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A Silicon Tether Approach for Addition of Functionalized Radicals to Chiral α-Hydroxyhydrazones: Diastereoselective Additions of Hydroxymethyl and Vinyl Synthons

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Stereocontrolled additions of hydroxymethyl and vinyl groups to chiral α-hydroxyhydrazones can be achieved by radical cyclizations using bromomethyl or vinyl radical precursors tethered via a temporary silicon connection. Tin-mediated 5-exo radical cyclization of α-hydroxyhydrazones using a silicon-tethered bromomethyl group, followed by oxidative removal of the tether, provides *anti*-2-hydrazino 1,3-diols in good yield. Tandem thiyl radical addition−cyclization of α-hydroxyhydrazones using a silicon-tethered vinyl group, followed by treatment with potassium fluoride, affords acyclic allylic *anti*-hydrazino alcohols in good yield. The thiyl addition−cyclization method has been successfully extended to the use of α,*β*-dihydroxyhydrazones without prior protection or hydroxyl differentiation. Diastereoselection in both reaction types increases with increasing *A* values of the appended groups, consistent with prediction by the Beckwith−Houk model for stereocontrol in 5-hexenyl radical cyclizations.

Introduction

Chiral α-branched amines are key substructures within 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 such as alkene oxidation or carbonyl reduction. It is worth noting that alkene oxidation methods (e.g., epoxidation, dihydroxylation, or aminohydroxylation) demand isomerically pure alkenes which can in turn require nontrivial syntheses and/or separations. In contrast, 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[7] (azomethines) under basic conditions often suffer competing aza-enolization.[8] These considerations make the discovery and development of mild, efficient C−C bond constructions for chiral α-branched amine synthesis an area of very active inquiry.[9]

Nonpolar radical additions[10] to C=N bonds[11] (Figure 1) could (a) circumvent imine aza-enolization problems,

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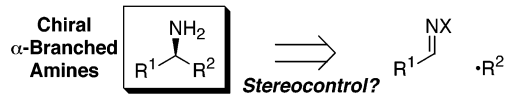

FIGURE 1. Carbon−carbon radical disconnection for synthesis of chiral α-branched amines.

(b) efficiently construct crowded C−C bonds, and (c) tolerate highly functionalized precursors. However, stereocontrolled intermolecular alkyl radical addition to C=N acceptors is rare.[12−14] Furthermore, intermolecular radical addition reactions are normally limited to unfunctionalized alkyl radicals; for example, synthetically viable intermolecular addition of vinyl radicals to C=N bonds has yet to be developed.

We envisioned a novel approach to radical addition to C=N bonds which would address these issues through the use of a temporary linkage to make the radical addition more favorable from an entropic standpoint, avoid side reactions resulting from premature radical quenching, and enforce some conformational constraints to aid in stereocontrol. Applications of silyl ethers as temporary tethers, initially introduced by Nishiyama and Stork for diastereoselective radical reactions,[15] have been extended to a variety of different stereocontrolled C−C bond construction reactions.[16] The wealth of precedents for preparation, utilization, and subsequent manipulations of the silicon tether suggested that this strategy would be a logical first choice as the temporary linkage.

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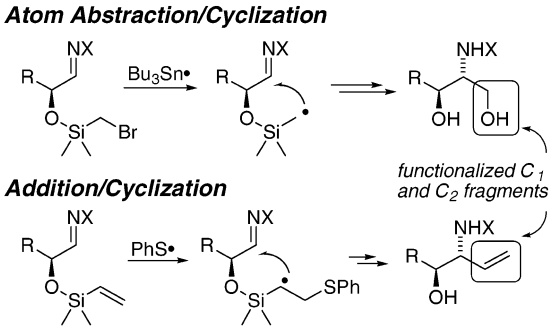


FIGURE 2. Silicon-tethered synthetic equivalents of hydroxymethyl and vinyl groups and their stereocontrolled radical addition to C═N bonds.

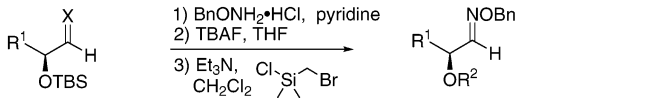
After removal of the tether, the net result would be an acyclic radical adduct; thus if the cyclization step were rendered diastereoselective, the overall process could be considered an indirect strategy for acyclic stereocontrol. Could the well-known high internal conformational diastereocontrol of 5-hexenyl radical cyclizations[10b] be harnessed for this *formal* acyclic stereocontrol of radical addition to C═N bonds?

Our plan was to engage the preexisting stereocenter of a chiral α-hydroxy ester[17] to direct the 5-*exo*-*trig* cyclization of an alkyl radical, tethered via a temporary silicon connection, to an imino acceptor (Figure 2). Subsequent removal of the tether would afford acyclic chiral α-branched amines. Importantly, the silicon tether would permit introduction of a variety of functionalized fragments.[18] As described in preliminary communications, we have exploited this hypothesis to achieve (a) hydroxymethyl group addition[19] through atom abstraction−cyclization of a silicon-tethered bromomethyl group, followed by Tamao oxidation; or (b) vinyl group addition[20] via a tandem thiyl addition−cyclization of a tethered vinyl group, followed by desilylative *β*-elimination of benzenethiolate. Here, we provide a full account, including additional exploratory experiments and expanded discussion, of this work which has led to two complementary approaches for stereocontrolled addition of functionalized radicals to α-hydroxyhydrazones.

Results

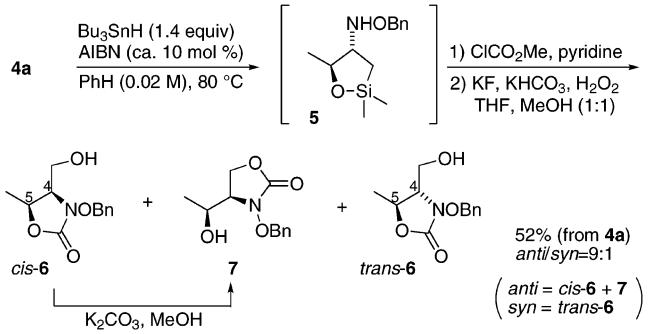
Hydroxymethyl Addition to Oxime Ethers. Our first test of the silicon tether approach for diastereoselective radical addition to α-hydroxyimino compounds involved the use of bromomethyldimethylsilyl (BDMS) ethers. These were chosen because halogen atom abstraction has a wealth of precedent for generating radicals for cyclization; the first studies could then exploit the most standard radical cyclization conditions (Bu_3SnH, AIBN [2,2′-azobis(isobutyronitrile)], PhH, 80 °C), which had already been shown to be successful in addition to various C═N acceptors. Cognizant of the seminal reports

SCHEME 1



1a (X=O, R^1=Me)
1b (X=O, R^1=Ph)
2a (X=NOBn, R^1=Me), 92% (*E*/*Z*=3:1)
2b (X=NOBn, R^1=Ph), 92% (*E*/*Z*=3:1)
3a (R^1=Me, R^2=H), 93% (*E*/*Z*=3.6:1)
3b (R^1=Ph, R^2=H), 95% (*E*/*Z*=4:1)
4a (R^1=Me, R^2=Si(Me)$_2$$CH_2$Br)
4b (R^1=Ph, R^2=Si(Me)$_2$$CH_2$Br)

SCHEME 2



of Bartlett,[21] Hart,[22] and Parker[23] in radical cyclizations to oxime ethers, we selected these readily available C═N radical acceptors for the initial study,

Silylation and DIBAL reduction of methyl lactate and methyl mandelate according to the known method[24] gave aldehydes **1a** and **1b** (Scheme 1), which condensed readily with O-benzylhydroxylamine to afford oxime ethers **2**. Desilylation gave α-hydroxyoxime ethers **3**, which upon treatment with bromomethyldimethylsilyl chloride in the presence of triethylamine provided bromomethylsilyl ethers **4**. These cyclization substrates were sensitive to purification and storage, and required rapid flash chromatography and immediate use in the next step. All of the oxime ethers were obtained as inseparable mixtures of *E* and *Z* isomers (*E*/*Z* ca. 3−4:1) with respect to the C═N bond.

Cyclizations under standard tin-mediated conditions led to material having ^{1}H NMR spectra suggesting its main component was oxasilacyclopentane **5**. The diastereomer ratio was estimated by ^{1}H NMR as 5:1 at this stage. However, a pure compound could not be isolated from this mixture; efforts to extract **5** into an acidic aqueous phase or chromatograph it on silica gel were thwarted by decomposition. Direct Tamao oxidation (KF, $KHCO_3$, H_2O_2, MeOH/THF) of the crude cyclization product gave a complex mixture. Because hydroxylamines are prone to oxidation, it seemed prudent to acylate the basic nitrogen before exposure to oxidant. Acylation of **5** could be achieved with methyl chloroformate and pyridine; Tamao oxidation of this product then gave a mixture of three oxazolidinones *cis*-**6**, *trans*-**6**, and **7** in an overall 52% yield from **4a** (Scheme 2). Although *cis*-**6** and **7** were each separated from the mixture by

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(22) (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. (b) Hart, D. J.; Krishnamurthy, R.; Pook, L. M.; Seely, F. L. *Tetrahedron Lett.* **1993**, *34*, 7819−7822.
(23) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628−4630.
(24) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

silica gel chromatography, *trans*-**6** was not obtained in pure form. After this two-stage derivatization, the anti/syn ratio was 9:1. Two similar derivatization experiments resulted in anti/syn ratios of 4.9:1 and 11.6:1, with low isolated yields. Because all three experiments began with the same crude cyclization material, the ratio of oxazolidinones apparently does not reflect the actual diastereomer ratio from radical cyclization.

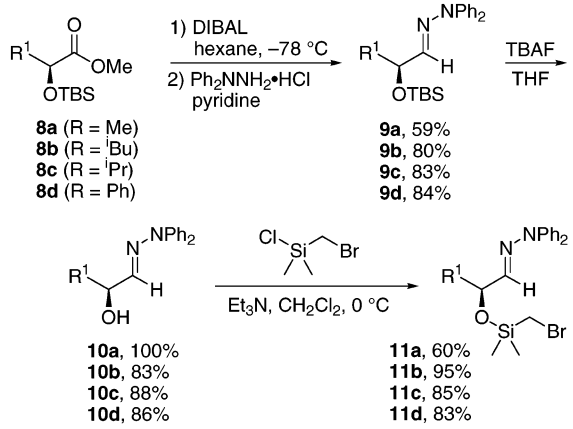
The relative configurations of oxazolidinones *cis*-**6** and *trans*-**6** were determined on the basis of simple correlations of ^{1}H NMR spectra to literature precedents. In numerous examples, including one case with *N*-alkoxy substitution, H4 and H5 of cis-4,5-disubstituted oxazolidinones are reliably shifted downfield by 0.1−0.5 ppm relative to the trans isomers.[25] This chemical shift difference was readily discerned for H4 and H5 of the **6** diastereomers. Accordingly, the isomer with downfield resonances (δ = 3.40, 4.57 ppm) was assigned the structure *cis*-**6**, and the one showing upfield resonances (δ = 3.20, 4.45 ppm) was assigned as *trans*-**6**.

