Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Science and Technology 702

Radical Cyclization Approaches to Pyrrolidines

BY

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CONTENTS

1. Introduction.

1.1 Pyrrolidines.

Pyrrolidines are well represented in naturally occurring alkaloids, and are also important in drug manufacturing. To mention but a few, there are pyrrolidine structural motifs in nicotine as well as in the beautiful polycyclic structure of strychnine. One of our own most basic building blocks, the amino acid proline, is also a pyrrolidine bearing a carboxylic acid side chain. Epibatidine is a naturally occurring alkaloid isolated from the poison arrow frog *Epipedobates tricolor* (Figure 1).

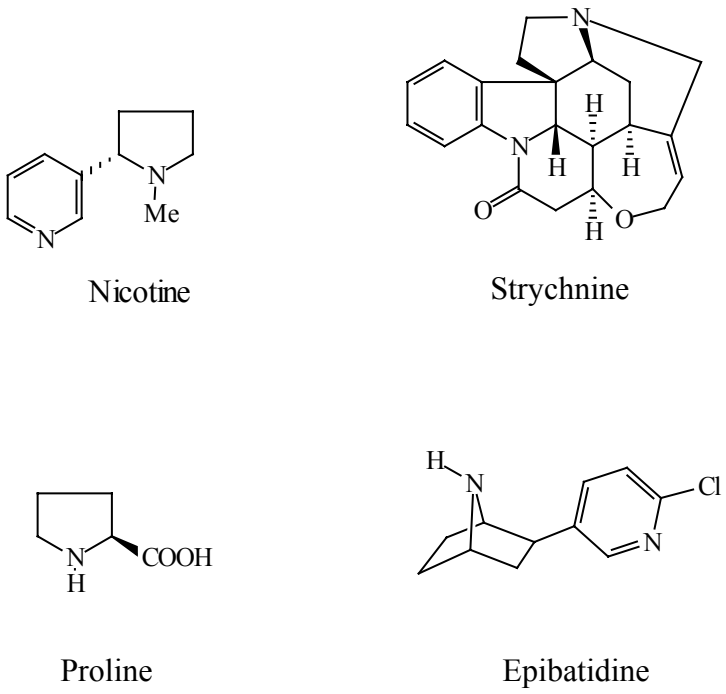


Figure 1. Some naturally occurring pyrrolidines.

By definition, pyrrolidines are heterocycles, but, due to their saturation, lack the special reactivity of their closest aromatic relative, pyrrole. Pyrrolidines behave as normal amines, and are often made from such. Synthetically, there are several distinctly different methods for their preparation, including organometallic methodologies as well as those of classical organic chemistry. Outlined below are some recent strategies for pyrrolidine synthesis.

1.1.1 Some recent synthetic pathways to pyrrolidines.

Pyrrolidines are ordinary amines. Thus, their synthesis can involve any chemical reaction that forms either a carbon-heteroatom or a carbon-carbon bond intramolecularly. Figure 2 shows a retrosynthetic analysis of pyrrolidine.

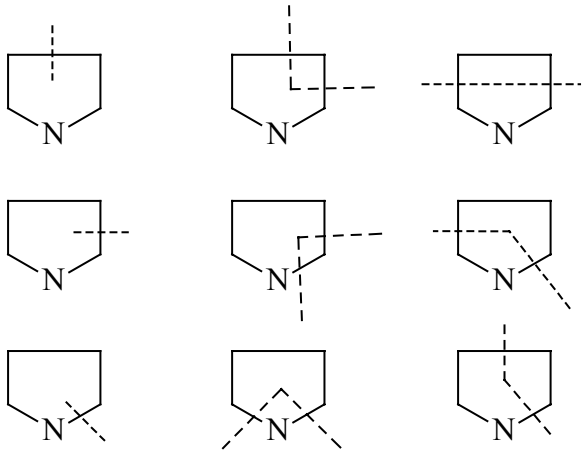


Figure 2. Retrosynthetic analysis of pyrrolidine. Bond formation can involve either ionic, radical or organometallic intermediates.

