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Unique Diastereoselectivity Trends in Aminyl Radical Cyclizations onto Silyl Enol Ethers

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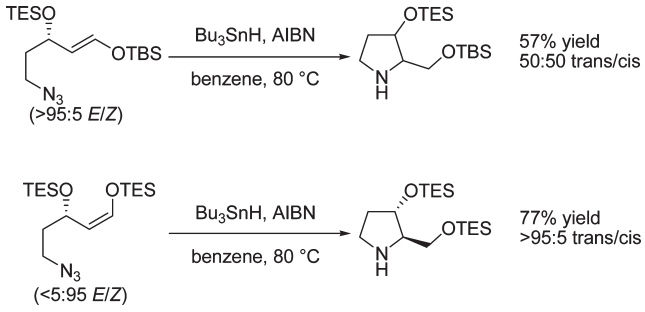

The cyclization of nitrogen-centered radicals onto silyl enol ethers is an efficient method for the synthesis of polyhydroxylated alkaloids as the 2-hydroxymethylpyrrolidine core can be readily accessed from a linear precursor. During our studies on the synthesis of polyhydroxylated alkaloid CYB-3, we found that the diastereoselectivity of the cyclization was dependent on a complex combination of sterics and olefin geometry. A more thorough understanding of the factors that lead to high diastereoselectivites would greatly expand the utility of this methodology in complex natural product synthesis. We have found that cyclization diastereoselectivities of substrates with alkyl or aryl substitution were excellent regardless of olefin geometry or substitution pattern. When electronegative substituents were introduced adjacent to the silyl enol ether, only *Z*-silyl enol ethers provide high diastereoselectivites. Temperature, steric size of the silyl group, and sterics and electronics of the metal hydride affected the selectivity to a lesser extent.

Introduction

Cyclizations between carbon-,[1] oxygen-,[2] and nitrogen-centered radicals[3] onto alkenes have been explored, and their highly predictable behavior with regard to both chemo- and diastereoselectivity make these methodologies valuable synthetic transformations. One class of cyclization acceptor that is relatively unexplored is silyl enol ethers.[4,5] Silyl enol ethers are synthetically useful radical acceptors as the cyclization products provide versatile alkoxy or siloxy functionalities.

(1) For reviews on carbon−radical cyclizations, see: (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541–3676. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.1, pp 715−777. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1996; Vol. 48, Chapter 2, pp 303−856. (d) Gansäuer, A.; Bluhm, H. *Chem. Rev*. **2000**, *100*, 2771–2788. and references therein.

(2) For the first example of oxygen-centered radical cyclizations, see: (a) Surzur, J. M.; Bertrand, M. P.; Nougier, R. *Tetrahedron Lett*. **1969**, *48*, 4197–4200. For recent reviews, see: (b) Hartung, J. *Eur. J. Org. Chem*. **2001**, 619–632. (c) Hartung, J.; Gottwald, T.; Špehar, K. *Synthesis* **2002**, 1469–1498 and references therein.

(3) For reviews on nitrogen-centered radicals, see: (a) Neale, R. S. *Synthesis* **1971**, 1–15. (b) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241–3260. (c) Stella, L. *Angew. Chem., Int. Ed. Engl*. **1983**, *22*, 337–350. (d) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem*. **1993**, *58*, 1–45. (e) Zard, S. Z. *Synlett* **1996**, 1148–1154. (f) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17534–17594. (g) Zard, S. Z. *Chem. Soc. Rev*. **2008**, *37*, 1603–1618. (h) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.2, pp 811−812. (i) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 51, pp 407−426. (j) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem.—Eur. J*. **2009**, *15*, 7830–7840.

(4) For select examples of carbon−radical cyclizations onto silyl enol ethers, see: (a) Urabe, H.; Kuwajima, I. *Tetrahedron Lett*. **1986**, *27*, 1355–1358. (b) Walkup, R. D.; Kane, R. R.; Obeyesekere, N. U. *Tetrahedron Lett*. **1990**, *31*, 1531–1534. (c) Fensterbank, L.; Mainetti, E.; Devin, P.; Malacria, M. *Synlett* **2000**, 1342–1344. (d) Zhu, H.; Wickenden, J. G.; Campbell, N. E.; Leung, J. C. T.; Johnson, K. M.; Sammis, G. M. *Org. Lett*. **2009**, *11*, 2019–2022.

(5) (a) Kim, S.; Kim, K. H.; Cho, J. R. *Tetrahedron Lett*. **1997**, *38*, 3915–3918. (b) Zlotorzynska, M.; Zhai, H.; Sammis, G. M. *Org. Lett*. **2008**, *10*, 5083–5086.

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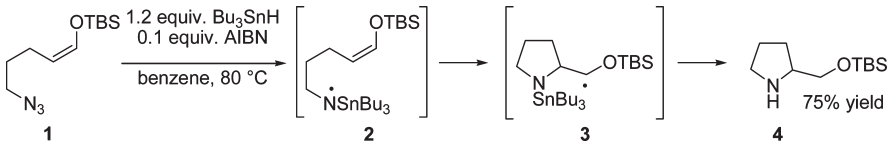
SCHEME 1. Cyclization of Azide 1 To Afford Pyrrolidine 4



However, not much is known about how the significant increase in electron density of the olefin affects the diastereoselectivity of 5-*exo* radical cyclizations.

In the course of our investigations into heteroatom-centered radical cyclizations onto silyl enol ethers,[5b,6] we recently reported the first example of a 5-*exo* aminyl radical cyclization onto a silyl enol ether (Scheme 1, **1**).[6] The tin-bound aminyl radical[7] cyclization proceeds in high yield to afford 2-siloxymethyl pyrrolidines. This new methodology was utilized as a key step in the syntheses of polyhydroxylated alkaloids[8] CYB-3 (Figure 1, **5**)[9,10] and 1,4-dideoxy-1,4-imino-D-ribitol (**6**).[11]

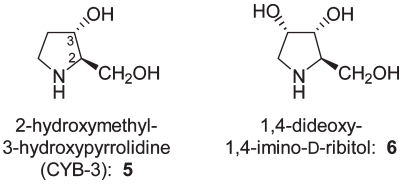
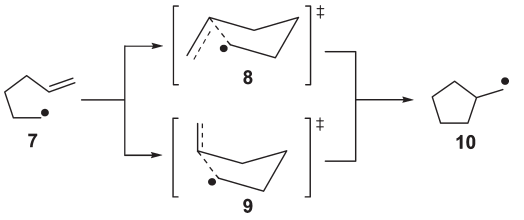


FIGURE 1. Polyhydroxylated alkaloids.

