Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions

Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic HAT Reactions

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Abstract

Spiro- and bridged bicyclic structures are in demand for their sp^3-rich frameworks that offer unique physiochemical properties and precisely positioned substituent groups. In order to rapidly access such molecules in a cross-coupling fashion we describe olefin-amine (OLA) reagents for the transformation of aldehydes and ketones into all three topological types of bicyclic N-heterocycles: bridged, spiro-, and fused rings. The OLA reagents are easily prepared and allow the synthesis of complex molecular frameworks under operationally simple conditions that tolerate a wide array of functional groups. Investigations into the Mn or Fe promoted reaction pathway support a metal hydride hydrogen atom transfer (MH-HAT) to generate a C-centered radical that undergoes addition to an unactivated imine, leading to an N-centered radical. A catalytic cycle featuring regeneration of the metal catalyst by O_2 and a second HAT to form the unprotected saturated N-heterocycle appears to be operative.

Introduction

Saturated N-heterocycles have emerged as one of the most popular and successful scaffolds for drug design and development.[1] In the past 3 years, more than 50% newly approved small molecule drugs (FDA) feature a saturated N-heterocycle.[2] While access to substituted, saturated N-heterocycles is often challenging, a number of new synthetic methods including intramolecular hydroamination,[3] decarboxylative cross-coupling,[4] and C–H functionalization[5] offer streamlined routes. In our own work, we have introduced SnAP[6] and SLAP[7] reagents that provide convenient access to saturated N-heterocycles from aldehydes and ketones; these reagents are already widely used in the pharmaceutical industry.

A remaining challenge is the direct synthesis of bicyclic saturated structures. As noted by pharmaceutical experts in recent review, "Key unsolved problems in synthetic chemistry include … concise synthesis of highly functionalized, constrained bicyclic amines".[8] Such scaffolds are prized for their ability to position binding groups in precise, three-dimensional orientations, which are topologically divided to three classes: spirocycles, bridged bicycles, and fused rings. Spirocycles have become a popular scaffold for pharmaceutical development[9] and the synthesis of bridged bicyclic compounds are in high demand[10] due to their unique physiochemical properties.[11] We have therefore targeted rapid, modular approaches to C-substituted variants of these bicyclic structures from widely available starting materials.

In this report we document the development, synthesis, and application of olefin amine (OLA) reagents for the synthesis of all three topological classes of bicyclic structures – bridged bicyclic, spirocyclic and fused bicyclic saturated N-heterocycles from aldehydes and ketones (Figure 1C).[12] The reactions are initiated by a Mn or Fe catalyzed H-atom transfer (HAT) reaction of olefins to give C-centered radicals that participate in cyclization, often via challenging reaction trajectories. The key C–C bond forming step – HAT promoted addition of olefins to unactivated imines – has not previously been reported. The resulting constrained saturated N-heterocycles – particularly the bridged bicyclic N-heterocycles – would be difficult to access by any established synthetic route.

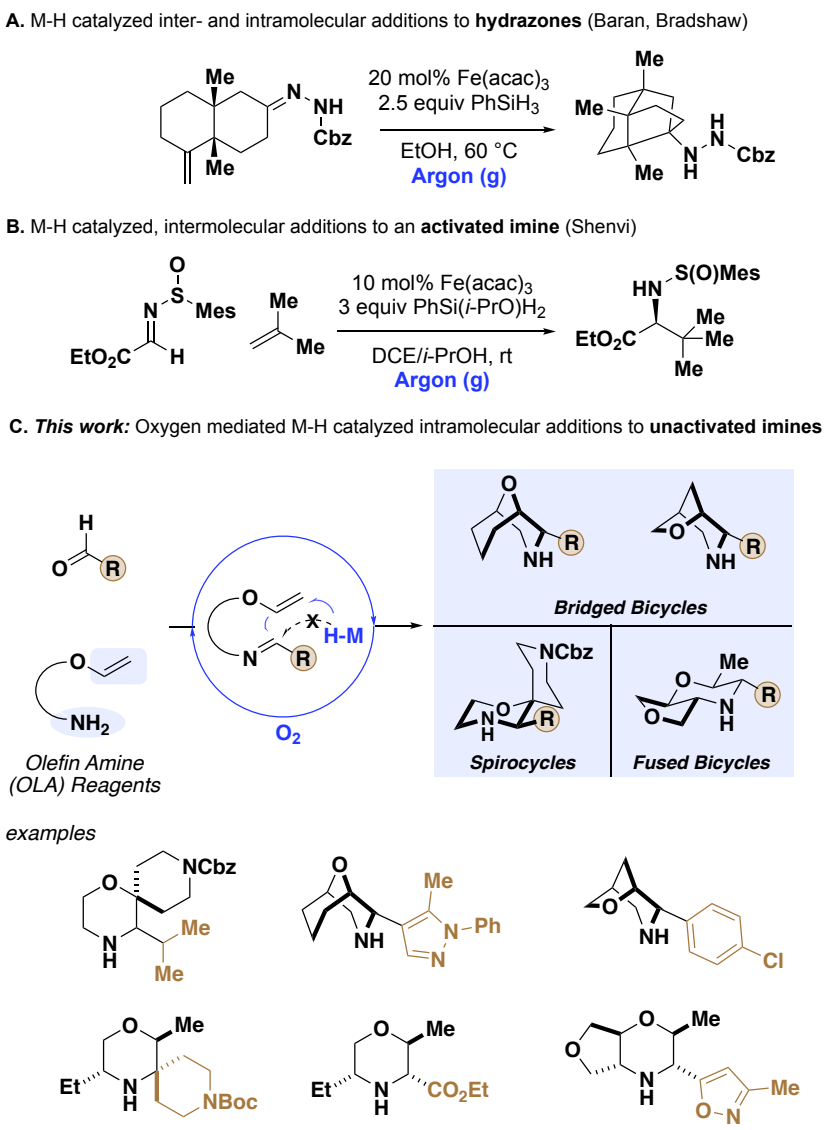


Figure 1. OLA reagents for the synthesis of C-substituted bicyclic structures.

