

Cite this: *Chem. Sci.*, 2022, 13, 7264

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 24th January 2022

Accepted 27th May 2022

DOI: 10.1039/d2sc00481j

rsc.li/chemical-science

# A redox-enabled strategy for intramolecular hydroamination†

Meredith A. Allen, Huy M. Ly, Geneviève F. O'Keefe and André M. Beauchemin \*

Metal- or acid-catalyzed intramolecular hydroamination and Cope-type intramolecular hydroamination, a distinct concerted approach using hydroxylamines, typically suffer from significant synthetic limitations. Herein we report a process for intramolecular hydroamination that uses a redox-enabled strategy relying on efficient *in situ* generation of hydroxylamines by oxidation, followed by Cope-type hydroamination, then reduction of the resulting pyrrolidine *N*-oxide. The steps are performed sequentially in a single pot, no catalyst is required, the conditions are mild, the process is highly functional group tolerant, and no chromatography is generally required for isolation. A robustness screen and a gram-scale example further support the practicality of this approach.

## Introduction

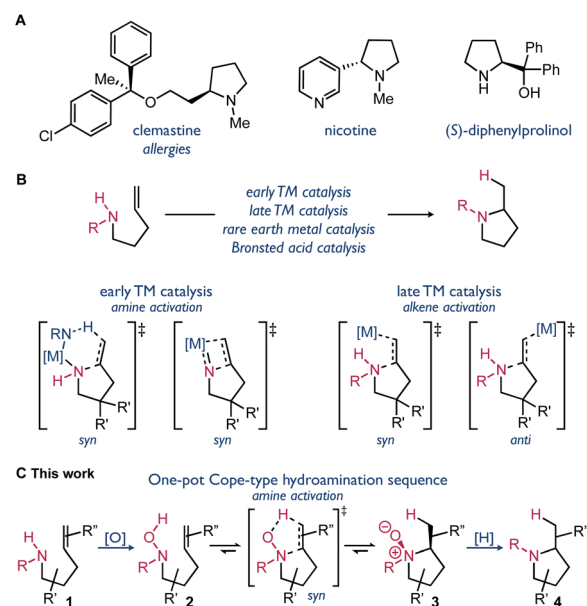
Amines are ubiquitous substructures within bioactive compounds. Cyclic amines, such as pyrrolidines and piperidines, are common motifs in pharmaceuticals and other fine chemicals (Scheme 1A).<sup>1</sup> The syntheses of saturated cyclic amines can be accomplished using a variety of C–C or C–N bond forming reactions. Examples of efficient methods include nitrene C–H insertion, N-centered radical addition, and hydroamination reactions.<sup>2</sup> Alkene hydroamination typically uses readily available reagents, amines and alkenes, and has high atom economy. Catalysis has often been required to overcome the high kinetic barrier of hydroamination reactions (Scheme 1B).<sup>2b,3</sup> The use of metal-catalyzed processes is still often impeded by harsh reaction conditions, poor functional group tolerance, complex ligand synthesis, and the requirement for specific substitution.<sup>4</sup>

Cope-type hydroamination is a distinct strategy using oxidized amines, hydroxylamines, to form pyrrolidine *N*-oxides upon concerted cyclization.<sup>5</sup> This reaction proceeds *via* a 5-membered transition state, resulting in a lower kinetic barrier for hydroamination. Cope-type hydroamination is a viable alternative to metal-catalyzed processes, however, it suffers from difficulties associated with the stability of the hydroxylamine reagent **2** and the isolation or reduction of the *N*-oxide product **3**.<sup>6</sup> This strategy for hydroamination has consequently been underappreciated.<sup>7</sup> Herein we report the first redox-transfer enabled approach to hydroamination, applied to the

synthesis of pyrrolidines. By using a synthetic sequence that avoids the isolation of the hydroxylamine and *N*-oxide intermediates (Scheme 1C), this methodology is designed to improve functional group tolerance and practicality relative to other intramolecular hydroamination methods.

## Results and discussion

After surveying the literature relating to oxidative hydroxylamine synthesis, it was clear that overoxidation would likely be



**Scheme 1** (A) Pyrrolidines in bioactive compounds and organo-catalysts; (B) general activation modes for catalyzed intramolecular hydroamination; (C) this work – one-pot synthesis of pyrrolidines *via* redox-enabled hydroamination.