There are numerous ways to close the five-membered ring. Therefore, it would be difficult to cover every possible synthetic strategy here. However, the recent literature shows a preference for certain routes for the preparation of pyrrolidines. Some of them, such as the 1,4-disubstitution of a carbon fragment by nucleophilic amines, can be considered classic. Although many of the below methods can be performed with good stereocontrol, no particular attention will be given to asymmetric pyrrolidine synthesis. Figure 3 outlines the most commonly encountered approaches to pyrrolidines - intramolecular substitution:

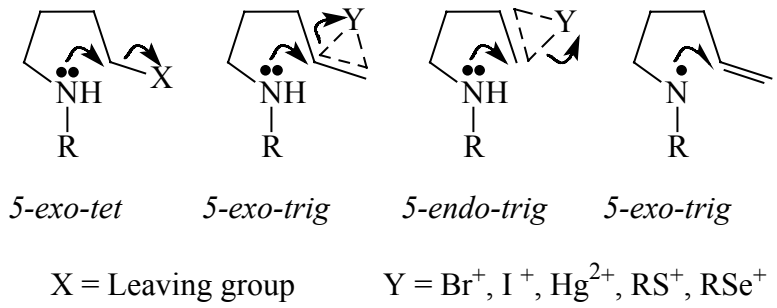


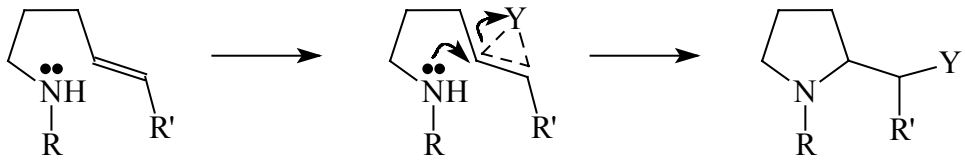
Figure 3. The general picture for *5-exo-tet*, *5-exo-trig* and *5-endo-trig* cyclisation.

Reasons for the successful application of these methodologies are of course the high nucleophilicity of nitrogen and the favourable rate of cyclization. Five-membered rings form

6 times faster than six-membered ones, 6000 times faster than four-membered ones and 83 times faster than three-membered ones.[1a] Extra driving force is also provided by the favourable entropy change accompanying intramolecular substitution and by steric relief upon cyclization (if the heteroatom carrying carbon is also substituted by other groups).[1b]

A classic example of the *5-exo-tet* reaction is the *Hoffman-Löffler-Freytag* reaction,[2] where chloramines form pyrrolidines by generating the leaving group (the chloride from the chloramine) *in situ* on the δ-carbon. There are also examples of tosyl[3] and hydroxyl (via the *Mitsunobu* reaction)[4] leaving groups.

The *5-exo-trig* cyclization approach is commonly used for pyrrolidine synthesis. This reaction can either be ionic or radical. The ionic pathway has been used more frequently than the radical one and also works better (Scheme 1):



$Y = Br^+, I^+, Hg^{2+}, RS^+, RSe^+$

Scheme 1. Ionic *5-exo-trig* cyclization with nitrogen as a nucleophile.

This process is similar to the *iodolactonization* reaction. An electrophilic species adds across the unsaturated bond and activates it towards nucleophilic attack. The most commonly used electrophiles for this type of ring-closure are shown in Scheme 1.[5]

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[1] [a)]Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591. [b)]Kirby, A. J. in 'Advances in Physical Organic Chemistry', eds. Gold, V.; Bethell, D. Academic press, 1980, vol. 17, 183.

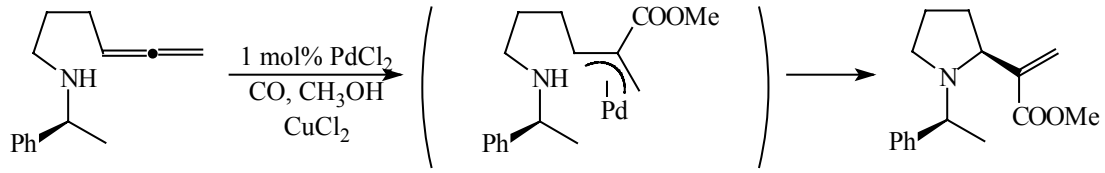
[2] Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.

[3] [a)]Lin, G. -q.; Shi, Z. –c. *Tetrahedron Lett.* **1995**, *36*, 9537. [b)]Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 3637.

