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

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### Abstract

A convergent and stereodivergent pathway to highly substituted 1-aza-7-oxabicyclo[2.2.1]heptanes is described. This process begins with a coupling reaction between an allylic alcohol, aldehyde, and LiHMDS for the production of stereodefined primary homoallylic amines. Subsequent *N*-oxidation and condensation with formaldehyde or a 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. The control of stereochemistry in these reactions is proposed to result from both the control of nitron geometry, and a selective partitioning of reaction pathway between direct [3+2] cycloaddition, or 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.<sup>1</sup> Here, we describe a convergent, asymmetric, and stereodivergent entry into tri- and tetrasubstituted 1-aza-7-oxabicyclo[2.2.1]heptanes (**6** and **7**), precursors to complex 4-hydroxypiperidines, 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) the establishment of a three-component coupling reaction for the stereoselective synthesis of primary homoallylic amines, and 2) control of path selectivity in annulation chemistry of highly substituted homoallylic nitrones.

Since LeBel and Lumma's early reports,<sup>2</sup> and Oppolzer's subsequent investigation of regio- and stereoselectivity,<sup>3</sup> 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, on reductive cleavage of the  $\sigma_{N-O}$  bond, 4-hydroxypiperidines.<sup>4</sup> The vast majority of applications in this regard describe intramolecular reactions of sparsely functionalized homoallylic nitrones, with few reports describing 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) difficulties associated with accessing the requisite highly substituted and stereodefined

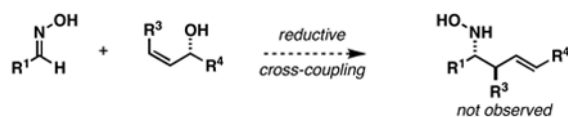
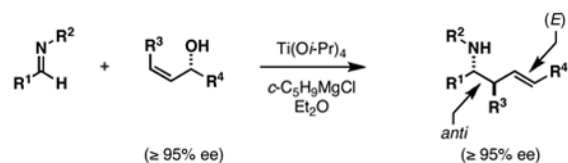
Correspondence to: Glenn C. Micalizio.

#### SUPPORTING INFORMATION PARAGRAPH:

Experimental procedures and tabulated spectroscopic data for new compounds (PDF) are available free of charge via the Internet at <http://pubs.acs.org/page/jacsat/submission/authors.html>.

homoallylic nitron starting materials, and 2) lack of stereochemical control in the cycloaddition reaction.<sup>5</sup>

Our investigations in this area began by developing a synthetic method suitable for the preparation of highly substituted and stereodefined homoallylic hydroxylamines. Previous studies in our laboratory have established an asymmetric route to stereodefined homoallylic secondary amines based on the union of preformed imines with chiral allylic alcohols (eq 1).<sup>6</sup> While a sequence of deprotection (removal of R<sup>2</sup>) and *N*-oxidation could render this process useful to intersect with the annulation chemistry of homoallylic nitrones, we opted to pursue a more direct means to accomplish this goal; namely coupling of allylic alcohols with preformed oximes (eq 2). Unfortunately, all attempts to accomplish such a bond construction were met with failure.



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-imine<sup>7</sup> 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(*O*-*i*-Pr)<sub>4</sub> and *c*-C<sub>5</sub>H<sub>9</sub>MgCl (Et<sub>2</sub>O, –78 to –40 °C). Subsequent addition of a preformed allylic lithium alkoxide results in overall reductive cross-coupling and, on aqueous work-up, delivers primary homoallylic amines with outstanding levels of regio- and stereocontrol. This reaction proceeds effectively with a variety of aromatic and aliphatic aldehydes, and delivers stereodefined (*E*)-*anti*-homoallylic amines as single diastereomers in 53–87% yield.

With a robust stereoselective process for the convergent assembly of complex primary homoallylic amines secured, we turned our attention to the evaluation of intramolecular nitron annulation chemistry as a means to generate highly substituted heterocycles. After oxidation of homoallylic amine **10** to the corresponding hydroxylamine **29**,<sup>8</sup> heating with formaldehyde at 50 °C leads to a complex product mixture (eq 3, 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). Here, the isomeric cycloadduct **33** is produced in 74% yield with very high levels of stereoselection ( $ds \geq 20:1$ ).