Results

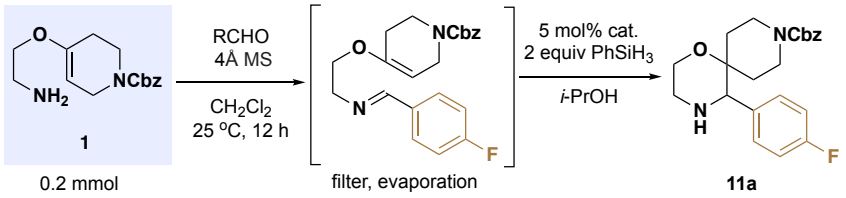
In prior work from our group, we have established that C-centered radicals, generated by single electron oxidation of organosilicons or organostannes, undergo additions to unactivated imines. In order to access more complicated ring structures, we sought alternative methods for radical generation and turned to the well-known Mukaiyama hydration of olefins[13] and further developments by Carreira,[14] Boger,[15] Baran,[16] Shenvi,[17] Shigehisa,[18] Herzon,[19,] Bradshaw [20] and others to a growing number of Mn-, Fe- and Co-catalyzed radical hydrofunctionalizations of olefins.[21] These reactions are generally based on the Halpern mechanism[22] featuring carbon-centered radicals generated from the olefins by hydrogen atom transfer (HAT) via metal hydride (MH) species. Although both inter- and intramolecular M–H catalyzed additions to hydrazones (Figure 1A) have been reported by

Baran[16d] and Bradshaw,[20b] the same conditions were reportedly not suitable for additions to simple imines.[20b] This is likely due to the relatively poor reactivity of unactivated imines in radical additions, which are known to be several orders of magnitude less reactive than hydrazones.[23] Very recently, Shenvi reported M–H catalyzed intermolecular additions of olefins to activated imines (Figure 1B),[17b] but our desired reactions cannot accommodate a sulfonyl group on the imine. Furthermore, the majority of intramolecular HAT-promoted reactions, including the elegant intramolecular additions to hydrazones, occur as 5- or 6-*exo* processes, rather than the 6- or 7-*endo* reactions required for our target structures.

By focusing on intramolecular reactions, we hoped to form stabilized C-centered radicals by hydrogen-atom transfer and engage these in a cyclization to give an N-centered radical, which could be further reduced to afford the desired saturated N-heterocycles. In order to access the topologically challenging spiro- and bridged bicyclic structures we also required the cyclization to occur via contorted transition states that are less kinetically accessible than prior efforts.

Establishment of Conditions for Cyclization of OLA-Imine. For our initial studies, we targeted the synthesis of spirocyclic morpholines with OLA reagent **1**. Imine formation between **1** and 4-fluorobenzaldehyde proceeded smoothly in the presence of the enol ether; simple filtration and evaporation afforded the imine with no requirement for further purification. With the readily accessible OLA-imine, we attempted the cyclization in degassed isopropanol with catalytic amount of $Fe(acac)_3$ (acac = acetylacetonate) and equimolar amount of $PhSiH_3$ as reducing reagent, under Ar or N_2 atmosphere (Table 1 entry 1). These conditions, similar to Shenvi's or Bradshaw's for additions reactions to activated C=N bond (Figure 1A,B), afforded only trace amounts of product from unactivated OLA-imine. In contrast, using an air atmosphere gave desired product **11a** in high yield (entry 2). $Mn(dpm)_3$ (dpm = dipivaloylmethane) performed better than $Fe(acac)_3$ in most cases (entry 3), but the iron catalyst is still useful for many substrates. Further screening established that performing the cyclization at higher temperature afforded better yields, particularly on larger scales (entry 4). Attempts to use Buchwald's Cu-based catalysts, which have been applied to intramolecular additions of styrenes to imines,[24] or Co(salen) catalyst used for intermolecular addition to phenyl sulfonyl oxime,[14b] proved unsuccessful in this case. Our screening studies highlighted the tolerance of the reaction to higher temperatures, wet solvents, and oxygen, rendering this reaction easily executed.