Chemical behavior established the relative configuration of monosubstituted oxazolidinone **7** and corroborated the assignments of *cis*- and *trans*-**6**. Different exposures to the basic Tamao oxidation conditions gave dramatically different ratios of **7** and *cis*-**6**, while the amounts of *trans*-**6** were similar. This suggested that the monosubstituted oxazolidinone **7** was configurationally related to *cis*-**6** and that these constitutional isomers are interconverted by transesterification under the Tamao oxidation conditions. This isomerization only occurs with one of the disubstituted oxazolidinones, providing evidence in favor of the indicated assignments. Torsional strain associated with the vicinal substituents should differentiate the cis and trans oxazolidinone isomers; in this scenario the relief of strain by transesterification of *cis*-**6** to the monosubstituted isomer would appear more favorable. In further support of this assignment, exposure of isomerically pure cis-**6** with K_2CO_3/MeOH indeed produced **7**.

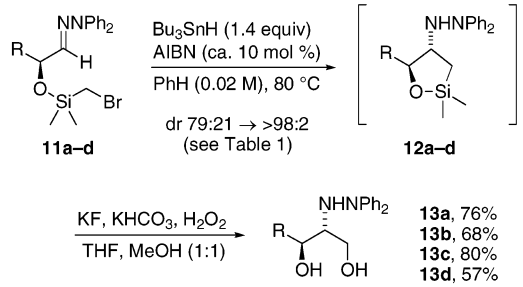
Although these preliminary results suggested the potential utility of the silicon tether for diastereocontrolled radical addition to C=N bonds, some problems were noted. First, an attempt to apply the multistep procedure to mandelate derivative **3b** failed to give synthetically useful yields, casting some doubt on the versatility of the sequence. Second, the diastereoselectivities of the cyclizations were obscured by the multistep follow-up sequence leading to **6**. Finally, from a more practical standpoint, the oxime ethers were obtained as inseparable *E*/*Z* mixtures in all cases. Other imino derivatives were considered in an effort to avoid these problems.

Hydroxymethyl Addition to Hydrazones. We turned to hydrazones in hopes of improving on the results

SCHEME 3



SCHEME 4



observed with oxime ethers. Hydrazone cyclization substrates were prepared using standard transformations from the α-silyloxy esters **8** (Scheme 3), as described above for the oxime ethers. The intermediate aldehydes obtained by DIBAL reduction were condensed with *N*,*N*-diphenylhydrazine to afford the corresponding hydrazones **9**, followed by desilylation to give **10**. Installation of the bromomethylsilyl radical precursor group conveniently provided cyclization substrates **11** in good overall yield. Although these bromomethylsilyl ethers were somewhat unstable, they could be briefly exposed to silica gel in order to obtain partially purified materials suitable for the subsequent radical cyclizations. Hydrazones **9**−**11** were essentially single isomers (>98:2) with respect to the C=N bond;[26] only the lactate-derived compounds (**9a**−**11a**) contained detectable traces (<5%) of a minor isomer.

Cyclization of bromides **11** using standard tin hydride conditions (1.4 equiv of Bu_3SnH, 10 mol % AIBN, PhH, 0.02 M) resulted in very clean, efficient C−C bond construction to furnish heterocycles **12** (Scheme 4, Table 1). These cyclic silanes were unstable to normal silica gel chromatography but could be stored indefinitely in benzene at −5 °C without significant decomposition. In the same flask, Tamao oxidation[27] for oxidative removal of the tether[28] (KF, $KHCO_3$, H_2O_2) then smoothly delivered *anti*-2-hydrazino-1,3-diols **13** in good yields. It is worth noting that the Tamao oxidation occurs cleanly in the presence of an unprotected hydrazine; this contrasts with the behavior of hydroxylamine **5** described above.

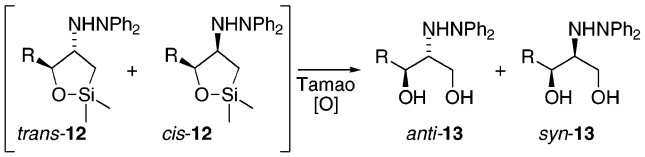
(25) Oh, J. S.; Park, D. Y.; Song, B. S.; Bae, J. G.; Yoon, S. W.; Kim, Y. G. *Tetrahedron Lett.* **2002**, *43*, 7209−7212. Ncube, A.; Park, S. B.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3625−3636. Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510−12517. Merino, P.; Castillo, E.; Franco, S.; Merchán, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301−12322. Deng, J. G.; Hamada, Y.; Shioiri, T. *Synthesis* **1998**, 627−638. Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271−3274. Falb, E.; Nudelman, A.; Hassner, A. *Synth. Commun.* **1993**, *23*, 2839−2844. Moreno-Mañas, M.; Padros, I. *J. Heterocycl. Chem.* **1993**, *30*, 1235−1239. Foglia, T. A.; Swern, D. *J. Org. Chem.* **1968**, *34*, 1680−1684.

(26) 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.

(27) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 315−321.

(28) Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1−64.

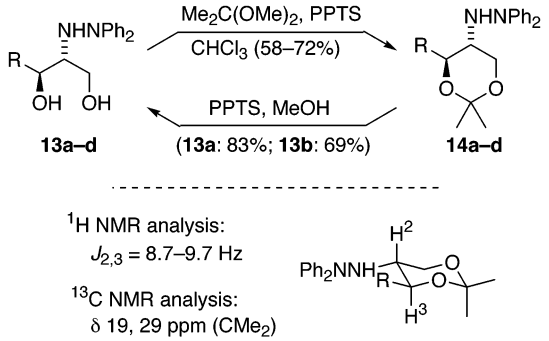
TABLE 1. Diastereomer Ratios in Cyclization and Tamao Oxidation Sequence from Bromomethyldimethylsilyl Ethers 11a−d (Scheme 4)



entry	R	oxasilacyclopentane product, ratio (trans/cis)[a]	2-hydrazino 1,3-diol product, ratio (anti/syn)[a]
1	Me	**12a**, 80:20	**13a**, 79:21
2	*i*Bu	**12b**, 88:12	**13b**, 85:15
3	*i*Pr	**12c**, 95:5	**13c**, 96:4[b]
4	Ph	**12d**, >98:2[c]	**13d**, >98:2[c]

[a] Ratios from integration of ^{1}H NMR spectra. [b] Ratio of isolated diastereomers. [c] Minor isomer not detected.

SCHEME 5



Diastereoselectivities of the cyclizations were revealed by independent analyses which were found to give consistent results. Examination of cyclic silanes **12** by ^{1}H NMR spectroscopy gave a direct measure of the diastereomer ratios. A separate measurement was made after Tamao oxidation; the results were very similar. Although **13a** and **13b** could not be obtained in diastereomerically pure form at this stage, the diastereomeric products *syn*-**13c** and *anti*-**13c** could be separated after Tamao oxidation; the ratio of isolated diastereomers was nearly identical to the ratio determined spectroscopically at the cyclic silane stage.

For further stereochemical analysis of the hydroxymethyl adducts, 1,3-diol acetonides **14** (Scheme 5) were prepared by treatment with dimethoxypropane (PPTS, $CHCl_3$). During this preparation of **14a** from **13a**, small amounts of a material tentatively identified as a 4,5-disubstituted 1,3-dioxolane (i.e., a five-membered cyclic O,N-acetal) were observed; this material was converted to **14a** on standing. For **13a** and **13b**, which were used as diastereomeric mixtures, this procedure offered the benefit of easy chromatographic separation of the anti and syn diastereomers of acetonides **14a** and **14b**. Hydrolysis (PPTS, MeOH) then gave access to the diastereomerically pure major isomers **13a** and **13b**.

Relative configurations of diols **13** were readily ascertained via NMR spectra of the corresponding acetonides. Analysis of ^{1}H NMR spectra of the major isomers **14a−d** revealed large vicinal coupling constants ($J_{2,3}$ = 8.7−9.7 Hz) in all cases, consistent with the assignment of anti configurations.[29] The reliability of this assignment was verified by the dramatic differences in chemical shifts of the acetonide methyl groups in ^{13}C NMR spectra characteristic of axial and equatorial orientations; this confirmed the predominance of chair conformations.[30]

Configurational Integrity. Mosher ester analysis confirmed that the integrity of the preexisting stereocenter was maintained through the sequence to diols **13b** and **13c** (>96% ee). Thus, the α-hydroxy and α-silyloxy hydrazones in these sequences are configurationally stable under the conditions employed in this study. However, alcohol **10d**, wherein the phenyl group can promote enolization, suffered significant racemization at some point en route to **13d**. Mosher ester analysis of **13d** showed only 33% ee. It is most likely that the racemization occurs during silylation using triethylamine as a base. Unfortunately, an attempt to confirm this was unsuccessful: significant decomposition occurred during preparation of the Mosher ester from α-hydroxyhydrazone **10d**. Nevertheless, it can be concluded that, so long as additional carbanion-stabilizing functionality is not present to facilitate enolization (as in **10d**), the silicon tether strategy for radical addition to α-hydroxyhydrazones preserves the configurational integrity of the starting α-hydroxyester.

Tandem Thiyl Addition−Cyclization: Vinyl Addition to Hydrazones. Having shown that conformational constraints can be harnessed via a temporary silicon connection to achieve *formal* acyclic stereocontrol in hydroxymethyl addition, we sought a method to introduce a functionalized two-carbon fragment. We recognized that intermolecular addition of heteroatom radicals to an alkene or alkyne can initiate a cyclization event when a second radical acceptor moiety is appropriately situated.[31,32] This led to the hypothesis that stannyl or thiyl radical addition to a vinyl group, temporarily tethered to a chiral α-hydroxyhydrazone, would lead to an alkyl radical which could cyclize with excellent stereocontrol.[33,34] Because chlorodimethylvinylsilane is inexpensive and commercially available in large quantities, its derived vinylsilyl ethers appeared to be attractive starting points to test this hypothesis.

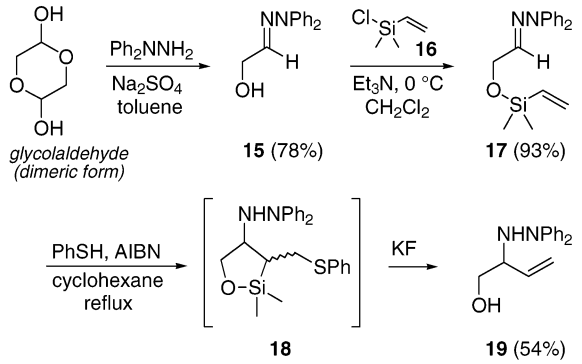
(29) Coupling constants of acetonides have previously been used to elucidate the relative configurations of various 2-amino-1,3-diols. Devijver, C.; Salmoun, M.; Daloze, D.; Braekman, J. C.; De Weerdt, W. H.; De Kluijver, M. J.; Gomez, R. *J. Nat. Prod.* **2000**, *63*, 978−980. Mancini, I.; Guella, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 51−58. Mori, K.; Uenishi, K. *Liebigs Ann. Chem.* **1994**, 41−48. Barrett, A. G. M.; Rys, D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1009−1017. 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*, 1909−1914. Herold, P.; *Helv. Chim. Acta* **1988**, *71*, 354−362.

