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# A Regio- and Diastereoselective Intramolecular Nitrone Cycloaddition for Practical 3- and 2,3-Disubstituted Piperidine Synthesis from γ-Butyrolactone

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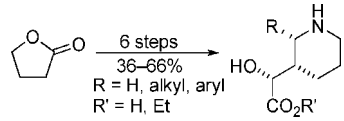


A fast and efficient route for diversity-oriented synthesis of 3- and 2,3-disubstituted piperidines, featuring an intramolecular nitrone cycloaddition with high regio- and diastereoselectivity, was achieved in six steps and 36−66% overall yield from commercially available γ-butyrolactone or 1,4-butanediol. A new *N*-alkenyl nitrone enoate was used in this intramolecular nitrone cycloaddition, and the regioselectivity, diastereoselectivity, and reversibility of this cycloaddition were investigated.

## Introduction

Piperidine-containing compounds are frequently observed in nature and used as bioactive agents, prompting ongoing interest in synthetic methods allowing for efficient access to functionalized piperidines.[1] Both 3- and 2,3-disubstituted piperidines are interesting classes of bioactive piperidine.[1a,d,g,2] As these compounds are used in medicinal and clinical applications,[1a] efficient and versatile methods amenable to accessing this class of compounds with selectivity are desirable. Recent 3- and 2,3-disubstituted piperidine syntheses have used strategies including tandem hydrozirconation−iodination−cyclization of *N*-allyl β-amino esters,[2a] ring opening of chiral epoxy alcohols,[2b] ring expansion of β-lactams,[2c] stereoselective Ireland−Claisen rearrangement and Michael addition,[2d] and cross-coupling and cyclization of olefins and imines.[2e]

The tandem nitrone cycloaddition/N−O bond reduction strategy is well represented in the syntheses of heterocycles such as azepanes, pyrrolidines, piperidones, indolizidines, and piperidines.[3−5] The efficiency of these transformations, however, can be limited by the regio- and stereochemical fidelity of the nitrone cycloaddition. This prompted our interest in examining the practical utility of this strategy in accessing substituted piperidines. Herein reported is a rapid entry to new 3- and 2,3-disubstituted piperidines, featuring an intramolecular nitrone cycloaddition between an *N*-alkenyl nitrone and an enoate dipolarophile.[4] This six-step sequence (Scheme 1) proceeded

(1) For recent reviews of piperidine synthesis, see: (a) Kaellstroem, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601–635. (b) De Risi, C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry* **2008**, *19*, 131–155. (c) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207. (d) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80. (e) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101–130. (f) Fraser, H. L.; Floyd, M. B.; Sosa, A. C. B. *Prog. Heterocycl. Chem.* **2005**, *17*, 261–303. (g) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (h) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (i) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun. (Cambridge, U.K.)* **1998**, 633–640.

(2) For recent reports of 3- and 2,3-disubstituted piperidine synthesis, see: (a) Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 2473–2476. (b) Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem.* **2008**, 1789–1796. (c) D'Hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4575–4584. (d) Garrido, N. M.; García, M.; Díez, D.; Sánchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687–1690. (e) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514–7516. (f) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3619–3622. (g) Davis, F. A.; Ramachandar, T. *Tetrahedron Lett.* **2008**, *49*, 870–872. (h) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun. (Cambridge, U.K.)* **2006**, 2156–2158. (i) Liang, N.; Srinivas, P.; Datta, A. *Tetrahedron Lett.* **2005**, *46*, 7221–7223. (j) Pedersen, C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 115–122. (k) For selected recent reports on the biological activities of 3- and 2,3-disubstituted piperidines, see: Nencetti, S.; Demontis, G. C.; Mazzoni, M. R.; Betti, L.; Banti, I.; Rossello, A.; Lapucci, A. *J. Pharm. Pharmacol.* **2008**, *59*, 1439–1445. (l) Jin, J.; Wang, Y.; Wang, F.; Shi, D.; Erhard, K. F.; Wu, Z.; Guida, B. F.; Lawrence, S. K.; Behm, D. J.; Disa, J.; Vaidya, K. S.; Evans, C.; McMillan, L. J.; Rivero, R. A.; Neeb, M. J.; Douglas, S. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2860–2864.

(3) For reviews, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285. (b) Gothelf, K. V.; Jørgensen, K. A. In *The Chemistry of Heterocyclic Compounds, Volume 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002. (c) Jones, R. C. F.; Martin, J. N. In *The Chemistry of Heterocyclic Compounds, Volume 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909. (e) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425. (f) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, New York, 1991; Vol. 4, pp 1111−1168. (g) Confalone, P. N.; Huie, E. M. *Org. React. (N.Y.)* **1988**, *36*, 1–173. (h) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403. (i) Oppolzer, W. *Angew. Chem., Int. Ed.* **1977**, *16*, 10–23. (j) Padwa, A. *Angew. Chem., Int. Ed.* **1976**, *15*, 123–180. (k) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495. (l) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565–632.



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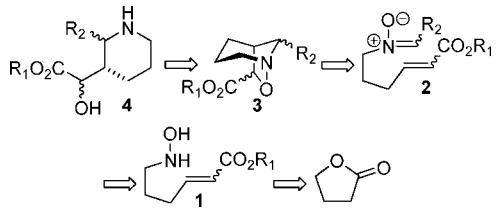
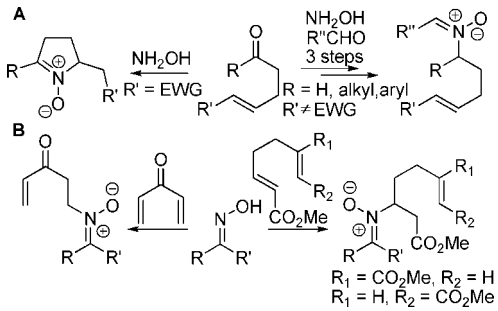
**SCHEME 1. Retrosynthetic Analysis of the Route to 3- and 2,3-Disubstituted Piperidines from γ-Butyrolactone**



**SCHEME 2. Previous *N*-4-Alkenyl Nitrone Syntheses Have Used (A) Oxime Formation and Reduction[4a–f,h–j,l,m,q] or (B) 1,3-Azaprotio Cyclotransfer[4g,k,n–p]**



with good to excellent regio- and diastereoselectivity and furnishes 3- and 2,3-disubstituted piperidine cores in 36−66% overall yield from commercially available synthons such as γ-butyrolactone or 1,4-butanediol. The key step was envisioned to be the construction of the isoxazolidine **3** from an *N*-alkenyl nitrone **2**.

This approach required resolution of three issues: first, a practical preparation of the *N*-alkenyl hydroxylamine **1** from γ-butyrolactone, second, the suppression of the competing intramolecular Michael addition during the formation of nitrone **2** from **1**, and third, the regio- and diastereoselectivity of the cycloaddition of **2** to provide **3**.

## Results and Discussion

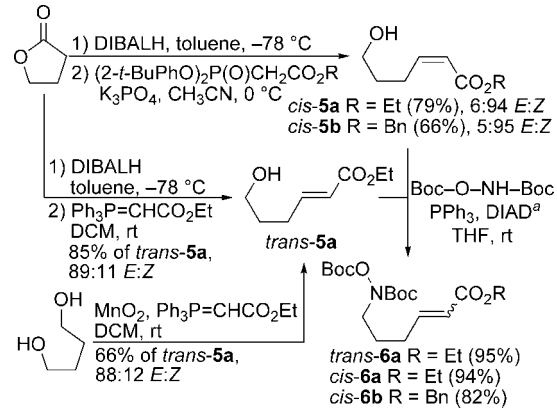
**Preparation of the Nitrone Precursors.** *N*-4-Alkenyl nitrone formation has been accomplished via either oxime formation followed by reduction[4a−f,h−j,l,m,q] or 1,3-azaprotio cyclotransfer[4g,k,n−p] (Scheme 2).