Table 1. Optimization of reaction conditions

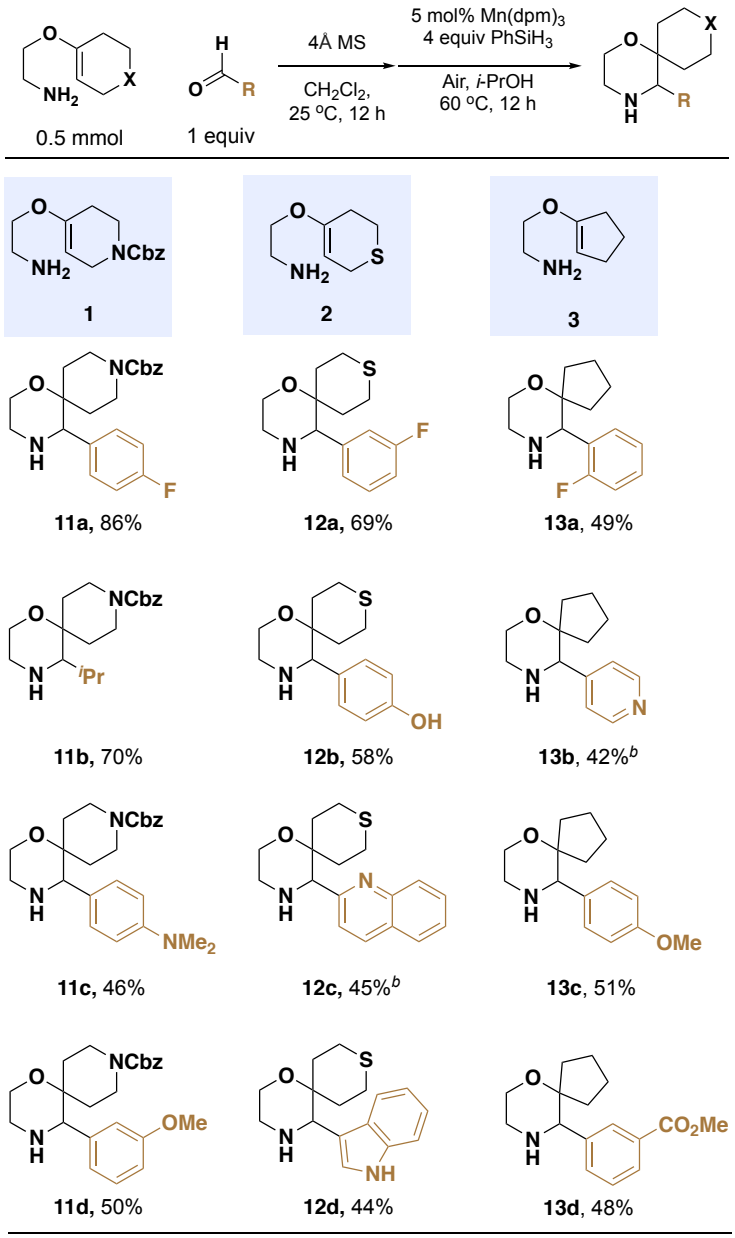


entry	coditions	yields[a]
1	**Argon** or N_2, $Fe(acac)_3$, rt	<5%
2	**Air**, $Fe(acac)_3$, rt	78%
3	**Air**, $Mn(dpm)_3$, rt	86%
4[b]	**Air**, $Mn(dpm)_3$, 60 °C	94% (86%[c])

[a] Yield values refer to isolated yields after purification. [b] Reaction with 4 equiv $PhSiH_3$ for 8 h. [c] Reaction with 0.5 mmol scale

Synthesis of saturated spirocyclic morpholines. We easily prepared OLA reagents **1–3** from commercially available ketones using Lewis acid-promoted cyclic ketal opening reaction as a key step (see SI for detailed synthetic procedures). With these reagents, we examined the synthesis of a variety of spirocyclic morpholines **11**–**13** with a spirocyclic carbon atom adjacent to the morpholine O-atom, the regioisomer of the product of SnAP morpholine reagents with ketones.[6b] We tested the reactions with aryl, heteroaryl and aliphatic aldehydes (Table 2). The reaction proceeded well with both electron-rich and electron-poor aryl aldehydes to give moderate to good yields of the spirocyclic products and exhibited excellent tolerance for unprotected functional groups including tertiary amines (**11c**), free phenols (**12b**), and unprotected indoles (**12d**). For substrates containing aromatic N-heterocycles (**12c**, **13b**), we found that $Fe(dibm)_3$ (dibm = diisobutyrylmethane) and the inclusion of K_2HPO_4[16b] – as employed by others with pyridine-containing reactants[25] – gave improved yields.

Table 2. OLA Reagents for the synthesis of spirocycles.



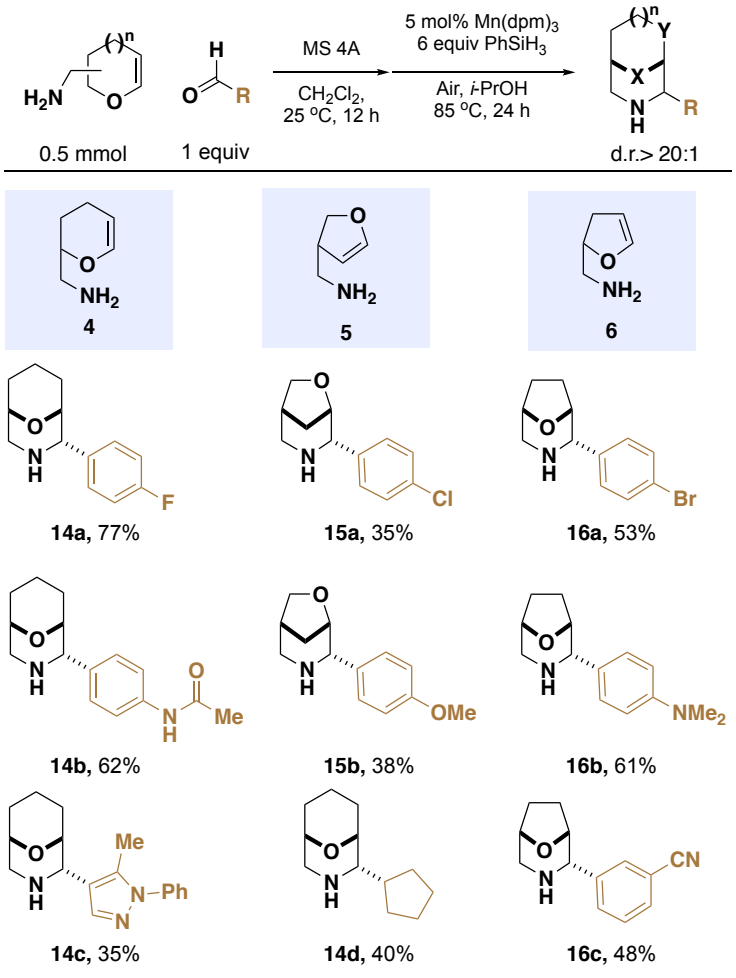
[a] Yield values refer to isolated yields after purification. [b] $Fe(dibm)_3$ instead of $Mn(dpm)_3$, 6 equiv of $PhSiH_3$ and 1 equiv K_2HPO_4 additive was used. Reaction for 24 hours.

Synthesis of bridged bicyclic N-heterocycles.

