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Tandem thiyl radical addition and cyclization of chiral hydrazones using a silicon-tethered alkyne

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Abstract—A diastereoselective method for addition of a *trans*-2-(phenylthio)vinyl group to α-hydroxy hydrazones is presented. An ethynyl group, tethered to α-hydroxy hydrazones via a silicon tether, undergoes thiyl radical addition and cyclization under neutral tin-free conditions. In the same pot, desilylation with potassium fluoride or tetrabutylammonium fluoride affords (*E*)-vinylsulfides. The one-pot process is the synthetic equivalent of an acetaldehyde Mannich reaction with acyclic stereocontrol.
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Polyhydroxylated amines are found in a variety of common compound classes of interest for their biological activity, including sphingolipids,[1] hydroxylated pyrrolidines and piperidines ('azasugars'),[2] and aminosugars.[3] Asymmetric synthesis of amino alcohols also provides access to chiral auxiliaries and ligands for asymmetric catalysis.[4]

A carbon–carbon bond construction approach to α-branched amines may create both a stereogenic center and a C–C bond in a single synthetic transformation. We have exploited radical addition to C=N bonds as a general strategy;[5,6] the radical intermediates are non-basic, avoiding aza-enolization,[7] and are chemoselective and can be generated under mild conditions, avoiding some of the problems inherent in additions of carbanion-type organometallic reagents to aldehyde imino derivatives.[8] Acyclic stereocontrol of alkyl radical addition to C=N acceptors is rare, appearing only in the last 6 years.[9–11] We have found that hydroxymethyl[12] and vinyl[13] units can be installed with 'formal acyclic stereocontrol' using a temporary silicon tether to allow conformational constraints to control diastereoselectivity in radical cyclization (Fig. 1).

Because no viable intermolecular additions of vinyl or aryl radicals to C=N bonds are yet available, installation of these unsaturated groups warrants a temporary silicon tether approach,[14] which renders the addition intramolecular. Here, we report a new variant of this strategy which engages a tethered alkyne for tandem thiyl radical addition–cyclization to install a 2-(phenylthio)vinyl fragment in diastereoselective fashion.

Intermolecular addition of heteroatom radicals to an alkene or alkyne can initiate a cyclization event when a second radical acceptor moiety is appropriately situated.[15] Previously we have shown that thiyl radical addition to a vinylsilane temporarily tethered to a chiral α-hydroxyhydrazone facilitates such a cyclization with excellent stereocontrol. Subsequent fluoride-induced thiolate elimination occurred during removal of the silicon tether, returning the vinyl functionality. We hypothesized that an analogous sequence might take place at a higher oxidation level using an ethynylsilane as the silicon-tethered radical precursor group, a reaction type which, to our knowledge, is without direct precedent.[16] Because of the additional options available for functionalization of alkynes, an ethynyl group addition would be a potentially useful complement to our vinyl addition methodology.

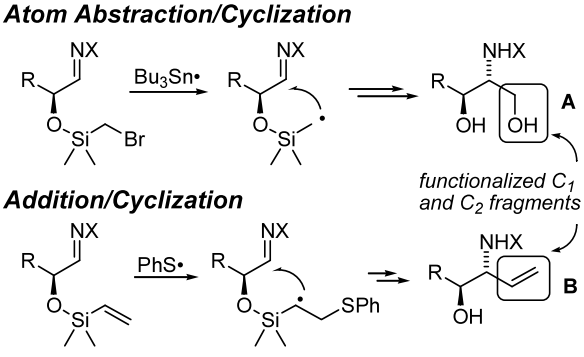

Figure 1.

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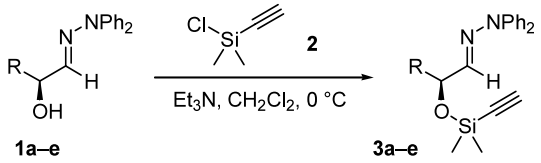
To test this hypothesis, we began by silylating glycolaldehyde *N*,*N*-diphenylhydrazone[13] (**1a**, Scheme 1) with chloroethynyldimethylsilane **2**[17] to afford addition–cyclization substrate **3a**[18] (83% yield). Treatment with thiophenol and AIBN (cyclohexane, reflux) resulted in efficient C–C bond construction to furnish a cyclic silane, which was not amenable to standard flash chromatography on silica gel. Exposure to fluoride led to removal of the silicon tether, but surprisingly, none of the alkyne was observed. In contrast to our previous work with the vinylsilane, the thiolate elimination did not occur; simple protodesilylation was observed instead, preserving the sulfide functionality in a 2-(phenylthio)vinyl adduct **4a**[18] (68% yield, two steps). The one-pot process accomplishes addition of a functionalized vinyl radical to a C=N bond under neutral conditions, without toxic and difficult-to-remove stannane reagents.



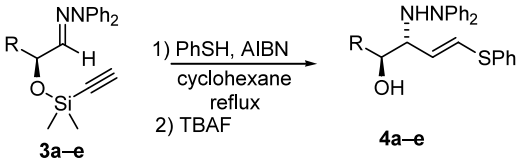
a: R = H (83%); **b**: R = Me (93%); **c**: R = ^{i}Bu (86%); **d**: R = ^{i}Pr (90%); **e**: R = Ph (83%)

Scheme 1.

Although the planned elimination to form the alkyne was not realized, we were cognizant of some advantages of the vinylsulfide functional group for further manipulations. Specifically, because vinylsulfides are aldehyde equivalents, these reactions can be considered the radical equivalent of an acetaldehyde Mannich reaction.[19] Furthermore, a vinylsulfide can undergo direct acid-catalyzed cyclization with a remote hydroxyl group to afford cyclic hemithioacetals (i.e. thioglycosides).[20]

Next we explored the diastereoselectivity of the process using cyclization substrates **3b**–**3d**[18,21] (Scheme 2), easily prepared from enantiomerically pure α-hydroxy hydrazones **1b**–**1d**[12,13] by silylation with **2**. Sequential treatment with thiophenol/AIBN and refluxing methanolic KF led to allylic *anti*-hydrazino alcohols **4b**–**4d**.[18] Subsequently, we found that tetrabutylammonium fluoride was a preferred fluoride source in this reaction, excising the silicon tether smoothly and in improved yield at room temperature. Silyl ether **3e** reacted in similar fashion, though less cleanly. In this case, even though some inseparable by-products prevented accurate determination of the product ratio, only a trace of (*E*)-*syn*-**4e**, and no trace at all of (*Z*)-*syn*-**4e** was detected in the crude product mixture by ^{1}H NMR. In all cases, the *anti*/*syn* diastereoselectivity in this process ranged upward from about 4:1 (Table 1) and is clearly correlated with the steric demand of the substituent R.

In preliminary stages of this work, only the *E*-alkene[22] was observed after removal of the silicon tether and



a: R = H (68%); **b**: R = Me (64%); **c**: R = ^{i}Bu (51%); **d**: R = ^{i}Pr (68%); **e**: R = Ph (70%)

Scheme 2.

Table 1. Product ratios and diastereoselectivities of tandem radical addition/cyclization of **3a**–**3e**

Entry	R	Product ratio[a]	dr[b]
1	H	1.4:1[c]	–
2	Me	71.8:6.6:19.2:2.3	78:22
3	^{i}Bu	74.4:11.3:11.2:3.1	86:14
4	^{i}Pr	87.0:8.7:3.6:<1	96:4
5	Ph	90.1:9.9:<1:0	>98:2[d]

Conditions: (1) 1.2 equiv. PhSH added via syringe pump, 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. See Ref. 27 for a representative example. (2) 2.2 equiv. TBAF in THF, rt, 1 h.

[a] Ratios (*E*-*anti*:*Z*-*anti*:*E*-*syn*:*Z*-*syn*) from integration of 500 MHz ^{1}H NMR spectra of product mixtures, given in order of elution on SiO_2 (hexane/EtOAc).

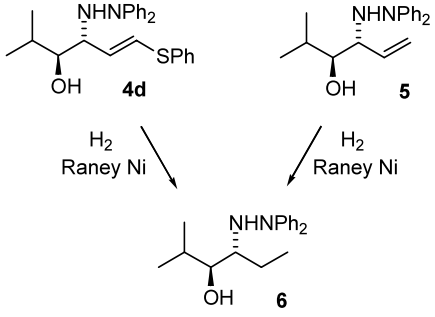
[b] Diastereomer ratio (*anti*/*syn*), sum of *E* and *Z* isomers.

[c] *E*/*Z* ratio (*anti*/*syn* not applicable).

[d] Trace amount of isomer (*E*)-*syn*-**3e** was detected by ^{1}H NMR.

chromatographic purification. We suspected that the minor *Z*-isomer might be formed to some extent. Indeed, in some experiments involving more rapid addition of PhSH, significant amounts of *Z*-alkene products were found upon careful chromatography. Because the formation of the *Z*-alkene was suppressed by maintaining a lower concentration of PhSH, it is reasonable to speculate that the *E*-alkene is susceptible to alkene isomerization via an addition–elimination mechanism after the key C–C bond construction.

The relative configuration of **4d** was assigned by chemical correlation with the corresponding vinyl adduct **5**, lacking the sulfide. Upon treatment with Raney nickel, both **4d** and **5** were converted to the same saturated



Scheme 3.

product **6** (Scheme 3). This established the *anti* relative configuration of **4d**.[23]

The favored *anti* diastereomer is that predicted by the Beckwith–Houk model,[24] i.e. the preferred chair-like transition state with minimized allylic strain. The minor *syn* product would be expected from disfavored chair-axial and/or boat conformations. Interestingly, the selectivity of these ethynylsilane addition/cyclization reactions is slightly lower than that observed in the corresponding reactions of vinylsilanes, which proceed via 5-*exo* cyclization of an alkyl radical.[13] Considering the differences in reactivity of alkenyl and alkyl radicals, the slightly lower selectivity in this work may be attributable to an earlier chair-like transition state, which would presumably exhibit diminished energetic differences between chair–equatorial and the competing chair–axial and/or boat conformations (Fig. 2).

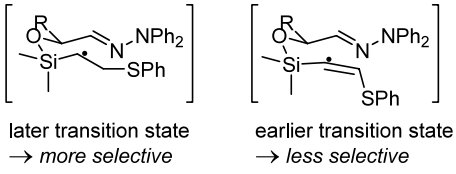
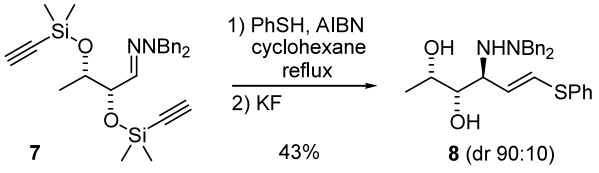


Figure 2.

The enantiomeric purity of **4b**–**4d** depends on that of the starting α-hydroxy acid or ester used to prepare **1b**–**1d**. Previously, in studies of hydroxymethyl addition,[12] Mosher ester analysis of **A** (see Fig. 1) showed that there is complete retention of configuration from an α-hydroxy acid or α-hydroxy ester via **1b**–**1d** (but not **1e**) through the sequence analogous to Schemes 1 and 2.[25]

Lastly, the use of a diol can be accommodated by the silicon-tethered radical addition strategy, even without prior hydroxyl differentiation. Thus, the bis-silylated diol **7**[26] led to aminodiol **8**[18] upon thiyl addition/cyclization followed by treatment with fluoride (Scheme 4). The adduct in this case is an open-chain derivative of L-daunosamine,[3] suggesting the potential of this method for synthesis of polyhydroxylated amines of biological importance.



Scheme 4.

In conclusion, we have shown that the 2-(phenylthio)-vinyl group can be installed via diastereoselective tin-free radical addition to α-hydroxyhydrazones. Employing a silicon-tethered ethynyl group, the tandem process is the synthetic equivalent of an acetaldehyde Mannich reaction with acyclic stereocontrol. Since intermolecular vinyl radical addition methods are currently unavailable, this silicon-tethered approach offers a potentially valuable alternative.[27]

Acknowledgements

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21. Hydrazones were obtained as single C=N bond isomers (>98:2).
22. The olefin configurations were assigned on the basis of 1D NOE data and vicinal coupling constants of **4d** (*E*-**4d**: $J=15$ Hz, *Z*-**4d**: $J=9$ Hz). For all compounds **4**, the olefinic vicinal coupling constants were either 15 Hz or 9 Hz, and olefin isomers were assigned by analogy to **4d**.
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25. The α-hydroxy- and α-silyloxy hydrazones without additional carbanion-stabilizing functionality are configurationally stable under these conditions (>96% ee, Mosher ester analysis). However, alcohol **1e**, wherein the phenyl group can promote enolization, suffered significant racemization.
26. Bis-ethynylsilyl ether **7** was prepared from crotonaldehyde in three steps. Massari, S. E. Diastereoselective Vinyl Addition to Chiral Hydrazones via Tandem Thiyl Radical Addition and Silicon-Tethered Cyclization. M.S. Thesis, University of Vermont, 2001.
27. **Representative procedure**: A solution of ethynylsilyl ether **3c** (204 mg, 0.56 mmol) in cyclohexane (5.6 mL) was deoxygenated (N_2, via syringe needle) for ca. 10 min, then heated to reflux. A solution of 2,2′-azobis(isobutyronitrile) (AIBN, 10 mg, 0.06 mmol) and thiophenol (0.080 mL, 0.78 mmol) in benzene (0.8 mL), was added via syringe pump (0.34 mL/h). Additional portions of AIBN (3×10 mg) were added in 3 h intervals until the reaction was complete (as judged by TLC), then the cooled reaction mixture was concentrated. The residue was dissolved in THF (1 M) and treated with tetrabutylammonium fluoride (1.5 mL, 1 M in THF, 1.5 mmol) at room temperature for ca. 1 h. When complete (as judged by TLC), the reaction was diluted with hexane, washed with water, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/ethyl acetate) furnished the vinyl sulfide **4c** as a mixture of diastereomers (157 mg, 67%), from which the major diastereomer (*E*)-*anti*-**4c** (120 mg, 51% yield) was isolated by radial chromatography (hexane/ethyl acetate) as a pale yellow oil: $[\alpha]_D^{28}=-12.0$ (*c* 1.25, $CHCl_3$); IR (film, $CHCl_3$) 3447, 3060, 2955, 1588, 1495, 1272, 1071, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 9H), 7.14–7.11 (m, 4H), 7.05–7.00 (m, 2H), 6.35 (d, $J=15.1$ Hz, 1H), 5.90 (dd, $J=15.2$, 8.9 Hz, 1H), 4.09 (s, 1H), 4.00–3.95 (m, 1H), 3.52 (dd, $J=8.9$, 2.4 Hz, 1H), 2.35 (s, 1H), 1.80–1.72 (m, 1H), 1.45 (ddd, $J=14.0$, 9.3, 5.6 Hz, 1H), 1.12 (ddd, $J=13.1$, 8.1, 3.6 Hz, 1H), 0.92 (d, $J=6.7$ Hz, 3H), 0.89 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ?147.96, 134.65, 129.96, 129.28, 129.08, 128.79, 127.70, 126.93, 122.72, 120.36, 68.70, 65.28, 41.85, 24.65, 23.34, 22.08; MS (CI) *m*/*z* (relative intensity) 419 ([M+H]$^+$, 80%), 164 (100%). Anal. calcd for $C_{26}H_{30}N_2OS$: C, 74.60; H, 7.22; N, 6.69. Found: C, 74.32; H, 7.28; N, 6.43.