

Supporting Information for:

C–H Amination of Arenes with Hydroxylamine

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SUPPORTING INFORMATION

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General Information

NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^1H ; 100.71 MHz for ^{13}C), a Varian vnmrs 500 (500.01 MHz for ^1H ; 125.75 MHz for ^{13}C) or a Varian vnmrs 700 MHz (699.76 MHz for ^1H ; 175.95 MHz for ^{13}C) spectrometer. ^1H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak (CDCl_3 : ^1H NMR = 7.26, ^{13}C NMR = 77.16, Methanol- d_4 : ^1H NMR = 3.31, ^{13}C NMR = 49.15). ^1H multiplicities are reported as follows: singlet (s), broad singlet (br), doublet (d), triplet (t), quartet (q), pentet (pent) multiplet (m), sextet (sext), septet (sept), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt). Coupling constants (J) are reported in Hz. GCMS analysis was performed on a Shimadzu GCMSQP2010 gas chromatograph mass spectrometer. The products were separated on a 30 m length x 0.25 mm id RESTEK XTI-5 column coated with a 0.25 μm film. Helium was employed as the carrier gas with a constant column flow of 1.5 mL/min. The injector temperature was held constant at 250 $^\circ\text{C}$. The GC oven temperature program for low molecular weight compounds was as follows: 32 $^\circ\text{C}$ hold 5 min, ramp 15 $^\circ\text{C}/\text{min}$ to 250 $^\circ\text{C}$, hold for 1.5 min. Melting points were determined with a MelTemp 3.0 (Laboratory Devices, Inc) and are uncorrected. High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer.

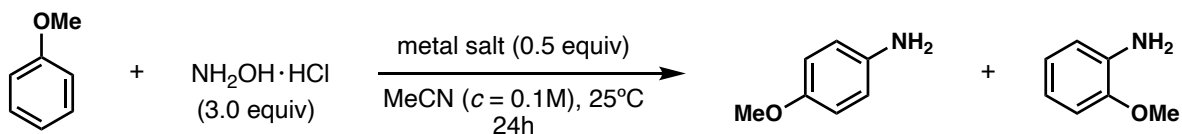
All reactions were performed using oven-dried (150 $^\circ\text{C}$) round-bottomed flasks or new reaction vessels unless otherwise stated. Reactions were carried out under an inert atmosphere of nitrogen with dry solvents, unless otherwise stated. Dichloromethane, pentane, diethyl ether, ethyl acetate, toluene, acetonitrile and hexanes were obtained from Fisher Scientific and used as received. CDCl_3 was purchased from Cambridge Isotope Laboratories. Anhydrous acetonitrile was purchased from Sigma-Aldrich and used as received. Titanium trichloride (12% in aqueous HCl) was purchased from Sigma-Aldrich and transferred to a Schlenk flask for long term storage. Titanium(III) sulfate (20% in 1-4% sulfuric acid) was purchased from Alfa Aesar. Sulfuric acid 95-98% was purchased from VWR Chemicals (supplier BDH) and used as received.

Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using ultraviolet light as a visualizing agent and an acidic mixture of *p*-anisaldehyde or a basic mixture of potassium permanganate and heat as developing agents.

Reaction Optimization

Mediator Screen

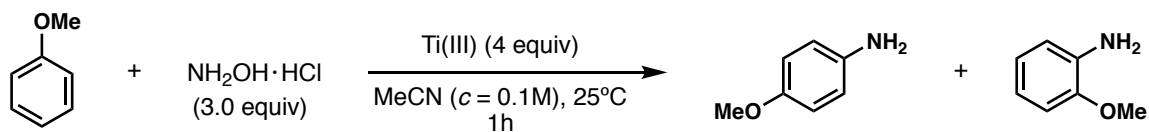
Hydroxylamine hydrochloride (0.3 mmol) and the corresponding metal salt were added to a reaction vial and placed under an atmosphere of nitrogen. A solution of anisole (0.10 mmol) in acetonitrile (0.50 mL) was added in 1 portion, and the reaction was stirred vigorously under nitrogen for 24 h at rt (25 °C). After this time, the reaction was basified with sodium hydroxide (20%) and extracted with ethyl acetate. The internal standard 1,3,5-trimethoxybenzene was added, and the crude mixture was analyzed by GC.



Metal	Salts	Yield (%) ^b
Fe(II)	FeF ₂ , FeCl ₂ , FeBr ₂ , Fe(oxalate) ₂ , Fe(OAc) ₂ , FeSO ₄ , Fe(BF ₄) ₂ , ferrocene	0
Fe(III)	Fe ₂ (SO ₄) ₃ , FeF ₃ , FeBr ₃ , Fe(OTf) ₃ , Fe(acac) ₃ , Fe(NO ₃) ₃	0
Cu(I)	Cu[MeCN] ₄ OTf, Cu[MeCN] ₄ PF ₆ , CuCl, CuI	0
Cu(II)	CuF ₂ , CuCl ₂ , CuBr ₂ [*] , Cu(OAc) ₂ , CuO	0
Mn(II)	MnCl ₂ , Mn(OAc) ₂ , Mn(OTf) ₂ , MnSO ₄	0
Mn(III)	Mn(OAc) ₃	0
Cr	CrCl ₂ , CrCl ₃	0
Co	CoCl ₂ , CoBr ₂ , Co(BF ₄) ₂ , CoF ₃	0
Ni(II)	NiCl ₂ , Ni(OAc) ₂ , Ni(acac) ₂ , Ni(OTf) ₂ , Ni(BF ₄) ₂	0
Ti(III)	Cp ₂ TiCl ^c TiCl ₃ (THF) ₃ ^c	0 13%

^a Conditions: substrate (0.1 mmol), NH₂OH·HCl (0.3 mmol), MeCN (0.5 mL), metal salt (0.05 mmol), room temperature, 24 h; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard; ^c 1 equiv of Ti(III) used * significant amount of bromo-anisole observed by GCMS

Additional Optimization



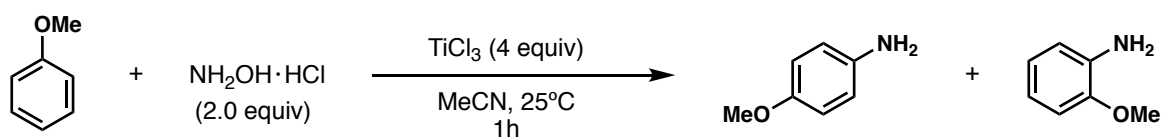
		Conditions	o:p	mono:di	Yield (%) ^b
conc: 0.1M		added in 1 portion	-	-	0
		added in over 20min	1:1.41	-	7
		10 equiv. H ₂ SO ₄ , added in 1 portion	-	-	0
		10 equiv. H ₂ SO ₄ , added over 20 min	1:2.18	4.12:1	39
		2eq NH ₂ OH·HCl, 10 equiv. H ₂ SO ₄ , added in 1 portion	0	0	0
		2eq NH ₂ OH·HCl, 10 equiv. H ₂ SO ₄ , added over 20 min	1:2.09	- ^c	32
conc: 0.5M		added in 1 portion	0	0	0
		added in over 20min	1:1.12	-	15
		10 equiv. H ₂ SO ₄ , added in 1 portion	1:1.25	-	16
		10 equiv. H ₂ SO ₄ , added over 20 min	1:3.27	1:1.78	65
		2eq NH ₂ OH·HCl, 10 equiv. H ₂ SO ₄ , added in 1 portion	1:1.55	-	18
		2eq NH ₂ OH·HCl, 10 equiv. H ₂ SO ₄ , added over 20 min	1:2.07	2.61:1	73

^a Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), MeCN (x mL), Ti(III) (0.4 mL for 0.4 mmol of NH₂OH·HCl and 0.6 mL for 0.6 mmol of NH₂OH·HCl), room temperature, 1 h; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard; ^c trace diamination.

Note: yields refer to the combined yield of mono and di-aminated products

Summary: The reaction yield improved with increasing reaction concentration and slow introduction of the titanium solution. The addition of sulfuric acid was found to be critical to ensure good yields of the product. Visually, the presence of sulfuric acid significantly reduced the decolorization of the titanium solution and the amount of titanium solution needed to reach the purple end-point color. Excess hydroxylamine in this case resulted in significant over reaction, which reduced the yield of the desired product.