Despite the significant studies on the diastereoselectivities of radical cyclizations onto alkenes,[1−3] little is known about the effects substituents have on 5-*exo* cyclizations onto silyl enol ethers. Indeed, during our synthetic studies, we observed some atypical substituent effects in regard to sterics and olefin geometry.[6] Typically, the diastereoselectivity of radical cyclizations is predicted on the basis of computational studies on radical cyclization transition states by Beckwith[12] and Houk.[13] The premise behind these studies

SCHEME 2. Chairlike (8) and Boatlike (9) Transition States for Radical 5-*Exo* Cyclizations



is that 5-*exo* cyclizations can be analyzed through both chairlike (**8**) and boatlike (**9**) transition states (Scheme 2). Regardless of the substitution pattern, the overall cyclization diastereoselectivity can be predicted through energy minimization of these transition states. Supported by extensive empirical evidence,[1,13] this model for radical cyclization has emerged as a powerful and predictable tool in organic synthesis.[14]

While substituent effects in carbon-centered radical cyclizations onto alkenes have been thoroughly studied,[1] the tin-bound aminyl radical analogue may provide different selectivity trends when cyclizing onto an electron-rich olefin, such as a silyl enol ether. Herein, we report an investigation into how sterics, temperature, hydride source, silyl enol ether geometry, and electronics of the substituent affect the overall diastereoselectivity of this cyclization.

Results and Discussion

We started our investigations with siloxy substitution at C_3 as the corresponding substituted pyrrolidine is a common core in many of the polyhydroxylated alkaloids (Figure 1).[8] A general synthesis for the preparation of 3-siloxy-substituted cyclization precursors is presented in Scheme 3. Synthesis of the *tert*-butyldimethylsiloxy-substituted cyclization substrates began with known enantioenriched diol **11**.[15] Conversion of the primary alcohol to the iodide followed by protection of the secondary alcohol with a siloxy group afforded ester **12** in excellent yield. A subsequent DIBAL reduction of the ester followed by silyl enol ether formation provided **13** as a 40:60 mixture of *E*- to *Z*-isomers. Displacement of the iodide with azide afforded the key cyclization precursor **14**.

According to the Beckwith−Houk studies, there are four transition states that should be analyzed for this cyclization: chair transition states **15** and **18** and boat transition states **17**

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(7) For initial studies on azides as precursors for tin-bound aminyl radicals, see: (a) Kim, S. G.; Joe, H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328–3329. (b) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521–5522.

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(9) Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 738–740.

(10) CYB-3 has been found to exhibit modest glycosidase inhibition: Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. J. *Life Sci.* **1986**, *39*, 645–650.

(11) For early syntheses of 2-hydroxymethyl-3-hydroxypyrrolidine and protected derivatives, see: (a) Ikota, N.; Hanaki, A. *Heterocycles* **1988**, *27*, 2535–2537. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866–1875. For recent, enantioselective syntheses of 2-hydroxymethyl-3-hydroxypyrrolidine, see: (c) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929–2947. (d) Toumi, M.; Couty, F.; Evano, G. *Tetrahedron Lett.* **2008**, *49*, 1175–1179. (e) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996–2003. (f) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572–575. (g) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610–6615.

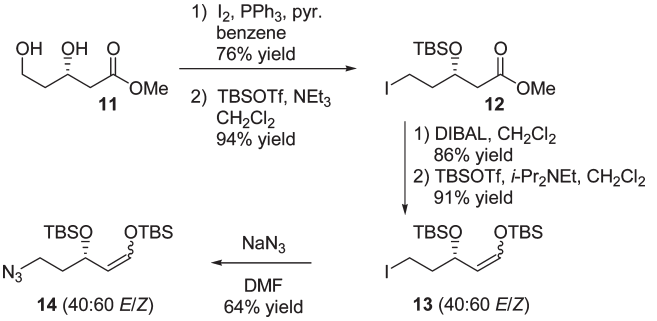
(12) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941.

(13) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

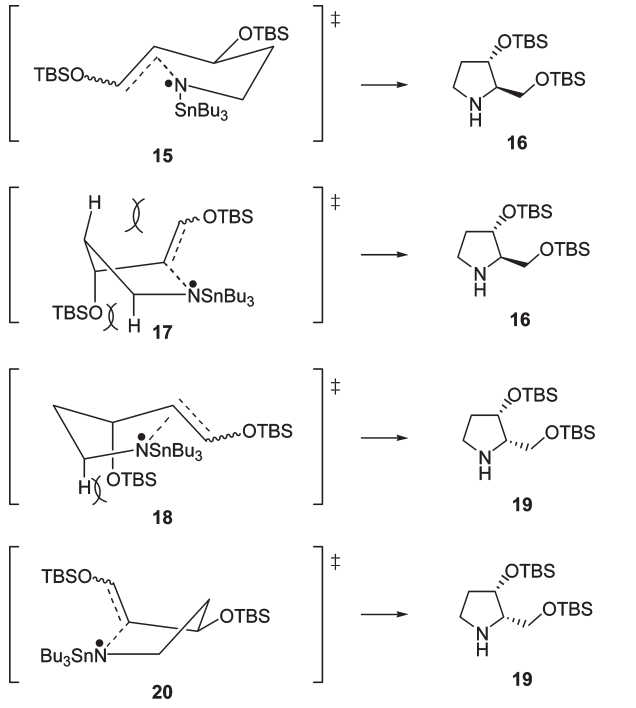
(14) For reviews on the use of radicals in natural product synthesis, see: (a) Curran, D. P. *Synthesis* **1988**, 417–439. (b) Curran, D. P. *Synthesis* **1988**, 440–513. (c) Jasperse, C. P.; Curran, D.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286 and references therein.

(15) For a synthesis of (*S*)-methyl-3,5-dihydroxypentanoate, see: Loubinaux, B.; Sinnes, J. -L.; O'Sullivan, A. C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549–3558.

SCHEME 3. Synthesis of Cyclization Precursor 14



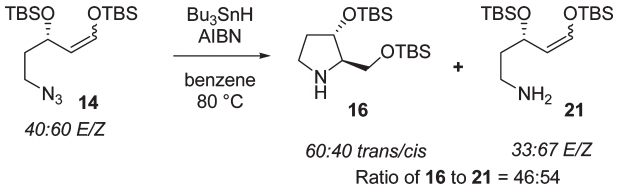
SCHEME 4. Beckwith−Houk Transition States for the Cyclization of Azide 14



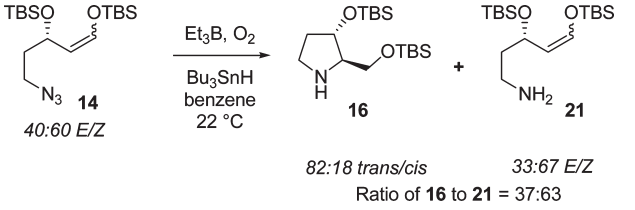
and **20** (Scheme 4). Of the two chair transition states, **15** should be lower in energy than **18** through simple minimization of steric interactions of the siloxy substitutent. Likewise, boat transition state **20** should be lower in energy than **17** through simple steric minimization. Furthermore, boat-transition state **20** does not have more significant steric interactions than are present in chair transition state **18**. On the basis of these models, and on analogous oxygen-centered radical[5b,16] cyclizations onto simple alkenes, it was expected that cyclization of the nitrogen-centered radical should provide the *trans*-pyrrolidine **16** as the major diastereomer.