[4] [a)]Van Betsbrugge, J.; Tourwé, D.; Kaptein, B.; Kierkels, H.; Broxterman, R. *Tetrahedron* **1997**, *53*, 9233. [b)]Barry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *J. Chem. Soc.*, *Chem. Commun.* **1997**, 2141.

[5] [a)]Ihara, M.; Haga, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1983**, *105*, 7345. [b)]Webb II, R. R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 1357. [c)]Takahara, H.; Bandoh, H.; Momose, T. *J. Org. Chem.* **1992**, *57*, 4401. [d)]Coldham, I.; Warren, S. *J. Chem. Soc.*, *Perkin Trans. 1*, **1993**, 1637. [e)]Terao, K.; Toshimitsu, A.; Uemura, S. *J. Chem. Soc.*, *Perkin Trans. 1*, **1986**, 1837. [f)]Tamaru, Y.; Kawamura, S.; Bando, T.; Kunitada, T.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491. [g)]Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1983**, *48*, 3644. [h)]Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc.*, *Chem. Commun.* **1998**, 2207. [i)]Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.

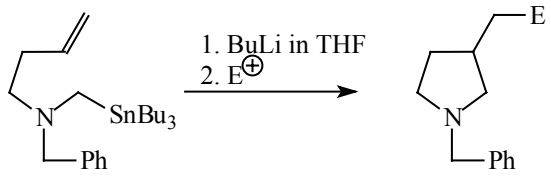
Several metal-catalysed variations of this theme have been reported.[6] Intramolecular nucleophilic attack on a π-allyl palladium complex is shown in Scheme 2.



Scheme 2. Palladium catalyzed pyrrolidine synthesis.

There are also some interesting reactions of γ-aminoacetylenes with titanium(IV),[7] γ-aminoallenes with silver(I) and γ-aminoolefins with lanthanides.[8]

The approach using the α-carbon as an electrophile or nucleophile has not been used as extensively as the methodology described above, but some interesting examples exist. Some cases rely on an anion stabilizing group (carbonyl, carboxyl) next to the charge created. α-Aminostannanes can be used to form anions via metal exchange.[9] The resulting organolithium compound then adds to the double bond (Scheme 3):



Scheme 3. An organostannane as a source of a carbanion.

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[6] [a]Larock, R. C.; Yang, H. *J. Org. Chem.* **1994**, *59*, 4172. [b]Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1994**, *35*, 9537. [c]Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652. [d]Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724. [e]Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *39*, 5081. [f]Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421.

[7] Fairfax, D.; Stein, M.; Livinghouse, T.; Jensen, M. *Organometallics* **1997**, *16*, 1523.

[8] [a]Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983. [b]Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295.

[9] [a]Coldham, I.; Hufton, R.; Rathmell, R. E. *Tetrahedron Lett.* **1997**, *38*, 7617. [b]Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R. E.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621.

There are several radical variations of this pathway as well. To mention a few, radical precursors such as α-chlorides, -sulfides, -isocyanates and -thiocyanates have been used.[10] SmI_2 has a large reducing capacity. It can easily donate electrons to unsaturated heteroatom-carbon bonds and thereby initiate radical reactions.[11]

The other major intramolecular pathway to pyrrolidines involves formation of the 3C-4C bond (Figure 4):

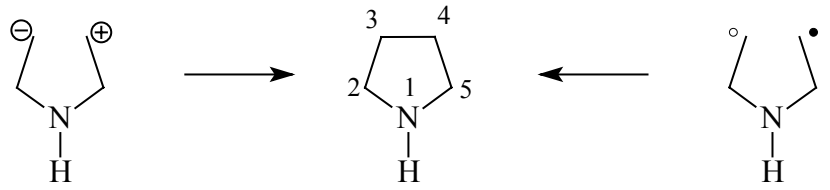

Figure 4. 3C-4C bond formation.

Some synthetic alternatives to accomplish this are the following:

1. Ring-closure by way of transition metal catalysed metathesis.
2. Ring-closure by way of ene- or metallo-ene reactions.
3. Ring-closure by way of reductive metal catalysis.
4. Ring-closure by way of radical cyclization.