Acid Equivalent Screen:



Acid	[anisole]	o:p ratio	mono:diamination	Yield (%) ^b
H ₂ SO ₄ , 1 equiv	0.50 M	1:1.92	-	15
H ₂ SO ₄ , 2 equiv	0.50 M	1:2.17	4.5:1	25
H ₂ SO ₄ , 5 equiv	0.50 M	1:2.21	1.9:1	34
H₂SO₄, 10 equiv	0.50 M	1:2.07	2.6:1	73
H ₂ SO ₄ , 15 equiv	0.50 M	1:1.96	2.6:1	66
H ₂ SO ₄ , 20 equiv	0.50 M	1:2.16	1.6:1	40

^a Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), MeCN (x mL), TiCl₃ (0.4 mL, added over 20min), room temperature, 1 h; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard

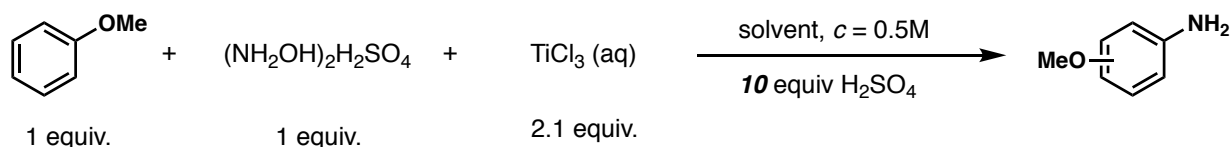
Reaction Concentration Screen:

Acid	[anisole]	o:p ratio	mono:diamination	Yield (%) ^b
H ₂ SO ₄ , 10 equiv	0.10 M	1:2.09	-	34
H ₂ SO ₄ , 10 equiv	0.25 M	1:2.04	2.8:1	51
H₂SO₄, 10 equiv	0.50 M	1:2.07	2.6:1	73
H ₂ SO ₄ , 10 equiv	0.75 M	1:2.08	2.1:1	65
H ₂ SO ₄ , 10 equiv	1.0 M	1:2.17	2.7:1	51

^a Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), MeCN (x mL), TiCl₃ (0.4 mL, added over 20min), room temperature, 1 h; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard

Note: yields refer to the combined yield of mono and di-aminated products

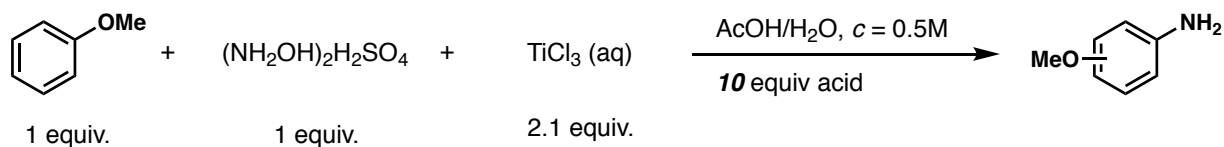
Solvent and Acid Screens



Solvent	Mono (%)	o:p ratio	diamination (%)	Total ^b (%)	Comments
AcOH/H ₂ O (5:2)	54	1:2.2	21	76	
MeCN	48	1:2.1	24	73	
HFIP	-	-	-	-	no SM or pdt by GC
MeOH*	30	1:3.3	-	30	
DMF*	36	1:5.1	-	36	
THF*	18	1:1.4	-	4	

Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), solvent (0.4 mL), conc. H₂SO₄ (2.0 mmol), TiCl₃ (0.4 mL, added over 20min), room temperature, 1 h; ^a solvents used was not dried or degassed previously; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard; * these solvents are known to react with aminyl radicals to form carbon-based radicals

Note: yields refer to the combined yield of mono and di-aminated products

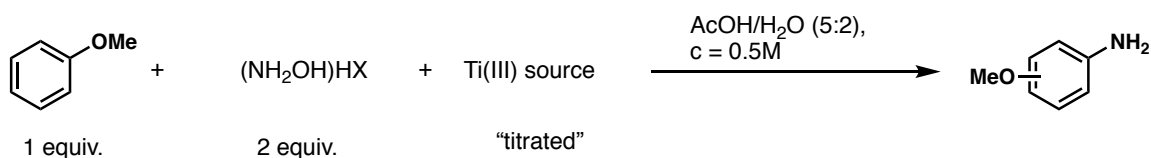


Acid	mono (%)	o:p ratio	Comments
H ₂ SO ₄	54	1:2.2	Additional ~21% of diaminated product
H ₃ PO ₄	9	1:4.1	
HCl	15	1:1.3	
HBr	-	-	
HBF ₄	5	1:2.8	
TfOH	5	1:0.6	
TFA	3	ortho	
TsOH	3	1:1.9	
MsOH	31	1:2.1	

Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), solvent (0.4 mL), acid (2.0 mmol), TiCl₃ (0.4 mL, added over 20min), room temperature, 1 h; ^a determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Note: Sulfuric acid was found to be uniquely suitable for this reaction, with other acids (over a range of pK_a) being significantly less effective.

Screen of Various Ti(III) Solutions and Hydroxylamine Salts

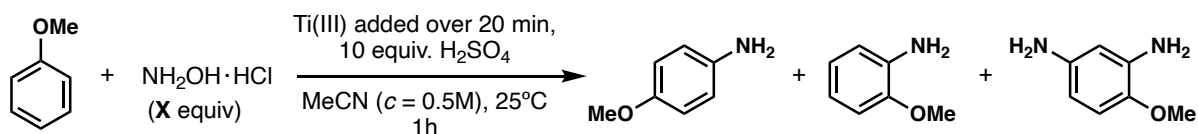


	Ti(III) source	(NH ₂ OH)HX	mono (%)	o:p ratio	diamination	Total ^a (%)
no H ₂ SO ₄	Ti ₂ (SO ₄) ₃	(NH ₂ OH) ₂ H ₂ SO ₄	3	1:0.5	-	3
	TiCl ₃	(NH ₂ OH) ₂ H ₂ SO ₄	6	1:0.42	-	6
	TiCl ₃	(NH ₂ OH)HCl	4	1:0.2	-	4
10 equiv. H ₂ SO ₄	Ti ₂ (SO ₄) ₃	(NH ₂ OH) ₂ H ₂ SO ₄	25	1:3.7	2	28
	TiCl ₃	(NH ₂ OH) ₂ H ₂ SO ₄	48	1:2.6	16	65
	TiCl₃	(NH₂OH)HCl	54	1:2.2	21	76

Conditions: substrate (0.2 mmol), NH₂OH·HCl (0.4 mmol), solvent (x mL), TiCl₃ (0.4 mL, added over 20min), room temperature, 1 h; ^a determined by GC using 1,3,5-trimethoxybenzene as internal standard.

Notes: Commercial titanium(III) chloride (in hydrochloric acid) was found to be optimal, although titanium(III) sulfate was also effective. Interestingly, hydroxylamine sulfate gave consistently lower yields compared to hydroxylamine hydrochloride.

Yields refer to the combined yield of mono and di-aminated products



NH ₂ OH·HCl Equivalence	ortho (%) ^b	para (%) ^b	di-amine (%) ^b	o:p	mono:di	Total (%) ^b
2eq NH ₂ OH·HCl	18	36	20	1:2.07	2.61:1	73
3eq NH ₂ OH·HCl	8	22	38	1:2.70	1:1.27	67
4eq NH ₂ OH·HCl	4	14	57	1:3.40	1:3.08	75

^a Conditions: substrate (0.2 mmol), NH₂OH·HCl (x mmol), MeCN (0.4 mL), Ti(III) (0.4 mL for 0.4 mmol of NH₂OH·HCl, 0.6 mL for 0.6 mmol of NH₂OH·HCl, 0.7 mL for 0.8 mmol of NH₂OH·HCl), room temperature, 1 h; ^b determined by GC using 1,3,5-trimethoxybenzene as internal standard.

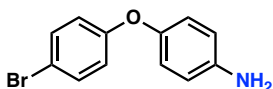
Substrate Limitations

The following substrates were examined under the standard amination conditions. However, low conversion were noted.

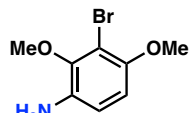
Low conversions (< 30%):



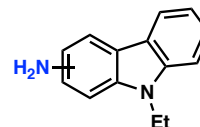
~ 10% conversion



~ 10% conversion

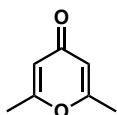


~ 21% conversion

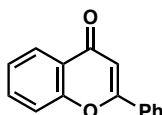


~10% conversion
mono + diamine

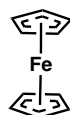
No reactions/ incompatibility:



<5% conversion



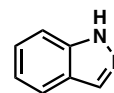
0% conversion



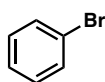
0% conversion



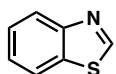
0% conversion



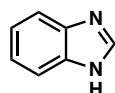
100% conversion;
no desired amination



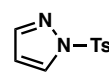
0% conversion



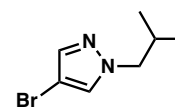
0% conversion



0% conversion



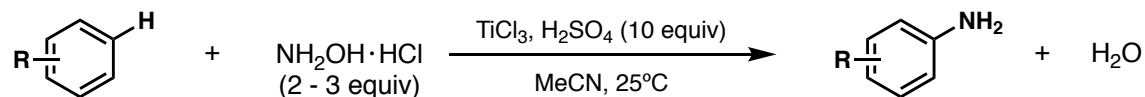
100% conversion;
no desired amination



0% conversion;
no desired amination

Experimental Procedures for Amination

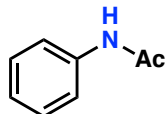
General Procedure for Amination



The appropriate arene (1.0 mmol) and hydroxylamine hydrochloride (2.0 or 3.0 mmol) were suspended in acetonitrile (2.0 mL). The reaction was immersed in a rt (25 °C) water bath. Concentrated sulfuric acid (10 mmol) was added dropwise, and the reaction was stirred for 10 min open to air. After this time, the reaction was sealed with a rubber septum, and the headspace was purged for 1 min with nitrogen. Titanium trichloride (12% in aqueous HCl) was added via a syringe pump (addition rate of 4 mL/h) until the purple color of the titanium trichloride solution persisted for more than 10 min. The reaction was stirred for an additional 10 min before the addition of saturated aqueous sodium citrate (3 mL). Sodium hydroxide (20% aqueous) was then added slowly until the reaction mixture became basic, and the resulting solution was then extracted with ethyl acetate (5 x 10 mL). The combined organic phases were dried over magnesium sulfate and purified by column chromatography over silica.