Centre for Catalysis Research and Innovation, Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie-Curie, Ottawa, ON, K1N 6N5, Canada. E-mail: andre.beauchemin@uottawa.ca

† Electronic supplementary information (ESI) available: Complete experimental procedures, characterization data, and NMR spectra. See <https://doi.org/10.1039/d2sc00481j>

a problem to address in the reaction optimization.<sup>8</sup> We therefore focused on developing mild oxidation conditions that could also facilitate hydroamination. Inherently, rapid cyclization would prevent overoxidation of the hydroxylamine. Mild reduction conditions were also required to ensure functional group tolerance. Fortunately, several recent reports use boron-containing reagents for mild and selective reduction of *N*-oxides.<sup>9</sup> With a longstanding interest in the Cope-type hydroamination field, we were also aware of the strong solvent effects for the equilibrium between hydroxylamine and *N*-oxide, with alcohol solvents often significantly benefitting reactivity.<sup>10</sup> Using a urea hydrogen peroxide adduct (UHP) in 2,2,2-trifluoroethanol (TFE), we expected that efficient amine oxidation to the corresponding hydroxylamine could be achieved as inspired by analogous reactivity oxidizing sulfides and alkenes.<sup>11</sup> Thus optimization began with the objective of achieving a one-pot reaction sequence that would avoid isolation of the intermediates (Table 1). Gratifyingly, efficient and selective oxidation was observed, hydroamination proceeded smoothly, and the following reduction occurred quantitatively using B<sub>2</sub>pin<sub>2</sub> (Table 1, entry 1).

Using 1.2 equivalents of the oxidant and reductant proved optimal (Table 1, entries 1–3). Including the reductant along with the oxidant and amine in a single step procedure led to no desired product (entry 4). The boron reductant was instead selectively oxidized under the reaction conditions. These results therefore supported continuing optimization efforts using a one-pot, two-step procedure where amine oxidation and hydroamination occur separately from *N*-oxide reduction (see ESI, Tables S1–S4 for more details<sup>†</sup>). Modifying the oxidant to aqueous hydrogen peroxide had minimal effect on the overall yield (entry 5). The benefits of a good safety profile and minimal by-products of UHP (water) led us to continue using UHP for

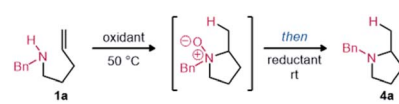
reaction optimization. Changing the solvent from TFE to other fluorinated or non-fluorinated alcohols led to reduced yields (entries 6 and 7). Lowering the reaction temperature led to an incomplete oxidation within the same reaction time (entry 8). Modifying the reductant to a less reactive, though widely available, *o*-tolylboronic acid led to no reduction (entry 9). Using hypodiboric acid as a reductant also led to a high yield (entry 10) and facilitated isolation. Indeed, the product **4a** could be isolated in high purity after aqueous workup. Due to the simple isolation and better atom economy, hypodiboric acid was selected as the reductant.

With an optimal one-pot procedure in hand (Table 1, entry 10), the scope of this hydroamination sequence was then explored. Given that carbon substitution has been thoroughly evaluated in prior Cope and metal-catalyzed intramolecular hydroamination reports, our efforts focused on varying nitrogen substitution. Substitution with various *N*-alkyl substitution (Scheme 2, **4a–4g**).<sup>12</sup> Modest diastereoselectivity can be obtained when using chiral amines (**4f–4g**).<sup>13</sup> This selectivity could possibly be elaborated into a chiral auxiliary-based route towards enantiopure  $\alpha$ -substituted pyrrolidines. 2,5-Disubstituted pyrrolidine also formed in high yield under the reaction conditions with good *cis* diastereoselectivity (**4h**). Proximal alkene substitution, known to increase the rate of Cope-type hydroamination, had minimal effect on the product formation (**4i**). Conversely, terminal methyl substitution, known to decrease the rate of hydroamination, led to lower yields of the corresponding pyrrolidine under the optimized reaction conditions (**4j**).<sup>5,14</sup> Notably, *trans*-substitution (**1j'**) led to only trace product formation, with mostly degradation occurring, while *cis*-substituted amine **1j'** formed a modest yield of pyrrolidine **4j** via the two-step reaction sequence at 60 °C. Gratifyingly, aryl-substituted amines also underwent hydroamination (**4k–4m**). Aromatic substitution is largely missing from the Cope-type hydroamination literature, potentially due to the reduced nucleophilicity of aniline nitrogen atoms and the propensity of arylhydroxylamines to dimerize.<sup>15</sup>

