

Convergent and Stereodivergent Synthesis of Complex 1-Aza-7-oxabicyclo[2.2.1]heptanes

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Supporting Information

ABSTRACT: A convergent and stereodivergent pathway to highly substituted 1-aza-7-oxabicyclo[2.2.1]heptanes is described. It begins with a coupling reaction involving allylic alcohol, aldehyde, and LiHMDS to produce stereodefined primary homoallylic amines. Subsequent N-oxidation and condensation with formaldehyde or glyoxylate defines a convenient entry to densely functionalized homoallylic nitrones whose intramolecular annulation can be controlled to deliver one of two distinct heterocyclic skeletons, each with $\geq 20:1$ stereoselection. Control of the stereochemistry in these reactions results from both control of the nitrone geometry and selective partitioning of the reaction pathway between direct $[3 + 2]$ cycloaddition and tandem $[3,3]$ rearrangement/ $[3 + 2]$ cycloaddition.

Alkaloids are a broad class of natural products that possess a diverse array of biological properties. While examples include a vast array of molecular architectures, structurally complex polycyclic alkaloids have played a prominent role in the development of modern organic chemistry, providing inspiration for the development of synthetic methods suitable for the preparation of their intricate stereodefined skeletons. Densely functionalized piperidines are a common motif in complex alkaloids (Figure 1), and despite the variety of chemical methods available to access this type of nitrogen-containing heterocycle, the asymmetric synthesis of highly substituted piperidines remains a significant challenge in chemical synthesis.¹ Here we describe a convergent, asymmetric, and stereodivergent entry into tri- and tetrasubstituted 1-aza-7-oxabicyclo[2.2.1]heptanes (6 and 7) that derives from the union of an allylic alcohol (3) with two carbonyl electrophiles (1 and 5) and LiHMDS (2) (Figure 2). These studies are based on two central advances: (1) establishment of a three-component coupling reaction for the stereoselective synthesis of primary homoallylic amines and (2) control of the path selectivity in the annulation chemistry of highly substituted homoallylic nitrones.

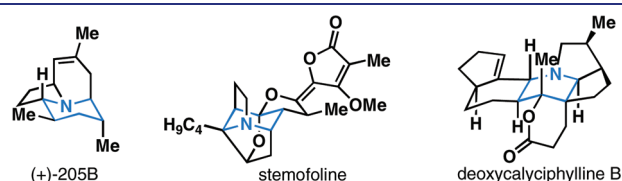


Figure 1. Piperidine-containing polycyclic alkaloids.

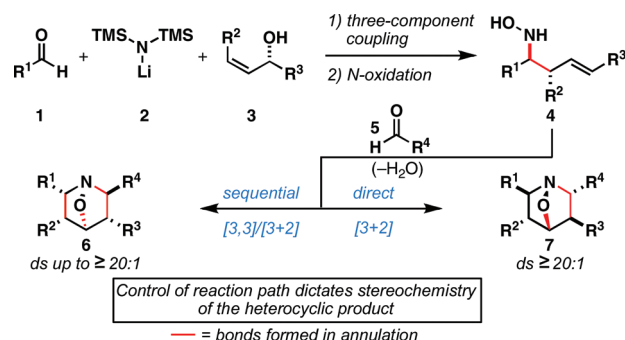
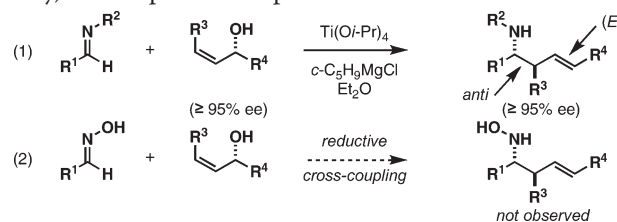


Figure 2. Convergent route to 1-aza-7-oxabicyclo[2.2.1]heptanes.

