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A tertiary amine synthesis *via* a hydroxylamine alkylation/catalytic reduction sequence

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Overalkylation is a common side reaction that typically prevents the synthesis of tertiary *N*-methylamines from secondary amines, using alkyl iodides and other reactive electrophiles. Herein, we present an indirect approach featuring hydroxylamines, using a reaction sequence involving alkylation, followed by an optimized, catalytic *in situ* reduction of the *N*-oxide intermediate to give the desired *N*-methyl tertiary amine. An optimized isolation of these products is also reported.

N-Methyl tertiary amines are a common motif in many pharmaceutical and natural products (Scheme 1A), making them important target compounds for synthetic chemists.[1] Given the importance of *N*-methyl tertiary amines, many approaches have been developed for their synthesis (Scheme 1B). Although the formation of tertiary amines may seem conceptually simple, the direct alkylation of secondary amines *via* S_N2 reactions is often plagued by overalkylation.[2] This problem arises from the nucleophilicity of the amine increasing as it becomes more substituted, making the products more reactive than the starting materials.[3] Overalkylation is a more common synthetic challenge for reactions with iodomethane, and related reactive alkylating agents that lack the steric hindrance that could help reduce overalkylation.[4] A variety of systems have been developed to reduce the overalkylation using iodomethane, however these can be overall substrate dependent and/or moderate yielding.[5] Selective *N*-methylation of secondary amines is often achieved in good yield using a reductive amination approach using formaldehyde and a range of reducing agents, including $NaBH_3CN$,[6a] $Zn(BH_4)_2$,[6b] $NaBH(OAc)_3$,[6c] and others.[6d] The Eschweiler–Clarke reaction of secondary amines with formaldehyde, using formic acid as reductant, has also been a common way to form *N*-methylamines.[6e] Recent advances in the Eschweiler–Clarke reaction have reported using H_2 with heterogenous catalysts,[6f] the use an iridium catalyst to enhance the rate of the reduction step,[6g] as well as a simplified reaction using only formaldehyde and high heat.[6h] Metal catalyzed processes have also been developed, especially with the use of methanol in a borrowing hydrogen strategy.[7] These processes tend to give overall very high mono-*N*-methylation selectivity, however, do require the use of more forcing conditions and the use of precious metal catalysts, such as rhodium and iridium.[8] These strategies have been expanded to different C1-electrophiles, such as formic acid,[9] carbon dioxide,[10] and dialkyl phosphites.[11] Carbamates have also been used as late-stage methyl group precursors in the synthesis of complex molecules.[12] Indeed, carbamates may be reduced to the methylamine group, but also often act as a protecting group for the nitrogen atom throughout the synthesis. This protecting group strategy led us to wonder if hydroxylamines could be used in a similar fashion (Scheme 1B). The use of disubstituted hydroxylamines as nucleophiles in alkylation reactions has been reported sporadically,[13] but this reactivity has not been thoroughly investigated, perhaps due to the fact that such reactions afford *N*-oxide products. An example of *N*-methylation of a dialkylhydroxylamine using iodomethane was reported by Shvo in 1981, giving the corresponding *N*-oxide in low yield while using forcing conditions.[13c] Alkyl bromides were also explored and showed moderate reactivity.[13d–g] Dialkylhydroxylamines demonstrated moderate reactivity with propylene oxide to form 2-hydroxypropyl *N*-oxides.[13i] The conjugate *N*-addition of mono-substituted hydroxylamines onto various Michael acceptors has been thoroughly reported in the literature,[13j–l] however, the same cannot be said with the dialkyl derivatives. In these cases, only the thermodynamic *O*-addition products have been observed, due to the fast Cope-elimination of the kinetic *N*-oxide product (the *N*-addition product).[13l] Another contributing factor to this gap in the literature may be inefficient synthetic methodology and challenging isolation for accessing the hydroxylamine starting materials. Our group has a long-standing interest in the synthesis and reactivity of hydroxylamines, notably in the context of Cope-type hydroamination reactions.[14] We have recently published methodology enabling a direct, oxidative synthesis and isolation of *N*,*N*-disubstituted hydroxylamines from the parent amines (Scheme 1D).[15] In paral-