Substrates including Lewis basic functional groups were well tolerated in contrast to related examples from metal-catalyzed processes (**4n–4u**).<sup>16</sup> Products with heterocyclic substituents (**4n–4o**), alcohols and ethers (**4p–4t**) were isolated in good yields under modified reaction conditions. When an alkylamine substituent was included (**1u**), excess oxidant could be used to oxidize both nitrogen atoms, then complete reduction could occur using excess reductant, forming the corresponding pyrrolidine in an adequate yield (**4u**).

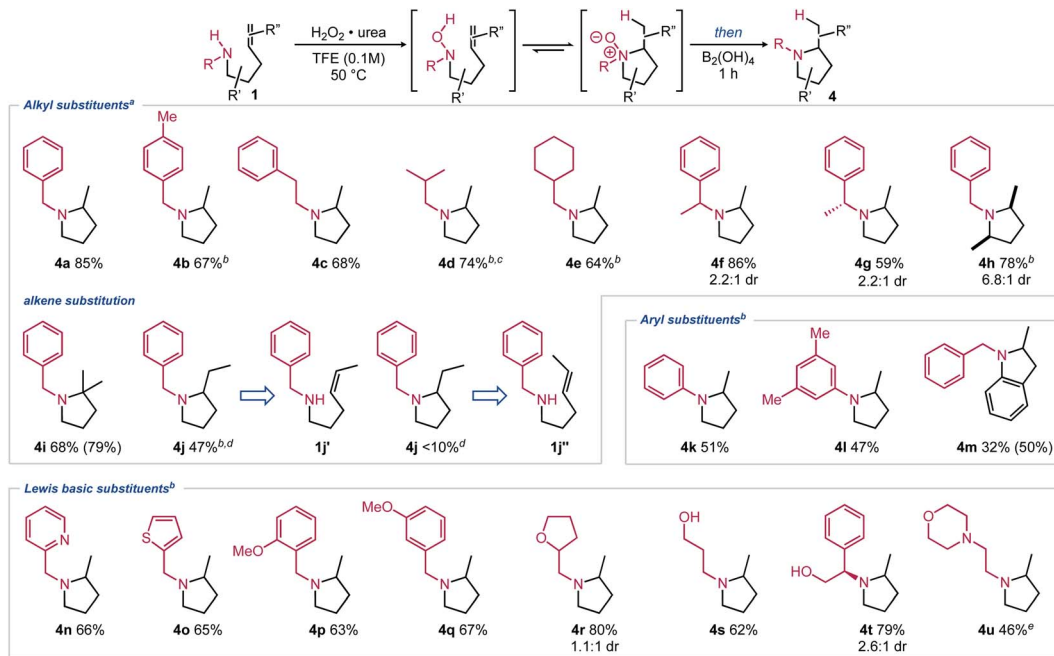
When 2-allylanilines (**1m**, **1v**) were used as reagents for this reaction sequence, significant conformational effects were observed (Scheme 3). While mono-substituted aniline **1v** formed no indoline upon oxidation to the corresponding hydroxylamine, the *N*-benzyl variant **1m** formed a modest yield of pyrrolidine (**4m**). These results can be rationalized by considering the equilibrium of sp<sup>2</sup>-N hindered rotation of the R vs. OH substituents of the hydroxylamine intermediate. While the *N*-benzylhydroxylamine (**2m**) favours the reactive conformer **2'**, the mono-substituted hydroxylamine variant (**2v**) should