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 vs. sigmatropic rearrangement (Figure 4).<sup>5a,b,9</sup> 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 nitrene **A**. After isolation of the rearranged product **30**, heating in toluene at 120 °C results in a stereodivergent annulation via **D** to deliver **33**, uncontaminated 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  $\alpha$ - to the intermediate nitrene ( $dr \geq 20:1$ ). Entries 3 and 4 depict annulation events that deliver products of identical stereochemistry as that seen in entries 1 and 2, albeit 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 the tetrasubstituted heterocycle **42** in 80% yield ( $dr = 4:1$ ).<sup>10</sup>

The stereochemical control of the annulation events depicted in Table 2 derives from the enhanced propensity of the initially formed nitrenes to undergo [3,3]-sigmatropic rearrangement, with subsequent [3+2] cycloaddition occurring by way of the transposed nitrene (via **D**; Figure 4). With this model in mind, we speculate that more electron rich nitrenes in intermediate **D** have the potential to isomerize to the (*E*)-*O* nitrene—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**  $\rightarrow$  **C**; Figure 4) is not driven by thermodynamic stabilization of the resulting conjugated nitrene, attempted annulation reactions with formaldehyde or acetaldehyde result in a complex mixture of reaction products.

In an attempt to broaden the scope of this convergent route to complex heterocycles we aimed to define an alternative means to control the mechanistic course of these annulation processes. Specifically, we sought to identify conditions suitable to promote direct [3+2] annulation of the initially formed nitrene as a path to heterocycles of a distinct substitution and stereochemistry. Without a mechanistically lucid means by which to pursue this goal, we opted to drastically change the electronic and stereochemical features of the initially formed nitrene **A** (Figure 4).

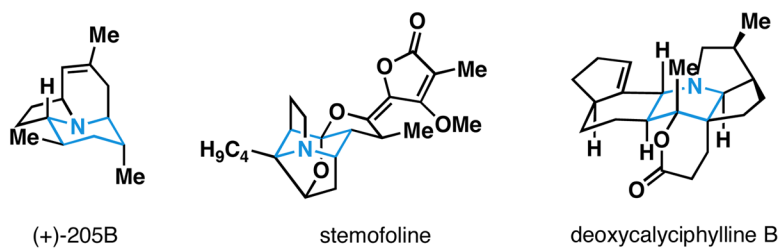
With this goal in mind, the related annulation of homoallylic hydroxylamines with ethylglyoxal was explored. Compared to nitrenes resulting from condensation of hydroxylamines with formaldehyde or acetaldehyde, nitrenes derived from glyoxalates are electronically and stereochemically distinct. While more electron deficient, these nitrenes prefer an (*E*)-geometry in hydrocarbon solvents and exist in rapid equilibrium with their (*Z*)-isomers.<sup>11</sup>

As illustrated in Table 3, we were delighted to find that annulation with ethylglyoxal 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. Cycloaddition proceeds with hydroxylamines that have neighboring aliphatic- as well as aromatic- substitution, and delivers stereodefined

