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Evaluation of 2-(piperidine-1-yl)-ethyl (PIP) as a protecting group for phenols: Stability to *ortho*-lithiation conditions and boiling concentrated hydrobromic acid, orthogonality with most common protecting group classes, and deprotection via Cope elimination or by mild Lewis acids

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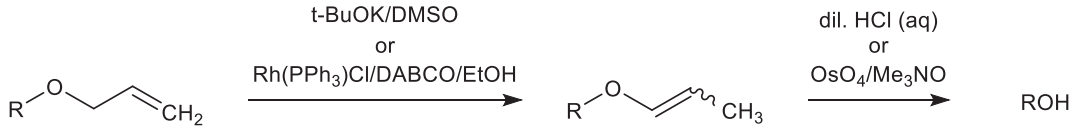
ABSTRACT

A new protecting group, 2-(piperidine-1-yl)-ethyl (PIP), was evaluated as a protecting group for phenols. The PIP group was stable to *ortho*-lithiation conditions and refluxing with concentrated hydrobromic acid. Deprotection was accomplished by two routes, oxidation to *N*-oxides followed by Cope elimination (CE) and subsequent hydrolysis or ozonolysis of the vinyl ether or one-step deprotection by BBr_3•Me_2S. The PIP group is orthogonal to the *O*-benzyl, *O*-acetyl, *O*-*t*-butyldiphenylsilyl, *O*-methyl, *O*-*p*-methoxybenzyl, *O*-allyl, *O*-tetrahydropyranyl and *N*-*t*-butoxy carbonyl groups. The CE step was systematically studied and was found to give higher yields when the reaction was performed in the presence of silylating agents.

1. Introduction

The manipulation of complex organic molecules with many functional groups creates a need for many different protecting groups. [1]. A protecting group that is stable to strong acids and bases, nucleophiles and electrophiles and that can be removed under mild conditions is very desirable to organic chemists. Moreover, orthogonality of protecting groups to many other protecting groups is a highly desirable property. [2].

"Assisted removal" is an important concept in protecting group chemistry. [1]. One example is the deprotection of allyl ethers such as **1** via isomerization with a base or transition metal salts to vinyl ethers **2.** These vinyl ethers can then be cleaved with acid or through oxidation to the parent hydroxy compounds **3** (eq 1). [1].



1 **2** **3**

For 2-(phenylselenyl)ethyl protected compounds, deprotection of **4** is accomplished via oxidation to selenoxides **5** followed by

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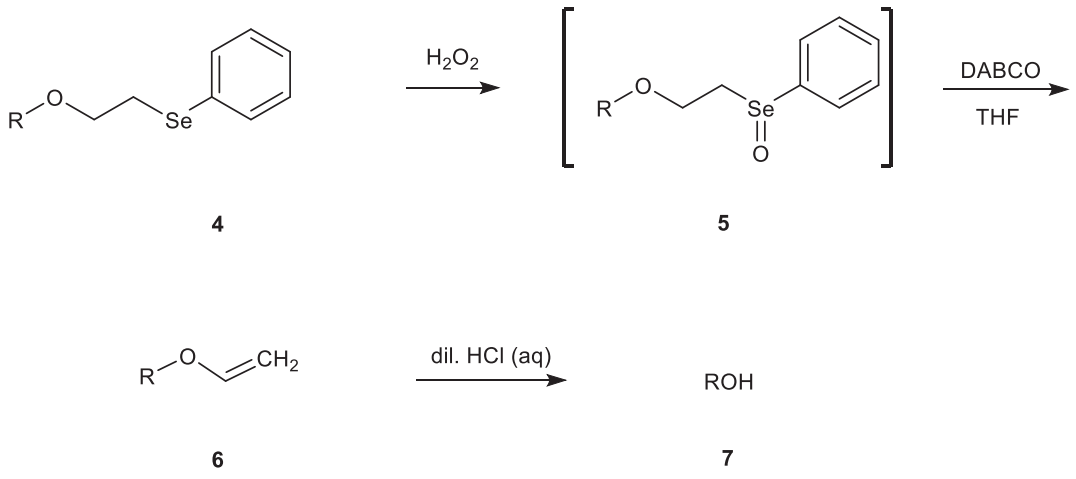
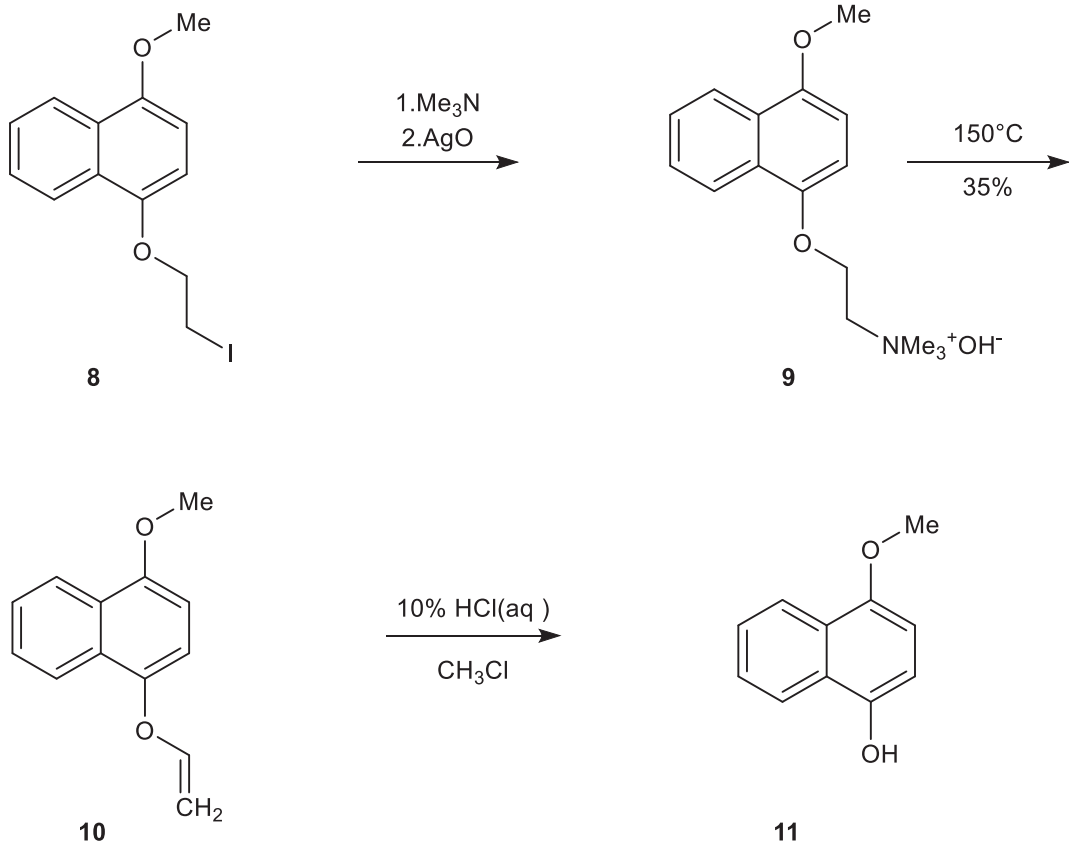
elimination to vinyl ethers **6**, are subsequently hydrolyzed to the parent hydroxy compounds **7** (eq 2). [1].



The greatest similarity to the 2-(piperidine-1-yl)-ethyl (PIP) group described in the literature is in the work by Laatsch. [3]. In that study, 2-iodoethoxy naphthalene **8** is reacted with trimethylamine to give a quaternary ammonium iodide, which is treated with silver oxide, and the resulting trimethylammonium hydroxide **9** is subjected to Hoffman elimination conditions to yield vinyl ether **10**. The yield in the elimination step is only 35%. The vinyl ether is then hydrolyzed with acid to hydroxy naphthalene **11** (eq 3).

Herein, I report that the PIP group has high stability under harsh conditions and can be deprotected under mild oxidative conditions via oxidation to *N*-oxide, Cope elimination (CE) and subsequent cleavage of the formed vinyl ether. It can also be selectively deprotected directly by $BBr_3 \bullet Me_2S$.



2. Results and discussion

2.1. Protecting phenols with the PIP group

Phenols are efficiently protected with the PIP group via alkylation with 1-(2-chloroethyl)-piperidine hydrochloride and K_2CO_3 as the base, as demonstrated for *p*-nitrophenol in Scheme 1.

For sensitive phenols, Cs_2CO_3 and sonication gives similar yield and the reaction can be performed at ambient temperature (see compound **2a** Table 2).

2.2. The Cope elimination PIP-deprotection route

The first step in the deprotection of the PIP group via the CE route is oxidation to the *N*-oxide (Scheme 2).

In the workup of **13**, before evaporation, hexamethyldisilazane (HMDS) was added to remove moisture, and **13** was isolated in its non-hydrated form. HMDS was chosen as the drying agent because the excess reagent and byproducts formed could be removed upon evaporation. The ^1H NMR peak at 3.14 ppm attributed to H_2O present in the *N*-oxide monohydrate **13b** sample not treated with HMDS before evaporation is absent from the spectrum of the HMDS-treated sample **13** (see Supporting Info.).

2.3. Study of cope-elimination

It has been reported that anhydrous conditions greatly facilitate CE [4a-c]· because water hydrogen bonds to the *N*-oxide and interferes with the reaction.

This effect could also be applicable to the 1-hydroxypiperidine (**15**) byproduct formed in the reaction. I theorized that silylating agents such as *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA), HMDS, and *N,O*-bis(trimethylsilyl)acetamide (BSA) would.

1. Remove any trace moisture in the *N*-oxide.
2. Silylate the 1-hydroxypiperidine formed and prevent it from interfering with the CE process by hydrogen bonding to or reduction of the *N*-oxide. [5].

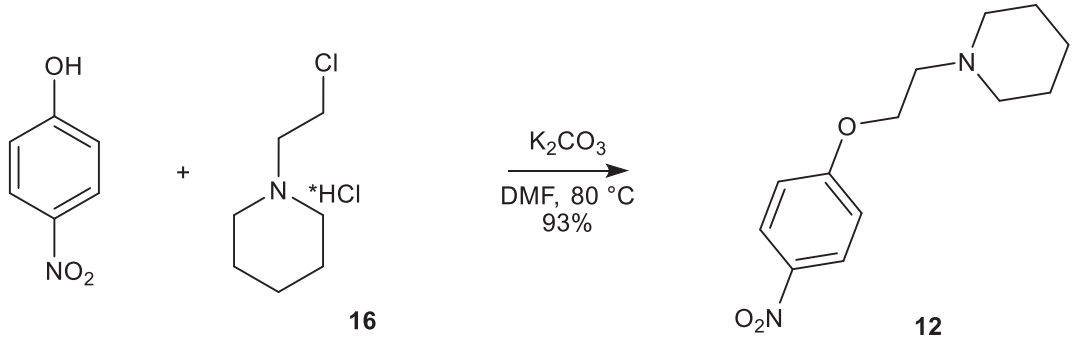
A systematic study in which **13** was heated under varying conditions to induce CE was conducted. The results of this study are summarized in Table 1.

When **13** was refluxed in dry toluene without an additive, vinyl ether **14** was isolated in 66% yield (run 1). When 1 equiv. of water was present, the yield decreased to 46% (run 2).

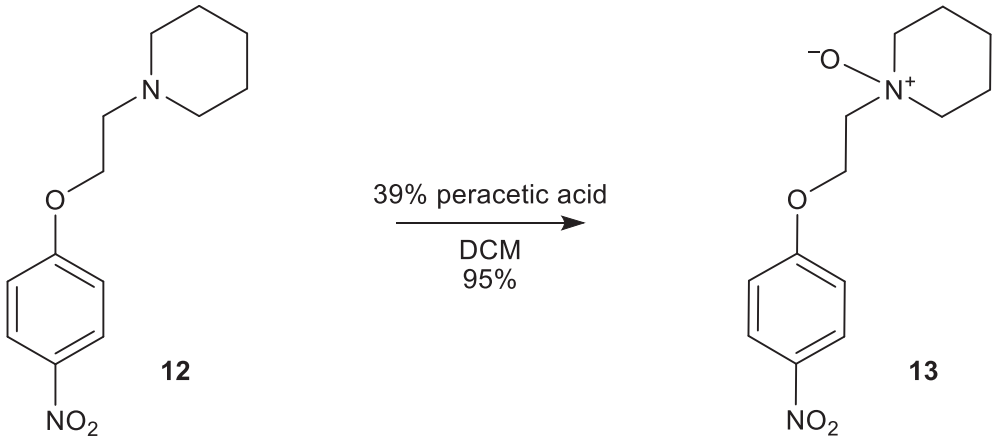
The low yield obtained in the presence of 1 equiv. of water can explain why the synthesis of vinyl ethers via CE has not, to my knowledge, been reported in the literature, as *N*-oxides are often isolated in their non-anhydrous form. [6].

When 1 equiv. of **15** was present, the yield decreased to approximately 41% (run 4). However, if the reaction was run in the presence of 1 equiv. of BSA and 1 equiv. of **15**, the yield was similar to that without any additive (run 14), indicating that BSA neutralizes the negative effect of **15**. The natural explanation for this effect is that BSA silylates **15**, thus neutralizing its negative effect on the yield.

When 1 equiv. of BSTFA was added, the yield was 85%, which was similar to the yields obtained with 2 or 3 equiv. (runs 8, 9, and 10). The addition of 10 equiv. of CaH_2 did not increase the yield (run 12) and did not protect against the negative effect of **15** (run 13).

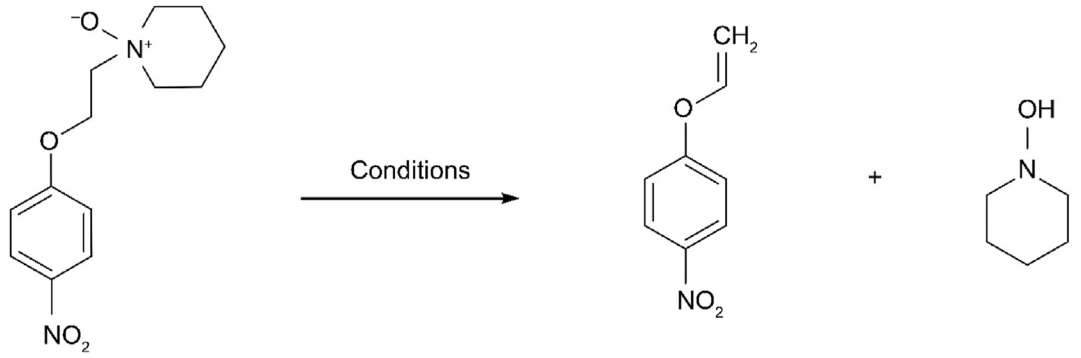


Scheme 1. PIP Protection of *p*-Nitrophenol.



Scheme 2. First Step in the Deprotection of the PIP Group, Oxidation to the *N*-Oxide.

Table 1
Study of cope Elimination[a].



13 **14** **15**

run	additive	equiv.	**yield of** 14 **(%)**
1	–		66
2[b]	H_2O	1	46
3[b]	H_2O	2	43
4	**15**	1	41
5	**15**	2	31
6	HMDS	3	69
7	BSTFA	0.5	64
8	BSTFA	1	85
9	BSTFA	2	88
10	BSTFA	3	84
11	BSA	3	81
12[c]	CaH_2	10	69
13[d]	CaH_2 + **15**	10 + 1	35
14	BSA + **15**	1 + 1	63
15	HMDS + **15**	1 + 1	42
16	4A MS		Complex mixture

[a] Reactions run in a 0.1 M PhMe solution at reflux temperature.
[b] **13** was first dissolved in dichloromethane (DCM), H_2O was then added, and the solution was finally sonicated for 30 min. PhMe was added, DCM was evaporated, and the solution was refluxed.
[c] **13** was dissolved in DCM/PhMe, CaH_2 was added, and the solution was stirred overnight; then, DCM was evaporated, and the solution was refluxed.
[d] **13** was dissolved in DCM/PhMe, CaH_2+**15** was added, and the solution was sonicated for 60 min. DCM was evaporated and the solution was refluxed.