The oxime formation and reduction method is limited by the spontaneous cyclization of *N*-4-alkenyl oximes with double bonds substituted by electron-withdrawing groups (EWGs) (Scheme 2A).[6] Furthermore, a general procedure for the preparation of the ketone or aldehyde precursors has not been reported, with the starting point typically from allyl halides and alcohols,[4b,c] various esters and ketones,[4a,d–f,h,i,l,m] an oxazolidinone,[4j] and D-arabinose.[4q]

The 1,3-azaprotio cyclotransfer reaction developed by Grigg et al.[4g,k,n–p] is an elegant method for accessing *N*-4-alkenyl nitrones containing electron-deficient dipolarophiles (Scheme 2B). However, the necessary presence of two sites where 1,3-azaprotio cyclotransfer can take place introduces the additional complication of regioselectivity in the reaction of oximes with nonsymmetrical 1,5-dienes.

It was speculated that either γ-butyrolactone or 1,4-butanediol, both commercially available, could serve as cost-effective starting points for *N*-4-alkenyl nitrone synthesis. An ancillary advantage of the former starting material is that substituted

**SCHEME 3. Preparation of *cis*- and *trans*-*N*-4-Alkenyl Boc-Protected Hydroxylamines 6[a]**



[a] Diisopropyl azodicarboxylate (DIAD).

γ-butyrolactones are also easily accessible.[7] The sequence (Scheme 3) commenced with the reduction of γ-butyrolactone using DIBALH in toluene to give tetrahydrofuran-2-ol, which was used directly in the *Z*-selective Horner−Wadsworth−Emmons reaction employing Touchard's[8] modified Ando phosphonoacetates.[9]

The reaction proceeded with excellent *Z* selectivities for both the ethyl and benzyl olefins, providing *cis*-**5a** and *cis*-**5b** in 79% and 66% isolated yields, respectively, over two steps. The corresponding trans olefin, *trans*-**5a**, could be prepared with *E* selectivity (89:11 *E*:*Z*) in 85% yield over two steps via a DIBALH reduction and Wittig olefination. The alternative route, involving a one-pot $MnO_2$ oxidation and Wittig olefination of 1,4-butanediol,[10] provided *trans*-**5a** in 66% yield after 2 days at room temperature.

(4) For previous syntheses of *N*-4-alkenylnitrones, as well as reports of their use in the synthesis of piperidine and azepane natural products, see: (a) Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722–6723. (b) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, *45*, 4391–4394. (c) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497–3509. (d) Holmes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265–6. (e) LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363–8. (f) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393–1405. (g) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991**, *47*, 8297–8322. (h) Holmes, A. B.; Hughes, A. B.; Smith, A. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 633–43. (i) Collins, I.; Nadin, A.; Holmes, A. B.; Long, M. E.; Man, J.; Baker, R. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2205–2215. (j) Rudge, A. J.; Collins, I.; Holmes, A. B.; Baker, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2320–2322. (k) Saba, I. S.; Frederickson, M.; Grigg, R.; Dunn, P. J.; Levett, P. C. *Tetrahedron Lett.* **1997**, *38*, 6099–6102. (l) Hems, W. P.; Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1393–1396. (m) Tan, C.-H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1397–1400. (n) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P. *Chem. Commun. (Cambridge, U.K.)* **2000**, 2035–2036. (o) Dunn, P. J.; Graham, A. B.; Grigg, R.; Saba, I. S.; Thornton-Pett, M. *Tetrahedron* **2002**, *58*, 7701–7713. (p) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P.; Thornton-Pett, M. *Tetrahedron* **2002**, *58*, 7727–7733. (q) Moutel, S.; Shipman, M.; Martin, O. R.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2005**, *16*, 487–491.

(5) For a review on the use of *N*-alkenyl nitrones in natural product synthesis, see: (a) Holmes, A. B.; Bourdin, B.; Collins, I.; Davison, E. C.; Rudge, A. J.; Stork, T. C.; Warner, J. A. *Pure Appl. Chem.* **1997**, *69*, 531–536.

(6) For an example, see page 6937 of: Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929–6952.

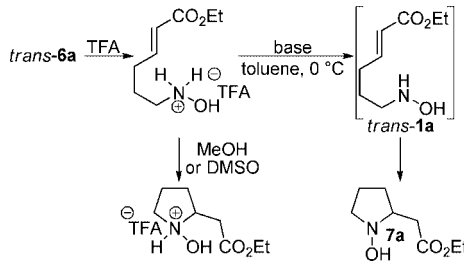
(7) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292.

(8) (a) Touchard, F. P.; Capelle, N.; Mercier, M. *Adv. Synth. Catal.* **2005**, *347*, 707–711. (b) Touchard, F. P. *Eur. J. Org. Chem.* **2005**, 1790–1794.

(9) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939. (c) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408. (d) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.

(10) Phillips, D. J.; Pillinger, K. S.; Li, W.; Taylor, A. E.; Graham, A. E. *Chem. Commun. (Cambridge, U.K.)* **2006**, 2280–2282.

**SCHEME 4. Deprotection of *trans*-6a and Reactions of the Resulting Hydroxylamine**




Synthesis of the Boc-protected hydroxylamines **6** was achieved by a Mitsunobu reaction between **5** and Boc-protected hydroxylamine,[11] the latter prepared according to the procedure of Stazak,[12] and proceeded in 82−95% yield. As mentioned previously, the alternative route via oxime formation and reduction would lead to rapid intramolecular cyclization.[6]

In summary, this synthesis provided *cis*- and *trans*-**6** on a multigram scale and 54−75% overall yield in only three steps from the readily available $\gamma$-butyrolactone.

**Formation of Nitrone Cycloadduct *trans*-3a from *trans*-1a with Suppression of the Competing Michael Addition.** Removal of the Boc groups was readily achieved in neat TFA. The resulting TFA salt, however, was not stable due to the proximity of the enone ester and hydroxylamine moieties (Scheme 4).[13] Complete decomposition to **7a** in the presence of base at 0 °C in toluene occurred in less than 15 min. In polar solvents such as methanol or DMSO, immediate decomposition of the salt was observed by $^1$H NMR spectroscopy, even in the absence of base.

Hydroxylamines are known to cyclize intramolecularly in the presence of an olefin.[13] When the olefin is unactivated, the cyclization proceeds via a "reverse Cope" mechanism,[13c−g] as shown in Scheme 5A. This cyclization is sensitive to the alkyl substituents on the olefin[13f] due to a tight 5-exo-trig transition structure. When the olefin is not substituted or monosubstituted at C-4 (**8a**, **8b**), the cyclization occurs rapidly at elevated temperatures.[13b] If the olefin substitution is at C-5 in the trans geometry (**8c**), the cyclization is prevented by steric hindrance. In the case of hydroxylamine cyclization in the presence of an activated olefin such as **10** (Scheme 5B), the mechanism switches to a Michael addition via a 6-endo-trig transition structure.[13e] These precedents, taken together, suggest that Michael addition is the most likely pathway for the intramolecular cyclization of hydroxylamine *trans*-**1a**.

Using *trans*-**1a**·TFA as a model substrate, a series of conditions were screened to suppress this Michael addition by promoting nitrone formation with use of excess formaldehyde (Table 1).

Conditions previously used[4b,c,q] for the cycloaddition of *N*-4-alkenyl nitrones derived from formaldehyde were first examined.

