Published in final edited form as:

Angew Chem Int Ed Engl. 2018 November 12; 57(46): 15162–15166. doi:10.1002/anie.201809799.

Mannich-type Reactions of Cyclic Nitrones: Effective Methods for the Enantioselective Synthesis of Piperidine-containing Alkaloids

Vladislav G. Lisnyak, Tessa Lynch-Colameta, Scott A. Snyder

Department of Chemistry, University of Chicago, 5735 S. Ellis Avenue, Chicago, IL, 60637 (USA)

Abstract

Although there are dozens of biologically active 2-substituted and 2,6-disubstituted piperidines, only a limited number of approaches exist for their synthesis. Herein is described two Mannich-type additions to nitrones, one using β -ketoacids under catalyst-free conditions and another using methyl ketones in the presence of chiral thioureas, which can generate a broad array of such 2-substituted materials, as well as other ring variants, in the form of β -*N*-hydroxy-aminoketones. Both processes have broad scope, with the latter providing products with high enantioselectivity (up to 98%). The combination of these methods, along with other critical steps, has enabled 8-step total syntheses of the 2,6-disubstituted piperidine alkaloids (–)-lobeline and (–)-sedinone.

Graphical Abstract

Despite their prevalence, 2- and 2,6-disubstituted piperidines are challenging to prepare asymmetrically, particularly when they possess β -functionalization. Herein, two new approaches based on the use of cyclic nitrones provides the means to readily fashion an array of such materials, one of which proceeds with high enantioselectivity (up to 98% ee) using a chiral thiourea promoter. Of note, their sequential use has enabled 8-step total syntheses of both (–)-lobeline and (–)-sedinone from a common intermediate.

Keywords

catalysis; piperidine; enantioselective; nitron; total synthesis

Although piperidine rings are a ubiquitous structural feature of alkaloid-based natural products and pharmaceuticals, equally common is their possession of 2- or 2,6-substitution patterning that includes a β -carbonyl and/or alcohol functionality.^[1] Molecules such as those drawn in Scheme 1 (**1–7**) are representative examples isolated from a diverse array of plants and insects.^[2] Biosynthetically, these side-chains are believed to arise via Mannich-type additions of carbonyl-derived nucleophiles onto piperidine-derived iminium intermediates.^[2f,3] Scheme 1 provides two approaches that can proceed with enantiocontrol in a laboratory setting. The first utilizes L-proline to effect direct Mannich-type reactions between imines **8** and varied ketones **9** (primarily methyl) to produce aminoketones of type **10**, noting that only one example where $R_3 = H$ has been described.^[4] The second utilizes a chiral copper (I)-conjugated Brønsted base pair to catalyze a stepwise ring-opening/aldol addition/dehydration cascade followed by a stereodefining *aza*-Michael reaction^[5] starting from cyclic hemiaminal **11** and methyl ketones **12**.^[6] While both approaches possess significant power, these methods only work effectively if the intermediates have appropriate stability, noting that the synthesis of some starting materials can be step intensive, particularly for more complex piperidines and related azacycles. As such, we wondered whether a complementary, and potentially more general, method could be developed utilizing cyclic nitrones as an iminium surrogate. That conjecture was based on the fact that such species are readily prepared in one step via oxidation of their corresponding secondary amines^[7] or hydroxylamines (more mild),^[8] are reasonably stable compounds that exist in cyclic form exclusively as the more reactive *E*-isomers,^[9] and are well documented to accept a variety of nucleophiles.^[10] Herein, we show that nitrones, both cyclic and acyclic, are indeed effective substrates for Mannich-type additions with β -ketoacids, simply upon dissolution, as well as an array of methyl ketones when appropriate promoters are added. When chiral thioureas are used as catalysts in the latter process, the reaction proceeds with good to excellent enantiocontrol and can serve as a foundational method to generate key chiral centers leading to the rapid and stereocontrolled total synthesis of 2,6-disubstituted natural products such as (–)-lobeline (**3**) and (–)-sedinone (**4**).