The addition of 3 equiv. of BSA is advantageous because it leads to approximately the same yield as the addition of BSTFA but is more economical. The addition of 3 equiv. of HMDS did not significantly increase the yield (run 6) and did not protect from the negative effect of **15** (run 15), probably because HMDS is a less efficient silylating agent for this system.

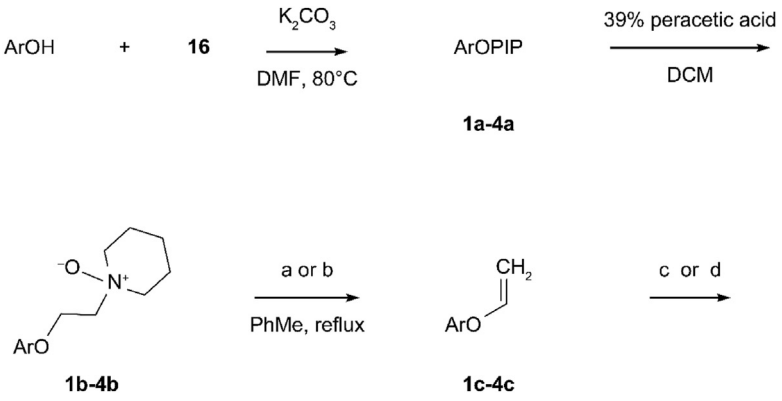
In runs 4, material with a Rf value on thin-layer chromatography (TLC) above that of **13** but much more polar than **14** was isolated in 22% yield through silica gel chromatography and was found to be amine **12**. This material was formed in all runs except for 8, 9, 10 and 11. **15** apparently reduced the *N*-oxide and thereby reduced the yield of CE, which could be hindered by silylation of **15**. Currently, there is no experimental proof that **15** hydrogen bonds to the *N*-oxide and thus reduces the yield. No silylated **15** was detected or isolated and the reason for this is likely that TMS ethers are not stable under the workup or purifying conditions used. When the reaction was performed in the presence of ground 4A MS, the solution became brown and resulted in a complex mixture containing only trace **14** (run 16).

2.4. Protection and de-protection of some phenols

A set of phenols were protected and deprotected, and the results of these experiments are summarized in Table 2.

The protection step gave yields above 90% in all cases and no chromatography was necessary. Oxidation to N-oxide was also very efficient. The Cope elimination step gave, as in Table 1, better yield in all the examples when the reaction was run in presence of 3 equiv. BSA then with no BSA. The *N*-oxide **4b** was not isolated because it slowly degraded upon storage. The final step, hydrolysis of the vinyl ether, also gave yields above 90% in all cases.

Table 2
Protection and deprotection of some Phenols.



entry	Ar	yield (%)		(%)		(%)			(%)	
1	3-NO_2Ph	**1a**	96	**1b**	95	**1c**	64[a]	78[b]	**1d**[d]	95
2	2-MeOPh	**2a**	95, 91[f]	**2b**	88	**2c**	52[a]	80[b]	**2d**[c]	91
3	2-Naphtyl	**3a**	96	**3b**	95	**3c**	63[a]	77[b]	**3d**[c]	95
4	4-CHOPh	**4a**	95	**4b**	NI[e]	**4c**	48[a]	69[b]	**4d**[c]	96

Conditions: (a) No BSA. (b) 3 equiv. of BSA. (c) 90% HOAc (aq). (d) HOAc/H_2O/TFA 90:10:1. (e) Not stable, not isolated. (f) Cs_2CO_3, sonication, ambient temperature.

2.5. Investigation of the orthogonality of the PIP group

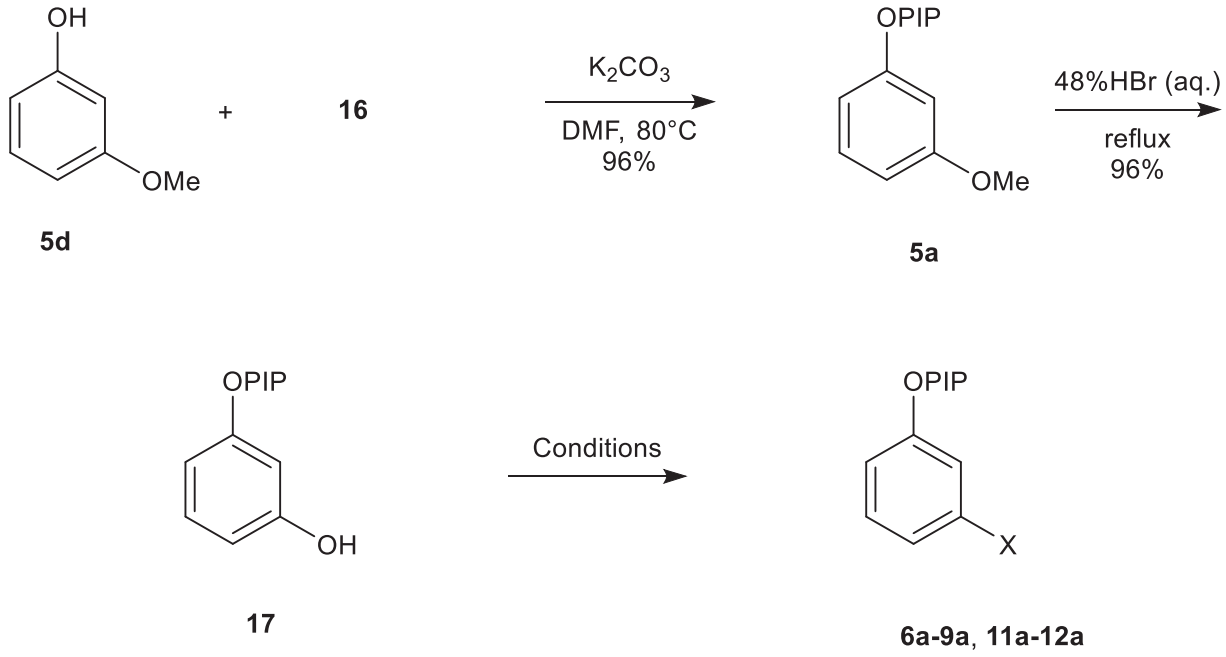
To test the orthogonality of the PIP group, compounds **5a-12a** were synthesized. **5d** was alkylated in the usual way to give compound **5a**, and the methyl ether was hydrolyzed by boiling conc. HBr (aq) to afford compound **17**. Interestingly, only demethylation was observed, and the PIP group was stable to these conditions (*vide infra*). Then, **17** was protected with some common protecting groups to give compounds **6a-9a** and **11a-12a** (Scheme 3).

Compound **10a** was synthesized via reduction of *p*-nitro compound **12** with iron in 90% HOAc (aq), followed by protection of the amino group with Boc_2O (Scheme 4).

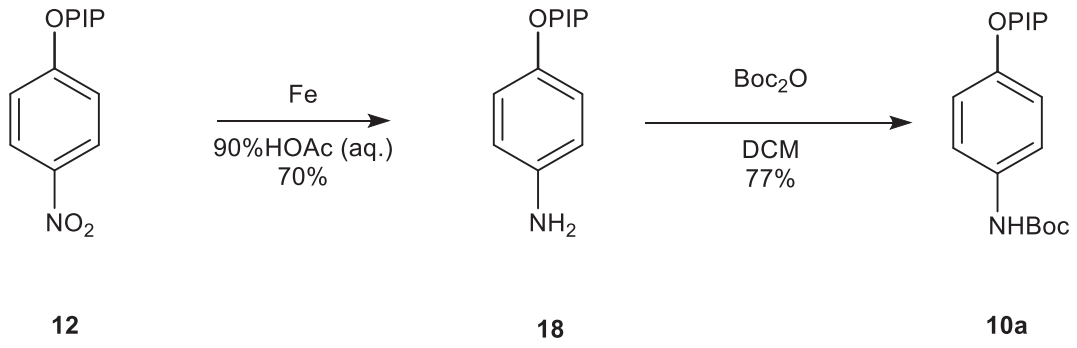
First, deprotection of the PIP group was investigated, and the results of these experiments are summarized in Table 3.

Conditions: (a) 1.2 equiv. of 39% peracetic acid in acetic acid/DCM. (b) PhMe, 3 equiv. of BSA, reflux. (c) DMF, 3 equiv. of BSA, 120 °C. (d) 90% HOAc reflux. (e) O_3/MeOH (f) HOAc/H_2O/TFA 90:10:1 reflux. (g) O_3/DCM then 90% HOAc (aq) + MeOH. (h) Not stable, use immediately. (i) 3,6-(2-pyridyl)-1,2,4,5-tetrazine/DMF/H_2O, *vide infra*.

The oxidation to amine oxide was generally very fast (2–4 min), and the product was formed in high yield. Allyl-protected compound **11a** did not epoxidize to any significant extent, and the tetrahydropyran (THP) group in **12a** was stable to peracetic acid

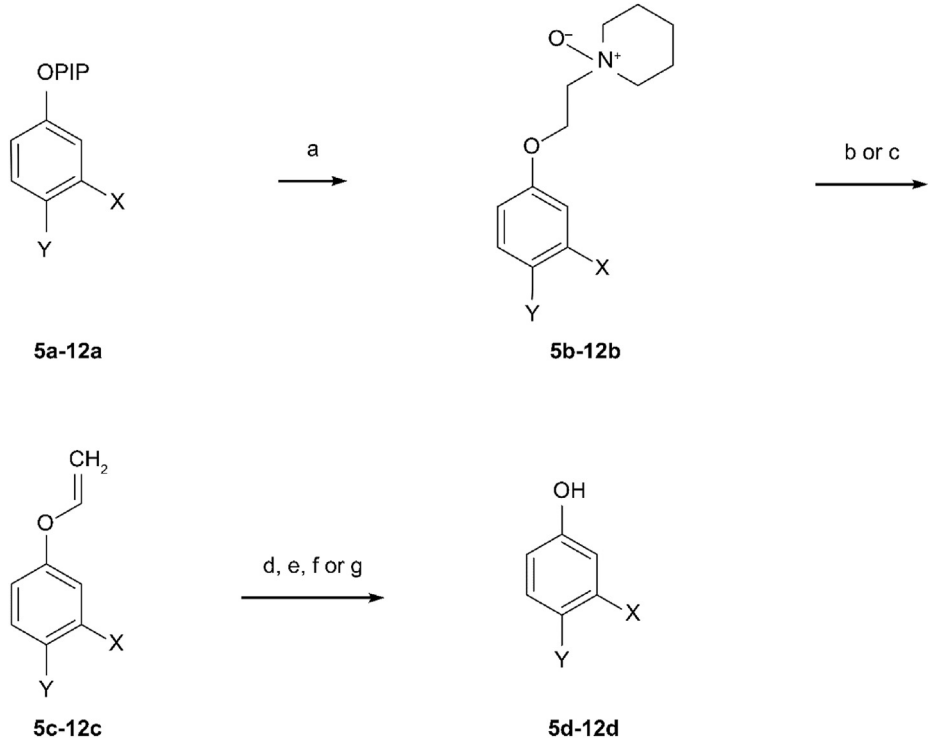


Scheme 3. Protection of Resorcinol with the PIP group and some common protecting groups.



Scheme 4. Synthesis of *O*-PIP, *N*-Boc Protected *p*-Aminophenol.

Table 3
Deprotection of the PIP group in presence of some common classes of protecting Groups.



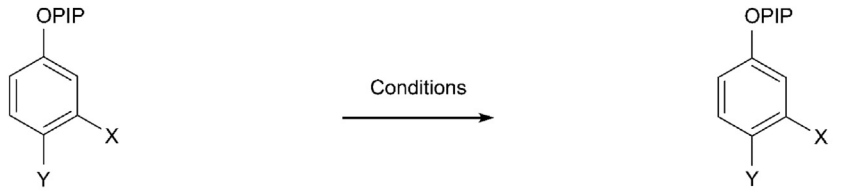
entry	STM	X	Y	yield (%)		(%)		(%)		overall yield (%)
1	**5a**	OMe	H	**5b**[a]	95	**5c**[b]	69	**5d**[d]	90	59
2	**6a**	OAc	H	**6b**[a, h]	—	**6c**[b]	51	**6d**[e]	94	46
3	**7a**	OBn	H	**7b**[a]	95	**7c**[b]	82	**7d**[f]	98	76
4	**8a**	OPMB	H	**8b**[a]	96	**8c**[b]	79	**8d**[g]	69	53
5	**9a**	OtBDPS	H	**9b**[a]	84	**9c**[b]	71	**9d**[g]	95	57
6	**10a**	H	NHBoc	**10b**[a]	88	**10c**[c]	66	**10d**	88[g], 55[i]	51, 32
7	**11a**	O-Allyl	H	**11b**[a]	95	**11c**	74	**11d**[d]	87	58
8	**12a**	OTHP	H	**12b**[a]	95	**12c**	68	**12d**[i]	60	39

during the reaction. CE was performed in toluene for all samples except for compound **10b**, which was heated in dimethylformamide (DMF) due to solubility issues. The vinyl ethers had different stabilities; 90% HOAc (aq) was not sufficient for hydrolysis in some cases, so HOAC/H_2O/TFA (90:10:1) was used instead. Compounds **8c-10c** were ozonolyzed in DCM, and the presumed ozonides were treated with 90% HOAc (aq)+ MeOH. The ozonides decomposed to phenols without reduction, which may have been a result of hydrolysis of the presumed acid-sensitive "ortho-ester like" ozonides. Ozonolysis of compound **6c** in MeOH gave the phenol in the absence of acid. Compounds **10c** and **12c** were cleaved to phenols via inverse electron-demand Diels-Alder (IEDDA) retro-Diels-Alder elimination reaction (*vide infra*).

Deprotection of the other protecting groups was achieved under standard conditions, and the results of these experiments are summarized in Table 4.

Deprotection generally resulted in nice yields, which reflects the high stability of the PIP group under various conditions. **17** Is very

Table 4
Deprotection of some common classes of protecting groups in the presence of the PIP Group.



5a-12a

17 X = OH, Y = H
18 X = H, Y = NH_2

entry	STM		product		yield (%)
1[a]	**5a**	X = OMe, Y = H	**17**	X = OH, Y = H	83
2[b]	**6a**	X = OAc, Y = H	**17**	X = OH, Y = H	95
3[c]	**7a**	X = OBn, Y = H	**17**	X = OH, Y = H	91
4[f]	**8a**	X = OPMB, Y = H	**17**	X = OH, Y = H	69
5[d]	**9a**	X = OtBDPS, Y = H	**17**	X = OH, Y = H	98
6[e]	**10a**	X = H, Y = NHBoc	**18**	X = H, Y = NH_2	93
7[g]	**11a**	X = O-Allyl, Y = H	**17**	X = OH, Y = H	84
8[h]	**12a**	X = OTHP	**17**	X = OH, Y = H	96

Conditions: [a]48% HBr (aq) reflux. [b]NH_3/MeOH. [c]H_2-PdC/MeOH, atmospheric pressure. [d]TBAF/THF r.t. [e]60% TFA/DCM r.t. [f]AcOH reflux. [g]Conc. HCl (aq) 75 °C. [h]90% HOAc (aq) refl.

polar and in some cases some yield was probably lost in the chromatography purification step.