Compound Synthesis and Characterization

N-phenylacetamide (SI-1)



A modification of the general procedure was followed using benzene (156 mg, 2.0 mmol, 2.0 equiv) and hydroxylamine hydrochloride (69.5 mg, 1.0 mmol, 1.0 equiv) as starting materials. After concentrating via rotary evaporation, the reaction was dissolved in dichloromethane (5.0 mL) and treated with acetic anhydride (1.5 equiv) and triethylamine (2.0 equiv) at rt for 5 h. Then, the reaction was quenched with saturated sodium bicarbonate (3 mL) and extracted with dichloromethane (3 x 5 mL), and the organic extracts were dried over magnesium sulfate. Purification by column chromatography (hexanes/EtOAc 4:1) afforded the product as a cream colored solid (13 mg, 10%).

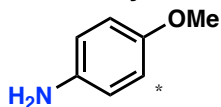
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.44 (br s, 1H), 7.31 (t, $J = 7.7$ Hz, 2H), 7.10 (t, $J = 7.4$ Hz, 1H), 2.16 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 168.5, 138.0, 129.1, 124.4, 120.0, 24.7.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{10}\text{NO}^+$ 136.0757; found 136.0755.

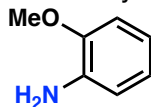
The characterization data matched that of the commercial sample.

2-methoxyaniline (2b), 4-methoxyaniline (2a), 4-methoxybenzene-1,3-diamine (2c)



The general procedure was followed using anisole (108 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude mixture was purified by flash column chromatography (hexanes/EtOAc 4:1 to 1:1 to 0:1) to afford 2-methoxyaniline as a pale yellow oil (20.1 mg, 16%), 4-methoxyaniline as a light gray solid (42 mg, 34%), and 4-methoxybenzene-1,3-diamine as a gray solid that darkens rapidly in air (32 mg, 23%).

2-methoxyaniline (2b)

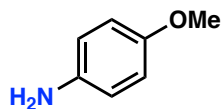


$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.84–6.77 (m, 2H), 6.77–6.71 (m, 2H), 3.86 (br s, 3H), 3.79 (s, 2H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 147.4, 136.3, 121.2, 118.6, 115.1, 110.6, 55.5.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{NO}^+$ 124.0757; found 124.0756.

4-methoxyaniline (2a)



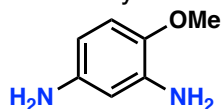
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.78–6.71 (m, 2H), 6.69–6.61 (m, 2H), 3.75 (s, 3H), 3.42 (br s, 2H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 152.9, 140.1, 116.5, 114.9, 55.9.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{NO}^+$ 124.0757; found 124.0759.

The characterization data matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

4-methoxybenzene-1,3-diamine (**2c**)

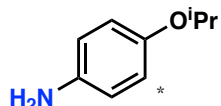


$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.61 (d, $J = 8.3$ Hz, 1H), 6.13 (d, $J = 2.7$ Hz, 1H), 6.07 (dd, $J = 8.4, 2.7$ Hz, 1H), 3.77 (s, 3H), 3.53 (br s, 4H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 141.0, 140.8, 137.2, 112.4, 104.9, 103.5, 56.4.

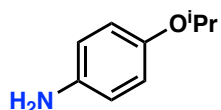
HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{11}\text{N}_2\text{O}^+$ 139.0866; found 139.0865.

4-isopropoxyaniline (**3a**), 4-isopropoxybenzene-1,3-diamine (**3b**)



The general procedure was followed using isopropoxybenzene (136 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude mixture was purified by flash column chromatography (hexanes/EtOAc 4:1 to 3:1) to afford 4-isopropoxyaniline (60.5 mg, 40%) first, followed by 4-isopropoxybenzene-1,3-diamine (38.7 mg, 22%) as light yellow oils that darkened upon storage on the benchtop.

4-isopropoxyaniline (**3a**)



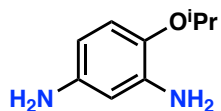
$^1\text{H NMR}$: (500 MHz, CDCl_3): δ 6.74 (d, $J = 8.7$ Hz, 2H), 6.63 (d, $J = 8.7$ Hz, 2H), 4.37 (hept, $J = 6.1$ Hz, 1H), 3.42 (br s, 2H), 1.29 (d, $J = 6.1$ Hz, 6H).

$^{13}\text{C NMR}$: (126 MHz, CDCl_3): δ 151.0, 140.3, 118.0, 116.5, 71.2, 22.3.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{14}\text{NO}^+$ 152.1070; found 152.1071.

The characterization data matched that found in the literature (*Organometallics* **2007**, *26*, 5627–5635).

4-isopropoxybenzene-1,3-diamine (**3b**)

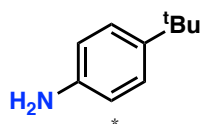


$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.64 (d, $J = 8.4$ Hz, 1H), 6.12 (d, $J = 2.7$ Hz, 1H), 6.04 (dd, $J = 8.4, 2.7$ Hz, 1H), 4.31 (hept, $J = 6.1$ Hz, 1H), 3.70 (br s, 1H), 3.38 (br s, 1H), 1.30 (d, $J = 6.1$ Hz, 6H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 141.3, 138.9, 138.6, 117.2, 105.2, 103.4, 72.3, 22.5.

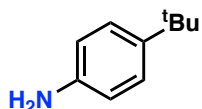
HRMS : (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{15}\text{N}_2\text{O}^+$ 167.1179; found 167.1177.

4-(*tert*-butyl)aniline (**4a**), 3-(*tert*-butyl)aniline (**4b**)



The general procedure was followed using *tert*-butylbenzene (134 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude oil was purified by flash column chromatography (hexanes/EtOAc 4:1 to 3:1) to afford an isomeric mixture of the title compounds (**4a** : **4b** 1.82 : 1) as a yellow oil (77.5 mg, 52%).

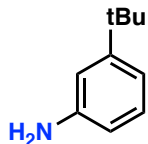
4-(*tert*-butyl)aniline (**4a**)



$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.20 (d, $J = 8.5$ Hz, 2H), 6.66 (d, $J = 8.5$ Hz, 2H), 3.58 (br s, 2H), 1.29 (s, 9H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 143.9, 141.5, 126.2, 115.1, 34.0, 31.7.

3-(*tert*-butyl)aniline (**4b**)



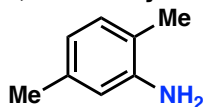
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.11 (t, $J = 7.8$ Hz, 1H), 6.82 (ddd, $J = 7.8, 1.9, 1.0$ Hz, 1H), 6.74 (t, $J = 2.1$ Hz, 1H), 6.53 (ddd, $J = 7.8, 2.3, 1.0$ Hz, 1H), 3.58 (br s, 2H), 1.30 (s, 9H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 152.6, 146.2, 129.1, 116.0, 112.6, 112.5, 34.7, 31.4.

HRMS : (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{16}\text{N}^+$ 150.1277; found 150.1278.

The characterization data matched that found in the literature (*Angew. Chem. Int. Ed.* **2019**, *58*, 526–531).

2,5-dimethylaniline (**5**)



The general procedure was followed using *para*-xylene (106 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford the title compound (84 mg, 70%) as a light yellow oil.

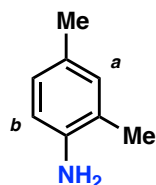
¹H NMR (500 MHz, CDCl₃): δ 6.95 (d, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.52 (s, 1H), 3.55 (br s, 2H), 2.26 (s, 3H), 2.14 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 144.5, 136.7, 130.4, 119.5, 119.4, 115.8, 21.2, 17.0.

HRMS: (ESI) *m/z* [M+H]⁺ calcd. for C₈H₁₂N⁺ 122.0964; found 122.0963.

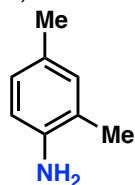
The characterization data matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

2,4-dimethylaniline (**6a**), 2,6-dimethylaniline (**6b**), 3,5-dimethylaniline (**6c**)



The general procedure was followed using *meta*-xylene (106 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford an inseparable mixture (**6a** : **6b** : **6c** 7.74 : 1.82 : 1) of the title compounds (72 mg, 60%) as a light yellow oil. The purified spectra was compared to commercially obtained samples of the individual isomers to confirm their identities.