Cyclization of azide **14** afforded pyrrolidines **16** and **19** as a 60:40 ratio of *trans*- to *cis*-isomers (Scheme 5), a diastereoselectivity significantly lower than what has been previously

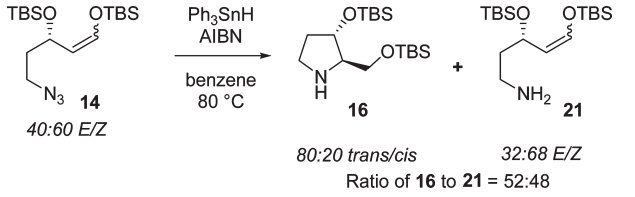
SCHEME 5. Cyclization of Azide 14 To Afford Pyrrolidine 16 and Acyclic Amine 21



SCHEME 6. Cyclization of Azide 14 To Afford Pyrrolidine 16 and Acyclic Amine 21



SCHEME 7. Cyclization of Azide 14 To Afford Pyrrolidine 16 and Acyclic Amine 21



observed for both carbon and oxygen-centered radical cyclizations. In addition, pyrrolidine **16** was formed in a virtually equimolar ratio with acyclic amine **21** presumably arising from trapping of the nitrogen radical prior to cyclization. This yield was also significantly lower than expected compared to cyclization of simple azide **1**.

In an effort to increase the diastereoselectivity of the cyclization, we next examined the effects of lowering the reaction temperature. We focused on a different initiation method (Scheme 6) as azobisisobutyronitrile (AIBN) requires elevated temperatures for radical formation. Treatment of azide **14** with triethylborane and oxygen at ambient temperature[17] in the presence of tributyltin hydride formed pyrrolidine **16** with increased diastereoselectivity. However, there was also a significant increase in the amount of acyclic amine **21**.

We hypothesized that we may be able to increase the ratio of pyrrolidine **16** to amine **21** by decreasing the electron density of the tin-bound nitrogen-centered radical. A more electrophilic nitrogen-centered radical is expected to have faster rates of cyclization with the electron-rich silyl enol ether. Cyclization of azide **14** with triphenyltin hydride led to a slight increase in the ratio of cyclized pyrrolidine **16** and amine **21** (Scheme 7). It also afforded an increase in the diastereoselectivity, presumably due to the increased steric bulk around the nitrogen-centered radical.

Formation of acyclic amine **21** may be due to steric congestion in the transition state **15**, thus lowering cyclization rates.

(16) For representative diastereoselectivity studies, see: (a) Hartung, J.; Hiller, M.; Schmidt, P. *Chem.—Eur. J.* **1996**, *2*, 1014–1023. (b) Hartung, J.; Kneuer, R.; Laug, S.; Schmidt, P.; Špehar, K.; Svoboda, I.; Fuess, H. *Eur. J. Org. Chem.* **2003**, 4033–4052. (c) Hartung, J.; Stowasser, R.; Vin, D.; Bringmann, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2820–2823.

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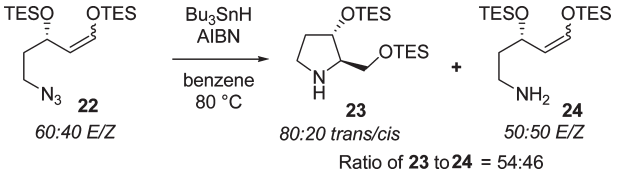
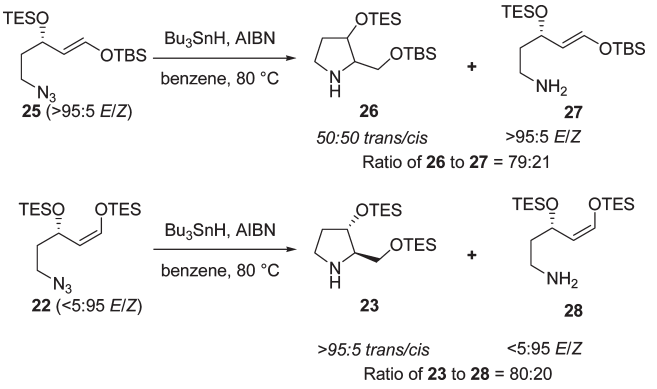
SCHEME 8. Cyclization of Azide 22 To Afford Pyrrolidine 23 and Acyclic Amine 24



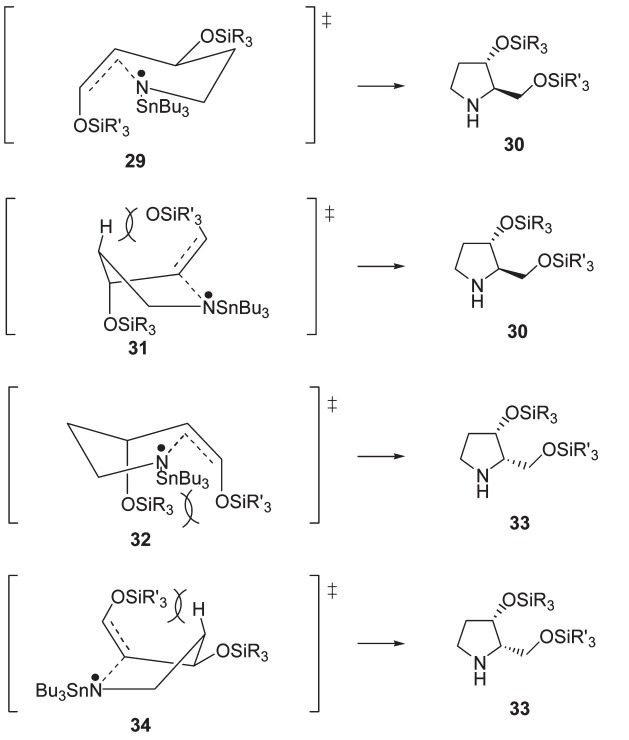
SCHEME 9. Cyclization of Azides 25 and 22 To Afford Pyrrolidines 26 and 23