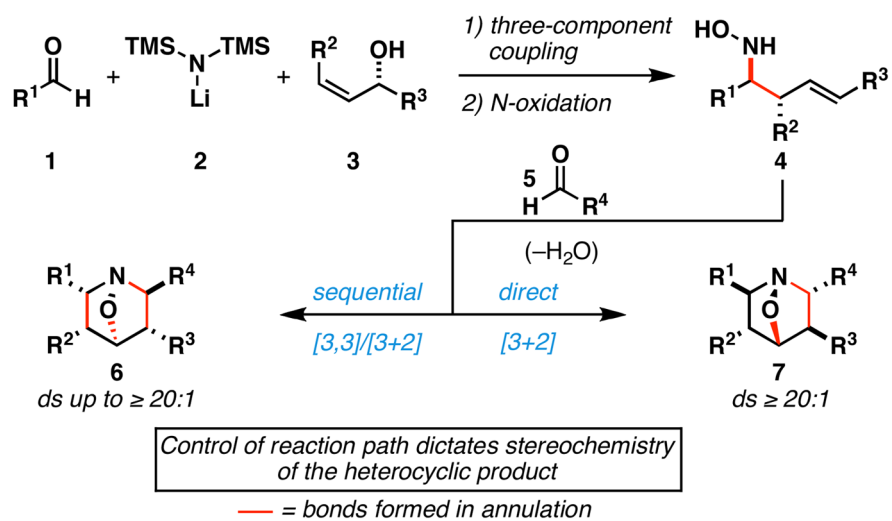


## References

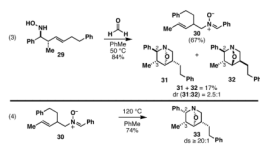
1. For reviews, see: a) Buffat MGP. *Tetrahedron*. 2004; 60:1701–1729. b) Weintraub PM, Sabol JS, Kane JM, Borchering DR. *Tetrahedron*. 2003; 59:2953–2989. c) Baliah V, Jeyaraman R, Chandrasekaran. *Chem Rev*. 1983; 83:379–423.
2. a) LeBel NA, Slusarczuk GMJ, Spurlock LA. *J Am Chem Soc*. 1962; 84:4360–4361. b) Lumma WC. *J Am Chem Soc*. 1969; 91:2820–2821.
3. Oppolzer W, Siles S, Snowden RL, Bakker BH, Petrzilka M. *Tetrahedron*. 1985; 41:3497–3509.
4. For an example, see: Hoffmann RW, Endesfelder A. *Liebigs Ann Chem*. 1986; 11:1823–1826.
5. For a discussion concerning the observation of products derived from aza-Cope/intramolecular [3+2] nitrono cycloaddition, see: (a) Wuts PGM, Jung YW. *J Org Chem*. 1988; 53:1957–1965. (b) Merino P, Mannucci V, Tejero T. *Eur J Org Chem*. 2008:3943–3959. For a review of [3+2] nitrono cycloaddition, see: (c) Confalone PN, Huie EM. *Org React*. 1988; 36:1–173.
6. (a) Takahashi M, McLaughlin M, Micalizio GC. *Angew Chem Int Ed*. 2009; 48:3648–3652. (b) Umemura S, McLaughlin M, Micalizio GC. *Org Lett*. 2009; 11:5402–5405. [PubMed: 19877599] (c) Yang D, Micalizio GC. *J Am Chem Soc*. 2009; 131:17548–17549. [PubMed: 19950989] (d) Chen MZ, McLaughlin M, Takahashi M, Tarselli MA, Yang D, Umemura S, Micalizio GC. *J Org Chem*. 2010; 75:8048–8059. [PubMed: 21069994]
7. (a) Hart DJ, Kanai K, Thomas DG, Yang TK. *J Org Chem*. 1983; 48:289–294. (b) Ha DC, Hart DJ, Yang TK. *J Am Chem Soc*. 1984; 106:4819–4825.
8. Berman AM, Johnson JS. *J Org Chem*. 2006; 71:219–224. [PubMed: 16388639]
9. For a computational assessment related to the competition between [3,3]-rearrangement and [3+2]-cycloaddition reactions of homoallylic nitrones, see: Merino P, Tejero T, Mannucci V. *Tetrahedron Lett*. 2007; 48:3385–3388.
10. See Supporting Information for details.
11. (a) Inouye Y, Hara J, Kakisawa H. *Chem Lett*. 1980:1407–1410. (b) Inouye Y, Takaya K, Kakisawa H. *Bull Chem Soc Jpn*. 1983; 56:3541–3542. It has also been proposed that intermolecular [3+2] cycloaddition reactions occur faster by way of (E)-nitrones: (c) Burdisso M, Gandolfi R, Grünanger P. *J Org Chem*. 1990; 55:3427–3429.
12. These observations do not exclude control by the Curtin-Hammett principle where reversible [3,3]-rearrangement of the initially formed glyoxylate-based nitrono is irrelevant in determining product distribution.