Encouraged by these results, we turned to the more challenging case of bridged-bicycle formation (Table 3). The construction of bridged bicyclic products requires the addition of the C-radical – generated by hydrogen atom transfer – to the imine by a congested, transannular trajectory. OLA reagent **4** was conveniently prepared from the commodity chemical 3,4-dihydro-2H-pyran-2-methanol**.** In the model reaction of **4** and 4-fluorobenzaldehyde, we found higher reaction temperatures (85 °C) were advantageous for

forming [3.3.1]-bicyclic compound **14a** in high yield. The ability to work at elevated temperatures highlights an advantage of this system; related efforts with SnAP reagents failed in part due to the poor stability of the copper complexes at increased temperatures. We also tested the coupling of OLA reagent **4** with heteroaryl and aliphatic aldehydes, which gave moderate yields of bridged bicycles **14c** and **14d**. In all cases, only one diastereoisomer with the substituent group at the equatorial position of the bridged cycle was formed, as confirmed by an X-ray structure of **14b**. We also prepared OLA reagents **5** and **6** from the corresponding lactones via reduction and elimination. These reagents were competent reaction partners with both electron-rich and electron-poor aldehydes, providing [3.2.1]-bicyclic compounds **15** and **16** as single diastereomers in moderate to good yields.

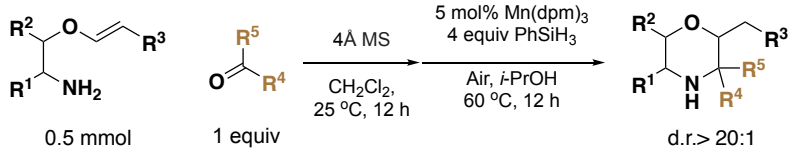
Table 3. OLA reagents for bridged bicycles.



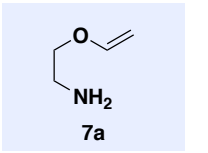
[a] Yield values refer to isolated yields after purification.

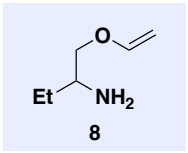
Synthesis of oligosubstituted mono- and fused- morpholines. Many of the OLA reagents are simple to prepare – particularly in comparison to the substituted SnAP reagents – rendering them attractive starting materials for stereochemically-defined substituted morpholines. To demonstrate this, we tested simpler OLA reagents including commercially available compound **7a** and **7b**, readily prepared **8** and **9** for the synthesis of di- and tri-substituted morpholines, and reagent **10** for the synthesis of fused cycles (Table 4). These reactions worked well and delivered the products as single diastereomers (structures determined by crystallography and NMR). Aldehydes from aromatic N-heterocycles including isoxazoles (**17b**, **19b**), pyridines (**18c**), unprotected imidazoles (**18d**), and even unprotected ketones (**17a**) were readily tolerated. We also found that ketones could be employed as substrates when the ketimine formation was performed with $Ti(O\textit{i}\text{-}Pr)_4$ and the cyclization conducted at 85 °C to afforded disubstituted spirocyclic morpholine **18f.** Medium-sized rings are also accessible via the corresponding OLA reagents **7b** and **7c**, which afforded oxazepane **21a**, **21b** and oxazocane **22**, albeit with diminished yields as the ring size increased.

Table 4 . OLA Reagents for mono- and fused cycles



0.5 mmol | 1 equiv | d.r.> 20:1


7a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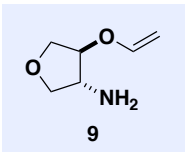
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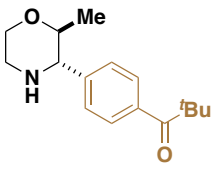
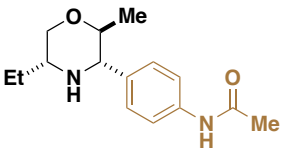
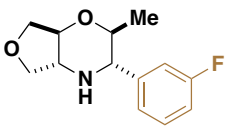
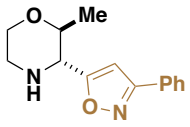
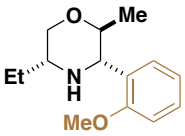
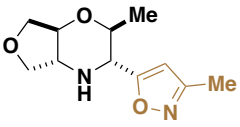

17a, 50%[b,c]

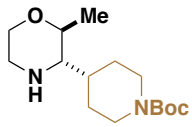

18a, 57%[c,d]

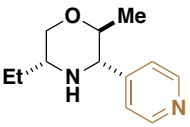

19a, 60%

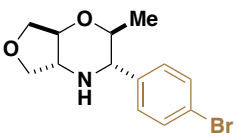

17b, 45%

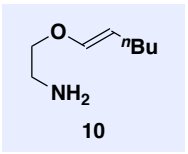

18b, 55%[c,d]


19b, 60%


17c, 57%


18c, 42%[c,d]


19c, 81%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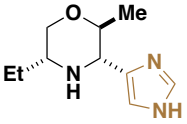
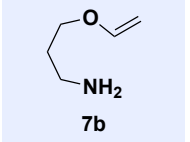
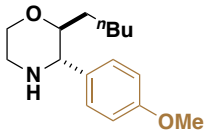
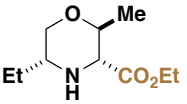
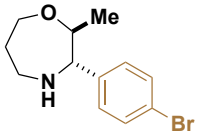
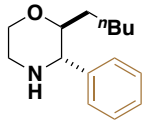

18d, 40%[c,d]

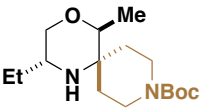

7b

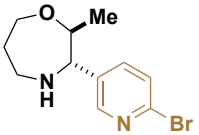

20a, 41%

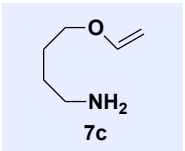

18e, 75%[b,c,e]

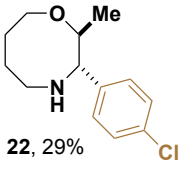

21a, 42%


20b, 48%


18f, 45%[c,d,f,g]