2.6. Stability of a PIP protected phenol to basic conditions

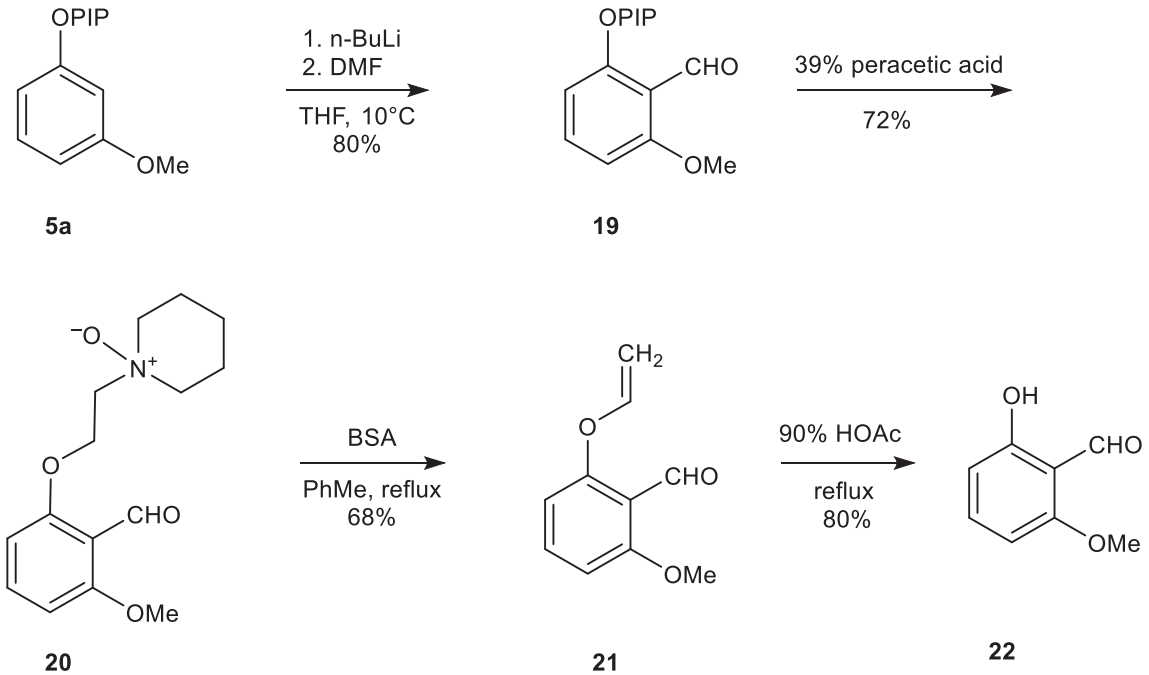
The PIP group is clearly very stable to basic conditions. Compound **5a** was *ortho*-lithiated with *n*-BuLi in THF, and the lithiated derivative was quenched with DMF to afford aldehyde **19** in 80% yield. This compound was deprotected via CE to phenol **22** (Scheme 5).

2.7. Stability to Brönsted Acids

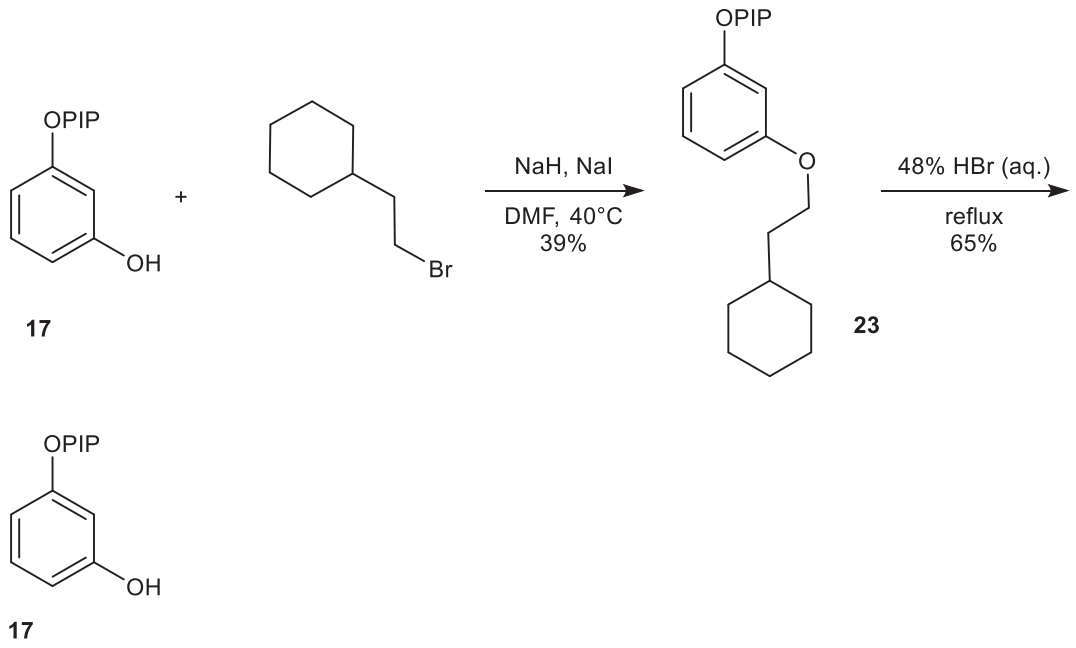
A methyl ether can be selectively hydrolyzed by refluxing in hydrobromic acid in the presence of the PIP group, as demonstrated in Scheme 3.

To determine whether this result is because the PIP group is more sterically hindered than the methyl group, compound **23** was synthesized and exposed to the same hydrolysis conditions (Scheme 6).

The hydrolysis of compound **23** is very selective, and no significant amount of resorcinol or 3-methoxyphenol was detected by



Scheme 5. *Ortho*-Lithiation of a PIP Protected Phenol.



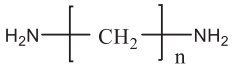
Scheme 6. Comparison of Acid-Stability of the PIP Group and 2-Cyclohexylethyl.

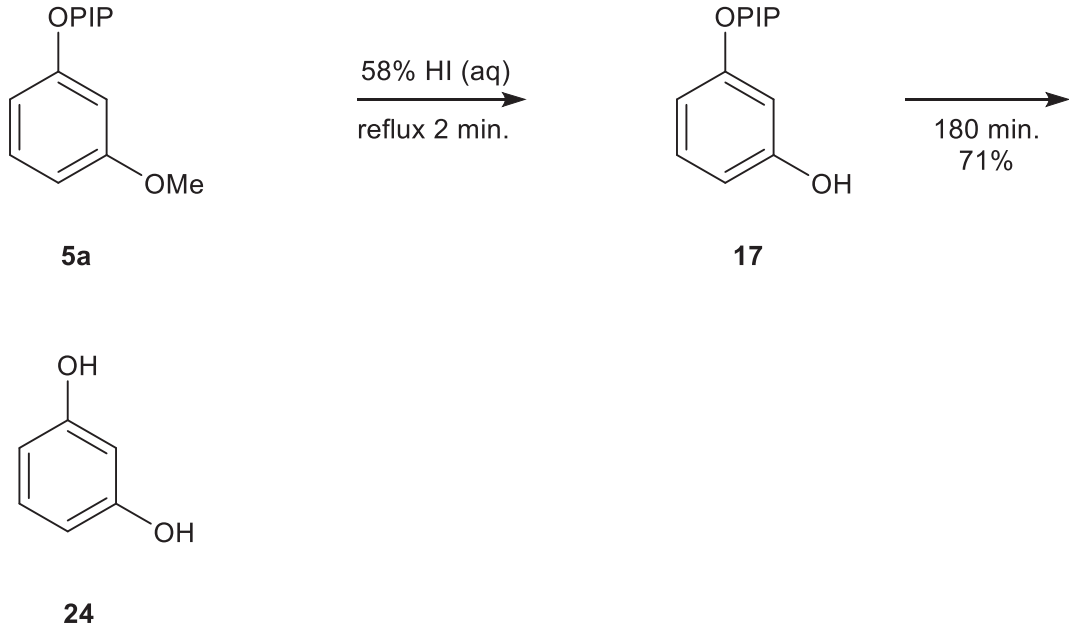
Table 5
Comparison of pKa_1 and pKa_2 of Diaminoalkanes and Hydrazine.

n	pKa_1	pKa_2	Ka_2/Ka_1
0	8.0	−1.0	1,000,000,000
2	10.172	7.564	406
3	10.94	9.03	81
4	11.15	9.71	28
5	10.25	9.13	13
6	11.857	10.762	12

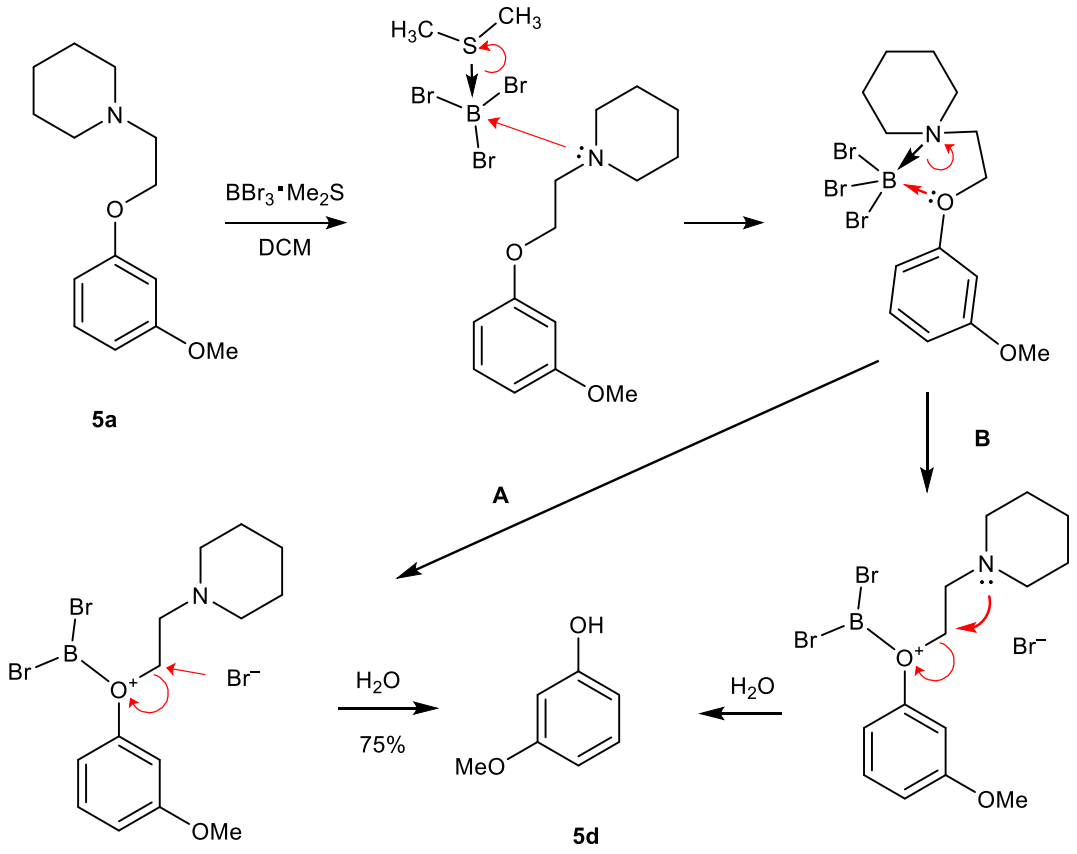
TLC. This experiment indicates that the selective hydrolysis of methyl ether is not a consequence of steric hindrance.

The explanation for this selectivity is that the positive charge first formed on the piperidine nitrogen repels formation of a charge on the PIP-ether oxygen. This same effect was also observed in diaminoalkanes and hydrazine and can be visualized as the difference between pKa_1 and pKa_2, as shown in Table 5 [7a–d].The effect was small when $n > 2$, but for ethylendiamine ($n = 2$), in which the distance between the nitrogen and oxygen is similar to that in the PIP protected phenols, the effect is considerable. For hydrazine ($n = 0$), the effect is very large.





Scheme 7. Hydrolysis of the PIP Group with Brönsted Acids.



Scheme 8. Deprotection of the PIP Group by Lewis Acid.

Table 6
Deprotection of the PIP group by lewis acid.

entry	STM		product	yield (%)
1	**5a**[a]	X = OMe, Y = H	5d	75
2	**6a**[b]	X = OAc, Y = H	6d	50[c]
3	**7a**[b]	X = OBn, Y = H	7d	70
4	**12a**[b]	X = OTHP, Y = H	12d	51

Conditions: [a]1.16 equiv. Lewis acid/DCM, ambient temperature. [b]1.0 equiv. Lewis acid/DCM, ambient temperature. [c]Based on 26% recovered 6a.

When compound **5a** was refluxed for 2 min in conc. hydroiodic acid, the methyl ether was hydrolyzed. PIP ether required 3 h of reflux to be hydrolyzed, and resorcinol was isolated in 71% yield, indicating that PIP is a very stable protecting group (Scheme 7).

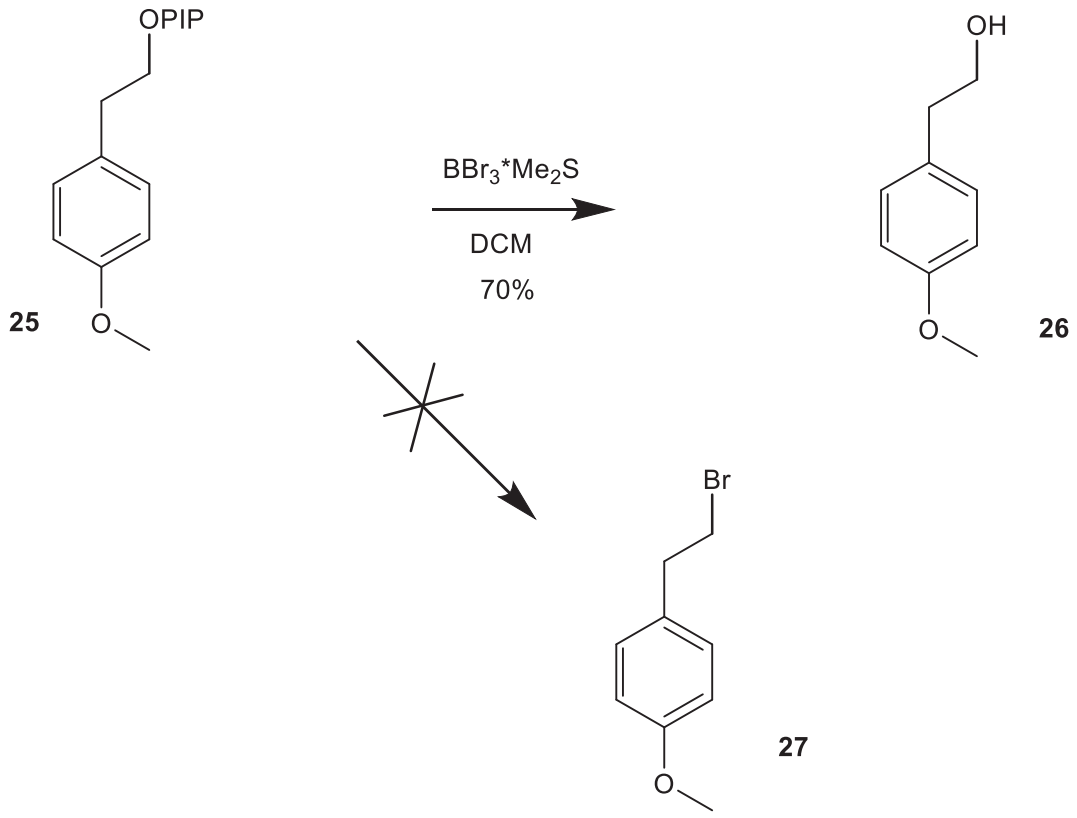
2.8. Stability to Lewis Acids

When compounds **5a, 6a, 7a,** and **12a** were treated with BBr_3•Me_2S at ambient temperature in DCM, the ether groups on PIP were selectively hydrolyzed. The proposed mechanism for this reaction with **5a** as an example is outlined in Scheme 8, and the yields are presented in Table 6. Structures for compounds **6a**, **7a** and **12a** are presented in Table 3.