To test this hypothesis, we synthesized azide **22** using a similar protocol as azide **14**.[18] Indeed, cyclization of azide **22** afforded an increased ratio of pyrrolidine **23** to amine **24** (Scheme 8) compared to cyclization of the TBS analog under similar conditions (Scheme 5). Despite the improved yields using cyclization precursor **22**,[19] the diastereoselectivity was still significantly lower than comparable cyclizations with oxygen-centered radicals.[5b,16]

The decreased diastereoselectivities in all of these cyclizations could arise from the difference in selectivities for the *E*- and *Z*-silyl enol ethers. To test this hypothesis, we synthesized both the *E*- and *Z*-silyl enol ethers **22** and **25** (Scheme 9). These substrates were synthesized according to Scheme 3 with the exception of the silyl enol ether formation step. Synthesis of the *E*-silyl enol ether was accomplished using TBSCl and DBU in dichloromethane at 35 °C to form the thermodynamic product. The *Z*-silyl enol ether was prepared using TESCl and DBU at 0 °C to form the *Z*-enriched product which was subsequently purified using flash chromatography. Cyclization of *E*-silyl enol ether **25** afforded pyrrolidine **26** in moderate yield with no diastereoselectivity while cyclization of *Z*-silyl enol ether **22** afforded pyrrolidine **23** in excellent yield exclusively as the *trans*-isomer (Scheme 9). While there is a slight contribution to diastereoselectivity from the difference in steric size between the silyl enol ether substituents (Schemes 5 and 8) the dramatic difference in selectivities in the cyclizations of azides **25** and **22** suggests that the geometry of the silyl enol ether is the dominant factor in the diastereoselectivity of this reaction.

SCHEME 10. Beckwith−Houk Transition States for the Cyclization of *Z*-Silyl Enol Ethers



The high selectivity for the cyclization of *Z*-silyl enol ether **22** can be understood using the standard Beckwith−Houk transition states (Scheme 10). Chair transition state **29**, which provides the observed *trans*-substituted pyrrolidine, has few major steric interactions. The siloxy substituent at C_3 is in the equatorial position and the silyl enol ether is oriented to minimize $A^{1,3}$-strain. Transition states **32** and **34**, which lead to the *cis*-substituted pyrrolidine, should both be significantly higher in energy than **29**. Chair transition state **32** has significant $A^{1,3}$ -strain between the siloxy substitutents.

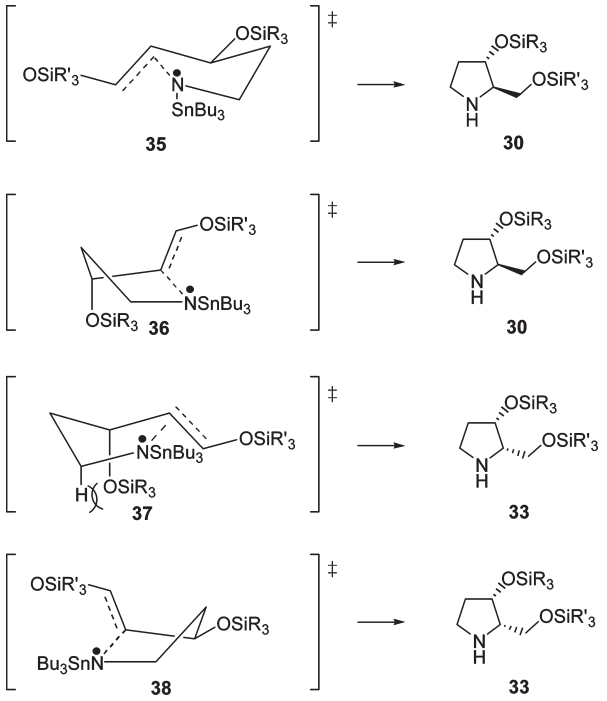
The poor diastereoselectivity when cyclizing *E*-silyl enol ether **25** is much more difficult to understand using the Beckwith−Houk transition states. Chair transition state **35**, leading to *trans*-substituted pyrrolidine **30**, has few major steric interactions (Scheme 11). The alternative chair transition state (**37**) should be slightly higher in energy as the *A* value for a *tert*-butyldimethylsiloxy group is 1.06 kcal/mol.[20] While transition state **36** should be high in energy, boat transition state **38** also has reduced steric interactions between the silyl enol ether substituents and the rest of the substrate compared to the chair transition state **37**. Though transition states **37** and **38** are closer in energy to **35** than for *Z*-silyl enol ether **22**, the cyclization should still favor the *trans*-pyrrolidine as cyclization of alkoxy radicals with substitution at C_3 provide excellent selectivity to the corresponding tetrahydrofuran. The lack of selectivity in the cyclization of azide **25** indicates steric minimization is likely not the sole factor in reaction diastereoselectivity.

(18) The enolization was accomplished by treatment with TESCl and DBU at ambient temperature. See the Supporting Information for further details.

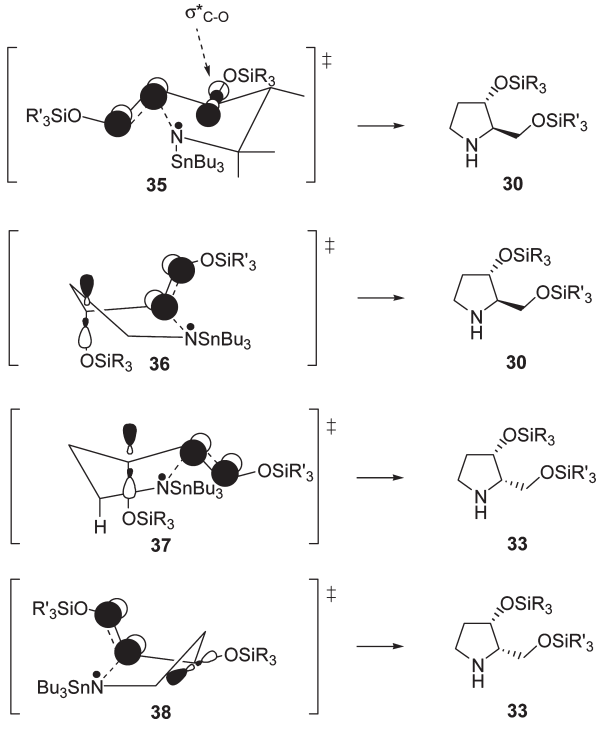
(19) The *Z*- to *E*-ratios of amines **21** and **24** were slightly higher than the *Z*- to *E*-ratios of azide-containing silyl enol ethers **14** and **22**. This suggests that the rate of cyclization of the *Z*-silyl enol ether is slightly slower than the cyclization rate of *E*-silyl enol ether.