Metathesis is catalysed by different metals. Some recent examples include the use of ruthenium complexes (although the product of this reaction is unsaturated in the ring), and chromium in the form of a Fischer carbene complex.[12]

Oppolzer and co-workers have shown that intramolecular ene reactions can be used for the preparation of substituted pyrrolidines. Both unactivated and activated enophiles react.[13]

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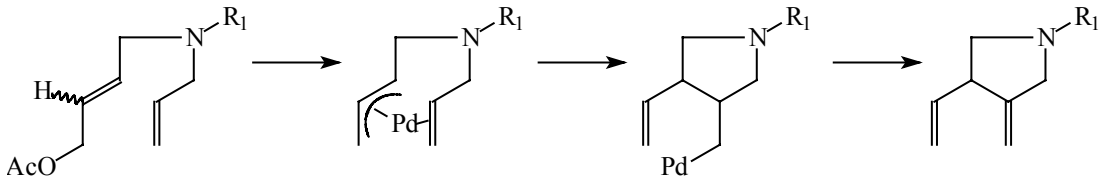
[10] [a)]Clive, D. L. J.; Yang, W. *J. Chem. Soc., Chem. Commun.* **1996**, 1605. [b)]Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 219. [c)]Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. [d)]Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 455.

[11] [a)]Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1383. [b)]Baldwin, J. E.; MacKenzie Turner, J. E.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9411, 9425.

[12] [a)]Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. [b)]Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1998**, 1315. [c)]Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. [d)]Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7996. [e)]Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291. [f)]Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1995**, *36*, 9501. [g)]Bates, R. W.; Rama-Devi, T.; Ko, H-H. *Tetrahedron* **1995**, *51*, 12939. [h)]Dötz, K. H.; Schäfer, T. O.; Harms, K. *Synthesis* **1992**, 146.

[13] [a)]Oppolzer, W.; Pfenninger, E.; Keller, K. *Helv. Chim. Acta.* **1973**, *56*, 1807. [b)]Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. [c)]Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. [d)]Oppolzer, W.; Mirza, S. *Helv. Chim. Acta.* **1984**, *67*, 730.

Nickel, palladium and platinum can also be used to catalyse the ene reaction (metallo-ene reaction). In these processes, an olefin is coupled to a π-allyl-palladium complex[14] as shown in Scheme 4:



Scheme 4. Palladium catalysed ene reaction.

Similarly, the coupling of an olefin to an acetylene is catalysed by palladium(0).[15] Nickel(0) works in the same manner.[16] Zirconium complexes have been found to dimerize unsaturated bonds (including both C=C and C=O) intramolecularly to form five-membered zirconacycles. These can be transformed to pyrrolidines.[17] Titanium[18] and cobalt[19] complexes work in a similar fashion.

Radical carbon-carbon bond formation has also found use in the formation of the C3-C4 bond of pyrrolidines. As exemplified in Scheme 5, carbon-carbon bond formation is often the result of a *5-exo-trig* or *5-exo-dig* cyclization.

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[14] [a)]Oppolzer, W.; Gaudin, J-M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Raynham, T. M.; Robyr, C. *Tetrahedron Lett.* **1988**, *29*, 4709. [b)]Oppolzer, W.; Keller, T. H.; Kuo, D. L.; Pachinger, W. *Tetrahedron Lett.* **1990**, *31*, 1265. [c)]Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C. Y. *Tetrahedron Lett.* **1988**, *29*, 6433. [d)]Oppolzer, W.; Keller, T. H.; Bedoya-Zurita, M.; Stone, C. *Tetrahedron Lett.* **1989**, *30*, 5883.

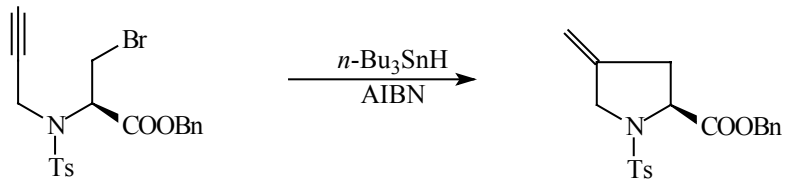
[15] [a)]Oppolzer, W.; Birkinshaw, T. N.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 6995. [b)]Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033. [c)]Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron* **1988**, *44*, 4321. [d)]De Riggi, I.; Surzur, J-M.; Bertrand, M. P. *Tetrahedron* **1988**, *44*, 7119. [e)]Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007. [f)]Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109.