**SCHEME 5. (A) Examples of the Reverse Cope cyclization of Unactivated *N*-4-Alkenylhydroxylamines.[13b] (B) Michael Addition over Reverse Cope Cyclization in an Activated *N*-4-Alkenylhydroxylamine[13e]**

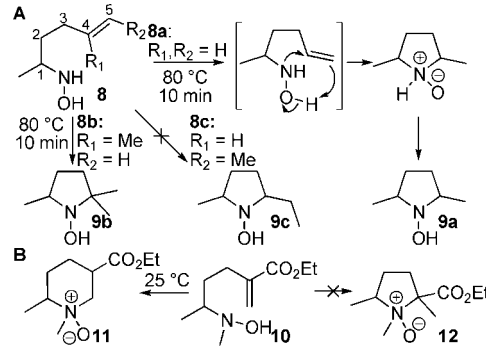
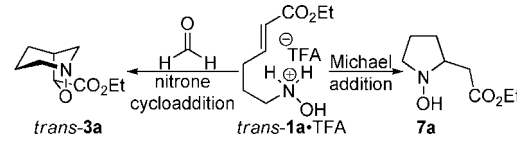



**TABLE 1. Nitrone Formation and Cycloaddition vs Michael Addition**




| entry[a] | solvent | $T$ (°C) | equiv of $(CH_2O)_n$ | **3a/7a**[b] | yield of *trans*-**3a** (%) |
|---|---|---|---|---|---|
| 1 | toluene | 0−110 | 10[c] | *d* | 25−32[e] |
| 2 | toluene | 60 | 2 | <99:1 | n.d.[f] |
| 3 | toluene | 80 | 2 | <99:1 | 90 |
| 4 | toluene | 100 | 2 | <99:1 | n.d.[f] |
| 5 | toluene | 110 | 2 | <99:1 | n.d.[f] |
| 6 | $CHCl_3$ | 60 | 2 | 70:30 | n.d. |
| 7 | toluene | 25 | 10 | >1:99 | *g* |
| 8 | toluene | 0 | 10 | >1:99 | *g* |

[a] All reactions were performed using MS3Å powder and 2 equiv of diisopropylethylamine (DIEA) to liberate the TFA salt. [b] Ratios were estimated by $^1$H NMR spectroscopy of the reaction mixtures after workup. [c] Gaseous formaldehyde was generated from the specified equivalents of $(CH_2O)_n$ according to the procedure of Oppolzer.[4b,c] [d] Ratio estimation was precluded by the formation of a complex reaction mixture. [e] Range of yields from three attempts. [f] Yield was not determined, but crude $^1$H NMR spectra and crude masses obtained after workup were similar to those of entry 3. [g] No *trans*-**3a** was detectable in the reaction mixture.

These involved first forming the nitrone by bubbling gaseous formaldehyde, generated by heating paraformaldehyde ($(CH_2O)_n$) above 120 °C, through the reaction mixture at 0 °C, and then allowing the cycloaddition to occur by heating the reaction to 110 °C overnight. Unfortunately, complex reaction mixtures and low isolated yields were obtained (entry 1). Only when formaldehyde was generated in situ from excess $(CH_2O)_n$ in toluene, at temperatures greater than 60 °C, was nitrone formation, followed by rapid intramolecular cycloaddition to form *trans*-**3a**, preferred over the competing intramolecular Michael addition to **7a** and other decomposition reactions (entries 2−5). Raising the reaction temperature above 60 °C did not result in yield improvement, on the basis of the nearly identical NMR spectra of the crude reaction mixtures (entries 2−5). Use of a more polar solvent or lower reaction temperature led to more of the cyclization adduct **7a** (entries 6−8).

The stereo- and regiochemistry of the cycloadduct *trans*-**3a** were elucidated by 2D-NMR spectroscopy (Figure 1A). The correlation between axial H-3 (H-3$_{ax}$) and H-6 indicated that the trans stereochemistry of the dipolarophile had been preserved. Evidence for the shown regiochemistry of *trans*-**3a** was

(11) For a discussion of this strategy for hydroxylamine synthesis, see: (a) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593–2595. (b) Knight, D. W.; Leese, M. P.; De Kimpe, N *Tetrahedron Lett.* **2001**, *42*, 2597–2600.

(12) Staszak, M. A.; Doecke, C. W. *Tetrahedron Lett.* **1993**, *34*, 7043–7044.

(13) Intramolecular cyclization of *N*-4-alkenylhydroxylamines was first reported by House, who proposed a radical mechanism for the reaction: (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1975**, *41*, 855–863. (b) Black, D.; St., C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. The reaction was shown to proceed via a reverse-Cope mechanism by Ciganek and Oppolzer. (c) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007–9. (d) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139–3140. (e) Ciganek, E.; Read, J. M., Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795–802. (f) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803–7. (g) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243–269.

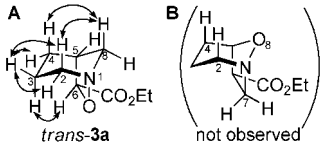
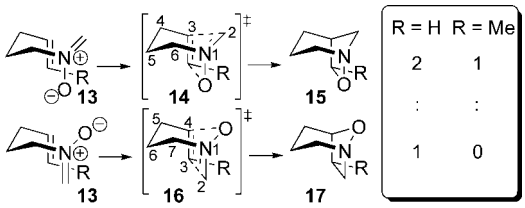



**FIGURE 1.** (A) Correlations observed in *trans*-**3a** from 2D-NOESY data. (B) Unobserved regioisomer.

**SCHEME 6. Regioselectivity from Two Transition Structures during Intramolecular Cycloaddition of *N*-4-Alkenyl Nitrones[4b,c]**



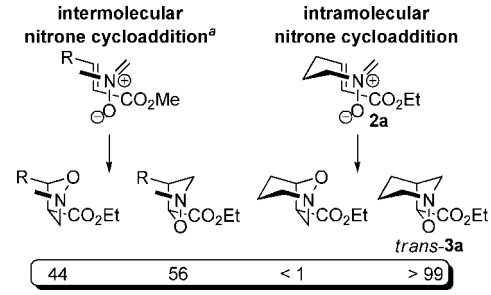

provided by the correlations between H-8$_{ax}$ and H-4$_{ax}$ and H-2$_{ax}$. In the regioisomer that was not observed (Figure 1B), the positions of C-8 and the oxygen atom of the N−O bond are reversed, and thus both equatorial H-8 (H-8$_{eq}$) and H-8$_{ax}$ would lie on the opposite face of the molecule to H-4$_{ax}$ and H-2$_{ax}$.

While the high diastereoselectivity of this nitrone cycloaddition was expected, the regioselectivity was mechanistically intriguing. Regioselectivity of nitrone cycloadditions is well-known to diverge from that of typical cycloaddition reactions.[14] Studies using frontier molecular orbital theory on the regiochemical outcomes of nitrone cycloadditions have deconvoluted the complex stereoelectronic nature of the substituent effect in the intermolecular case.[15] The case with intramolecular nitrone cycloadditions is further complicated by steric factors, although efforts continue to be made in finding rules of general applicability.[3] Oppolzer and co-workers have observed that, in intramolecular nitrone cycloadditions of *N*-alkenyl nitrones, regioselectivity was sometimes the opposite of that seen in the intermolecular homologues and could not be explained by stereoelectronic considerations alone.[4b,c]

The unusual regioselectivity pattern for intramolecular *N*-4-alkenyl cycloaddition was explained by an entropically favored six-membered ring transition structure (**14**, Scheme 6).[4b,c]

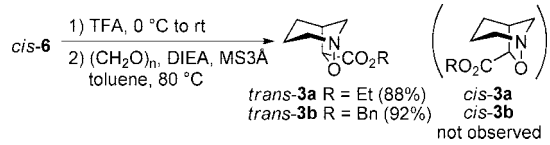
As carbon−carbon bond formation is likely to be more developed than carbon−oxygen bond formation in the transition state,[4b,c,16] a six-membered ring transition structure (**14**), defined by the dominant carbon−carbon bond formation, would be entropically favored over a seven-membered ring transition structure **16**, resulting in **15** as the major regioisomer, rather than **17**. This kinetic advantage was invoked to account for the regioselectivities observed in some intramolecular nitrone cycloaddition reactions.[4b,c] When the dipolarophile moiety in **13** is unsubstituted at the terminal carbon of the alkene (Scheme 6, R = H), this entropic control is in competition with the stereoelectronic control, leading to a mixture of regioisomers in the intramolecular mode. When there is a methyl substituent at the terminal carbon (**13**, R = Me), the dipolarophile moiety

**SCHEME 7. Reversal of Regioselectivity in an Intramolecular Nitrone Cycloaddition[a]**




[a] R = CH(OBn)CH$_3$, data from Annunziata et al.[18]

**SCHEME 8. Attempted Preparation of *cis*-3a and *cis*-3b**




is effectively disubstituted at both ends with alkyl groups. With little direction from stereoelectronic control,[17] regioselectivity in this case is controlled through the entropically favored six-membered ring transition structure (Scheme 6, R = Me), leading to the exclusive formation of **15**.