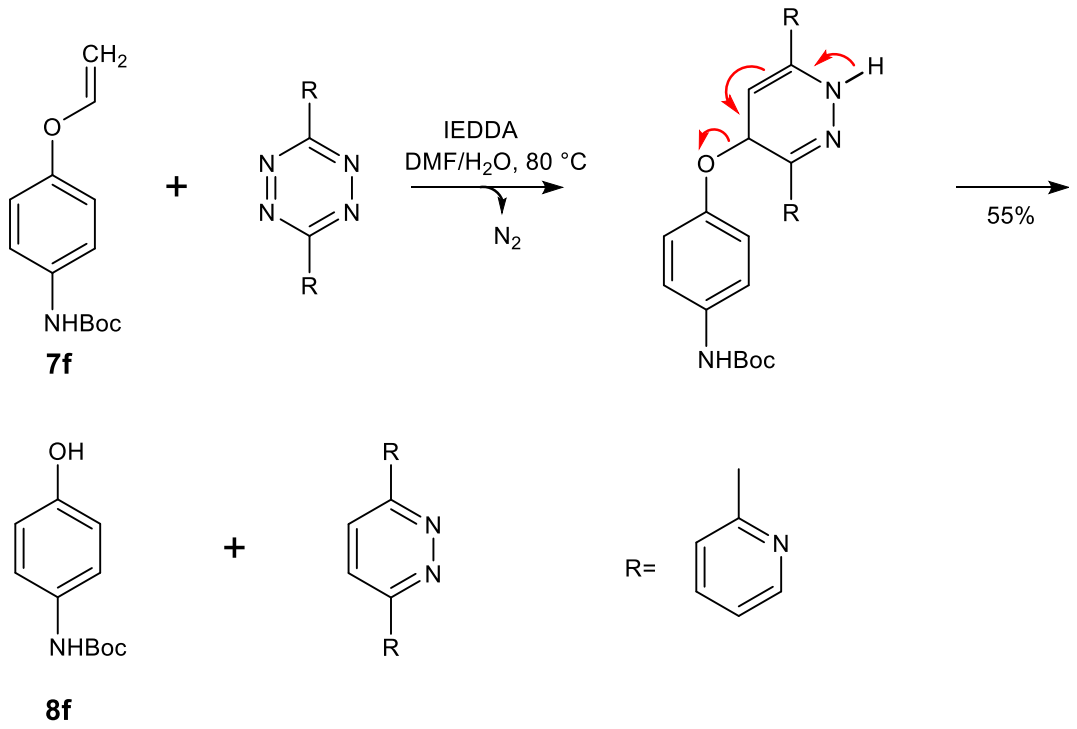
Piperidine nitrogen substitutes for dimethyl sulfide; thereafter, the nitrogen is displaced by the ether oxygen of the PIP to form a cyclic transition state. The ether bond in the PIP is then attacked by the bromide ion (Mechanism A) or the nitrogen atom in the piperidine ring (Mechanism B). The reaction is very selective, and no significant amount of **17** was detected by TLC. To explain this finding, one must assume that the displacement of dimethyl sulfide by nitrogen and the formation of the cyclic transition state are kinetically favored and faster than attack by the methyl ether oxygen on the Lewis acid. This offers an important alternative PIP-deprotection route, as the reaction is so selective that even the highly acid-sensitive THP group in **12a** is spared. As outlined in Scheme 9, when compound **25** was treated with BBr_3•Me_2S, compound **26** was isolated in 70% yield (calculated from the 24% recovery of **25**), suggesting that Mechanism B is predominant, at least in this case, since otherwise, bromo-compound **27** and alcohol **26** would form in a 1:1 M ratio (the experimentally observed molar ratio was 1:170). This experiment also showed that the PIP group can be used to protect alcohols. The BBr_3•Me_2S reagent is relatively mild, and hydrolyzing aryl methyl ethers by refluxing for 12–24 h in dichloroethane (DCE) with a 4-fold molar excess of the reagent is generally required, as demonstrated by Williard et al. [9] This reagent is surprisingly stable and must be thoroughly hydrolyzed in the workup, or it will contaminate the product even after 2 rounds of chromatography.

2.9. Deprotection of vinyl ethers by the inverse electron-demand Diels-Alder/Retro Diels-Alder elimination reaction

Staderini et al. [10] showed that vinyl ethers can be de-caged via an IEDDA/retro-Diels-Alder elimination reaction using 3,6-(2-pyridyl)-1,2,4,5-tetrazine in DMF/H_2O. When these conditions were applied to compounds **10c** and **12c,** compounds **10d** and **12d** were isolated in 55 and 60% yields, respectively (Scheme 10 and Table 3). This reaction is an alternate way to hydrolyze vinyl ether when the starting material is sensitive to acid or if ozone cannot be used.



Scheme 9. Comparison of Mechanism A and B, Deprotection of a PIP Protected Alcohol with Lewis Acid.



Scheme 10. Deprotection of a Vinyl Ether by Inverse-Electron Demand Diels-Alder/Retro Diels Alder Elimination Reaction.

3. Conclusions

In summary, the PIP group was evaluated as a protecting group for phenols. The protection step was relatively mild and fast and generally resulted in yields greater than 90% in the examples presented herein. Deprotection was accomplished with a very mild three-step process via CE or with a one-step procedure with a mild Lewis acid, and yields of approximately 50–70% were achieved with both methods. The fact that the PIP group is both orthogonal to sensitive protecting groups, such as N-Boc, O-THP and O–Ac, and stable to *ortho*-lithiation conditions as well as boiling concentrated hydrobromic acid is a strength of this innovation. PIP is also orthogonal to *O*-allyl groups, so alkenes do not epoxidize under the conditions used in the CE-deprotection route, as the oxidation of the PIP group to an *N*-oxide is much faster. If the substrate is very sensitive to acid or ozone, hydrolysis of the vinyl ether can be accomplished via an IEDDA/retro Diels-Alder elimination reaction. Lewis acid deprotection involves treatment with BBr_3•Me_2S, and an O–Me, O-Bn, O–Ac and O-THP group can be present on the aromatic nucleus; this is perhaps a more important deprotection route than the CE route because it is a one-step procedure and gives approximately the same yields. The finding that CE results in higher yields of vinyl ether when run in the presence of silylating agents because the reduction of the *N*-oxide can be suppressed by the byproduct hydroxylamine can prove useful when CE is performed on other types of substrates. The chemistry presented herein also provides access to highly functionalized vinyl aryl ethers. The mechanism analysis of the BBr_3•Me_2S deprotection route also involved one example in which an alcohol is protected with the PIP group and subsequently deprotected.

4. Experimental section

4.1. General experimental section

Tetrahydrofuran (THF), dimethyl formamide (DMF) and toluene were stored over 4 Å molecular sieves prior to use. Potassium carbonate was oven dried at 300 °C for 3 h and ground to a fine powder in a porcelain mortar and pestle prior to use. All other solvents and reagents were used as received. NMR spectra were obtained at the indicated fields as solutions in $CDCl_3$ or MEOD unless otherwise indicated. TLC was performed on 0.2 mm Alugram Sil G/UV_{254} 60 Å silica gel plates using 254 nm UV light for monitoring and plates dipped in a 0.5% aqueous potassium permanganate solution when the UV absorbance was low. This method facilitated distinguishing alkenes from ozonides. Ozone was generated with a Sander Certizon 50 ozone generator. Flash chromatography was performed on 40–63 μm 60 Å silica gels with the reported eluents. Melting points were uncorrected.

4.1.1. PIP-protection of phenols, general reaction and isolation procedure for electron-poor substrates, method A

1-(2-(3-Nitrophenoxy)ethyl)piperidine (**1a**). [11]. 3-Nitrophenol (1.00 g, 7.19 mmol) was dissolved under stirring in DMF (50 ml) in a 250 ml Erlenmeyer flask. K_2CO_3 (4.00 g, 28.94 mmol) was added, and the mixture was heated on a magnetic stirrer to 80 °C under heavy stirring for 5 min. **16** (1.59 g, 8.64 mmol) was added, and the solution was stirred at 80 °C for 15 min. The solution was cooled to ambient temperature, and conc. NH_4OH (aq) (15 ml) was added to quench any remaining **16**, and the solution was stirred for 60 min. The solution was diluted with H_2O (50 ml) and extracted with Et_2O (4*30 ml). The organic phase was subjected to acid-base partitioning with 5% HCl (aq) (100 ml) and 5% NH_4OH (aq) (150 ml), followed by extraction with Et_2O (4*50 ml) (for sensitive compounds, 0.5 M citric acid and 0.5 M $NaHCO_3$ can be used). The organic phase was diluted with hexane (20 ml), dried with Na_2SO_4 and filtered and evaporated under reduced pressure, and the residue was dried in vacuo to give 1.72 g (96%) of the title compound as an oil. The spectra were consistent with those of a commercial sample.

3-Nitrophenol (**1d**). [12]. **1a** (1.53 g, 6.11 mmol) was dissolved in DCM (50 ml). The solution was stirred, and 39% peracetic acid (in HOAc) (1.25 ml, 7.31 mmol) was added. The solution was stirred for 5 min. Then, 1 M K_2CO_3 (aq) (20 ml) was added, and the solution was stirred for 2 min. The solution was filtered through phase-separator (PS) paper, and the remaining aqueous phase was extracted with DCM (5*10 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette in the filter funnel as the organic phase passed through the PS-filter. The organic phases were combined, and HMDS (6.00 ml) was added. The solution was evaporated at reduced pressure to give **1b** (1.54 g, 95%) as a semi-crystalline solid. The broad ^{1}H NMR signal at 2.8 ppm was attributed to water, and the compound was highly hygroscopic. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.3, 2.2 Hz, 1H), 7.76 (t, J = 2.3 Hz, 1H), 7.45 (t, J = 8.2 Hz, 1H), 7.26 (dd, J = 8.3, 2.5 Hz, 1H), 4.82–4.65 (m, 2H), 3.68–3.54 (m, 2H), 3.40–3.30 (m, 2H), 3.26 (td, J = 11.8, 11.2, 3.3 Hz, 2H), 2.41–2.24 (m, 2H), 1.81–1.73 (m, 1H), 1.69 (dt, J = 14.5, 4.5 Hz, 2H), 1.46 (dd, J = 10.0, 3.5 Hz, 1H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 21.1, 22.0, 62.4, 66.9, 68.4109.7, 116.3, 130.2, 149.1, 158.3; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{13}H_{18}N_2O_4$, 267.1339; found, 267.1339. **1b** (0.27 g, 1.01 mmol) was suspended in toluene. BSA (0.73 ml, 3.00 mmol) was added, and the solution was stirred and heated in an oil bath to reflux for 25 min. The solution was evaporated under reduced pressure and purified by column chromatography by elution with EtOAc/hexane (1:7) to give 0.13 g (78%) of **1c** [8] as an oil, and the spectra were consistent with published data. **1c** (0.13 g, 0.79 mmol) was dissolved in HOAc/H_2O/TFA (90:10:1, 3 ml). The solution was refluxed for 45 min. The solution was evaporated at reduced pressure, and the crystalline residue was dried in vacuo. Yield, 0.104 g (95%); mp, 95–97 °C; Lit., 97 °C. The spectra were consistent with those of a commercial sample.

3-Nitrophenol (**1d**). The reaction was as above, but BSA was omitted in the **1b**-**1c** step, and the yield in this step decreased to 64%. The yields of the other steps were the same as above. The spectra were consistent with those described above.

4.1.2. PIP protection of phenols, general reaction and isolation procedure for electron-rich substrates, method B

1-(2-(2-Methoxyphenoxy)ethyl)piperidine (**2a**). [11]. 2-Methoxyphenol (2.00 g, 16.11 mmol) was dissolved in DMF (100 ml) in a 250 ml Erlenmeyer flask. The solution was heated on a magnetic stirrer to 80 °C under heavy stirring, and K_2CO_3 (8.91 g, 64.47 mmol) was added. The mixture was stirred at 80 °C for 10 min, and **16** (5.93 g, 32.21 mmol) was added. The mixture was stirred at 100 °C for 10 min K_2CO_3 (4.60 g, 33.28 mmol) was added, and the solution was stirred at 100 °C for 20 min. The solution was cooled to ambient temperature, and conc. NH_4OH (aq) (35 ml) was added to quench any remaining excess of **16**. The solution was stirred for 60 min. The solution was diluted with water (150 ml) and extracted with Et_2O (4*50 ml). The organic phase was subjected to acid-base partitioning with 5% HCl (aq) (100 ml) and 5% NH_4OH (aq) (150 ml), followed by extraction with Et_2O (4* 50 ml) (for sensitive compounds, 0.5 M citric acid (aq) and 0.5 M $NaHCO_3$ (aq) can be used). The solution was diluted with hexane (20 ml), dried with Na_2SO_4, filtered and evaporated. The residual gum was dried in vacuo to give 3.61 g (95%) of the title compound. The spectra are consistent with those of a commercial sample.

4.1.3. PIP protection with cesium carbonate/sonication. General reaction and isolation procedure

1-(2-(2-Methoxyphenoxy)ethyl)piperidine (**2a**). 2-Methoxyphenol (0.093 g, 0.75 mmol) was dissolved in DMF (2 ml) under N_2 atmosphere and stirring. Cesium carbonate (0.78 g, 2.4 mmol) and **16** (0.18 g, 0.98 mmol) was added. The solution was sonicated for 90 min at ambient temperature. The solution was diluted with H_2O (20 ml) and was extracted with Et_2O (3*20 ml). The combined organic phase was washed with H_2O (2*20 ml) and was dried with Na_2SO_4, filtered and evaporated to give 0.16 g (91%) of the title compound. Spectra as above.

2-Methoxyphenol (**2d**). [12]. **2a** (3.65 g, 15.51 mmol) was dissolved in DCM (40 ml) under stirring. Then, 39%, peracetic acid (in HOAc) (3.10 ml, 18.12 mmol) was added, and the solution was stirred for 10 min. Next, 1 M K_2CO_3 (48 ml) was added, and the solution was stirred for 2 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (6*20 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (17.00 ml) was added to the organic phase, and the solution was evaporated at reduced pressure to give 3.42 g (88%) of **2b** as a semicrystalline solid; ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.08–6.79 (m, 4H), 4.73–4.52 (m, 2H), 3.83 (s, 3H), 3.67–3.63 (m, 2H), 3.43–3.20 (m, 4H), 2.43–2.14 (m, 2H), 1.70 (td, J = 9.4, 8.8, 4.2 Hz, 3H), 1.45 (s, 1H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 21.2, 22.0, 55.7, 62.8, 66.5, 68.5, 111.8, 114.1, 120.9, 121.9147.3, 149.4. HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{14}H_{21}NO_3$, 252.1594; Found, 252.1595. **2b** (0.25 g, 1.00 mmol) was suspended in toluene (9 ml). BSA (0.73 ml, 3.00 mmol) was added, and the solution was heated to reflux in an oil bath under stirring. The solution was heated to reflux for 30 min. The solution was evaporated under reduced pressure, and the residual oil was purified by column chromatography and eluted with EtOAc/hexane (1:20) to give 0.12 g (80%) of **2c** [13] as an oil. The spectra were consistent with published data. **2c** (0.12 g, 0.80 mmol) was dissolved in 90% HOAc (aq) (4 ml). The solution was heated to reflux under stirring in an oil bath for 10 min. The solution was evaporated under reduced pressure to give 0.09 g (91%) of the title compound as an oil. The spectra are consistent with those of a commercial sample.

2-Methoxyphenol (**2d**). The reaction was performed as above, but BSA was omitted in the **2b**-**2c** step. The yield was identical to those above except for the **2b**-**2c** step, where it decreased to 52%.

1-(2-(Naphthalen-2-yloxy)ethyl)piperidine (**3a**). [11]. The title compound was prepared by Method B and was isolated as a crystalline solid (3.40 g (96%) from 2.00 g (13.90 mmol) of 2-naphthol). Mp, 48–49 °C. Lit., 48–49 °C; the spectra were consistent with those of a commercial sample.