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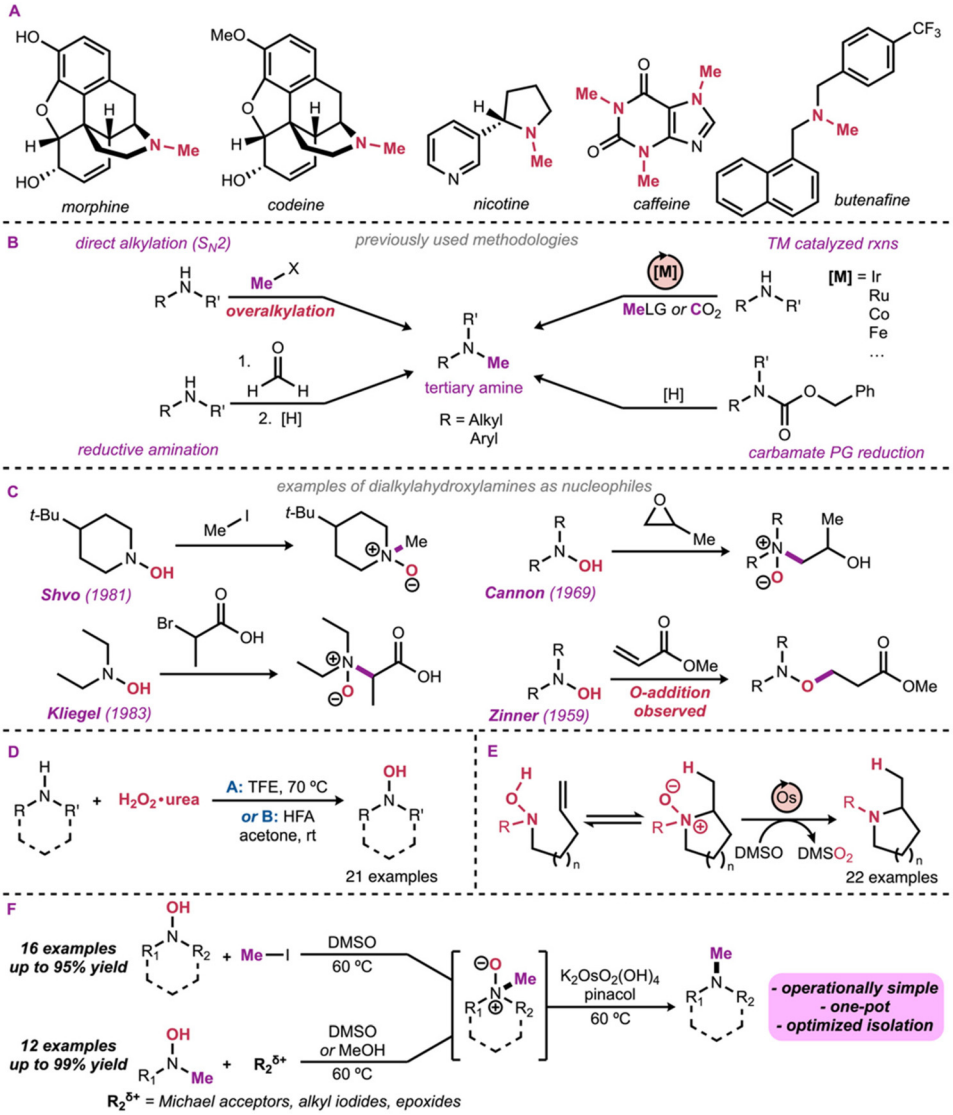
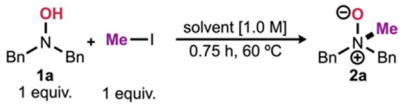


