 (s, 1H), 3.90 (s, 1H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -137.61 ppm (m, 1F). **EI-MS:** m/z 142 (M^+), 127.

Following the procedure of Clark and Miller,[6] 2-fluoro-6-methoxyphenol 13.0 g (91 mmol) was added to a solution of 19.5 g (160 mmol) 40% dimethylamine and 11.7 mL (160 mmol) of 37% formaldehyde in 91 mL of absolute ethanol. The reaction mixture was heated at reflux for 2 hours, cooled to room temperature, and concentrated under vacuum to a white solid. The solid was triturated with ether to afford 17.25 g (95%) of N,N-dimethyl-3-hydroxy-4-methoxy-5-fluorobenzylamine as a white solid that was used without purification in the following step. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 6.67 (t, *J* = 4.6 Hz, 1H), 3.90 (s, 1H), 3.32 (s, 1H), 2.23 (s, 3H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -138.08 (dd, *J* = 11.1, 1.7 Hz).

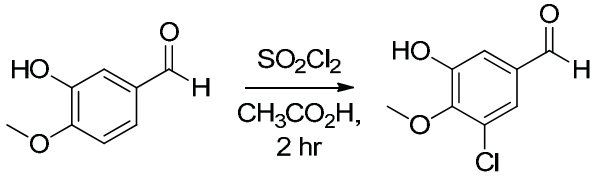
Iodomethane (100 mL) was added to a solution of 20.0 g (100 mmol) *N,N*-Dimethyl-3-hydroxy-4-methoxy-5-fluorobenzylamine in $CHCl_3$ (900 mL). The mixture was stirred overnight at room temperature. The solution was filtered to afford 32.7 g (95% yield) 1-(3-fluoro-4-hydroxy-5-methoxyphenyl)-N,N,N-trimethylmethanaminium iodide as an off-white solid that was used in the following step without purification. **^{1}H NMR (300 MHz, DMSO)** δ 9.78 (d, *J* = 1.8 Hz, 1H), 7.14 – 6.86 (m, 2H), 4.41 (d, *J* = 7.0 Hz, 2H), 3.85 (d, *J* = 2.7 Hz, 3H), 3.13 – 2.84 (m, 9H). **^{19}F NMR (282 MHz, DMSO)** δ -135.24 (dd, *J* = 25.8, 10.4 Hz).

A solution of 25.4 g (74 mmol) 1-(3-fluoro-4-hydroxy-5-methoxyphenyl)-N,N,N-trimethyl-methanaminium iodide was dissolved in acetic acid (65 mL) and H_2O (65 mL) and heated to reflux. Hexamethylenetetramine 40 g (285 mmol) was added to the refluxing solution in one portion. The

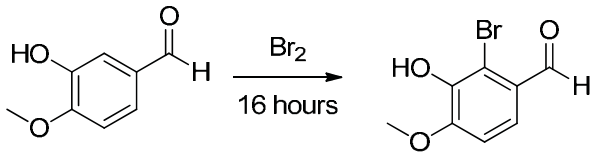
mixture was stirred at reflux for 2 hours at which time concentrated HCl (16.4 mL) was added. The solution was stirred an additional 5 minutes, cooled, and extracted with ether (3 X 175 mL). The organic layer was washed with H_2O (2 X 175 mL), dried over $MgSO_4$, and concentrated under vacuum to give 9.00 g (72% yield) of **3a** as a white powder. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.75 (s, 1H), 7.35 (d, *J* = 10.3 Hz, 1H), 7.31 (s, 1H), 3.88 (s, 3H). **^{19}F NMR (282 MHz, C_6D_6)** δ -134.71 (d, *J* = 10.2 Hz).



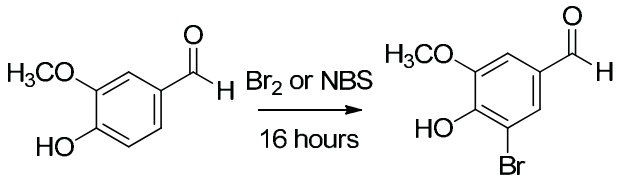
***2-Chloro-isovanillin (2-chloro-3-hydroxy-4-methoxybenzaldehyde)*.** Neat sulfuryl chloride (14.85 g, 110 mmol, 1.1 eq.) was added dropwise over 5 minutes to a solution of isovanillin (15.00 g, 100 mmol, 1 eq) in 120 mL of glacial acetic acid in an ice-water bath. After 2 hours of stirring with ice-water bath cooling, the reaction was filtered, washed with cold acetic acid, and dried under vacuum to afford 14.16 g of white solid. HPLC and ^{1}H-NMR indicate indicated the presence of unreacted isovanillin. This solid was dissolved in boiling ethanol and recrystallized to yield 11.91 g (80%) of fluffy white needles (mp = 200.0 – 209.9 °C). ^{1}H-NMR indicated <1% isovanillin after one recrystallization. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 10.19 (s, 1H, CHO), 9.83 (d, *J* = 31.4 Hz, 1H, OH), 7.41 (d, *J* = 8.6 Hz, 1H, ArH), 7.12 (d, *J* = 8.6 Hz, 1H, ArH), 3.93 (s, 3H, OCH_3); **^{1}H-NMR (300 MHz, DMSO-*d_6*):** δ 10.19 (s, 1H, CHO), 9.89 (s, 1H, OH), 7.42 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.12 (d, *J* = 8.6 Hz, 1H, Ar-H), δ 3.93 (s, 3H, OMe); **EI-MS *m/z*:** 187 (M+2), 185 (M+, 100%), 171, 157, 143, 129, 115, 107, 99, 79, 65, 51. **UV-Vis:** 215.3, 237.2, 283.8 nm.



***5-Chloro-vanillin (3-chloro-4-hydroxy-5-methoxybenzaldehyde)*.** Neat sulfuryl chloride (14.85 g, 8.89 mL, 110 mmol, 1.1 eq.) was added dropwise over a 5 minute period to a solution of 15.00 g (100 mmol, 1 eq.) of vanillin (4-hydroxy-3-methoxybenzaldehyde) in 120 mL of glacial acetic acid in an ice water bath (0– 2°C). After two hours of stirring with ice bath cooling, the reaction mixture was vacuum filtered, rinsed with chilled glacial acetic acid and dried under vacuum to afford a clumpy white solid. HPLC and ^{1}H-NMR indicate the presence of vanillin starting material. The solid was dissolved in hot ethanol, recrystallized, vacuum filtered, rinsed with cold ethanol and dried under vacuum to yield to product as 12.59 g (85%) of a chunky, white, crystalline solid (mp =163.0–170.0 °C). Product was 98% pure by as estimated by ^{1}H-NMR. Minor contaminating species included ~1% each of vanillin and di-chloro-vanillin. **^{1}H-NMR (300 MHz, DMSO-*d_6*):** δ 10.54 (s, 1H, OH), δ 9.79 (s, 1H, CHO), δ 7.60 (s, 1H, Ar-H), δ 7.40 (s, 1H, Ar-H), δ 3.91 (s, 3H, OMe); **EI-MS *m/z*:** 187 (M+2), 185 (M+, 100%), 173, 171, 157, 143, 115, 107, 99, 79, 65, 51. **UV-Vis:** 237.2, 278.3, 302.3 nm.



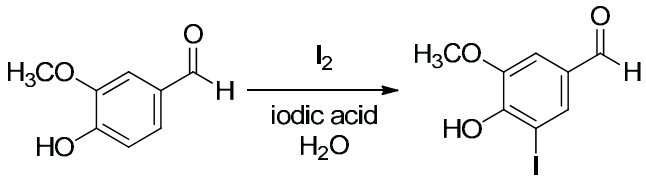
2-Bromo-isovanillin (2-bromo-3-hydroxy-4-methoxybenzaldehyde). Liquid Br_2 (36.85 g, 11.6 mL, 225 mmol, 1.5 equiv.) was added dropwise at a rate of 0.1 mL/min over a period of 2 hours, using a syringe pump or addition funnel, to a three-neck flask, equipped with septum and overhead stirring assembly, containing a solution of isovanillin, 3-hydroxy-4-methoxybenzaldehyde (22.8g, 150 mmol), in 75 mL of CCl_4 and 75 mL of $CHCl_3$. The reaction mixture was allowed to stir overnight (approximately 12 hours) at room temperature. The resulting reddish brown precipitate was vacuum filtered and rinsed with 50 mL of a 1:1 solution of CCl_4 and $CHCl_3$. After removing solvent under reduced pressure, the precipitate was dissolved in 300 mL of ethyl acetate (EtOAc) to give a bright yellow solution. This extract was washed with 150 mL of brine, 50 mL of 10% w/v sodium thiosulfate, and twice more with brine (2 x 150 mL portions).The organic phase was dried with $MgSO_4$, vacuum-filtered, and solvent was removed by under reduced pressure at room temperature. The recovered white solid was recrystallized in ethanol and vacuum filtered to afford 22.11 g (60%) of a fine, grainy, white solid, 2-bromo-3-hydroxy-4-methoxybenzaldehyde (mp = 204.5–210.4°C). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 10.11 (s, 1H, CHO), δ 9.94 (s, 1H, OH), δ 7.42 (d, *J* =8.6 Hz, 1H, Ar-H), δ 7.15 (d, *J* = 8.6 Hz, 1H, Ar-H), δ 3.93 (s, 3H, OMe); **EI-MS *m/z*:** 232 (M+2), 231(100%), 230 (M+), 229, 214, 201,189, 187, 173, 161,159, 150, 143, 131, 122, 107, 94, 79, 78, 77, 63, 51; **UV-Vis:** 215.3, 239.1, 297.4 nm.