2-Naphthol (**3d**). [12]. **3a** (3.43 g, 13.4 mmol) was dissolved in DCM (50 ml) under stirring. Then, 39% peracetic acid (in HOAc) (2.50 ml, 14.62 mmol) was added, and the solution was stirred for 10 min. Next, 1 M K_2CO_3 (aq) (50 ml) was added, and the solution was stirred for 2 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (6*25 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (15 ml) was added to the combined organic phases, and the solution was evaporated at reduced pressure to give 3.45 g (95%) of **3b** as a crystalline hygroscopic solid (mp 58–59 °C). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.79–7.69 (m, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.09 (dd, J = 8.9, 2.6 Hz, 1H), 4.84–4.64 (m, 2H), 3.79–3.55 (m, 2H), 3.34 (dt, J = 10.1, 4.6 Hz, 2H), 3.26 (td, J = 11.9, 11.1, 3.2 Hz, 2H), 2.30 (qd, J = 10.2, 8.3, 4.6 Hz, 2H), 1.85–1.55 (m, 3H), 1.43 (dd, J = 9.9, 3.5 Hz, 1H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 21.2, 22.0, 61.5, 66.6, 66.7, 107.1, 118.3, 123.9, 126.5, 126.8, 127.5, 129.1, 129.5, 134.3, 155.6; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{17}H_{21}NO_2$, 272.1645; Found, 272.1651. **3b** (2.70 g, 9.95 mmol) was suspended in toluene (50 ml) under stirring, BSA (7.33 ml, 28.00 mmol) was added, and the solution was heated to reflux in an oil bath for 30 min. The solution was evaporated under reduced pressure, and the residual oil was purified by column chromatography by elution with EtOAc/hexane (1:25) to give 1.30 g (77%) of **3c** [14] as an oil. The spectra were consistent with published data.

3c (0.52 g, 3.06 mmol) was dissolved in 90% HOAc (aq) (15 ml). The solution was heated to reflux under stirring in an oil bath for 30 min. The solution was evaporated under reduced pressure to give 0.42 g (95%) of the title compound as a tan crystalline solid (mp, 121–123 °C; Lit., 123 °C). The spectra were consistent with those of a commercial sample.

2-Naphthol (**3d**). The reaction was performed as above, but BSA was omitted in the **3b**-**3c** step, and the yield in this step decreased to 63%. Yield in the other steps were identical to those above. The spectra were the same as described above.

4-(2-(Piperidin-1-yl*)ethoxy)benzaldehyde* (**4a**). [15]. The title compound was prepared by Method A and was isolated as a gum (3.57 g (93%) from 2.00 g (16.40 mmol) of 4-hydroxybenzaldehyde). The spectra were consistent with those of a commercial sample.

4-Hydroxybenzaldehyde (**4d**). [12]. **4a** (0.50 g 2.14 mmol) was dissolved in DCM (20 ml). The solution was stirred, and 39% peracetic acid (in HOAc) (0.43 ml 2.51 mmol) was added. The solution was stirred for 3 min. Conc. NH_4OH (aq) (4 ml) (in this case, it appeared to work better than 1 M K_2CO_3) was added, and the solution was stirred for 1 min. The phases were separated, and the aqueous phase was extracted with DCM (5*20 ml) in a separatory funnel. The organic phase was dried with $MgSO_4$ and filtered. HMDS (2 ml) was added, and the solution was evaporated at reduced pressure to give **4b** as a gum. This material was not stable over an extended time, did not give rise to good NMR spectra due to degradation and was used immediately in the next step. HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{14}H_{19}NO_3$, 250.1438; Found, 250.1434. The gum was dissolved in DCM (3 ml). The solution was diluted with toluene (30 ml), and BSA (2.1 ml, 8.60 mmol) was added. The solution was heated until the DCM evaporated, and the solution was refluxed for 20 min. The solution was evaporated at reduced pressure, and the residual gum was purified by column chromatography by elution with EtOAc/hexane (1:7) to give 0.22 g (69%, 2 steps) of **4c** [13] as an oil. The spectra are consistent with published data. **4c** (0.19 g, 1.28 mmol) was dissolved in 90% HOAc (aq) (3 ml). The solution was stirred and heated to reflux in an oil bath for 4 h and was left at ambient temperature overnight. The solution was evaporated at reduced pressure, the residue was dissolved in Et_2O (2 ml), and the solution was filtered through a plug of cotton and evaporated to give 0.15 g (96%) of the title compound as a crystalline solid (mp, 112–115 °C; Lit., 112–116 °C). The spectra were consistent with those of a commercial sample.

4-Hydroxybenzaldehyde (**4d**). The reaction was performed as above, but BSA was omitted in the **4b**-**4c** step, and the yield for **4a**-**4c** decreased to 48%. The yield in the last step was the same as that reported above. The spectra were the same as described above.

1-(2-(3-Methoxyphenoxy)ethyl)piperidine (**5a**). The title compound was prepared according to Method B (7.21 g (30.64 mmol) (95%) from 3-methoxyphenol (4.00 g, 32.23 mmol)). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.16 (t, J = 8.2 Hz, 1H), 6.57–6.36 (m, 3H), 4.08 (t, J = 6.1 Hz, 2H), 3.78 (s, 3H), 2.76 (t, J = 6.1 Hz, 2H), 2.50 (s, 4H), 1.60 (p, J = 5.6 Hz, 4H), 1.44 (t, J = 6.0 Hz, 2H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.2, 25.9, 55.0, 55.2, 57.9, 101.0, 106.3, 106.7, 129.8, 160.1, 160.8; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{14}H_{21}NO_2$, 236.1645; Found, 236.1651.

3-Methoxyphenol (**5d**). [12]. **5a** (1.00 g, 4.25 mmol) was dissolved in DCM (20 ml). Next, 39% peracetic acid (in HOAc) (0.87 ml,

5.09 mmol) was added under stirring. The solution was stirred for 5 min. Then, 1 M K_2CO_3 (20 ml) was added, and the solution was stirred for 4 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (5 * 10 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (5 ml) was added, and the solution was evaporated under reduced pressure to give 1.01 g (95%) **5b** as a gum; ^{1}H NMR (800 MHz, MeO-d4) δ 7.18 (t, J = 8.2 Hz, 1H), 6.55 (dd, J = 8.2, 2.4 Hz, 2H), 6.52 (t, J = 2.4 Hz, 1H), 4.63–4.42 (m, 2H), 3.77 (s, 3H), 3.72–3.66 (m, 2H), 3.43 (td, J = 11.7, 3.1 Hz, 2H), 3.37–3.32 (m, 2H), 2.16 (qd, J = 11.0, 5.6 Hz, 2H), 1.72 (ddt, J = 13.6, 9.5, 4.4 Hz, 3H), 1.57–1.43 (m, 1H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 22.0, 22.6, 55.7, 62.6, 67.0, 69.5, 102.1, 107.8, 108.0, 131.1, 160.5, 162.5, 176.8; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{14}H_{21}NO_3$ 252.1594; Found, 252.1592. **5b** (0.19 g, 0.76 mmol) was suspended in toluene (7.5 ml) under stirring. BSA (0.55 ml, 2.25 mmol) was added, and the solution was heated to reflux in an oil bath under stirring for 30 min. The solution was evaporated under reduced pressure, and the residual oil was purified by column chromatography by elution with EtOAc/hexane (1:4) to give 0.079 g (69%) of **5c** [16] as an oil. The spectra were consistent with published data. **5c** (0.079 g, 0.53 mmol) was dissolved in HOAc (90%) (aq) (2 ml). The solution was stirred and heated to reflux in an oil bath for 30 min. The solution was evaporated at reduced pressure to give 0.059 g (90%) of the title compound as an oil. Trace HOAc was removed by aspirator vacuum. The spectra were consistent with those of a commercial sample.

3-Methoxyphenol (**5d**). [12]. **5a** (1.03 g, 4.40 mmol) was dissolved in DCM (30 ml) under stirring in a N_2 atmosphere. BBr_3•Me_2S (1.60 g, 5.12 mmol) was added, and the solution was stirred for 15 min. The solution was diluted with conc. NH_4OH (aq) (6 ml) and MeOH (20 ml), stirred vigorously for 10 min and left overnight. On day 2, the solution was extracted with DCM (3*40 ml), and the organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The residual solid was dissolved in MeOH/H_2O (2:1, 50 ml), and this solution was refluxed for 60 min to hydrolyze the traces of boron reagent. The solution was evaporated at reduced pressure, and the residue was purified with chromatography by elution with EtOAc/hexane (1:2) to give 0.39 g (71%) of the title compound as an oil. The spectra were consistent with those of a commercial sample.

3-(2-(Piperidin-1-yl*)ethoxy)phenyl acetate* (**6a**). **17** (0.50 g, 2.26 mmol) was suspended in Ac_2O (4 ml). The mixture was heated to reflux under stirring for 5 min. The solution was cooled, and MeOH (15 ml) was added, and the solution was left overnight. The solution was diluted with DCM (50 ml) and water (50 ml), stirred and neutralized with $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with DCM (3*30 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography by elution with EtOAc/hexane/triethylamine (TEA) (5:15:1) (the column was packed with EtOAc/hexane 1:3) to give 0.41 g (69%) of the title compound as an oil. ^{1}H NMR (800 MHz, MeO-d4) δ 7.05 (t, J = 8.0 Hz, 1H), 6.53–6.22 (m, 3H), 4.08 (t, J = 5.6 Hz, 2H), 2.78 (t, J = 5.7 Hz, 2H), 2.57 (s, 4H), 2.02 (s, 3H), 1.64 (p, J = 5.7 Hz, 4H), 1.49 (t, J = 6.0 Hz, 2H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 20.5, 24.9, 26.4, 55.9, 58.9, 66.1, 103.0, 106.7, 109.1, 130.8, 130.9, 159.7, 161.3, 161.4, 173.4; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{15}H_{21}NO_3$, 264.1594; Found, 264.1593.

3-Hydroxyphenyl acetate (**6d**). [12]. **6a** (0.22 g, 0.84 mmol) was dissolved in DCM (4 ml) under stirring. Then, 39% peracetic acid (in HOAc) (0.17 ml, 0.99 mmol) was added, and the solution was stirred for 4 min. The solution was evaporated under reduced pressure and co-evaporated with toluene/MeOH (1:1, 15 ml). The residue was dissolved in DCM (3 ml), and HMDS (1 ml) was added. The solution was evaporated under reduced pressure, and the residue was dried in vacuo to give **6b**, which was used immediately because it was not stable for storage and did not give rise to good NMR spectra because of degradation. HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{15}H_{21}NO_4$, 280.1543; Found, 280.1552. The gum was dissolved in DCM (3 ml), and the solution was diluted with toluene (7 ml). BSA (0.84 ml, 3.43 mmol) was added, and the solution was heated until the DCM evaporated. The solution was refluxed for 25 min under stirring. The solution was evaporated under reduced pressure, and the residual oil was purified by column chromatography and eluted with EtOAc/hexane (1:7) to give 0.076 g (51%, 2 steps) of **6c** as an oil. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.30 (t, J = 8.2 Hz, 1H), 6.87 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 6.81 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 6.76 (t, J = 2.3 Hz, 1H), 6.61 (dd, J = 13.7, 6.0 Hz, 1H), 4.80 (dd, J = 13.7, 1.8 Hz, 1H), 4.47 (dd, J = 6.1, 1.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 96.1, 110.7, 114.3, 116.2, 130.0, 147.6, 151.5, 157.5, 169.2. **6c** (0.11 g, 0.62 mmol) was dissolved in MeOH (7.5 ml). Ozone mixed with air was bubbled through the solution under stirring for 60 min at ambient temperature at a rate of 50 mg ozone/h. The solution was left for 240 min. The solution was evaporated at reduced pressure to give 0.089 g (94%) of the title compound as a crystalline solid (mp, 54–55 °C; Lit., 55–56 °C). The spectra were consistent with those of a commercial sample.

3-Hydroxyphenyl acetate (**6d**). [12]. **6a** (0.40 g, 1.52 mol) was dissolved in DCM (5 ml) under stirring in a N_2 atmosphere in a flame-dried Schlenk tube. BBr_3•Me_2S (0.49 g, 1.57 mmol) was added. The solution was stirred for 10 min. The solution was poured into a mixture of $NaHCO_3$ (1.2 g), H_2O (5 ml) and MeOH (30 ml). The mixture was stirred for 4 h, diluted with H_2O (30 ml) and extracted with DCM (4*20 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The residual oil was purified with column chromatography by elution with a stepwise gradient EtOAc/hexane (1:3)-EtOAc/TEA (9:1) to give 0.086 g (50%) of the title compound as an oil (based on 0.104 g recovered **6a**); spectra as above.

1-(2-(3-Benzyloxy)phenoxy)ethyl)piperidine (**7a**). **17** (0.50 g, 2.26 mmol) was dissolved in DMF (25 ml) under stirring in a N_2 atmosphere. NaH (60% in oil, 0.12 g, 3.00 mmol) was added, and the solution was heated to 55 °C for 5 min. Benzyl bromide (0.30 ml, 2.52 mmol) was added, and the solution was stirred at RT for 20 min. The solution was diluted with H_2O (40 ml) and Et_2O (40 ml), and the phases were separated. The aqueous phase was extracted with Et_2O (3*20 ml), and the combined organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography and eluted with EtOAc/hexane/TEA (5:15:1) (the column was packed with EtOAc/hexane 1:3) to give 0.52 g (74%) of the title compound as a gum. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 2H), 7.39–7.34 (m, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.16 (td, J = 8.2, 1.7 Hz, 1H), 6.60–6.54 (m, 2H), 6.52 (dd, J = 8.1, 2.4 Hz, 1H), 5.03 (s, 2H), 4.07 (td, J = 6.0, 1.5 Hz, 2H), 2.75 (dd, J = 7.1, 5.5 Hz, 2H), 2.49 (s, 4H), 1.60 (p, J = 5.2 Hz, 4H), 1.44 (q, J = 6.8, 6.2 Hz, 2H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.2, 25.9, 55.0, 57.9, 65.9, 70.0, 101.9106.3, 107.1, 127.5, 127.9, 128.5, 129.8, 136.9, 159.96, 160.04; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{20}H_{25}NO_2$, 312.1958; Found, 312.1955.

3-(Benzyloxy)phenol (**7d**). [12]. **7a** (0.39 g, 1.25 mmol) was dissolved in DCM (15 ml). Next, 39% peracetic acid (in HOAc) (0.34 ml, 1.99 mmol) was added, and the solution was stirred for 4 min. Then, 1 M K_2CO_3 (8 ml) was added, and the solution was stirred for 2 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (5 * 10 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (2 ml) was added to the organic phase, which was evaporated at reduced pressure to give 0.39 g (95%) of **7b** as a gum. ^{1}H

NMR (800 MHz, MeO-d_4) δ 7.36–7.33 (m, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.11 (td, J = 8.2, 2.1 Hz, 1H), 6.56 (dd, J = 8.2, 2.4 Hz, 1H), 6.53 (t, J = 2.4 Hz, 1H), 6.52–6.42 (m, 1H), 4.99 (s, 2H), 4.44 (q, J = 4.1 Hz, 2H), 3.63–3.55 (m, 2H), 3.32 (td, J = 11.5, 10.8, 2.8 Hz, 2H), 2.08 (tt, J = 10.6, 5.1 Hz, 2H), 1.70–1.58 (m, 3H), 1.51–1.37 (m, 1H); . ^{13}C NMR (201 MHz, MeO-d4) δ 22.0, 22.6, 62.6, 67.0, 69.5, 71.0, 103.1, 108.1, 109.0, 128.5, 128.9, 129.5131.2, 138.6, 160.5, 161.5; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{20}H_{25}NO_3$, 328.1907; Found, 328.1902. **7b** (0.39 g, 1.19 mmol) was suspended in toluene (7.5 ml). BSA (0.88 ml, 3.6 mmol) was added, and the solution was heated to reflux under stirring for 35 min. The solution was evaporated, and the resulting gum was purified by column chromatography by elution with EtOAc/hexane (1:20) to give 0.22 g (82%) of **7c** [17] as an oil. The spectra were consistent with those of a commercial sample. **7c** (0.079 g, 0.35 mmol) was dissolved in HOAc/H_2O/TFA (90:10:1), and the solution was heated to reflux under stirring for 4 min. The solution was evaporated under reduced pressure to give 0.069 g (98%) of the title compound as an oil. The spectra were consistent with those of a commercial sample.

