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Pyrrolidines from β-Aminoselenides via Radical Cyclization. Diastereoselectivity Control by the N-Substituent

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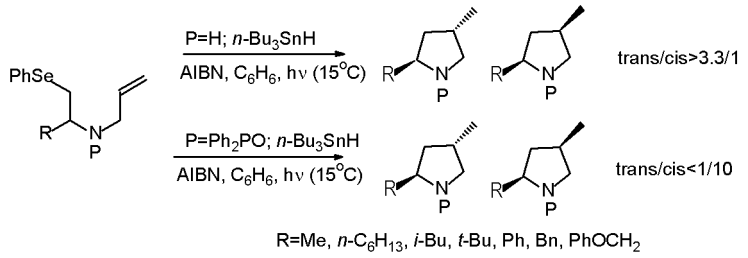
ABSTRACT



***N*-Allyl-β-aminoalkyl phenyl selenides—precursors of 3-aza-5-hexenyl radicals—were prepared by ring opening of *N*-allylaziridines with benzeneselenol under acidic conditions or by sodium cyanoborohydride reduction of *N*-allylimines of α-phenylselenenyl ketones. The effect of various N-protective groups (acyl, sulfonyl, or phosphinoyl) on diastereoselectivity in thermally or photochemically initiated 3-aza-5-hexenyl reductive radical cyclization was studied. Whereas N-unprotected derivatives afforded *trans*-2,4-disubstituted pyrrolidines with good selectivity, the diphenylphosphinoyl group directed cyclization to occur in a highly cis-selective manner.**

The problem of controlling the stereochemical outcome of radical reactions is currently receiving considerable attention.[1] Substrate-controlled diastereoselection can often be achieved when the controlling stereocenter is incorporated into a cyclic radical. For acyclic diastereoselection, significant levels of selectivity have also been obtained in radical addition and reduction reactions using preexisting chiral centers,[2] chiral auxiliaries,[3] or chiral Lewis acids.[4] In the two former cases, selectivity is often enhanced by preorganization of the substrate through Lewis acid[5] or solvent[6] complexation or intramolecular hydrogen bonding.[7] Attempts to control

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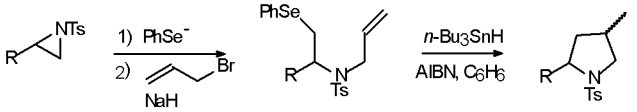
diastereoselectivity in free-radical cyclization reactions have so far been less successful.

Diastereoselectivity is governed primarily by conformational and steric effects as described by the Beckwith−Houk transition state model.[8] Thus, 1- or 3-substituted 5-hexenyl radicals afford predominantly cis-disubstituted products, whereas 2- or 4-substituted radicals give mainly trans-disubstituted ones. However, the selectivity in simple systems rarely exceeds 4:1 in favor of the major diastereomer. Recent successful strategies to perturb Beckwith−Houk diastereoselectivities in intramolecular radical cyclization reactions are based on Lewis acid coordination,[9] variation in the hydrogen atom donor,[10] or the stereochemical influence of the anomeric effect.[11]

The model for radical cyclization proposed by Beckwith and Houk is also applicable to various types of heterocycle construction (e.g., tetrahydrofuran[12] and pyrrolidine[13] synthesis). Some time ago, we reported the preparation of 2,4-disubstituted *N*-tosylpyrrolidines from *N*-tosylaziridines via benzeneselenolate ring opening, *N*-allylation, and reductive radical cyclization (Scheme 1).[14] In disagreement with the

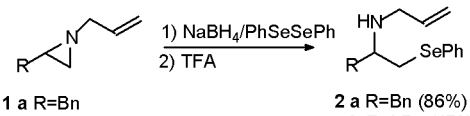
Scheme 1



Beckwith−Houk rules, the products were obtained predominantly (2/1−3/1) as cis isomers. These results prompted us to study the N-substituent as a tool for controlling the diastereoselectivity in various types of azaalkenyl radical cyclizations.[15] The results presented in the following for 3-aza-5-hexenyl radicals show that the N-substituent has a dramatic effect on the stereochemical outcome of cyclization.