Table 1 Pyrrolidine synthesis optimization<sup>a</sup>

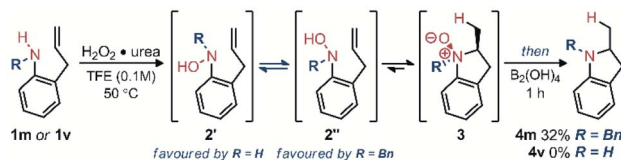


Entry	Oxidant (equiv.)	Reductant	Solvent	Yield <sup>b</sup> (%)
1	UHP (1.0)	B <sub>2</sub> pin <sub>2</sub>	TFE	71
2	UHP (1.2)	B <sub>2</sub> pin <sub>2</sub>	TFE	91
3	UHP (1.5)	B <sub>2</sub> pin <sub>2</sub>	TFE	70
4 <sup>c</sup>	UHP (1.2)	B <sub>2</sub> pin <sub>2</sub>	TFE	0
5	30% aq. H <sub>2</sub> O <sub>2</sub> (1.2)	B <sub>2</sub> pin <sub>2</sub>	TFE	84
6	UHP (1.2)	B <sub>2</sub> pin <sub>2</sub>	HFIP	70
7	UHP (1.2)	B <sub>2</sub> pin <sub>2</sub>	MeOH	30
8 <sup>d</sup>	UHP (1.2)	B <sub>2</sub> pin <sub>2</sub>	TFE	33
9	UHP (1.2)	<i>o</i> -tolylB(OH) <sub>2</sub>	TFE	0
10 <sup>e</sup>	UHP (1.2)	B <sub>2</sub> (OH) <sub>4</sub>	TFE	85 <sup>f</sup>

<sup>a</sup> Conditions: amine **1a** in solvent (0.1 M), then oxidant added, 50 °C, 16 h. Reductant then added (1.2 equiv.), rt, 30 min. <sup>b</sup> <sup>1</sup>H NMR yield of **4a** using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> B<sub>2</sub>pin<sub>2</sub> and UHP added together. <sup>d</sup> Reaction stirred at rt instead of 50 °C. <sup>e</sup> Reduction step stirred at 50 °C, 1 h. <sup>f</sup> Isolated yield. B<sub>2</sub>pin<sub>2</sub>: bis(pinacolato)diboron. HFIP: 1,1,1,3,3,3-hexafluoroisopropanol.



**Scheme 2** Scope of pyrrolidines **4** synthesized via redox-enabled hydroamination reaction sequence. Isolated yields shown with <sup>1</sup>H NMR yields using 1,3,5-trimethoxybenzene as an internal standard shown in parentheses. (a) Conditions from Table 1, entry 10; (b) 2.2 equiv. of B<sub>2</sub>(OH)<sub>4</sub> was added; (c) isolated as the HCl salt; (d) at 60 °C; (e) 2.2 equiv. of UHP and 3.2 equiv. of B<sub>2</sub>(OH)<sub>4</sub> were added.



**Scheme 3** Conformational effects for aniline reagents towards the synthesis of indolines.

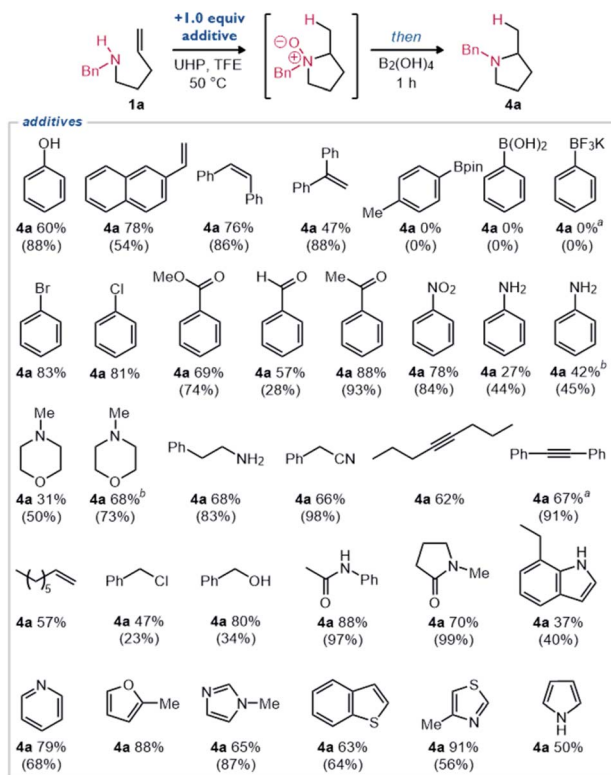
favour the unreactive conformer **2'**, leading to no observed hydroamination reaction products.