21b, 33%


7c

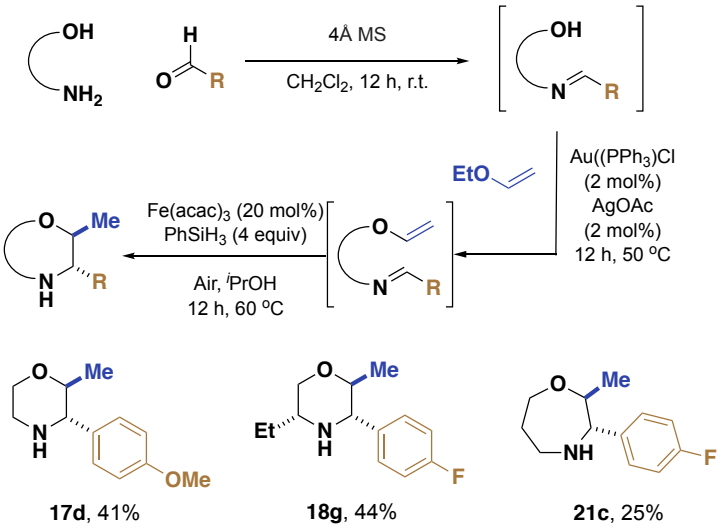

22, 29%

[a] Yield values refer to isolated yields after purification. [b] Reaction at 25 °C. [c] Reaction for 24 h. [d] 6 equiv $PhSiH_3$ was used. [e] EtOH instead of *i*-PrOH. [f] condition for ketimine formation: 2 equiv $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2, 25 °C, 4 h. [g] reaction at 85 °C.

Telescoped synthesis of saturated rings from amino alcohols and aldehydes

In preliminary studies, we have established that morpholines and oxazepanes can be formed by telescoping the synthesis of the OLA reagent, imine-formation, and cyclization in a three-component coupling of aldehydes, amino alcohols, and ethyl vinyl ether. Condensation of the amino alcohol with an aldehyde, followed by gold-catalyzed vinylation, afforded the crude imine intermediate without further purification (Scheme 2). For the cyclization step, we found $Mn(dpm)_3$ was not compatible with this reaction sequence but $Fe(acac)_3$ promoted the synthesis of 2-Me substituted products **17d**, **18g,** and **21c** as single diasteroisomers in moderate yield. Although the overall yields are somewhat lower, this tandem 3-component approach from commodity chemicals may find use in the preparation of libraries.

Scheme 2. Telescoped 3-component coupling of amino alcohols, aldehydes and ethyl vinyl ether

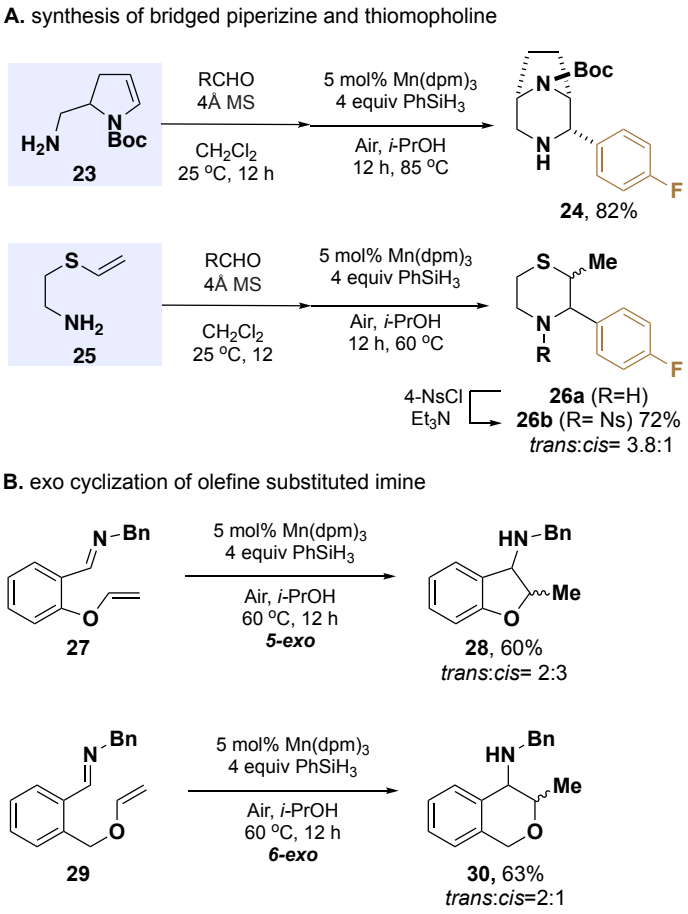


OLA reagents for the synthesis of other heterocycles and amines. These catalytic conditions were also suitable for the synthesis of other classes of saturated N-heterocycles from alternative OLA reagents (Scheme 3A). Starting from reagent **23**, we obtained bridged piperizine **24** as single diastereomer in good yield. OLA reagent **25** – synthesized from 1,4-thioxane in two steps – participates in the cyclization in an unexpectedly non-selective manner to give thiomorpholines **26a** as an inseparable mixtures of diastereomers.

Nosylation afforded products **26b** and allowed us to separate and characterize the diastereomers.

Although we were primarily focused on cyclization that occur in an *endo* fashion, we were also pleased to find that these conditions could be applied to *exo*-cyclizations of imines (Scheme 3B). Following the Baldwin-Beckwith rule[26], the reaction of **27** and **29** lead to secondary amines **28** and **30,** respectively, as mixtures of diastereomers. These conditions complement Bradshaw's *exo*-cyclization of hydrazones,[20b] which afford primary amines after reduction, by directly forming the exocyclic secondary amines.

Scheme 3. Other applications of OLA-imine cyclization



Mechanistic consideration. We carried out a series of control experiments to better understand the reaction pathway, particularly the role of an oxygen-atmosphere on the success of the cyclizations. Attempts at intermolecular coupling of simple enol ethers and imines gave no addition products (Scheme 4A), and efforts to reduce these starting materials with $Mn(dpm)_3$ gave no observable reduction products. The $Mn(dpm)_3$ catalyst also could not promote the intermolecular coupling between enol ethers and methyl acrylate (see SI). These observations highlight the unique relationship of $Mn(dpm)_3$ catalyst, the electron-rich olefin, and the imine in the successful cyclization reaction.