**Figure 1.**  
Piperidine-containing polycyclic alkaloids.

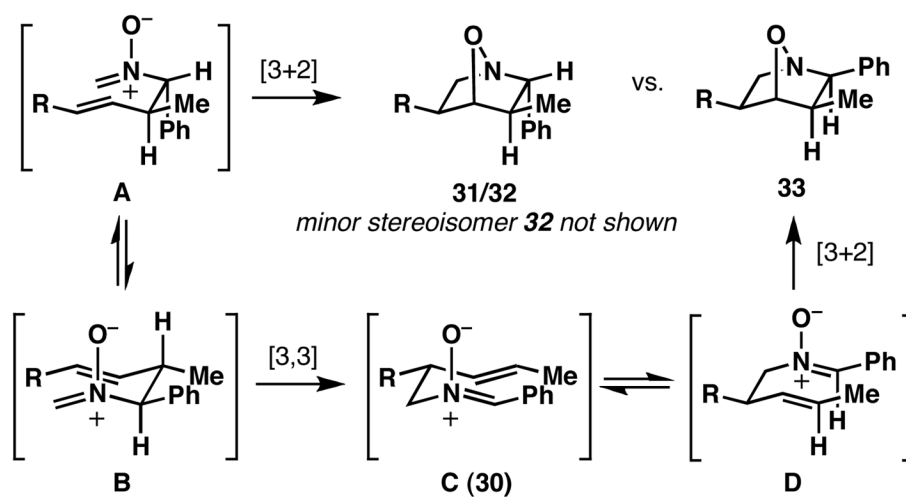


**Figure 2.**  
Convergent route to 1-aza-7-oxabicyclo[2.2.1]heptanes.

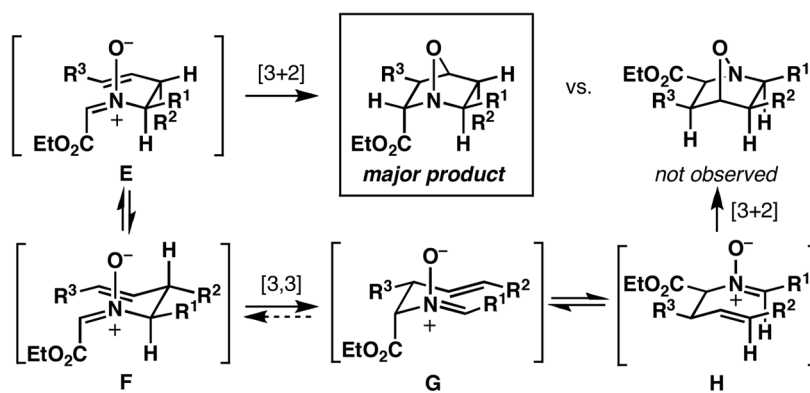


**Figure 3.**  
Stereochemical complexity of nitrono cycloaddition.

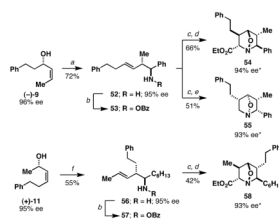




**Figure 4.**  
Direct [3+2] vs. tandem [3,3]/[3+2].




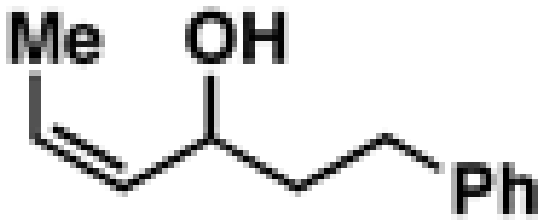

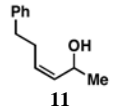
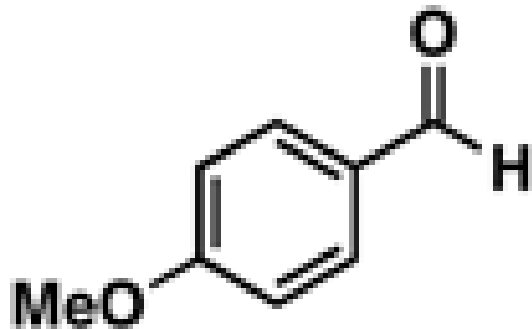
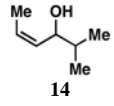
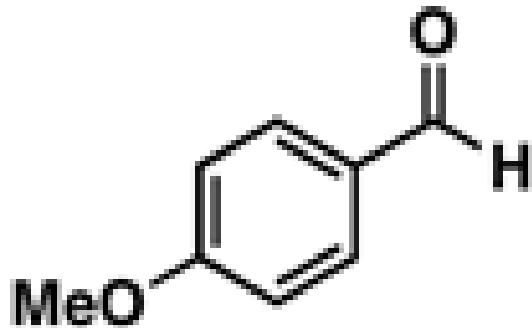
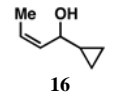
**Figure 5.**  
Stereoselective annulation with ethylglyoxylate.