5-Bromo-vanillin (3-bromo-4-hydroxy-5-methoxybenzaldehyde). *Method 1, bromination with elemental bromine*: Vanillin, 3-methoxy-4-hydroxybenzaldehyde (22.8 g, 150 mmol), was dissolved in 75 mL of CCl_4 and 75 mL of $CHCl_3$ in a three-neck flask equipped with septum and overhead stirring assembly. Liquid Br_2 (36.77 g, 11.6 mL, 225 mmol, 1.5 equiv.) was added dropwise at a rate of 0.1mL/min over a period of 2 hours by either addition funnel or syringe pump. As a large amount of solid orange precipitate forms during the course of the reaction, which slows or stops mixing, adequate stirring is important to minimize over-bromination. The reaction mixture was allowed to stir overnight (approximately 12 hours) at room temperature. The resulting orange precipitate was vacuum-filtered and rinsed with 50 mL of a 1:1 solution of CCl_4 and $CHCl_3$. After removing solvent *in vacuo*, the precipitate was dissolved in 300 mL of ethyl acetate (EtOAc) to give a bright orange/yellow solution. This extract was washed with 150 mL of brine, 50 mL of 10% w/v sodium thiosulfate, and twice more with brine (2 x 150 mL portions). The organic phase was dried with $MgSO_4$, vacuum filtered, and solvent was removed under reduced pressure in a room temperature bath. The recovered white solid was recrystallized in ethanol and vacuum filtered to afford (27.72 g, 75%) of a fine, grainy, white solid, 3-bromo-4-hydroxy-5-methoxybenzaldehyde (mp = 163.5–168.3°C).

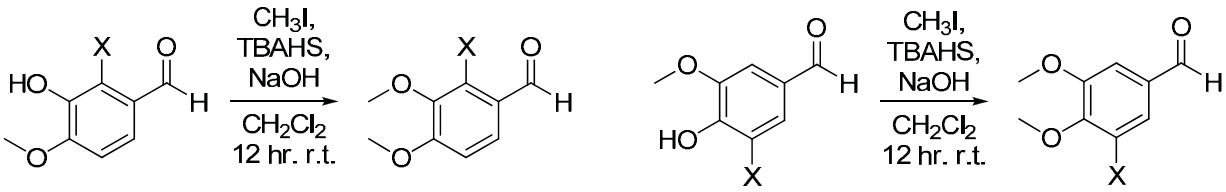
*Method 2, bromination with N-bromo-succinamide***:** Vanillin (30 g, 197 mmol) was dissolved in acetonitrile (250 mL) in a 600-mL beaker with stirring by magnetic stirbar. *N*-bromo succinimide (35.1 g, 197 mmol) was added to the solution. Precipitate was apparent after 30 minutes. Stirring continued at room temperature overnight. The reaction mixture was quenched with brine (10 mL) and stirred for 15 minutes. Ether (100 mL) was added to aid in transferring to a separatory funnel. The solid precipitate was not transferred but was washed with ether. These extracts were also added to the separatory funnel. The combined organic layers were washed twice with equal volumes of 10% w/v sodium thiosulfate solution and thrice with equal volumes of brine, dried over $MgSO_4$, and concentrated *in vacuo*. The oil was recrystallized from ethanol to give the product as an off-white powder (24.5 g, 106 mmol, 54%).

^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ 10.75 (s, 1H, OH), 9.78 (s, 1H, CHO), 7.72 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 3.91 (s, 3H, OMe); **EI-MS *m/z*:** 232 (M+2), 230 (M+, 100%), 217, 215, 203, 201, 189, 187, 161, 159, 143, 135, 107, 94, 79, 78, 77, 63, 51. **UV-Vis:** 236.6, 282.0, 299.2 nm.

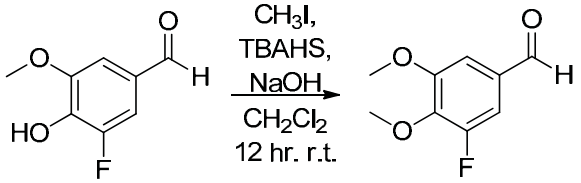


***5-Iodo-vanillin (3-Iodo-4-hydroxy-5-methoxybenzaldehyde)*.** Vanillin (38.1 g, 250 mmol) and iodine (25.4 g, 100 mmol) were added to a 1 L round bottom flask containing minimal EtOH. Iodic acid (8.8 g, 50 mmol) was dissolved in minimal amount of water (50 mL), and added to the flask containing the vanillin-iodine mixture. The flask was placed in a water bath at a constant temperature of 35 °C and stirred. The thick consistency of the reaction mixture requires overhead mechanical stirring. While reacting, minimal amounts of EtOH and distilled H_2O were occasionally used to wash solids down the sides of the flask. After 1.5 hours, the reaction was judged to be complete by HPLC. The cream-colored solid was washed in a Buchner funnel with 1.5 L of saturated sodium thiosulfate (NaS_2O_3) and 0.5 L of deionized H_2O. The remaining solid was recrystallized in EtOH yielding 42.2 g (97.7%) of light yellow prism-shaped crystals. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.74 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 3.89 (s, 3H). **EI-MS *m/z*:** 278 (M+), 263, 249, 235, 221, 207, 189, 179, 165, 151, 135, 122, 107, 91, 79, 62, 51. **UV-Vis:** 228.7, 297.4 nm.

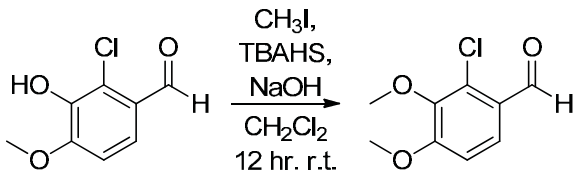
Methylation reactions



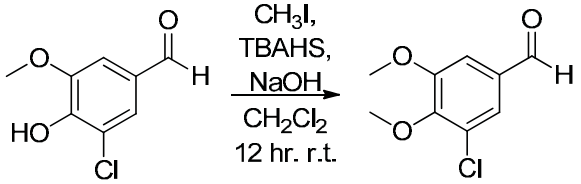
General methylation procedure. Following an adaptation of the procedure of McKillop et al.[7], an aqueous solution of 1.20 g of NaOH (30 mmol, 3.0 eq.) in 50 mL of deionized water was added to a stirring solution of 2.31 g (10 mmol) of 2-bromo-isovanillin (2-bromo-3-hydroxy-4-methoxy-benzaldehyde) in 50 mL of dichloromethane. Next, phase transfer catalyst was added, as 3.40 g of either tetrabutylammonium hydrogen sulfate (TBAHS, 10.0 mmol, 1.0 eq.) or recycled catalyst (assuming that the recovered catalyst is tetrabutylammonium hydroxide, 2.6 g is 10 mmol, 1.0 eq). Once dissolved, 17 g (120 mmol, 12 eq.) of methyl iodide was then added to the mixture and the reaction was allowed to stir at room temperature. Reaction progress was monitored by HPLC. As monitored by HPLC, reaction progress generally showed complete turnover to product with no side products by 3 hours, however the solution was typically allowed to stir overnight for convenience. The reaction mixture was extracted with 3 x 50 mL portions of CH_2Cl_2. The combined organic extracts were washed with brine and deionized water, dried over $MgSO_4$, filtered, and concentrated by evaporation under reduced pressure to yield a either a white or yellow solid. To remove catalyst, the solid was first ground to a fine powder with a mortar and pestle. This solid was poured on top of a 2 – 3 cm layer of dry silica gel in a 3 – 4 cm (I.D.) sintered glass fritted Buchner funnel. The solid was extracted with 1:5 ethyl acetate:hexanes in 75 mL portions by pouring the solvent mixture over the dry solids with vacuum suction to collect the solution in a round bottom flask. Allow the solids to dry between solvent portions for best separation. The first 1250 mL typically contained 85 - 95% of pure product. The combined eluent was evaporated to dryness under reduced pressure to afford a dense, white, flakey solid (2.06 g, 90%). If the product was found to contain non-halogenated contaminants from the previous step, pure halogenated product was easily obtained by recrystallization from hexanes. The phase transfer catalyst, presumably a mixture of tetrabutylammonium salts, was recovered by either scooping it out of the filter or by eluting with ethyl acetate.



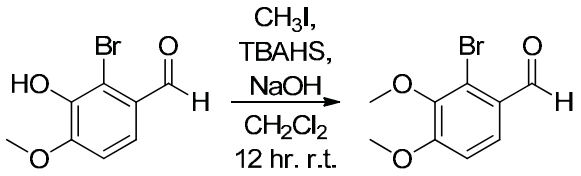
***3-fluoro-4,5-dimethoxybenzaldehyde (3b)*.** From 3.10 g (11.7 mmol) of 5-fluoro-vanillin (3-chloro-4-hydroxy-5-methoxybenzaldehyde) methylation afforded 3.27 g (97.5%) of a fluffy, white solid; **mp** = 51.2–53.0 °C; **^{1}H-NMR (300 MHz, DMSO-d_6)** δ 9.88 (d, *J* = 1.6 Hz, 1H), 7.48 – 7.43 (m, 2H), 3.92 – 3.90 (m, 6H). ; **^{19}F NMR (282 MHz, DMSO-d_6):** δ -128.87 (d, *J* = 10.1 Hz). **EI-MS *m/z*:** 184 (M+), 169, 155, 137, 125, 113, 95, 83, 70, 59, 50.



