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A Silicon Tether Approach for Diastereocontrol in Radical Addition to Chiral Hydrazones

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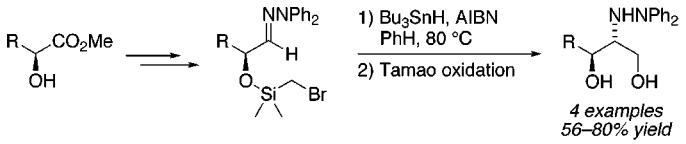
ABSTRACT



A radical carbon–carbon bond construction approach to chiral α-branched amines is presented. Stereocontrolled radical addition to chiral hydrazones can be achieved by virtue of conformational constraints imposed during cyclizations using a temporary silicon connection. Oxidative removal of the tether completes the hydroxymethylation process to afford *anti*-2-hydrazino-1,3-diols in good yield. The 1,2-induction increases with increasing *A* values of the appended groups, consistent with prediction by the Beckwith–Houk model for stereocontrol in 5-hexenyl radical cyclizations.

Chiral α-branched amines are key features within bioactive amino alcohols such as sphingolipids and aminosugars; direct and efficient synthetic strategies exploiting carbon−carbon bond construction with acyclic stereocontrol hold considerable promise for streamlined preparation of these valuable targets.[1] Currently common are indirect routes involving stepwise C−C and C−N bond constructions and often a third separate asymmetric induction step (e.g., alkene epoxidation or carbonyl reduction).[2] In contrast, a strategy exploiting retrosynthetic C−C bond disconnection of α-branched amines (Figure 1) creates both a stereocenter and a C−C bond *in one synthetic transformation*.

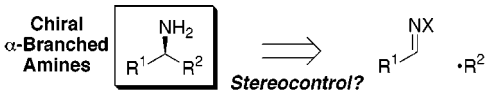


Figure 1. Carbon−carbon disconnection for synthesis of chiral α-branched amines.

Application of the C−C bond construction strategy has been underdeveloped, largely because additions of carbanionic reagents to aldehyde imino derivatives[3] (azomethines) often suffer competing aza-enolization.[4] New C−C bond constructions for chiral α-branched amine synthesis are consequently in high demand.[5]

To address the general problem of acyclic chiral α-branched amine synthesis, nonpolar radical additions to C=N bonds[6]

(1) Reviews of methods for amino alcohol synthesis: Reets, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. For ionic C−C bond construction approaches, see: Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219. Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

(2) Recent examples in natural product synthesis: Boger, D. L.; Ledeboer, M. W.; Kume, M. *J. Am. Chem. Soc.* **1999**, *121*, 1098. Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1999**, *64*, 2789. Deng, J.; Hamada, Y.; Shioiri, T. *Synthesis* **1998**, 627.

(3) Reviews: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. Selected recent examples: Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portunovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555. Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138.

(4) Even organocerium reagents, considered relatively nonbasic nucleophiles, can promote aza-enolization of hydrazones. Enders, D.; Diez, E.; Fernandez, R.; Martin-Zamora, E.; Munoz, J. M.; Pappalardo, R. R.; Lassaleta, J. M. *J. Org. Chem.* **1999**, *64*, 6329.

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(Figure 1) could (a) circumvent imine aza-enolization problems, (b) efficiently construct crowded C−C bonds, and (c) tolerate highly functionalized precursors. However, acyclic stereocontrol of radical additions to C═N is virtually unknown.[7] Could the well-known high internal conformational diastereocontrol of 5-hexenyl radical cyclizations[8] be harnessed for *formal* acyclic stereocontrol of radical addition to C═N bonds? To test this hypothesis, the preexisting stereocenter of a chiral α-hydroxy ester would serve to direct the 5-*exo*-*trig* cyclization of a radical tethered via a temporary silicon connection[9] (Figure 2). Subsequent oxidative removal