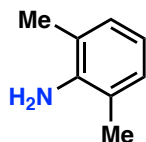
2,4-dimethylaniline (**6a**)



¹H NMR (700 MHz, CDCl₃): δ 6.90 (d, *J* = 2.1 Hz, 1H), 6.87 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 3.50 (br s, 2H, overlapping with another isomer), 2.25 (s, 3H, overlapping with another isomer), 2.16 (s, 3H).

¹³C NMR (176 MHz, CDCl₃): δ 142.1, 131.2, 127.9, 127.4, 122.6, 115.2, 20.5, 17.5.

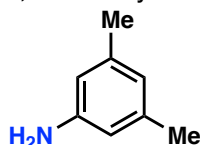
2,6-dimethylaniline (**6b**)



$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.97 (d, $J = 7.4$ Hz, 2H), 6.67 (t, $J = 7.4$ Hz, 1H), 3.50 (s, 2H, overlapping with another isomer), 2.20 (s, 3H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 142.8, 128.3, 121.8, 118.1, 17.6.

3,5-dimethylaniline (**6c**)

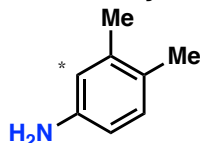


$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.44 (s, 1H), 6.35 (s, 2H), 3.50 (s, 2H, overlapping with another isomer), 2.25 (s, 6H, overlapping with another isomer).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 146.4, 139.1, 120.6, 113.2, 21.4.

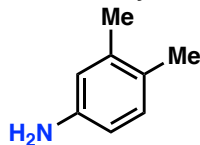
HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{12}\text{N}^+$ 122.0964; found 122.0963.

3,4-dimethylaniline (**7a**), 2,3-dimethylaniline (**7b**)



The general procedure was followed using *ortho*-xylene (106 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude mixture was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford an inseparable mixture of the title compounds (96.8 mg, 80%) as a light yellow oil (**7a** : **7b** = 2 : 1).

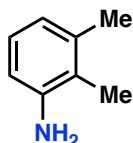
3,4-dimethylaniline (**7a**)



$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.96 (d, $J = 7.9$ Hz, 1H), 6.56 (d, $J = 2.5$ Hz, 1H), 6.50 (dd, $J = 7.9, 2.5$ Hz, 1H), 3.54 (br s, 2H), 2.24 (s, 3H), 2.21 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 144.2, 137.4, 130.4, 126.6, 117.0, 112.7, 19.9, 18.8.

2,3-dimethylaniline (**7b**)



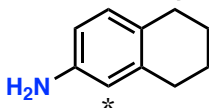
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.98 (t, $J = 7.7$ Hz, 1H), 6.68 (d, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 3.54 (br s, 2H), 2.32 (s, 3H), 2.12 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 144.6, 137.2, 126.6, 121.0, 120.7, 113.3, 20.6, 12.8.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{12}\text{N}^+$ 122.0964; found 122.0963.

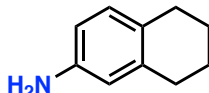
The characterization data matched that of a commercial source.

5,6,7,8-tetrahydronaphthalen-2-amine (**8a**), 5,6,7,8-tetrahydronaphthalen-1-amine (**8b**)



The general procedure was followed using 1,2,3,4-tetrahydronaphthalene (132 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford an inseparable mixture of the title compounds (96.8 mg, 66%) as a light yellow oil (**8a** : **8b** = 3 : 1).

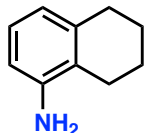
5,6,7,8-tetrahydronaphthalen-2-amine (**8a**)



$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.87 (d, $J = 8.2$, 1H), 6.49 (d, $J = 8.1$ Hz, 1H), 6.44 (s, 1H), 3.52 (br s, 2H), 2.71–2.64 (m, 4H), 1.81–1.70 (m, 4H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 143.9, 138.0, 130.0, 127.5, 115.6, 113.3, 29.6, 28.7, 23.7, 23.4.

5,6,7,8-tetrahydronaphthalen-1-amine (**8b**)



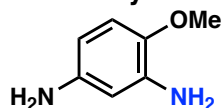
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.96 (td, $J = 7.7, 3.4$ Hz, 1H), 6.57 (dt, $J = 7.8, 2.2$ Hz, 1H), 6.53 (d, $J = 7.8$ Hz, 1H), 3.52 (br s, 2H), 2.75 (m, 2H), 2.47 (t, $J = 6.5$ Hz, 2H), 1.91–1.85 (m, 2H), 1.77 (m, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 144.4, 138.2, 126.0, 121.9, 119.7, 112.2, 30.0, 24.2, 22.9, 22.9.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{14}\text{N}^+$ 148.1121; found 148.1121.

The characterization data matched that found in the literature (*Chem. Eur. J.* **2017**, *23*, 563–567).

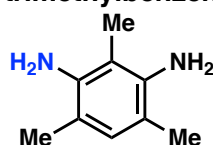
4-methoxybenzene-1,3-diamine (9)



The general procedure was followed using 4-methoxyaniline (123 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 1:2 to 1:4) to afford 4-methoxybenzene-1,3-diamine as a grey solid that darkens rapidly in air (112 mg, 81%).

The ^1H NMR, ^{13}C NMR, and HRMS spectra were identical to compound **xx** reported above and matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

trimethylbenzene-1,3-diamine (10)



The general procedure was followed using 2,4,6-trimethylaniline (135 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 1:2 to 1:4) to afford the title compound as a yellow foam (94 mg, 62%).

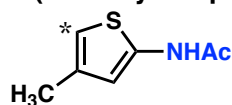
^1H NMR (500 MHz, CDCl_3): δ 6.69 (s, 1H), 3.46 (s, 4H), 2.11 (s, 6H), 2.03 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 141.1, 129.4, 112.6, 107.0, 17.3, 11.0.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{15}\text{N}_2^+$ 151.1230; found 151.1231.

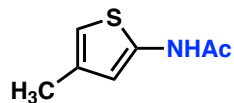
Melting Point: 52–53.5 °C

N-(4-methylthiophen-3-yl)acetamide (11a), *N*-(3-methylthiophen-2-yl)acetamide (11b)



A modified procedure was followed using 3-methylthiophene (98 mg, 1.0 mmol) and hydroxylamine hydrochloride (208 mg, 3.0 mmol, 3.0 equiv) as starting materials. The crude reaction was concentrated, and the resulting residue was dissolved in dichloromethane (5.0 mL) and treated with acetic anhydride (1.5 equiv) and triethylamine (2.0 equiv) at rt for 5 h. Subsequently, the reaction was quenched with saturated sodium bicarbonate (3 mL) and extracted with dichloromethane (3 x 5 mL), and the organic extracts were dried over magnesium sulfate. Purification by column chromatography (hexanes/EtOAc 2:1 to 1:1) afforded an inseparable mixture of the products as a cream colored solid (**11a** : **11b** 1.33 : 1, 79 mg, 51%).

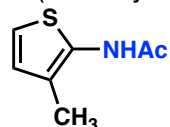
N-(4-methylthiophen-3-yl)acetamide (**11a**)



$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 10.98 (s, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 2.12 (s, 3H), 2.03 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, $\text{DMSO-}d_6$): δ 166.2, 139.7, 133.5, 112.4, 111.8, 22.6, 15.7.

N-(3-methylthiophen-2-yl)acetamide (**11b**)



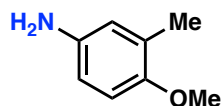
$^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 10.06 (s, 1H), 6.90 (d, $J = 5.5$ Hz, 1H), 6.69 (d, $J = 5.5$ Hz, 1H), 2.13 (s, 3H), 2.09 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, $\text{DMSO-}d_6$): δ 167.1, 133.3, 127.1, 121.2, 117.0, 22.5, 12.9.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{NOS}^+$ 156.0478; found 156.0478.

The melting points were not taken as the products were isolated as an inseparable mixture by flash column chromatography.

4-methoxy-3-methylaniline (12)



The general procedure was followed using 1-methoxy-2-methylbenzene (122 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 3:1 to 2:1) to afford the title compound as a yellow solid (109 mg, 80%).

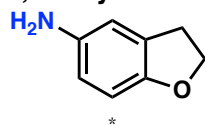
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.67 (d, $J = 8.4$ Hz, 1H), 6.56–6.53 (m, 1H), 6.51 (dd, $J = 8.4, 2.9$ Hz, 1H), 3.76 (s, 3H), 3.36 (br s, 2H), 2.17 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 151.2, 139.7, 127.8, 118.7, 113.2, 111.7, 56.1, 16.4.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{12}\text{NO}^+$ 138.0913; found 138.0913.

The characterization data matched that found in the literature (*Chem. Eur. J.* **2017**, *23*, 563–567).