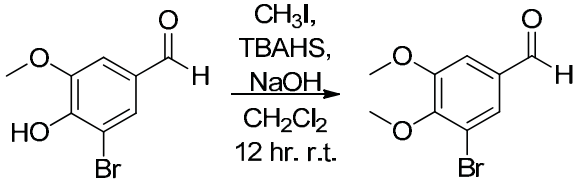
***2-Chloro-3,4-dimethoxybenzaldehyde (3c)*.** From 2.00 g (10.7 mmol) of 2-chloro-isovanillin (2-chloro-3-hydroxy-4-methoxybenzaldehyde) methylation afforded 1.98 g (92%) of a fluffy, white solid; mp = 68.0-69.0 °C (recrystallized from hexanes with 78% recovery); **^{1}H-NMR (300 MHz, DMSO-*d*$_6$):** δ 10.19 (s, 1H, CHO), 7.68 (d, J= 8.8 Hz., 1H, Ar-H), 7.24 (d, J=8.8 Hz., 1H, Ar-H), 3.95 (s, 3H, OMe), 3.79 (s, 3H, OMe); **EI-MS *m/z*:** 203, 202 (M+2), 200 (M+, 100%), 199, 187, 185, 172, 167, 158, 156, 149, 141, 135, 131, 129, 121, 115, 113, 107, 99, 93, 85, 79, 78, 74, 65, 60, 51, 50; **UV-Vis:** 211.0, 233.6, 282.0 nm.



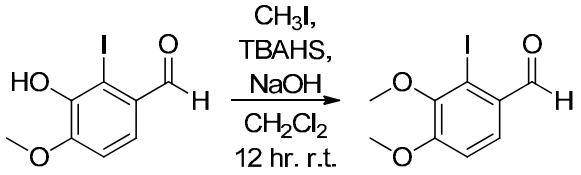
***3-Chloro-4,5-dimethoxybenzaldehyde (3d)*.** From 2.10 g (11.2 mmol) of 5-chloro-vanillin (3-chloro-4-hydroxy-5-methoxybenzaldehyde) methylation afforded 2.17 g (96%) of dense, white, flakey solid; mp = 54.5-55.5 °C (recrystallized from hexanes with 80% recovery); **^{1}H-NMR (300 MHz, DMSO-*d*$_6$):** δ 9.90 (s, 1H, CHO), 7.66 (s, J=1.75 Hz., 1H, Ar-H), 7.53 (s, J=1.75 Hz., 1H, Ar-H), 3.93 (s, 3H, OMe), 3.87 (s, 3H, OMe); **EI-MS *m/z*:** 202 (M+2), 200 (M+), 199, 187, 185, 171, 159, 157, 149, 141, 135, 131, 129, 121, 116, 114, 107, 99, 94, 93, 85, 79, 78, 77, 74, 65, 60, 51; **UV-Vis:** 234.8, 268.5, 304.2 nm.



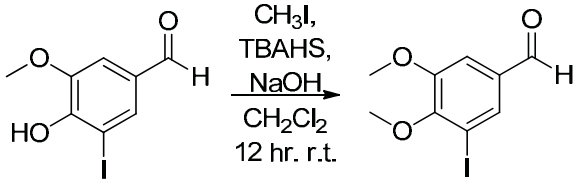
***2-Bromo-3,4-dimethoxybenzaldehyde (3e)*.** From 5.09 g (22.0 mmol) 2-bromo-isovanillin (2-bromo-3-hydroxy-4-methoxybenzaldehyde) methylation afforded 5.19 g (96%) of a dense, white, flakey solid; mp = 83.0-84.0 °C (no recrystallization); **^{1}H-NMR (300 MHz, DMSO-*d*$_6$):** δ 10.11 (s, 1H, CHO), 7.68 (d, J=8.8 Hz., 1H, Ar-H), 7.27 (d, J=8.8 Hz., 1H, Ar-H), 3.95 (s, 3H, OMe), 3.78 (s, 3H, OMe); **EI-MS *m/z*:** 246 (M+2), 245, 244 (M+, 100%), 243, 231, 229, 216, 207, 202, 200, 187, 185, 175, 173, 163, 160, 159, 158, 157, 150, 149, 143, 137, 131, 129, 122, 116, 107, 94, 79,78, 77, 65, 50; **UV-Vis:** 238.5, 280.1, 299.8 nm.



***3-Bromo-4,5-dimethoxybenzaldehyde (3f)*.** From 2.50 g (10.8 mmol) of 5-bromo-vanillin (3-bromo-4-hydroxy-5-methoxybenzaldehyde) methylation afforded 2.47 g (93%) white, fluffy solid; mp = 59.8-61.3 °C; **^{1}H-NMR (300 MHz, DMSO-*d_6*):** δ 9.89 (s, 1H, CHO), 7.78 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 3.92 (s, 3H, OMe), 3.85 (s, 3H, OMe); **EI-MS *m/z*:** 247 (M+2), 246, 245 (M+), 244 (100%), 243, 231, 229, 215, 207, 203, 202, 201, 200, 199, 197, 187, 185, 175, 173, 163, 160, 157, 150, 145, 143, 135, 129, 122, 116, 107, 101, 94, 86, 79,78, 73, 63, 51; **UV-Vis:** 223.8, 272.1, 229.9, 272.8 nm.



***2-Iodo-3,4-dimethoxybenzaldehyde (3g)*.** From 2.78g (10 mmol) **of** 2-iodo-isovanillin (2-iodo-3-hydroxy-4-methoxybenzaldehyde) methylation afforded 2.65 g (90%) of a dense, white, flakey solid; **^{1}H-NMR (300 MHz, DMSO-*d_6*):** δ 9.90 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 3.93 (s, 3H), 3.75 (s, 3H). **UV-Vis**: 227.5, 292.4 nm.

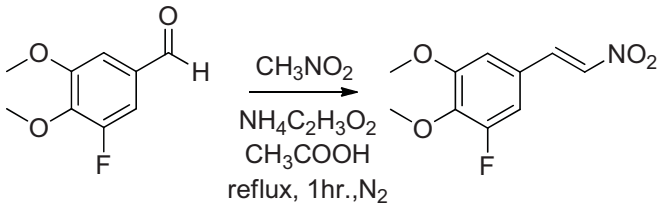


***3-Iodo-4,5-dimethoxybenzaldehyde (3h)*.** From 2.78g (10 mmol) of 5-iodo-vanillin (3-iodo-4-hydroxy-5-methoxybenzaldehyde) methylation afforded 2.83 g (97%) of a white, fluffy solid; **^{1}H-NMR (300 MHz, DMSO-*d_6*):** δ). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (d, *J* = 2.4 Hz, 1H), 8.48 (t, *J* = 2.1 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 4.49 (d, *J* = 2.3 Hz, 3H), 4.44 (d, *J* = 2.4 Hz, 3H). **EI-MS *m/z*:** 292 (M+), 277, 264, 245, 233, 221, 206, 189, 177, 166, 150, 135, 122, 107, 94, 77, 62, 51; **UV-Vis:** 228.1, 297.5 nm.

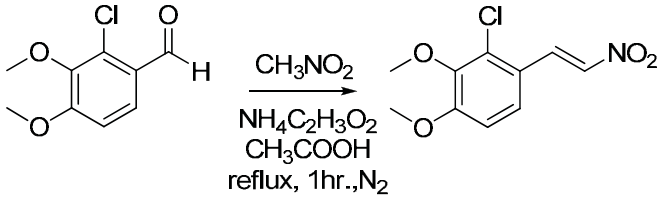
Nitroaldol (Henry) reactions

Method A: General procedure for nitroaldol reaction. Aldehyde (4 mmol) was added to a round bottom flask containing a solution of 0.3 g (4 mmol, 1 eq.) of ammonium acetate (fresh commercial solid works well, however it must be recrystallized from glacial acetic acid if it appears wet) dissolved in 1.1 mL (20 mmol, 5 eq.) of nitromethane, 3.0 mL (56 mmol, 14 eq.) of glacial acetic acid, and small number of 3Å molecular sieves. The flask was attached to a condenser with septum and the assembly was lowered into a sand bath. The reaction mixture was allowed to gently reflux at 90–100 °C with stirring for one hour. After removing the molecular sieves, the resulting bright yellow solution was partitioned between 10 mL of brine and extracted with 3 x 25 mL portions of ethyl acetate. Organic extracts were combined and rinsed with 3 X 50 mL portions of deionized water, dried over $MgSO_4$, vacuum filtered, and concentrated under vacuum to afford a dense yellow crystalline solid. Unless otherwise specified, all isolated products were free of starting material, side products, and ammonium acetate by ^{1}H-NMR and

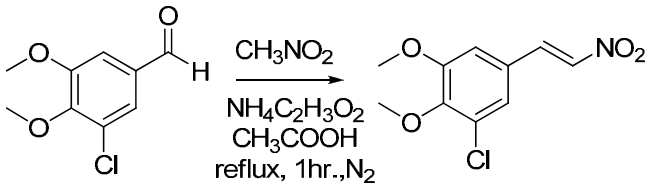
HPLC-UV. If further purification is required due to the presence of minor side products, the nitrostyrene may be recrystallized by dissolving in minimal methanol and adding distilled water at room temperature. All reported melting points were from crude isolated solid.



5-fluoro-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4b). 145 mg (0.78 mmol) of 3-fluoro-4,5-dimethoxybenzaldehyde (**3b**) was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 95-100 °C for 1.5 hours resulting in a bright yellow solution. Isolation afforded a dense, flakey bright yellow crystalline solid (175 mg, 98%). **^{1}H NMR (300 MHz, DMSO-*d*$_6$):** δ 8.28 (d, J = 13.6 Hz, 1H), 8.06 (d, J = 13.6 Hz, 1H), 7.52–7.43 (m, 2H), 3.90–3.85 (m, 6H). **^{19}F NMR (282 MHz, DMSO-*d*$_6$):** δ -130.54 (d, *J* = 11.1 Hz).