Scheme 1 (A) Bioactive molecules containing *N*-methyl motif. (B) Existing methodologies for methylation of secondary amines. (C) Selected examples of *N*,*N*-dialkylhydroxylamines as nucleophiles. (D) Recently developed methodologies for 2° hydroxylamine synthesis (HFA = hexafluoroacetone; TFE = 2,2,2-trifluoroethanol). (E) Osmium-catalyzed reduction for hydroaminations. (F) Current work featuring a hydroxylamine alkylation/catalytic reduction sequence for the synthesis of *N*-methyl tertiary amines.

lel, we discovered that *N*-oxides can be chemoselectively reduced in the presence of hydroxylamines, allowing challenging hydroamination reactions and access to cyclic tertiary amines (Scheme 1E).[16] These advances led us to explore the alkylation of hydroxylamines to give the corresponding *N*-oxides and subsequent catalytic reduction, thereby expanding the diversity of tertiary amines accessible with this strategy. Herein, we report the transformation of hydroxylamines to their corresponding tertiary amines *via* an *N*-alkylation/catalytic *N*-oxide reduction sequence, with the specific goal of synthesizing *N*-methyl tertiary amines (Scheme 1F).

Given the importance of *N*-methylamines, we sought the development of mild, but reliable conditions to alkylate various *N*,*N*-dialkylhydroxylamines to form the *N*-oxide intermediate, followed by efficient catalytic reduction conditions to form the desired products. Selected optimization data is presented in Tables 1 & 2. In early optimization toward a suitable reaction sequence, alkylation of secondary hydroxylamines proceeded rapidly to form *N*-oxide **2a** quantitatively using a 1 : 1 ratio of hydroxylamine to methyl iodide[13a,b] in DMSO (entry 1). Less polar solvents showed mixed reactivity, with acetone and tetrahydrofuran showing the best reactivity, 26 and 27% respectively (entries 2 & 3). Dichloroethane gave a 3% yield (entry 4), while acetonitrile resulted in a complex, intractable mixture (entry 5).[17] When solvent polarity was further increased, dimethylformamide showed an increase in the desired reactivity (75%; entry 6). Protic solvents were also evaluated. Methanol, ethanol and isopropanol gave similar results,

Table 1 Solvent screening for alkylation step[a]



Entry	Solvent	Yield[b] (%)
1	DMSO	>99
2	Acetone	26
3	Tetrahydrofuran	27
4	1,2-Dichloroethane	3
5	Acetonitrile	N.D.
6	*N*,*N*-Dimethylformamide	75
7	Methanol	53
8	Ethanol	49
9	Isopropanol	35
10	2,2,2-Trifluoroethanol	0
11	1,1,1,3,3,3-Hexafluoroisopropanol	0

[a] Hydroxylamine (1 equiv.) in the solvent (1.0 M), then MeI (1 equiv.) added, 60 °C, 0.75 h. [b] ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard.

Table 2 Optimization table for reduction[a]

Entry	Deviation from standard conditions	Yield[b] (%)
1	None	>99
2	1 or 2 equiv. of pinacol w/ cat.	72 or 76
3	Ethylene glycol or (*S*,*S*)-(−)-hydrobenzoin	90 or 62
4	B_2pin_2 (1 equiv.)	>99
5	Morpholin-4-ol w/ EtI or EtBr	18 or <5
6	NaBr 1 equiv. w/ reductant	59
7	Bis-2-ethylhexyl-NOH (1 g) 6 h or 18 h	14 or (97)[c]