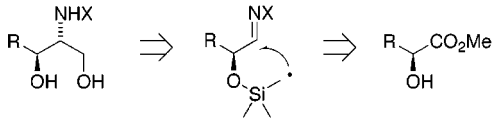
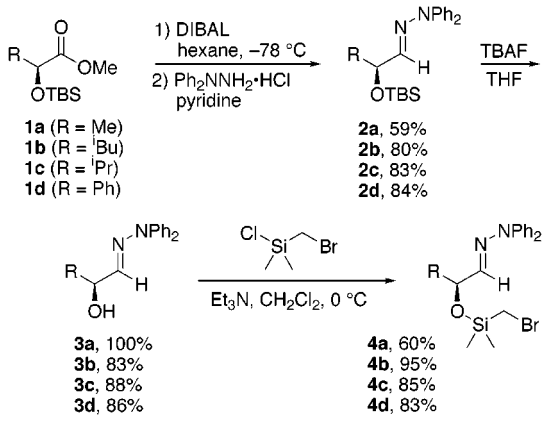


Figure 2. Silicon tether approach to stereocontrolled radical addition to C═N bonds.

of the tether[10] would afford acyclic chiral α-branched amines.[11] Here I disclose initial experiments which confirm the viability of the silicon tether approach for stereoselective hydroxymethylation of hydrazones and explore substituent effects on diastereocontrol.

From readily available enantiomerically pure α-silyloxy esters **1a**−**d**,[12] standard transformations led conveniently to cyclization substrates **4** in good overall yields (Scheme 1).

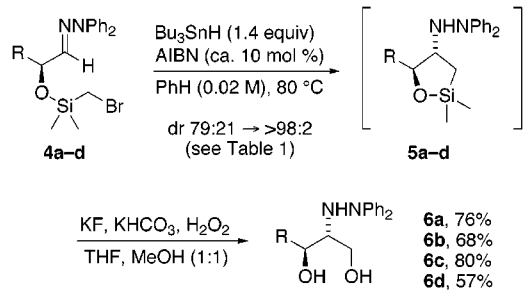
Scheme 1. Preparation of Hydrazone Cyclization Substrates



Silylation and DIBAL reduction gave aldehydes which condensed readily with *N*,*N*-diphenylhydrazine to afford the corresponding hydrazones **2**.[13,14] Desilylation gave α-hydroxy hydrazones **3**,[13] which upon treatment with bromomethyldimethylsilyl chloride in the presence of triethylamine provided radical cyclization substrates **4**.[15,16]

Cyclization of bromides **4** using standard tin hydride conditions (1.4 equiv of Bu_3SnH, 10 mol % of AIBN, PhH, 0.02 M) resulted in very clean, efficient C−C bond construction to furnish unstable cyclic silanes **5** (Scheme 2). In the

Scheme 2. Silicon-Tethered Radical Addition to Hydrazones



same flask, Tamao oxidation[17] (KF, $KHCO_3$, H_2O_2) then smoothly delivered *anti*-2-hydrazino-1,3-diols **6**[13] in good yields. The cyclic silane intermediates were unstable to normal silica gel chromatography but were examined easily

(5) Mild, stereoselective additions to aldehyde imino derivatives are a prominent current challenge. For notable efforts and leading references, see: Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.

(6) (a) Review of radical cyclizations to C═N acceptors: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Intermolecular radical addition to C═N acceptors: Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174 and references therein. (c) General reviews of radical reactions in organic synthesis: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

(7) Only two studies showing acyclic stereocontrol in radical addition to C═N acceptors have appeared to date: Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1789. Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. For acyclic stereocontrol in radical addition to C═C bonds, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163 and references therein.

(8) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: New York; 1995.

(9) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. Reviews: Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. For a recent nonradical application to amino alcohol synthesis, see: Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J.* **1998**, *4*, 2501.

(10) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1.

(11) Importantly, the silicon tether should permit introduction of a variety of functionalized fragments in addition to hydroxymethyl. Tamao, K.; Maeda, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4984.

(12) Esters **1** are prepared easily by standard methods from commercially available hydroxy acids or amino acids.

(13) All structures **2**, **3**, **6**, and **7** are consistent with combustion analyses, spectroscopic data (^1H and ^{13}C NMR, IR, MS), and optical rotation. See Supporting Information.

(14) Hydrazones **2**−**4** were essentially single isomers (>98:2) with respect to the C═N bond; only **2a**−**4a** contained detectable traces (<5%) of a minor isomer. Aldehyde hydrazones are generally obtained as *E* isomers. Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; pp 275−339.

(15) Cyclization substrates **4** were purified rapidly by flash chromatography and used immediately in the next step.

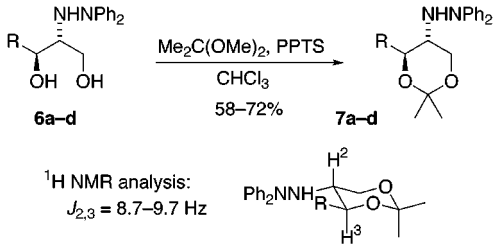
(16) Mosher ester analysis confirmed that the integrity of the preexisting stereocenter was maintained through the sequence to diols **6b** and **6c** (>96% ee). However, alcohol **3d**, wherein the phenyl group can promote enolization, suffered significant racemization en route to **6d**. The α-hydroxy and α-silyloxy hydrazones without additional carbanion-stabilizing functionality are configurationally stable under these conditions.

(17) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, p 315.

by ^{1}H NMR spectroscopy and stored indefinitely in benzene at −5 °C without significant decomposition.

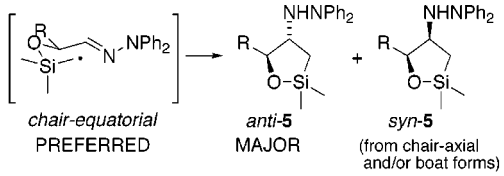
Relative configuration was ascertained upon conversion of diols **6** to the corresponding 1,3-diol acetonides **7**[13] (Scheme 3). Large vicinal coupling constants (^{1}H NMR, $J_{2,3}$ = 8.7−9.7 Hz) revealed *anti* configurations.[18] Predominant chair conformations were confirmed by appropriate acetonide chemical shifts (^{13}C NMR).[19]

Scheme 3. Relative Configurations of 2-Hydrazino-1,3-diols



The Beckwith−Houk model[20] predicts enhancement of diastereoselectivity upon increasing substituent steric demand in 4-substituted 5-hexenyl radical cyclizations. The present method was conceived in expectation that a similar transition state model would apply. Indeed, experimental support for this is seen in the correlation of diastereoselectivity with substituent *A* values[21] (Table 1). A preferred chairlike transition state with a pseudoequatorial substituent minimizing allylic strain is consistent with the observed product distributions; the minor *syn* product would be expected from disfavored chair-axial and/or boat conformations.[22]

Table 1. Correlation of Cyclization Diastereoselectivity with Substituent A Values



entry	R	*A* value[a] (kcal/mol)	product, ratio (anti:syn)[b]
1	Me	1.6	**5a**, 80:20 [**6a**, 79:21]
2	^{i}Bu	1.8 (est.)	**5b**, 88:12 [**6b**, 85:15]
3	^{i}Pr	2.2	**5c**, 95:5 [**6c**, 96:4][c]
4	Ph	2.9	**5d**, >98:2[d] [**6d**, >98:2][d]

[a] *A* values are free energy differences between equatorial and axial chair cyclohexanes.[21] Values for R are assumed similar here in order to show the trend within the series. [b] Ratios from integration of ^{1}H NMR spectra. [c] Gravimetric ratio of separated diastereomers. [d] Minor isomer not detected.

In conclusion, a method for stereocontrolled radical addition to chiral hydrazones has been designed and implemented which, in conjunction with established methods for reductive cleavage of hydrazine N−N bonds,[23] constitutes a novel nonpolar complement to ionic methods for acyclic amino alcohol synthesis. This carbon−carbon bond construction approach to chiral α-branched amine synthesis features the temporary silicon connection for formal acyclic stereocontrol of radical addition to C=N bonds.

Acknowledgment. I thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Additional support was provided by the University of Vermont.

Supporting Information Available: Experimental procedures and complete analytical data for compounds **2**, **3**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Mori, K.; Uenishi, K. *Liebigs Ann. Chem.* **1994**, 41. Barrett, A. G. M.; Rys, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1009. Han, B. H.; Kim, J. C.; Park, M. K.; Park, J. H.; Go, H. J.; Yang, H. D.; Suh, D.-Y.; Kang, Y.-H. *Heterocycles* **1995**, *41*, 1909. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354.

(19) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

(20) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(21) Bushweller, C. H. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995.

(22) Cyclohexane terminology for 5-hexenyl radical transition states is the current convention. See ref 8 for discussion.

(23) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1996**, *116*, 7447. Martin, S. F.; Hom, R. K. *Tetrahedron Lett.* **1999**, *40*, 2887. Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219.