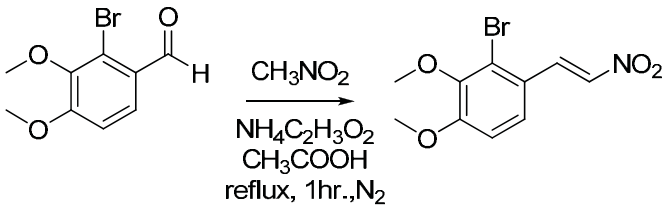


2-chloro-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4c). 803 mg (4.00 mmol) of 2-Chloro-3,4-dimethoxybenzaldehyde (**3c**) was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 89-90 °C for one hour resulting in a bright yellow solution. Isolation afforded a dense, flakey bright yellow crystalline solid (973 g, 99%). **mp** = 84.6-88.1 °C (lit. 88-91 °C [21]); **^{1}H-NMR (300 MHz, DMSO-*d*$_6$):** δ 8.23 (s, 2H, C=CH), 7.88 (d, J=9.29 Hz, 1H, Ar-H), 7.20 (d, J=9.29 Hz., 1H, Ar-H), 3.93 (s, 3H, OMe), 3.78 (s, 3H, OMe); **^{1}H-NMR (300 MHz, CDCl$_3$):** 8.40 (d, J= 13.70 Hz., 1H, C=CH), 7.60 (d, J=13.70 Hz., 1H, C=CH), 7.40 (d, J=8.83 Hz., 1H, Ar-H), 6.90 (d, J=8.83 Hz., 1H, Ar-H), 3.97 (s, 3H, OMe), 3.91 (s, 3H, OMe); **UV-Vis:** 253, 351 nm.

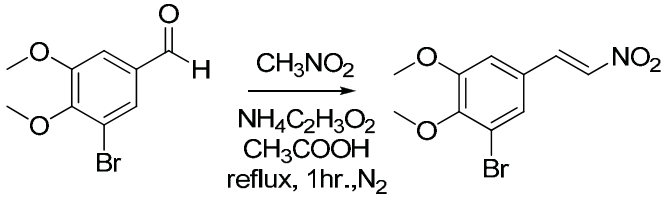


5-chloro-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4d). 804 mg (4.00 mmol) of 3-Chloro-4,5-dimethoxybenzaldehyde (**3d**) was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 89-90 °C for one hour resulting in resulting in a bright yellow solution. Isolation afforded a dense, flakey bright yellow crystalline solid a fluffy, bright yellow crystalline solid 900 mg (92%). **mp** =

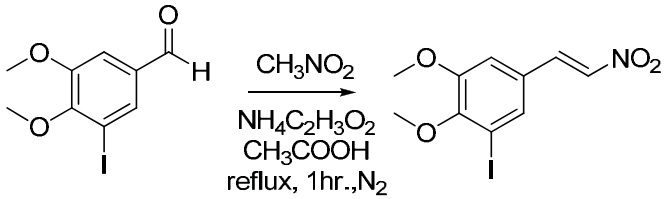
149.4-155.5 °C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 8.32 (d, J=13.62 Hz., 1H, C=CH), 8.07 (d, J=13.62 Hz., 1H, C=CH), 7.64 (s, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 3.90 (s, 3H, OMe), 3.82 (s, 3H, OMe); **UV-Vis**: 248.2, 335.0 nm.



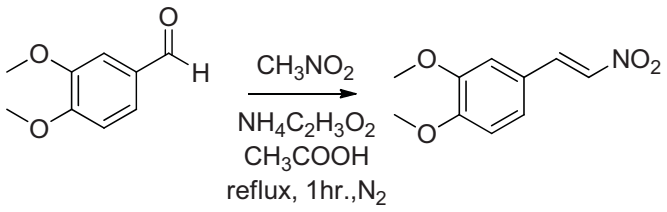
***2-bromo-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4e)*.** 800 mg (3.26 mmol) of 2-Bromo-3,4-dimethoxybenzaldehyde (2e) was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 100 °C for one hour resulting in resulting in a bright yellow solution. Isolation afforded a dense yellow crystalline solid 933 mg (99%). **mp** = 84.9-87.8 °C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 8.26 (d, J=13.35 Hz., 1H, C=CH), 8.19 (d, J=13.35 Hz., 1H, C=CH), 7.87 (d, J= 9.14 Hz., 1H, Ar-H), 7.22 (d, J= 9.14 Hz., 1H, Ar-H), 3.93 (s, 3H, OMe), 3.77 (s, 3H, OMe); **UV-Vis:** 257.4, 355.0 nm.



***5-bromo-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4f)*.** 975.0 mg (4 .00 mmol) of 3-Bromo-4,5-dimethoxybenzaldehyde (**3f**) was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 90 °C for one hour resulting in resulting in a bright yellow solution. Isolation afforded a fluffy, bright yellow crystalline solid (1.075 g, 94%). **mp** =150-153.2 °C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 8.32 (d, J=13.5 Hz., 1H, C=CH), 8.06 (d, J=13.5 Hz., 1H, C=CH), 7.76 (s, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 3.89 (s, 3H, OMe), 3.81 (s, 3H, OMe); **UV-Vis:** 211.6, 245.8, 335.7 nm.



5-Iodo-3,4-dimethoxy-1-(2-nitrovinyl)benzene (4h). 1.16 g (3.97 mmol) of 2-Iodo-3,4-dimethoxybenzaldehyde was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 100 °C for one hour resulting in resulting in a bright yellow solution. Isolation afforded a dense yellow crystalline solid 1.105 g (83%). **^{1}H NMR (300 MHz, DMSO-d_6):** δ 8.35 (d, J = 13.6 Hz, 1H), 8.09 (d, J = 13.6 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H); **UV-Vis:** 220.2, 358.6, 369.9 nm.



3,4-dimethoxy-1-(2-nitrovinyl)benzene (4i). 10.00 g (60.2 mmol) of 3,4-dimethoxybenzaldehyde was reacted following Nitroaldol Reaction Method A. The reaction was maintained at 100 °C for one hour resulting in resulting in a bright yellow solution. Isolation afforded a flakey yellow crystalline solid 12.18 g (97%). **^{1}H-NMR (300 MHz, DMSO-*d*$_6$):** δ 8.16 (d, J = 13.3 Hz, 1H), 8.03 (d, J= 13.5 Hz, 1H), 7.48 (s, 1H), 7.30 (d, 1.7 Hz, 1H), 6.85 (d, J = 1.7 Hz, 1H), 3.82 (s, 3H). **UV-Vis:** 217.7, 259.9, 376 nm.

Method B: General nitroaldol reaction procedure with free phenols.

Aldehyde (20 mmol) and ammonium acetate (10 mmol) were mixed in 70 mL of nitromethane in a sealed glass high-pressure reaction vessel (Ace glass 8648 pressure vessels with 5846 PTFE plugs). The reaction was mixed by magnetic stirring while immersed in an oil bath maintained at the temperature and time specified for each compound. *Caution: This reaction builds-up pressure, use of a blast shield is recommended.* After the stated time, the vessel was allowed to cool to room temperature before opening. The reaction mixture was transferred to a round bottom flask (solids were dissolved in ethyl acetate when necessary). The organic layer was washed with a small amount of brine, dried over $MgSO_4$, vacuum filtered, and evaporated to dryness under reduced pressure. All isolated products were free of starting material, side products, and ammonium acetate by ^{1}H-NMR and HPLC-UV. If further purification was required, products may be recrystallized from ethanol.

Notes on nitroaldol condensation in the presence of phenol moieties.

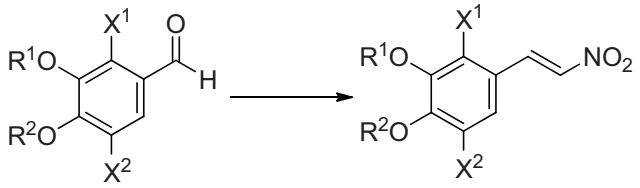
This method represents a general procedure for large scale nitroaldol condensation in the presence of unprotected phenol moieties. High yield nitroaldol condensation with the halogenated phenol 2-bromo-5-hydroxy-4-methoxybenzaldehyde with catalytic ammonium acetate has been previously reported at reflux temperature (105 °C)[8]. However, in our hands this procedure did not yield high conversion for our aldehydes (5-fluoro-vanillin was the notable exception). Instead, reflux with phenols generally achieved 30–60% completion as monitored by HPLC. When allowed to react for longer times, significant amounts of unidentified side products accumulated.

Heating the reaction in sealed high-pressure glassware at 130–160 °C, above the boiling point of nitromethane, represents a general improvement over reflux. All reactions were generally complete after 60 minutes. Although this method worked well for nitroaldol condensation in the presence of free phenols, it requires significant excess of nitromethane (900–1500 equivalents), which makes large scale application somewhat cost prohibitive. Moreover, the free phenol was not suitable our specific application. For these reasons, Method B was not explored further, but other researchers may find it to

be a useful option for overcoming the problem of incomplete nitrostyrene reaction with less-reactive aldehydes and ketones. See Table S1 for results.

This method is similar to the high-yield, microwave-assisted nitroaldol condensation described by Rodríguez and Pujol.[9] Using the identical (CEM Discover microwave system outfitted with external infrared temperature monitoring), their procedure provided near quantitative conversion of halogenated aldehydes **6b – 6f**. However, we were unable to scale the reported procedure beyond 2 mmols. Microwave reactions in sealed reaction vessels at 4 mmol scale generated side products and incomplete conversion. Low conversion to nitrostyrene product was observed when a 10 mmol at ca. 105 °C in an open round bottom flask. We found that this inability to scale-up was due to instrument problems with accurate monitoring and control of the reaction temperature for a large scale reaction with only infrared thermometer monitoring in this model microwave reactor. For successful reactions, the instrument reported the reaction temperature as 90 °C, however we found that the internal temperature was actually around 130 °C, above the boiling point of nitromethane. We concluded that the microwave reactor was actually maintaining the conditions of our Method B and not the 90 °C temperature indicated by the instrument's infrared thermometer.