Selenium-based radical precursors suitable for this investigation were prepared by two different routes. In contrast to *N*-tosylaziridines, *N*-alkylaziridines are not ring-opened by benzeneselenolate generated by sodium borohydride reduction of diphenyl diselenide. However, on addition of trifluoroacetic acid, ring opening occurred regioselectively from the sterically least hindered side. Thus, aziridines **1**, prepared by allylation of the corresponding N-unsubstituted aziridines, were converted to *β*-(allylamino)alkyl phenyl selenides **2** in fair yields as shown in Scheme 2. In another

Scheme 2



1 **a** R=Bn
b R=i-Bu
c n-C_6H_{13}
d $PhOCH_2$

2 **a** R=Bn (86%)
b R=i-Bu (47%)[a]
c R=n-C_6H_{13} (45%)[a]
d R=$PhOCH_2$ (83%)
[a] One-pot allylation/ring opening

approach, readily prepared[16] α-(phenylselenenyl) ketones **3** were condensed with allylamine in the presence of titanium tetrachloride as a dehydrating agent.[17] Subsequent in situ sodium cyanoborohydride reduction of the imines **4** afforded the desired radical precursors **5** (Scheme 3).

Scheme 3

3 **a** R=Me
b R=Ph
c R=*t*-Bu

4 **a** R=Me
b R=Ph
c R=*t*-Bu

5 **a** R=Me (34%)[a]
b R=Ph (58%)[a]
c R=*t*-Bu (37%)[a]
[a] Over two steps

For initial screening of the effect of various N-protecting groups on diastereoselectivity in 3-aza-5-hexenyl radical cyclization, aminoselenide **2a** was reacted with a selection of acylating, sulfonylating, and phosphinoylating agents (Table 1). Reductive radical cyclization was then effected in 60−93% yields in benzene with thermal (80 °C) or photochemical (15 °C) initiation in the presence of AIBN and tri-*n*-butylstannane. Diastereoselectivities were determined by ^{1}H NMR, sometimes after acidic hydrolysis of the N-protecting groups. As shown in Table 1, cyclization of the N-unprotected compound afforded predominantely the

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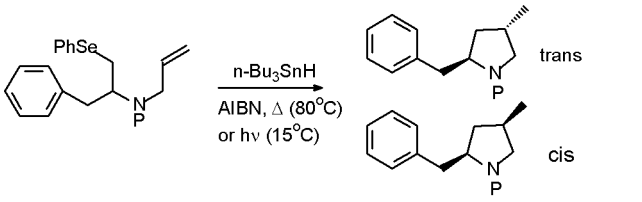
Table 1. Diastereoselectivities in the Reductive Radical Cyclization of N-Protected 2-Benzyl-3-aza-5-hexenyl Phenyl Selenides at 80 and 15 °C



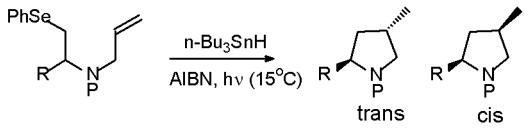
P	cis/trans-ratio[a] (80°C)	yield (%)[b] (80°C)	cis/trans-ratio[a] (15°C)	yield (%)[b] (15°C)
H	1/2.6	60	1/3.8	92
EtC(=O)	2.2/1	88	2.7/1	82
i-PrC(=O)	2.6/1	83	3.2/1	80
t-BuC(=O)	2.0/1	93	2.0/1	87
PhC(=O)	4.4/1	72	7.1/1	89
4-MeC$_6$H$_4$SO$_2$	3.0/1	77	4.0/1	78
Ph$_2$P(=O)	10/1	79	24/1	81

[a] As determined by ^{1}H NMR
[b] isolated yield

trans isomer, whereas most of the N-protecting groups directed cyclization to occur in a moderately (2.0−4.4/1 at 80 °C and 2.0−7.1/1 at 15 °C) cis-selective fashion. In contrast, cyclization of the diphenylphosphinoyl-protected aminoselenide was highly (10/1) cis-selective already at 80 °C and even more so (24/1) at 15 °C.

