ORGANIC LETTERS

2009
Vol. 11, No. 5
1059−1061

Stereocontrol in *N*-Directed Hydroboration: Synthesis of Amino Alcohols Related to the Piperidine Alkaloids

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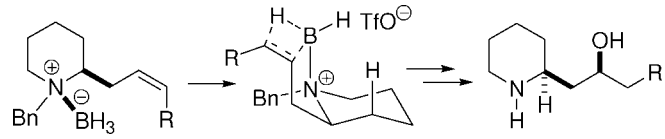
Received December 2, 2008

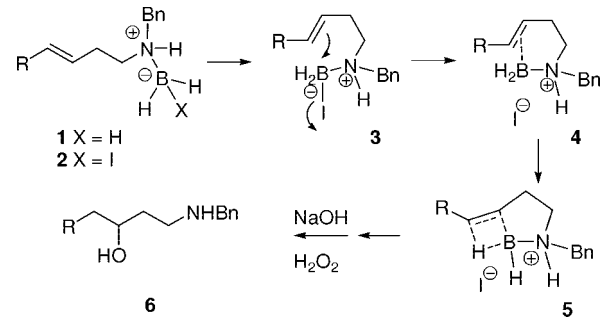
ABSTRACT



Treatment of 2-(2′-alkenyl)-piperidine boranes with iodine or triflic acid induces internal hydroboration with high regiocontrol, even with a terminal alkene (R = H). Good stereocontrol is possible for the *N*-benzyl substrates. Comparisons with acyclic model structures show that the source of regiocontrol with the terminal alkene is due to a steric effect of the axial piperidine C(3,5) hydrogens that destabilize the competing bridged bicyclic transition state.

Recent publications from our laboratory have described the amine-directed intramolecular hydroboration reaction from unsaturated amine borane complexes **1** activated by molecular iodine.[1,2] The key event is an S_N2-like displacement of a leaving group by the nucleophilic alkene, as shown in the conversion of the activated iodoborane complex **2** to an olefin π-complex ion pair **4**, followed by 4-center hydroboration (HB) to give **6** (Scheme 1). We now report applications of this technique to piperidine substrates that provide opportunities for stereocontrol as well as regiocontrol in the HB step.[3] The optimized methodology has been evaluated in the context of amino alcohols related to the piperidine alkaloids where

Scheme 1. Mechanistic Considerations



diastereoselectivity of HB can be deduced by NMR comparisons with known structures.[4−7]

According to our prior investigation, the major product of homoallylic amine borane activation with I_2 is formed via the fused bicyclic transition state **5**, provided that the

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(2) Scheideman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* **2008**, *130*, 8669.

(3) Stereoselective amine HB: (a) Lyle, R. E.; Carle, K. R.; Ellefson, C. R.; Spicer, C. K. *J. Org. Chem.* **1970**, *35*, 802. Stern, P.; Trska, P.; Ferles, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2267. Stereoselective N-EWG HB: (b) Fujita, Y.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1964**, *86*, 1844. Dicko, A.; Montury, M.; Baboulene, M. *Tetrahedron Lett.* **1987**, *28*, 6041. Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027. Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991**, *113*, 4042. Sibi, M. P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115. Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815.

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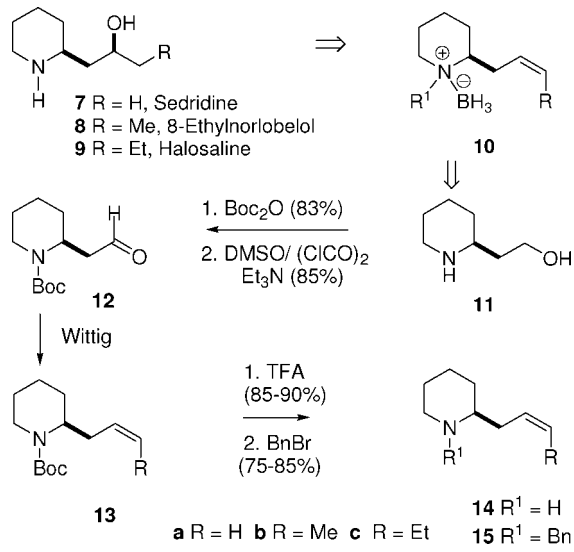
10.1021/ol802781c CCC: $40.75
Published on Web 01/30/2009

substituent R is an alkyl group. Therefore, access to the piperidine alkaloids **8** or **9** would be readily predicted from a homoallylic amine precursor **10**, but regiocontrol issues would be expected in the case where R= H, corresponding to sedridine (**7**; Scheme 2).