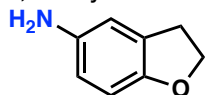
2,3-dihydrobenzofuran-5-amine (13a), 2,3-dihydrobenzofuran-5,7-diamine (13b)



*

The general procedure was followed using dihydrobenzofuran (135 mg, 1.0 mmol) and hydroxylamine hydrochloride (173.7 mg, 2.5 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 2:1 to 1:1) to afford 2,3-dihydrobenzofuran-5-amine as a yellow solid (74.3 mg, 55%), followed by 2,3-dihydrobenzofuran-5,7-diamine as a brown solid (18.7 mg, 12%).

2,3-dihydrobenzofuran-5-amine (**13a**)



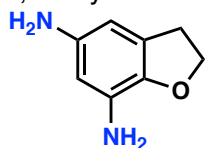
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.63–6.58 (m, 2H), 6.46 (dd, $J = 8.5, 2.3$ Hz, 1H), 4.49 (t, $J = 8.6$ Hz, 2H), 3.39 (br s, 2H), 3.13 (t, $J = 8.6$ Hz, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 153.3, 140.0, 127.9, 114.8, 112.8, 109.4, 71.0, 30.4.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{10}\text{NO}^+$ 136.0757; found 136.0756.

The characterization data matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

2,3-dihydrobenzofuran-5,7-diamine (**13b**)



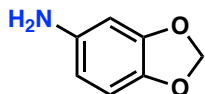
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.08–6.03 (m, 1H), 5.97–5.93 (m, 1H), 4.49 (t, $J = 8.6$ Hz, 2H), 3.44 (s, 4H), 3.10 (t, $J = 8.6$ Hz, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 141.1, 140.9, 130.8, 127.6, 102.5, 102.5, 71.1, 31.1.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}^+$ 151.0866; found 151.0865.

Melting Point: 114–116 °C (decomposition)

benzo[*d*][1,3]dioxol-5-amine (**14**)



The general procedure was followed using benzo[*d*][1,3]dioxole (122 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials and glacial acetic acid (instead of acetonitrile) as the solvent. The crude product was purified by flash column chromatography (hexanes/EtOAc 2:1 to 1:1) to afford the title compound as a yellow solid (78 mg, 57%).

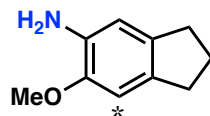
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.62 (d, $J = 8.2$ Hz, 1H), 6.29 (d, $J = 2.2$ Hz, 1H), 6.13 (dd, $J = 8.2, 2.3$ Hz, 1H), 5.86 (s, 2H), 3.47 (br s, 2H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 148.3, 141.5, 140.5, 108.7, 107.0, 100.8, 98.2.

HRMS: (ESI) m/z $[M+H]^+$ calcd. for $C_7H_8NO_2^+$ 138.0550; found 138.0549.

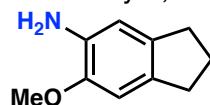
The characterization data matched that found in the literature (*Chem. Eur. J.* **2017**, *23*, 563–567).

6-methoxy-2,3-dihydro-1*H*-inden-5-amine (15a), 5-methoxy-2,3-dihydro-1*H*-inden-4-amine (15b)



The general procedure was followed using 5-methoxy-2,3-dihydro-1*H*-indene (148.2 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 3:1 to 2:1) to afford a mixture of the title compounds as a wet, pale yellow solid (73.3 mg, 45%, **15a** : **15b** = 2 : 1).

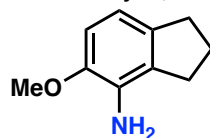
6-methoxy-2,3-dihydro-1*H*-inden-5-amine (15a)



1H NMR (500 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.63 (s, 1H), 3.83 (s, 3H), 3.69 (br s, 2H), 2.91–2.77 (m, 4H), 2.05 (pent, $J = 7.4$ Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.5, 136.2, 134.6, 134.0, 111.3, 107.2, 55.9, 32.9, 32.7, 25.9.

5-methoxy-2,3-dihydro-1*H*-inden-4-amine (15b)



1H NMR (500 MHz, $CDCl_3$): δ 6.66 (d, $J = 8.0$ Hz, 1H), 6.62 (d, $J = 8.0$ Hz, 1H), 3.84 (s, 3H), 3.69 (br s, 2H), 2.87 (t, $J = 7.5$ Hz, 2H), 2.74 (t, $J = 7.4$ Hz, 2H), 2.12 (p, $J = 7.4$ Hz, 2H).

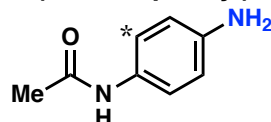
^{13}C NMR (126 MHz, $CDCl_3$): δ 145.8, 137.3, 132.2, 129.5, 113.3, 109.2, 56.2, 32.7, 29.7, 25.7.

HRMS: (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{14}NO^+$ 164.1070; found 164.1071.

The characterization data matched that found in the literature (*Chem. Eur. J.* **2017**, *23*, 563–567).

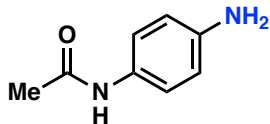
The melting points were not taken as the products were isolated as an inseparable mixture by flash column chromatography.

***N*-(2-aminophenyl)acetamide (16a), *N*-(4-aminophenyl)acetamide (16b)**



The general procedure was followed using *N*-phenylacetamide (135 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude products were purified by flash column chromatography (hexanes/EtOAc 1:1 to 1:3) to afford an inseparable mixture of the title compounds (**16a** : **16b** = 2.44 : 1) as a yellow solid (66 mg, 44%).

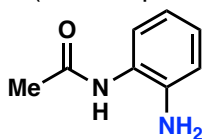
N-(2-aminophenyl)acetamide (**16a**)



$^1\text{H NMR}$ (500 MHz, DMSO- d_6): δ 9.10 (s, 1H), 7.14 (dd, J = 7.8, 1.5 Hz, 1H), 6.91–6.85 (m, 1H), 6.70 (dd, J = 7.9, 1.4 Hz, 1H), 6.52 (td, J = 7.6, 1.5 Hz, 1H), 4.83 (s, 2H), 2.03 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, DMSO- d_6): δ 168.1, 141.9, 125.7, 125.3, 123.5, 116.1, 115.8, 23.3.

N-(4-aminophenyl)acetamide (**16b**)



$^1\text{H NMR}$ (500 MHz, DMSO- d_6): δ 9.46 (s, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 8.7 Hz, 2H), 4.80 (br s, 2H), 1.94 (s, 3H).

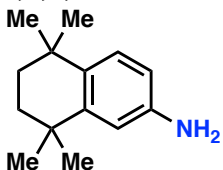
$^{13}\text{C NMR}$ (126 MHz, DMSO- d_6): δ 167.1, 144.6, 128.6, 120.8, 113.8, 23.7.

HRMS : (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}^+$ 151.0866; found 151.0866.

The melting points were not taken as the products were isolated as an inseparable mixture by flash column chromatography.

The characterization data matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-amine (17)



The general procedure was followed using 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (188 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford the title compound as a pale orange solid (172.6 mg, 85%).

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.10 (dd, J = 8.3, 1.6 Hz, 1H), 6.64 (t, J = 2.0 Hz, 1H), 6.52 (dd, J = 8.4, 2.0 Hz, 1H), 3.50 (br s, 2H), 1.65 (s, 4H), 1.25 (s, 6H), 1.24 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3): δ 146.0, 143.8, 135.5, 127.5, 113.7, 113.0, 35.4 (2C), 34.4, 33.7, 32.2 (2C), 32.0 (2C).

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{22}\text{N}^+$ 204.1747; found 204.1749.

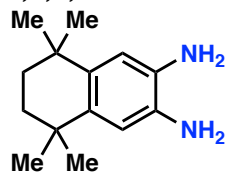
The characterization data matched that found in the literature. (*Org. Lett.* **2013**, *15*, 1378–1381).

Scale-up procedure for compound 17:

The scale-up procedure was adapted from the general procedure without further optimization.

1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (1.88 g, 10.0 mmol) and hydroxylamine hydrochloride (2.08 mg, 30.0 mmol) were suspended in dry acetonitrile (20 mL). The resulting solution was immersed in a rt (25 °C) water bath, and concentrated sulfuric acid was added slowly (5.33 mL, 100 mmol). The water bath was removed, and the reaction was allowed to warm to rt (25 °C). The reaction flask was then sealed with a septum, and the headspace was flushed with nitrogen for 5 min. TiCl_3 (12% in aqueous HCl) was added via a syringe pump (addition rate of 20 mL per hour) until the purple color of the TiCl_3 solution persisted for more than 10 min. During the addition, the reaction temperature was routinely checked, and the addition rate was adjusted to ensure the temperature was kept below 30 °C. The reaction was stirred for an additional 10 min before saturated aqueous sodium citrate (30 mL) was added. Sodium hydroxide (20%) was then added slowly until the reaction turned basic. The reaction mixture was subsequently extracted with ethyl acetate (5 x 20 mL). The combined organic phases were then dried over magnesium sulfate and purified by column chromatography over silica. The product was isolated as a pale orange solid (1.65 g, 81.5%) together with a smaller fraction of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2,3-diamine, **17b** (196 mg, 9%) which was isolated as a pale yellow solid that turned brown after prolonged storage on the benchtop.