Since LeBel and Lumma's early reports² and Oppolzer's subsequent investigation of regio- and stereoselectivity,³ intramolecular cycloaddition of homoallylic nitrones has been accepted as a general strategy for the synthesis of substituted 1-aza-7-oxabicyclo[2.2.1]heptanes and, upon reductive cleavage of the σ_{N-O} bond, 4-hydroxypiperidines.⁴ The vast majority of applications in this regard have involved intramolecular reactions of sparsely functionalized homoallylic nitrones, and few reports have described the utility of this cycloaddition for the stereoselective synthesis of densely functionalized 1-aza-7-oxabicyclo[2.2.1]heptanes. This apparent lack of utility was thought to be due in part to (1) the difficulties associated with accessing the requisite highly substituted and stereodefined homoallylic nitrone starting materials and (2) the lack of stereochemical control in the cycloaddition reaction.⁵

We began with the development of a synthetic method for preparing highly substituted and stereodefined homoallylic hydroxylamines. Previous studies in our laboratory had established an asymmetric route to stereodefined homoallylic secondary amines based on the union of preformed imines with chiral allylic alcohols (eq 1).⁶ While a deprotection (removal of R^2)/N-oxidation sequence could allow this process to intersect with the annulation chemistry of homoallylic nitrones, we opted to pursue a more direct approach, namely, coupling of allylic alcohols with preformed oximes (eq 2). Unfortunately, all attempts to accomplish such a bond construction failed.



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Table 1. Primary Homoallylic Amines from Ti-Mediated Coupling^a

entry	aldehyde	allylic alcohol	yield (%)	product
1			80	
2			76	
3			70	
4			83	
5			87	
6			72	
7			56	
8			53	
9			63	

^a Reaction conditions: RCHO (2 equiv), LiHMDS (2 equiv) (−78 °C for aliphatic RCHO, −10 °C for aromatic RCHO), then Ti(Oi-Pr)₄ (2–3 equiv), RLi or RMgCl (4–6 equiv), then lithium alkoxide of allylic alcohol (1 equiv) (−78 °C to rt). For specific examples, see the Supporting Information. Note: products are racemic.

To circumvent this impediment in reactivity, we pursued an alternative coupling reaction capable of delivering a stereodefined primary homoallylic amine, a product whose subsequent N-oxidation would deliver homoallylic hydroxylamines without the need for intermediate protecting-group manipulations. As depicted in Table 1, in situ generation of a TMS-imine⁷ proved compatible with Ti-mediated allylic alcohol-based reductive cross-coupling, defining a three-component coupling process for the synthesis of stereodefined primary homoallylic amines. Overall, exposure of an aldehyde to LiHMDS is followed by introduction of Ti(Oi-Pr)₄ and *c*-C₅H₉MgCl (Et₂O, −78 to −40 °C). Subsequent addition of a preformed allylic lithium alkoxide results in overall reductive cross-coupling and, upon aqueous workup, delivers primary homoallylic amines with outstanding levels of regio- and stereocontrol. This reaction proceeds effectively with a variety of aromatic and aliphatic aldehydes and

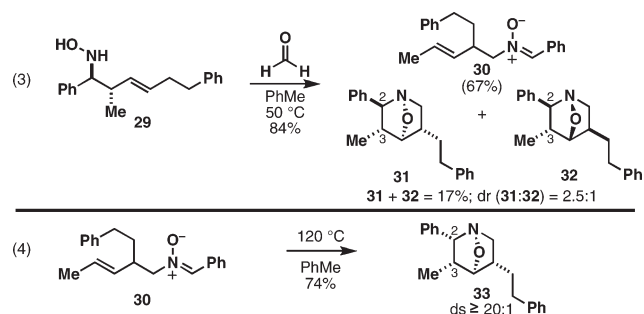


Figure 3. Stereochemical complexity of nitron cycloaddition.