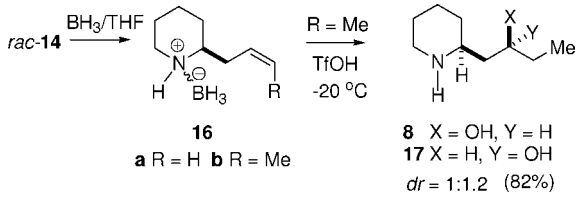
Scheme 2. Synthesis of *rac*-2-(2′-Alkenyl)-piperidines



Our investigation began with conversion of racemic 2-piperidineethanol **11** into the protected aldehyde **12**, followed by Wittig olefination (KO*t*Bu/THF) to afford the alkenes **13a**−**c**. Structures **13b** and **13c** were obtained as 9:1 and 13:1 *Z*:*E* mixtures, respectively, and were used as such in the following steps. Deprotection and benzylation then provided the desired 2-(2′-alkenyl)-piperidine substrates **14** and **15**.

Treatment of the N−H piperidines **14** (Scheme 3) with THF-borane at −20 °C afforded amine boranes **16** as diastereomer mixtures. The terminal alkene **16a** could not

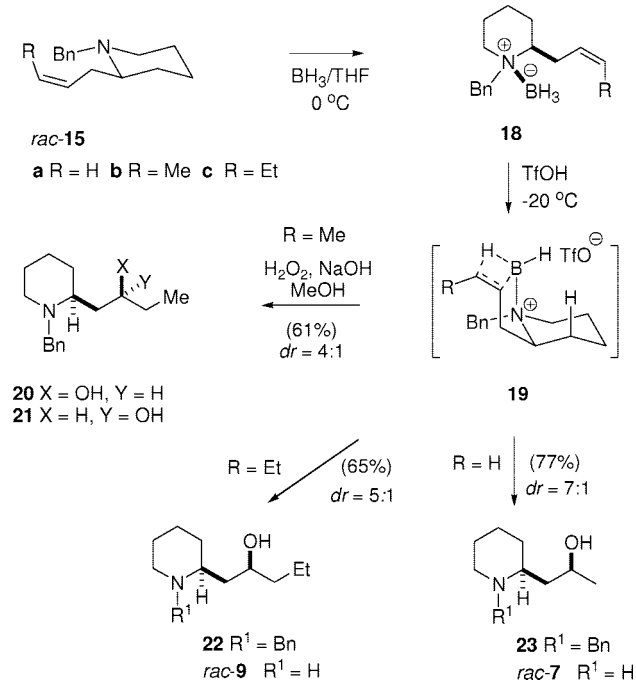
Scheme 3. Intramolecular Hydroboration from **14**



be purified due to partial decomplexation at rt, but the disubstituted alkene analogs **16b** and **16c** survived chromatography and were isolated as diastereomer mixtures (ca. 2:1 dr). Activation of **16b** with iodine or with TfOH gave aminoalcohol products after oxidative workup. However, the diastereomer ratio of **8**:**17** was only 1:1.2 according to NMR comparisons.[5] Because the diastereomers of the amine borane **16b** are not separable, we could not determine whether the low dr is due to inherently low selectivity, or due to opposite diastereofacial preferences for each diastereomer.

An alternative approach was pursued in an attempt to improve diastereoselectivity at the stage of amine borane complexation. Presumably, the reaction of **14b** with THF/borane occurs with low diastereoselectivity because there is little energy difference between the nitrogen invertomers (axial vs equatorial lone pairs in the chairlike structure).[8] Better conformational control was expected starting with the *N*-benzyl substrate, so **15b** was evaluated in the complexation step with THF/borane (Scheme 4). Assuming that **15b** reacts

Scheme 4. Intramolecular Hydroboration from **15**



via the more stable all-equatorial conformer (lone pair axial), the major product should be **18b** (axial BH_3 subunit). The exact dr was difficult to measure because the starting amine **15b** contains 11% of the isomeric *E*-alkene, but comparison of the *N*-benzyl signals indicated a ratio of ca. 8:1 in favor of the isomer **18b** as shown in Scheme 4.

Upon activation of **18b** with TfOH (−20 °C, 16 h) followed by oxidative workup, the products **20** and **21** were obtained in an improved ratio of 4:1, this time favoring the

(6) Maio, W. A.; Sinishtaj, S.; Posner, G. H. *Org. Lett.* **2007**, *9*, 2673.

(7) Extensive synthetic work targetting piperidine alkaloids is described in ref 4. For selected recent studies, see: (a) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (c) Lesma, G.; Crippa, S.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron* **2004**, *60*, 6437. (d) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva, S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2225.

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stereochemistry corresponding to *rac*-8-ethylnorlobelol-I (**8**) according to NMR comparisons after debenzylation with $Pd(OH)_2/H_2$.[5] Initial attempts to activate **18b** with iodine gave similar dr, but these experiments were less reproducible and afforded variable amounts of recovered amine **15b**. Our earlier study demonstrated that the recovery of unreacted amines is due to formation of ammonium salts via competing protonation of the amine borane B−N bond by HI, formed during the first stage of iodine activation of the B−H bond.[2] Evidently, the TfOH activation procedure is more selective for the desired protonation at B−H vs B−N for the tertiary *N*-benzylamine **18b**.