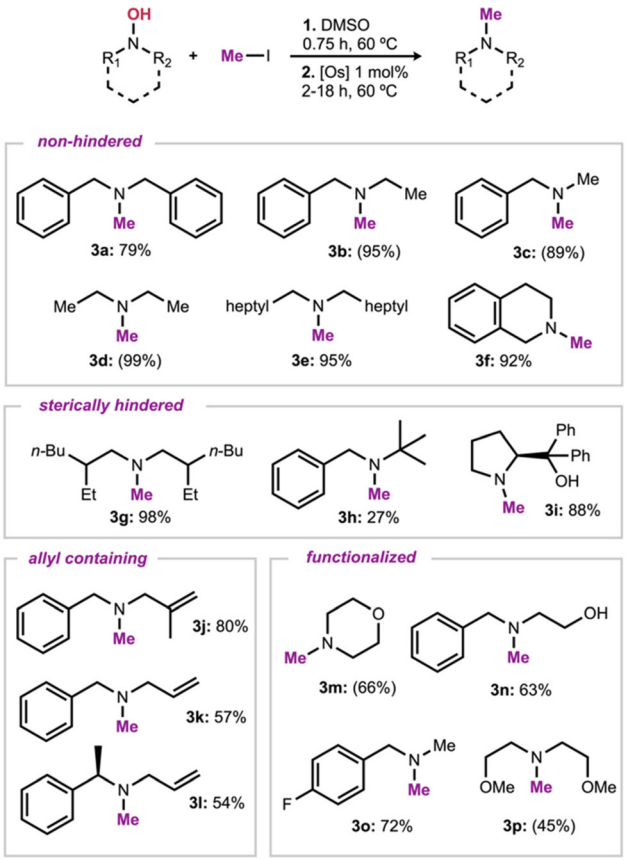
[a] Alkylation: hydroxylamine (1 equiv.) in DMSO (1.0 M), then MeI (1 equiv.) added, 60 °C, 0.75 h. Reduction: [Os] DMSO solution (1 mol%) was added, 60 °C, 2 h. [b] ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yields are shown parentheses.

with 53, 49 and 35% *N*-oxide formation being observed, respectively (entries 7–9). The use of TFE and HFIP was also evaluated, as they are shown to aid hydroamination reactions by stabilizing the formed *N*-oxides.[18] With both these solvents, no reaction was observed, likely resulting from the stabilization of the hydroxylamines (entries 10 & 11). Thus, DMSO was used for the alkylation step, which added to the simplicity of the one-pot process, as it also acts as the stoichiometric reductant in the next step.

Building on our recent work for the subsequent catalytic reduction,[16] it was found that modified conditions using 1 mol% of an osmium catalyst (prepared from $K_2OsO_2(OH)_4$ with 3 equivalents of pinacol; see SI for additional details) for 2 h at 60 °C resulted in a quantitative reduction of the *N*-oxide by NMR, and oxidation of DMSO to dimethylsulfone ($DMSO_2$). With this, the catalytic conditions previously developed for cyclic *N*-oxides[16] were optimized to allow efficient reduction of acyclic *N*-oxides (Table 2, entry 1), making the desired reaction sequence possible. Lowering the equivalents of pinacol ligand in the osmium catalyst solution had a detrimental impact on the reduction, lowering the yield to 72% and 76% for 1 and 2 equivalents, respectively (entry 2). Varying the ligand from pinacol to ethylene glycol resulted in a slight decrease in yield to 90%, whereas the change to (*S*,*S*)-(−)-hydrobenzoin showed a significant decrease to 62% yield (entry 3). The use of different reductants was also explored. B_2pin_2 is a known *N*-oxide stoichiometric reducing agent,[19] which led the desired amine in high yield (entry 4). B_2pin_2 was not used for the remainder of the development due to it not being amenable to catalytic reductions, as well as its lower chemoselectivity. Alkyl bromides were also explored as alkylating agents. Initially using morpholin-4-ol, it was found that the alkylation proceeded comparably to its iodide equivalent, however no reduction was observed (entry 5). We hypothesized that the bromide ion was poisoning the catalyst, preventing it from reducing the *N*-oxide.[20] Thus a reaction with added NaBr present during the reduction step was performed, for which a lower yield of 59% was obtained (entry 6), lending support to this hypothesis. During the evaluation of the scope of the sequence (*vide infra*), it was found that the yield decreased for more hindered substrates (such as **1g**); the alkylation was efficient, but the reduction of sterically bulky *N*-oxides was much slower. Fortunately, increasing the reaction time to 18 h allowed the reduction to go to completion (entry 7).