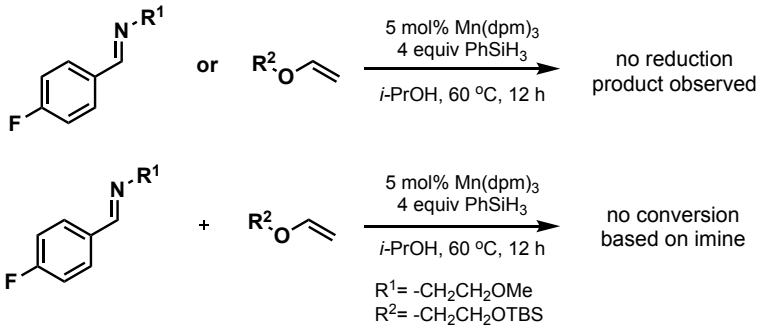
We studied the influence of various silanes and reaction conditions on the cyclization to form **17e** (Scheme 4B). In the absence of *i*-PrOH, $PhSiH_3$ gave poor conversion in 1,2-dichloroethane, while Shenvi's silane,[17a] $PhSi(i\text{-}PrO)H_2$, restored the reactivity, highlighting the need to form a more active silane. Reactions performed in degassed solvent under N_2 atmosphere, instead of air, proceed to full conversion only when stoichiometric amounts of $Mn(dpm)_3$ were provided, revealing a key role for oxygen in catalyst turnover.[17d] Attempts to use other oxidants, such as TBHP, failed to afford products under N_2.

Based on extensive prior mechanistic work from Halpern, Baran, Shenvi, and others, the reaction most likely begins by in situ generation of active metal hydride (M–H) species from Mn (III) or Fe (III) and a silane. Metal hydride hydrogen atom transfer (MH HAT) to the electron-rich olefin provides Mn(II) [or Fe(II)] and the heteroatom-stabilized radical **II** – similar to the species postulated to be involved in SnAP chemistry. This HAT process was demonstrated by the reaction with $PhSiD_3$ gave deuterated product **31**. Radical **II** undergoes Beckwith rule[26] breaking 6/7/8-*endo*-trig cyclization to give N-centered radical **III**.

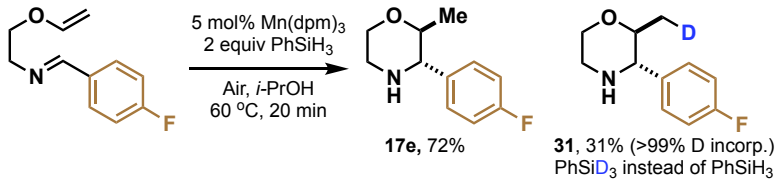
Our group has demonstrated that copper or photoredox catalyzed additions of C-centered radicals to unactivated imines requires subsequent reduction of the relatively stable N-centered radical formed by the initial addition, a challenging process that can complicate catalyst turnover. We initial postulated that the catalytic cycle could be completed by an inner sphere single electron transfer between radical **III** and Mn (II) (Scheme 4C, Path I). This process, however, is not likely to be operative due to the requirement of oxygen and the large reduction potential gap between Mn (III) ($E_{1/2}^{III/II}$ ~ 0.39 V vs SCE) and N-centered radical **III** ($E_{1/2}^{red}$ = –1.70 V vs SCE for dialkylaminyl radical[7]). Based on this consideration, oxidation of the catalyst and reduction of radical **III** are thought to be independent events.

Scheme 4. Control experiments and proposed catalytic cycle

A. reduction and intermolecular addition of simple imine and vinyl ether



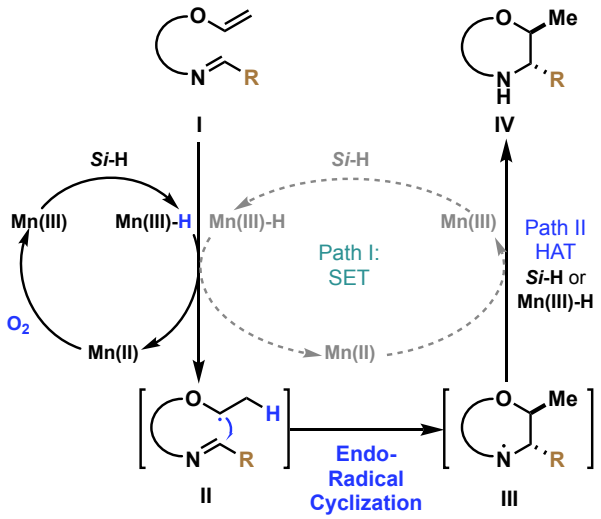
B. control experiments



Entry	Deriviation from above	Yield*
1	$ClCH_2CH_2Cl^b$ instead of *i*-PrOH, 3 h	43%
2	$PhSi(i\text{-}PrO)H_2$, $ClCH_2CH_2Cl^b$, 3 h	66%
3	under $N_2{}^c$, 5 mol% $Mn(dpm)_3$	<5%
4	under $N_2{}^c$, 50 mol% $Mn(dpm)_3$	33%
5	under $N_2{}^c$, 100 mol% $Mn(dpm)_3$	60%

[a] yield determined by crude NMR. [b] dry $ClCH_2CH_2Cl$ used. [c] degassed *i*-PrOH used.