Overall, this substrate scope is largely composed of products with nitrogen substitution not present in the Cope-type or transition metal-catalyzed intramolecular hydroamination literature. Intramolecular Cope-type hydroamination has historically been limited by difficult hydroxylamine reagent synthesis, leading to examples largely limited to methyl and benzyl nitrogen substitution.<sup>5,6</sup> Transition metal catalysis does not suffer from this issue, however, few reported examples use Lewis basic alkylamines or other Lewis basic atoms.<sup>16</sup> Additionally, geminal dialkyl substituents are common to affect a Thorpe–Ingold bias to promote cyclization. The reported redox-enabled Cope-type intramolecular hydroamination methodology is significantly less limited by substitution requirements. Additionally, most pyrrolidines could be isolated in high purity using this methodology without using chromatography (see ESI for more details†).

To further evaluate the functional group tolerance of this hydroamination methodology, a robustness screen was performed (Scheme 4).<sup>17</sup> Using the optimized reaction conditions

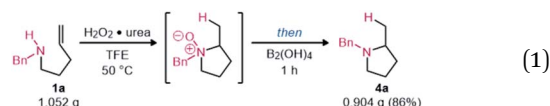
with amine **1a** (Table 1, entry 10), we measured the yield of pyrrolidine **4a** when including 1.0 equivalents of various additives. Minimal changes were observed when phenol or aryl alkenes were added. Aryl boronic acid, ester, and trifluoroborate salt were not tolerated, as boron was completely oxidized under the reaction conditions. The inclusion of aryl halides, carbonyl-containing functional groups, and nitro groups generally led to no change in the yield of observed product. The inclusion of aniline or a secondary amine led to minimal observed product. Although, when the equivalents of oxidant and reductant were increased to 2.2, the product was again observed in higher yields. As similarly observed for the morpholine-substituted amine substrate (Scheme 2, **1u**), we found that when both nitrogen atoms could be oxidized, the reaction proceeded smoothly, then global reduction afforded pyrrolidine **4a** efficiently. This entry served to help validate the procedure for this robustness screen to accurately predict functional group tolerance. Primary amines, nitriles, alkynes, alkenes, alkyl chlorides, alcohols, and amides were generally well-tolerated functional groups. Various nitrogen, oxygen and sulfur-containing heterocycles were also well-tolerated. Reduced yields were observed when *N*-oxidation (e.g., aniline and *N*-methylmorpholine), *N*-alkylation (e.g., benzyl chloride), or other oxidation (e.g., pyrrole, indole) could occur readily. Overall, these reaction conditions were observed to be highly robust as demonstrated by generally high product yields even in the presence of many common functional groups. These results demonstrate that this redox-enabled strategy for hydroamination is quite general, practical, and highly functional group tolerant.





**Scheme 4** Robustness screen examining functional group compatibility. The standard reaction is undertaken in the presence of one molar equivalent of the given additive. The yield of **4a** is given as a <sup>1</sup>H NMR yield using 1,3,5-trimethoxybenzene as an internal standard (additive remaining in parentheses – value not included for volatile additives). (a) Partial solubility of additive; (b) 2.2 equiv. of UHP and Bz(OH)<sub>4</sub> were added.

Finally, this hydroamination methodology was evaluated on a gram scale using amine **1a**. The resulting pyrrolidine **4a** was still isolated in good yield after an aqueous workup (eqn (1)). The HCl salt could also easily be formed to produce a solid product.



## Conclusions

In summary, secondary amines can undergo an efficient metal-free hydroamination to form pyrrolidines *via* a redox-enabled approach, featuring a concerted hydroamination reaction. Importantly, the undesirable issues associated with the synthesis and isolation of hydroxylamines and *N*-oxides are avoided using a one-pot sequence relying on new conditions to selectively oxidize secondary amines. The reaction conditions are highly functional group tolerant, as additionally demonstrated by a robustness screen, in contrast to many related transition metal-catalyzed hydroamination variants.

Diastereoselective examples and gram scale reactivity are also reported. Overall, this work provides an improved method to form pyrrolidines and illustrates a practical redox-enabled process applied to hydroamination. While this stoichiometric process follows many of the principles of green chemistry due to the high atom economy, low reagent toxicity, and chromatography-free isolation, a catalytic oxygen transfer process is currently under investigation and will be reported in due course.