Although the formation of these model tertiary amines was optimized, the isolation was not trivial. The presence of iodide, DMSO, $DMSO_2$ and osmium proved to be a purification challenge. The iodine was quenched post-reaction using an aqueous sodium thiosulfate solution. Column chromatography was ineffective, and while different additives and solvent systems were attempted, little success was obtained.[21] Liquid–liquid extraction was found to be the most effective way to separate the amines from the undesired starting materials and by-products. Basification using aqueous NaOH or KOH, followed by extraction with dichloromethane and several washes with a saturated aqueous NaCl solution allowed for isolation of high purity tertiary amines. The removal of DMSO this way enabled the isolation of the more volatile amines.[22]

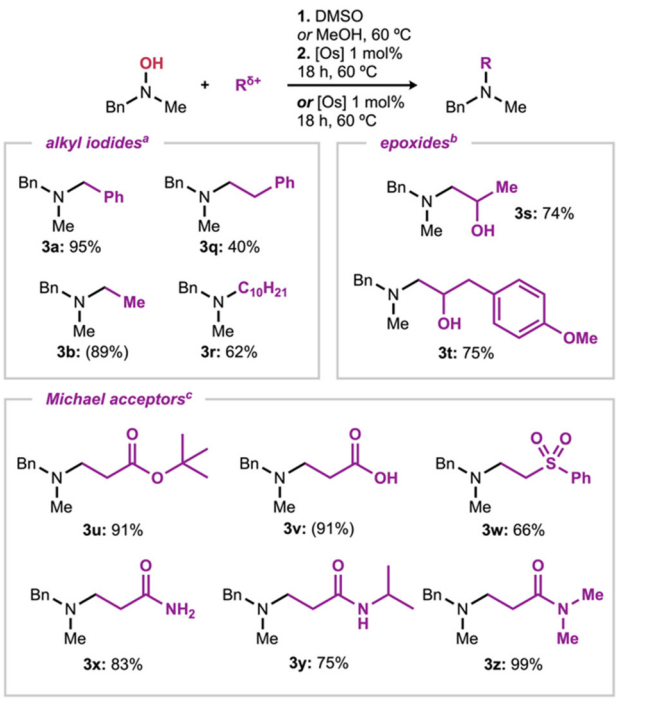
With suitable conditions and isolation procedures, evaluation of the substrate scope of the reaction sequence was conducted by reacting various hydroxylamines with iodomethane (Scheme 2). *N*,*N*-Dibenzylhydroxylamine gave a good isolated yield of **3a** (79%). Variation of one of the benzyl groups for an ethyl or methyl group resulted in a consistently higher NMR yield of 95% & 89%, respectively. Less hindered products were obtained in higher yields (entries **3d** & **3e** 99% & 95%, respectively). This method also proved efficient with cyclic amine **3f** (92%). A hydroxylamine with increased steric hinderance at the β-position reacted efficiently, allowing formation of the parent amine with a minimal decrease in yield relative to its less hindered counterparts (**3g**, 98% yield). A low isolated yield was obtained for **3h**, 27%, which is not unexpected due to the



Scheme 2 Applicability of the hydroxylamine methylation/reduction sequence for the synthesis of *N*-methyl tertiary amines. Hydroxylamine (1 equiv.) in DMSO (1.0 M); MeI (1 equiv.), 60 °C, 0.75 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 2–18 h. Isolated yields. ^{1}H NMR yields shown in brackets using 1,3,5-trimethoxybenzene as an internal standard. Trace aldehyde can be observed in the spectra of **3a**, **3h**, **3j**, **3k** and **3n**.