[16] [a)]Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. [b)]Cancho, Y.; Martín, J. M.; Martínez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221. [c)]Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824. [d)] Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449.

[17] [a)]Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615. [b)]Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643. [c)]Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5469.

[18] Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785.

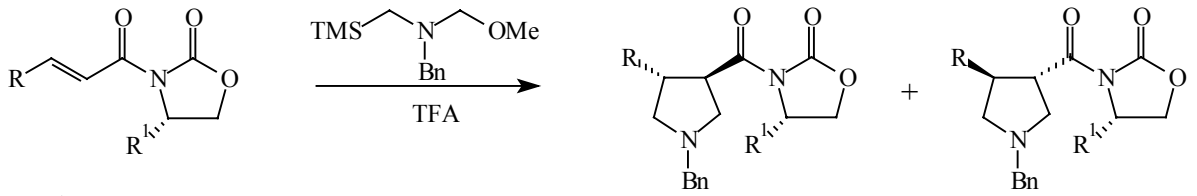
[19] [a)]Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169. [b)]Belanger, D.; O'Mahony, D. J. R.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637.



Scheme 5. *5-Exo-dig* cyclization for pyrrolidine synthesis.

Carbon centred radicals have been formed either by tin hydride mediated chain reactions[20] (like the one above), by fragmentation of a suitable radical precursor or by intermolecular addition to an unsaturated bond. A relatively new methodology of radical formation involves single electron transfer from samarium to a carbonyl group.[21]

The [2+3] cycloaddition reaction has been diligently explored for pyrrolidine synthesis. Azomethine ylides or imine anions are frequently used in the reaction. Often, the ylide or anion precursor contains silicon or tin (Scheme 6): [22]



R^1 = *i*-Pr, Bn, Ph

Scheme 6. [2+3] cycloaddition for pyrrolidine synthesis.

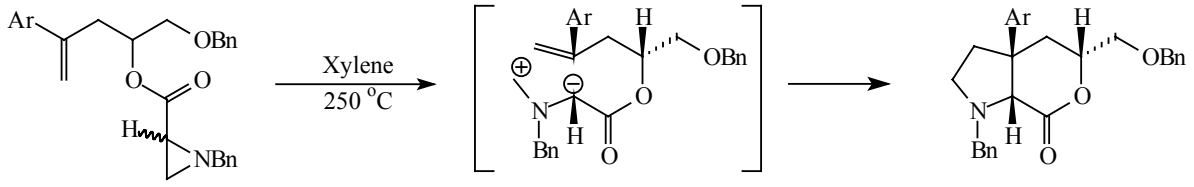
If one of the α-carbons carries anion stabilising groups, the ylid forms when acid or base is present. In some instances the cycloaddition has been catalysed with silver or lithium.[23] A

[20] [a)]Soucy, F.; Wernic, D.; Beaulieu, P. *J. Chem. Soc.*, *Perkin Trans. 1*, **1991**, 2885. [b)]Adlington, R. M.; Mantell, S. J. *Tetrahedron* **1992**, *48*, 6529. [c)]Esch, P. M.; Heimstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659. [d)]Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269. [e)]Bertrand, M-P.; Gastaldi, S.; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229. [f)]Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc.*, *Chem. Commun.* **1993**, 125. [g)]Ryu, I.; Kurihara, A.; Muraoka, H.; Tsunoi, S.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 7570. [h)]Castagnino, E.; Corsano, S.; Barton, D. H. R. *Tetrahedron Lett.* **1989**, *30*, 2983. [i)]Vogler, B.; Bayer, R.; Meller, M.; Kraus, W.; Shell, F. M. *J. Org. Chem.* **1989**, *54*, 4165. [j)]Brumwell, J. E.; Simpkins, N. S.; Terret, N. K. *Tetrahedron Lett.* **1993**, *34*, 1219.

[21] [a)]Baldwin, J. E.; MacKenzie-Turner, S. C.; Moloney, M. G. *Tetrahedron Lett.* **1992**, *33*, 1517. [b)]Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H.; Naito, T. *Tetrahedron* **1998**, *54*, 5883.