As shown in Scheme 1, we began our investigations by exploring whether cyclic nitrones of type **14** could provide an alternative to the well-established decarboxylative Mannich-type reaction between cyclic imines and β -ketoacids (i.e. the Schöpf reaction).^[11] Given that this imine variant is known to be slow, low-yielding, and pH-dependent with side reactions often observed,^[11,12] we anticipated that an alternative and broadly effective variant, even in racemic format, could be of value. Pleasingly, we found that **14** and **15** could readily merge, without any added catalyst,^[13] simply upon stirring in CH_2Cl_2 at 23 °C.

Table 1 provides the products synthesized (**19–27**), where no further optimization was performed from our initial condition hit given the generally smooth and high yielding outcomes (50–90%); the one exception was product **26**, obtained in 34% yield from a conjugated starting material. Of note, nitrones of different ring sizes and acyclic systems

(which tend to be less reactive)^[9] worked well with several β -ketoacids; products **23** and **24** are of particular significance given challenges observed for adding heterocycles and hindered alkyl-containing β -ketoacids onto imines.^[14] Finally, the success of a pregnenolone-derived β -ketoacid to form **27** (77% yield, *dr* = 2:1) highlights the ability to use the reaction for late-stage functionalization.

We next performed several screens to determine if these transformations could proceed with enantiocontrol. Unfortunately, all efforts with β -ketoacids as well as several additional probes using β -ketoesters failed. Our first effective hit came when we changed the nucleophile partner to a simple ketone, using enamine activation^[15] to promote this slower-to-achieve union. As shown in Table 2, when nitrone **28** was coupled with an excess of acetone (**29**) in CH_2Cl_2 in the presence of L-proline (**30**, 20 mol %), **31** was formed in 60% yield and 54% *ee* (measured after derivatization of the hydroxylamine, see Supporting Information). However, subsequent exploration of the more challenging, and arguably more useful from the standpoint of complex molecule synthesis,^[2f] reaction with acetophenone (**32**) proved to be rather poor under these conditions (7% yield, 12% *ee*). As a result, all further optimizations were performed with ketone **32**.

We quickly found that chiral primary amine catalysts such as **34** and **35** could dramatically enhance *ee* (80–86%), albeit with no yield improvement (10–25%). Inspired by reports from both Schreiner^[16] and Takemoto^[17] showing that thiourea-based hydrogen bonding catalysts^[18] can increase the rate of both [3+2]-cycloadditions and nucleophilic additions to nitrones, we then tested bifunctional catalyst **36**.^[19] Pleasingly, it provided a further increase in enantioselectivity (90% *ee*), but still with no improvement in yield (26%). Interestingly, the analogous squaramide **37**^[20] performed worse (20% yield, 65% *ee*). Ultimately, varying the thiourea side-chain resulted in a significant increase in both parameters, with Jacobsen catalyst **38**^[21] affording **33**^[22] in 45% yield and 88% *ee*. Further screening with this promoter (see SI) showed that when the loading of the catalyst and benzoic acid additive were increased to 20 mol % and 40 mol %, respectively, the desired product was obtained in 84% yield and 90% *ee* (Table 3).

As presented in the remainder of Table 3, use of these optimized conditions with a range of 6-membered cyclic nitrones^[23] bearing varied substituents at the 2-, 3-, and 4-positions afforded products **40–43** in good yields and up to 98% *ee*. Of particular note, a “heterocyclic” nitrone^[24] also reacted successfully to afford an effective synthesis of **44**. As denoted in Table 4, different electron-rich and -deficient acetophenones were also tested with nitrone **28** to afford **46–51** in good to moderate yields (54–70%) and high enantioselectivity (86–93% *ee*). Pleasingly, these same conditions were readily extended to alkyl methyl ketones to generate **31** and **52–59**, similarly in good to moderate yields (51–90%) and high enantioselectivity (94–96% *ee*).^[25] Of note, while additional substitution at the ketone α -position did decrease yield in some cases, the enantioselectivity remained high with excellent regiocontrol using a range of unique substituents, including fluorine and methoxy groups. The formation of **58**, in fact, is in contrast to the preferential product generated under enamine catalysis,^[21b,26] highlighting an element of complementarity.