higher steric hindrance on the α-carbon, decreasing the efficiency of the reduction reaction. When using a cyclic hydroxylamine with reduced steric hindrance at the α-position but higher on the β-carbon, we see this trend continue as high isolated yields were observed (**3i**, 88%). Allylic hydroxylamines were also evaluated and showed good reactivity, with isolated yields for **3j** and **3k** of 80 and 57% respectively. A lower yield was obtained for amine **3l** (54%), which is, again, consistent with a more challenging reduction step. Functional group tolerance was also explored. A morpholine derivative **3m** was obtained in a 66% NMR yield. The tolerance of substrates with pendant alcohols was evaluated, and good yields were obtained with the benzylethanolamine derivative **3n**, and the diphenylprolinol derivative **3i** (63% and 88%, respectively). These results show that products that could coordinate to the osmium catalyst[23] can be tolerated under the reaction conditions. Fluorinated amine **3o** was also obtained in good yield (72%), in line with the result obtained with the non-functionalized analogue **3a**. The tolerance of ether groups was further evaluated, and acyclic amine **3p** was prepared (45% yield).

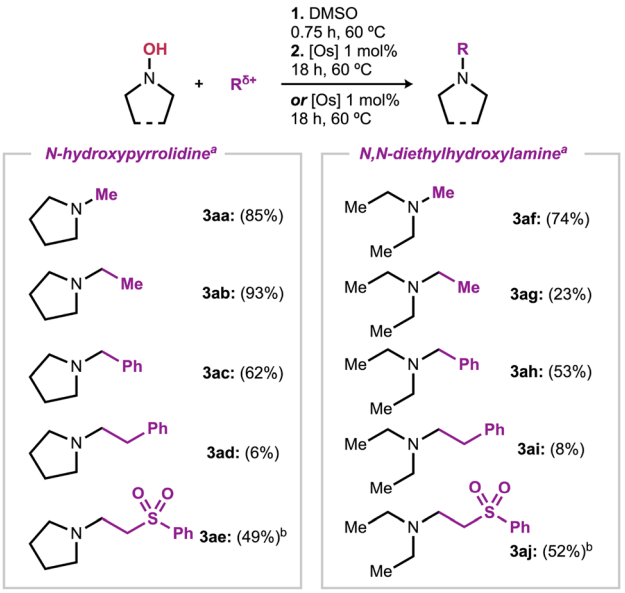
As previously mentioned, it was observed that the overall sequence suffered in yield during the reduction step when higher steric bulk was present around the *N*-oxide. In order to expand the scope of the reaction sequence forming *N*-methyl tertiary amines, the reaction of *N*-methylbenzylhydroxylamine with various alkylating agents, and subsequent reduction, was then studied (Scheme 3). This approach allowed us to expand the possible alkylating agents being used. The use of benzyl, ethyl and decyl iodide in the two-step process resulted in moderate to excellent overall yields of the corresponding amines, 95, 89 and 62%, respectively (**3a**, **3b** & **3r**). More notably, in the case of **3a** and **3b**, previous scope entries (from Scheme 2) were re-synthesized in similar or greater yields. Surprisingly, the reaction with phenethyl iodide with *N*-methylbenzylhydroxylamine to yield **3q**, gave a lower-than-expected yield of the reduced product, 40%. This trend is consistent with other alkylation/reductions performed with phenethyl iodide (see **3ad** & **3ai**).[24] Epoxides were also explored as electrophiles to form the corresponding amino alcohols. Using a modified alkylation procedure, in which methanol was used as a solvent,[13g] **3s** and **3t** were obtained in high yields, 74 and 75%, respectively. Michael acceptors were of interest due to



Scheme 3 Expansion of the hydroxylamine alkylation/reduction sequence for the synthesis of *N*-methyl tertiary amines. (a) Reaction with alkyl iodides: hydroxylamine (1 equiv.) in DMSO (1.0 M); alkyl iodide (1 equiv.), 60 °C, 0.75–2 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 18 h. (b) Reaction with epoxides: hydroxylamine (1 equiv.) in MeOH (4.5 M); epoxide (1 equiv.), 60 °C, 6 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 18 h. (c) Reaction with Michael acceptors: hydroxylamine (1 equiv.) in DMSO (1.0 M); Michael acceptor (3 equiv.); [Os] DMSO solution (1 mol%), 60 °C, 18 h. Isolated yields. ^{1}H NMR yields shown in brackets using 1,3,5-trimethoxybenzene as an internal standard.