## Data availability

All experimental data, including additional reaction optimization data and detailed experimental procedures, is available in the ESI.†

## Author contributions

M. A. Allen and A. M. Beauchemin conceived the project. The reaction conditions were optimized by M. A. Allen and G. F. O'Keefe, and the purification procedure was determined by M. A. Allen and H. M. Ly. Substrates were synthesized by M. A. Allen, H. M. Ly and G. F. O'Keefe. The scope reported and robustness screen data were obtained by M. A. Allen and H. M. Ly. M. A. Allen wrote the manuscript with input from all authors and edited it with A. M. Beauchemin.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We would like to gratefully acknowledge the support of the University of Ottawa and NSERC (Discovery grant to A. M. B., PGS-D scholarship to M. A. A., and USRA to G. F. O.).

## Notes and references

- (a) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
- (a) J. Bariwalab and E. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 9283; (b) A. Trowbridge, S. M. Walton and M. J. Gaunt, *Chem. Rev.*, 2020, **120**, 2613.
- (a) T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (b) E. Bernoud, C. Lepori, M. Mellah, E. Shulz and J. Hannedouche, *Catal. Sci. Technol.*, 2015, **5**, 2017; (c) L. Rocard, D. Chen, A. Stadler, H. Zhang, R. Gil, S. Bezzenine and J. Hannedouche, *Catalysts*, 2021, **11**, 674.
- Specific substitution requirements often include a dialkyl substituent for a Thorpe–Ingold bias or an aryl or amide substituent on nitrogen to reduce its Lewis basicity.
- (a) N. J. Cooper and D. W. Knight, *Tetrahedron*, 2004, **60**, 243; (b) A. M. Beauchemin, *Org. Biomol. Chem.*, 2013, **11**, 7039.