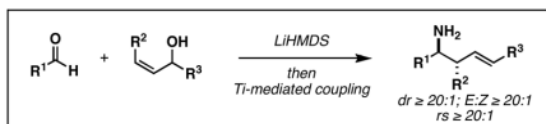
**Figure 6.**

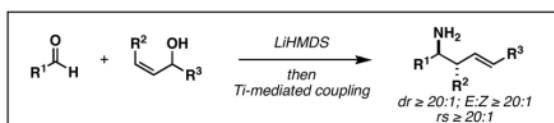
Asymmetric entry to 1-aza-7-oxabicyclo[2.2.1]heptanes. *Reaction conditions:* a) PhCHO, LiHMDS, THF ( $-10\text{ }^{\circ}\text{C}$ ), then  $\text{Ti}(\text{O}i\text{-Pr})_4$ ,  $c\text{-C}_5\text{H}_9\text{MgCl}$ , then Li-alkoxide of allylic alcohol (1 equiv) ( $-78\text{ }^{\circ}\text{C}$  to rt); b)  $(\text{BzO})_2$ ,  $\text{K}_2\text{HPO}_4$ , DMF, rt; c)  $\text{NH}_2\text{NH}_2$ , EtOH; d) ethylglyoxylate, PhMe,  $4\text{ \AA}$  mol. sieves,  $100\text{ }^{\circ}\text{C}$ ; e)  $(\text{CH}_2\text{O})_n$ , PhMe,  $4\text{ \AA}$  mol. sieves,  $50\text{ }^{\circ}\text{C}$ ; f)  $\text{C}_6\text{H}_{13}\text{CHO}$ , LiHMDS, THF ( $-78\text{ }^{\circ}\text{C}$ ), then  $\text{Ti}(\text{O}i\text{-Pr})_4$ ,  $c\text{-C}_5\text{H}_9\text{MgCl}$ , then Li-alkoxide of allylic alcohol (1 equiv) ( $-78\text{ }^{\circ}\text{C}$  to rt). \* % ee determined by Mosher ester analysis of derivatives, see Supporting Information for details.

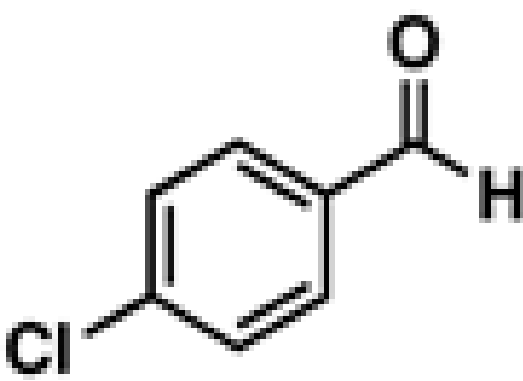
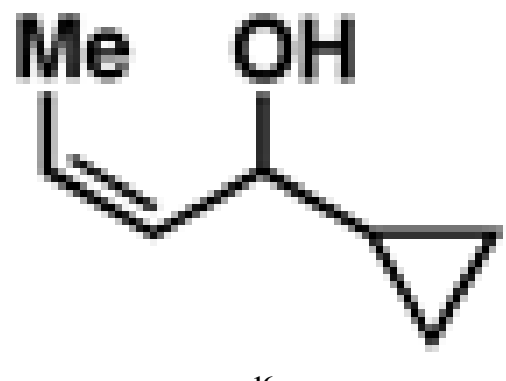
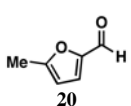
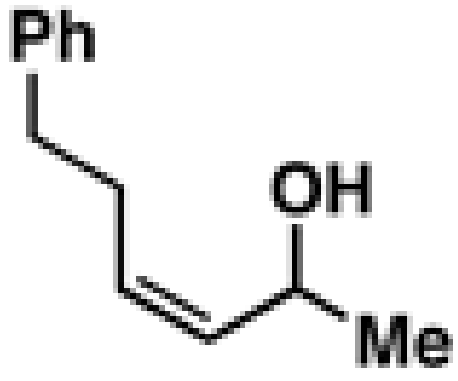
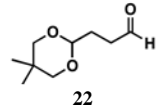
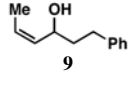
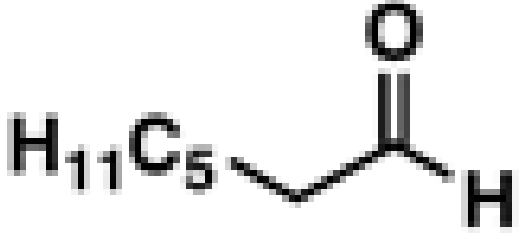
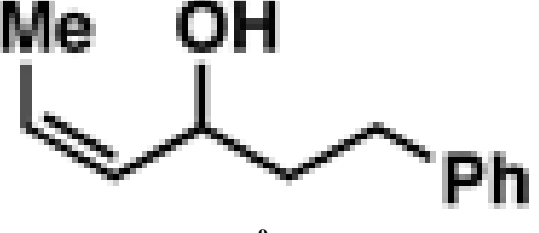
Table 1