the reports of *N*-alkylation being the faster transformation, however due to its reversibility (*via* the Cope elimination), the thermodynamically favored *O*-alkylation was observed.[13j] The reducing catalyst was added to the reaction mixture from the beginning with the Michael acceptors to permit the chemoselective reduction of the *N*-oxide as it formed. This strategy was successful in obtaining the *N*-alkylated product as the sole product. The *tert*-butyl acrylate derivative **3u** was isolated in high yield (91%). Acrylic acid also resulted in good reactivity, affording an amino acid derivative in high NMR yield of 91% (**3v**). The reaction with vinyl sulfone also resulted in good yields, 66% (**3w**). Acrylamide derivatives were also well tolerated. Acrylamide afforded the product in 83% isolated yield (**3x**). Mono- and di-substituted acrylamide derivatives were also obtained in high yields, 75 and 99% respectively (**3y** & **3z**). These results demonstrate that the reaction sequence and catalytic reduction conditions are applicable to form a diverse group of cyclic and acyclic tertiary amines. The results also show the broad applicability of reactions with alkyl iodides, epoxides, and Michael acceptors to form *N*-oxides efficiently. Remarkably, the osmium catalyzed reductions described above proceeded with high chemoselectivity during the reduction step, avoiding the formation of oxidized byproducts derived from further oxidation of the *N*-methyl tertiary amines.[25]

We elected to study the steric effects on the reduction step in a systematic fashion. To delineate the reactivity of the alkylation/reduction sequence of tertiary amines for reagents with varying steric hindrance, the structurally analogous *N*-hydroxypyrrolidine and *N*,*N*-diethylhydroxylamine were tested using various alkylating agents (Scheme 4). Unsurprisingly, the methylation of *N*-hydroxypyrrolidine and subsequent reduction of the *N*-oxide intermediate resulted in high yield, 85% (**3aa**). The reaction sequence with ethyl iodide also worked in high yield, 93% (**3ab**), which was surprising as the ethylation of morpholin-1-ol was quite inefficient (Table 2, entry 5). Reaction sequences initiated by alkylation of *N*-hydroxypyrroline with benzyl iodide (**3ac**) and vinyl sulfone (**3ae**) gave the corresponding amines in decreased yields, 62 and 49%, respectively. The reaction sequence with phenethyl iodide (**3ad**) only gave a 6% yield, with the presence of 14% styrene from the competing Cope-elimination reaction, suggesting this is due to an unstable *N*-oxide intermediate.[24] When methylating the acyclic variant *N*,*N*-diethylhydroxylamine, the reduction of the *N*-oxide worked comparably to that of the *N*-hydroxypyrrolidine analog (74%, **3af**). However, a significantly lower yield was observed when ethyl iodide was used, giving only 23% of reduced acyclic amine **3ag**, in contrast to the 93% observed with the *N*-hydroxypyrrolidine derivative (**3ab**). Benzylation of the *N*,*N*-diethylhydroxylamine resulted in a modest yield of 53% for the overall sequence (**3ah**), and the reduction of the phenethyl reaction sequence was equally as inefficient as for *N*-hydroxypyrrolidine, 8% (**3ai**). The reduction of the conjugate addition product of the *N*,*N*-diethylhydroxylamine onto the vinyl sulfone was observed in a moderate yield, 52% (**3aj**). This set of experiments provided additional insight into the steric