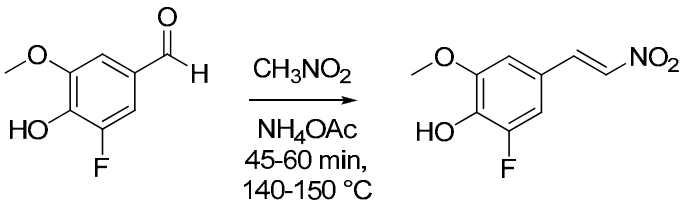
Table S1[a]



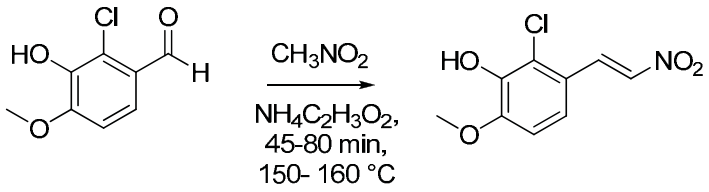
6a - 6e **7a - 7e**

Product	R^1	R^2	X^1	X^2	conversion[b] (isolated yield)
6a	CH_3	H	H	F	100% (98%)
6b	H	CH_3	Cl	H	99.6% (97%)
6c	CH_3	H	H	Cl	94% (95%)
6d	H	CH_3	Br	H	96% (94%)
6e	CH_3	H	H	Br	99.6% (84%)
6f	CH_3	H	H	I	98% (92%)

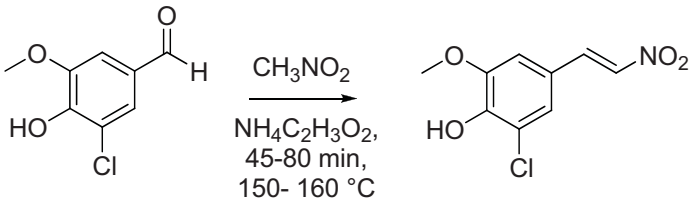
a. Yields for nitroaldol condensation of aldehydes with unprotected phenol moieties by Method B.
b. Conversion was estimated from disappearance of initial amount of starting material by HPLC.



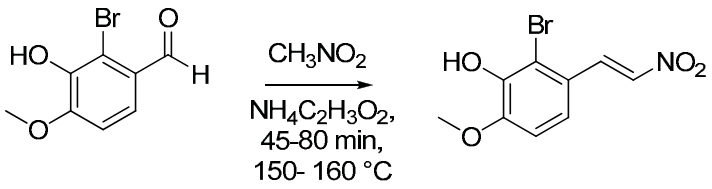
5-Fluoro-vanillin nitrostyrene (2-fluoro-6-methoxy-4-(2-nitrovinyl)phenol) (6a). 1.70 g (10.0 mmol) of 2-fluoro-isovanillin (2-fluoro-3-hydroxy-4-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B at 140 – 150 °C for 60 minutes resulting in a yellow/orange solution. After evaporation of solvent, 2.10 g (98% yeild) of **6a** was collected as a yellow solid without the need for further purification. **^{1}H NMR (300 MHz, DMSO-*d*$_6$):** δ 8.09 (dd, J = 45.6, 13.3 Hz, 2H), 7.41 (d, J = 11.6 Hz, 1H), 7.35 (s, J = 11.8 Hz, 1H), 3.85 (s, 3H). **^{19}F NMR (282 MHz, DMSO-*d*$_6$):** δ -135.35 (d, J = 11.5 Hz).



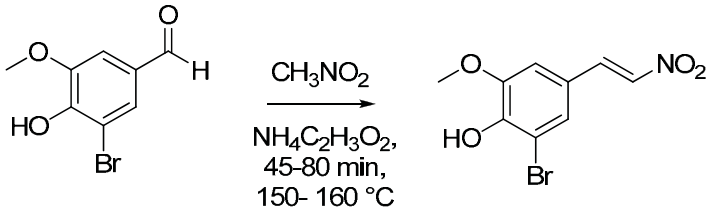
***2-Chloro-isovanillin nitrostyrene (2-chloro-6-methoxy-3-(2-nitrovinyl)phenol) (6b)*.** 1.87 g (10.0 mmol) of 2-chloro-isovanillin (2-chloro-3-hydroxy-4-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B at 150 – 160 °C for 45 minutes resulting in a yellow/orange solution. After evaporation of solvent, 2.22 g (97%) of **6b** was collected as a yellow solid without the need for further purification. **^{1}H-NMR (300 MHz, acetone-*6*):** δ 8.71(s, 1H, OH), δ 8.38 (d, J= 13.5 Hz., 1H, C=CH), δ 7.94 (d, J= 13.5 Hz., 1H, C=CH), δ 7.55 (d, J= 8.5 Hz.,1H, Ar-H), δ 7.10 (d, J=8.5 Hz.,1H, Ar-H), δ 4.00 (s, 3H, OMe); **UV-Vis:** 212, 261, 368 nm.



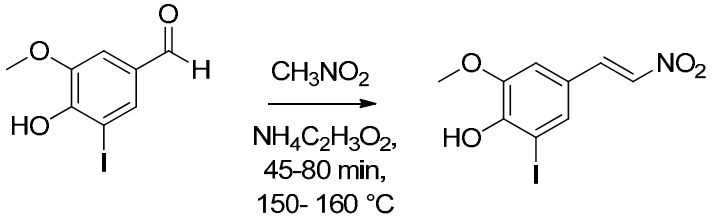
5-chloro-vanillin-nitrostyrene (2-chloro-6-methoxy-4-(2-nitrovinyl)phenol) (6c). 1.86 g (10.0 mmol) of 2-chloro-isovanillin (2-chloro-3-hydroxy-4-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B at 150 – 160 °C for approximately 80 minutes resulting in a yellow/orange solution. After evaporation of solvent, 2.17 g (95%) was collected as a powdery, reddish/orange solid without the need for further purification. **UV-Vis:** 210.4, 253.7, 366.8 nm.



2-bromo-isovanillin-nitrostyrene (2-bromo-6-methoxy-3-(2-nitrovinyl)phenol) (6c). 230 mg (1.00 mmol) of 2-bromo-isovanillin (2-bromo-3-hydroxy-4-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B with 38 mg (0.5 mmol, 0.5 eq.) of ammonium acetate in ~50.0 mL (931 mmol, 931 eq.) of nitromethane at 150-160 °C for 60 minutes resulting reddish/orange solution. After evaporation of solvent, 258 mg (94%) was collected as a powdery, bright yellow/orange solid without further purification. **^{1}H-NMR (300 MHz, acetone-d_6):** δ 8.85 (s, 1H, OH), 8.42 (d, J= 13.5 Hz., 1H, C=CH), 7.90 (d, J= 13.5 Hz., 1H, C=CH), 7.56 (d, J= 8.5 Hz.,1H, Ar-H), 7.12 (d, J=8.5 Hz.,1H, Ar-H), 4.00 (s, 3H, OMe); **UV-Vis:** 211.0, 264.2, 368.6 nm.

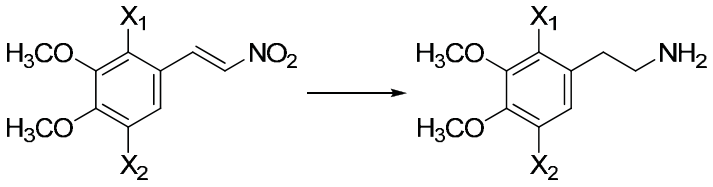


5-Bromo-vanillin nitrostyrene ((E)-2-bromo-6-methoxy-4-(2-nitrovinyl)phenol) (6d). 2.31 g (10.0 mmol) of 5-bromo-vanillin (3-bromo-4-hydroxy-5-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B at 150 – 160 °C for 60 minutes resulting reddish/orange solution. After evaporation of solvent, 2.31 g (84%) was collected as a powdery, reddish/orange solid without the need for further purification. **UV-Vis:** 212.3, 253.1, 367.4 nm.



5-iodo-vanillin-nitrostyrene (2-iodo-6-methoxy-4-(2-nitrovinyl)phenol) (6f). 556 mg (2.0 mmol) of 5-iodo-vanillin (3-iodo-4-hydroxy-5-methoxybenzaldehyde) was reacted following Nitroaldol Reaction Method B with 77 mg (1.0 mmol, 0.5 eq.) of ammonium acetate in ~40.0 mL of nitromethane at 150 – 160 °C for 60 minutes resulting reddish/orange solution. After evaporation of solvent, 590 mg (92%) was collected as a powdery, bright yellow/orange solid without further purification. **UV-Vis:** 220, 370, 258 nm.

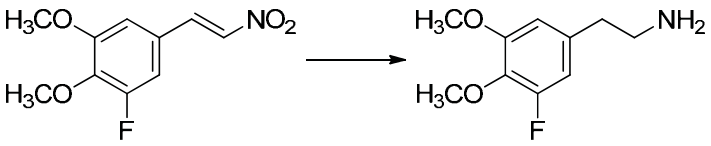
Reduction reactions



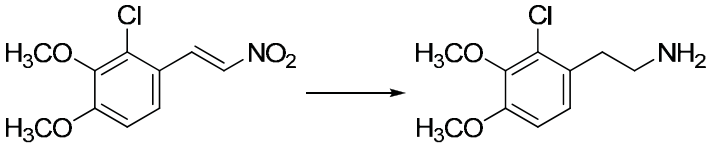
General procedure for Zn-HCl reduction of nitrostyrenes.