3-(Benzyloxy)phenol (**7d**). [12]. **7a** (1.02 g, 3.30 mmol) was dissolved in DCM under stirring in a N_2 atmosphere in a flame-dried round-bottom flask. BBr_3•Me_2S (1.03 g, 3.30 mmol) was added. The solution was stirred for 25 min. The solution was diluted with conc. NH_4OH (aq) (6 ml) and stirred for 3 min. The mixture was poured into a mixture of MeOH (40 ml), H_2O (30 ml) and $NaHCO_3$ (4.2 g). The mixture was boiled for 20 min, and some of the MeOH boiled off. The mixture was cooled to ambient temperature and extracted with DCM (3*25 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The residual oil was purified by column chromatography by elution with EtOAc/hexane (1:4) to give 0.46 g (70%) of the title compound as an oil. The spectra were the same as described above.

1-(2-(3-((4-Methoxybensyl)oxy)phenoxy)ethyl)piperidine (**8a**). **17** (1.00 g, 4.52 mmol) was dissolved in DMF (20 ml) under a N_2 atmosphere with stirring. NaH (0.24 g, 6.00 mmol) was added, and the solution was heated to 70 °C in an oil bath. The solution was cooled to ambient temperature. *p*-MeOBnCl (0.78 g, 5.00 mmol) was added, and the solution was stirred for 2 h. The solution was diluted with Et_2O (40 ml) and H_2O (40 ml). The aqueous phase was extracted with Et_2O (3*20 ml), and the combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography by eluting with EtOAc/hexane/TEA (5:15:1) (the column was packed with EtOAc/hexane 1:3) to give 0.60 g (39%) of the title compound as a crystalline solid (mp 48–52 °C). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.42–7.30 (m, 2H), 7.15 (t, J = 8.2 Hz, 1H), 7.00–6.83 (m, 2H), 6.61–6.44 (m, 3H), 4.95 (s, 2H), 4.07 (t, J = 6.1 Hz, 2H), 3.81 (s, 3H), 2.75 (t, J = 6.1 Hz, 2H), 2.49 (s, 4H), 1.60 (p, J = 5.6 Hz, 4H), 1.44 (d, J = 6.0 Hz, 2H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.2, 25.9, 55.0, 55.3, 57.9, 65.9, 69.8, 101.9, 107.05, 107.13, 114.0, 129.0, 129.2, 129.8, 159.4, 160.0; HRMS ESI + *m/z* $[M+H]^+$ Calcd For $C_{21}H_{27}NO_3$ 342.2064 Found 342.2068.

3-((4-Methoxybenzyl)oxy)phenol (**8d**). [18]. **8a** (0.27 g, 0.79 mmol) was dissolved in DCM (15 ml) under stirring. Then, 39% peracetic acid (in HOAc) (0.16 ml, 0.94 mmol) was added, and the solution was stirred for 4 min. Next, 1 M K_2CO_3 (2 ml) was added, and the mixture was stirred for 4 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (7*2 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (2 ml) was added to the combined organic phase and evaporated at reduced pressure to give 0.27 g (96%) of **8b** as a gum. ^{1}H NMR (800 MHz, MeO-d_4) δ 7.35–7.30 (m, 2H), 7.17 (t, J = 8.2 Hz, 1H), 6.93–6.87 (m, 2H), 6.61 (dd, J = 8.2, 2.3 Hz, 1H), 6.58 (t, J = 2.4 Hz, 1H), 6.55 (dd, J = 8.2, 2.4 Hz, 1H), 4.96 (s, 2H), 4.54–4.46 (m, 2H), 3.78 (s, 3H), 3.67–3.60 (m, 2H), 3.38 (td, J = 11.7, 2.8 Hz, 2H), 3.30–3.27 (m, 2H), 2.14 (tt, J = 10.6, 5.3 Hz, 2H), 1.69 (dt, J = 7.6, 4.7 Hz, 3H), 1.55–1.41 (m, 1H); ^{13}C NMR (201 MHz, MeO-d4) δ 22.0, 22.6, 55.7, 62.6, 67.0, 69.5, 70.8, 103.1, 108.0, 109.1, 114.9, 130.3, 130.5, 131.1, 160.5, 160.9, 161.6; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{21}H_{27}NO_4$, 358.2013; Found, 358.2009. **8b** (0.16 g, 0.45 mmol) was suspended in toluene (5 ml). BSA (0.33 ml, 1.40 mmol) was added, and the solution was refluxed for 45 min. The solution was evaporated at reduced pressure, and the residue was purified by column chromatography by elution with EtOAc/hexane (1:7) to give 0.091 g (79%) of **8c** as a crystalline solid (mp 56–58 °C); ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.37–7.30 (m, 2H), 7.20 (t, J = 8.2 Hz, 1H), 6.94–6.87 (m, 2H), 6.69 (dd, J = 8.4, 2.4 Hz, 1H), 6.64–6.56 (m, 3H), 4.96 (s, 2H), 4.77 (dd, J = 13.7, 1.7 Hz, 1H), 4.42 (dd, J = 6.1, 1.7 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 55.3, 69.9, 95.3, 104.1, 109.3, 109.6, 114.0, 128.7, 129.2, 130.0, 147.9, 157.9, 159.5, 160.0. **8c** (0.043 g, 0.17 mmol) was dissolved in DCM (7 ml), and ozone in air was bubbled through the solution at a rate of 50 mg ozone/h for 20 min. The reaction was closely monitored by TLC (**8c** has a R_f value of 0.45 (EtOAc/hexane 1:4), and ozonide has a R_f value of 0.30). The ozone was discontinued immediately when the starting material was completely consumed. Then, 90% HOAc (aq) (0.5 ml) and MeOH (0.5 ml) were added, and the solution was left overnight. On day 2, TLC showed 100% conversion of ozonide to the title product (R_f 0.25). The solution was washed with H_2O (2*5 ml), dried with Na_2SO_4, filtered and evaporated at reduced pressure to give 0.027 g (69%) of the title compound as a semi-crystalline solid. The overall yield was 53%. The spectra were consistent with those of a commercial sample.

1-(2-3-((tert-Butyldiphenylsilyl)oxy)phenoxy)ethyl)piperidine (**9a**). **17** (1.00 g, 4.52 mmol) was dissolved in DMF (15 ml) under a N_2 atmosphere with stirring. *tert*-Butylchlorodiphenylsilane (1.92 g, 6.99 mmol), TEA (2.00 ml) and 4-(dimethylamino)pyridine (DMAP) (0.12 g) were added. The solution was stirred and heated to 70 °C for 3 h in an oil bath. The solution was cooled and diluted with Et_2O (50 ml) and water (50 ml). The mixture was stirred for 4 min, and the phases were separated. The aqueous phase was extracted with Et_2O (3*30 ml). The combined organic phase was dried with Na_2SO_4 and filtered. The solution was evaporated at reduced pressure. The residue was purified with column chromatography and eluted with EtOAc/hexane/TEA (20:80:5) (the column was packed with EtOAc/hexane 1:3) to give 1.31 g (63%) of the title compound as a syrup. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.75–7.64 (m, 4H), 7.44–7.38 (m, 2H), 7.35 (t, J = 7.5 Hz, 4H), 6.94 (d, J = 8.8 Hz, 1H), 6.42 (dd, J = 7.3, 2.0 Hz, 1H), 6.38–6.30 (m, 2H), 3.86 (t, J = 6.2 Hz, 2H), 2.63 (t, J = 6.2 Hz, 2H), 2.41 (s, 4H), 1.57 (p, J = 5.7 Hz, 4H), 1.43 (d, J = 6.2 Hz, 2H), 1.09 (s, 9H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 19.4, 24.2, 25.9, 26.5, 54.9, 57.7, 65.7, 106.3, 107.8, 112.2, 127.7, 127.7, 129.4, 129.8, 133.0, 135.5, 156.6, 159.7; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{29}H_{37}NO_2Si$, 460.2666; Found 460.2686.

3-((tert-Butyldiphenylsilyl)oxy)phenol (**9d**). [11]. **9a** (0.94 g, 2.04 mmol) was dissolved in DCM (20 ml). Next, 39% peracetic acid (in HOAc) (0.48 ml, 2.81 mmol) was added under stirring for 4 min. Then, 1 M K_2CO_3 (10 ml) was added, and the solution was stirred for 3 min. The solution was filtered through phase-separator paper, and the aqueous phase was extracted in the filter funnel with DCM (7*3 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (2 ml) was added to the organic phase, and this solution was evaporated at reduced pressure to give 0.92 g (84%) of **9b** as a gum that contained 1 equiv. of HOAc. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.72–7.67 (m, 4H), 7.45–7.40 (m, 2H), 7.36 (t, J = 7.3 Hz, 4H), 6.96 (t, J = 8.2 Hz, 1H), 6.39 (ddd, J = 33.1, 8.2, 2.3 Hz, 2H), 6.30 (t, J = 2.4 Hz, 1H), 4.41–4.35 (m, 2H), 3.77–3.72 (m, 2H), 3.60 (dt, J = 11.9, 4.4 Hz, 2H), 3.20–3.09 (m, 2H), 2.28–2.14 (m, 2H), 1.72 (dd, J = 9.2, 4.6 Hz, 1H), 1.65 (dt, J = 14.6, 4.5 Hz, 2H), 1.41 (s,

1H), 1.09 (s, 9H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 19.4, 20.9, 21.7, 26.5, 61.3, 65.5, 67.3, 106.4, 107.3, 113.0, 127.8, 129.7, 129.9, 132.7, 135.5, 156.8, 158.3; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{29}H_{37}NO_3Si$, 476.2615; Found, 476.2624. **9b** (0.54 g, 1.01 mmol) was suspended in toluene (7.5 ml) under stirring. BSA (0.83 ml, 3.40 mmol) was added, and the solution was heated to reflux for 35 min. The solution was evaporated at reduced pressure, and the resulting gum was purified by column chromatography by elution with EtOAc/hexane (1:20) to give 0.27 g (71%) of **9c** as an oil. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.74–7.67 (m, 4H), 7.45–7.38 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 4H), 6.99 (t, *J* = 8.2 Hz, 1H), 6.51 (s, 1H), 6.47–6.35 (m, 3H), 4.64 (dd, *J* = 13.7, 1.6 Hz, 1H), 4.31 (dd, *J* = 6.1, 1.6 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 19.4, 26.5, 94.9, 108.9, 109.8, 114.6, 127.8, 129.7, 129.9, 132.7, 135.5, 147.9, 156.7, 157.5; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{24}H_{26}O_2Si$, 375.1775; Found, 375.1775.

9c (0.096 g, 0.26 mmol) was dissolved in DCM/90% HOAc (aq) (2:1, 10 ml), and ozone in air was bubbled through the solution at a rate of 50 mg ozone/h for 45 min. The starting material had a R_f value of 0.80 (EtOAc/hexane 1:4), and the ozone was discontinued when this material was completely converted to the corresponding presumed ozonide (R_f 0.70). MeOH (2.5 ml) was added, and the solution was left overnight. The next day, the ozonide was completely hydrolyzed to the title compound (R_f 0.60). The solution was diluted with H_2O (10 ml), and the mixture was extracted with EtOAc/hexane (1:4, 3*15 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure to give 0.086 g (95%) of the title compound as an oil. The spectra were consistent with those of a commercial sample.

tert-Butyl(4-(2-piperidin-1-yl*)ethoxy)phenyl)carbamate* (**10a**). [19]. **18** (1.59 g, 7.22 mmol) was dissolved in DCM (40 ml). Boc_2O (2.20 g, 10.08 mmol) was added, and the solution was left overnight. The solution was evaporated at reduced pressure, and the residue was purified by column chromatography by eluting with EtOAc/hexane/TEA (10:20:3) (the column was packed with EtOAc/hexane 1:2) to give 1.72 g (74%) of the title compound as a crystalline solid (mp 78–80 °C). ^{1}H NMR (800 MHz, MeO-d_4) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.92–6.72 (m, 2H), 4.07 (t, *J* = 5.7 Hz, 2H), 2.74 (t, *J* = 5.7 Hz, 2H), 2.66–2.38 (m, 4H), 1.62 (p, *J* = 5.7 Hz, 4H), 1.50 (s, 11H). ^{13}C NMR (201 MHz, MeO-d_4) δ 25.0, 26.4, 28.8, 55.9, 59.0, 66.6, 80.5, 115.7, 121.7, 133.7, 155.6, 156.0.

4-Tert-butyl(4-hydroxyphenyl)carbamate (**10d**). [12]. **10a** (0.36 g, 1.12 mmol) was dissolved in DCM (25 ml) under stirring. Then, 39% peracetic acid (in HOAc) (0.26 ml,1.52 mmol) was added, and the solution was stirred for 4 min. Next, 1 M K_2CO_3 (4.2 ml) was added, and the mixture was stirred for 4 min. The solution was filtered through PS paper, and the aqueous phase was extracted in the filter funnel with DCM (7*4 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the PS-filter. HMDS (2 ml) was added to the organic phase, and the solution was evaporated at reduced pressure to give 0.33 g (88%) of **10b** as a crystalline solid (mp 186–188 °C). ^{1}H NMR (800 MHz, MeO-d4) δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.97–6.70 (m, 2H), 4.62–4.38 (m, 2H), 3.69–3.58 (m, 2H), 3.39 (td, *J* = 11.6, 2.8 Hz, 2H), 3.30–3.24 (m, 2H), 2.16 (dd, *J* = 10.9, 3.8 Hz, 2H), 1.79–1.65 (m, 3H), 1.50 (s, 10H); ^{13}C NMR (201 MHz, MeO-d4) δ 22.0, 22.1, 22.7, 63.0, 67.1, 69.7, 80.6, 115.8, 121.7, 134.3, 155.1, 155.6; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{18}H_{27}N_2O_4$, 336.2044; Found, 336.2038. **10b** (0.14 g, 0.42 mmol) was dissolved in DMF (7 ml) under stirring. BSA (0.31 ml, 1.27 mmol) mmol) was added, and the solution was heated to 120 °C for 50 min. The solution was then cooled to ambient temperature, and H_2O (20 ml) was added. The mixture was extracted with Et_2O (3*10 ml). The organic phase was washed with H_2O (2* 10 ml), dried with Na_2SO_4, filtered and evaporated at reduced pressure. The solid residue was purified by column chromatography by elution with EtOAc/hexane (1:7) to give 0.065 g (66%) of **10c** as a crystalline solid (mp 59–62 °C); ^{1}H NMR (800 MHz, MeO-d4) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.95–6.87 (m, 2H), 6.67 (dd, *J* = 13.7, 6.1 Hz, 1H), 4.61 (dd, *J* = 13.6, 1.5 Hz, 1H), 4.34 (dd, *J* = 6.1, 1.5 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (201 MHz, MeO-d4) δ 28.7, 80.8, 94.2, 118.5, 121.4, 136.0, 150.2, 153.6, 155.5; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{13}H_{17}NO_3$, 236.1281; Found, 236.1283.

10c (0.14 g, 0.60 mmol) was dissolved in DCM (5 ml) under stirring, and then ozone in air was bubbled through the solution at a rate of 50 mg/h for 30 min. HOAc (90%) (aq) (2 ml) and MeOH (2 ml) were added, and the solution was left at ambient temperature. On day 3, the solution was diluted with DCM (10 ml) and H_2O (10 ml). The solution was stirred for 3 min, and the phases were separated. The organic phase was washed with H_2O (10 ml), dried with Na_2SO_4, filtered and evaporated. The crystalline residue was washed with DCM (1 ml) and dried in vacuo to give 0.11 g (88%) of the title compound as a crystalline solid (mp, 141–143 °C; lit., 142–143 °C). The spectra were consistent with those of a commercial sample.

4-tert-Butyl(4-hydroxyphenyl)carbamate (**10d**). **10c** (0.066 g, 0.28 mmol) was dissolved in DMF (1.6 ml), and H_2O (0.4 ml) was added under stirring. 3,6-(Di(pyridine-2-yl)1,2,4,5-tetrazine (0.080 g, 0.34 mmol) was added, and the solution was stirred and heated to 60 °C for 570 min. The solution was cooled and diluted with Et_2O (5 ml) and H_2O (5 ml). The aqueous phase was extracted with Et_2O (3*5 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The solid residue was purified by column chromatography by elution with EtOAc/hexane (1:2) to give 0.032 g (55%) of the title compound as a crystalline solid. The spectra were the same as described above.