C. proposed catalytic cycle



We therefore considered a second pathway (Path II), based on Halpern's alkene hydrogenation studies. The presence of active H-atom source, including both silanes and M–H species, renders the direct reduction of **III** to form the final product **IV** by a second HAT a probable mechanism as it is polarity matched and favored by thermodynamic considerations (morpholine $BDE_{N\text{-}H}$> 95.3 kcal/mol[27] vs. $PhSiH_3$ $BDE_{Si\text{-}H}$= 91.3 kcal/mol[28]

vs. $BDE_{Mn\text{-}H} < 50$ kcal/mol[17c]). This double HAT pathway distinguishes it from the catalytic redox cycle in SnAP chemistry and HAT/SET[16c] (or PCET)[29] hybrid cycle in Fe-H catalyzed additions of enol ethers to acrylates.

Conclusion

In summary, we have developed a convenient, modular approach to the synthesis of C-substituted N-heterocycles including challenging bridged bicyclic and spirocyclic examples. The catalytic reaction proceeds by a chemoselective hydrogen atom transfer reaction that generates C-centered radicals by reduction of electron-rich olefin in the presence of imines and a second HAT that reduces the resulting N-centered radical. Based on preliminary experiments, the same principles should be applicable to the synthesis of other attractive targets, including other saturated N-heterocycles and related frameworks attractive for drug discovery.[30]

Supporting Information

Experimental procedures, characterization data NMR spectra for all new compounds (PDF)

X-ray crystallographic data for 7 compounds including **14b**, **18a**, ***trans*-26b**, ***cis*-26b**, **32** (nosylated **15b**), **33** (nosylated **19c**), and **34** (nosylated **24**).

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References

(1) Marson, C. M. Saturated Heterocycles with Applications in Medicinal Chemistry. *Advances in Heterocyclic Chemistry* **2017**, *121*, 13–33.

(2) During 2016-2018, FDA approved 86 small molecule drugs, 44 of which contained a saturated N-heterocycle. For further information, see: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/

(3) For selected examples of intramolecular hydroamination, see: (a) Mai, D. N.; Wolfe, J. P. Asymmetric palladium-catalyzed carboamination reactions for the synthesis of enantiomerically enriched 2-(arylmethyl)- and 2 (alkenylmethyl)pyrrolidines. *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159. (b) Zhai, H.; Borzenko, A.; Lau, Y. Y.; Ahn, S. H.; Schafer, L. L. Catalytic asymmetric synthesis of substituted morpholines and piperazines. *Angew. Chem. Int. Ed.* **2012**, *51*, 12219–12223.

(4) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. Dual catalysis. Merging photoredox with nickel catalysis: coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **2014**, *345*, 437–440. (b) Zhai, H.; Borzenko, A.; Lau, Y. Y.; Ahn, S. H.; Schafer, L. L. Catalytic asymmetric synthesis of substituted morpholines and piperazines. *Angew. Chem. Int. Ed.* **2012**, *51*, 12219–12223. (c) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. Practical Ni-Catalyzed Aryl-Alkyl Cross-Coupling of Secondary Redox-Active Esters. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177.

(5) For selected examples of C-H functionalization of saturated N-heterocycles, see: (a) Joe, C. L.; Doyle, A. G. Direct Acylation of C(sp(3))-H Bonds Enabled by Nickel and Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 4040–4043. (b) Perry, I. B.; Brewer T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco D. A.; MacMillan, D. W. Direct arylation of strong aliphatic C-H bonds. *Nature* **2018**, *560*, 70–75.

(6) For reviews, see: (a) Luescher, M. U.; Geoghegan, K.; Nichols, P. L.; Bode, J. W. SnAP Reagents for a Cross-Coupling Approach to the One-Step Synthesis of Saturated N-Heterocycles. *Aldrichimica Acta* **2015**, *48*, 43–48. For a recent example, see: (b) Saito, F.; Trapp, N.; Bode, J. W. Interative Assembly of Polycyclic Saturated Heterocycles from Monomeric Building Blocks *J. Am. Chem. Soc.* **2019**, *141*, 5544–5554.

(7) Hsieh, S. Y.; Bode, J. W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **2016**, *18*, 2098–2101.

(8) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The importance of synthetic chemistry in the pharmaceutical industry. *Science* **2019**, *363*, 244-244.

(9) Zheng, Y.; Tice C. M.; Singh S. B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Let.* **2014**, *24*, 3673–3682.

(10) Cakmak, M.; Mayer, P.; Trauner, D. An efficient synthesis of loline alkaloids *Nature Chemistry* **2011**, *3*, 543–545.

(11) For selected examples of bridged cycles with unique physiochemical properties, see: (a) Levterov, V. V.; Michurin, O.; Borysko, P. O.; Zozulya, S.; Sadkova, I. V.; Tolmachev, A. A.; Mykhailiuk, P. K. Photochemical In-Flow Synthesis of 2,4-Methanopyrrolidines: Pyrrolidine Analogues with Improved Water Solubility and Reduced Lipophilicity. *J. Org. Chem.* **2018**, *83*,14350–14361 (b) Degorce, S. L.; Bodnarchuk, M. S.; Cumming I. A.; Scott J. S. Lowering Lipophilicity by Adding Carbon: One-Carbon Bridges of Morpholines and Piperazines. *J. Med. Chem.* **2018**, *61*, 8934–8943.

(12) During the submission of this manuscript, Gaunt reported an elegant synthesis of N-protected spirocyclic amines by cyclization of iminiums and olefins under visible-light promoted photoredox catalysis and a Hantzsch ester as the HAT reagent: Floden, N. J.; Trowbridge, A.; Willcox, D., Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined synthesis of C(sp^3)–H rich *N*-heterospirocycles enabled by visible-light-mediated photocatalysis. *J. Am. Chem. Soc.* **2019**, Just Accepted Manuscript, DOI: 10.1021/jacs.9b03372 (Published 10 May 2019).

(13) Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular-Oxygen and Phenylsilane by the Use of Bis(Acetylacetonato)Cobalt(II). *Chem. Lett.* **1989**, *18*, 1071–1074.