(30) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9−17.

(31) Reviews: Miyata, O.; Naito, T. *C. R. Acad. Sci. Paris, Chim.* **2001**, *4*, 401−421. Naito, T. *Heterocycles* **1999**, *50*, 505−541. For selected recent examples, see: Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213−224. Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459−4479. Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199−6207. Depature, M.; Diewok, J..; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2000**, 275−280. Ryu, I.; Ogura, S.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 1515−1518. Depature, M.; Siri, D.; Grimaldi, J.; Hatem, J.; Faure, R. *Tetrahedron Lett.* **1999**, *40*, 4547−4550. Marco-Contelles, J.; Rodriguez, M. *Tetrahedron Lett.* **1998**, *39*, 6749−6750.

(32) For cyclizations of C=N acceptors initiated by intermolecular addition of alkyl radicals, see: Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071−4074. Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618−5626. Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835−3838.

SCHEME 6

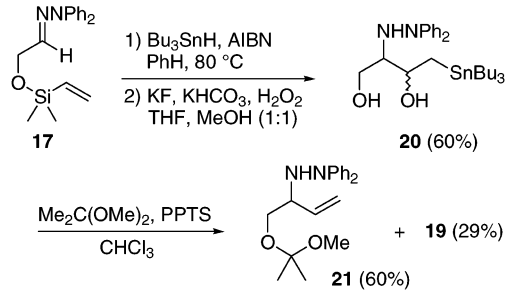


For an initial feasibility study, we began with glycolaldehyde dimer, which was condensed with diphenylhydrazine to provide α-hydroxyhydrazone **15** (78%). Silylation with chlorodimethylvinylsilane (**16,** Scheme 6) provided the addition/cyclization substrate **17** (93% yield). Treatment of **17** with thiophenol and AIBN (cyclohexane, reflux) resulted in very clean, efficient C−C bond construction to furnish cyclic silane **18** as a mixture of diastereomers (Scheme 6). Like its analogues **5** and **12**, **18** was not amenable to standard flash chromatography on silica gel. In the same flask, **18** was smoothly converted to allylic hydrazino alcohol **19** (racemic) by the action of excess KF (54% yield, 2 steps). This one-pot process (**17** → **19**) achieves vinyl addition to a C=N bond under neutral conditions, without toxic and difficult-to-remove stannane reagents.

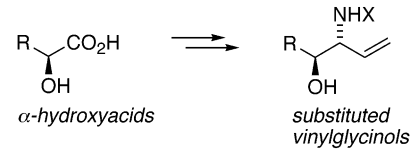
The formation of **19** can be rationalized by a tandem process entailing thiyl (PhS•) addition to the terminal carbon of the alkene of **17**, followed by cyclization of the resulting α-silylalkyl radical to form an aminyl radical. Quenching of the cyclized aminyl radical by hydrogen atom abstraction from thiophenol would generate **18** and a thiyl radical, propagating a radical chain. Upon treatment of **18** with fluoride, *β*-elimination of thiolate presumably occurs from an intermediate fluorosilicate, regenerating the alkene functionality during the desilylation.[35] Radical addition products bearing sulfur could not be found after the fluorodesilylation.

A similar tandem sequence was explored using stannyl radicals. Addition−cyclization of **17** with tributyltin hydride and AIBN (Scheme 7) appeared to lead to the desired addition/cyclization process as judged by ^{1}H NMR spectra. However, further attempted transformations (fluorodesilylation or Tamao oxidation) of the cyclic product gave complex mixtures and generally low yields. In one case, Tamao oxidation in refluxing methanol−THF occurred in 60% yield to furnish tin-containing diol **20**

SCHEME 7



SCHEME 8



as a diastereomeric mixture. When this diol was exposed to acidic transacetalization conditions (dimethoxypropane, PPTS), a mixture of alkenes **19** and **21** was formed.[36] Without precautions to exclude acid and adventitious moisture, the mixed acetal **21** was rapidly hydrolyzed during ^{1}H NMR analysis in $CDCl_3$ to afford **19** along with equimolar amounts of methanol and acetone. The formation of alkenes **19** and **21** along with loss of the tributyltin presumably occurs by a cationic *β*-elimination process during acetonide formation. Although the net result indicated successful C−C bond construction, the tin-mediated process was discontinued in favor of further pursuit of the thiyl addition-cyclization reactions; the latter seemed more attractive because of the opportunity to avoid the use of toxic tin reagents.

Chiral α-hydroxy acids could be envisioned as precursors for chiral α-hydroxyhydrazones analogous to achiral glycolaldehyde derivative **17**. The overall sequence involving the thiyl addition−cyclization reaction would then lead to substituted vinylglycinols. These are potentially useful differentially functionalized allylic amino alcohol building blocks; the parent structure (Scheme 8, R = X = H) is a chiral building block of well-documented utility.[37]

Toward this end, we explored the diastereoselectivity of the tandem thiyl addition-cyclization process using cyclization substrates **22a**−**d**[38] (Scheme 9), easily prepared from enantiomerically pure α-hydroxy hydrazones **10a**−**d** by silylation with **16**. Reductive cyclization occurred upon treatment with thiophenol/AIBN, affording

(33) 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 by Matsuda et al. For examples, see: Kodama, T.; Shuto, S.; Nomura, M.; Matsuda, A. *Chem. Eur. J.* **2001**, *7*, 2332−2340. Shuto, S.; Yahiro, Y.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 5547−5557 and references therein.

(34) A nonradical silicon-tethered strategy using BF_3•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*, 2289−2292.

(35) For a similar fluorodesilylative *β*-elimination of a *β*-phenylseleno group, see: Sugimoto, I.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1999**, *64*, 7153−7157.

(36) In this experiment, cyclic hemiaminal **25** was also formed in low yield.

(37) For selected alternative preparations and applications, see: Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99−102, and references therein. See also: Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802−1815. Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12−13. Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329−6343. Chandrasekhar, S.; Raza, A.; Takhi, M. *Tetrahedron: Asymmetry* **2001** *13*, 423−428. Sabat, M.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1209−1212. Sabat, M.; Johnson, C. R. *Org. Lett.* **2000**, *2*, 1089−1092. Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887−5890. Harris, M. C. J.; Jackson, M.; Lennon, I. C.; Ramsden, J. A.; Samuel, H. *Tetrahedron Lett.* **2000**, *41*, 3187−3191. Monache, G. D.; Misiti, D.; Salvatore, P.; Zappia, G.; Pierini, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2653−2659.

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

SCHEME 9

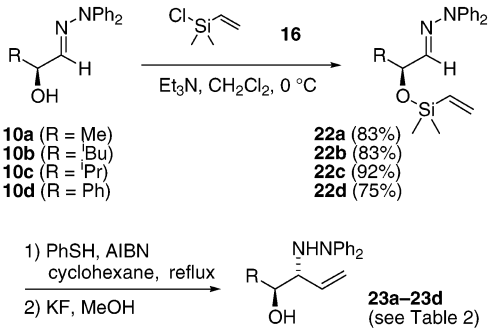
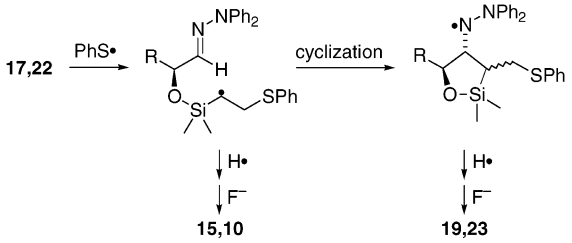


TABLE 2. Yields and Selectivities of Thiyl Addition−Cyclization of Hydrazones 22a−d (Scheme 9)[a]

entry	R	product, yield[b] (%)	ratio (anti/syn)[c]
1	Me	**23a**, 77	90:10
2	^{i}Bu	**23b**, 67	94:6
3	^{i}Pr	**23c**, 61	98:2
4[d]	^{i}Pr	**23c**, 89	>98:2[d,e]
5	Ph	**23d**, 49	>98:2[e]

[a] Conditions: 1.2 equiv of PhSH, 10 mol % AIBN, 0.1−0.3 mmol of 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, yield and ratio after isolation by crystallization. [e] Minor isomer not detected.

SCHEME 10



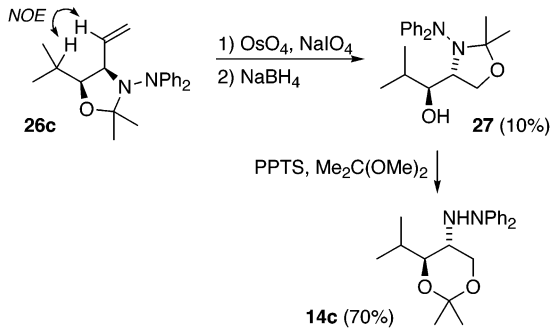
cyclic silane intermediates similar to **18**.[39] Exposure to KF led to allylic *anti*-hydrazino alcohols **23a**−**d** (Table 2). Diastereomers *anti*-**23a** and *syn*-**23a** were readily separated by chromatography. For characterization purposes, pure *anti*-**23b** was obtained by conversion to its acetonide derivative (vide infra), chromatographic separation, and hydrolysis.

A promising indication for multigram material throughput was observed upon increasing the scale to ca. 5 g (Table 2, entry 4). Crystalline, diastereomerically pure **23c** was obtained in a significantly improved yield (89% after crystallization).

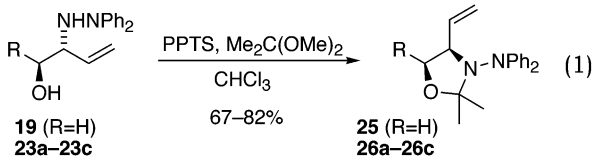
Variable amounts of α-hydroxyhydrazones **10** or **15** (ca. 3−10% yield) were generally observed as byproducts after the fluorodesilylation stage of the thiyl addition−cyclization process. As judged by ^{1}H NMR analysis, alkenes were absent prior to treatment with fluoride. Thus, the recovery of this material can be attributed to hydrogen atom abstraction to quench the α-silyl radical prior to cyclization, leading to the product of simple addition of thiophenol (Scheme 10).[40] Fluorodesilylation of the uncyclized thiophenol adducts would regenerate the α-hydroxyhydrazones **15** (R = H, from **17**) or **10** (R = alkyl or aryl, from **22**).

(39) Unfortunately, ^{1}H NMR analysis of the cyclic silane intermediate did not give a clear indication of the diastereomer ratio.

SCHEME 11



Conversion of **19** and **23a**−**c** to their 2,2-dimethyloxazolidine (acetonide) derivatives was facile (eq 1). Using 1 equiv of PPTS and excess 2,2-dimethoxypropane, the acetonides **25** and **26a**−**c** were formed smoothly in synthetically useful yields on milligram scale. Using 10 mol % PPTS, the reaction of **23c** was scaled up to 0.5 g with similar results (75% yield).