Equally critical, although the oxidation state of the products is higher than that found in most natural targets, as well as materials produced using iminium intermediates, the hydroxylamine moiety serves to protect against *in situ* racemization.^[27] For example, with **33** only 3% *ee* was lost following 20 h of standing in MeOH at 23 °C. When stored neat at –20 °C, all products sampled (**31**, **33**, **46**, **50**, and **51**) were configurationally stable after several months except for those bearing electron-withdrawing substituents on the aromatic ring (**47–49**). Moreover, unlike the parent secondary amines that normally require an additional Boc-protection step in order to be purified,^[4] **16**, **39**, and **45** can be chromatographed directly.^[28] Additionally, as tested with **31** and **33**, the N–OH bond can be readily cleaved with Zn/AcOH (see SI) to provide the corresponding free amine.

Finally, we sought to explore the power of these methods to accomplish total syntheses of (–)-lobeline (**3**, cf. Scheme 1) and (–)-sedinone (**4**). While the former target has been prepared numerous times,^[29] the most efficient syntheses from Boehringer Ingelheim, Birman, and Stoltz at 2, 5 and 11 steps, respectively took advantage of the target's inherent symmetry. By contrast, non-symmetric (–)-sedinone (**4**) has been synthesized twice, as a racemate in 9 steps from commercial materials and in optically active form as a partial synthesis from (–)-norsedamine (**1**).^[30] Our approach sought the first unified solution capable of accessing both targets and numerous analogs, given the known therapeutic value of **3** as a potent antagonist at nicotinic acetylcholine receptors.^[2f,31]

As noted in Scheme 2, those efforts commenced with application of the developed catalytic protocol for the preparation of **33**, previously conducted on 0.5 mmol scale, to now generate gram quantities in a single pot. While the yield dropped slightly on 10 mmol scale (84% to 70%), the enantioselectivity did not change (90% *ee*). Next, a *syn*-reduction of **33** was achieved using Zn(BH₄)₂^[32] to deliver the desired alcohol as a 9:1 mixture of diastereomers about the new chiral center, with subsequent silylation (TBSOTf, *i*-Pr₂NEt) affording **60** in 67% yield over two steps without significant deterioration in enantiomeric excess (89% *ee*). Pleasingly, crystals of **60** proved suitable for diffraction, confirming its absolute (*S,S*)-configuration and, by analogy, all the other products as shown in Tables 2–4.

With an eye towards using the β-ketoacid variant of the nitron addition, hydroxyamine **60** was then oxidized with high regioselectivity using IBX^[8d] to afford a 4:1 ratio of aldonitrone **61** and its corresponding ketonitrone (undrawn). By contrast, application of more common oxidation agents, such as HgO^[33] or MnO₂,^[8c] provided little or no regiocontrol. Next, separate addition of the two requisite β-ketoacids (**15**, R = Ph or Me) to crude nitron **61** smoothly afforded the corresponding disubstituted hydroxylamines, but predominantly with a *trans*-2,6-arrangement on the piperidine ring (~4:1 *dr* for both).^[34] Subsequent efforts to effect reductive cleavage of their N–O bonds indeed produced the desired secondary amines, but these products were prone to equilibration, likely via retro-*aza*-Michael/*aza*-Michael pathways,^[29ab,35] to ultimately favor the 2,6-*cis*-isomers.^[36] Unfortunately, all attempts to *N*-alkylate these *cis*-isomers were unsuccessful; by contrast, the *trans*-isomers participated in reductive amination readily. Based on these results and on the fact that the *trans*-isomers can be converted into *cis*-isomers at a later stage (*vide infra*),^[29e] we developed a one-pot procedure combining these two operations to minimize isomerization by using Zn/AcOH in the presence of aqueous formaldehyde.^[37] This

operation afforded *N*-methylamines **62** and **63** in 75% and 76% yield, respectively, from common intermediate **61**. For these products, equilibration was still observed, with the *dr* of **62** being batch dependent (~1:1), while **63** was less prone to epimerization (*dr* = 1:5.4 favoring the *trans*-isomer). Finally, after acidic TBS removal^[35] and subsequent basic work-up, we obtained the desired aminoalcohol intermediates (i.e. **3** and **4**) with the same *dr* as the silylated starting materials.