1-(2-(3-(Allyloxy)phenoxy)ethyl)piperidine (**11a**). **17** (0.300 g, 1.36 mmol) was dissolved in DMF (6.0 ml) under a N_2 atmosphere, and NaH (60% in mineral oil, 0.065 g, 1.63 mmol) was added under stirring. The solution was heated in a polyethylene glycol (PEG) bath to 120 °C for 4 min. The mixture was cooled to ambient temperature and stirred for 15 min. Allyl iodide (0.272 g, 1.62 mmol) was added, and the mixture was stirred for 25 min. The solution was diluted with H_2O (20 ml) and extracted with Et_2O (3* 25 ml). The organic phase was subjected to acid-base partitioning with HOAc (6.0 ml in 20 ml H_2O) and conc. NH_4OH (aq) (10 ml in 30 ml H_2O). The organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure to give 0.24 g (68%) of the title compound as an oil; ^{1}H NMR (800 MHz, MeOD) δ 7.14 (t, *J* = 8.1 Hz, 1H), 6.55–6.45 (m, 3H), 6.05 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.39 (dd, *J* = 17.3, 1.7 Hz, 1H), 5.24 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.51 (d, *J* = 5.2 Hz, 2H), 4.09 (t, *J* = 5.6 Hz, 2H), 2.76 (t, *J* = 5.7 Hz, 2H), 2.55 (s, 4H), 1.63 (p, *J* = 5.7 Hz, 4H), 1.48 (s, 2H). ^{13}C NMR (201 MHz, MeO-d4) δ 25.0, 26.4, 55.9, 58.9, 66.3, 69.8, 102.8, 107.9, 108.2, 117.4, 130.9, 135.0, 161.31, 161.34; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{16}H_{23}NO_2$, 262.1807; Found, 262.1807.

3-(Allyloxy)phenol (**11d**). [11]. **11a** (0.16 g, 0.61 mmol) was dissolved in DCM (4 ml) under stirring. Then, 39% peracetic acid (in HOAc) (0.10 ml, 0.61 mmol) was added, and the solution was stirred for 2 min. TEA (0.2 ml) was added to protect the alkene from possible epoxidation if excess peracetic acid was present, and the solution was stirred for 1 min. Next, 1 M K_2CO_2 (2.0 ml) was added, and the mixture was stirred for 4 min. The mixture was filtered through PS paper, and the aqueous phase was extracted with DCM (7*5.0 ml) in the filter funnel by siphoning the mixture back and forth with a single-use 5 ml polyethylene Pasteur pipette as the organic phase passed through the PS-filter. The organic phase was mixed with HMDS (1.0 ml), and the solution was evaporated at reduced pressure to give 0.17 g (0.16 g, 95%) of **11b** as a semi-crystalline solid. ^{1}H NMR (800 MHz, MeOD) δ 7.18 (t, *J* = 8.1 Hz, 1H), 6.66–6.46 (m, 3H), 6.14–5.93 (m, 1H), 5.39 (dd, *J* = 17.3, 1.7 Hz, 1H), 5.24 (dt, *J* = 10.6, 1.5 Hz, 1H), 4.52 (dt, *J* = 5.7, 1.9 Hz, 4H),

3.72–3.61 (m, 2H), 3.39 (ddd, J = 12.8, 11.3, 2.8 Hz, 2H), 3.30–3.22 (m, 2H), 2.16 (qd, J = 10.8, 3.9 Hz, 2H), 1.71 (dt, J = 14.3, 5.0 Hz, 3H), 1.50 (tdd, J = 11.4, 7.8, 4.9 Hz, 1H); ^{13}C NMR (201 MHz, MeOD) δ 22.1, 22.7, 62.7, 67.1, 69.7, 69.8, 102.9, 108.0, 108.8, 117.4, 131.1, 134.9, 160.5, 161.4; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{16}H_{23}NO_3$, 278.1757; Found, 278.1756. **11b** (0.15 g, 0.54 mmol) was suspended in toluene (6.0 ml). BSA (0.39 ml, 1.60 mmol) was added, and the solution was refluxed for 36 min. The solution was evaporated at reduced pressure, and the oily residue was purified by column chromatography by elution with EtOAc/hexane (1:20) to give 0.066 g (70.1%) of **11c** as an oil; ^{1}H NMR (800 MHz, MeOD) δ 7.21 (t, J = 8.1 Hz, 1H), 6.71 (dd, J = 13.6, 6.1 Hz, 1H), 6.66 (ddd, J = 8.3, 2.4, 0.9 Hz, 1H), 6.61–6.55 (m, 2H), 6.05 (ddt, J = 17.3, 10.5, 5.2 Hz, 1H), 5.39 (dd, J = 17.3, 1.7 Hz, 1H), 5.25 (dd, J = 10.6, 1.5 Hz, 1H), 4.70 (dd, J = 13.7, 1.5 Hz, 1H), 4.53 (dt, J = 5.1, 1.6 Hz, 2H), 4.41 (dd, J = 6.1, 1.5 Hz, 1H). ^{13}C NMR (201 MHz, MeOD) δ 69.9, 95.2, 104.9, 110.1, 110.5, 117.5, 131.2, 134.8, 149.3, 159.4, 161.4.

11c (0.054 g, 0.31 mmol) was dissolved in 90% HOAc (aq) (3.0 ml), and the solution was refluxed for 30 min. The solution was evaporated at reduced pressure to give 0.040 g (87%) of the title product. The spectra were consistent with those of a commercial sample.

1-(2-(3-((Tetrahydro-2H-pyran-2-yl*)oxy)phenoxy)ethyl)piperidine* (**12a**). **17** (1.00 g, 4.52 mmol) was mixed with *p*-TSA*H_2O (0.936 g, 4.92 mmol) in a Schlenk flask in vacuo, and the mixture was stirred and heated until a melt formed (approx. 60 °C) and the bubbling stopped. The mixture was cooled to ambient temperature, and toluene (3 ml), DCM (9 ml) and DMSO (2 ml) were added. The mixture was sonicated for 2 min. 3,4-Dihydro-2H-pyrane (2.24 ml, 24.6 mmol) was added, and the mixture was stirred for 1 h. Then, 3,4-dihydro-2H-pyrane (1.00 ml, 11.00 mmol) was added, and the solution was stirred for 1.5 h. At this point, a clear solution was formed. The solution was poured into a mixture of conc. NH_4OH (aq) (9 ml) and Et_2O (150 ml) under stirring. The aqueous phase was extracted with Et_2O (3*25 ml). The combined organic phase was washed with H_2O (1*40 ml), dried with Na_2SO_4, filtered and evaporated at reduced pressure. The resulting oil was purified by column chromatography by elution with EtOAc/hexane/TEA (10:10:1) to give 0.91 g (66%) of the title compound as an oil; ^{1}H NMR (700 MHz, MeOD) δ 7.14 (t, J = 8.5 Hz, 1H), 6.66–6.59 (m, 2H), 6.56 (ddd, J = 8.3, 2.3, 1.0 Hz, 1H), 5.39 (t, J = 3.4 Hz, 1H), 4.10 (t, J = 5.7 Hz, 2H), 3.91–3.84 (m, 1H), 3.61–3.55 (m, 1H), 2.76 (t, J = 5.6 Hz, 2H), 2.55 (s, 4H), 2.03–1.94 (m, 1H), 1.86 (dddd, J = 13.5, 10.5, 4.4, 3.0 Hz, 1H), 1.79 (dddd, J = 13.0, 6.1, 4.6, 3.4 Hz, 1H), 1.72–1.61 (m, 6H), 1.59 (ddt, J = 11.8, 7.4, 4.3 Hz, 1H), 1.49 (q, J = 5.9 Hz, 2H); ^{13}C NMR (201 MHz, MeOD) δ 20.0, 25.0, 26.35, 26.44, 31.5, 55.9, 59.0, 63.2, 66.4, 97.8, 104.4, 108.7, 110.1, 130.8, 159.7, 161.2; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{18}H_{27}NO_3$, 306.2069; Found, 306.2069.

3-((Tetrahydro-2H-pyran-2-yl*)oxy)phenol* (**12d**). [15]. **12a** (0.135 g, 0.44 mmol) was dissolved in DCM (6 ml) under stirring. Next, 39% peracetic acid (in HOAc) (0.091 ml, 0.53 mmol) was added, and the solution was stirred for 4 min. Then, 1 M K_2CO_3 (aq) (3.5 ml) was added, and the solution was stirred for 4 min. The mixture was filtered through PS paper, and the aqueous phase was extracted with DCM (7*10 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette in the filter funnel as the organic phase passed through the PS- filter. HMDS (2.0 ml) was added to the combined organic phase, and the solution was evaporated at reduced pressure to give 0.135 g (95%) of **12b** as a semi-crystalline solid; ^{1}H NMR (800 MHz, MeOD) δ 7.22–7.12 (m, 1H), 6.71–6.65 (m, 2H), 6.60 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 5.41 (t, J = 3.4 Hz, 1H), 4.55–4.49 (m, 2H), 3.87 (ddd, J = 11.4, 9.4, 3.0 Hz, 1H), 3.69–3.62 (m, 2H), 3.59 (dtd, J = 11.5, 4.2, 1.2 Hz, 1H), 3.40 (ddd, J = 13.8, 11.0, 2.8 Hz, 2H), 3.35–3.23 (m, 4H), 2.16 (qd, J = 10.8, 3.8 Hz, 2H), 2.07–1.94 (m, 1H), 1.91–1.75 (m, 2H), 1.75–1.61 (m, 5H), 1.61–1.53 (m, 1H), 1.51 (tdd, J = 11.1, 7.7, 4.4 Hz, 1H); ^{13}C NMR (201 MHz, MeOD) δ 19.9, 22.1, 22.7, 26.3, 31.5, 62.7, 63.1, 67.1, 69.7, 97.7, 104.5, 108.7, 110.6, 131.0, 159.8, 160.4; HRMS ESI + m/z $[M+H]^+$ Calcd for $C_{18}H_{27}NO_4$, 322.2018; Found, 322.2018. **12b** (0.111 g, 0.345 mmol) was suspended in toluene (9.0 ml). BSA (0.30 ml, 1.23 mmol) was added, and the mixture was heated under stirring in a PEG bath to reflux for 35 min. The solution was evaporated at reduced pressure, and the resulting oil was purified by chromatography by elution with EtOAc/hexane (1:20) to give 0.052 g (68%) of **12c** as an oil; ^{1}H NMR (700 MHz, MeOD) δ 7.21 (t, J = 8.2 Hz, 1H), 6.76 (ddd, J = 8.3, 2.3, 0.8 Hz, 1H), 6.73–6.70 (m, 1H), 6.70–6.68 (m, 1H), 6.62 (ddd, J = 8.1, 2.4, 0.9 Hz, 1H), 5.41 (t, J = 3.4 Hz, 1H), 4.70 (dd, J = 13.7, 1.5 Hz, 1H), 4.41 (dd, J = 6.1, 1.5 Hz, 1H), 3.88 (ddd, J = 11.4, 9.4, 3.0 Hz, 1H), 3.60 (dtd, J = 11.4, 4.1, 1.2 Hz, 1H), 2.04–1.94 (m, 1H), 1.86 (dddd, J = 13.5, 10.5, 4.4, 3.0 Hz, 1H), 1.83–1.76 (m, 1H), 1.72–1.63 (m, 2H), 1.63–1.54 (m, 1H)); ^{13}C NMR (201 MHz, MeOD) δ 19.9, 26.3, 31.4, 63.1, 95.2, 97.8, 106.5, 110.9, 112.3, 131.1, 149.5, 159.2, 159.7. **12c** (0.030 g, 0.0137 mmol) was suspended in DMF (1.0 ml), and H_2O (0.2 ml) was added. 3,6-Di-2-pyridyl-1,2,4,5-tetrazine (50 mg, 0.212 mmol) was added, and the mixture was heated in a PEG bath to 60 °C for 4.5 h. The mixture was diluted with EtOAc/hexane (1:2, 10 ml) and washed with H_2O (1*20 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated. The resulting solid was purified by column chromatography by elution with EtOAc/hexane (1:2) to give 0.016 g (60%) of the title compound as an oil. The spectra were consistent with those of a commercial sample.

3-((Tetrahydro-2H-pyran-2-yl*)oxy)phenol* (**12d**). **12a** (0.50 g, 1.64 mmol) was dissolved in DCM under stirring in a N_2 atmosphere in a flame-dried round-bottom flask. BBr_3•Me_2S (0.51 g, 1.64 mmol) was added, and the solution was stirred for 10 min. The solution was diluted with conc. NH_4OH (aq) (2 ml) and stirred for 3 min. The mixture was poured into a mixture of MeOH (40 ml), H_2O (30 ml) and $NaHCO_3$ (4.2 g) and boiled for 20 min. DCM and some of the MeOH were boiled off. The mixture was cooled to ambient temperature and extracted with DCM (3*25 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The residual oil was purified by column chromatography by elution with EtOAc/hexane (1:3) to give 0.162 g (51%) of the title compound as an oil. The spectra were the same as described above.

1-(2-(4-Nitrophenoxy)ethyl)piperidine (**12**). [20]. 4-Nitrophenol (2.00 g, 14.40 mmol) was dissolved in DMF (50 ml) under stirring in an Erlenmeyer flask. K_2CO_3 (5.96 g, 43.12 mmol) was added, and the mixture was heated to 90 °C on a magnetic stirrer. **16** (2.65 g, 14.4 mmol) was added, and the solution was stirred for 30 min. The solution was cooled, water (100 ml) was added, and the solution was extracted with Et_2O (4*40 ml). The organic phase was subjected to acid-base partitioning with 5% HCl (aq) (100 ml) and 5% NH_4OH (aq) (150 ml), followed by extraction with Et_2O (4* 60 ml). The solution was diluted with hexane (40 ml), dried with Na_2SO_4, filtered and evaporated. The crystalline residue was dried in vacuo to give 3.40 g (94%) of the title compound. The spectra were consistent with published data. mp, 62–64 °C; Lit., 63–64 °C.

4.1.4. Isolation of reduced N-oxide, Table 1, run 4

1-(2-(4-Nitrophenoxy)ethyl)piperidine (**12**). **13** (0.18 g, 0.68 mmol) was suspended in toluene (6.8 ml) in a flame-dried Schlenk flask under a N_2 atmosphere. 1-Hydroxypiperidine (0.070 g, 0.69 mmol) and HMDS (0.43 ml, 2.05 mmol) were added, and the mixture was heated to reflux in an oil bath under stirring for 15 min. The solution was evaporated at reduced pressure, and the residual oil was purified by column chromatography by elution with EtOAc/MeOH/H_2O/TEA (56:4:2:1) to give 0.037 g

(22%) of the title compound (mp, 61–63 °C; Lit., 63–64 °C). The spectra were the same as described above.

1-(2-(4-Nitrophenoxy)ethyl)piperidine 1-oxide (**13**)**. 12** (1.53 g, 6.11 mmol) was dissolved in DCM (50 ml). The solution was stirred, and 39% peracetic acid (in HOAc) (1.25 ml, 7.31 mmol) was added. The solution was stirred for 5 min. Then, 1 M K_2CO_3 (aq) (25 ml) was added, and the solution was stirred for 4 min. The solution was filtered through PS paper, and the remaining aqueous phase was extracted with DCM (7*10 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette in the filter funnel as the organic phase passed through the PS-filter. HMDS (6.00 ml) was added to the organic phase, and the solution was evaporated at reduced pressure to give 1.55 g (95%) of the title compound as a deliquescent semi-crystalline solid. ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.20 (d, J = 9.2 Hz, 2H), 7.04 (d, J = 9.2 Hz, 2H), 4.88–4.68 (m, 2H), 4.09–3.98 (m, 2H), 3.66 (dd, J = 11.9, 4.9 Hz, 2H), 3.49–3.43 (m, 2H), 2.25 (qd, J = 11.1, 5.7 Hz, 2H), 1.79 (dt, J = 9.5, 4.1 Hz, 3H), 1.54 (dddd, J = 11.3, 7.9, 5.7, 2.9 Hz, 1H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 20.9, 21.4, 62.4, 65.9, 67.6, 114.7, 126.0, 142.1, 162.3; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{13}H_{18}N_2O_4$, 267.1339; Found, 267.1335.