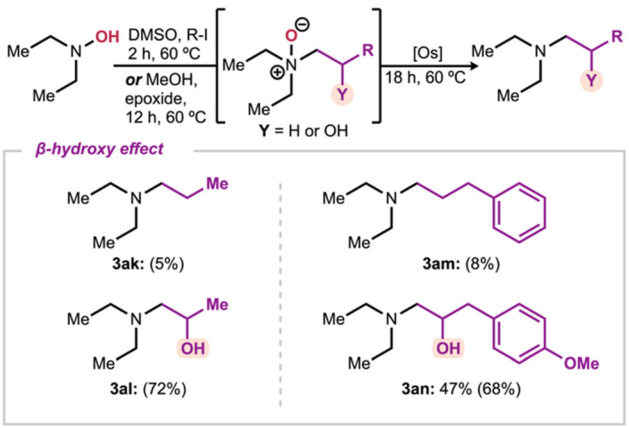


Scheme 4 Delineating the reactivity of the alkylation/reduction sequence for the synthesis of tertiary amines for reagents with varying steric hindrance. (a) Reactions with alkyl iodides: hydroxylamine (1 equiv.) in DMSO (1.0 M); alkyl iodide (1 equiv.), 60 °C, 0.75–2 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 18 h. (b) Reaction with phenyl vinyl sulfone: hydroxylamine (1 equiv.) in DMSO (1.0 M); phenyl vinyl sulfone (3 equiv.); [Os] DMSO solution (1 mol%), 60 °C, 18 h. ^{1}H NMR yields shown in brackets using TMB as an internal standard.

limitations of the reduction of the *N*-oxide with the osmium catalyst, showing the impact of steric hindrance and proximal electron-withdrawing groups on the reduction step. These findings are aligned with previous observations,[16] as well as what is reported in the literature.[26]

Interestingly, the systematic variation above also allowed comparison of the reactivity of relatively similar substrates (Scheme 5). For example, while products **3ak** and **3al** have similar substituents, it is the most hindered product containing an additional hydroxyl group that is formed more efficiently (5 & 72%). We see the same trend when comparing **3am** to **3an**, showing an improvement in yields from negligible to moderate (8 & 68%). These results suggest that the presence of an alcohol functionality in the β-position is beneficial for the reduction reactivity, possibly due to a directed reduction. While this warrants additional investigation, the ability of osmium to participate in directed catalytic oxidation reactions has been reported.[27]

In summary, a new approach for the *N*-methylation of dialkylhydroxylamines using iodomethane and the subsequent reduction of the corresponding *N*-oxides using an osmium catalyst and DMSO has been developed. A complementary alkylation approach of *N*-methyl-*N*-benzylhydroxylamine using alkyl iodides, epoxides and Michael acceptors was also developed to form *N*-methyl tertiary amines. Insight into the steric limitations for the reduction of the *N*-oxide intermediates has also been reported. The reported methods demonstrated compatibility with alkenes, alcohols, ethers, esters, amides and



Scheme 5 Comparison of reactivity highlighting the beneficial effect of a β-hydroxyl group. Reaction with alkyl iodide: hydroxylamine (1 equiv.) in DMSO (1.0 M); alkyl iodide (1 equiv.), 60 °C, 0.75–2 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 18 h. Reaction with epoxides: hydroxylamine (1 equiv.) in MeOH (4.5 M); epoxide (1 equiv.), 60 °C, 6 h. [Os] DMSO solution (1 mol%) was added, 60 °C, 18 h. Isolated yields. ^{1}H NMR yields shown in brackets using TMB as an internal standard.

fluorinated functional groups. Limitations include the difficult isolation of very volatile amines as well as decreased yields in the reduction of highly sterically encumbered *N*-oxides. Overall, this methodology demonstrates the utility of various secondary hydroxylamines for the selective formation of tertiary amines in a one-pot reaction. It further shows that the recently developed conditions for osmium catalyzed *N*-oxide reduction are chemoselective, as seen with the tolerance of reactive functional groups (*i.e.* alkenes, secondary hydroxylamines, Michael acceptors). This method can facilitate the formation of complex nitrogen-containing molecules, amine *N*-oxides, and *N*-methyl tertiary amines, which have high relevance for the pharmaceutical industry.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article has been included as part of the supplementary information (SI). Supplementary information: Table S1, general procedures, full characterization data for all new compounds, ^{1}H and ^{13}C NMR spectra, and further experimental details. See DOI: https://doi.org/10.1039/d5ob01902h.

Acknowledgements

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