Our goal now was to convert these mixtures into the desired *cis*-isomers. Encouraged by recent research using crystallization-induced dynamic resolution (CIDR),^[38] we attempted to recrystallize their free bases. Pleasingly, slow evaporation of **3** in MeOH at 4 °C for several weeks exclusively afforded *cis*-disposed (–)-lobeline (**3**) in 90% yield over the final 2 steps. Similar techniques, however, did not work for **4**, presumably due its greater configurational stability. We ultimately found that three rounds of equilibration in MeOH (to 1:1 *dr*) with selective precipitation of the *cis*-isomer in hexanes/EtOAc afforded (–)-sedinone (**4**) in 73% yield over 2 steps.

In conclusion, we have developed two distinct methods for Mannich-type additions to nitrones. These approaches encompass diverse substrate scope and potential for late-stage functionalizations, with one also affording opportunities for enantioselective syntheses with cyclic six-membered nitrones to generate the corresponding β-*N*-hydroxy-aminoketones in up to 98% *ee*. As a result of the oxidation state of the products, purification is facile and racemization is slow. Finally, the serial execution of both methods, coupled with other unique operations, has enabled 8-step total syntheses of (–)-lobeline (**3**) and (–)-sedinone (**4**) from a common intermediate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Dr. Alexander Filatov and Mr. Andrew McNeece for X-ray analysis of **60**, and Dr. Antoni Jurkiewicz and Dr. C. Jin Qin for assistance with NMR and mass spectrometry, respectively. We also thank Dr. Michael Rombola for **37** and Ms. Elizabeth Kelley for assistance with the preparation of **28** and **38**. Financial support for this work came from the University of Chicago and the National Institutes of Health (NIH R01-124295A).

References

- [1]. a)Schneider MJ, Pyridine and piperidine alkaloids: an update, in: Alkaloids: chemical and biochemical perspectives (Ed.: Pelletier SW), Pergamon, Oxford, UK, 1996, 10, 155–299;b)Michael JP, Nat. Prod. Rep. 2008, 25, 139; [PubMed: 18250900] c)O'Hagan D, Nat. Prod. Rep. 2000, 17, 435; [PubMed: 11072891] d)Vitaku E, Smith DT, Njardarson JT, J. Med. Chem. 2014, 57, 10257. [PubMed: 25255204]
- [2]. a)Marion L, Lavigne R, Lemay L, Can. J. Chem. 1951, 29, 347; [PubMed: 14831019] b)Franck B, Chem. Ber. 1959, 92, 1001;c)Denne WA, Johns SR, Lamberton JA, Mathieson AM, Snares H, Tetrahedron Lett. 1972, 13, 1767;d)Colau B, Hootele C, Can. J. Chem. 1983, 61, 470;e)Huang Q, Attygale AB, Meinwald J, Houck MA, Eisner T, J. Nat. Prod. 1998, 61, 598; [PubMed: 9599256] f)Felpin F-X, Lebreton J, Tetrahedron 2004, 60, 10127;g)Hu Y, Zhang C, Zhao X, Wang Y, Feng D, Zhang M, Xie H. J. Nat. Prod. 2016, 79, 252. [PubMed: 26710212]