Relative configuration of *anti*-**23c** was determined by a combination of chemical correlation experiments and NOE difference spectra using the diastereomerically pure acetonide **26c**. Lemieux−Johnson oxidation,[41] followed by borohydride reduction of the intermediate aldehyde, gave a low yield of acetonide **27** (Scheme 11). Exposure to the typical acetonide-forming conditions then converted this to **14c**, the configuration of which had already been established (see Scheme 5). Strong NOE enhancements were observed between the isopropyl methine and the internal olefinic hydrogen of **26c**,[42] providing further support for the assigned structure.

Diastereocontrol. The Beckwith−Houk model[43] 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[44] (Table 3). A transition state resembling chairlike conformation **A** (Scheme 12), 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

(40) The premature hydrogen abstraction process would be expected to be suppressed by slow addition of the thiophenol.

(41) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478−479.

(42) The NOE enhancement was 10% at the internal vinyl hydrogen upon irradiation of the isopropyl methine; the inverse enhancement was 8% at the isopropyl methine.

(43) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974.

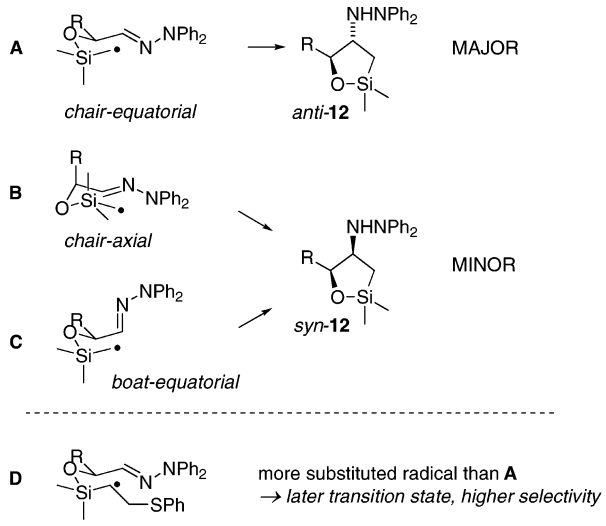
(44) Bushweller, C. H. In *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York, 1995.

TABLE 3. Correlation of Substituent *A* Values with Diastereoselectivity in Hydroxymethyl and Vinyl Addition

entry	R	*A* value (kcal/mol)[a]	dr of **13**[b]	dr of **23**[c]
1	Me	1.6	79:21	90:10
2	^{i}Bu	1.8 (est)	85:15	94:6
3	^{i}Pr	2.2	96:4	98:2
4	Ph	2.9	>98:2[d]	>98:2[d]

[a] Free energy differences between equatorial and axial chair conformers of the monosubstituted cyclohexane. [b] Hydroxymethyl addition; ratios determined as described in Table 1. [c] Vinyl addition; ratios determined as described in Table 2. [d] Minor isomer not detected.

SCHEME 12

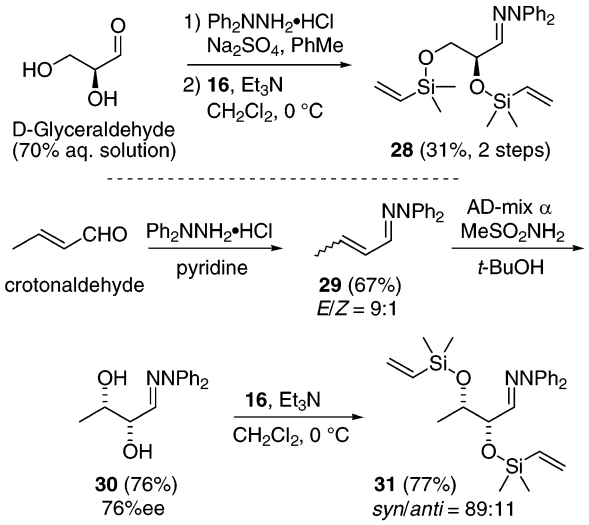


disfavored chair-axial (**B**) and/or boat (**C**) conformations.[45] Boat-axial conformations are considered to have negligible contributions to stereocontrol in 5-hexenyl radical cyclizations.[10b]

The diastereoselectivity of vinyl addition, 90:10 or higher in all cases, is also attributable to the conformational constraints described above. The vinyl additions occurred with consistently higher stereoselectivity in comparison to hydroxymethyl addition. This fact may be rationalized by considering the relative reactivities of the two radical intermediates **A** and **D** (Scheme 12). If the more reactive silylmethyl radicals **A** are assumed to have earlier transition states than the more substituted alkyl radicals **D**, this might elicit a decreased contribution from the cyclohexane-like conformational constraints described above and a decreased differentiation of the diastereomeric transition states leading to the alternative anti and syn products.

Vinyl Addition to α,β-Dihydroxyhydrazones. We expected that α,β-dihydroxyhydrazones, which would support two tethered vinyl groups, could also undergo vinyl transfer stereoselectively. In this case, either 5-exo or 6-exo cyclization could be initiated by thiyl addition to either of the two tethered vinylsilanes. No evidence of 6-endo cyclization was found in the experiments described above, so 6-endo or 7-endo cyclizations may be regarded as unlikely. Indeed, only a few examples of radical addition at the nitrogen atom of imino acceptors have been reported, facilitated through polarity effects or engineered through modifications to radical reactivity. Here, in the absence of any unusual regiocontrol factors, 5-exo cyclization through the proximal silyl ether linkage would be expected to predominate, considering the more rapid rates relative to 6-exo cyclization. Rates of 5-exo cyclization in related hydrazones with carbon tethers have been determined by competition experiments to be about 100 times faster than the corresponding 6-exo cyclizations.[46]

SCHEME 13



(AD-mix α: $K_2OsO_4•2H_2O$, $(DHQ)_2PhAl$, $K_3Fe(CN)_6$, K_2CO_3)

To test the feasibility of this approach, two bis-(vinylsilyloxy)hydrazone cyclization precursors were synthesized from glyceraldehyde and crotonaldehyde. Hydrazone **28** (Scheme 13) was prepared by condensation of commercially available aqueous D-glyceraldehyde with diphenylhydrazine, followed by silylation of both hydroxyl groups with chlorosilane **16**. Another diol precursor was obtained from *E*-crotonaldehyde, which was condensed with diphenylhydrazine to furnish hydrazone **29** in 67% yield as a ca. 9:1 mixture of olefin isomers (Scheme 13).[47] Sharpless asymmetric dihydroxylation (AD)[48] afforded the resulting diol in 76% yield as a mixture of *syn*- and *anti*-diol diastereomers; the major *syn*-diol **30** was formed in 76% ee.[49,50] The minor *anti*-diol was not unexpected considering the small amount of *Z*-olefin present in the precursor. Bis-silylation of the *syn*-diol with **16** furnished cyclization substrate **31** in 77% yield (syn/anti = 89:11).

Vinyl addition to bis-silylated substrate **28** (Scheme 14) occurred upon treatment with thiophenol/AIBN; fluorodesilylation using KF furnished hydrazino diol **32** with

(45) (a) Boat-axial conformations are considered to have negligible contributions to stereocontrol in 5-hexenyl radical cyclizations.[10b] (b) Cyclohexane terminology for 5-hexenyl radical transition states is the current convention.[10b]

(46) For kinetic data, see: Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514−6516.

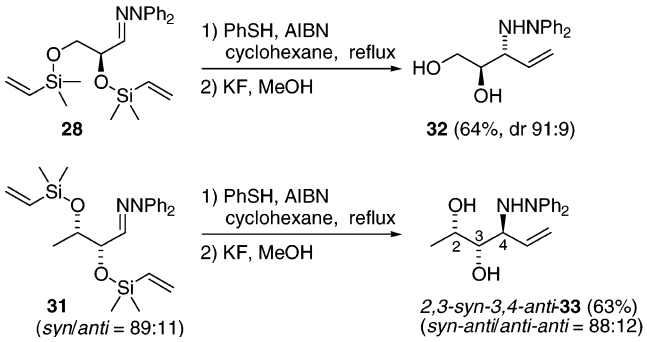
(47) The *E*- and *Z*-isomers were inseparable at this point. Although only the major isomer is shown in the following steps, minor diastereomers were present as judged by ^{1}H NMR spectra.

(48) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(49) Enantiomeric excess and absolute configuration were assessed through ^{1}H NMR analysis of the corresponding bis-Mosher esters (see the Supporting Information).

(50) To our knowledge, this is the first example of asymmetric dihydroxylation in the presence of a hydrazone.

SCHEME 14

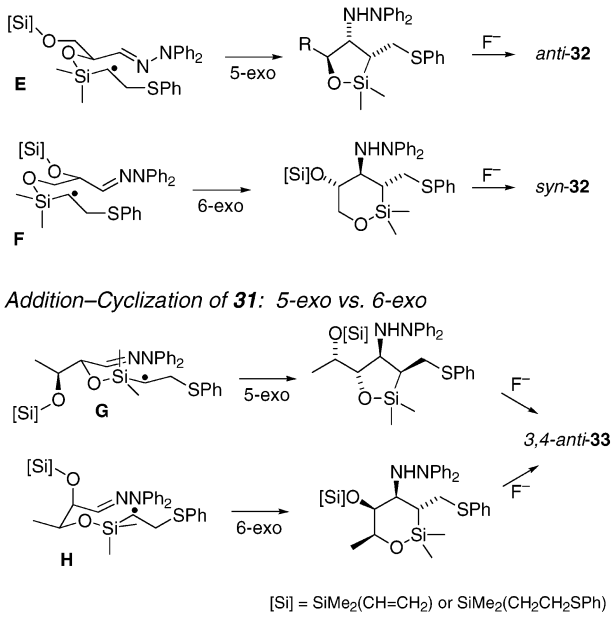


high selectivity (dr 91:9) as observed in the monosilylated substrates. Cyclization substrate **31** also underwent the addition-cyclization process to afford **33** (dr 88:12) in 63% yield after chromatographic purification. Another diastereomer was present, carried through from the syn/anti mixture of **31** (dr 89:11) employed in this experiment.[51] For this reason, the stereochemical outcome is not entirely unambiguous in this case. However, both *syn*-**31** and *anti*-**31** appeared to undergo highly diastereospecific vinyl addition; only two of the four possible diastereomers of **33** were found, and they were present in the same ratio as the starting material. Also, a key point is clearly established by the vinyl additions of Scheme 14: The two hydroxyls of D-glyceraldehyde or dihydroxyhydrazone **30** do not require protection or differentiation prior to this radical vinylation sequence. It should be noted also that **32** and **33** are potentially useful chiral building blocks bearing differentially functionalized termini.

Relative configurations of diols **32** and **33** were assigned by analogy to the hydrazino alcohols **13** and **23** described above. Mechanistic considerations support both of these assignments (Scheme 15). First, the D-glyceraldehyde-derived **32** could arise through either 5-exo or 6-exo cyclization of **28**, which could be initiated by thiyl addition to either α-vinylsilyloxy or *β*-vinylsilyloxy groups, respectively. Assuming the C−C bond formations (i.e., the cyclization steps) are irreversible, the faster 5-exo cyclization via **E** should predominate and the Beckwith−Houk model can be invoked as described above to predict *anti*-**32** as the major product. The 6-exo pathway from **28** via **F** would result in the corresponding *syn*-**32**, with low stereoselectivity expected because of the low *A* value of the silyloxy substituent. Accordingly, the highly stereoselective formation of *anti*-**32** (91:9) lends support to the suggestion of a preferred 5-exo pathway and justification for the application of the Beckwith−Houk model for predicting the anti configuration. Cyclization substrate **31** also could potentially cyclize via either 5-exo or 6-exo modes, with the 5-exo route via **G** predicted to be kinetically preferred, leading to 3,4-*anti*-**33**. In this case, however, the competition between the pathways would be nullified by their convergence to the same configuration. In the 6-exo mode, the additional methyl group of **31** (compared to **28**) should enforce a preference for the alternative chair conformer **H** with the smaller silyloxy

(51) A mixture of syn and anti diols (dr 9:1) was employed. These inseparable isomers resulted from the 9:1 ratio of inseparable *E*- and *Z*-olefins used in the asymmetric dihydroxylation.