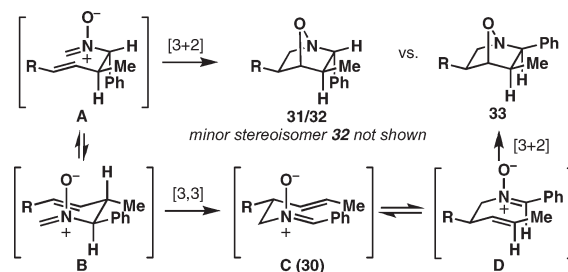


Figure 4. Direct [3 + 2] cycloaddition versus tandem [3,3] rearrangement/[3 + 2] cycloaddition.

delivers stereodefined (*E*)-*anti*-homoallylic amines as single diastereomers in 53–87% yield.

Having secured a robust stereoselective process for the convergent assembly of complex primary homoallylic amines, we turned our attention to the evaluation of intramolecular nitron annulation chemistry as a means of generating highly substituted heterocycles. After oxidation of homoallylic amine **10** to the corresponding hydroxylamine **29**,⁸ heating with formaldehyde at 50 °C leads to a complex product mixture (eq 3 in Figure 3). While the rearranged nitron **30** is formed in 67% yield, cycloadducts **31** and **32** are generated in 17% combined yield without substantial stereoselection (*ds* = 2.5:1). Interestingly, after isolation of nitron **30**, heating at 120 °C in toluene results in a highly stereoselective annulation (eq 4 in Figure 3). Here the isomeric cycloadduct **33** is produced in 74% yield with very high levels of stereoselection (*ds* ≥ 20:1).

The difference in 2,3 stereochemistry between **33** and the cycloadducts **31** and **32** is consistent with a complex competition in reaction mechanism due to the relative rate of cycloaddition versus sigmatropic rearrangement (Figure 4).^{5a,b,9} For example, initial exposure of **29** to formaldehyde at 50 °C leads primarily to the product of [3,3] rearrangement (**30**), with the minor cycloadducts **31** and **32** deriving from direct [3 + 2] cycloaddition of the intermediate nitron **A**. After isolation of the rearranged product **30**, heating in toluene at 120 °C results in a stereodivergent annulation via **D** to deliver **33** without contamination by cycloadduct **31** or **32**.

This tandem [3,3]-sigmatropic rearrangement/[3 + 2] cycloaddition is a useful stereoselective process for the production of densely functionalized 2-aryl-substituted 1-aza-7-oxabicyclo[2.2.1]heptanes (Table 2). Entries 1 and 2 demonstrate that the stereoselection of this process is highest with electron-deficient aromatics α to the intermediate nitron (*dr* ≥ 20:1). Entries 3 and 4 depict annulation events that deliver products having stereochemistry identical to that seen in entries 1 and 2, albeit

Table 2. Stereoselective Synthesis of 2,3-syn-3,4-syn-4,5-syn-5,6-anti-1-Aza-7-oxabicyclo[2.2.1]heptanes^a

entry	homoallylic hydroxylamine	R ³ CHO	yield (%)	dr	product
1			61	≥20:1	
2			60	≥20:1	
3			66	6:1 ^b	
4			61	6:1 ^b	
5			80	4:1	

^aNotes: (1) The initial sigmatropic rearrangement for the reactions summarized in entries 1 and 2 occurred in <2 h, whereas the substrates depicted in entries 3 and 4 required up to 48 h. Similarly, the subsequent [3 + 2] annulation in entries 3 and 4 required prolonged heating in comparison with entries 1 and 2 (48 h at 120 °C vs 12 h at 120 °C). (2) The products are racemic. ^bThe minor product is epimeric at the highlighted (*) position.

with compromised levels of stereocontrol (dr = 6:1). Finally, entry 5 provides a glimpse of the potential utility of this process for the synthesis of fully substituted heterocyclic systems. In this more complex example, reaction with an aliphatic aldehyde produces tetrasubstituted heterocycle **42** in 80% yield (dr = 4:1).¹⁰