- [3]. a)Gupta RN, Spenser ID, Can. J. Chem. 1967, 45, 1275;b)Hemscheidt T, Spenser ID, J. Am. Chem. Soc. 1990, 112, 6360;c)Bunsupa S, Yamazaki M, Saito K, Front. Plant Sci. 2012, 3, 239. [PubMed: 23112802]
- [4]. Monaco MR, Renzi P, Schietroma DMS, Bella M, Org. Lett. 2011, 13, 4546. [PubMed: 21812495]
- [5]. a)For selected examples of intramolecular aza-Michael reactions, see: Carlson EC, Rathbone LK, Yang H, Collett ND, Carter RG, J. Org. Chem. 2008, 73, 5155; [PubMed: 18529081] b)Fustero S, del Pozo C, Mulet C, Lazaro R, Sánchez-Roselló M, Chem. Eur. J. 2011, 17, 14267; [PubMed: 22083999] c)He W, Hu J, Wang P, Chen L, Ji K, Yang S, Li Y, Xie Z, Xie W, Angew. Chem. Int. Ed. 2018, 57, 3806;d)Roy TK, Parhi B, Ghorai P, Angew. Chem. Int. Ed. 2018, 57, 9397.
- [6]. Shi S-L, Wei X-F, Shimizu Y, Kanai M, J. Am. Chem. Soc. 2012, 134, 17019. [PubMed: 23039221]
- [7]. a)Murahashi S-I, Shiota T, Tetrahedron Lett. 1987, 28, 2383;b)Murahashi S-I, Mitsui H, Shiota T, Tsuda T, Watanabe S, J. Org. Chem. 1990, 55, 1736;c)Goti A, Nannelli L, Tetrahedron Lett. 1996, 37, 6025.
- [8]. a)Goti A, De Sarlo F, Romani M, Tetrahedron Lett. 1994, 35, 6571;b)Cicchi S, Goti A, Brandi A, J. Org. Chem. 1995, 60, 4743;c)Cicchi S, Marradi M, Goti A, Brandi A, Tetrahedron Lett. 2001, 42, 6503;d)Matassini C, Parmeggiani C, Cardona F, Goti A, Org. Lett. 2015, 17, 4082. [PubMed: 26225452]
- [9]. a)Huisgen R, Seidl H, Brüning I, Chem. Ber. 1969, 102, 1102;b)Ali Sk. A., Khan JH, Wazeer MIM, Perzanowski HP, Tetrahedron 1989, 45, 5979.
- [10]. a)For reviews, see: Lombardo M, Trombini C, Synthesis 2000, 6, 759;b)Merino P, Tejero T, Synlett 2011, 14, 1965 For recent examples, see:c)Postikova S, Tite T, Levacher V, Brière J-F, Adv. Synth. Catal. 2013, 355, 2513;d)Juste-Navarro V, Prieto L, Delso I, Manzano R, Tejero T, Reyes E, Vicario JL, Merino P, Adv. Synth. Catal. 2017, 359, 4122.
- [11]. Schöpf C, Braun F, Burkhardt K, Dummer G, Müller H, Liebigs Annalen 1959, 626, 123.
- [12]. a)Wisse JH, De Klonia H, Visser BJ, Rec. Trav. Chim. Pays-Bas 1964, 83, 1265;b)Cragg JE, Herbert RB, Jackson FB, Moody CJ, Nicolson IT, J. Chem. Soc. Perkin Trans. 1982, 1, 2477;c)Devijver C, Macours P, Braekman J-C, Daloze D, Pasteels JM, Tetrahedron 1995, 51, 10913.
- [13]. a)Similar reactions usually require a catalyst or promoter: Zhong F, Jiang C, Yao W, Xu L-W, Lu Y, Tetrahedron Lett. 2013, 54, 4333;b)Jia C-M, Zhang H-X, Nie J, Ma J-A, J. Org. Chem. 2016, 81, 8561; [PubMed: 27562019] c)Liu Y-J, Li J-S, Nie J, Ma J-A, Org. Lett. 2018, 20, 3643 For a catalyst-free precedent, see: [PubMed: 29847943] d)Böhm M, Proksch K, Mahrwald R, Eur. J. Org. Chem. 2013, 6, 1046.
- [14]. a)Grisar JM, Claxton GP, Stewart KT, Synthesis 1974, 284;b)Grisar JM, Claxton GP, Stewart KT, MacKenzie RD, Kariya T, J. Med. Chem. 1976, 19, 1195. [PubMed: 994149]
- [15]. a)For recent reviews, see: Mukherjee S, Yang JW, Hoffmann S, L B, Chem. Rev. 2007, 107, 5471; [PubMed: 18072803] b)Bertelsen S, Jørgensen KA, Chem. Soc. Rev. 2009, 38, 2178; [PubMed: 19623342]
- [16]. Wittkopp A, Schreiner PR, Chem. Eur. J. 2003, 9, 407. [PubMed: 12532289]
- [17]. Okino T, Hoashi Y, Takemoto Y, Tetrahedron Lett. 2003, 44, 2817.
- [18]. a)For selected, recent reviews, see: Doyle AG, Jacobsen EN, Chem. Rev. 2007, 107, 5713; [PubMed: 18072808] b)Serdyuk OV, Heckel CM, Tsogoeva SB, Org. Biomol. Chem. 2013, 11, 7051. [PubMed: 24057617]
- [19]. a)Mei K, Jin M, Zhang S, Li P, Liu W, Chen X, Xue F, Duan W, Wang W, Org. Lett. 2009, 11, 2864; [PubMed: 19485350] b)Zhang X-J, Liu S-P, Lao J-H, Du G-J, Yan M, Chan ASC, Tetrahedron: Asymmetry 2009, 20, 1451;c)Uehara H, Barbas CF, Angew. Chem. Int. Ed. 2009, 48, 9848.
- [20]. Konishi H, Lam TY, Malerich JP, Rawal VH, Org. Lett. 2010, 12, 2028. [PubMed: 20359172]
- [21]. a)Wenzel AG, Jacobsen EN, J. Am. Chem. Soc. 2002, 124, 12964; [PubMed: 12405820] b)Huang H, Jacobsen EN, J. Am. Chem. Soc. 2006, 128, 7170; [PubMed: 16734464] c)Puglisi A, Raimondi L, Benaglia M, Bonsignore M, Rossi S, Tetrahedron Lett. 2009, 50, 4340.
- [22]. The structural assignment of 33 was confirmed after N–O reductive cleavage (see SI for details).