In the case of the nitrone **2a** here, the dipolarophile moiety is substituted by an EWG (Scheme 7, intramolecular nitrone cycloaddition) and is thus substituted at both ends with groups of opposite electronic characteristics. While this intramolecular cycloaddition has not been reported, an intermolecular analogue is known (Scheme 7, intermolecular nitrone cycloaddition).[18] In the intermolecular case, the stereoelectronic direction is weak, resulting in little preference for either regioisomer. If Oppolzer's hypothesis of entropic control is applicable here, the intramolecular nitrone cycloaddition of **2a** should show a higher level of regioselectivity preference for *trans*-**3a** than that in the intermolecular case. The only question that remained was the extent to which this change in regioselectivity would occur. The formation of *trans*-**3a** as the only detectable regioisomer (Scheme 7, intramolecular nitrone cycloaddition) is consistent with Oppolzer's rationale and affirms entropic considerations as the dominant control over stereoelectronics in these intramolecular nitrone cycloadditions.

**Diastereoselectivity of the Intramolecular Nitrone Cycloaddition of *cis*-6.** With conditions for the preparation of *trans*-**3a** from *trans*-**6a** developed, preparation of the diastereomeric isoxazolidines *cis*-**3** from *cis*-**6** was attempted using these conditions. However, the TFA salts obtained after deprotection of *cis*-**6** did not lead to the expected cis cycloadducts. Instead, the diastereomeric ethyl and benzyl esters *trans*-**3a** and *trans*-**3b**, respectively, were formed (Scheme 8).

Thus, in contrast to the expected[3] outcome (Figure 2), both *trans*- and *cis*-*N*-4-alkenyl hydroxylamines were found, under these reaction conditions, to undergo nitrone formation and intramolecular cycloaddition to form the trans cycloadducts.

A plausible mechanism behind this loss of stereochemical fidelity is shown in Scheme 9.

(14) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798–5800.
(15) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57–64. (b) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287–7301. (c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315. (d) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81–90.
(16) Magnuson, E. C.; Pranata, J. *J. Comput. Chem.* **1998**, *19*, 1795–1804.
(17) Houk, K. N.; Domelsmith, L. N.; Strozier, R. W.; Patterson, R. T. *J. Am. Chem. Soc.* **1978**, *100*, 6531–6533.
(18) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Eur. J. Org. Chem.* **1998**, 1823–1832.

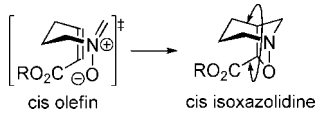
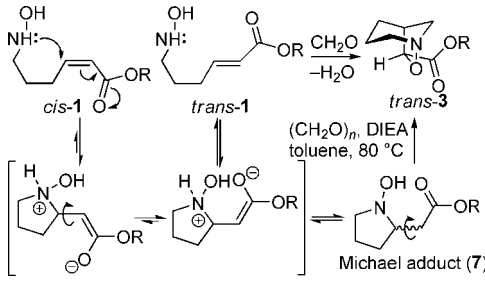



**FIGURE 2.** Diastereoselectivity expected in the nitrone cycloaddition of *cis*-**3**.

**SCHEME 9. Mechanism for the Formation of *trans*-3 from *cis*-1 via Reversible Michael Addition and Double-Bond Isomerization**



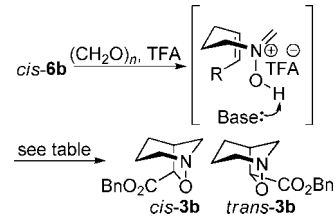

Upon release of the free hydroxylamine, *cis*-**1** undergoes rapid intramolecular Michael addition to form a zwitterionic intermediate. This either undergoes bond rotation and retro-Michael addition to form the thermodynamically more stable *trans*-**1** or proton transfer to form Michael adduct **7**. The Michael addition is reversible, as confirmed by an experiment in which **7a** (R = Et) was subjected to cycloaddition conditions (Scheme 9). After 20 h of heating at 80 °C, quantitative formation of *trans*-**3a** was observed by $^1$H NMR spectroscopy. In the presence of excess formaldehyde and dehydrating agent, the nitrone is formed irreversibly. The exclusive formation of *trans*-**3a** suggests that the isomerization of the enoate *cis*-**1** via the reverse Michael reaction occurs much faster than nitrone formation. This is consistent with previous observations regarding the instability of *cis*- and *trans*-**1**·TFA, even in the absence of base.

To circumvent this isomerization problem, conditions were sought that would promote nitrone formation while avoiding the Michael reaction. As the $^1$H NMR ($CDCl_3$) spectrum of the TFA salt obtained after deprotection of the Boc-protected hydroxylamines *cis*-**6** indicated that the *Z*-geometry of the double bond was conserved, formation of the nitrone by inclusion of 2 equiv of $(CH_2O)_n$ during the deprotection step was attempted. After removal of the TFA under reduced pressure, the $^1$H NMR spectrum of the crude oil obtained indicated the nitrone had been formed, with doublets at 6.75 and 6.50 ppm observed in $CDCl_3$, and that the *Z*-geometry of the double bond was conserved. Although neat TFA has not been used previously as a solvent in nitrone formation, it is known that this reaction can exhibit general acid catalysis.[19] While stable over a period of a few hours, extensive nitrone decomposition was observed by $^1$H NMR after 26 h at room temperature.

With conditions for nitrone formation developed, nitrone cycloaddition was performed at 80 °C in dry toluene or $CH_3CN$. However, no cycloadduct was detected in the reaction mixture (Table 2, entries 1 and 2). On the hypothesis that residual TFA was protonating the nitrone and thereby preventing cycloaddition from occurring, a variety of organic and inorganic bases were investigated as additives (entries 3−16).

(19) For studies on the mechanism of nitrone formation, see: (a) Fett, R.; Simionatto, E. L.; Yunes, R. A. *J. Phys. Org. Chem.* **1990**, *3*, 620–626. (b) Travalon, S. A.; Brighente, I. M. C.; Yunes, R. A. *Int. J. Chem. Kinet* **2002**, *34*, 685–692, and references cited therein.

**TABLE 2. Optimization of Nitrone Cycloaddition Yield and Diastereomeric Ratio**




| entry[a] | base (equiv) | solvent | *T* (°C) | *cis*-**3b** (% yield)[b] | dr (cis/trans)[b] |
|---|---|---|---|---|---|
| 1 | n/a | toluene | 80 | <1 | n.d. |
| 2 | n/a | $CH_3CN$ | 80 | <1 | n.d. |
| 3 | 2,6-lutidine (2) | $CH_3CN$ | 80 | 9 | 13:87 |
| 4 | pyridine | pyridine | 80 | <1 | <1:99 |
| 5 | DIEA (2) | toluene | 80 | 12 | 18:82 |
| 6 | DIEA (2) | $CH_3CN$ | 80 | 34 | 70:30 |
| 7 | DBU (2) | $CH_3CN$ | 80 | 44 | 73:27 |
| 8 | $K_3PO_4$ (30) | $CH_3CN$ | 80 | 45 | >99:1 |
| 9 | $K_2CO_3$ (30) | $CH_3CN$ | 80 | 55 | 82:18 |
| 10[c] | $K_3PO_4$ (30) | $CH_3CN$ | 80 | 62 | 91:9 |
| 11[c] | $K_2CO_3$ (30) | $CH_3CN$ | 80 | 62 (64[d]) | 92:8 |
| 12[c] | $K_3PO_4$ (5) | $CH_3CN$ | 80 | 51 | 70:30 |
| 13[c] | $K_3PO_4$ (30) | THF | 67 | 58 | 87:13 |
| 14[c,e] | $K_2CO_3$ (30) | $CH_3CN$ | 80 | 72 (65[d]) | 91:9 |
| 15[c,e] | A-A21 (30)[f] | $CH_3CN$ | 80 | 67 | 83:17 |
| 16[c,e] | A-A21 (10)[f] | $CH_3CN$ | 80 | 65 | 84:16 |

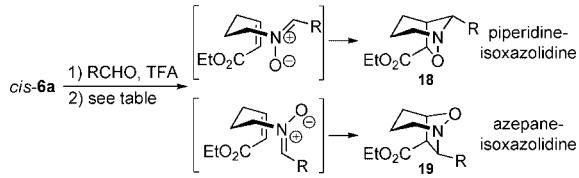
[a] Reactions were performed on a 0.1 mmol scale. [b] Estimated by $^1$H NMR spectroscopy. [c] MS3Å were used. [d] Isolated yield. [e] $CH_3CN$ was distilled from $P_2O_5$ onto MS3Å. [f] Amberlyst A-21.