(20) Eliel, E. L.; Satici, H. *J. Org. Chem.* **1994**, *59*, 688–689.

SCHEME 11. Beckwith−Houk Transition States for the Cyclization of *E*-Silyl Enol Ethers

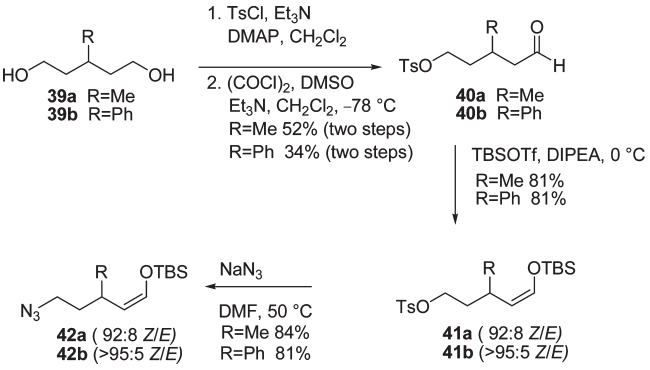


SCHEME 12. Stereoelectronic Interaction in Beckwith−houk Transition States for the Cyclization of *E*-Silyl Enol Ethers

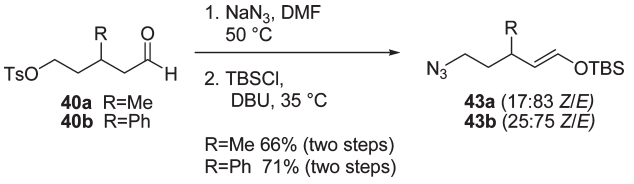


A possible explanation for the low diastereoselectivity during the cyclization of azide **25** is a stereoelectronic interaction in one of the transition states (Scheme 12). In chair transition state **35**, the σ^*_{C-O} of the siloxy group is in alignment with the π-system of the silyl enol ether, which will lead to decreased electron density of the olefin. This interaction is not present in transition state **37** as the σ^*_{C-O} of the siloxy group and the π-system of the silyl enol ether are orthogonal. Similarly, there is either poor or no overlap between the σ^*_{C-O} and the olefin in boat transition states **36** and **38**. Since the nitrogen-centered radical is slightly electrophilic, the cyclization rate of transition state **35** should be slowed in comparison with transition states **37** and **38** due to the decreased electron density in the olefin. Presumably, the stereoelectronic interactions are comparable to the higher steric demand in transtion states **37** and **38**, leading to similar rates of cyclization. This interaction is also present in transition state **29**, but the steric interactions are apparently sufficiently severe to outweigh the stereoelectronic effects.

SCHEME 13. Synthesis of Cyclization Precursors 42a and 42b



SCHEME 14. Synthesis of Cyclization Precursors 43a and 43b

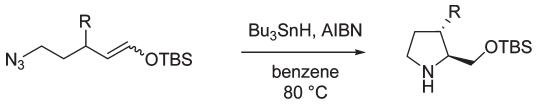


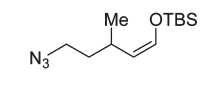
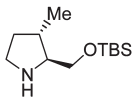
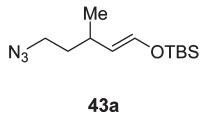
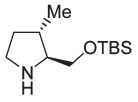
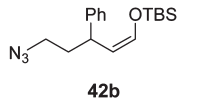
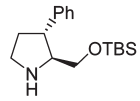
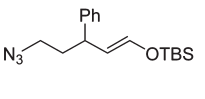
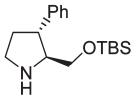
To test this hypothesis, we next investigated substrates with alkyl and aryl substitution at C_3. The σ^* of these substituents are less accessible for interaction with the π-system as they are higher in energy. Synthesis of these substrates began from readily accessible diols (Scheme 13, **39a** and **39b**) Monotosylation and Swern oxidation afforded aldehydes **40a** and **40b**, which were subjected to TBSOTf and diisopropylethylamine at 0 °C to afford *Z*-enriched silyl enol ethers **41a** and **41b**. The cyclization precursors (**42a** and **42b**) were synthesized by a final displacement of the tosylate with sodium azide.

The *E*-silyl enol ethers (**43a** and **43b**) were synthesized using an analogous procedure except the final two steps had to be reversed as the enolization conditions necessary for *E*-selectivity led to elimination of the tosylate (Scheme 14). Displacement of tosylate **40** followed by treatment with TBSCl and DBU at 35 °C afforded *E*-enriched silyl enol ether **43a** and **43b** in good yields.

Cyclization of *Z*-silyl enol ethers (**42a** and **42b**) proceeded with high diastereoselectivity to yield pyrrolidines **44a** and **44b** (Table 1, entries 1 and 3). Methyl substitution (**42a**) provided the cyclized product in high yield and excellent diastereoselectivity. Increasing the steric size to a phenyl group afforded pyrrolidine **44b** in excellent yields. Only the *trans*-isomer could be detected by ^{1}H NMR spectroscopy.

TABLE 1. Cyclization of Methyl- and Phenyl-Substituted Substrates



entry	substrate[a]	product[b]	Isolated yield (%)[c]	d.r.[d]
1	 **42a**	 **44a**	71	93:7
2	 **43a**	 **44a**	72	79:21
3	 **42b**	 **44b**	68	>95:5
4	 **43b**	 **44b**	70	>95:5

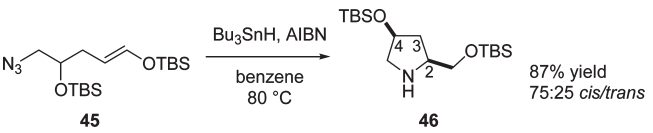
[a]Reactions were carried out on >0.25 mmol scale. [b]The relative stereochemistry was determined by derivatization of the product and comparison to known compounds. See the Supporting Information for experimental details. [c]Isolated yields of the mixture of diastereomers after flash chromatography. [d]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of purified products.