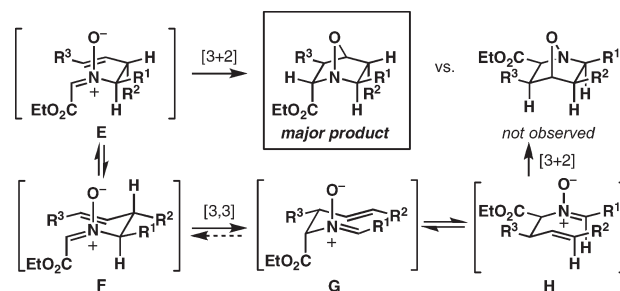
The stereochemical control of the annulation events depicted in Table 2 derives from the enhanced propensity of the initially formed nitrones to undergo [3,3]-sigmatropic rearrangement, with subsequent [3 + 2] cycloaddition occurring by way of the transposed nitrone (via **D** in Figure 4). With this model in mind, we speculate that more electron-rich nitrones in intermediate **D** have the *potential* to isomerize to the (*E*)-*O*-nitrone, a process that we reason is *in part* responsible for the decreased levels of stereoselection observed in entries 3 and 4 of Table 2. In cases where the initial [3,3] rearrangement (**B** → **C** in Figure 4) is not driven by thermodynamic stabilization of the resulting conjugated nitrone, attempted annulation reactions with formaldehyde or acetaldehyde result in a complex mixture of products.

To broaden the scope of this convergent route to complex heterocycles, we aimed to define an alternative means of controlling the mechanistic course of these annulation processes. Specifically, we sought to identify conditions that would promote the direct [3 + 2] annulation of the initially formed nitrone as a path to heterocycles having distinct substitution and stereochemistry.

Table 3. Stereoselective Synthesis of 2,3-anti-3,4-syn-4,5-anti-5,6-anti-1-Aza-7-oxabicyclo[2.2.1]heptanes^a

entry	homoallylic hydroxylamine	yield (%)	dr	product
1		64	≥20:1	
2		55	≥20:1	
3		64	≥20:1	
4		52	≥20:1	
5		60	≥20:1	

^aProducts are racemic.

**Figure 5. Stereoselective annulation with ethyl glyoxylate.**

Without a mechanistically lucid means of pursuing this goal, we opted to make drastic changes in the electronic and stereochemical features of the initially formed nitrone **A** (Figure 4).

With this goal in mind, the related annulation of homoallylic hydroxylamines with ethyl glyoxylate was explored. In comparison with nitrones resulting from condensation of hydroxylamines with formaldehyde or acetaldehyde, nitrones derived from glyoxylates are electronically and stereochemically distinct. While they are more electron-deficient, these nitrones prefer an *E* geometry in hydrocarbon solvents and exist in rapid equilibrium with their *Z* isomers.¹¹

As illustrated in Table 3, we were delighted to find that annulation with ethyl glyoxylate defines a stereochemically unique path to highly substituted heterocycles, in this case delivering 1-aza-7-oxabicyclo[2.2.1]heptane products containing a 2,3-anti-3,4-syn-4,5-anti-5,6-anti stereochemical relationship.