- [23]. 5-membered nitrones under these conditions suffered from poor yields (<10%) due to the relatively slower reaction rate consistent with the same observation for [3+2]-cycloadditions (cf. ref. 9b). When the same conditions were applied to a 7-membered nitrone, only a small amount of desired product was observed along with decomposition, perhaps due to prolonged acidic treatment: Imada Y, Okita C, Maeda H, Kishimoto M, Sugano Y, Kaneshiro H, Nishida Y, Kawamorita S, Komiya N, Naota T, *Eur. J. Org. Chem.* 2014, 26, 5670.
- [24]. a)Elsworth JF, Lamchen M, *J. Chem. Soc. C.* 1968, 2423;b)Ali Sk. A., Almuallem HA, *Tetrahedron* 1992, 48, 5273.
- [25]. At this stage, the optical rotation, and thus absolute configuration of 31, was confirmed after reductive cleavage of the N–O bond (see SI for details).
- [26]. a)Cheng L, Han X, Huang H, Wong MW, Lu Y, *Chem. Comm.* 2007, 4143;b)Ayats C, Hensler AH, Dibello E, Pericàs MA, *ACS Catal.* 2014, 4, 3027.
- [27]. a)Galimovskiy F, Bianchetti G, Weiser R, *Monatsch. Chem.* 1953, 84, 1221;b)Schöpf C, Kauffmann T, Berth P, Bundschuh W, Dummer G, Fett H, Habermehl G, Wieters E, Wüst W, Liebigs *Annalen* 1957, 608, 88;c)Chen L-J, Hou D-R, *Tetrahedron: Asymmetry* 2008, 19, 715.
- [28]. For some products (20, 22, 24, and 26) we obtained their O-benzoylated adducts for structure confirmation (see SI) due to the complicating equilibrium between cyclic and acyclic forms in CDCl₃. For example, see: Pesciaioli F, De Vincentiis F, Galzerano P, Bencivenni G, Bartoli G, Mazzanti A, Melchiorre P, *Angew. Chem. Int. Ed.* 2008, 47, 8703.
- [29]. a)Compère D, Marazano C, D BC, *J. Org. Chem.* 1999, 64, 4528;b)Felpin F-X, Lebreton J, *J. Org. Chem.* 2002, 67, 9192; [PubMed: 12492320] c)Klingler F-D, Sobotta R, 2006, U.S. Patent 2006014791;d)Birman V, Jiang H, L X, *Org. Lett.* 2007, 9, 3237; [PubMed: 17658751] e)Krishnan S, Bagdanoff JT, Ebner DC, Ramtohul YK, Tambar UK, Stoltz BM, *J. Am. Chem. Soc.* 2008, 130, 13745. [PubMed: 18798630]
- [30]. Driessens F, Hootelè C, *Can. J. Chem.* 1991, 69, 211.
- [31]. a)Dwoskin LP, Crooks PA, *Biochem. Pharmacol.* 2002, 63, 89; [PubMed: 11841781] b)Zheng G, Dwoskin LP, Deacuic AG, Norrholm SD, Crooks PA, *J. Med. Chem.* 2005, 48, 5551. [PubMed: 16107155]
- [32]. Pilli RA, Dias LC, *Synth. Commun.* 1991, 21, 2213.
- [33]. a)Gossinger E, *Tetrahedron Lett.* 1980, 21, 2229;b)Ali Sk. A., *Tetrahedron Lett.* 1993, 34, 5325 Any attempt to reproduce the result reported by Ali for his substrates 14b, 15b did not succeed in our hands. Instead, we observed a 1:1 mixture of regioisomers.
- [34]. This value was established at the final stage when epi-4 was isolated as the major product.
- [35]. Zheng G, Dwoskin LP, Crooks PA, *J. Org. Chem.* 2004, 69, 8514. [PubMed: 15549833]
- [36]. Ryan J, Šiau iulis M, Gomm A, Maciá B, O'Reilly E, Caprio V, *J. Am. Chem. Soc.* 2016, 138, 15798. [PubMed: 27960354]
- [37]. Silva RA, Estevam IHS, Bieber LW, *Tetrahedron Lett.* 2007, 48, 7680.
- [38]. Amara Z, Bernadat G, Venot P-E, Retailleau P, Troufflard C, Drège E, Le Bideau F, Joseph D, *Org. Biomol. Chem.* 2014, 12, 9797. [PubMed: 25320963]