SCHEME 15



substituent axial. After cyclization and fluorodesilylation, both pathways should lead to the same diastereomer; this stereoconvergency model is consistent with the very high diastereoselectivity (>98:2 with respect to the new stereocenter) observed in formation of **33**. In all the vinyl additions, the stereocenter generated adjacent to the Si atom is not preserved after fluorodesilylation, and therefore it is premature to draw any definitive conclusions from this work about the stereocontrol at this center during cyclization. However, it can be assumed that an equatorial orientation of the radical subsituent is preferred, as shown in the transition states **D**−**H**.

Conclusion

In conclusion, a method for stereocontrolled radical addition to chiral hydrazones has been designed and implemented, which, in conjunction with various established methods for reductive cleavage of hydrazine N−N bonds,[52] 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. The hydroxymethyl group can be added to a range of chiral α-hydroxyhydrazones using a bromomethylsilyl ether as a radical precursor via tin-mediated halogen atom abstraction. The vinyl group can be added using a vinylsilyl ether which is activated for radical cyclization by thiyl radical addition. In the latter case, the method has been successfully extended to the

(52) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927−2931. Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266−6267. Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219−1222. Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447−7448. Martin, S. F.; Hom, R. K. *Tetrahedron Lett.* **1999**, *40*, 2887−2890. Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* **2000**, *56*, 8673−8678. Deniau, E.; Enders, D. *Tetrahedron* **2001**, *57*, 2581−2588. Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197−7200.

use of α,β-dihydroxyhydrazones without prior protection or hydroxyl differentiation. Stereoselectivity in both these processes is consistent with predictions by the Beckwith-Houk model for 5-exo cyclizations of substituted 5-hexenyl radicals.

Experimental Section[53]

Hydroxymethyl Addition to Oxime Ethers. (*S*)-2-(*tert*-Butyldimethylsilyloxy)propanal *O*-Benzyloxime (2a). A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal[24] (**1a**) (0.5 g, 2.6 mmol) and *O*-benzylhydroxylamine hydrochloride (0.48 g, 3.0 mmol) in pyridine (1 mL) was stirred at ambient temperature for 40 h. After concentration in vacuo to remove most of the pyridine, the mixture was partitioned between aq $NaHCO_3$ and CH_2Cl_2. Drying over Na_2SO_4, concentration, and gradient flash chromatography (hexane → 10:1 hexane/EtOAc) furnished **2a** (715 mg, 92% yield, inseparable 3:1 *E*/*Z* mixture) as a colorless oil. *E*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.29 (m, 6H), 5.07 (s, 2H), 4.41 (quintet, *J* = 6.4 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 137.6, 128.3, 128.2, 127.8, 75.8, 66.6, 25.8, 22.4, 18.1, −4.6, −4.9. *Z*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 5.6 Hz, 1H), 5.07 (ABq, Δν = 8.5 Hz, *J* = 12.4 Hz, 2H), 5.02−4.96 (m, 1H), 1.28 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 137.9, 127.9, 76.1, 63.0, 25.8, 21.0, 18.1, −4.9, −5.0; some resonances were not resolved from those of the major isomer. *E*/*Z* mixture: IR (film, ATR) 2955, 1471, 1254, 1089 cm^{-1}; MS (APCI-LCMS, H_2O/MeOH) *m*/*z* (relative intensity) 294 ([M + H]$^+$, 100), 162 (22). Anal. Calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.18; H, 9.42; N, 4.84.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylethanal *O*-Benzyloxime (2b). A solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylethanal[24] (**1b**) (536 mg, 2.14 mmol) and *O*-benzylhydroxylamine hydrochloride (0.38 g, 2.4 mmol) in pyridine (1 mL) and toluene (1 mL) was stirred at ambient temperature for 36 h. After concentration in vacuo to remove most of the pyridine, the mixture was partitioned between aq $NaHCO_3$ and CH_2Cl_2. Drying over Na_2SO_4, concentration, and gradient flash chromatography (hexane → 5:1 hexane/EtOAc) furnished **2b** (702 mg, 92% yield, inseparable 3:1 *E*/*Z* mixture) as a colorless oil. *E*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.30 (m, 11H), 5.37 (d, *J* = 7.6 Hz, 1H), 4.54 (s, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 140.9, 137.3, 128.4, 128.3, 128.2, 127.8, 127.6, 125.8, 75.9, 72.2, 25.8, 18.2, −4.6, −4.9. *Z*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 6.3 Hz, 1H), 6.07 (d, *J* = 6.3 Hz, 1H), 5.17 (ABq, Δν = 7.6 Hz, *J* = 11.0 Hz, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 140.7, 137.7, 128.2, 128.0, 127.8, 127.6, 126.0, 76.3, 67.3, 25.8, 18.2, −4.6, −4.9; some resonances were not resolved from those of the major isomer. *E*/*Z* mixture: IR (film, ATR) 3045, 2954, 1453, 1253, 1005 (s) cm^{-1}; MS (APCI-LCMS, H_2O/MeOH) *m*/*z* (relative intensity) 356 ([M + H]$^+$, 100), 256 (30), 224 ([M − OTBS]$^+$, 92). Anal. Calcd for $C_{21}H_{29}NO_2Si$: C, 70.94; H, 8.22; N, 3.94. Found: C, 71.16; H, 8.35; N, 4.04.

(*S*)-2-Hydroxypropanal *O*-Benzyloxime (3a). A solution of **2a** (42 mg, 0.14 mmol) and tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.17 mL, 0.17 mmol) in THF (1.7 mL) was stirred at ambient temperature for 1 h. Concentration in vacuo and flash chromatography (5:1 hexane/EtOAc) furnished **3a** (23.3 mg, 93% yield, inseparable 3.6:1 *E*/*Z* mixture) as a colorless oil. *E*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 4.7 Hz, 1H), 7.38−7.30 (m, 5H), 5.08 (s, 2H), 4.42 (qd, *J* = 6.6, 4.8 Hz, 2.22 (br s, 1H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 137.2, 128.4, 128.3, 128.0, 76.1, 65.6, 21.1. *Z*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 5.0 Hz, 1H), 5.12 (s, 3H), 4.89−4.84 (m, 1H), 1.33 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 76.4, 62.5, 20.0; some resonances were not resolved from those of the major isomer. *E*/*Z* mixture: IR (film, ATR) 3400 (br), 2926, 1454, 1021 cm^{-1}; MS (APCI-LCMS, H_2O/MeOH) *m*/*z* (relative intensity) 180 ([M + H]$^+$, 100). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.45; H, 7.37; N, 7.57.

(*S*)-2-Hydroxy-2-phenylethanal *O*-Benzyloxime (3b). A solution of **2b** (352 mg, 0.99 mmol) and TBAF (1 M in THF, 1.2 mL, 1.2 mmol) in THF (12 mL) was stirred at ambient temperature for 1 h. Concentration in vacuo and flash chromatography (5:1 hexane/EtOAc) furnished **3b** (227 mg, 95% yield, inseparable 4:1 *E*/*Z* mixture) as a colorless oil. *E*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 5.3 Hz, 1H), 7.43−7.28 (m, 10H), 5.34 (d, *J* = 5.1 Hz, 1H), 5.14 (s, 2H), 2.60 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 139.6, 137.2, 128.7, 128.4, 128.3, 128.2, 128.0, 126.4, 76.3, 71.7. *Z*-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 5.5 Hz, 1H), 5.86 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 140.0, 137.3, 128.6, 128.0, 76.5, 68.0; some resonances were not resolved from those of the major isomer. *E*/*Z* mixture: IR (film, ATR) 3413 (br), 3032, 1453, 1010 (s) cm^{-1}; MS (APCI-LCMS, H_2O/MeOH) *m*/*z* (relative intensity) 242 ([M + H]$^+$, 100), 224 ([M − OH]$^+$, 58). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.28; H, 6.37; N, 5.72.

Oxazolidinones *cis*-6, 7, and *trans*-6. A solution of α-hydroxyoxime **3a** (196 mg, 1.09 mmol) in dry CH_2Cl_2 (1.1 mL) at 0 °C was treated sequentially with Et_3N (0.20 mL, 1.4 mmol) and bromomethyldimethylsilyl chloride (0.20 mL, 1.4 mmol). After 0.5 h at 0 °C, the mixture was diluted with ether (2 mL) and filtered through a short plug of silica gel (elution with ether). Rapid flash chromatography (10:1 hexane/EtOAc) gave bromomethylsilyl ether **4a** (297 mg, 83%) which was used directly for the subsequent step. A portion of **4a** (170 mg, 0.515 mmol), tributyltin hydride (0.19 mL, 0.67 mmol), and 2,2′-azobis(isobutyronitrile) (AIBN, 20 mg, 0.12 mmol) in benzene (18 mL) was deoxygenated (N_2 via needle) for ca. 10 min and then heated at reflux for 1.5 h. Additional AIBN (20 mg, 0.12 mmol) was added in two portions at 0.5 h intervals. The colorless crude intermediate cyclic silane (**5**, dr 5:1 by ^{1}H NMR) was obtained as a solution in benzene. A portion of the cyclic silane (0.023 M in benzene, 4.0 mL, 0.092 mmol) was concentrated to remove benzene and then treated with pyridine (11 μL, 0.14 mmol) and methyl chloroformate (11 μL, 0.14 mmol) in CH_2Cl_2 (0.3 mL) at ambient temperature for ca. 12 h. The reaction mixture was partitioned between CH_2Cl_2 and H_2O, dried (Na_2SO_4), and concentrated. The residue was dissolved in THF/methanol (1:1, 0.5 mL) and treated with KF (15 mg, 0.26 mmol) and $KHCO_3$ (20 mg, 0.20 mmol) at ambient temperature for 15 min, followed by addition of H_2O_2 (30%, 0.1 mL, 0.88 mmol). After 8 h, the emaining H_2O_2 was quenched with aqueous $Na_2S_2O_3$ (20%, 0.5 mL), and the reaction mixture was diluted with ether, dried over Na_2SO_4, and concentrated. Gradient flash chromatography (hexane → EtOAc) afforded a mixture of oxazolidinones *cis*-**6**, **7**, and *trans*-**6** (17 mg, 52%[54] from **4a**) as a colorless oil. Radial chromatography resolved *cis*-**6** and **7**, but *trans*-**6** could not be obtained in pure form. Monosubstituted oxazolidinone **7** (anti): [α] $^{29}_D$ +112 (*c* 0.17, $CHCl_3$); IR (film, ATR) 3450 (br), 1760 (s), 1210 (s), 1074 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.40 (m, 5H), 5.04 (ABq, Δν = 33 Hz, *J* = 11.5 Hz, 2H), 4.22 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.17 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.78 (qd, *J* = 6.7, 2.3 Hz, 1H), 3.53 (ddd, *J* = 8.3, 8.3, 2.3 Hz, 1H), 1.45 (br s, 1H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 135.5, 19.9, 129.2, 128.8, 77.4, 63.1 (2C), 61.2, 17.3; MS *m*/*z* (relative intensity) 238 ([M + H]$^+$, 100). Disubstituted oxazolidinone *trans*-**6** (syn): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (ABq, Δν = 17.8 Hz, *J* = 11.6 Hz, 2H), 4.44 (dq,

(53) A general statement describing materials and methods is provided in the Supporting Information.