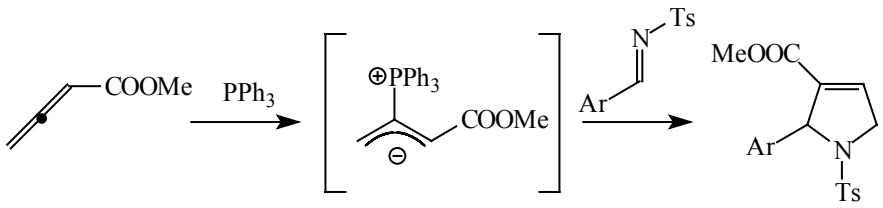
[22] [a)]Katritzky, A. R.; Köditz, J.; Lang, H. *Tetrahedron* **1994**, *50*, 12571. [b)]Pandey, G.; Bagul, T. D.; Lakshmaiah, G. *Tetrahedron Lett.* **1994**, *35*, 7439. [c)]Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527. [d)]Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431. [e)]Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354. [f)]Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329. [g)]Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. [h)]Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1995**, *36*, 9409.

related method takes advantage of the ring-opening equilibrium of anion stabilised aziridines (Scheme 7): [24]



Scheme 7. Ring-opening equilibrium of anion stabilized aziridine.

Related to the [2+3] concerted cyclization shown above is the [2+3] cyclization of imines[25] (Scheme 8). As yet, few examples of this methodology are known.



Scheme 8. [2+3] cycloaddition of an imine.

Strictly speaking, this is a dihydropyrrole synthesis. However, the product can easily be reduced to a pyrrolidine. Other examples involve metals and a precursor that allows for π-allyl complexation or S_N2'substitution (Scheme 9).[26]

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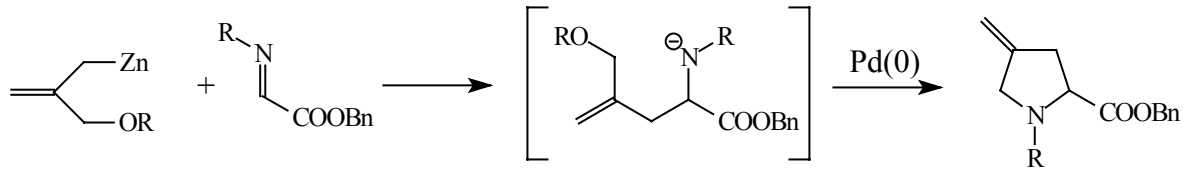
[23] [a)]Overman, L. E.; Tellew, J. E. *J. Org. Chem.* **1996**, *61*, 8338. [b)]Wittland, C.; Arend, M.; Risch, N. *Synthesis* **1996**, 367. [c)]Schneider, M-R.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 8493. [d)]Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005. [e)]Barkley, J. V.; Gilchrist, T. L.; Rocha Gonsalves, A. M. d'A.; Pinhoe Melo, T. M. V. D. *Tetrahedron* **1995**, *51*, 13455. [f)]Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1995**, *51*, 13347. [g)]Pätzel, M.; Galley, G.; Jones, P. G.; Chrapkowsky, A. *Tetrahedron Lett.* **1993**, *34*, 5707. [h)]Ayerbe, M.; Arrieta, A.; Cossío, F. P.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795. [i)]Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. [j)]Martel, S. R.; Wisedale, R.; Gallagher, T.; Hall, L. D.; Mahon, M. F.; Bradburry, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309. [k)]Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H-P. *Chem. Eur. J.* **1995**, *1*, 150. [l)]Coldham, I.; Collins, A. J.; Mould, R. J.; Robinson, D. E. *Synthesis* **1995**, 1147.

[24] [a)]Hashimura, K.; Tomita, S.; Hiroya, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2291. [b)]Gaebert, C.; Mattay, J. *Tetrahedron* **1997**, *53*, 14297. [c)]Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4. [d)]Sharp, M. J.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 3651. [e)]La Porta, P.; Capuzzi, L.; Bettarini, F. *Synthesis* **1994**, 287.

[25] Yamago, S.; Nakamura, M.; Wang, X. Q.; Yanagawa, M.; Tokumitsu, S.; Nakamura, E. *J. Org. Chem.* **1998**, *63*, 1694.



Scheme 9. Metal assisted [2+3] cyclization of an imine.