For every 1.0 mmol of nitrostyrene, 2 mL of methanol, 800 mg of zinc dust (12 mmol), and 2 mL of 37% HCl (24 mmol) were used. Methanol was vigorously stirred in an ice bath maintained <0 °C (ice/NaCl or freezer-chilled commercial antifreeze). HCl, zinc dust, and nitrostyrene were slowly added over the course of 30 minutes in alternating small portions taking care that the temperature did not rise above 0 °C. For large-scale reactions (>25 mmol), HCl was added continuously by syringe pump. After addition was complete, any solids on the side were washed into the solution with a small amount of methanol. All starting material was consumed within one hour of complete reagent addition as monitored by HPLC and observed by complete disappearance of the initial yellow color. At this point, an intermediate and the phenethylamine product generally dominate the mixture as observed by HPLC. The intermediate is typically converted to product after 4 hours of total stirring at 0 °C. The reaction is typically complete 4–6 hours after the yellow color has disappeared. The reaction may stir for as long as 16 hours in a 4 °C refrigerator without significant formation of side products. If HPLC is not available to monitor the reaction, we suggest adding an additional 200 mg of zinc dust (3 mmol) and 0.6 mL (7 mmol) of concentrated HCl for every 1.0 mmol of nitrostyrene after 5 hours and stir for an additional hour to ensure complete reaction. Once complete, the excess solid zinc was removed by filtration through filter paper. *Note that filtering through celite, silica gel, or alumina at this stage leads to product decomposition.* The solution was made basic by dropwise addition of saturated sodium hydroxide in methanol, while maintaining the temperature below 5 °C, until the pH was greater than 11 by pH paper. Next, 10 mL of $CHCl_3$ was added (per mmol of reactant). Solid anhydrous $MgSO_4$ was added to dry the organic layer. The organic extract was filtered by filter paper. The remaining paste was extracted two more times with $CHCl_3$ and filtered. The combined organic extracts were evaporated *in vacuo* to yield phenethylamine as an amber oil. In cases when an oil was not obtained at the final step, the material was dissolved in minimal $CHCl_3$ and the remaining inorganic salts were completely precipitated by addition of diethyl ether. After filtration and evaporation, a salt-free oil was obtained.

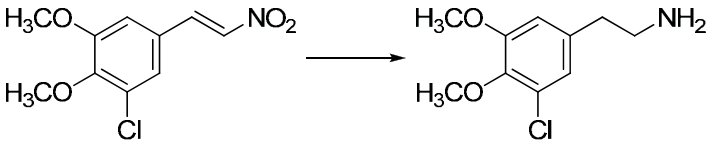
The phenethylamine products may be converted to solid HCl salts by dissolving the free base in minimal cold diethyl ether, carefully adding one equivalent of concentrated HCl, and evaporating to dryness under vacuum.



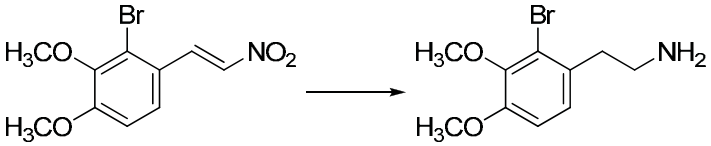
5-fluoro-3,4-dimethoxy-phenethylamine (5b). 750 mg (3.3 mmol) of compound **4b** was reacted following the general procedure for Zn-HCl reduction to yield 766 mg (83%) as an oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 6.85 – 6.68 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H). **^{19}F NMR (282 MHz, methanol-*d*$_4$):** δ -132.92 (d, *J* = 10.4 Hz). **HRMS** ($C_{10}H_{16}NO_2F^+$): calc. 200.1086 $[M+H]^+$; found 200.1088.



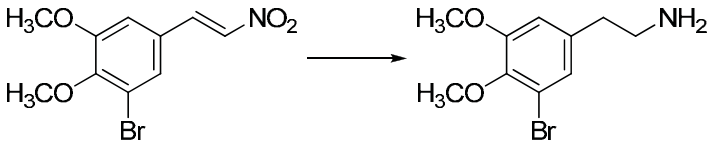
2-chloro-3,4-dimethoxy-phenethylamine (5c). 517 mg (2.4 mmol) of compound **4c** was reacted following the general procedure for zinc reduction to yield 434 mg (74%) as an oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$)** δ 7.01 (d, *J* = 8.4 Hz, 1H), 6.88 (d, J = 8.5 Hz 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.94 (d, J = 5.6 Hz, 2H), 2.83 (d, J = 5.4 Hz, 2H). **HRMS** ($C_{10}H_{15}NO_2Cl^+$): calc. 216.0791 $[M+H]^+$; found 216.0795.



5-chloro-3,4-dimethoxy-phenethylamine (5d). 487 mg (2.0 mmol) of compound **4d** was reacted following the general procedure for zinc reduction to yield 376.5 mg (87%) as a yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$)** δ 6.93 (d, J = 1.9 Hz, 1H), 6.90 (d, J = 1.9 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.14 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H). **HRMS** ($C_{10}H_{15}NO_2Cl^+$): calc. 216.0791 $[M+H]^+$; found 216.0791.



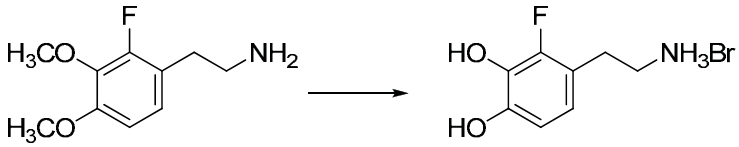
2-bromo-3,4-dimethoxy-phenethylamine (5e). 288 mg (1.0 mmol) of compound **4e** was reacted following the general procedure for zinc reduction to yield 201.3 mg (77%) as yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$)** δ 6.96 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 2.97 (dd, J = 10.4, 3.8 Hz, 2H), 2.84 (dd, J = 10.5, 3.9 Hz, 2H). **^{13}C NMR (75 MHz, methanol-*d*$_4$)** δ 146.93, 143.65, 126.48, 121.82, 121.78, 114.61, 40.61, 32.20. **HRMS** ($C_{10}H_{15}NO_2Br^+$): calc. 260.0286 and 262.0266 $[M+H]^+$; found 260.0288 262.0267.



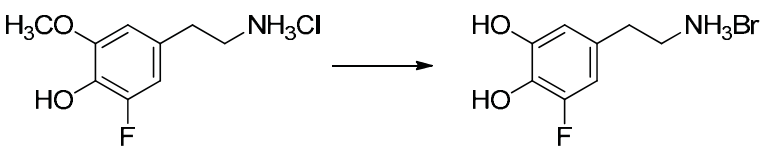
5-bromo-3,4-dimethoxy-phenethylamine (5f). 288 mg (1.0 mmol) of compound **4f** was reacted following the general procedure for zinc reduction to yield 216.1 mg (83%) as a yellow colored solid. **^{1}H NMR (300 MHz, methanol-*d*$_4$)** δ 7.10 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.19 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H). **HRMS** ($C_{10}H_{15}NO_2Br^+$): calc. 260.0286 and 262.0266 $[M+H]^+$; found 260.0292 and 262.0277.

Catechol demethylation reactions

Method A. General demethylation procedure by HBr reflux. For every 1 mmol of mono- or dimethoxy-phenethylamine, 10 mL of concentrated (37%) HBr was refluxed for 20 minutes to degas any dissolved oxygen. The top of the condenser was closed off from the atmosphere and connected to an oil bubbler. The methoxy phenol ether was added and the mixture was refluxed for 3 hours. The excess hydrobromic acid was removed by vacuum and the resulting product was dissolved in methanol (15 mL) and evaporated to dryness under vacuum. This step was repeated again using methanol (15 mL), followed by H_2O (15 mL), and finally methanol (15 mL). After the final evaporation the product was placed in a vacuum desiccator overnight to yield dopamine analogs as their hydrobromide salts. Slow diffusion of ether into an isopropanol solution works well to recrystallize the products if analytical purity is required for further applications. However, recovery is significantly lower.

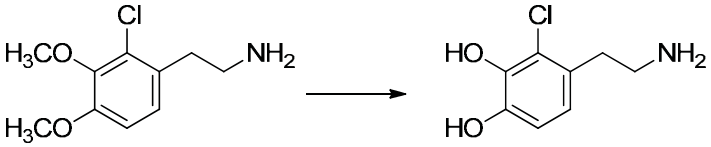


2-fluoro-dopamine-HBr (1a). Following the general procedure above (Method A), 0.250 g (1.26 mmol) of 2-fluoro-3,4-dihydroxy-phenethylamine was reacted as above to yield 0.330 g (104%) of **1a** as a white powdery solid. NMR revealed that there were significant no organic contaminants, however quantitative NMR analysis revealed that the product was 87.9% pure by mass, thus the recovered yield was 91%. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)**: δ 9.40 (s, 1H), 9.00 (s, 1H), 7.87 (s, 3H), 6.57-6.49 (m, 2H), 2.97-2.90 (m, 2H), 2.80-2.75 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 151.01 (d, *J* = 237.9 Hz), 146.97 (d, *J* = 5.6 Hz), 133.85 (d, *J* = 14.3 Hz), 119.45 (d, *J* = 5.4 Hz), 115.15 (d, *J* = 14.1 Hz), 111.47 (d, *J* = 2.6 Hz), 40.42 (s), 31.17 (s). **^{19}F NMR (282 MHz, DMSO-*d*$_6$)**: δ -143.69 (dd, *J* = 6.2, 1.2 Hz). **HRMS** ($C_8H_{11}NO_2F^+$): calc. 172.0774 $[M+H]^+$; found 172.0772.