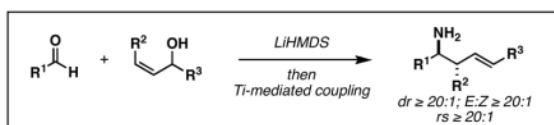
Primary homoallylic amines from Ti-mediated coupling.

entry	aldehyde	allylic alcohol	yield (%)
1	 8	 9	80
2	 8	 11	76
3	 13	 14	70
4	 13	 16	83





entry	aldehyde	allylic alcohol	yield (%)
5	 <p>18</p>	 <p>16</p>	87
6	 <p>20</p>	 <p>11</p>	72
7	 <p>22</p>	 <p>9</p>	56
8	 <p>24</p>	 <p>9</p>	53

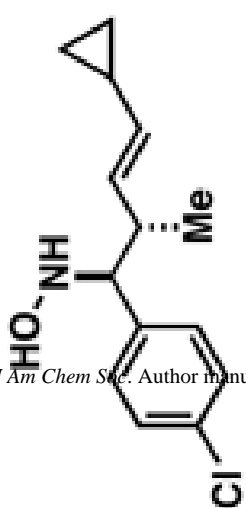

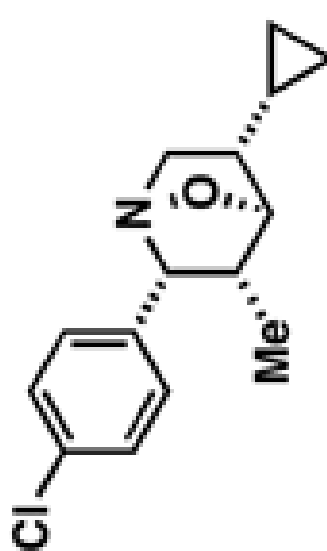
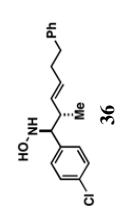
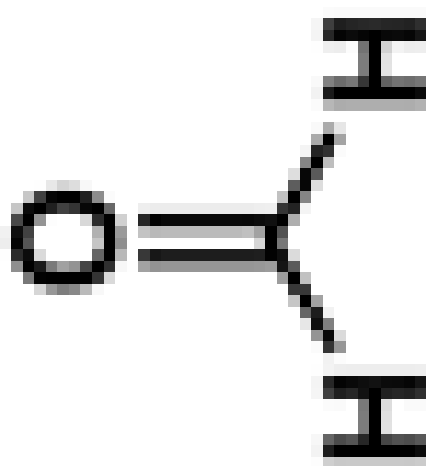
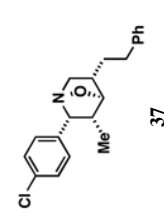