We next examined the effect of the geometry of the silyl enol ether acceptor on the diastereoselectivity of the cyclization for substrates with the same substitution pattern (Table 1). As was observed in substrates with siloxy substituents, *E*-silyl enol ether **43a** cyclized in much lower diastereoselectivity (entry 2) than did the corresponding *Z*-diastereomer **42a** (entry 1). However, the difference in diastereoselectivity between the *Z*- and *E*-silyl enol ethers with a methyl substituent was not as pronounced as what was observed for the siloxy substituted substrates. Furthermore, this drop in selectivity was not observed in the cyclization of the phenyl substituted *E*-silyl enol ether **43b** (entry 4),[21] which cyclized to give exclusively the *trans*-isomer. As the A-value for a methyl substituent (1.74 kcal/mol)[22] is only moderately higher than a siloxy substitutent (1.06 kcal/mol), sterics alone do not explain the increase in selectivity between the cyclizations of azides **25** and **43a**. However, it is consistent with the stereoelectronic interaction shown in transition state **35** (Scheme 12) as the siloxy substituent has a significantly lower energy σ^* orbital.

(21) The σ^*_{C-C} of phenyl substituents have been demonstrated to be acceptors in nucleophilic additions to acyclic carbonyls: Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667–1668. In 6-membered rings, the sterics of the phenyl ring override the stereoelectronic component: Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.

(22) Booth, H.; Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 278–280.

SCHEME 15. Cyclization of Azide 45 To Afford Pyrrolidine 46



45 **46**

To further investigate whether the steric difference between methyl and siloxy groups is sufficient to explain the difference in selectivities in the cyclization of azides **25** and **43a**, we cyclized azide **45** (Scheme 15). Since the siloxy substituent is homoallylic to the silyl enol ether, there should be no stereoelectronic interaction between the π-system and the σ^*_{C-O} of the silyl ether. The cyclization diastereoselectivity should therefore be governed exclusively by steric minimization. If indeed the siloxy substituent does not have a sufficiently high A-value to impart any diastereoselectivity, there should be an equimolar amount of the *cis* and *trans* diastereomers formed. However, the cyclization provided a 75:25 ratio of *cis* to *trans* isomers. Furthermore, substrates with substitution at C_3 are known to cyclize in higher diastereoselectivity than those with substitution at the C_4.[12,13] Thus, the 50:50 mixture obtained for the cyclization of azide **25** cannot be explained by a simple steric minimization argument.

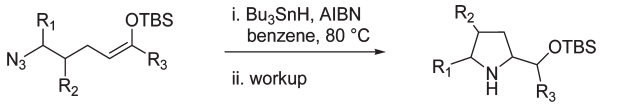
We next investigated the scope of alkyl and aryl substitution at C_4 and C_5 to determine if these substrates were consistent with the Beckwith−Houk studies on radical cyclization diastereoselectivity (Table 2).[23] We began by examining phenyl substitution on the silyl enol ether (entry 1). Cyclization of silyl enol ether **47a** provided desired pyrrolidine **48a** in good yield and in a 90:10 ratio of *erythro* to *threo* isomers, which is substantially higher than was observed with analogous oxygen-centered radical cyclizations.[5b]

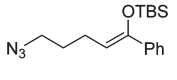
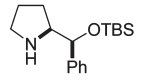
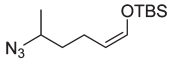
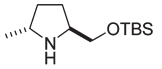
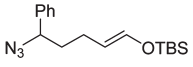
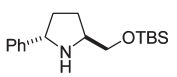
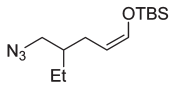
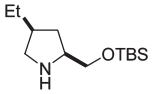
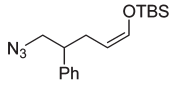
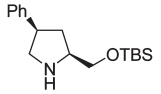
Substrates **47b** and **47c** (entries 2−3) were used to examine how substituents at C_5 would influence the yield and diastereoselectivity. Methyl substituent **47b** cyclized in excellent yield, but only in a 65:35 ratio of *trans*- to *cis*-isomers. Increasing the steric size of the substituent from methyl (**47b**) to phenyl (**47c**) provided comparable yields and a remarkable increase in diastereoselectivity (entry 3). The diastereoselectivity again was higher than what was observed for analogous oxygen-centered radical cyclizations.[5b] The diastereomers obtained were in accordance with the Beckwith-Houk studies.

We next examined whether possible β-fragmentation pathways would provide lower yields of cyclized product. Substrate **47d** (entry 4) cyclized to desired pyrrolidine **48d** in high yield with no fragmentation product observed by ^{1}H NMR spectroscopy. Products resulting from 1,5-hydrogen abstraction were also not observed. The cyclization also proceeded in a 72:28 ratio of *cis*- to *trans*-isomers. Phenyl substituted substrate **47e** cyclized in high yield. The increase in steric size also provided an increase in diastereoselectivity to an 89:11 ratio of *cis*- to *trans*-isomers. As in previous entries, the selectivity observed was consistent with the Beckwith−Houk studies. Despite the added stabilization of the β-fragmentation product, no other products were observed by ^{1}H NMR spectroscopy. Thus, in addition to high

(23) Analogous oxygen-centered radical cyclizations onto silyl enol ethers (ref 5b) were consistent with the Beckwith−Houk model for diastereoselectivity.

TABLE 2. Cyclization of Methyl- and Phenyl-Substituted Substrates



entry	substrate[a]	product[b]	isolated yield (%)[c]	d.r.[d]
1	 **47a**	 **48a**	62	90:10
2	 **47b**	 **48b**	78	65:35
3	 **47c**	 **48c**	66[e]	84:16
4	 **47d**	 **48d**	79	72:28
5	 **47e**	 **48e**	77	89:11

[a]Reactions were carried out on >0.25 mmol scale. [b]The relative stereochemistry was determined by derivatization of the product and comparison to known compounds. See the Supporting Information for experimental details. [c]Isolated yields of the mixture of diastereomers after flash chromatography. [d]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [e]Isolated yield of the *trans*-stereoisomer. The *cis*-isomer was also isolated in 12% yield.

diastereoselectivity, these cyclizations also exhibit a high level of chemoselectivity.

Conclusion

We have found conditions to achieve high diastereoselectivities for cyclizations between tin-bound aminyl radicals and silyl enol ethers regardless of the substituent or substitution pattern. While temperature, source of hydride, and sterics of the substituent all influenced the cyclization selectivity, the geometry of the silyl enol ether had the most dramatic effect on selectivity. Cyclizations of *Z*-silyl enol ethers provide high diastereoselectivities for all substrates examined. However, the diastereoselectivity using *E*-silyl enol ethers was significantly lower when an electronegative substituent was adjacent to the silyl enol ether. The low diastereoselectivities in cyclizations of *E*-silyl enol ethers with electron-withdrawing substituents are likely due to a combination of small steric differentiation between the transition states and a stereoelectronic interaction that decreases the electron density from the olefin. Cyclization diastereoselectivities of substrates with alkyl or aryl substitution were excellent regardless of olefin geometry or substitution pattern. Efforts to further explore this cyclization methodology in the context of natural product synthesis are currently underway.