To probe the directing effect of the diphenylphosphinoyl group in other systems, the remaining aminoselenides **2** and **5** were reacted with diphenylphosphinic chloride in methylene chloride containing triethylamine and DMAP (the radical precursor with R = *t*-Bu could not be prepared in this way). The unprotected *β*-aminoalkyl phenyl selenides and their diphenylphosphinoylated derivatives were then subjected to radical cyclization at 15 °C in benzene with photochemical initiation in the presence of AIBN and tri-*n*-tributyltin hydride. As shown in Table 2, unprotected compounds afforded *trans*-2,4-disubstituted pyrrolidines with fair to high selectivity (cis/trans = 1/3.3−1/20) whereas the *N*-diphenylphosphinoylated compounds gave the corresponding *cis*-2,4-disubstituted pyrrolidines with even higher diastereoselectivity (cis/trans = 10/1−20/1) in good yields. The assignment of cis/trans isomers was based on NOESY and NOE experiments on diphenylphosphinoylated compounds. The yields reported in Table 2 for unprotected compounds are those obtained after radical cyclization and *N*-diphenylphosphinoylation.

Table 2. Diastereoselectivities in the Reductive Radical Cyclization of 3-Aza-5-hexenyl Phenyl Selenides and Their Corresponding *N*-Diphenylphosphinoyl-Protected Derivatives at 15 °C



R	P	yield (%)[a]	cis/trans-ratio (15°C)
Me	H	59[b]	1/3.8
Me	Ph$_2$P(=O)	78	18/1
n-C$_6$H$_{13}$	H	86[b]	1/4
n-C$_6$H$_{13}$	Ph$_2$P(=O)	85	20/1
i-Bu	H	91[b]	1/3.3
i-Bu	Ph$_2$P(=O)	84	17/1
t-Bu	H	59[b]	< 1/20
t-Bu	Ph$_2$P(=O)	-[c]	-
Ph	H	61[b]	1/10
Ph	Ph$_2$P(=O)	88	10/1
PhOCH$_2$	H	75[b]	1/14.3
PhOCH$_2$	Ph$_2$P(=O)	72	20/1

[a] isolated yield
[b] overall cyclization/diphenylphosphinoylation yield
[c] the radical precursor could not be prepared by the methodologies developed

At present, we can only speculate as to the reasons for the high diastereoselectivities in the cyclization reactions. The predominant formation of *trans*-2,4-disubstituted pyrrolidines from unprotected compounds is in accord with the predictions based on the Beckwith−Houk transition state model. The high selectivity with the phenoxymethyl side chain (cis/trans = 1/14.3) could be due to intramolecular hydrogen bonding as shown in Figure 1, favoring an equatorial orientation of the substituent.

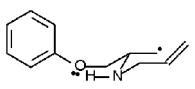


Figure 1.

The preference for formation of *cis*-2,4-disubstituted pyrrolidines in the radical cyclization of N-protected β-aminoalkyl phenyl selenides may be explained by $A^{1,2}$-strain between the protecting group and the 2-substituent[18] in the chair-equatorial conformation (Figure 2, exemplified with the bulky diphenylphosphinoyl group). Thus, the chair-axial transition state, leading to the 2,4-*cis*-disubstituted pyrrolidine, becomes energetically more favorable. Usually, boat transition states for radical cyclization are only ca. 1 kcal/mol higher in energy than the corresponding chair conformations. Therefore, it is hard to say which of the chair-equatorial or boat-axial conformations contribute most to the formation of the minor *trans*-2,4-disubstituted pyrrolidine.

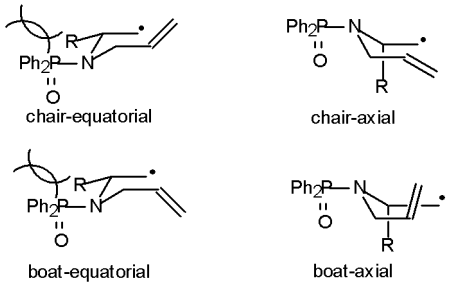


Figure 2.

In the present paper we have demonstrated the usefulness of the N-substituent for controlling the diastereoselectivity in 3-aza-5-hexenyl radical cyclization. By running the reactions at 15 °C with photochemical initiation[19] and by using a hydrogen or a bulky diphenylphosphinoyl protecting group, high levels of diastereoselectivity in the formation of *trans*- and *cis*-2,4-disubstituted pyrrolidines, respectively, can be obtained. It is important to emphasize that the methodology described in this paper is also well suited for asymmetric synthesis. The required enantiomerically pure aziridines of the type used in Scheme 2 are already available. It would also be possible to perform enantioselective reduction of the imines shown in Scheme 3 to obtain enantiomerically pure β-aminoalkyl phenyl selenides.

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

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