(54) Note that the theoretical yield is based on the portions of crude material used for each step.

J = 8.1, 6.3 Hz, 1H), 3.47 (ddd, J = 12.4, 4.1, 3.0 Hz, 1H), 3.34 (ddd, J = 12.5, 9.0, 2.3 Hz, 1H), 3.19 (ddd, J = 8.04, 2.5, 2.5 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H); some resonances were not resolved from those of the major isomer. Disubstituted oxazolidinone *cis*-**6** (anti): $[\alpha]^{29}_D$ −9.5 (*c* 0.11, $CHCl_3$); IR (film, ATR) 3444 (br), 1754 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.37 (m, 5H), 5.00 (ABq, $\Delta\nu$ = 46 Hz, J = 11.3 Hz, 2H), 4.55 (qd, apparent quintet, J = 6.7 Hz, 1H), 3.87 (dd, J = 12.3, 3.8 Hz, 1H), 3.63 (dd, J = 12.3, 2.3 Hz, 1H), 3.43−3.39 (m, 1H), 1.65 (br s, 1H), 1.44 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 135.5, 129.5, 128.9, 128.6, 78.2, 72.1, 62.1, 58.0, 14.9; MS *m*/*z* (relative intensity) 238 ($[M + H]^+$, 100). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.57; H, 6.44; N, 5.82.

Hydroxymethyl Addition to Hydrazones. General Procedure C: 2-Hydrazino-1,3-diols 13. A solution of α-hydroxyhydrazone (e.g., **10a**−**d**[55]) in dry CH_2Cl_2 (ca. 1 M) at 0 °C was treated sequentially with Et_3N (1.3 equiv) and bromomethyldimethylsilyl chloride (1.3 equiv). Copious white precipitate formed immediately. After being warmed to room temperature over 0.5 h, the mixture was diluted with ether (ca. 4 mL/mmol Et_3N) and filtered through a short plug of silica gel (elution with ether). Rapid flash chromatography (20:1 then 10:1 hexane/EtOAc) gave bromomethylsilyl ether **11** as a colorless oil which was used immediately in the next step (prolonged storage or prolonged exposure to silica gel led to decomposition). A solution of the bromomethylsilyl ether **11** and tributyltin hydride (1.4 equiv) in benzene (ca. 0.02 M) was deoxygenated (N_2 via needle) for ca. 10 min. AIBN (10 mol %) was added, and the mixture was deoxygenated for 5 min and then heated at reflux for 0.5 h. If TLC indicated incomplete reaction at this point, additional AIBN was added and heating was continued for another 0.5 h. Concentration of the reaction mixture afforded the colorless crude intermediate cyclic silane **12**, which was analyzed by ^1H NMR to determine the diastereomer ratio (integral ratios for Si*Me*$_2$ and C*H*NHNPh$_2$ resonances). A solution of the cyclic silane **12** in THF/methanol (1:1, ca. 0.1 M) was treated at room temperature with KF (3.5 equiv), $KHCO_3$ (2 equiv) and H_2O_2 (30% aqueous solution, 10 equiv). After 0.5−2 d, the mixture was diluted with an equal volume of ether, and 50% aqueous $Na_2S_2O_3$ (ca. 0.2 mL/mmol H_2O_2) was added. The mixture was filtered through Celite with the aid of additional ether, concentrated, partitioned between CH_2Cl_2 and brine, and dried (Na_2SO_4). Concentration and gradient flash chromatography (hexane → EtOAc) provided 2-hydrazino-1,3-diol **13**.

(2*R*,3*S*)-(+)-2-(*N*,*N*-Diphenylhydrazino)butane-1,3-diol (13a, R = Me). From **10a** (361 mg, 1.02 mmol) via general procedure C was obtained **11a** (215 mg, 60% yield) as a colorless viscous oil. From **11a** (59 mg, 0.15 mmol) was obtained **13a** (30.9 mg, 76% yield, 79:21 diastereomeric ratio). These isomers were separated via acetonide **14a**, which was hydrolyzed (PPTS, methanol) to give an analytical sample of the major diol *anti*-**13a** (anti/syn = 90:10) as a colorless viscous oil: $[\alpha]^{27}_D$ +25 (*c* 0.71, $CHCl_3$); IR (film) 3390 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 4H), 7.19−7.15 (m, 4H), 7.05−7.01 (m, 2H), 4.53 (br s, 1H), 4.16−4.10 (m, 1H), 3.92−3.81 (m, 2H), 3.01 (ddd, J = 6.8, 3.7, 3.4 Hz, 1H), 2.60 (br s, 1H), 2.11 (br s, 1H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 129.3, 122.9, 120.6, 67.0, 62.5, 60.6, 18.6; MS *m*/*z* (relative intensity) 273 ($[M + H]^+$, 100), 168 (90) (diastereomeric mixture). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.27; H, 7.38; N, 10.08.

(2*R*,3*S*)-(+)-2-(*N*,*N*-Diphenylhydrazino)-5-methylhexane-1,3-diol (13b, R = ^{i}Bu). From **10b** (70 mg, 0.25 mmol) via general procedure C was obtained **11b** (103 mg, 83% yield) as a colorless viscous oil. From **11b** (103 mg, 0.238 mmol) was obtained **13b** (51 mg, 68% yield, 85:15 diastereomeric ratio by ^1H NMR, major isomer >96% ee by Mosher ester analysis). These isomers were separated via acetonide **14b**, which was hydrolyzed (PPTS, methanol) to give an analytical sample of the major diol *anti*-**13b** as a colorless viscous oil: $[\alpha]^{27}_D$ +21 (*c* 0.83, $CHCl_3$); IR (film) 3400 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.20−7.17 (m, 4H), 7.05−7.01 (m, 2H), 4.65 (br s, 1H), 4.05−4.00 (m, 1H), 3.88−3.80 (m, 2H), 2.99 (ddd, J = 6.2, 3.7, 3.2 Hz, 1H), 2.57 (br s, 1H), 2.19 (br s, 1H), 1.70−1.60 (m, 1H), 1.50 (ddd, J = 13.9, 9.6, 5.5 Hz, 1H), 1.17 (ddd, J = 13.5, 8.6, 3.7, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 129.3, 122.8, 120.5, 68.9, 62.0, 60.7, 41.9, 24.9, 23.4, 22.0; MS *m*/*z* (relative intensity) 315 ($[M + H]^+$, 80), 168 (100). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.57; H, 8.33; N, 8.91. Found: C, 72.75; H, 8.32; N, 8.87.

(2*R*,3*S*)-(+)-2-(*N*,*N*-Diphenylhydrazino)-5-methylhexane-1,3-diol (13c, R = ^{i}Pr). From **10c** (93 mg, 0.347 mmol) via general procedure C was obtained **11c** (124 mg, 85% yield) as a colorless viscous oil. From **11c** (123 mg, 0.293 mmol) was obtained **13c**, which was further purified by radial chromatography to afford *syn*-**13c** (3 mg) and *anti*-**13c** (68 mg, 80% combined yield, 96:4 diastereomeric ratio, anti isomer >96% ee by Mosher ester analysis) as colorless viscous oils. Minor diastereomer *syn*-**13c**: IR (film) 3401 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.28 (m, 4H), 7.20−7.18 (m, 4H), 7.05−7.00 (m, 2H), 4.65 (br s, 1H), 3.91 (dd, J = 11.5, 2.4 Hz, 1H), 3.67−3.60 (m, 1H), 3.52 (dd, J = 5.6, 5.3 Hz, 1H), 3.12 (ddd, J = 6.4, 3.3, 3.3 Hz, 1H), 2.26 (br s, 1H), 2.10 (br s, 1H), 1.96−1.87 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 129.3, 122.9, 120.7, 76.5, 61.8, 59.4, 29.9, 19.7, 16.5; MS *m*/*z* (relative intensity) 301 ($[M + H]^+$, 85), 300 (M^+, 30), 170 (95), 168 (100). Major diastereomer *anti*-**13c**: $[\alpha]^{20}_D$ +33 (*c* 1.3, $CHCl_3$); IR (film) 3410 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.30 (m, 4H), 7.19−7.16 (m, 4H), 7.06−7.02 (m, 2H), 4.47 (br s, 1H), 3.88−3.80 (ABX, J_{AB} = 11.4 Hz, J_{AX} = 3.7 Hz, J_{BX} = 6.1 Hz, $\Delta\nu_{AB}$ = 15.9 Hz, 2H), 3.54 (dd, J = 8.7, 3.0 Hz, 1H), 3.17 (ddd, J = 6.2, 3.6, 3.5 Hz, 1H), 2.86 (br s, 1H), 2.40 (br s, 1H), 1.77−1.68 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 129.3, 122.8, 120.6, 76.1, 60.4, 59.3, 30.3, 19.5, 18.8; MS *m*/*z* (relative intensity) 301 ($[M + H]^+$, 100), 300 (M^+, 45), 170 (98), 168 (65). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.73; H, 8.24; N, 9.16.

(2*R*,3*S*)-(−)-2-(*N*,*N*-Diphenylhydrazino)-3-phenylpropane-1,3-diol (13d, R = Ph). From **10d** (104 mg, 0.344 mmol) via general procedure C was obtained **11d** (129 mg, 85% yield) as a colorless viscous oil. From **11d** (129 mg, 0.285 mmol) was obtained **13d** (54 mg, 57% yield, single diastereomer by ^1H NMR, 33% ee by Mosher ester analysis) as a colorless viscous oil. $[\alpha]^{25}_D$ −5.4 (*c* 0.14, $CHCl_3$, 33% ee); IR (film) 3390 (br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 9H), 7.12−7.08 (m, 4H), 7.05−7.00 (m, 2H), 5.00 (dd, J = 5.2, 2.1 Hz, 1H), 4.34 (br s, 1H), 3.84 (ddd, J = 11.5, 5.7, 5.7 Hz, 1H), 3.76 (br d, J = 11.5 Hz, 1H), 3.22 (ddd, J = 5.3, 5.3, 4.1 Hz, 1H), 2.92 (br s, 1H), 2.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 140.5, 129.3, 128.6, 127.9, 126.2, 122.8, 120.5, 73.0, 63.4, 60.6; MS *m*/*z* (relative intensity) 335 ($[M + H]^+$, 40), 170 (30), 168 (30), 107 (100). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.56; H, 6.75; N, 8.25.

Tandem Thiyl Addition−Cyclization: Vinyl Addition to Hydrazones. General Procedure E: Preparation of α-(Vinyl)silyloxyhydrazones 17 and 22a−d. A solution of an α-hydroxyhydrazone (e.g., **15**,[55] **10a**−**d**[55]) in dry CH_2Cl_2 (ca. 1 M) at 0 °C was treated sequentially with Et_3N (1.3 equiv) and chlorodimethylvinylsilane (**16**, 1.3 equiv). White precipitate formed immediately. After being warmed to room temperature over 5 h, the mixture was diluted with ether (ca. 4 mL/mmol Et_3N) and filtered through a short plug of silica gel (elution with ether). Flash chromatography (10:1 hexane/EtOAc) gave silyl ethers **17** and **22** as colorless oils.

2-(Dimethylvinylsilyloxy)ethanal *N*,*N*-Diphenylhydrazone 17. From **15** (300 mg, 1.32 mmol), **16** (0.23 mL, 1.71

(55) For preparation of this compound, see the Supporting Information.

mmol), and Et_3N (0.24 mL, 1.71 mmol) by general procedure E was obtained **17** (381 mg, 93% yield) as a colorless oil: IR (film) 3067, 2958, 1595, 1495 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.36 (m, 4H), 7.14−7.11 (m, 2H), 7.11−7.09 (m, 4H), 6.51 (t, J = 5.1 Hz, 1H), 6.11 (dd, J = 20.0, 14.7 Hz, 1H), 6.03 (dd, J = 14.7, 4.1 Hz, 1H), 5.79 (dd, J = 20.0, 4.1 Hz, 1H), 4.34 (d, J = 5.1 Hz, 2H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 137.1, 136.4, 133.4, 129.6, 124.2, 122.3, 63.5, −2.0; MS (CI) m/z (relative intensity) 311 ([M + H]$^+$, 100%), 168 (50). Anal. Calcd for $C_{18}H_{22}SiN_2O$: C, 69.64; H, 7.14 N, 9.02. Found: C, 69.92; H, 7.26; N, 8.91.

(*S*)-(−)-2-(Dimethylvinylsilyloxy)propanal *N*,*N*-Diphenylhydrazone (22a, R = Me). From **10a** (718 mg, 3.00 mmol), **16** (0.53 mL, 3.90 mmol), and Et_3N (0.54 mL, 3.90 mmol) by general procedure E was obtained **22a** (813 mg, 83% yield) as a colorless oil: $[\alpha]^{29}_D$ −21.8 (*c* 1.85, $CHCl_3$); IR (film) 3050, 2969, 1591, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48−7.45 (m, 4H), 7.24−7.21 (m, 6H), 6.55 (d, J = 5.9 Hz, 1H), 6.26 (dd, J = 20.3, 14.8 Hz, 1H), 6.11 (dd, J = 14.8, 3.8 Hz, 1H), 5.90 (dd, J = 20.3, 3.8 Hz, 1H), 4.72−4.69 (m, 1H) 1.45 (d, J = 6.3 Hz, 3H), 0.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 140.9, 137.9, 133.1, 129.7, 124.3, 122.4, 69.5, 22.6, −1.1, −1.2; MS (CI) m/z (relative intensity) 325 ([M + H]$^+$, 100), 168 (M, 20). Anal. Calcd for $C_{19}H_{24}SiN_2O$: C, 70.33; H, 7.45; N, 8.63. Found: C, 70.37; H, 7.48; N, 8.49.

(*S*)-(−)-2-(Dimethylvinylsilyloxy)-4-methylpentanal *N*,*N*-Diphenylhydrazone (22b, R = ^{i}Bu). From **10b** (750 mg, 2.65 mmol), **16** (0.47 mL, 3.44 mmol), and Et_3N (0.48 mL, 3.44 mmol) by general procedure E was obtained **22b** (810 mg, 83% yield) as a colorless oil: $[\alpha]^{29}_D$ −13.2 (*c* 1.41, $CHCl_3$); IR (film) 3050, 2956, 1595, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.37 (m, 4H), 7.17−7.14 (m, 2H), 7.11−7.09 (m, 4H), 6.35 (d, J = 6.5 Hz, 1H), 6.15 (dd, J = 20.2, 14.7 Hz, 1H), 6.03 (dd, J = 14.7, 3.7 Hz, 1H), 5.79 (dd, J = 20.2, 3.7 Hz, 1H) 4.49 (ddd, J = 8.1, 6.2, 6.2 Hz, 1H), 1.75−1.67 (m, 1H), 1.55 (ddd, J = 13.8, 8.1, 6.1 Hz, 1H), 1.38 (ddd, J = 13.5, 7.6, 5.9 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.21 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 140.7, 137.9, 133.0, 129.7, 124.2, 122.4, 71.9, 45.3, 24.2, 23.1, 22.4, −1.1; MS (CI) m/z (relative intensity) 367 ([M + H]$^+$, 100), 168 (M, 20). Anal. Calcd for $C_{22}H_{30}SiN_2O$: C, 72.08; H, 8.25; N, 7.64; O. Found: C, 72.35; H, 8.33; N, 7.48.

(*S*)-(+)-2-(Dimethylvinylsilyloxy)-3-methylbutanal *N*,*N*-Diphenylhydrazone (22c, R = ^{i}Pr). From **10c** (140 mg, 0.522 mmol), **16** (0.09 mL, 0.68 mmol), and Et_3N (0.09 mL, 0.68 mmol) by general procedure E was obtained **22c** (170 mg, 92% yield) as a colorless oil: $[\alpha]^{29}_D$ +15.0 (*c* 1.38, $CHCl_3$); IR (film) 3050, 2958, 1594, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.37 (m, 4H), 7.15−7.14 (m, 2H), 7.11−7.09 (m, 4H), 6.35 (d, J = 6.9 Hz, 1H), 6.15 (dd, J = 20.3, 13.8 Hz, 1H), 6.00 (dd, J = 13.8, 2.8 Hz, 1H), 5.80 (dd, J = 20.3, 2.8 Hz, 1H), 4.05−4.10 (m, 1H), 1.75−1.70 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 140.2, 138.1, 132.9, 129.8, 124.2, 122.4, 78.6, 33.8, 18.4, −1.1, −1.2; MS (CI) m/z (relative intensity) 353 ([M + H]$^+$, 100), 168 (11). Anal. Calcd for $C_{21}H_{28}SiN_2O$: C, 71.54; H, 8.00; N, 7.96. Found: C, 71.67; H, 8.05; N, 8.05.

(*S*)-(−)-2-(Dimethylvinylsilyloxy)-2-phenylacetaldehyde *N*,*N*-Diphenylhydrazone (22d, R = Ph). From **10d** (520 mg, 1.72 mmol), **16** (0.31 mL, 2.23 mmol), and Et_3N (0.31 mL, 2.23 mmol) by general procedure E was obtained **22d** (500 mg, 75% yield) as a colorless oil: $[\alpha]^{29}_D$ −74.4 (*c* 1.17, $CHCl_3$); IR (film) 3060, 2959, 1592, 1495 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.24 (m, 8H), 7.20−7.10 (m, 1H), 7.05−7.02 (m, 6H), 6.42 (d, J = 6.7 Hz, 1H), 6.15 (dd, J = 20.3, 14.9 Hz, 1H), 6.10 (dd, J = 14.9, 3.9 Hz, 1H), 5.75 (dd, J = 20.3, 3.9 Hz, 1H), 5.50 (d, J = 6.7 Hz, 1H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 142.0, 139.6, 137.6, 133.4, 129.8, 128.3, 127.3, 126.0, 124.4, 122.4, 75.3, −1.1, −1.2; MS (CI) m/z (relative intensity) 387 ([M + H]$^+$, 52), 168 (15). Anal. Calcd for $C_{24}H_{26}SiN_2O$: C, 74.57; H, 6.78; N, 7.25. Found: C, 74.86; H, 6.85; N, 7.29.

(*R*)-(+)-2,3-Bis(dimethylvinylsilyloxy)propanal *N*,*N*-Diphenylhydrazone (28). A solution of d-glyceraldehyde *N*,*N*-diphenylhydrazone (29 mg, 0.11 mmol) in dry CH_2Cl_2 (1.1 mL) at 0 °C under nitrogen was treated sequentially with Et_3N (0.040 mL, 0.29 mmol) and **16** (0.048 mL, 0.29 mmol). A white precipitate formed immediately. After being warmed to room temperature over 5 h, the mixture was diluted with an equal volume of ether and filtered through a short plug of silica gel (elution with ether). Flash chromatography (10:1 hexane/EtOAc) gave **28** (33 mg, 70% yield) as a colorless oil: $[\alpha]^{29}_D$ +31.7 (*c* 1.28, $CHCl_3$); IR (film) 3050, 2958, 1592, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42−7.39 (m, 4H), 7.17−7.12 (m, 6H), 6.42 (d, J = 6.2 Hz, 1H), 6.21−6.10 (m, 2H), 6.13−6.00 (m, 2H), 5.81−5.77 (m, 2H), 4.53−4.45 (m, 1H), 3.70 (d, J = 5.5 Hz, 2H), 0.24 (s, 3H), 0.23 (s, 3H), 0.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 137.9, 137.7, 137.3, 133.1, 133.0, 129.6, 124.1, 122.3, 74.0, 66.0, −1.3, −1.4, −2.0, −2.1; MS (CI) m/z (relative intensity) 425 ([M + H]$^+$, 100), 409 (54). Anal. Calcd for $C_{23}H_{32}N_2O_2Si_2$: C, 65.05; H, 7.59; N, 6.59. Found: C, 65.29; H, 7.78; N, 6.44.

(2*S*,3*S*)-2,3-Bis(dimethylvinylsilyloxy)butanal *N*,*N*-Diphenylhydrazone (31). To a solution of diol **30** (1.46 g, 5.41 mmol), Et_3N (2.10 mL, 15.1 mmol), and DMAP (64.4 mg, 0.394 mmol) in toluene (75 mL) was added **16** (1.88 mL, 13.6 mmol) at ambient temperature. After 2 h, the reaction mixture was concentrated and partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography afforded silyl ether **31** (1.844 g, 77% yield) as a colorless oil containing a mixture of syn and anti diastereomers (dr 89:11). Major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.36 (m, 4H), 7.16−7.14 (m, 2H), 7.10−7.08 (m, 4H), 6.37 (d, J = 6.9 Hz, 1H), 6.20−6.05 (m, 2H), 6.05−5.90 (m, 2H), 5.80−5.70 (m, 2H), 4.22 (dd, J = 6.9, 6.3 Hz, 1H), 3.80 (dddd, apparent quintet, J = 6.3 Hz, 1H), 1.07 (d, J = 6.3 Hz, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.152 (s, 3H), 0.147 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 138.2, 138.1, 137.9, 132.8, 132.6, 129.6, 124.1, 122.3, 77.8, 71.2, 19.6, −1.2, −1.3. Diastereomeric mixture: IR (film) 3050, 2962, 1593, 1496 cm^{-1}; MS (CI) m/z (relative intensity) 439 ([M + H]$^+$, 100), 337 (86), 168 (34). Anal. Calcd for $C_{24}H_{34}N_2O_2Si_2$: C, 65.71; H, 7.91; N, 6.39. Found: C, 66.11; H, 7.92; N, 6.39.

General Procedure F: Tandem Thiyl Radical Addition−Cyclization and Elimination. A solution of silyl ether and thiophenol (1.2 equiv) in cyclohexane (ca. 0.1 M) was deoxygenated (nitrogen via needle) for ca. 10 min. AIBN (10 mol %) was added, and the mixture was deoxygenated for 5 min and then heated at reflux for 2−3 h. If TLC indicated incomplete reaction at this point, additional AIBN was added and heating continued for another 15 h. After concentration of the reaction mixture, a solution of the residual oil in THF (ca. 0.15 M) was treated at room temperature with a saturated KF/MeOH solution (14 mL/mmol silyl ether). After 20 h, the solution was diluted with hexane, washed with water, dried (Na_2SO_4), and concentrated. Diastereomer ratios were determined by integration of ^1H NMR spectra prior to flash chromatography (10:1 → 5:1 hexane/EtOAc), which afforded the hydrazino alcohols **19** and **23a**−**d** as mixtures of diastereomers.

***N*-(Diphenylamino)vinylglycinol (19).** From **17** (77 mg, 0.25 mmol), thiophenol (0.03 mL, 0.30 mmol), and AIBN (4 mg, 0.025 mmol) by general procedure F was obtained racemic **19** (34 mg, 54% yield) as a colorless oil: IR (film) 3391 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.28 (m, 4H), 7.17−7.15 (m, 4H), 7.02−7.01 (m, 2H), 5.90 (ddd, J = 17.7, 10.5, 7.5 Hz, 1H), 5.30−5.15 (m, 2H), 4.22 (s, 1H), 3.80−3.71 (m, 1H), 3.70−3.58 (m, 2H), 1.95 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 135.7, 129.1, 122.5, 120.4, 118.8, 63.9, 61.9; MS (CI) m/z (relative intensity) 255 ([M + H]$^+$, 42), 165 (100), 183 (27). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.31; H, 7.14; N, 10.78.

(2*S*,3*R*)-3-(*N*,*N*-Diphenylhydrazino)-4-penten-2-ol (23a). From **22a** (94 mg, 0.29 mmol), thiophenol (0.03 mL, 0.35

mmol), and AIBN (4 mg, 0.029 mmol) by general procedure F was obtained **23a** as a mixture of diastereomers (60 mg, 77% yield, anti/syn = 90:10) as a pale yellow oil. For characterization, both pure diastereomers were obtained via acetonide **26a**. Major diastereomer (*anti*-**23a**): $[\alpha]^{31}_{D}$ +48.5 (*c* 1.98, $CHCl_3$); IR (film) 3435 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.30 (m, 4H), 7.15−7.13 (m, 4H), 7.04−7.01 (m, 2H), 5.93 (ddd, *J* = 17.3, 10.4, 8.4 Hz, 1H), 5.33 (dd, *J* = 10.4, 1.8 Hz, 1H), 5.26 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.10 (dddd, *J* = 6.5, 6.5, 6.5, 2.7 Hz, 1H), 4.20−3.50 (br s, 1H), 3.43 (dd, *J* = 8.4, 2.7 Hz, 1H), 2.55 (br s, 1H), 1.18 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 133.5, 129.2, 122.6, 120.4, 120.3, 66.53, 66.48, 18.1. Minor diastereomer (*syn*-**23a**): IR (film) 3401 (br, s), 1588, 1496, 1272, 1073, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.26 (m, 4H), 7.16−7.15 (m, 4H), 7.11−6.95 (m, 2H), 5.73 (ddd, *J* = 17.2, 10.3, 8.7 Hz, 1H), 5.18 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.15 (dd *J* = 17.2, 1.4 Hz, 1H), 4.50 (br s, 1H), 3.90−3.86 (m, 1H), 1H), 3.35 (dd, *J* = 7.9, 7.9 Hz, 1H), 2.10 (br s, 1H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 135.9, 129.0, 122.4, 120.6, 119.5, 69.5, 67.2, 20.4. Diastereomeric mixture: MS (CI) *m*/*z* (relative intensity) 269 ($[M + H]^+$, 100), 168 (98), 183 (36). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.27; H, 7.67; N, 10.18.

(3*R*,4*S*)-3-(*N*,*N*-Diphenylhydrazino)-6-methyl-1-hepten-4-ol (23b). From **22b** (400 mg, 1.09 mmol), thiophenol (0.13 mL, 1.31 mmol), and AIBN (17 mg, 0.11 mmol) by general procedure F was obtained **23b** as a mixture of diastereomers (232 mg, 68% yield, anti/syn = 94:6) as a pale yellow oil. For characterization, the pure major diastereomer was obtained via acetonide **26b**. Major diastereomer (*anti*-**23b**): $[\alpha]^{27}_{D}$ +26.3 (*c* 0.58, $CHCl_3$); IR (film) 3447 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (m, 4H), 7.13−7.11 (m, 4H), 7.03−7.00 (m, 2H), 5.87 (ddd, *J* = 19.1, 10.4, 8.6 Hz, 1H), 5.30 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.22 (dd, *J* = 19.1, 1.8 Hz, 1H), 4.04 (s, 1H), 4.01−3.96 (m, 1H), 3.40 (dd, *J* = 8.5, 2.3 Hz, 1H), 2.42 (dd, *J* = 2.1, 1.1 Hz, 1H), 1.79−1.71 (m, 1H), 1.44 (ddd, *J* = 13.9, 9.3, 5.5 Hz, 1H), 1.11−1.05 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 133.5, 129.2, 122.6, 120.3, 120.1, 68.2, 65.8, 41.6, 24.6, 23.4, 22.0; MS (CI) *m*/*z* (relative intensity) 311 ($[M + H]^+$, 98), 168 (M, 100), 183 (33). Diastereomeric mixture: Anal. Calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.44; H, 8.41; N, 8.92.

(3*S*,4*R*)-4-(*N*,*N*-Diphenylhydrazino)-2-methyl-5-hexen-3-ol (23c). From **22c** (5.00 g, 14.17 mmol), thiophenol (1.74 mL, 17.00 mmol), and AIBN (232 mg, 1.42 mmol) by general procedure F was obtained *anti*-**23c** as a single diastereomer after crystallization from hexane (3.77 g, 89% yield). In a smaller scale experiment, the crude product had a diastereomer ratio of 98:2 (anti/syn). Major diastereomer (*anti*-**23c**): mp 100−102 °C (from hexane/ether); $[\alpha]^{29}_{D}$ +64.6 (*c* 1.51, $CHCl_3$); IR (film) 3554 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.30 (m, 4H), 7.13−7.11 (m, 4H), 7.01−7.04 (m, 2H), 5.95 (ddd, *J* = 19.1, 10.4, 8.7 Hz, 1H), 5.32 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.27 (dd, *J* = 19.0, 1.4 Hz, 1H), 3.93 (br s, 1H), 3.61 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.50 (dd, *J* = 9.1, 1.7 Hz, 1H), 2.70 (s, 1H), 1.65 (dddd, *J* = 9.1, 6.6, 6.6, 6.6 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 133.2, 129.2, 122.7, 120.5, 120.0, 75.2, 63.2, 30.1, 19.7, 18.3; MS (CI) *m*/*z* (relative intensity) 297 ($[M + H]^+$, 90), 168 (100), 183 (30). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.09; H, 8.20; N, 9.45.

(1*S*,2*R*)-2-(*N*,*N*-Diphenylhydrazino)-1-phenyl-3-buten-1-ol (23d). From **22d** (75 mg, 0.19 mmol), thiophenol (0.02 mL, 0.23 mmol), and AIBN (3 mg, 0.019 mmol) by general procedure F was obtained **23d** as mixture of diastereomers (38 mg, 59% yield, anti/syn = >98:2) as pale yellow oil: IR (film) 3447 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.26 (m, 11H), 7.09−7.07 (m, 2H), 6.95−7.05 (m, 2H), 5.86 (ddd, *J* = 18.4, 10.4, 8.1 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.10 (d, *J* = 17.3 Hz, 1H), 4.93 (d, *J* = 4.5 Hz, 1H), 4.08 (s, 1H), 3.63 (dd, *J* = 8.1, 4.6 Hz, 1H), 2.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 140.2, 134.0, 129.1, 128.1, 127.5, 126.4, 122.6, 120.3, 120.3, 72.7, 66.8; MS (CI) *m*/*z* (relative intensity) 331 ($[M + H]^+$, 46), 170 (100), 168 (60). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.45; H, 6.72; N, 8.76.

(2*R*,3*R*)-3-(*N*,*N*-Diphenylhydrazino)-4-penten-1,2-diol (32). From **28** (75 mg, 0.19 mmol), thiophenol (0.02 mL, 0.23 mmol), and AIBN (3 mg, 0.019 mmol) by general procedure F was obtained **32** after flash chromatography (10:1 → 1:1 hexane/EtOAc) as a mixture of diastereomers (16 mg, 64% yield, anti/syn = 91:9) as a colorless oil: IR (film) 3399 (br, s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.28 (m, 4H), 7.13−7.11 (m, 4H), 7.03−7.00 (m, 2H), 5.90 (ddd, *J* = 18.8, 10.4, 8.4 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.22 (d, *J* = 18.2 Hz, 1H), 3.98−3.95 (m, 1H), 3.70 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.63−3.60 (m, 2H), 2.70 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 133.8, 129.2, 122.8, 120.4, 120.1, 71.8, 63.8, 63.2; MS (CI) *m*/*z* (relative intensity) 285 ($[M + H]^+$, 77), 168 (100). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.32; H, 7.16; N, 9.41.

(2*S*,3*S*,4*S*)-4-(*N*,*N*-Diphenylhydrazino)-5-hexene-2,3-diol (33). From **32** (106.7 mg, 0.244 mmol, syn/anti = 89:11), thiophenol (60 μL, 0.58 mmol), and AIBN (2.7 mg, 0.016 mmol) by general procedure F was obtained **33** (46.2 mg, 63% yield) as a colorless oil as an 88:12 diastereomeric mixture. Major diastereomer (2*S*,3*S*,4*S*)-**33**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (m, 4H), 7.12−7.10 (m, 4H), 7.04−7.00 (m, 2H), 5.92 (ddd, *J* = 18.8, 10.3, 8.4 Hz, 1H), 5.35−5.20 (m, 2H), 3.82 (dddd, apparent quintet, 1H), 3.65−3.60 (m, 2H), 2.90−2.60 (br s, 2H), 1.70−1.45 (br s, 1H), 1.11 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 133.5, 129.3, 122.8, 120.5, 120.1, 75.1, 67.8, 63.2, 18.4. Diastereomeric mixture: IR (film) 3401 (br, s) cm^{-1}; MS (CI) *m*/*z* (relative intensity) 299 ($[M + H]^+$, 48), 168 (100). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.34; H, 7.48; N, 9.30.

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Supporting Information Available: Experimental procedures (including general procedures A, B, D, and G) and characterization data for **9**, **10**, **14**, **15**, **20**, **21**, **25**−**27**, **29**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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