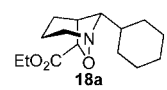
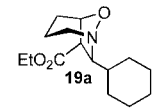
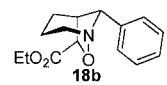
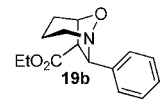
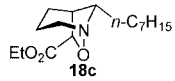
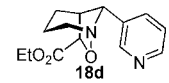
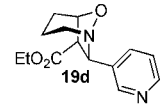
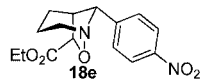
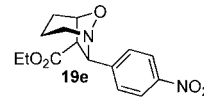
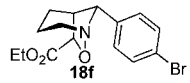
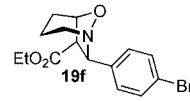
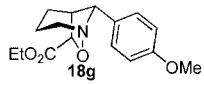
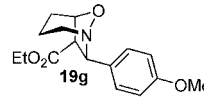
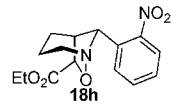
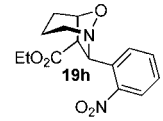
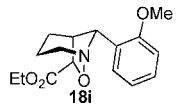
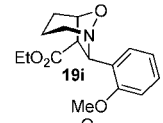
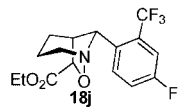
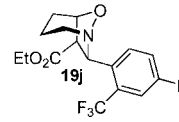
The results (Table 2) indicated that the dr obtained depended primarily on how rapid and efficient the removal of TFA was. If any TFA remained, significant isomerization of *cis*-**6b** was observed. Thus, weak bases, such as 2,6-lutidine (entry 3) and pyridine (entry 4), allowed the cycloaddition to occur but gave the undesired trans diastereomer as the major product. With the stronger base[20] diisopropylethylamine (DIEA) in a nonpolar solvent such as toluene, the trans cycloadduct was also the major product (entry 5). This may reflect slower acidity-quenching in nonpolar solvents. Indeed, using the same base but switching to the more polar $CH_3CN$ gave the cis diastereomer as the major product, although the yield remained poor (entry 6). The stronger base DBU gave only marginal improvement in yield and dr (entry 7). Possible acid- or base-catalyzed isomerization of *cis*-**3b** after cycloaddition was ruled out by the fact that no difference in yield or dr was observed with reaction times between 15 min and 3 h at temperatures between 60 and 110 °C.

One limitation of the use of organic bases was the impracticality of using a larger number of equivalents. Therefore, large excesses of inorganic bases, which are much less soluble and thus easily removed by filtration, were investigated. When 30 equiv of anhydrous $K_3PO_4$ was used, a dramatic improvement in dr was observed (entry 8), with no *trans*-**3b** detected in the crude reaction mixture. The less basic $K_2CO_3$ gave a reduced dr but a much cleaner reaction and thus a higher overall yield (entry 9). Use of 3 Å molecular sieve (MS3Å) powder with $K_2CO_3$ or $K_3PO_4$ resulted in a significant increase in yield (entries 10 and 11), and while the dr was reduced with $K_3PO_4$, it was increased with $K_2CO_3$.[21] Reducing the equivalents of $K_3PO_4$ lowered both yield and dr (entry 12), and changing the solvent to anhydrous THF gave a slightly lower yield and dr (entry

(20) Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019–1028.

**TABLE 3. Preparation of Disubstituted Piperidine− and Azepane−Isoxazolidines**




| entry [a] | solvent | $t$ (°C) | $t$ (h) | conv (%) [b] | piperidine-isoxazolidine | yield (%) [c] | azepane-isoxazolidine | yield (%) [c] | **18/19** [b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 80 | 2.5 | 46 |  **18a** | - [d] |  **19a** | - [d] | - [d] |
| 2 | $CH_3CN$ | 80 | 20 | > 95 | | 85 | | - [d] | 91:9 |
| 3 | $CH_3CN$ | 80 | 72 | 53 |  **18b** | - [d] |  **19b** | - [d] | 92:8 |
| 4 | toluene | 110 | 20 | > 95 | | 71 | | 23 | 72:28 |
| 5 | $CH_3CN$ | 80 | 19 | > 95 |  **18c** | 84 | - [e] | - [e] | - [e] |
| 6 | toluene | 110 | 16 | > 95 |  **18d** | 64 |  **19d** | 34 | 70:30 |
| 7 | toluene | 110 | 20 | > 95 |  **18e** | 58 |  **19e** | 31 | 63:37 |
| 8 | toluene | 110 | 22 | > 95 |  **18f** | 65 |  **19f** | 29 | 70:30 |
| 9 | toluene | 110 | 14 | > 95 |  **18g** | 63 |  **19g** | 24 | 71:29 |
| 10 | toluene | 110 | 39 | > 95 |  **18h** | 69 |  **19h** | 24 | 74:26 |
| 11 | toluene | 110 | 14 | > 95 |  **18i** | 84 |  **19i** | 15 | 86:14 |
| 12 | toluene | 110 | 39 | > 95 |  **18j** | 65 |  **19j** | 8 | 86:14 |

[a] See the Experimental Section. [b] Ratios and conversions (conv) estimated from $^1$H NMR spectra of the crude reaction mixtures. [c] Isolated yields. [d] Yield/ratio was not determined. [e] The azepane regioisomer was neither detectable nor isolable.

13). However, a further increase in yield and dr was achieved by freshly distilling commercially available anhydrous $CH_3CN$ from $P_2O_5$ (entry 14). Alternate bases, such as an ion-exchange resin previously utilized[22] for TFA-scavenging, gave slightly cleaner reactions but reduced dr values (entries 15 and 16).

The applicability of these optimized conditions for nitrone formation and cycloaddition to a range of other aldehydes was then investigated using *cis*-**6a** (Table 3).

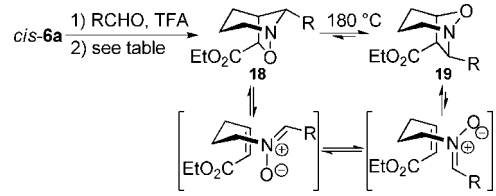
In the first examples attempted, using cyclohexanecarboxaldehyde and benzaldehyde as model aldehydes, complete formation of the nitrone−TFA salts was observed by $^1$H NMR after 30 min at room temperature in neat TFA.[23] When subjected to the previously optimized conditions using $K_2CO_3$ and MS3Å, **18a** was formed in high isolated yield (85%) after 20 h refluxing in $CH_3CN$ along with the regioisomeric azepane-isoxazolidine **19a** (entries 1 and 2).[24] The benzaldehyde-derived nitrone was significantly less reactive, with only 53% conversion observed

(21) MS3Å are much more effective dessicants for $CH_3CN$ than MS4Å or any commonly used dessicant apart from $P_2O_5$: (a) Burfield, D. R.; Gan, G.-H.; Smithers, R. H. *J. Appl. Chem. Biotechnol.* **1977**, *28*, 23–30. (b) Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42*, 3060–3065.