(14) (a) Waser, J.; Carreira, E. M. Catalytic hydrohydrazination of a wide range of alkenes with a simple Mn complex. *Angew. Chem. Int. Ed.* **2004**, *43*, 4099–4102. (b) Gaspar, B.; Carreira, E. M. Cobalt catalyzed functionalization of unactivated alkenes: regioselective reductive C-C bond forming reactions. *J. Am. Chem. Soc.* **2009**, *131*, 13214–13215.

(15) Leggans, E. K.; Barker, T. J.; Duncan, K. K.; Boger, D. L. Iron(III)/$NaBH_4$-mediated additions to unactivated alkenes: synthesis of novel 20'-vinblastine analogues. *Org. Lett.* **2012**, *14*,1428–1431.

(16) (a) Lo, J. C.; Yabe, Y.; Baran, P. S. A practical and catalytic reductive olefin coupling. *J. Am. Chem. Soc.* **2014**, *136*, 1304–1307. (b) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. Functionalized olefin cross-coupling to construct carbon–carbon bonds. *Nature* **2014**, *516*, 343–348. (c) Lo, J. C.; Baran, P. S. Fe-Catalyzed C-C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 2484–2503. (d) Dao, H. T.; Li, C.; Michaudel, Q.; Maxwell, B. D.; Baran, P. S. Hydromethylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2015**,*137*, 8046–8049.

(17) (a) Obradors, C.; Martinez, R. M.; Shenvi, R. A. Ph(*i*-PrO)SiH_2: An Exceptional Reductant for Metal-Catalyzed Hydrogen Atom Transfers. *J. Am. Chem. Soc.* **2016**, *138*, 4962-4971. (b) Matos, J. L. M.; Vásquez-Céspedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 16976–16981. (c) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vásquez-Céspedes, S.; Shevick, S. L.; Shenvi, R. A. The High Chemofidelity of Metal-Catalyzed Hydrogen Atom Transfer. *Acc. Chem. Res.* **2018**, *51*, 2628–2640. (d) Green, S. A.; Huffman, T. R.; McCourt, R. O., Van der Puy, V.; Shenvi, R. A. Hydroalkylation of Olefins To Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709–7714.

(18) Shigehisa, H.; Koseki, N.; Shimizu, N.; Fujisawa, M.; Niitsu, M.; Hiroya, K. Catalytic Hydroamination of Unactivated Olefins Using a Co Catalyst for Complex Molecule Synthesis *J. Am. Chem. Soc* **2014**, *136*, 13534–13537.

(19) Ma, X.; Herzon, S. B. Intermolecular Hydropyridylation of Unactivated Alkenes. *J. Am. Chem. Soc* **2016**, *138*, 8718–8721.

(20) (a) Saladrigas, M.; Bosch, C.; Saborit, G. V.; Bonjoch, J.; Bradshaw, B. Radical Cyclization of Alkene-Tethered Ketones Initiated by Hydrogen-Atom Transfer. *Angew. Chem. Int. Ed.* **2018**, *57*, 182–186. (b) Saladrigas, M.; Loren, G.; Bonjoch, J.; Bradshaw, B. Hydrogen Atom Transfer (HAT)-Triggered Iron-Catalyzed Intra- and Intermolecular Coupling of Alkenes with Hydrazones: Access to Complex Amines. *ACS Catal.* **2018**, *8*, 11619–11703.

(21) For review, see: (a) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912–9000. (b) Hoffmann, R. W. Markovnikov free radical addition reactions, a sleeping beauty kissed to life. *Chem. Soc. Rev.* **2016**, *45*, 577–583.

(22) Sweany, R. L.; Halpern, J. Hydrogenation of α-methylstyrene by hydridopentacarbonyl-manganese (I). Evidence for a free-radical mechanism**.** *J. Am. Chem. Soc.* **1977**, *99*, 8335–8337.

(23) Tauh, P.; Fallis, A. G. Rate Constants for 5-Exo Secondary Alkyl Radical Cyclizations onto Hydrazones and Oxime Ethers via Intramolecular Competition Experiments *J. Org. Chem.* **1999**, *64*, 6960–6968. (b) Kim, S,; Yoon, K.; Kim, Y. Kinetic studies of intramolecular addtions of alkyl radicals onto imines. *Tetrahedron* **1997**, *53*, 73-80.

(24) Ascic, E.; Buchwald, S. L. Highly Diastereo- and Enantioselective CuH-Catalyzed Synthesis of 2,3-Disubstituted Indolines. *J. Am. Chem. Soc.* **2015**, *137*, 4666–4669.

(25) Bordi, S.; Starr, J. T. Hydropyridylation of Olefins by Intramolecular Minisci Reaction. *Org. Lett.* **2017**, *19*, 2290–2293.

(26) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. Some guidelines for radical reactions. *J. Chem. Soc., Chem. Commun.* **1980**, 482–483.

(27) (a) Feng, Y.; Liu, L.; Wang, J.-T.; Zhao, S.-W.; Guo, Q.-X. Homolytic C-H and N-H Bond Dissociation Energies of Strained Organic Compounds. *J. Org. Chem.* **2004**, *69*, 3129–3138. (b) Hioe, J.; Šakić, D.; Vrček, V.; Zipse, H. The stability of nitrogen-centered radicals. *Org. Biomol. Chem.* **2015**, *13*, 157–169.

(28) Luo, Y.-R. Comprehensive Handbook of Chemical Bond Energies; CRC Press, London, 2007.

(29). Kim, D.; Wahidur Rahaman, S. M.; Mercado, B. Q.; Poli, R.; Holland, P. L. Roles of Iron Complexes in catalytic Radical Alkene Cross-Coupling: A Computational and Mechanistic Study. *J. Am. Chem. Soc.* **2019**, *141,* 7473-7485.

(30) Foley, D. J.; Nelson, A.; Marsden, S. P. Evaluating New Chemistry to Drive Molecular Discovery: Fit for Purpose? *Angew. Chem. Int. Ed.* **2016**, *55*, 13650–13657.

TOC graphic: