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# Diastereoselective Vinyl Addition to Chiral Hydrazones via Tandem Thiyl Radical Addition and Silicon-Tethered Cyclization

**Gregory K. Friestad* and Sara E. Massari**

*Department of Chemistry, University of Vermont, Burlington, Vermont 05405*

*gregory.friestad@uvm.edu*

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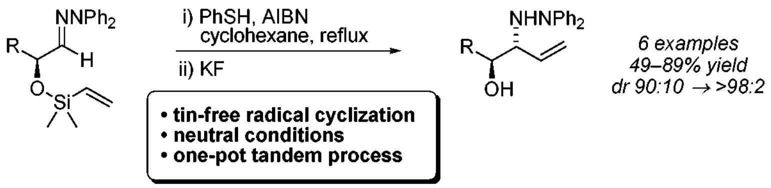
## ABSTRACT



**A diastereoselective method for addition of a vinyl group to α-hydroxy hydrazones under neutral tin-free radical cyclization conditions, leading to substituted vinylglycinols, is presented. Tandem thiyl radical addition/cyclization upon a silicon-tethered vinyl group followed by treatment with potassium fluoride accomplishes a one-pot neutral vinyl addition process to afford acyclic allylic *anti*-hydrazino alcohols in good yield.**

Chiral α-branched amines are a key feature of bioactive naturally occurring amino alcohols such as sphingolipids,[1] hydroxylated pyrrolidines and piperidines (“azasugars”),[2] and aminosugars.[3] Amino alcohols[4,5] are also components of commonly used chiral building blocks, auxiliaries, and ligands in asymmetric synthesis[4] and have been proposed as key binding motifs for design of biomimetic recognition processes.[6] When not available by direct reduction of amino acids, amino alcohols are often prepared by indirect routes involving various permutations of stepwise C−C and C−N bond constructions with a separate asymmetric induction step (e.g., alkene oxidation or carbonyl reduction).[7,8] In contrast,

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[1] For a review, see: Kolter, T.; Sandhoff, K. *Angew. Chem., Int Ed.* **1999**, *38*, 1532.

[2] Reviews: (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750−770. (b) *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998. (c) Nash, R. J.; Watson, A. A.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Tarrytown, NY, 1996; pp 345−376.

[3] (a) Review: Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35−67. (b) For selected recent syntheses, see: Sibi, M.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864. Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rubsam, F.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871.

[4] Reviews: Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

[5] Selected recent C−C bond construction approaches for synthesis of 1,2-amino alcohols: Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818. Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219.

[6] Wong, C.-H.; Hendrix, M.; Manning, D. D.; Rosenblum, C.; Greenberg, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 8319 and references therein.

[7] Alkene oxidation methods demand isomerically pure alkenes, which can in turn require nontrivial syntheses and/or separations.

[8] Representative examples: Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508. Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039. Inaba, T.; Yamada, Y.; Abe, H.; Sagawa, S.; Cho, H. *J. Org. Chem.* **2000**, *65*, 1623. 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.

[9] 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: Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875. Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.

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retrosynthetic C−C bond disconnection of α-branched amines (Figure 1) suggests inherently efficient syntheses may be available by creating both a stereogenic center and a C−C bond in a single synthetic transformation involving addition to a C═N bond. Application of such a C−C bond construction strategy has been underdeveloped, largely because additions of carbanionic reagents to aldehyde imino derivatives[9] (azomethines) under basic conditions often suffer competing aza-enolization.[10] New C−C bond constructions for chiral α-branched amine synthesis under mild conditions are consequently in high demand.[11]

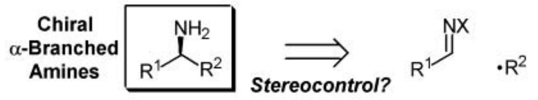

**Figure 1.** Carbon−carbon radical disconnection for synthesis of chiral α-branched amines.

Nonpolar radical addition reactions[12] with aldimine derivatives[13] (Figure 1) should avoid imine aza-enolization and tolerate highly functionalized precursors, complementing carbanion reagents. However, acyclic stereocontrol of alkyl radical addition to C═N acceptors is rare, appearing only in recent reports from our laboratories[14] and those of Naito[15] and Bertrand.[16] Furthermore, a synthetically viable intermolecular addition of vinyl or aryl radicals to C═N bonds has not yet been developed. Here we disclose a temporary silicon tether approach that formally achieves vinyl radical addition to hydrazones via a diastereoselective tandem addition, cyclization, and elimination process.

We have previously shown that conformational constraints can be harnessed via a temporary silicon connection[17] to achieve *formal* acyclic stereocontrol of radical addition to α-hydroxyhydrazones, leading to *anti*-hydrazino-1,3-diols (Figure 2).[18] Along with the hydroxymethyl group addition exemplified in these previous results, our synthetic objectives called for a method to introduce a functionalized two-carbon fragment. Intermolecular addition of heteroatom radicals to an alkene or alkyne can initiate a cyclization event when a second radical acceptor moiety is appropriately situated.[19] We hypothesized that thiyl radical addition to a vinylsilane temporarily tethered to a chiral α-hydroxyhydrazone would facilitate such a cyclization with excellent stereocontrol.[20,21]

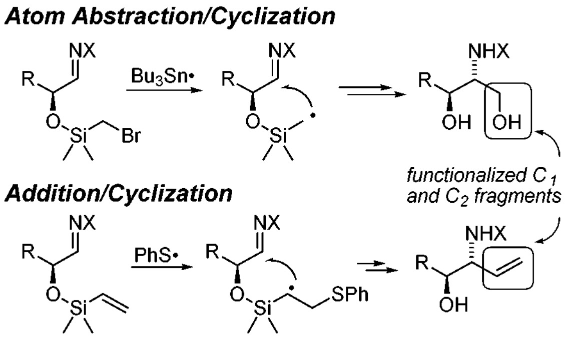

**Figure 2.** Silicon-tethered synthetic equivalents of hydroxymethyl and vinyl groups and their stereocontrolled radical addition to C═N bonds.

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(10) (a) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178. (b) 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.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 6329. (c) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 683. Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7.

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(15) Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1789. Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176.

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(17) 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 of silicon-tethered reactions: 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.

(18) Friestad, G. K. *Org. Lett.* **1999**, *1*, 1499.

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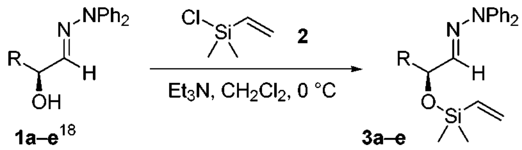
(20) This exploits a vinylsilane as a source of a *tethered radical*. Previously, intramolecular trapping of various cyclic radicals with a vinylsilane as a *tethered radical acceptor* has been reported. Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 5547 and references therein.

Subsequent thiolate elimination during excision of the tether would complete a tandem process comprising stereoselective vinyl addition to a hydrazone. The potentially valuable differentially functionalized allylic amino alcohol products may be regarded as substituted vinylglycinols; the parent structure (R = H) is a chiral building block of well-documented utility.[22]

For an initial feasibility study, we began with glycolaldehyde dimer, which was condensed with diphenylhydrazine to provide α-hydroxyhydrazone **1a**[23] (78%). Silylation with commercially available chlorodimethylvinylsilane (**2,** Scheme 1) provided the addition/cyclization substrate **3a**[23] (93% yield). Although treatment of **3a** with tributyltin hydride and AIBN [2,2′-azobis(isobutyronitrile)] appeared in preliminary experiments to lead to the desired addition/cyclization process as judged by $^1$H NMR spectra, further attempted transformations of the cyclic product gave complex mixtures and low yields. In contrast, treatment with thiophenol and AIBN (cyclohexane, reflux) resulted in very clean, efficient C−C bond construction to furnish cyclic silane **4a** (mixture of diastereomers by $^1$H NMR), which was not amenable to standard flash chromatography on silica gel. In the same flask, **4a** was smoothly converted to allylic hydrazino alcohol **5a**[23] (R = H, racemic) by the action of KF (54% yield, two steps). Presumably *β*-elimination of thiolate occurs from an intermediate fluorosilicate, regenerating the alkene functionality.[24] This one-pot process achieves vinyl addition to a C═N bond under neutral conditions, without toxic and difficult-to-remove stannane reagents.

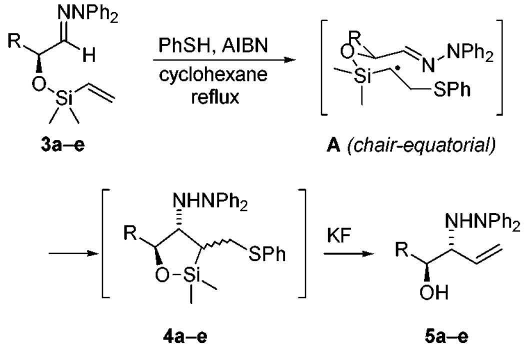
**Scheme 1.** Preparation of Hydrazone Cyclization Substrates



**a**: R = H (93%); **b**: R = Me (83%); **c**: R = $^i$Bu (83%);
**d**: R = $^i$Pr (92%), **e**: R = Ph (75%)

Next we explored the diastereoselectivity of the process using cyclization substrates **3b**−**e**[23,25] (Scheme 1), easily prepared from enantiomerically pure α-hydroxy hydrazones **1b**−**e**[18] by silylation with **2**. Sequential treatment with thiophenol/AIBN and KF led to allylic *anti*-hydrazino alcohols **5b**−**e**[23] (Table 1).[26,27] The diastereoselectivity, 90:10 or higher in all cases, is attributable to conformational constraints imposed by the silicon tether, leading to distinctions among transition states according to the Beckwith−Houk model[28] for 4-substituted 5-hexenyl radical cyclizations. A transition state resembling chairlike conformation **A**, wherein the pseudoequatorial orientation of substituent R minimizes allylic strain, is consistent with the observed *anti* diastereoselection. The minor *syn* product would be expected from disfavored chair-axial and/or boat conformations.[29,30]

**Table 1.** Yields and Selectivities of Radical Addition/Cyclization with Various R Groups[a]



| entry | R | yield,[b] product | ratio (anti:syn)[c] |
|---|---|---|---|
| 1 | H | 54%, **5a** | |
| 2 | Me | 77%, **5b** | 90:10 |
| 3 | $^i$Bu | 67%, **5c** | 94:6 |
| 4 | $^i$Pr | 61%, **5d** | 98:2 |
| 5[c] | $^i$Pr | 89%, **5d** | >98:2[d,e] |
| 6 | Ph | 49%, **5e** | >98:2[e] |

[a] Conditions: 1.2 equiv of PhSH, 10 mol % AIBN, 0.1−0.3 mmol hydrazone in refluxing cyclohexane (0.1 M); 2−3 h with TLC monitoring. If necessary (TLC), additional AIBN was added and the reaction was continued until complete. [b] Isolated yields of diastereomeric mixtures. [c] Ratios from integration of 500 MHz $^1$H NMR spectra. [d] Reaction run on 5 g scale; isolated yield and ratio were determined after crystallization (single diastereomer). [e] Minor isomer not detected.

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(21) A nonradical silicon-tethered strategy using $BF_3{\cdot}OEt_2$-induced vinylsilane addition to an acyliminium ion has been reported. Hioki, H.; Izawa, T.; Yoshizuka, M.; Kunitake, R.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2289.

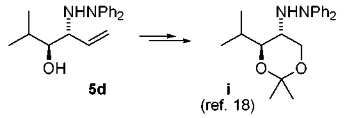
(22) For selected alternative preparations and applications, see: Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99 and references therein. See also: Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187. Monache, G. D.; Misiti, D.; Salvatore, P.; Zappia, G.; Pierini, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2653.

(23) Structures of new compounds **1a**, **1f**, **3**, and **5** are consistent with combustion analyses and spectroscopic data ($^1$H and $^{13}$C NMR, IR, MS) provided in the Supporting Information.

(24) For a similar fluorodesilylative *β*-elimination of a *β*-phenylseleno group, see: Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153.

(25) Hydrazones were obtained as single C═N bond isomers (>98:2).

(26) Relative configuration of **5d** was assigned by chemical correlation: Acetonide formation, Lemieux−Johnson oxidation, reduction, and acetonide equilibration led to known *anti*-2-hydrazino-1,3 diol acetonide **i** (see Supporting Information).



(27) Previous work established that epimerization of α-hydroxy hydrazones during a related sequence did not occur except when the anion-stabilizing phenyl group was present (i.e., **1e**). See ref 18.

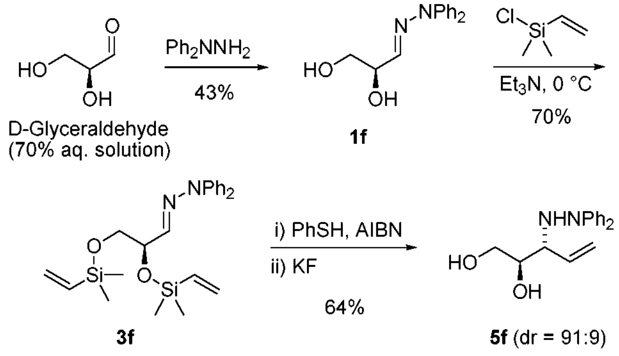
(28) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(29) Cyclohexane terminology for 5-hexenyl radical transition states is the current convention, see ref 12.

(30) We did not attempt to determine the relative configuration of the phenylthiomethyl substituent in **4**; this stereogenic center is lost during the subsequent elimination.

We expected that a D-glyceraldehyde hydrazone containing two tethered vinyl groups would also undergo vinyl transfer stereoselectively through the proximal silyl ether linkage via the more rapid 5-exo cyclization.[31] To test this hypothesis, hydrazone **1f**[23] (Scheme 2) was prepared by condensation of commercially available aqueous D-glyceraldehyde with diphenylhydrazine. Silylation of both hydroxyls afforded vinylation substrate **3f**,[23] wherein 5-exo or 6-exo cyclization could be initiated by thiyl addition to either of the vinylsilanes. In fact, radical vinylation proceeded as before with high selectivity (dr 91:9) to provide allylic hydrazino diol **5f**,[23] a potentially useful chiral building block with differentially functionalized termini. It is worth noting that the two hydroxyls of D-glyceraldehyde do not require protection or differentiation prior to this radical vinylation sequence.

**Scheme 2.** Vinyl Addition to d-Glyceraldehyde Hydrazone without Prior Hydroxyl Protection or Differentiation



Finally, a promising indication for multigram material throughput was observed upon increasing the scale to ca. 5 g (Table 1, entry 5). Crystalline, diastereomerically pure **5d** was obtained in a significantly improved yield (89% after crystallization). Further scale-up has not yet been attempted.

In conclusion, we have developed a carbon–carbon bond construction approach toward synthesis of chiral α-branched amines—specifically, substituted vinylglycinols—which exploits the temporary silicon connection and a tandem radical process for stereocontrolled vinyl addition to C═N bonds. This novel nonpolar acyclic amino alcohol synthesis complements existing methods, and its synthetic utility is under further examination.

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**Supporting Information Available:** Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) For kinetic data, see: Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514.