(22) Srinivasan, N.; Yurek-George, A.; Ganesan, A. *Mol. Diversity* **2005**, *9*, 291–293.

(23) Either in salt form or as the free bases, generated by the addition of excess DIEA, these nitrones were significantly more stable than their unsubstituted counterpart formed from formaldehyde, with no significant changes in their $^1$H NMR spectra observed after 6 days at room temperature.

**TABLE 4. Studies on Reversibility in the Intramolecular Nitrone Cycloaddition of Aliphatic and Aromatic Aldehyde-Derived Nitrones**




| entry[a] | solvent | $t$ (°C) | $t$ (h) | azepane-isoxazolidine product | yield of **19**(%)[b] | **18**/**19**[c] |
|---|---|---|---|---|---|---|
| 1 | DMSO | 110 | 18 | **19e** | *e* | *d* |
| 2 | DMAC | 110 | 24 | **19e** | *e* | *d* |
| 3 | DMSO | 110 | 22 | **19e** | *e* | 58:42 |
| 4 | DCB | 180 | 0.25 | **19e** | *e* | 54:46 |
| 5 | DCB | 180 | 2 | **19e** | *e* | 35:65 |
| 6 | DCB | 180 | 13 | **19e** | *e* | 13:87 |
| 7 | DCB | 180 | 29 | **19e** | 86 | <2:98 |
| 8 | DCB | 180 | 0.25 | **19a** | *e* | 87:13 |
| 9 | DCB | 180 | 40 | **19a** | 86 | 3:97 |
| 10 | DCB | 180 | 0.25 | **19d** | *e* | 61:39 |
| 11 | DCB | 180 | 40 | **19d** | 80 | <2:98 |
| 12 | DCB | 180 | 0.25 | **19j** | *e* | 80:20 |
| 13 | DCB | 180 | 16 | **19j** | *e* | 51:49 |
| 14 | DCB | 180 | 40 | **19j** | *e* | 31:69 |
| 15 | DCB | 180 | 80 | **19j** | 35 | 15:85 |

[a] See the Experimental Section. [b] Isolated yields. [c] Estimated from $^1$H NMR spectra of the crude reaction mixtures. [d] Decomposition was observed (see text). [e] Yield not determined.

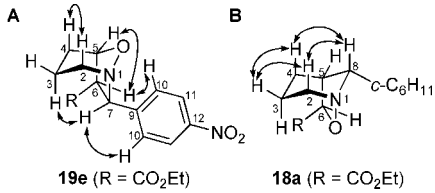



**FIGURE 3.** Key correlations observed in (A) **19e** and (B) **18a** from 2D-NOESY data.

after 72 h refluxing in $CH_3CN$ (entry 3). However, in toluene at 110 °C, the reaction was complete within 20 h, providing the piperidine− and azepane−isoxazolidines **18b** and **19b** in 71% and 23% isolated yields, respectively (entry 4).

Nitrones derived from octyl aldehyde (entry 5) and a variety of aryl aldehydes (entries 6−12) could also be converted to isoxazolidines in moderate to excellent isolated yields and with complete diastereoselectivity. The piperidine− and azepane−isoxazolidine regioisomers were always separable by flash column chromatography.

The regio- and stereochemistry of **18** and **19** were elucidated by 2D NMR spectroscopy. For the azepane−isoxazolidine **19e**, key correlations observed in the 2D NOESY data were those between H-3$_{ax}$ and H-7, H-7 and H-10, and H-10 and H-6, as well as the absence of any correlation between H-6 and H-3 (Figure 3A). Evidence for the axial orientation of H-8 in the piperidine isoxazolidines was provided by the correlations observed between H-8 and H-4$_{ax}$ and H-2$_{ax}$ (Figure 3B).

**Regioselectivity and Reversibility of the Nitrone Cycloaddition with Alkyl and Aryl Aldehydes.** Within the class of aryl aldehyde-derived nitrones (Table 3), a number of observations can be made regarding the regioselectivity and reversibility of this cycloaddition. Regioselectivity is not influenced by electron-donating substituents at the para position. In contrast, at both the para and ortho positions, electron-withdrawing substituents decrease the rate of cycloaddition and increase the proportion of the azepane regioisomer formed, although the piperidine−isoxazolidine was always the major product. Possibly due to steric hindrance in the transition structure leading to azepane formation, ortho-substituted aryl nitrones formed significantly more piperidine adduct than their para-substituted isomers (e.g., Table 3, entries 9 and 11).

In intermolecular cycloadditions with electron-deficient 1,2-disubstituted dipolarophiles, such as methyl crotonate, nitrones derived from aromatic or aliphatic aldehydes would be expected to give predominately the regioisomer resulting from addition of oxygen to the $\beta$-carbon.[25] Thus, as explained by Oppolzer, formation of the piperidine regioisomers as the major products in the intramolecular case results from entropic control,[4b,c] with, under these conditions, the kinetic product dominating.

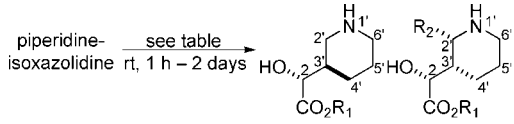
This led to the next issue of thermodynamic control and possible cycloaddition reversibility, given the differences in regioselectivity observed between $CH_3CN$ and toluene. For instance, going from 80 °C in $CH_3CN$ to 110 °C in toluene, the piperidine−azepane ratio decreased from 92:8 to 72:28 (Table 3, entries 3−4). In order to investigate this effect further, the cycloaddition was attempted in more polar and higher boiling solvents (Table 4).

In DMSO and *N,N*-dimethylacetamide (DMAC), complete decomposition was observed at 110 °C using the previously optimized cycloaddition conditions (entries 1 and 2), with neither **18e** nor **19e** detected in the $^1$H NMR spectrum of the crude reaction mixture. As the decomposition appeared to occur with formation of a dark residue on the $K_2CO_3$ after a few minutes of heating, cycloaddition in the absence of base was attempted. The TFA used in the deprotection step was removed by stirring the nitrone−TFA salt in dry $CH_2Cl_2$ with an alkylamine ion-exchange resin, which was removed after 15 min by filtration.

(24) When Oppolzer's[4b,c] conditions, or conditions previously discussed in this report (see Table 1) for the preparation of *trans*-**3a**, were employed, the Michael adduct **7a** was always obtained as the major product. This is likely due to the reduced reactivity of benzaldehyde and cyclohexanecarboxaldehyde compared to formaldehyde.

(25) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481–5484.

**TABLE 5. Results from Reductions of Piperidine−Isoxazolidines to Piperidines**




| entry [a] | piperidine-isoxazolidine | piperidine | conditions | yield (%) [b] |
|---|---|---|---|---|
| 1 | *trans*-**3a**•HCl | **20a** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 97 |
| 2 | *trans*-**3b** | **20b** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 97 |
| 3 | *cis*-**3b** | **21b** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 93 |
| 4 | *cis*-**3a**•HCl | **21a** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 86 |
| 5 | **18a**•HCl | **22a** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 97 |
| 6 | **18b**•HCl | **22b** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 96 |
| 7 | **18c**•HCl | **22c** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 91 |
| 8 | **18d** | **22d** | Zn, AcOH | 88 |
| 9 | **18e**•HCl | **22e** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 90 [c] |
| 10 | **18f** | **22f** | Zn, HCl (10%) | 98 |
| 11 | **18g**•HCl | **22g** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 93 |
| 12 | **18h**•HCl | **22h** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 83 [c] |
| 13 | **18i**•HCl | **22i** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 91 |
| 14 | **18j**•HCl | **22j** | Pd/C, $H_2$, *t*-BuOH–$H_2O$ | 95 |

[a] See the Experimental Section. [b] Isolated yield. [c] The $NO_2$ moiety of the corresponding isoxazolidine was reduced to an $NH_2$ group.

While significant decomposition was still observed when the cycloaddition was subsequently attempted without base in DMSO at 110 °C (entry 3), some isoxazolidine was visible in the crude $^1$H NMR spectrum, allowing estimation of the piperidine−azepane ratio. The ratio was similar to that observed at the same temperature in toluene (58:42 vs 63:37, respectively). Given the significant difference in polarity between toluene and DMSO, this indicated that the cycloaddition regioselectivity was not significantly influenced by solvent polarity.[26] Therefore, the less polar 1,2-dichlorobenzene (DCB) was used instead. After 2 h at 180 °C in DCB, inversion of regioselectivity was observed, with more azepane formed (entry 5, piperidine−azepane 35:65). The reaction also appeared to be significantly faster at this temperature, warranting an assessment of regioselectivity after 15 min (entry 4). As expected, since less time was allowed for cycloreversion, the piperidine−azepane ratio was higher at 54:46. While this reversibility has not been previously observed for *N*-4-alkenyl nitrones,[4] a number of examples exist for *C*-alkenyl nitrones.[27] Further evidence of reversibility was obtained by increasing the reaction time beyond 2 h (entries 6 and 7). Within 29 h, only trace amounts of the piperidine−isoxazolidine were detectable by $^1$H NMR spectroscopy, and the azepane−isoxazolidine was obtained in 86% isolated yield (entry 7). These results indicate that, as predicted by Oppolzer,[4b,c] the azepane−isoxazolidines **19**, resulting from stereoelectronic control, are the thermodynamically favored regioisomers in this cycloaddition.

(26) In the cycloaddition of an *N*-(3-oxo-4-pentenyl) nitrone, Grigg et al.[4o] observed an increase in regioselectivity from 1:1 in cyclohexane to 8:1 in DMSO and attributed this to the larger dipole moment of the preferred transition state.

(27) For examples of reversible intramolecular nitrone cycloadditions, see: (a) Horsley, H. T.; Holmes, A. B.; Davies, J. E.; Goodman, J. M.; Silva, M. A.; Pascu, S. I.; Collins, I. *Org. Biomol. Chem.* **2004**, *2*, 1258–1265. (b) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598–1602. For examples of reversible intermolecular nitrone cycloadditions, see: (c) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435–244. (d) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, C. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494–1514.

The reversibility of the cycloaddition was found to be general for aliphatic and aromatic nitrones, with those derived from cyclohexanecarboxaldehyde (entries 8 and 9) and pyridine-3-carboxaldehyde (entries 10 and 11) forming the corresponding azepane−isoxazolidines in good isolated yields within 40 h at 180 °C. Relatively hindered isoxazolidines such as the *ortho*-$CF_3$ substituted **18j**, which gave a high piperidine−azepane ratio of 86:14 at 110 °C in toluene, required longer periods at 180 °C for isomerization (entry 12−15). In this case, the low isolated yield appeared to result from decomposition of the nitrone at 180 °C when initially heated with base, as a dark, insoluble residue was formed on the $K_2CO_3$ and MS3Å. When the piperidine− and azepane−isoxazolidine cycloadducts **18j** and **19j** recovered after filtration were subsequently heated at 180 °C with MS3Å in the absence of base, no further decomposition was observed.

**N−O Bond Reduction.** With a regio- and diastereoselective route to the piperidine−isoxazolidines developed, the final step, N−O bond reduction, was investigated. When the ethyl ester isoxazolidines *trans*-**3a** and *cis*-**3a** were reduced as their free bases using Pd/C and hydrogen gas in *t*-BuOH-$H_2O$,[28] methanol, or ethanol, reproducible results could not be obtained, with varying amounts of decomposition observed (data not shown). In contrast, the benzyl ester isoxazolidines *trans*-**3b** and *cis*-**3b**, which form zwitterionic $\gamma$-amino acids, with the nitrogen center protonated, on reduction, were reproducibly obtained in excellent yield (Table 5, entries 2 and 3). On the assumption that the basicity of the ethyl ester piperidines might be causing their decomposition, *trans*-**3a** and *cis*-**3a** were reduced as their HCl salts. This procedure was reproducible and gave **20a** and **21a** in 97% and 86% yield, respectively (entries 1 and 4).

These conditions were used for reduction of the disubstituted piperidine−isoxazolidines **18a−j** (entries 5−14) and gave the corresponding piperidines in generally excellent yields. The *p*-bromoisoxazolidine **18f** underwent debromination as well as N−O bond cleavage to form **22b** in quantitative yield by $^1$H NMR spectroscopy. In this case, selectivity was achieved by using Zn in HCl (10%) instead, allowing the formation of **22f** in 98% yield (entry 10). The 3-pyridinylisoxazolidine **18d** was unstable as its HCl salt in the presence of Pd or Zn, with decomposition observed by TLC. However, Zn in acetic acid proved sufficiently mild, giving **22d** in 88% yield (entry 8).

In conclusion, a novel route for the diastereoselective synthesis of diversely substituted piperidines is presented. This sequence offers an efficient and rapid entry from readily available synthons using a new regio- and diastereoselective intramolecular nitrone cycloaddition with suppression of the competing Michael addition.

## Experimental Section

**General Procedure for the Preparation of *trans*-Isoxazolidines (Table 1).** TFA (70 equiv) was added to the Boc-protected hydroxylamine (1 equiv) at 0 °C. The solution was stirred at room temperature for 30 min. Most TFA was then removed in vacuo (35 °C, 10 Torr), and the resulting oil was further dried under high vacuum (rt, $5 \times 10^{-3}$ Torr). After 30 min, the oil was brought to atmospheric pressure and, under an atmosphere of dry argon, mixed with MS3Å powder (1.1 g mmol$^{-1}$) and $(CH_2O)_n$ (2 equiv) and then suspended in toluene (20 mL mmol$^{-1}$). The reaction vessel was immediately immersed in an oil bath preheated to 80 °C, and DIEA (2 equiv) was added to the mixture. After 3 h of vigorous stirring, heating was ceased, and once cooled to room temperature, the mixture was filtered. The residue was extracted with $CHCl_3$ and saturated aqueous $NaHCO_3$. After phase separation of the combined filtrates, the aqueous layer was further extracted with $CHCl_3$ (2 ×), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude isoxazolidine obtained was purified by flash column chromatography ($SiO_2$, 20−70% EtOAc in petroleum ether, 10% increments).

***rac*-(5*R*,6*R*)-Ethyl 7-Oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*trans*-3a).** Obtained as a yellow oil (664 mg, 90%): IR ($CHCl_3$) $\nu_{max}$ (cm$^{-1}$) 2951, 2869, 1741, 1458, 1374, 1294, 1109, 920; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.58 (s, 1H), 4.19 (m, 2H), 3.33 (dd, $J$ = 14.2, 6.0 Hz, 1H), 3.26 (br. dt, $J$ = 11.3, 2.9 Hz, 1H), 2.97 (d, $J$ = 11.4 Hz, 1H), 2.82 (br s, 1H), 2.76 (ddd, $J$ = 14.1, 12.0, 5.3 Hz, 1H), 1.93 (m, 1H), 1.85−1.68 (m, 2H), 1.55 (dt, $J$ = 14.0, 5.4 Hz, 1H), 1.27 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 171.4, 81.4, 61.2, 59.1, 55.8, 43.2, 27.9, 19.2, 14.1; HRMS (ESI) $m/z$ calcd for $C_9H_{16}NO_3$ $[M + H]^+$ 186.1130, found 186.1127.

**General Procedure for the Preparation of *cis*-Isoxazolidines (Tables 2 and 3).** TFA (70 equiv) was added to a mixture of *cis*-**6** (1 equiv) and aldehyde (2 equiv) at room temperature. After 15−45 min of stirring (15 min for $(CH_2O)_n$, 45 min for other aldehydes), excess TFA was removed in vacuo (35 °C, 10 Torr), and the residue was further dried under high vacuum (rt, $5 \times 10^{-3}$ Torr). After 30 min, the crude nitrone was put under an atmosphere of dry argon and dissolved in anhydrous solvent for cycloaddition (20 mL mmol$^{-1}$). The solution was immediately mixed with MS3Å (3.1 g mmol$^{-1}$) and $K_2CO_3$ (30 equiv) and subjected to the specified reaction conditions (Tables 2 and 3). Once cooled to room temperature, the mixture was diluted with $CH_2Cl_2$ (50 mL mmol$^{-1}$) and filtered. The residue was washed with $CH_2Cl_2$, and the combined filtrates were evaporated under reduced pressure to afford crude isoxazolidine, which was further purified according to the methods specified below.