5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2,3-diamine (17b)



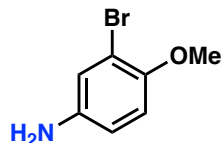
^1H NMR (700 MHz, CDCl_3): δ 6.63 (s, 2H), 3.29 (s, 4H), 1.63 (s, 4H), 1.23 (s, 12H).

^{13}C NMR (176 MHz, CDCl_3): δ 137.0 (2C), 132.8 (2C), 114.7 (2), 35.5 (2C), 33.8 (2C), 32.2 (4C).

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}^+$ 219.1856; found 219.1855.

Melting Point: 111–113 °C (decomposition)

3-bromo-4-methoxyaniline (18)



The general procedure was followed using 2-bromoanisole (186 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials and glacial acetic acid (instead of acetonitrile) as the solvent. The crude product was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford the title compound as a yellow oil (141 mg, 70%).

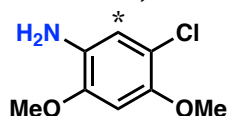
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.93 (d, $J = 2.7$ Hz, 1H), 6.74 (d, $J = 8.6$ Hz, 1H), 6.60 (dd, $J = 8.6, 2.8$ Hz, 1H), 3.81 (s, 3H), 3.46 (br s, 2H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 149.2, 141.2, 120.4, 115.2, 113.8, 112.5, 57.1.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_9\text{BrNO}^+$ 201.9862; found 201.9863.

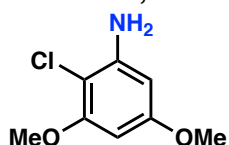
The characterization data matched that found in the literature (*Chem. Eur. J.* **2017**, *23*, 563–567).

2-chloro-3,5-dimethoxyaniline (19a), 5-chloro-2,4-dimethoxyaniline (19b)



The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (172 mg, 1.0 mmol) and hydroxylamine hydrochloride (139 mg, 2.0 mmol) as starting materials. The crude product mixture was purified by flash column chromatography (hexanes/EtOAc 4:1 to 3:2 to 2:3) to afford a yellow oil (**19a**, 24 mg, 13%), followed by a low-melting pale yellow solid (**19b**, 89 mg, 47%).

2-chloro-3,5-dimethoxyaniline (19a)

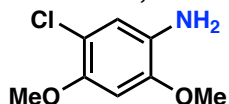


$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 6.72 (s, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.57 (s, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 147.86, 146.68, 130.81, 116.34, 114.12, 98.97, 57.63, 56.01.

HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{11}\text{ClNO}_2^+$ 188.0473; found 188.0473.

5-chloro-2,4-dimethoxyaniline (19b)



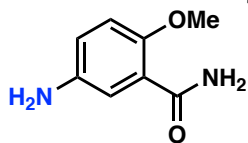
$^1\text{H NMR}$: (500 MHz, CDCl_3): δ 6.46 (s, 1H), 6.21 (s, 1H), 3.79 (s, 6H), 3.47 (s, 2H).

$^{13}\text{C NMR}$: (126 MHz, CDCl_3): δ 140.23, 130.41, 104.43, 99.73, 57.02.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{11}\text{ClNO}_2^+$ 188.0473; found 188.0473.

Melting Point: 34–36 °C

5-amino-2-methoxybenzamide (20)



The general procedure was followed using 2-methoxybenzamide (151 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 0:1) to afford the title compound as a white solid (157 mg, 95%).

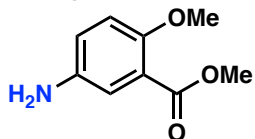
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 7.84 (br s, 1H), 7.55 (d, $J = 2.7$ Hz, 1H), 6.86–6.73 (m, 2H), 5.90 (br s, 1H), 3.89 (d, $J = 1.3$ Hz, 3H), 3.56 (br s, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 167.2, 151.2, 140.5, 121.3, 120.0, 118.8, 113.1, 56.6.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}^+$ 167.0815; found 167.0815.

Melting Point: 73–76 °C

methyl 5-amino-2-methoxybenzoate (21)



The general procedure was followed using methyl 2-methoxybenzoate (166 mg, 1.0 mmol) and hydroxylamine hydrochloride (208.5 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford the title compound as a pale yellow oil (128 mg, 71%).

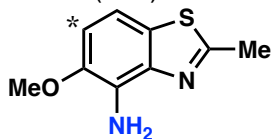
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.14 (dd, $J = 2.1, 1.2$ Hz, 1H), 6.85–6.78 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.50 (s, 2H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 166.9, 152.5, 139.7, 120.6, 120.4, 118.2, 114.2, 56.9, 52.2.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{12}\text{NO}_3^+$ 182.0812; found 182.0813.

The characterization data matched that found in the literature (*Adv. Synth. Catal.* **2010**, *352*, 2463–2473).

6-methoxy-2-methylbenzo[d]thiazol-7-amine (22a), 6-methoxy-2-methylbenzo[d]thiazol-5-amine (22b)



The general procedure was followed using 6-methoxy-2-methylbenzothiazole (89.5 mg, 0.50 mmol), hydroxylamine hydrochloride (105 mg, 1.5 mmol) as starting materials and acetonitrile (1 mL) as the solvent. The crude product was purified by flash column chromatography (hexanes/EtOAc 5:1 to 2:3)

to afford 6-methoxy-2-methylbenzo[*d*]thiazol-7-amine as a pale grey solid (39.2 mg, 40%), followed by 6-methoxy-2-methylbenzo[*d*]thiazol-5-amine as a tan solid (25.5 mg, 26%).

6-methoxy-2-methylbenzo[*d*]thiazol-7-amine (**22a**)



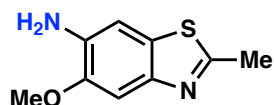
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 7.75 (d, $J = 8.6$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 4.30 (br s, 2H), 4.28 (s, 3H), 3.16 (s, 3H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 164.2, 148.8, 143.7, 129.6, 122.9, 112.1, 110.8, 56.7, 20.3.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{11}\text{N}_2\text{OS}^+$ 195.0587; found 195.0587.

Melting Point: 120–122 °C

6-methoxy-2-methylbenzo[*d*]thiazol-5-amine (**22b**)



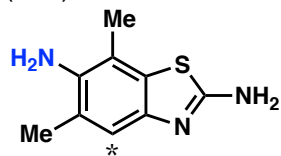
$^1\text{H NMR}$ (700 MHz, CDCl_3) δ 7.25 (s, 1H), 7.13 (s, 1H), 3.95 (br s, 2H), 3.90 (s, 3H), 2.75 (s, 3H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3) δ 164.5, 148.2, 146.9, 136.2, 125.2, 107.0, 101.9, 56.0, 20.0.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{11}\text{N}_2\text{OS}^+$ 195.0587; found 195.0585.

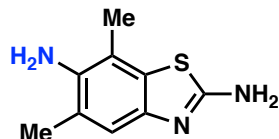
Melting Point: 113–115 °C

5,7-dimethylbenzo[*d*]thiazole-2,6-diamine (**23a**), 5,7-dimethylbenzo[*d*]thiazole-2,4-diamine (**23b**)



The general procedure was followed using 5,7-dimethylbenzo[*d*]thiazol-2-amine (89 mg, 0.50 mmol) and hydroxylamine hydrochloride (105 mg, 1.5 mmol) as starting materials and acetonitrile (1 mL) as the solvent. The crude products were purified by flash column chromatography (hexanes/EtOAc 1:1 to 0:1) to afford a mixture of the title compounds as a pale yellow powder (45 mg, 50%). A small sample was purified via preparative TLC (100% EtOAc as eluent) to separate the two isomers for further characterization.

5,7-dimethylbenzo[*d*]thiazole-2,6-diamine (**23a**)

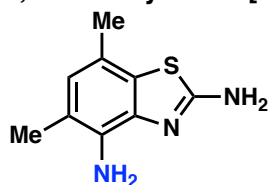


$^1\text{H NMR}$ (700 MHz, CD_3OD): δ 6.62 (s, 1H), 2.25 (s, 3H), 2.20 (s, 3H), NH_2 protons not observed due to rapid exchange.

$^{13}\text{C NMR}$ (176 MHz, CD_3OD): δ 167.8, 141.3, 134.1, 129.4, 125.7, 121.1, 121.0, 20.4, 17.1.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{12}\text{N}_3\text{S}^+$ 194.0746; found 194.0745.