Experimental Section

General Methods. All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran, diethyl ether, dichloromethane and benzene were purified by a solvent purification system. Thin-layer chromatography (TLC) was performed on UV_{254}-precoated TLC plates. Chromatographic separations were effected over silica gel. Triethylamine washed silica gel has been stirred with triethylamine prior to packing. All chemicals were purchased from commercial sources and used as received. Azide-containing silyl enol ethers, such as azides **1**, **14**, **25**, **42a**,**b**, **43a**,**b**, **45**, and **47a**−**e**, are benchstable for at least 2 weeks.

General Cyclization Procedure. A solution of Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), and silyl enol ether in degassed benzene[24] (0.05 M) was heated to 80 °C and stirred for 12 h, the solution was allowed to cool to room temperature, and the solvent was removed by rotary evaporation. Purification by flash chromatography afforded the cyclized product.

General Tosylation followed by Deprotection Procedure for Sterechemistry Determination. To a solution of pyrrolidine **48c** (25 mg) and *p*-toluenesulfonyl chloride (20 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added triethylamine (20 mg, 0.2 mmol). The resulting solution was stirred for 2 h, quenched with water (1 mL), and extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was removed by rotary evaporation to provide a pale yellow oil. Purification by flash chromatography (5% EtOAc in hexanes) provided the tosylate as a colorless oil, which was dissolved in MeOH (1 mL), and *p*-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol) was added. After being stirred for 4 h, the solution was diluted with Et_2O (2 mL) and washed with water (2 mL). The solvent was removed by rotary evaporation to provide a crude oil. The NMR spectra of the crude alcohols were compared with literature compounds.

2-(*tert*-Butyldimethylsilanyloxymethyl)pyrrolidine (4). Silyl enol ether **1**[6] (301 mg, 1.27 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (1% methanol in EtOAc) afforded 206 mg (75%) of pyrrolidine **4** as a yellow oil: IR (neat) 3354, 2954, 2857, 1652, 1418 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (dd, J = 10.0, 4.8 Hz, 1 H), 3.49 (dd, J = 10.0, 5.6 Hz, 1 H), 3.19−3.08 (m, 1 H), 2.96 (dt, J = 10.0, 6.4 Hz, 1 H), 2.81 (dt, J = 10.0, 7.2 Hz, 1 H), 2.57 (s, br, 1 H), 1.79−1.49 (m, 3 H), 1.56−1.46 (m, 1 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.6, 59.9, 46.4, 27.4, 25.8, 25.3, 18.2, −5.5; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{26}NOSiNa$ 216.1784, found 216.1785.

2-(*tert*-Butyldimethylsilanyloxymethyl)-3-methylpyrrolidine (44a). Silyl enol ether **42a** (375 mg, 1.0 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (5% methanol in EtOAc) gave 163 mg (71%) of pyrrolidine **44a** (*trans*/*cis* = 93:7) as a light yellow oil. The relative stereochemistry was determined by analogy to pyrrolidine **44b**: IR (neat) 3361, 2957, 1645, 1456, 1412 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (s, br, 1H), 3.78 (dd, J = 10.4, 4.8 Hz, 1H), 3.66 (dd, J = 10.4, 4.8 Hz, 1H), 3.17−3.04 (m, 2H), 2.91−2.81 (m, 1H), 2.08−1.95 (m, 2H), 1.03 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.054 (s, 3H), 0.045 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.7, 62.5, 44.9, 34.9, 33.5, 25.8,

(24) Benzene is a listed carcinogen within the EEC. Appropriate ventilation and safety precautions should be taken when working with this solvent.

18.2, 17.8, −5.5, −5.6; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{28}NOSi$ 230.1940, found 230.1946.

2-(*tert*-Butyldimethylsilanyloxymethyl)-3-phenylpyrrolidine (44b). Silyl enol ether **42b** (206 mg, 0.65 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (67% EtOAc in hexanes) gave 155 mg (82%) of pyrrolidine **44b** (*trans*/*cis* = >95:5) as a light yellow oil. The pyrrolidine was subjected to the general tosylation followed by deprotection procedure and the relative stereochemistry was confirmed by comparison to the desilylated alcohol:[25] IR (neat) 3317, 2928, 1651, 1456, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H), 3.71 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.52 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.21−3.12 (m, 2H), 3.11−3.04 (m, 1H), 2.97 (q, *J* = 8.8 Hz, 1H), 2.32−2.16 (m, 2H), 2.04−1.92 (m, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 128.4, 127.6, 126.1, 68.5, 62.9, 46.9, 46.5, 35.7, 25.9, 18.2, −5.5; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{17}H_{29}NONaSi$ 314.1916, found 314.1911.

2-(*tert*-Butyldimethylsiloxymethyl)-3-methylpyrrolidine (46). Silyl enol ether **45** (372 mg, 1.0 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (5% methanol in CH_2Cl_2) gave 300 mg (86%) of pyrrolidine **46** (*cis*/*trans* = 75:25) as a light yellow oil. The relative stereochemistry was determined by analogy to pyrrolidine **48d**: IR (neat) 2928, 2856, 1472, 1463, 1361, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36−4.31 (m, 1H), 3.64 (d, *J* = 5.4 Hz, 1.5H, *cis*), 3.57−3.35 (m, 0.25H, *trans*), 3.43−3.34 (m, 0.25H, *trans*), 3.17−3.04 (m, 1H), 2.90−2.83 (m, 1.5H, *cis*), 2.76−2.58 (m, 0.40H, *trans*), 2.06−1.99 (m, 1H), 1.86 (br, 1H), 1.46 (ddd, *J* = 10.5, 6.7, 3.8 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.06−0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.4, 65.6, 59.8, 55.8, 38.1, 25.9, 25.8, 25.2, 18.4, 18.1, −4.8, −5.4; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{40}NO_2Si_2$ 346.2598, found 346.2590.

2-[(*tert*-Butyldimethylsilanyloxy)phenylmethyl]pyrrolidine (48a). Silyl enol ether **47a** (309 mg, 0.97 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (3% methanol in EtOAc) gave 131 mg (50%) of *erythro* pyrrolidine **48a** as a colorless oil: IR (neat) 2955, 2856, 1471, 1253, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.45 (d, *J* = 6.8 Hz, 1H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.08−2.97 (m, 1H), 2.90−2.79 (m, 1H), 2.26 (s, br 1H), 1.80−1.61 (m, 2H), 1.49−1.32 (m, 2H), 0.88 (s, 9H), 0.04 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 128.0, 127.3, 126.8, 78.5, 66.0, 45.9, 27.2, 25.8, 24.5, 18.1, −4.5, −5.0; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2091.