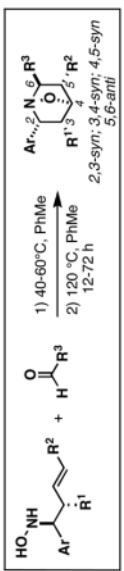
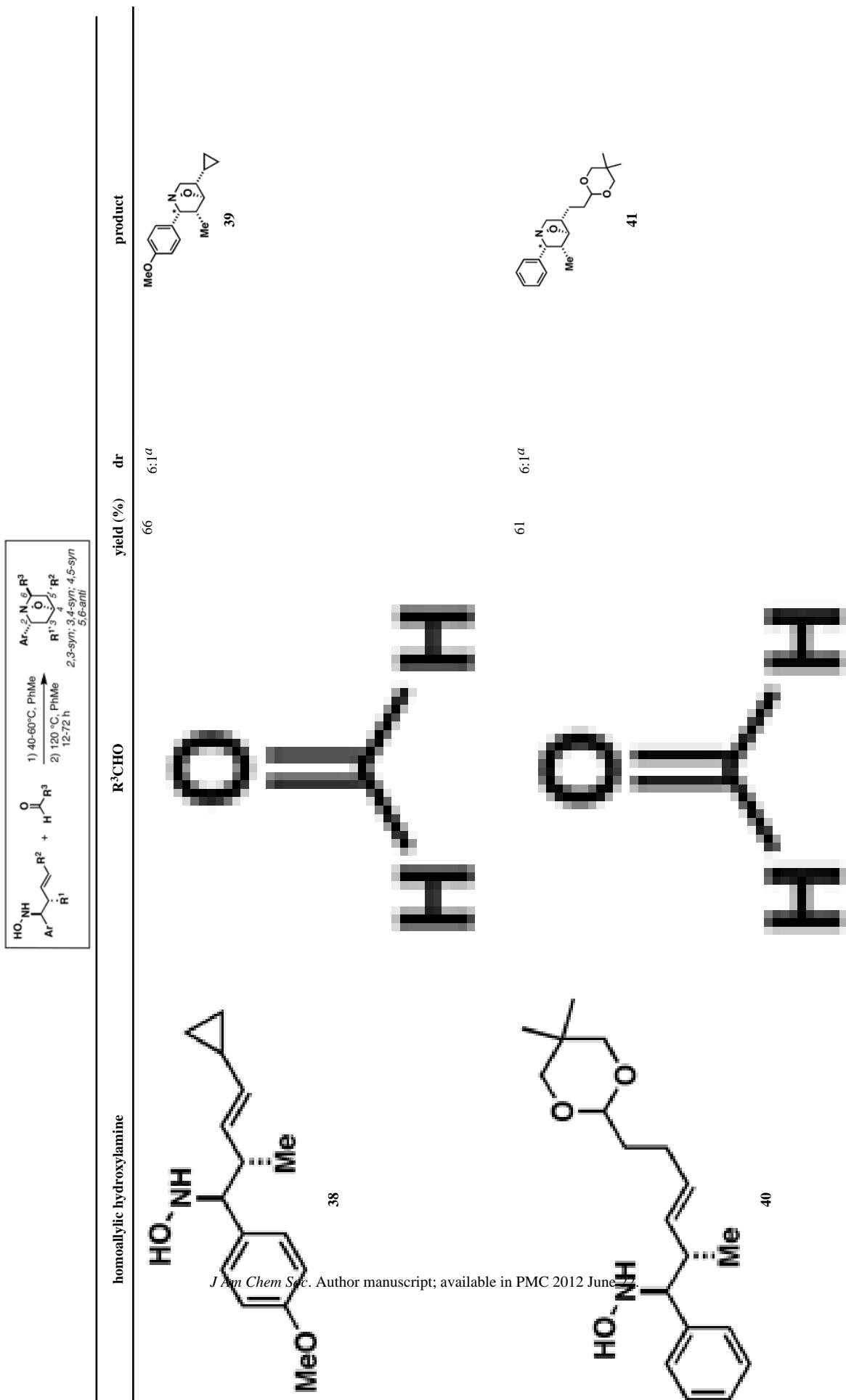
entry	aldehyde	allylic alcohol	yield (%)
9	<p style="text-align: center;">26</p>	<p style="text-align: center;">27</p>	63

*Reaction conditions:* RCHO (2 eq), LiHMDS (2 equiv), THF (−78 °C for aliphatic RCHO, −10 °C for aromatic aldehyde), then Ti(Oi-Pr)<sub>4</sub> (2–3 equiv), RLi or RMgCl (4–6 eq), then Li-alkoxide of allylic alcohol (1 equiv) (−78 °C to rt). For specific examples, see Supporting Information.  
*Note:* products are racemic.