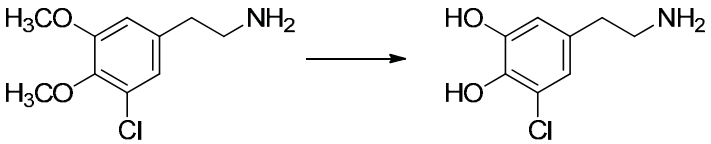


5-fluoro-dopamine-HBr (1b). Following the general procedure above, 0.290 g (1.3 mmol) of 2-fluoro-3-hydroxy-4-methoxyphenethylamine hydrochloride was reacted as above to yield 0.347 g (105%) of **1b** as powdery solid. NMR revealed that there were no organic contaminants, however quantitative NMR analysis revealed that the product was 85.3% pure by mass, thus the recovered yield was 89.6%. **^{1}H NMR (300 MHz, DMSO-*d*$_6$):** δ 9.47 (s, 1H), 8.92 (s, 1H), 7.81 (s, 3H), 6.55-6.53 (m, *J* = 1.8 Hz, 1H), 6.50-6.48 (m, *J* = 1.4 Hz, 2H), 3.04 – 2.85 (m, 2H), 2.78 – 2.62 (m, 2H). **^{1}H NMR (300 MHz, CDCl$_3$):** δ 7.87 (s, 5H), 6.52 (dd, *J* = 11.3, 1.8 Hz, 1H), 6.48 (d, *J* = 1.4 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.74 – 2.62 (m, 2H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$):** δ 152.41 (d, *J* = 237.2 Hz), 148.10 (d, *J* = 6.3 Hz), 132.34 (d, *J* = 14.3 Hz), 127.92 (d, *J* = 8.8 Hz), 112.31 (s), 107.17 (d, *J* = 19.3 Hz), 40.43 (s), 32.74 (s). **^{19}F NMR (282 MHz, DMSO-*d*$_6$):** δ -135.23 (dd, *J* = 11.2, 1.2 Hz). **HRMS** ($C_8H_{11}NO_2F^+$): calc. 172.0774 $[M+H]^+$; found 172.0774.

Method B: General demethylation procedure by BBr$_3$. Halogenated-3,4-dimethoxy-phenethylamine (1.0 mmol) was dissolved in minimal dry DCM (2 mL, dried over 3Å molecular sieves) and cooled to 0 °C by ice bath under nitrogen atmosphere. After cooling, BBr_3 in DCM (2.2 mL, 1 M solution) was added slowly via syringe to prevent vigorous reaction. The reaction was allowed to warm to room temperature and stirred for 1.5 hours. After this time, all reactions were observed to be complete by HPLC. If the reaction was incomplete, extra 0.2-1.0 equivalents of BBr_3 may be added. The reaction mixture was cooled again in an ice bath, quenched by slow addition of dry MeOH (dried over 3Å molecular sieves), and allowed to stir for 10 minutes. The resulting solution was concentrated *in vacuo*. The products were extracted by washing first with Et_2O and then dry MeOH to remove any borane byproducts and the leftover oil was dried under vacuum. The product can be precipitated by dissolving the oil in minimal acetonitrile followed by addition of minimal Et_2O until precipitation occurs.

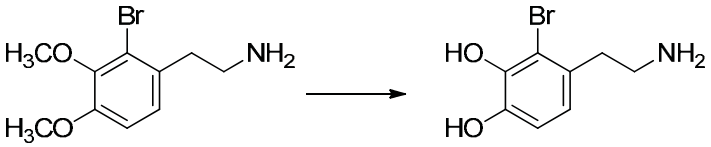


2-chloro-dopamine. 0.169 g (0.78 mmol) was reacted as above to yield 0.130 g (88.19%) of **1b** as a yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 6.81 – 6.71 (m, 2H), 3.16 (d, *J* = 5.1 Hz, 1H), 3.12 – 2.98 (m, 1H). **^{13}C NMR (75 MHz, methanol-*d*$_4$):** δ 145.44, 142.13, 125.24, 120.66, 120.45, 113.35, 39.30, 30.78. **HRMS** ($C_8H_{11}NO_2Cl^+$): calc. 188.0478 and 190.0449 $[M+H]^+$; found 188.0474 and 190.0446.

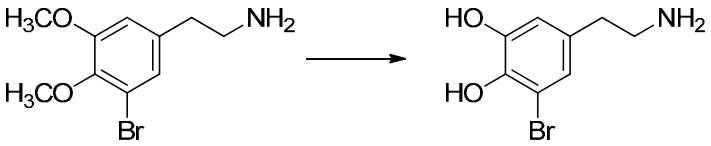


5-chloro-dopamine. 0.221 g (1 mmol) was reacted as above to yield 0.191 g (98.9%) of **1d** as a yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 6.75 (d, J = 2.0 Hz, 1H), 6.68 (d, J = 1.9 Hz, 1H), 3.14 (t, J = 7.6 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H). **^{13}C NMR (75 MHz, methanol-*d*$_4$):** δ 148.13, 142.24, 129.52, 122.02, 121.46,

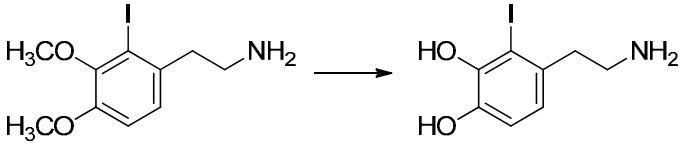
115.25, 41.96, 33.67. **HRMS** ($C_8H_{11}NO_2Cl^+$): calc. 188.0478 and 190.0449 $[M+H]^+$; found 188.0481 and 190.0450.



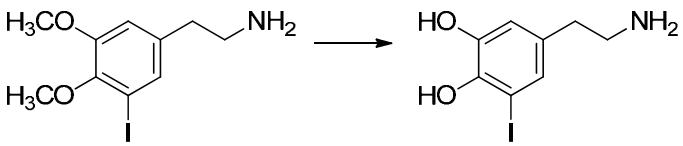
2-bromo-dopamine. 0.201 g (0.77 mmol) was reacted as above to yield 0.171 g (94.8%) of **1e** as a yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$)**: δ 6.73 (q, *J* = 8.2 Hz, 2H), 3.20 – 3.09 (m, 1H), 3.08 – 2.97 (m, 1H). **^{13}C NMR (75 MHz, methanol-*d*$_4$):** δ 146.93, 143.65, 126.48, 121.82, 121.78, 114.61, 40.61, 32.20. **HRMS** ($C_8H_{11}NO_2Br^+$): calc. 231.9973 and 233.9953 $[M+H]^+$; found 231.9975 and 233.9956.



5-bromo-dopamine. 0.216 g (0.8 mmol) was reacted as above to yield 0.175 g (90.8%) of **1f** as a yellow oil. **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 6.90 (d, J = 2.0 Hz, 1H), 6.72 (s, 1H), 3.11 (d, J = 8.0 Hz, 2H), 2.86 – 2.79 (m, 2H). **^{13}C NMR (75 MHz, methanol-*d*$_4$):** δ 146.25, 128.70, 123.32, 115.24, 114.58, 109.51, 40.52, 32.33. **HRMS** ($C_8H_{11}NO_2Br^+$): calc. 231.9973 and 233.9953 $[M+H]^+$; found 231.9972 and 233.9958.

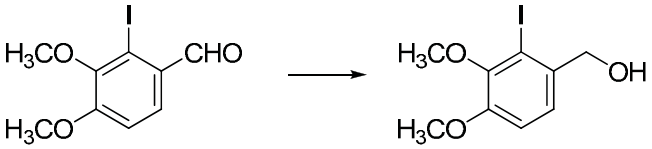


2-iodo-dopamine (1g). 2-iodo-3,4-dimethoxy-phenethylamine (0.5 mmol) was dissolved in minimal dry DCM (2 mL) and cooled to 0 °C under inert atmosphere. After cooling BBr_3 in DCM (1.1 mL, 1 M solution) was added slowly to prevent vigorous reaction. After addition the reaction was stirred at room temperature for 1.5 hours. Progress was monitored by HPLC. Reaction mixture was quenched with sieve-dried MeOH and allowed to stir for 10 minutes. The solution was concentrated under lowered atmosphere. Product was extracted by washing the concentrated solid with Et_2O to remove any borane byproducts and the leftover white powder was dried under vacuum to yield 2-iodo-dopamine (99.5%). **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 3.10 (s, 2H), 3.07 (d, *J* = 4.6 Hz, 2H). **^{13}C NMR (75 MHz, methanol-*d*$_4$):** δ 145.88, 143.51, 130.33, 120.63, 114.62, 89.33, 39.61, 37.44. **HRMS** ($C_8H_{11}NO_2I^+$): calc. 279.9835 $[M+H]^+$; found 279.9835.

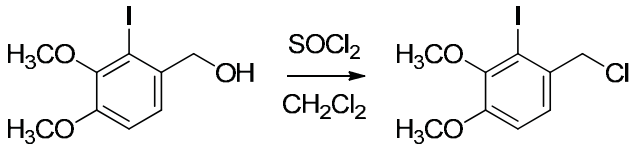


5-iodo-dopamine (1h). 5-iodo-3,4-dimethoxy-phenethylamine(1 mmol) was dissolved in minimal dry DCM (4 mL) and cooled to 0 ^{o}C under inert atmosphere. After cooling BBr_3 in DCM (2.2 mL, 1 M solution) was added slowly to prevent vigorous reaction. After addition the reaction was stirred at room temperature for 1.5 hours. Progress was monitored by HPLC. Reaction mixture was quenched with sieve-dried MeOH and allowed to stir for 10 minutes. The solution was concentrated under lowered atmosphere. Product was extracted by washing the concentrated solid with Et_2O and dry MeOH to remove any borane byproducts and the leftover white powder was dried under vacuum to yield 5-iodo-dopamine (98%). Additional precipitation of the dopamine product can be performed from ACN. **^{1}H NMR (300 MHz, methanol-*d*$_4$)**: δ 6.99 (d, *J* = 1.6p Hz, 1H), 6.66 (d, *J* = 1.5p Hz, 1H), 2.89-2.98 (m, 2H), 2.63-2.70 (m, 2H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$):** δ 145.06, 144.49, 130.18, 128.54, 116.03, 85.33, 31.88, 26.50. **HRMS** ($C_8H_{11}NO_2I^+$): calc. 279.9835 $[M+H]^+$; found 279.9835.