Further elution afforded 33 mg (12%) of pyrrolidine **48a** (*erythro*/*threo* = 50:50) as a light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.45 (d, *J* = 6.8 Hz, 0.5H), 4.45 (d, *J* = 6.8 Hz, 0.5H), 3.18 (q, *J* = 7.2 Hz, 1H), 3.21−3.19 (m, 1H), 3.08−2.97 (m, 2H), 2.91−2.73 (m, 1H), 2.03 (s, br 1H), 1.80−1.61 (m, 2H), 1.52−1.32 (m, 2H), 0.90 (s, 4.5H), 0.88 (s, 4.5H), 0.05 (s, 1.5H), 0.04 (s, 1.5H), −0.19 (s, 1.5H), −0.21 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 143.3, 128.0, 127.4, 127.3, 126.8, 126.5, 78.5, 77.2, 66.2, 66.0, 46.7, 45.9, 27.2, 27.1, 25.8, 25.0, 24.5, 18.1, −4.5, −5.0, −5.1.

2-(*tert*-Butyldimethylsilanyloxymethyl)-5-methylpyrrolidine (48b). Silyl enol ether **47b** (142 mg, 0.56 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (5% methanol in EtOAc) gave 99 mg (78%) of pyrrolidine **48b** (*trans*/*cis* = 65:35) as a light yellow oil. The relative stereochemistry was determined by analogy to pyrrolidine **48c**: IR (neat) 3364, 2927, 1645, 1462, 1379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 10.0, 4.8 Hz, 0.34H, *cis*), 3.56 (dd, *J* = 10.0, 4.8 Hz, 0.34H, *cis*), 3.51−3.45 (m, 1.3H, *trans*), 3.38−3.29 (m, 0.64H), 3.27−3.20 (m, 0.64H), 3.20−3.07 (m, 0.66H), 2.04 (s, br, 1H), 1.95−1.69 (m, 2H), 1.50−1.19 (m, 2H), 1.16 (d, *J* = 6.4 Hz, 3H, *cis*), 1.12 (d, *J* = 6.4 Hz, 3H, *trans*), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.0, 65.7, 60.5, 59.2, 54.9, 53.1, 33.8, 33.6, 27.9, 25.9, 21.5, 21.1, 18.3, −5.3, −5.4; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{28}NOSi$ 230.1940, found 230.1934.

2-(*tert*-Butyldimethylsilanyloxymethyl)-5-phenylpyrrolidine (48c). Silyl enol ether **47c** (280 mg, 0.88 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (20% EtOAc in hexanes) gave 169 mg (66%) of *trans*-pyrrolidine **48c** as a light yellow oil. The pyrrolidine was subjected to the general deprotection procedure, and the relative stereochemistry was confirmed by comparison to the desilylated alcohol:[26] IR (neat) 3330, 2928, 2856, 1673, 1462, 1255, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30−7.25 (m, 1H), 4.31 (t, *J* = 7.2 Hz, 2H), 3.63−3.53 (m, 3H), 2.29−2.20 (m, 1H), 2.15−2.01 (m, 2H), 1.78 (dq, *J* = 12.4, 8.8 Hz, 1H), 1.66−1.54 (m, 1H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 128.3, 126.7, 126.4, 66.2, 61.0, 59.6, 34.9, 27.8, 25.9, 18.3, −5.3; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2092.

Further elution afforded 31 mg (12%) of *cis*-pyrrolidine **48c** as a light yellow oil: IR (neat) 2954, 2856, 1255, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 4.17 (t, *J* = 7.2 Hz, 2H), 3.71 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.65 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.53 (quin, *J* = 6.0 Hz, 1H), 2.20−2.10 (m, 1H), 1.94−1.81 (m, 2H), 1.75−1.65 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 128.3, 126.8, 126.6, 66.7, 62.8, 60.3, 34.3, 27.8, 26.0, 18.4, −5.3; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2090.

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-ethylpyrrolidine (48d). Silyl enol ether **47d** (69 mg, 0.26 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (5% methanol in EtOAc) gave 49 mg (79%) of pyrrolidine **48d** (*cis*/*trans* = 72:28) as a light yellow oil. The relative stereochemistry was determined by analogy to pyrrolidine **48e**: IR (neat) 3300, 2957, 2857, 1463, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.64−3.46 (m, 2H), 3.27−3.18 (m, 1H), 3.16 (dd, *J* = 10.0, 7.2 Hz, 1H, *trans*), 3.03 (dd, *J* = 10.0, 7.2 Hz, 1H, *cis*), 2.56 (dd, *J* = 10.0, 7.2 Hz, 1H, *trans*), 2.45 (dd, *J* = 10.0, 8.4 Hz, 1H, *cis*), 2.08 (s, br, 1H), 2.07−1.92 (m, 2H), 1.74−1.63 (m, 1H), 1.43−1.32 (m, 1H), 1.08−0.98 (m, 1H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.09 (s, 9H), 0.06, (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.2, 65.9, 60.4, 59.6, 52.9, 52.0, 41.8, 41.0, 34.6, 34.0, 27.6, 27.4, 25.9, 18.3, 12.9, −5.4; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{30}NOSi$ 244.2097, found 244.2092.

2-(*tert*-Butyldimethylsilanyloxymethyl)-4-phenylpyrrolidine (48e). Silyl enol ether **47e** (203 mg, 0.64 mmol) was subjected to the general cyclization procedure. Purification by flash chromatography (5% methanol in EtOAc) gave 143 mg (77%) of pyrrolidine **48e** (*cis*/*trans* = 89:11) as a light yellow oil. The pyrrolidine was subjected to the general tosylation followed by deprotection procedure and the relative stereochemistry and dr were confirmed by comparison to the desilyled alcohol:[26] IR (neat) 3312, 2953, 2855, 1654, 1454, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.16 (m, 5H), 3.71 (dd, *J* = 10.0, 4.8 Hz, *cis*, 1H), 3.66 (dd, *J* = 10.0, 5.6 Hz, *cis*, 1H), 3.65 (dd, *J* = 10.0, 5.2 Hz, *trans*, 1H), 3.61 (dd, *J* = 10.0, 5.6 Hz, *trans*, 1H), 3.50−3.20 (m, 3H), 3.00−2.84 (m, 1H), 2.33−2.24 (m, 1H), 2.10−1.88 (m, 2H), 1.71−1.61 (m, 1H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 144.1, 128.4, 128.0, 127.3, 127.2, 126.2, 66.0, 65.8, 60.7, 60.3, 55.4, 54.2,

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45.9, 45.2, 36.8, 36.2, 25.9, 25.7, 18.3, −5.3; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2092.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.