***rac*-(5*R*,6*S*)-Ethyl 7-Oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (*cis*-3a).** Purified by flash column chromatography ($SiO_2$, 20−50% EtOAc in petroleum ether, 10% increments) and obtained as a yellow oil (106 mg, 69%): IR ($CHCl_3$/NaCl) $\nu_{max}$ (cm$^{-1}$) 2976, 2873, 1744, 1458, 1373, 1284, 1116, 902; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.59 (d, $J$ = 4.8 Hz, 1H), 4.30 (m, 2H), 3.46 (dd, $J$ = 14.3, 6.7 Hz, 1H), 3.38 (m, 1H), 3.18 (d, $J$ = 11.3 Hz, 1H), 2.89-2.79 (m, 2H), 2.13 (m, 1H), 1.87-1.69 (m, 2H), 1.42 (m, 1H), 1.32 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 169.6, 81.9, 61.4, 61.1, 56.2, 41.0, 25.1, 18.3, 14.3; MS (ESI) $m/z$ 186 $[M + H]^+$; HRMS (ESI) $m/z$ calcd for $C_9H_{16}NO_3$ $[M + H]^+$ 186.1130, found 186.1129.

***rac*-(5*S*,6*R*,8*S*)-Ethyl8-Cyclohexyl-7-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (18a).** Purified by flash column chromatography ($SiO_2$, 10−25% EtOAc in petroleum ether, 5% increments) and obtained as a colorless solid (33.6 mg, 85%): IR ($CH_2Cl_2$/NaCl) $\nu_{max}$ (cm$^{-1}$) 2929, 2854, 1747, 1450, 1373, 1278, 1207, 1038; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.51 (d, $J$ = 4.9 Hz, 1H), 4.26 (m, 2H), 3.52 (dd, $J$ = 14.1, 6.8 Hz, 1H), 2.87-2.78 (m, 2H), 2.60 (d, $J$ = 10.0 Hz, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 1.86 (m, 1H), 1.78-1.58 (m, 5H), 1.40-1.06 (m, 8H), 0.94-0.77 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.2, 80.4, 77.6, 61.0, 57.1, 41.6, 37.7, 30.8, 29.4, 26.9, 26.4, 26.0, 25.7, 17.9, 14.2; HRMS (MALDI-TOF) $m/z$ calcd for $C_{15}H_{26}NO_3$ $[M + H]^+$ 268.1913, found 268.1930.

**General Procedure for Reversibility Studies (Table 4).** The nitrone−TFA salt, prepared as described above, was put under an atmosphere of dry argon and dissolved in anhydrous 1,2-dichlorobenzene (20 mL mmol$^{-1}$). The solution was immediately mixed with MS3Å (3.1 g mmol$^{-1}$) and $K_2CO_3$ (30 equiv) and heated at 180 °C for 15 min. Once cooled to room temperature, the mixture was filtered and the residue extracted with $CH_2Cl_2$. The combined filtrates were concentrated in vacuo (50 °C, 10 Torr), and 1,2-dichlorobenzene was removed by Kugelrohr distillation (50 °C, 0.1

(28) This solvent system was previously used in N−O bond reduction during the synthesis of hydroxylated aminocycloheptanes: Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T *Org. Lett.* **2007**, *9*, 207–209.

Torr). The ratio **18/19** was estimated from the $^1$H NMR spectrum of the crude residue obtained. If isomerization to the azepane was not complete, the residue was redissolved in 1,2-dichlorobenzene under argon, mixed with MS3Å (3.1 g mmol$^{-1}$), and heated to 180 °C. The reaction was worked up as described previously after completion as indicated by TLC ($SiO_2$, visualization with iodine-modified Dragendorff's reagent[29]).

***rac*-(5*R*,6*R*,7*R*)-Ethyl7-Cyclohexyl-8-oxa-1-azabicyclo[3.2.1]octane-6-carboxylate (19a).** Purified by flash column chromatography ($SiO_2$, 5−12.5% EtOAc in petroleum ether, 2.5% increments) and obtained as a colorless oil (15.8 mg, 86%): IR ($CH_2Cl_2$/NaCl) $\nu_{max}$ (cm$^{-1}$) 2929, 2854, 1730, 1448, 1373, 1185, 1047; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.51 (m, 1H), 4.20 (m, 2H), 3.53 (m, 1H), 3.39−3.29 (m, 2H), 2.80 (m, 1H), 2.08−1.90 (m, 3H), 1.78−1.55 (m, 5H), 1.40−1.09 (m, 8H), 1.07−0.76 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 170.8, 77.7, 69.9, 60.9, 56.3, 55.9, 43.1, 30.5, 29.3, 26.5, 26.1, 26.0, 25.9, 15.3, 14.2; HRMS (MALDI-TOF) *m*/*z* calcd for $C_{15}H_{26}NO_3$ [M + H]$^+$ 268.1913, found 268.1932.

**General Procedure for N−O Bond Reduction Using Pd (Table 5).**[30] Pd/C (10%, 239 mg mmol$^{-1}$) was added to a solution of isoxazolidine in *t*-BuOH−$H_2O$ (5:1 v/v, 54 mL mmol$^{-1}$). The resulting mixture was stirred under an atmosphere of $H_2$ (balloon) until TLC ($SiO_2$, 10:1:0.2 $CH_2Cl_2$/MeOH/30% $NH_4OH$) indicated the reaction was complete and then filtered through a pad of diatomaceous earth. The filtercake was washed with MeOH, and the combined filtrates were concentrated under reduced pressure (50 °C, 10 Torr). The residue was purified as specified below.

***rac*-(*R*)-Ethyl 2-Hydroxy-2-((*R*)-piperidin-3-yl)acetate (20a).** Purification by flash chromatography ($SiO_2$, 18:1:1 $CHCl_3$/MeOH/30% $NH_4OH$) gave **20a** (31.4 mg, 97%) as colorless needles: IR ($CH_2Cl_2$/NaCl) $\nu_{max}$ (cm$^{-1}$) 3382 (br), 2938, 1732, 1446, 1370, 1117; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.22 (q, $J$ = 7.1 Hz, 2H), 4.03 (d, $J$ = 4.4 Hz, 1H), 2.96−2.88 (m, 2H), 2.77−2.53 (m, 2H), 1.87 (m, 1H), 1.82−1.72 (m, 2H), 1.56−1.42 (m, 2H), 1.24 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 174.6, 74.2, 61.4, 47.6, 46.5, 40.1, 27.8, 25.7, 14.2; HRMS (ESI) *m*/*z* calcd for $C_9H_{18}NO_3$ [M + H]$^+$ 188.1287, found 188.1281.

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**Supporting Information Available:** General experimental information; $^1$H and $^{13}$C NMR spectra of *cis*/*trans*-**3a**,**b**, *cis*/*trans*-**5a**,**b**, *cis*/*trans*-**6a**,**b**, **18a**−**j**, **19a**−**j**, **20a**,**b**, **21a**,**b**, and **22a**−**j**; 2D NMR spectra of *trans*-**3a**, *cis*-**3b**, **18a**, **19a**, **19e**, **20a**,**b**, and **21a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8018285

(29) Reagent C was used: Rubia, L. B.; Gomez, R. *J. Pharm. Sci.* **1977**, *66*, 1656–1657.

(30) In reductions where the HCl salt of the isoxazolidine was used (see Table 5), the isoxazolidine was first dissolved in a solution of 36% HCl (3.47 mL mmol$^{-1}$) in EtOH (17.4 mL mmol$^{-1}$), and excess HCl and EtOH were then removed under reduced pressure.