5,7-dimethylbenzo[d]thiazole-2,4-diamine (23b)

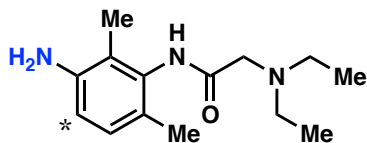


$^1\text{H NMR}$ (700 MHz, CD_3OD): δ 7.00 (s, 1H), 2.25 (s, 3H), 2.23 (s, 3H), NH_2 protons not observed due to rapid exchange.

$^{13}\text{C NMR}$ (176 MHz, CD_3OD): δ 165.4, 143.4, 137.7, 129.6, 121.8, 116.8, 114.2, 16.9, 15.7.

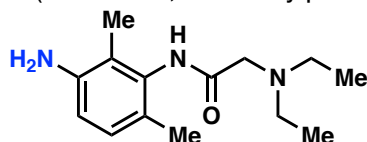
HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_{12}\text{N}_3\text{S}^+$ 194.0746; found 194.0745.

N-(3-amino-2,6-dimethylphenyl)-2-(diethylamino)acetamide (24a), *N*-(4-amino-2,6-dimethylphenyl)-2-(diethylamino)acetamide (24b)



The general procedure was followed using lidocaine (234 mg, 1.0 mmol) and hydroxylamine hydrochloride (208 mg, 3.0 mmol) as starting materials. The crude product was purified by flash column chromatography (hexanes/EtOAc 1:1 to 0:1) to afford an inseparable mixture of the title compounds (5.56 : 1) as a cream colored powder (199 mg, 80%).

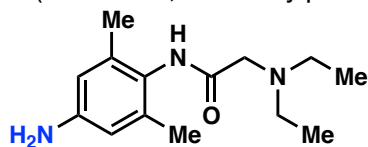
N-(3-amino-2,6-dimethylphenyl)-2-(diethylamino)acetamide (24a)



$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 8.90 (br s, 1H), 6.90 (d, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 3.53 (br s, 2H), 3.22 (s, 2H), 2.69 (q, $J = 7.1$ Hz, 4H), 2.13 (d, $J = 2.2$ Hz, 3H), 2.02 (s, 3H), 1.13 (t, $J = 7.2$ Hz, 6H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 170.6, 143.5, 134.3, 128.9, 124.8, 120.3, 114.4, 57.6, 49.1, 18.24, 12.8, 12.60.

N-(4-amino-2,6-dimethylphenyl)-2-(diethylamino)acetamide (**24b**)



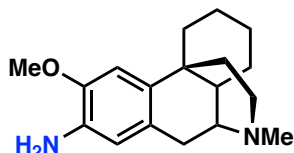
$^1\text{H NMR}$ (700 MHz, CDCl_3): δ 8.70 (br s, 1H), 6.41 (s, 2H), 3.52 (br s, 2H), 3.19 (s, 2H), 2.66 (t, $J = 7.1$ Hz, 4H), 2.12 (s, 6H), 1.12 (t, $J = 7.1$ Hz, 6H).

$^{13}\text{C NMR}$ (176 MHz, CDCl_3): δ 170.99, 145.4, 136.4, 125.1, 114.9, 57.6, 49.1, 18.7, 12.8.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}^+$ 250.1914; found 250.1916.

The melting points were not taken as the products were isolated as an inseparable mixture by flash column chromatography.

4-amino-dextromethorphan (**25**)



The general procedure was followed using dextromethorphan (135.6 mg, 0.5 mmol), hydroxylamine hydrochloride (104 mg, 1.5 mmol) as starting materials and acetonitrile (1 mL) as the solvent. Dextromethorphan was used as a free base, as described in the literature. The crude product was purified by flash column chromatography (EtOAc/MeOH/ Et_3N 1:0:0.05 to 19:1:0.5) to afford the title compound as a pale yellow gum (93 mg, 65%).

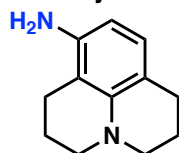
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.61 (s, 1H), 6.46 (s, 1H), 3.80 (s, 3H), 3.65 (br s, 2H), 2.86 (d, $J = 18.2$ Hz, 1H), 2.79 (dd, $J = 5.8, 3.2$ Hz, 1H), 2.58–2.52 (m, 1H), 2.45 (ddd, $J = 11.9, 4.8, 1.8$ Hz, 1H), 2.39 (s, 3H), 2.31–2.24 (m, 1H), 2.13 (td, $J = 12.3, 3.4$ Hz, 1H), 1.80 (dt, $J = 12.8, 3.2$ Hz, 1H), 1.71 (td, $J = 12.7, 4.8$ Hz, 1H), 1.65–1.59 (m, 1H), 1.49 (dt, $J = 8.5, 2.7$ Hz, 1H), 1.40–1.26 (m, 5H), 1.03 (t, $J = 7.2$ Hz, 1H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 146.6, 133.8, 130.0, 129.8, 114.3, 107.4, 58.3, 55.8, 47.5, 45.4, 42.8, 42.0, 36.8, 36.7, 26.7, 26.7, 23.7, 22.3.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}^+$ 287.2118; found 287.2117.

The characterization data matched that found in the literature (*ACS Catal.* **2016**, *6*, 8162–8165).

amino-julolidine (**26**)



Procedure for julolidine hydrochloride: Julolidine (0.5 g, 2.9 mmol, Alfa Aesar) was suspended in Et₂O (10 mL) and passed through a pipette silica plug (2 in). The silica plug was washed with more Et₂O (10 mL) to provide a pale yellow solution. Anhydrous HCl in Et₂O (2 M, 1.5 mL, 3.0 mmol) was then added dropwise, resulting in the precipitation of the julolidine HCl salt. The suspension was allowed to stand for 10 min, after which the precipitated solids were filtered and dried.

Procedure for amino-julolidine: The general procedure was followed using julolidine hydrochloride (104.5 mg, 0.5 mmol) and hydroxylamine hydrochloride (104 mg, 1.5 mmol) as starting materials and glacial acetic acid (1 mL) as the solvent. The crude product was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford the title compound as a brown oil (52 mg, 55%).

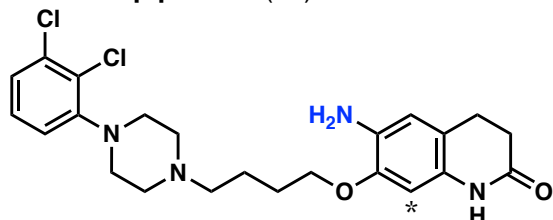
¹H NMR (700 MHz, CDCl₃): δ 6.65 (dt, *J* = 7.9, 0.9 Hz, 1H), 6.04 (d, *J* = 7.9 Hz, 1H), 3.43 (br s, 2H), 3.10–3.02 (m, 4H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.49 (t, *J* = 6.8 Hz, 2H), 2.08–2.00 (m, 2H), 2.00–1.92 (m, 2H).

¹³C NMR (176 MHz, CDCl₃): δ 143.9, 142.6, 127.2, 113.0, 107.1, 104.4, 50.7, 49.6, 27.4, 22.8, 22.4, 22.1.

HRMS: (ESI) *m/z* [M+H]⁺ calcd. for C₁₂H₁₇N₂⁺ 189.1386; found 189.1387.

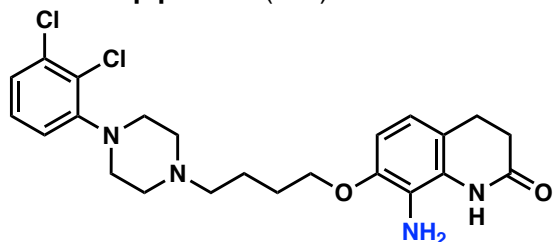
The characterization data matched that found in the literature (*Synlett* **2017**, *28*, 1652–1656.)

amino-azipiprazole (27)



The general procedure was followed using azipiprazole (89 mg, 0.2 mmol) and hydroxylamine hydrochloride (41 mg, 0.6 mmol) as starting materials, sulfuric acid (2 mmol) as an additive, and acetonitrile (0.4 mL) as the solvent. The crude product was purified by preparative TLC (CH₂Cl₂/MeOH/Et₃N 19:1:0.5) to yield **27a** as an off-white powder (contaminated with unreacted starting material) and **27b** as a yellow wax (60 mg, 65%). **27a** can be further purified via careful preparative TLC (EtOAc/MeOH/Et₃N 19.5:0.5:0.5) to obtain a pure, clear film (9.2 mg, 10%).

amino-azipiprazole (27a)

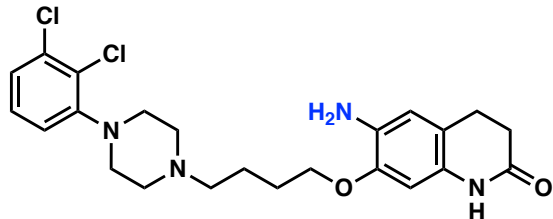


¹H NMR (700 MHz, CDCl₃): δ 8.65 (br s, 1H), 7.17–7.09 (m, 2H), 6.96 (dd, *J* = 7.3, 2.3 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.79 (br s, 2H), 3.08 (br s, 4H), 2.88 (dd, *J* = 8.4, 6.3 Hz, 2H), 2.65 (br s, 4H), 2.61–2.56 (m, 2H), 2.53–2.45 (m, 2H), 1.93–1.81 (m, 2H), 1.78–1.68 (m, 2H).