1-(2-(4-Nitrophenoxy)ethyl)piperidine 1-oxide hydrate (**13b**). 13 (0.50 g, 1.87 mmol) was left in a stoppered flask for 1 month. The content in the flask was dissolved in DCM (20 ml), and sufficient toluene to remove the hydrate was added (approximately 30 ml). The crystalline precipitate was collected on a filter, washed with Et_2O (2*5 ml) and dried with an aspirator vacuum to give 0.35 g (66%) of the title compound as white crystals. This material was not deliquescent and was stable in air (mp 73–77 °C); ^{1}H NMR (800 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 9.2 Hz, 2H), 4.87–4.50 (m, 2H), 3.76–3.55 (m, 2H), 3.32 (dd, J = 11.0, 5.5 Hz, 2H), 3.26 (dd, J = 10.9, 3.2 Hz, 2H), 3.14 (s, 2H), 2.46–2.19 (m, 2H), 1.72 (ddt, J = 51.3, 14.4, 4.6 Hz, 3H), 1.46 (dtd, J = 14.2, 10.6, 8.6, 5.2 Hz, 1H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 21.1, 22.0, 62.4, 66.9, 68.2, 114.5, 125.9, 141.9, 162.7. HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{13}H_{18}N3O_4$, 267.1339; Found, 267.1331.

4.1.5. Typical run, Table 1, run 9

1-Nitro-4-(vinyloxy)benzene (**14**). [21a,b]. **13** (0.20 g, 0.75 mmol) was suspended in toluene (7.5 ml) in a flame-dried Schlenk flask under stirring in a N_2 atmosphere. BSTFA (0.40 ml, 1.52 mmol) was added, and the solution was refluxed for 20 min. The solution was evaporated at reduced pressure, and the residual gum was purified by column chromatography by elution with EtOAc/hexane (1:3) to give 0.11 g (88%) of the title compound as a crystalline solid (mp, 55–56 °C; Lit., 55–56 °C). The spectra were consistent with previously reported data.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). [11]. **5a** (4.00 g, 17.00 mmol) was dissolved in HBr (48%) (aq) (10 ml), and the solution was heated to reflux for 70 min. The solution was cooled, poured into H_2O (35 ml) and neutralized with $NaHCO_3$ (7.40 g) under stirring. The separated solid was filtered and washed with ice-cold H_2O (3 ml) and Et_2O (10 ml). This solid was the first batch of **17**. The reaction solution was extracted with EtOAc (5*40 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated to give the second batch of **17**. The first and second batches of **17** were combined and sonicated with DCM (30 ml) for 10 min. The solid was collected on a filter and dried in vacuo to give 3.14 g (83%) of the title compound as a semi-crystalline solid. The spectra were consistent with those of a commercial sample.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **6a** (0.15 g, 0.57 mmol) was dissolved in NH_3/MeOH (5%, 6 ml) under stirring at ambient temperature. The solution was evaporated after 20 min, and the solid residue was dried at 50 °C at reduced pressure to remove the acetamide byproduct, yielding 0.12 g (95%) of the title compound as a solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **7a** (0.48 g, 1.54 mmol) was dissolved in MeOH (5 ml). Pd/C (5%, 0.15 g) was added, and the mixture was hydrogenated at ambient pressure under stirring for 60 min. The solution was filtered and evaporated at reduced pressure to give 0.31 g (91%) of the title compound as a solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **8a** (0.050 g, 0.15 mmol) was dissolved in HOAc. The solution was refluxed for 150 min, evaporated at reduced pressure and purified by column chromatography by elution with EtOAc/TEA/MeOH (90:10:5) (the column was packed with ETOAc) to give 0.023 g (69%) of the title compound as a solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **9a** (0.24 g, 0.52 mmol) was dissolved in THF (20 ml). Tetrabutylammonium fluoride (TBAF) (1 M in THF, 0.58 ml) was added, and the solution was stirred for 5 min. HOAc (56 μl) was added, and the solution was evaporated at reduced pressure. The residual gum was purified by column chromatography by elution with EtOAc/TEA/MeOH (90:10:5) (the column was packed with EtOAc) to give 0.113 g (98%) of the title compound as a solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **11a** (0.098 g, 0.375 mmol) was dissolved in conc. HCl (aq) (1.0 ml) and the solution was heated under stirring to 75 °C for 60 min. The solution was evaporated and the residue was dissolved in H_2O (1.5 ml). The solution was neutralized with $NaHCO_3$ and was filtered through PS paper. The remaining aqueous phase was extracted with EtOAc (6*3 ml) by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette in the filter funnel as the organic phase passed through the PS-filter. The combined organic phase was dried with Na_2SO_4, filtered and evaporated to give 0.070 g (84%) of the title compound as a semi-crystalline solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **12a** (0.158 g, 0.517 mmol) was dissolved in 90% HOAc (aq). The solution was heated to reflux for 1 min. The solution was evaporated and the residue was dissolved in H_2O. The solution was neutralized with $NaHCO_3$ and was extracted with EtOAc (6*3 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated to give 0.110 g (96%) of the title compound as a semi-crystalline solid. The spectra were the same as described above.

3-(2-(Piperidin-1-yl*)ethoxy)phenol* (**17**). **23** (0.15 g, 0.45 mmol) was dissolved in conc. HBr (aq) (1.0 ml), and the solution was heated under stirring to reflux in an oil bath for 70 min. The solution was cooled to ambient temperature, diluted with H_2O (7 ml) and neutralized with $NaHCO_3$ (2.00 g). The mixture was extracted with EtOAc (6*10 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The solid residue was purified with column chromatography by elution with EtOAc/TEA/MeOH (90:10:5) (the column was packed with EtOAc) to give 0.065 g (65%) of the title compound as a solid. The spectra were the same as described above.

4-(2-Piperidin-1-yl*)ethoxy)aniline* (**18**). [15,22]. **10a** (1.62 g, 5.06 mmol) was dissolved in DCM (4 ml) under stirring, and TFA (6 ml) was added. The solution was stirred for 15 min. The solution was diluted with H_2O (20 ml) and conc. NH_4OH (aq) (12 ml) was added under stirring. The organic phase was separated, and the aqueous phase was extracted with DCM (3*20 ml). The combined organic phase was diluted with hexane (20 ml), dried with Na_2SO_4, filtered and evaporated to give 1.04 g (93%) of the title compound as a crystalline solid (mp, 64–65 °C; Lit., 65–66.5 °C). The spectra were consistent with those of a commercial sample.

4-(2-Piperidin-1-yl*)ethoxy)aniline* (**18**). **12** (0.50 g, 2.00 mmol) was dissolved in 90% HOAc (aq) (8 ml) under stirring and heating to

50 °C. Fe (Dust, 0.50 g) was added, and the mixture was stirred at 50 °C for 30 min. The solution was cooled and diluted with Et_2O (40 ml), and conc. NH_4OH (aq) (20 ml) was added. The solution was stirred for 5 min. The phases were separated, and the aqueous phase was extracted with Et_2O (3*20 ml). The combined organic phase was diluted with hexane (30 ml), dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 0.31 g (70%) of the title compound as a crystalline solid. The spectra were the same as described above.

2-Methoxy-6-(2-piperidin-1-yl*)ethoxy)benzaldehyde* (**19**). **5a** (2.00 g, 8.50 mmol) was dissolved in THF (40 ml) under stirring in a N_2 atmosphere at 10 °C. *n*-BuLi (1.6 M in hexane, 8.00 ml, 12.80 mmol) was added. The solution was stirred for 10 min. DMF (4.00 ml) was added, and the solution was stirred for 5 min. The solution was diluted with H_2O (40 ml) and Et_2O (100 ml). The phases were separated, and the aqueous phase was extracted with Et_2O (3* 25 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure to give 1.79 g (80%) of the title compound as a syrup. ^{1}H NMR (800 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.42 (t, J = 8.4 Hz, 1H), 6.57 (dd, J = 8.5, 2.3 Hz, 2H), 4.18 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 2.82 (t, J = 6.0 Hz, 2H), 2.51 (s, 4H), 1.67–1.52 (m, 4H), 1.43 (s, 2H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.0, 25.9, 55.1, 56.0, 57.6, 67.3, 103.9, 104.8, 114.5, 135.8, 161.5, 162.0, 189.4; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{15}H_{21}NO_3$, 264.1594; Found, 264.1590.

2-Hydroxy-6-methoxybenzaldehyde (**22**). [12]. **19** (0.50 g, 1.90 mmol) was dissolved in DCM (15 ml) Then, 39% peracetic acid (in HOAc) (0.39 ml, 2.30 mmol) was added, and the solution was stirred for 5 min. Next, 1 M K_2CO_3 (aq) (6 ml) was added, and the solution was stirred for 2 min. The phases where separated by filtration through PS paper. The aqueous phase was extracted with DCM (6* 2 ml) in the PS filter by siphoning the mixture back and forth with a 5 ml single-use polyethylene Pasteur pipette as the organic phase passed through the filter. The combined organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure to give 0.38 g (72%) of **20** as a syrup; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{15}H_{21}NO_4$, 280.1543; Found, 280.1545. HMDS was not added before evaporation because adding it at that time seemed to increase the degradation of the sensitive *N*-oxide, and the material did not give rise to good NMR spectra. **20** (0.30 g, 1.07 mmol) was suspended in toluene (9 ml), BSA (1.60 ml, 6.5 mmol) was added, and the solution was refluxed for 30 min. The solution was evaporated at reduced pressure, and the residue was purified by column chromatography by elution with EtOAc/hexane (1:4) to give 0.13 g (68%) of **21** (mp, 36–38 °C). ^{1}H NMR (800 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.46 (t, J = 8.4 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.66–6.64 (m, 1H), 6.63 (dd, J = 13.7, 6.0 Hz, 1H), 4.84 (dd, J = 13.7, 2.0 Hz, 1H), 4.55 (dd, J = 6.1, 2.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 56.1, 97.1, 106.3, 109.0, 115.5, 135.6, 147.5, 159.1, 161.7, 188.7; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{10}H_{10}O_3$, 179.0703; Found, 179.0705. **21** (0.16 g, 0.90 mmol) was dissolved in 90% HOAc (aq) (7.5 ml). The solution was refluxed for 50 min and then evaporated under reduced pressure, and the residue was purified by column chromatography by elution with EtOAc/hexane (1:3) to give 0.11 g (80%) of the title compound as a semi-crystalline solid. The spectra were consistent with those of a commercial sample.

1-(2-(3-(2-Cyclohexylethoxy)phenoxy)ethyl)piperidine (**23**). **17** (0.81 g, 3.66 mmol) was dissolved in DMF (7 ml) under stirring in a N_2 atmosphere. NaH (60% in mineral oil) (0.18 g, 4.50 mmol) was added, and the mixture was heated to 50 °C. (2-Bromoethyl) cyclohexane (0.69 ml, 4.41 mmol) was added, and the mixture was stirred at 40 °C for 60 min. The solution was diluted with H_2O (10 ml) and extracted with Et_2O (3*30 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated. The residual syrup was purified by column chromatography by elution with EtOAc/hexane/TEA (9:9:1) to give 0.47 g (39%) of the title compound as an oil; ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.14 (t, J = 8.1 Hz, 1H), 6.54–6.42 (m, 3H), 4.08 (t, J = 6.1 Hz, 2H), 3.96 (t, J = 6.7 Hz, 2H), 2.76 (t, J = 6.1 Hz, 2H), 2.50 (s, 4H), 1.78–1.73 (m, 2H), 1.70 (dt, J = 13.3, 3.6 Hz, 2H), 1.66 (q, J = 6.8 Hz, 3H), 1.60 (p, J = 5.7 Hz, 4H), 1.53–1.46 (m, 1H), 1.44 (q, J = 5.6 Hz, 2H), 1.29–1.20 (m, 2H), 1.16 (d, J = 12.5 Hz, 1H), 1.00–0.93 (m, 2H). ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.2, 25.9, 26.2, 26.5, 55.0, 57.9, 65.88, 65.92, 101.5, 106.6, 106.9, 129.7, 160.0, 160.3; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{21}H_{33}NO_2$, 332.2584; Found, 332.2582.

Resorcinol (**24**). [12]. **5a** (0.15 g, 0.64 mmol) was dissolved in HI (aq) (58%, 4 ml) under stirring in a N_2 atmosphere. The solution was heated to reflux in an oil bath for 2 min. TLC (EtOAc/TEA 9:1) showed that **5a** (R_f 0.8) was 100% hydrolyzed to **17** (R_f 0.3, tailing). The solution was refluxed for 80 min. TLC showed that **17** was 100% hydrolyzed to the title compound (R_f 0.6). The solution was cooled and neutralized with $NaHCO_3$ (4 g) and then extracted with EtOAc (3*15 ml). The organic phase was dried with Na_2SO_4, filtered and evaporated at reduced pressure. The solid residue was purified by column chromatography by elution with an EtOAc/hexane gradient (1:2 to 1:1) to give 0.050 g (71%) of the title compound as a crystalline solid (mp 109–110 °C). The spectra and mp were consistent with those of a commercial sample.

1-(2-(4-Methoxyphenethoxy)ethyl)piperidine (**25**). 2-(4-Methoxyphenyl)ethan-1-ol (2.46 g, 16.16 mmol) was dissolved in DMF (35 ml) under stirring in a N_2 atmosphere. **16** (3.60 g, 19.60 mmol) and NaH (48% in mineral oil, 2.42 g, 48.4 mmol) were added, and the mixture was heated in a PEG bath to 80 °C for 20 min and cooled to ambient temperature. Conc. NH_4OH (aq) (9 ml) was added, and the solution was stirred for 80 min. The solution was diluted with H_2O (50 ml) and extracted with Et_2O (3*40 ml). The combined organic phase was washed with H_2O (2*30 ml), dried with Na_2SO_4, filtered and evaporated. The oily residue was purified by column chromatography by elution with EtOAc/TEA (20:1) to give 2.72 g (64%) of the title compound as an oil. ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.16–7.11 (m, 2H), 6.84–6.80 (m, 2H), 3.78 (s, 3H), 3.60 (t, J = 7.2 Hz, 2H), 3.57 (t, J = 6.1 Hz, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.53 (t, J = 6.1 Hz, 2H), 2.40 (s, 4H), 1.57 (p, J = 5.7 Hz, 4H), 1.41 (s, 2H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 24.2, 25.9, 35.3, 55.0, 55.2, 58.5, 68.8, 72.3, 113.7, 129.8, 129.9, 131.0, 158.0; HRMS ESI + *m/z* $[M+H]^+$ Calcd for $C_{16}H_{25}NO_2$, 264.1958; Found, 264.1962.

2-(4-Methoxyphenyl)ethan-1-ol **26** [12] and *1-(2-bromoethyl)-4-methoxybenzene* **27**. [12]. BBr_3•Me_2S (0.96 g, 3.10 mmol) was dissolved in DCM (20 ml) under stirring in a N_2 atmosphere in a flame-dried flask. **25** (0.41 g, 1.56 mmol) dissolved in DCM (2 ml) was added. The solution was stirred for 15 min, poured into a stirred mixture of $NaHCO_3$ (8 g)/H_2O (30 ml)/MeOH (40 ml) and heated to boiling for 30 min (The DCM was evaporated after 5 min) (It's very important to quench TLC-samples with aqueous $NaHCO_3$/MeOH solution before running TLC, otherwise more **27** will show). NH_4OH (aq) was avoided due to the risk of any formed **27** alkylating NH_3 and forming amine. The mixture was cooled and extracted with DCM (4*15 ml). The combined organic phase was dried with Na_2SO_4, filtered and evaporated. The oily residue was purified by column chromatography by elution with a stepwise gradient of EtOAc/hexane (1:7), EtOAc, EtOAc/TEA (9:1) to give 0.12 g (70% based on 0.10 g recovered starting material) of the title compound as an oil. As determined by careful examination of the TLC plates, 1.0 mg of **27** was isolated. The spectra for both compounds were consistent with those of commercial samples.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have

appeared to influence the work reported in this paper.

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