- 6 (a) A. R. Brown, C. Uyeda, C. A. Brotherton and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 6747; (b) W. Oppolzer, A. C. Spivey and C. G. Bochet, *J. Am. Chem. Soc.*, 1994, **116**, 3139; (c) H. O. House and L. F. Lee, *J. Org. Chem.*, 1976, **41**, 863; (d) E. Ciganek, J. M. Read Jr and J. C. Calabrese, *J. Org. Chem.*, 1995, **60**, 5795; (e) I. Dion, J.-F. Vincent-Rocan, L. Zhang, P. H. Cebrowski, M.-E. Lebrun, J. Y. Pfeiffer, A.-C. Bédard and A. M. Beauchemin, *J. Org. Chem.*, 2013, **78**, 12735; (f) N. P. Bainbridge, A. C. Currie, N. J. Cooper, J. C. Muir, D. W. Knight and J. M. Walton, *Tetrahedron Lett.*, 2007, **48**, 7782; (g) G. L. Ellis, I. A. O'Neil, V. E. Ramos, E. Cleator, S. B. Kalindjian, A. P. Chorlton and D. J. Tapolczay, *Tetrahedron Lett.*, 2007, **48**, 1683; (h) N. Henry and I. A. O'Neil, *Tetrahedron Lett.*, 2007, **48**, 1691; (i) I. A. O'Neil, E. Cleator, V. E. Ramos, A. P. Chorlton and D. J. Tapolczay, *Tetrahedron Lett.*, 2004, **45**, 3655.
- 7 Analogous oxygen state modification-based methodology for the functionalization of alcohols (borrowing hydrogen) has been extensively studied. For a recent review, see: B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta and L. C. Morrill, *ACS Cent. Sci.*, 2021, **7**, 570.
- 8 (a) Z. Rappoport and J. Liebman, *The chemistry of hydroxylamines, oximes, and hydroxamic acids*, Wiley, Chichester, England, 2009. For selected examples of oxidative hydroxylamine synthesis, see: ; (b) A. Banerjee and H. Yamamoto, *Chem. Sci.*, 2019, **10**, 2124; (c) A. M. Berman and J. S. Johnson, *J. Org. Chem.*, 2006, **71**, 219; (d) A. L. Biloski and B. Ganem, *Synthesis*, 1983, 537–538; (e) M. D. Wittman, R. L. Halcomb and S. J. Danishefsky, *J. Org. Chem.*, 1990, **55**, 1981; (f) J. Hill, A. A. Hettikankanamalage and D. Crich, *J. Am. Chem. Soc.*, 2020, **142**, 14820; (g) J. Hill and D. Crich, *Org. Lett.*, 2021, **23**, 6396; (h) R. W. Murray and M. Singh, *Synth. Commun.*, 1989, **19**, 3509; (i) I. A. O'Neil, E. Cleator and D. J. Tapolczay, *Tetrahedron Lett.*, 2001, **42**, 8247.
- 9 (a) R. Köster and Y. Morita, *Justus Liebigs Ann. Chem.*, 1967, **704**, 70; (b) G. W. Kabalka and H. C. Hedgecock, *J. Org. Chem.*, 1975, **40**, 1776; (c) S. Bae and M. K. Lakshman, *J. Org. Chem.*, 2008, **73**, 1311; (d) H. P. Kokatla, P. F. Thomson, V. R. Doddi and M. K. Lakshman, *J. Org. Chem.*, 2011, **76**, 7842; (e) C. Zhu, R. Wang and J. R. Falck, *Org. Lett.*, 2012, **14**, 3494; (f) A. L. Londregan, D. W. Piotrowski and J. Xiao, *Synlett*, 2013, **24**, 2695; (g) J. Kim and C. R. Bertozzi, *Angew. Chem., Int. Ed.*, 2015, **54**, 15777; (h) V. Gurram, H. K. Akula, R. Garlapati, N. Pottabathini and M. K. Lakshman, *Adv. Synth. Catal.*, 2015, **357**, 451; (i) S. Gupta, P. Sureshbabu, A. K. Singh, S. Sabiah and J. Kandasamy, *Tetrahedron Lett.*, 2017, **59**, 909.
- 10 (a) J. Moran, S. I. Gorelsky, E. Dimitrijevic, M.-E. Lebrun, A.-C. Bédard, C. Séguin and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2008, **130**, 17893; (b) A. M. Beauchemin, J. Moran, M.-E. Lebrun, C. Séguin, E. Dimitrijevic, L. Zhang and S. I. Gorelsky, *Angew. Chem., Int. Ed.*, 2008, **47**, 1410.
- 11 (a) N. Llopis, P. Gisbert and A. Baeza, *J. Org. Chem.*, 2020, **85**, 11072; (b) J. Legros, B. Crousse, D. Bonnet-Delphon and J.-P. Bégué, *Eur. J. Org. Chem.*, 2002, 3290; (c) K. Neimann and R. Neumann, *Org. Lett.*, 2000, **2**, 2861; (d) M. C. A. Van Vliet, I. W. C. E. Arends and R. A. Sheldon, *Synlett*, 2001, 248.
- 12 TFE solvation significantly contributes to the increased stability of several *N*-oxides (**3c–3g**, **3m–3p**) that could plausibly undergo Cope elimination to the corresponding secondary hydroxylamines. For examples of the increased stability of enamine or amine *N*-oxides in TFE, see: (a) D. Kang, S. T. Cheung, A. Wong-Rolle and J. Kim, *ACS Cent. Sci.*, 2021, **7**, 631; (b) Z. Mucsi, A. Szabó, I. Hermecz, A. Kucsman and I. G. Csizmadia, *J. Am. Chem. Soc.*, 2005, **127**, 7615.
- 13 For an example of low diastereoselectivity for an intramolecular Cope-type hydroamination, see ref. 6e. Diastereoselective 5-membered cyclizations with analogous exocyclic chiral centres have not yet been reported. See also ref. 5a.
- 14 D. St. C. Black and J. E. Doyle, *Aust. J. Chem.*, 1978, **31**, 2317–2322.
- 15 M. C. Bagley and J. Tovey, *Tetrahedron Lett.*, 2001, **42**, 351.
- 16 For an overview of recent intramolecular hydroamination examples within an enantioselective context, see: (a) A. M. M. M. Faisca Phillips, L. M. D. R. S. Martins and A. J. L. Pomberio, in *Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, ed. A. M. M. M. Faisca Phillips, Wiley, Hoboken, 1st edn, 2021, vol. 1, ch. 6, pp. 119–160. See also selected metal-catalyzed examples including ester, ether, alcohol, nitrile, thiophene, and furan functional groups: ; (b) A. Mukherjee, T. K. Sen, P. K. Ghorai and S. K. Mandal, *Organometallics*, 2013, **32**, 7213; (c) X. Shen and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2010, **49**, 564.
- 17 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597. To our knowledge, there are no reported examples of the evaluation of hydroamination reactions using a robustness screen.