^{13}C NMR (176 MHz, CDCl_3): δ 172.3, 151.4, 147.0, 134.2, 127.7, 127.6, 126.1, 124.7, 123.4, 118.7, 117.5, 117.4, 106.2, 68.6, 58.4, 53.5, 51.5, 31.4, 27.6, 25.4, 23.7.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{29}\text{Cl}_2\text{N}_4\text{O}_2^+$ 463.1662; found 463.1661.

amino-azipiprazole (27b)

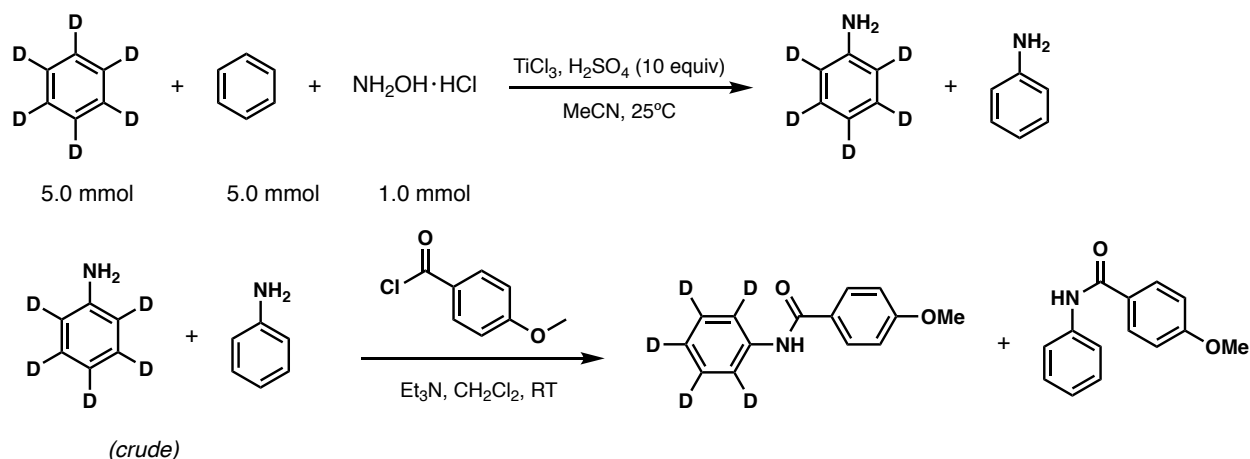


^1H NMR (700 MHz, CDCl_3): δ 8.33 (br s, 1H), 7.18–7.08 (m, 2H), 6.95 (dd, $J = 6.8, 2.8$ Hz, 1H), 6.53 (s, 1H), 6.27 (s, 1H), 3.99 (t, $J = 6.3$ Hz, 2H), 3.62 (br s, 2H), 3.07 (br s, 4H), 2.81 (dd, $J = 8.5, 6.6$ Hz, 2H), 2.65 (br s, 4H), 2.57 (dd, $J = 8.6, 6.5$ Hz, 2H), 2.52–2.44 (m, 2H), 1.91–1.81 (m, 2H), 1.77–1.67 (m, 2H).

^{13}C NMR (176 MHz, CDCl_3): δ 171.7, 151.4, 146.0, 134.1, 131.8, 129.0, 127.6, 127.6, 124.7, 118.7, 115.9, 114.9, 100.5, 68.6, 58.3, 53.4, 51.4, 31.3, 27.5, 25.0, 23.6.

HRMS: (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{29}\text{Cl}_2\text{N}_4\text{O}_2^+$ 463.1662; found 463.1662.

Kinetic Isotope Experiments



Benzene (5.0 mmol), benzene- d_6 (5.0 mmol), and hydroxylamine hydrochloride (1.0 mmol) were suspended in acetonitrile (2.0 mL). The reaction was immersed in a rt (25 °C) water bath. Concentrated sulfuric acid (10 mmol) was added dropwise, and the reaction was stirred open to air for 10 min. After this time, the reaction was capped, and the headspace was purged with nitrogen for 1 min. $TiCl_3$ (12% in aqueous HCl) was added via a syringe pump (addition rate: 4 mL/h) until the purple color of the titanium trichloride solution persisted for more than 10 min. The reaction was stirred for an additional 10 min before the addition of saturated aqueous sodium citrate (3 mL). Sodium hydroxide (20% aqueous) was then added slowly until the solution turned basic. The reaction was subsequently extracted with ethyl acetate (5 x 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed via rotary evaporation.

The resulting crude mixture of anilines was taken up in dry CH_2Cl_2 (5 mL). Triethylamine (1.5 mmol) was added, followed by *p*-anisoyl chloride (1.0 mmol). The reaction was stirred overnight at rt. The reaction was then quenched by the addition of saturated sodium bicarbonate and stirred for 30 min at rt. The reaction was washed with water (5 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were then dried over magnesium sulfate, concentrated via rotary evaporation, and purified by preparative TLC.

Based on the integration of the proton signals in the 1H NMR spectrum, the kinetic isotope effect was determined to be ~ 1.0 (**Figure S1**). The experiment was repeated 2 additional times with identical results.

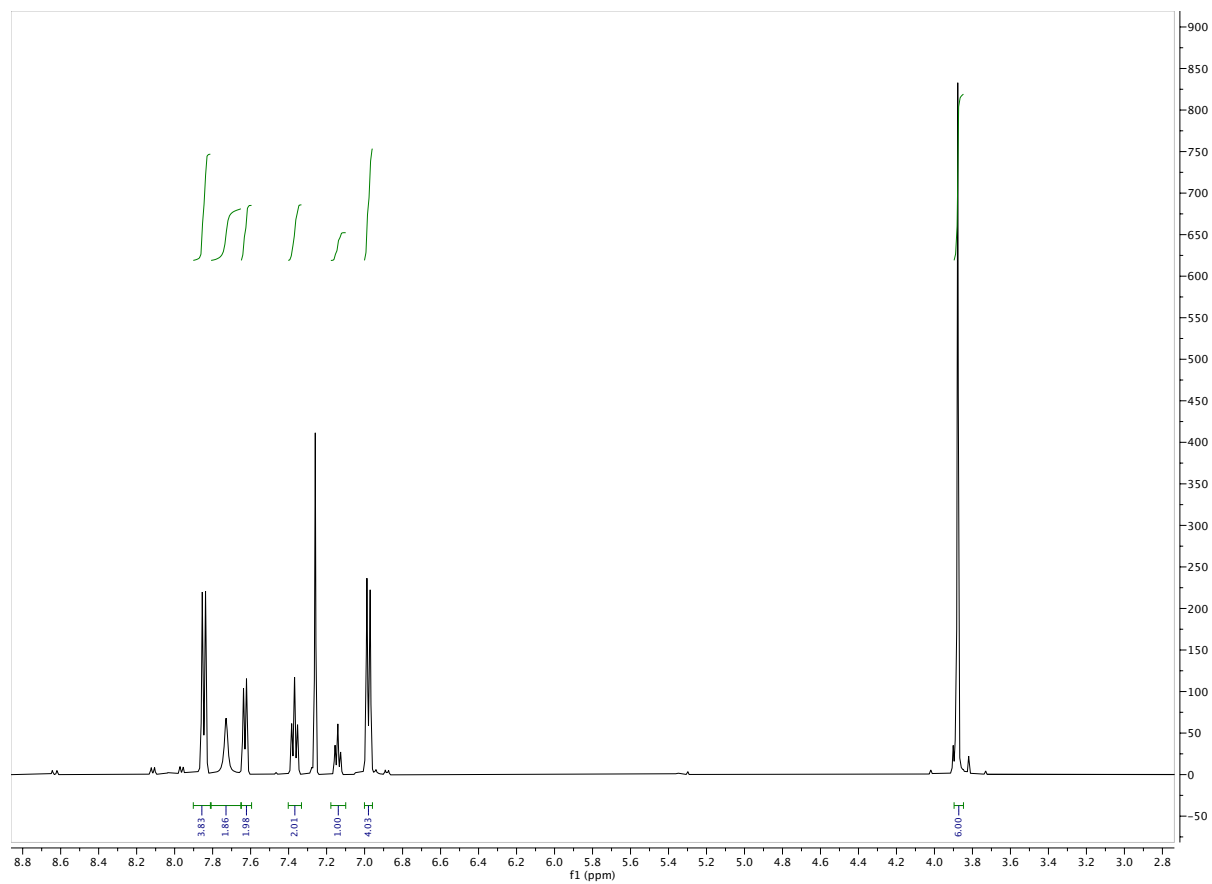


Figure S1. ¹H NMR of *d*₅-4-methoxy-*N*-phenylbenzamide and 4-methoxy-*N*-phenylbenzamide from KIE experiment.

References

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