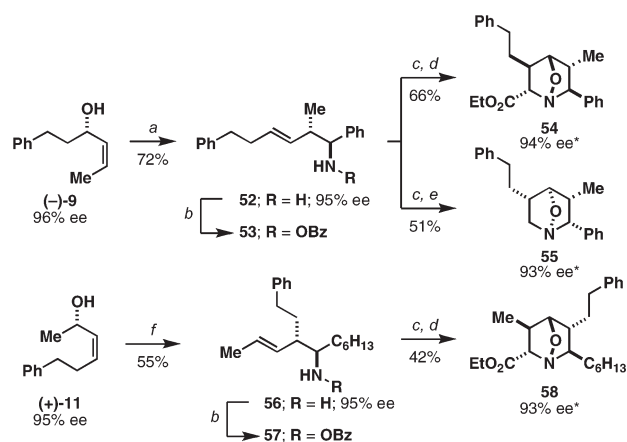


Figure 6. Asymmetric entry to 1-aza-7-oxabicyclo[2.2.1]heptanes. Reaction conditions: (a) PhCHO, LiHMDS (-10°C), then $\text{Ti}(\text{O}i\text{-Pr})_4$, $c\text{-C}_5\text{H}_9\text{MgCl}$, then lithium alkoxide of allylic alcohol (1 equiv) (-78°C to rt); (b) $(\text{BzO})_2$, K_2HPO_4 , DMF (rt); (c) NH_2NH_2 , EtOH; (d) ethyl glyoxylate, PhMe, 4 Å molecular sieves (100°C) (e) $(\text{CH}_2\text{O})_n$, PhMe, 4 Å molecular sieves (50°C , then 120°C) (f) $\text{C}_6\text{H}_{13}\text{CHO}$, LiHMDS (-78°C), then $\text{Ti}(\text{O}i\text{-Pr})_4$, $c\text{-C}_5\text{H}_9\text{MgCl}$, then lithium alkoxide of allylic alcohol (1 equiv) (-78°C to rt). The ee values labeled with * were determined by Mosher ester analysis of derivatives (see the Supporting Information for details).

Cycloaddition proceeds with hydroxylamines that have neighboring aliphatic as well as aromatic substitution and delivers stereodefined heterocycles in yields of 52–64% (entries 1–5; in all cases, no evidence could be found for the production of stereoisomeric cycloadducts).

The stereochemistry of the heterocycles depicted in Table 3 is consistent with a reaction sequence that proceeds by direct stereoselective intramolecular $[3 + 2]$ cycloaddition of the initially formed electron-deficient nitron **E**, uninterrupted by $[3,3]$ rearrangement (**F** \rightarrow **G** in Figure 5). While this provides a robust means of controlling the stereoselection in annulation events involving homoallylic nitrones derived from aliphatic aldehydes (entries 2 and 4), entries 1, 3, and 5 indicate that even when the substrate possesses neighboring aromatic substitution that has the potential to drive the $[3,3]$ -sigmatropic rearrangement, the reaction with ethyl glyoxylate proceeds in a highly stereoselective manner that is apparently uncomplicated by this process.¹² The facial selectivity of the cycloaddition is further supported by minimization of A-1,3 strain about the substituted nitron **E**, resulting in a pseudoequatorial disposition of R^1 and subsequently securing the orientation of R^2 and R^3 in the transition state for cycloaddition.

Finally, this sequence for the synthesis of complex 1-aza-7-oxabicyclo[2.2.1]heptanes is ideally suited for enantioselective synthesis. In accord with previous observations,⁶ Ti-mediated coupling of optically active allylic alcohols (Figure 6) proceeds with exquisite levels of stereocontrol and delivers optically active homoallylic amine products (**52** and **56**). As anticipated, a sequence of N-oxidation followed by nitron cycloaddition via either direct $[3 + 2]$ annulation or tandem $[3,3]$ rearrangement/ $[3 + 2]$ cycloaddition provides a convenient asymmetric entry to complex tri- and tetrasubstituted 1-aza-7-oxabicyclo[2.2.1]heptanes (**54**, **55**, and **58**).

In summary, we have described a convergent asymmetric entry to densely functionalized tri- and tetrasubstituted 1-aza-7-oxabicyclo[2.1.1]heptanes. This sequence is defined by (1) a

new diastereo- and enantioselective convergent synthesis of (*E*)-anti-homoallylic primary amines, (2) N-oxidation, and (3) a stereodivergent nitron annulation process. On the basis of the highly stereoselective nature of this synthesis pathway, the complexity of the resulting products, and the frequency with which substituted piperidines appear in alkaloids, we look forward to future applications of this method in target-oriented synthesis.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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