The same sequence of complexation and TfOH activation was also used with **15c**. Amine borane **18c** was obtained as the major isomer (9:1 dr) and treatment with TfOH gave **22** with 5:1 dr. The assignment was confirmed by debenzylation to give *rac*-**9** (halosaline) as the major diastereomer.[6] This outcome corresponds to preferred hydroboration via the fused transition state **19**, and is consistent with the stereochemistry assigned to **18b** and **18c**.

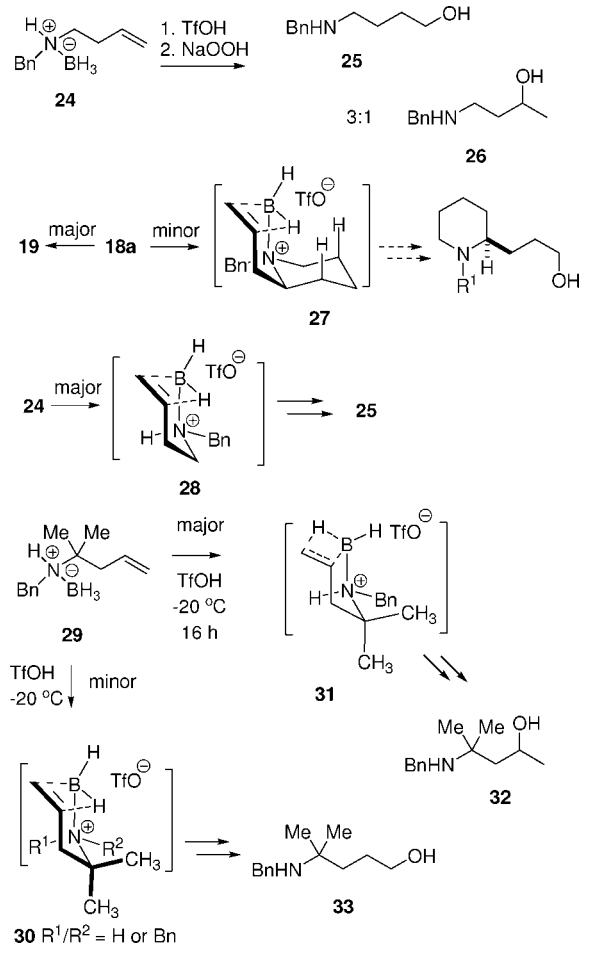
The major and minor amino alcohol diastereomers could not be separated in the above examples (**7**, **8**, **9**). If isomer separation is desired, this can be done as described in the literature using *N*-protected analogues.[7b,d]

In both of the above examples (**18b**,**c**) the regioisomeric amino alcohols could not be detected in the product mixture as expected.[2] However, the behavior of the terminal alkene **18a** was more surprising. By analogy with the prior studies using iodine activation of acyclic terminal alkenes such as **1** (R = H), the primary alcohol should be the major product. However, activation of **18a** using TfOH afforded the secondary alcohol **23** with high (>20:1) regioselectivity, similar to the results with **18b** and **18c**. Furthermore, **23** was obtained with the best dr (7:1) among the *N*-benzyl substrates **18a**−**c**.

To better understand the improved regioselectivity with **18a**, activation of the acyclic amine borane **24** was revisited, but using the same TfOH conditions as for the experiment with **18a** (Scheme 5). After oxidative workup, the amino alcohols **25** and **26** were obtained in a 3:1 ratio.[2] Thus, the TfOH activating agent is not responsible for the contrasting regioselectivity observed with **18a**.

An alternative explanation for the behavior of **18a** was considered, based on the steric environment adjacent to the ring nitrogen. The preference for product formation via the fused transition state **19a** suggests that the alternative bridged transition state **27** (Scheme 5) leading to a primary C−B bond is destabilized by axial C−H interactions as shown. Such interactions are absent in the analogous bridged TS **28** from **24**, resulting in hydroboration with the usual preference for boron bonding at the less substituted (primary) carbon. On the other hand, the more highly substituted acyclic substrate **29** would encounter the destabilizing steric repulsions in the bridged TS **30**, but not in the fused TS **31**. Accordingly, **29** was studied under conditions of both the iodine and TfOH activation conditions, followed by oxidative workup. In contrast to **24**, the secondary alcohol **32** was now the major product, and was obtained with excellent 18:1 regioselectivity (85%) using TfOH activation (16 h at −20 °C). The analogous iodine experiment gave lower 10:1 selectivity.

Scheme 5. Regioselectivity



Overall, our results are consistent with an intramolecular HB process that occurs with moderate to good diastereoselectivity (4−7:1 dr). Excellent regioselectivity is observed with all three substrates **18a**−**c**, and also with the *gem*-dimethyl-substituted acyclic terminal alkene **29**. In all of these examples, the major product corresponds to the preferred reaction via a fused bicyclic transition state for amine-directed hydroboration.

Acknowledgment. This work was supported by the National Institutes of Health (GM067146).

Supporting Information Available: Characterization of new compounds and key NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802781C