Scheme 1.

Selected piperidine-containing natural products, precedent for enantioselective functionalizations to generate such heterocycles, and two unique approaches based on using nitrones.

Scheme 2.

Total syntheses of (-)-lobeline (**3**) and (-)-sedinone (**4**) using both variants of the developed nitronium Mannich chemistry: a) **32** (3.0 equiv), **38** (20 mol %), BzOH (40 mol %), CH_2Cl_2 , 23 °C, 48 h, 70%, 90% *ee*; b) $\text{Zn}(\text{BH}_4)_2$ (1.2 equiv), THF, $-78 \rightarrow 0$ °C, 4 h, 9:1 *dr*; c) TBSOTf (1.1 equiv), *i*-Pr₂NEt (2.0 equiv), CH_2Cl_2 , 0 $\rightarrow$ 23 °C, 0.5 h, 67% over 2 steps, 89% *ee*; d) IBX (1.1 equiv), CH_2Cl_2 , -20 °C, 4 h, 99%, 4:1 *rr*; e) **15** (1.5 equiv), CH_2Cl_2 , 0 $\rightarrow$ 23 °C, 22 h; f) Zn (10 equiv), CH_2O (6.0 equiv), AcOH, 23 °C, 4 h, 75–76% over 2 steps, ~1:1 *dr* (*cis:trans*) (**62**), 1:5.4 *dr* (**63**); g) HCl (conc., 1.3 equiv), *i*-PrOH, 60 °C, 12 h; h) **3**: CIDR, MeOH, 4 °C, 2 weeks, 90% over 2 steps; **4**: MeOH, 23 °C, 12 h, then recrystallization (hexanes/EtOAc), 23 $\rightarrow$ -20 °C, 73% over 2 steps.

Table 1.Exploration of substrate scope with various nitrones (**14**) and β -ketoacids (**15**).^[a] ^[a] Reactions were performed with **14** (0.50 mmol) and **15** (0.76 mmol) in air^[b] 2 h reaction time;^[c] performed in MeOH;^[d] 1.5 equiv of **14** with 1.0 equiv of **15**.

Table 2.

Exploration of varied catalysts to achieve enantioselective addition of acetophenone (**32**) to nitron **28**.^[a]

^[a] Reactions were performed with **28** (0.5 mmol) and **32** (1.5 mmol) in air

^[b] without added BzOH.

Table 3.Exploration of nitron scope using **32** under optimized conditions.^[a] ^[a]Reactions were performed with **17** (0.5 mmol) and **32** (1.5 mmol) in air.

Table 4.

Exploration of substrate scope with nitron **28** using methyl ketones **12** under optimized conditions.^[a]

^[a] Reactions were performed with **28** (0.5 mmol) and **12** (1.5 mmol) in air

^[b] 16 h reaction time

^[c] ee was determined after *O*-benzoylation

^[d] combined yield

^[e] major regioisomer.