Preparation of 2-iodo-3,4-dimethoxy-phenethylamine (5g)

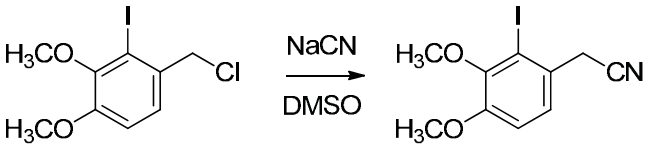


(2-iodo-3,4-dimethoxyphenyl)methanol. 3,4-dimethoxy-5-iodo-benzaladehyde (2.92g, 10 mmol) was dissolved in minimal EtOH and stirred in an ice bath. After the entire solid had dissolved, $NaBH_4$ (3.4g, ~10 mmol) was added to the mixture. The reaction progress was monitored by HPLC. After, 1.5 hours the complete reaction mixture was concentrated under vacuum to half its original volume and poured into a separating funnel containing water. The aqueous layer was extracted three times with DCM. It was then concentrated to give the final product as yellow oil (2.79 g, 9.5 mmol). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.40 – 7.27 (m, 1H), 7.02 (d, *J* = 1.7 Hz, 1H), 4.53 (s, 2H), 3.87 (s, 3H), 3.77 (s, 3H). **UV-Vis:** 216.5, 278.9 nm.

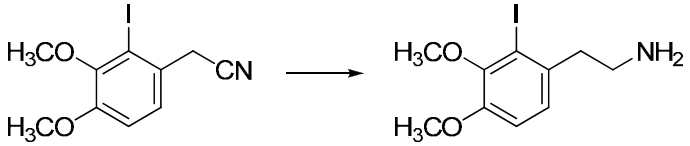


(2-iodo-3,4-dimethoxyphenyl)chloromethane. (2-iodo-3,4-dimethoxyphenyl)methanol (2.79 g, 9.5 mmol) obtained from the previous reaction was dissolved in CH_2Cl_2 and cooled to 0 °C in an ice bath. To the reaction an excess of thionyl chloride (3 mL) was added dropwise. After one hour, the reaction was concentrated *in vacuo* and dissolved in CH_2Cl_2. The organic layer was washed with water and brine. The organic layer was concentrated again under vacuum to afford a yellow oil (2.92 g, 8.55 mmol, 90%)

which crystalized upon standing. HPLC analysis of the crude reaction mixture indicated that ~10% of the starting material did not react during the chlorination procedure. **^{1}H NMR (300 MHz, DMSO-*d*$_6$):** δ 7.36 (dd, *J* = 8.4, 3.3 Hz, 1H), 7.09 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 2H), 3.86 – 3.80 (m, 3H), 3.72 – 3.66 (m, 3H). **UV-Vis:** 220.0, 281.4 nm.

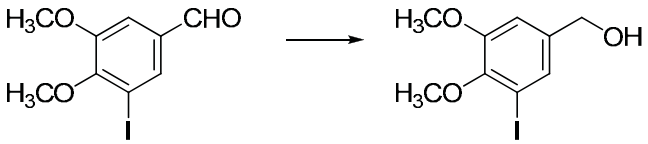


(2-iodo-3,4-dimethoxyphenyl)acetonitrile. (2-iodo-3,4-dimethoxyphenyl)chloromethane (2.66 g, 8.55 mmol) was dissolved in 150 mL of DMSO and allowed to stir. Sodium cyanide was added in excess to the mixture and allowed to stir for 2.5 hours. After the reaction was checked by HPLC the mixture was poured into a separating funnel and extracted with diethyl ether three times and washed with brine. The product was concentrated under vacuum to afford a white crystalline solid (2.24 g, 8.52 mmol, 99.6%). **^{1}H NMR (300 MHz, DMSO-*d*$_6$):** δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 3.96 (d, *J* = 15.8 Hz, 5H), 3.83 (s, 7H). **UV-Vis:** 215.9, 285.7 nm.

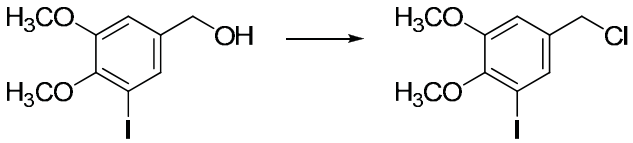


2-iodo-3,4-dimethoxy-phenethylamine (5g). (2-iodo-3,4-dimethoxyphenyl)acetonitrile (0.151 g, 0.5 mmol) from previous step was dissolved in minimal dry THF (1 mL) and transferred into an oven dried three neck flask fitted with a reflux condenser. Borane in THF (1 M, 2.2 mL, 1.1 eq per methoxy group) was added slowly to the mixture over of a time period of 10 minutes. The reaction mixture was then refluxed overnight at 55 °C. The progress was monitored by HPLC. Once the reaction was complete, the mixture was cooled to 0 °C and quenched with addition of H_2O (1 mL) and concentrated HCl (5 mL). After stirring for an additional hour, the mixture was diluted with H_2O (25 mL) and made basic by addition of concentrated NaOH. The mixture was then extracted three times with 97:3 DCM:MeOH and concentrated *in vacuo* to yield the product (0.48 mmol, 96%). To purify, the basic extract was dissolved in cold Et_2O with stirring, concentrated HCl was added dropwise to precipitate the product as an HCl salt. Filtration afforded a white solid 95% yield. **^{1}H NMR (300 MHz, methanol-*d*$_4$):** δ 7.06 (dd, *J* = 10.8, 8.4 Hz, 1H), 6.98 (dd, *J* = 8.4, 3.4 Hz, 1H), 5.51 (s, 3H), 3.88 – 3.83 (m, 3H), 3.80 – 3.76 (m, 3H), 3.27 (t, *J* = 7.2 Hz, 1H), 2.95 – 2.77 (m, 3H). **HRMS** ($C_{10}H_{15}NO_2I^+$): calc. 308.0148 $[M+H]^+$; found 308.0156. **UV-Vis:** 212.9, 279.5 nm.

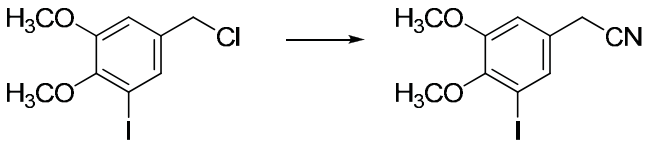
Preparation of 5-iodo-3,4-dimethoxy-phenethylamine (5h)



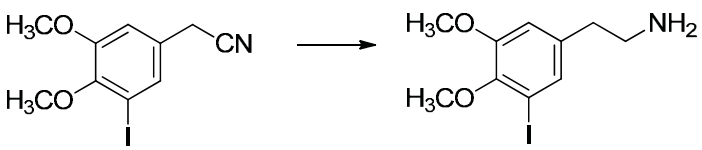
(5-iodo-3,4-dimethoxyphenyl)methanol. 3, 4-dimethoxy-5-iodo-benzaladehyde (2.92 g, 10 mmol) was dissolved in minimal EtOH and stirred in an ice bath. After the entire solid had dissolved $NaBH_4$ (3.4 g, ~10 mmol) was added to the mixture. The progress was monitored by HPLC. After, 1.5 hours the complete reaction mixture was concentrated under vacuum to half its volume and poured into a separating funnel containing water. Aqueous layer was extracted three times with DCM. It was then concentrated to give the final product as yellow oil (2.79 g, 9.5 mmol). **^{1}H NMR (300 MHz, DMSO-d_6):** δ 7.40 – 7.27 (m, 1H), 7.02 (d, *J* = 1.7 Hz, 1H), 4.53 (s, 2H), 3.87 (s, 3H), 3.77 (s, 3H). **UV-Vis:** 214.7, 285.1 nm.



(5-iodo-3,4-dimethoxyphenyl)chloromethane. (5-iodo-3,4-dimethoxyphenyl)methanol (2.78 g, 9.4 mmol) obtained from the previous reaction was dissolved in DCM and cooled to 0 °C in an ice bath. To the reaction an excess of thionyl chloride was added dropwise. After one hour the reaction was concentrated *in vacuo* and dissolved in DCM. The organic layer was washed with H_2O and brine. The organic layer was again concentrated *in vacuo* to afford a yellow colored oil (2.92 g, 8.55 mmol) which crystalized on standing. **^{1}H NMR (300 MHz, DMSO-d_6):** δ 7.36 (dd, *J* = 8.4, 3.3 Hz, 1H), 7.09 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 2H), 3.86 – 3.80 (m, 3H), 3.72 – 3.66 (m, 3H). **UV-Vis:** 218.9, 283.8 nm.



(5-iodo-3,4-dimethoxyphenyl)acetonitrile. The product from the previous reaction (2.92 g, 8.55 mmol) was dissolved in 150 mL of DMSO and allowed to stir. Sodium cyanide was added in excess (4.9 g, 10 mmol) to the mixture and allowed to stir for 2.5 hours. The reaction mixture was poured into a separatory funnel and extracted with diethyl ether three times and washed with brine. The product was concentrated *in vacuo* to give a white crystalline solid (2.24 g, 7.4 mmol). **^{1}H NMR (300 MHz, DMSO-d_6):** δ 7.31 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.69 (s, 2H). **UV-Vis:** 216.5, 285.7 nm.



5-iodo-3,4-dimethoxy-phenethylamine (5h). 3,4-dimethoxy-5-iodo-benzylnitrile (0.156 g, 0.5 mmol) was dissolved in minimal dry THF (1 mL) and transferred into a dry three neck flask with a reflux condenser. Borane in THF (1M, 2 mL) was added slowly to the mixture over of a time period of 10 minutes. The reaction mixture was then refluxed at 55 °C for two hours. Progress was monitored by HPLC. Once the reaction was complete the mixture was cooled to 0 °C and quenched with addition of H_2O (1 mL) and concentrated HCl (5 mL). After stirring for an additional hour the mixture was diluted with H_2O (25 mL) and made basic by addition of concentrated NaOH. Mixture was then extracted three times with DCM and concentrated under vacuum to yield the product (0.147 g, 0.48 mmol). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.22 (s, 1H), 6.74 (s, 1H), 5.32 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H). **HRMS** ($C_{10}H_{15}NO_2I^+$): calc. 308.0148 $[M+H]^+$; found 308.0151. **UV-Vis:** 214.1, 284.4 nm.

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