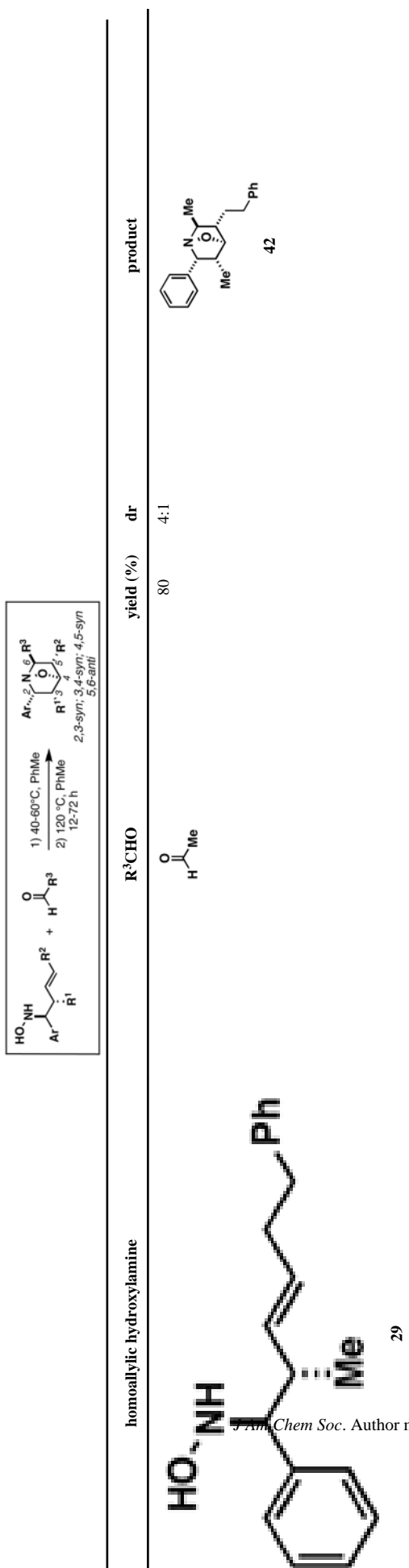
Table 2

selective synthesis of (2,3-syn-3,4-syn-4,5-syn-5,6-anti)-1-aza-7-oxabicyclo[2.2.1]heptanes.

homoallylic hydroxylamine	R <sup>3</sup> CHO	yield (%)	dr	product
 34	 H <sup>3</sup> CHO	61	≥20:1	 35
 36	 H <sup>3</sup> CHO	60	≥20:1	 37







product is epimeric at the highlighted (\*) position.

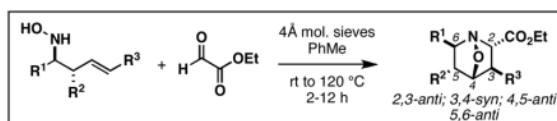
al sigmatropic rearrangement for reactions summarized in entries 1 and 2 occur in <2 h, whereas substrates depicted in entries 3 and 4 required up to 48 h. Similarly, the subsequent

ation in entries 3 and 4 require prolonged heating in comparison to entries 1 and 2 (48 h at 120 °C vs. 12 h at 120 °C). Note: products are racemic.

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.

entry	homoallylic hydroxylamine	yield (%)	dr	product
1	 43	64	≥20:1	 44
2	 45	55	≥20:1	 46
3	 47	64	≥20:1	 48



entry	homoallylic hydroxylamine	yield (%)	dr	product
4	 49	52	≥20:1	 50
5	 34	60	≥20:1	 51

Note: products are racemic.