The radical approach that we have chosen to investigate has clear advantages: 1) Aza-5-hexenyl radicals ring-close at very high rates favouring *exo* cyclization almost exclusively. This makes the synthesis unencumbered by side reactions. 2) Radical reactions are tolerant to many functional groups, and, thus, can be viewed upon as mild. 3) As a consequence of 1) and 2), radical ring-closures are often high-yielding reactions.

The main drawback of these reactions is the poor stereocontrol in the formation of pyrrolidines bearing substituents. Depending on the orientation relative to the radical bearing carbon, the diastereomeric ratios will vary greatly (*vide infra*). We have designed protocols to make either *cis* or *trans* 2,4-disubstituted pyrrolidines starting from aziridines. Since substantial amounts of these materials were needed, we have also investigated a short route to aziridines from olefins.

1.2 Radical chain reactions and the tin hydride method.

It is surprising to find that many undergraduate textbooks in organic chemistry include a chapter on radical chemistry as the last but one chapter – followed only by the magic treatise on photochemistry. Since it is a frequently used method in organic synthesis nowadays,[27] radical chemistry certainly deserves some more attention.

A criterion for performing successful radical reactions is that the desired reaction is faster than any competing reaction such as radical-radical recombination or radical-solvent reactions. Although the rates of radical-solvent reactions differ, radical reactions are tolerant to most solvents. Rate expressions for radical reactions are usually simpler than those for ionic reactions. This is because radical reactions are essentially insensitive to ion pairing, aggregation and solvent effects. By estimating the rate for radical-radical termination, a limitation for useful reactions can be calculated:

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[26] [a)]Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636. [b)]Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778. [c)]van der Heide, T. A. J.; van der Baan, J. L.; de Kimpe, V.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1993**, *34*, 3309.

$$R^{\bullet} + R^{\bullet} \xrightarrow{k_t} R{-}R \qquad \frac{d[R-R]}{dt} = k_t[R^{\bullet}][R^{\bullet}]$$

k_t can be approximated as diffusion controlled ~10^{10} M^{-1} s^{-1}. If the desired reaction is an addition to a double bond A=B:

$$R^{\bullet} + A{=}B \xrightarrow{k_a} R{-}A{-}B^{\bullet} \qquad \frac{d[R-A-B^{\bullet}]}{dt} = k_a[R^{\bullet}][A{=}B]$$

The limitation can then be expressed in the following way:

$$k_a[R^{\bullet}][A{=}B] > 10^{10}[R^{\bullet}]^2 \;;\; k_a[A{=}B] > 10^{10}[R^{\bullet}]$$

10^{-8} M is a reasonable estimate for the radical concentration $[R^{\bullet}]$ in a chain reaction. Therefore:

$$k_a[A{=}B] > 10^2$$

Similarly, there is a lower rate limit to reactions involved in a cyclization reaction. It is also noteworthy that radical reactions are sensitive to both reagent concentration and radical concentration. In fact, these are two factors that can be varied to control a radical chain reaction.

In executing radical reactions, care should be taken to strictly exclude oxygen in the reaction. Triplet oxygen reacts with all carbon-centred radicals at a rate approaching diffusion control. In contrast, moisture is not a problem since the O-H bond has high bond dissociation energy. This means that OH and NH groups do not need any protection in radical reactions.

Radical reactions are also very chemoselective and functional group tolerance is high. This is because of the mild reaction conditions. To boost selectivity, reactions can be carried out at temperatures as low as –78 ^{o}C. However, at these temperatures the chains can become too short for the reaction to be synthetically useful.

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[27] Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

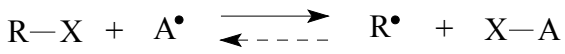
Since relative rates are so important in radical chemistry, one should take advantage of the vast body of absolute rate constants determined.[28] Prototype reactions can often serve as models for more complex reactions. Rate constants can be estimated using "radical clocks". A radical clock is a radical reaction where the absolute rate is known. To "clock" a reaction, it is run in competition with one of these reactions, and the product ratios determined. From these values the rate of the desired reaction can be calculated.

1.2.1 The chain reaction.

Since the radical concentration is always kept low, the chain reaction is ideal for obtaining high product yields in radical reactions. The chain is comprised of the initiation, propagation and termination steps. To initiate a chain, radicals have to be generated. This can be accomplished in many different ways, e.g. by photolysis or by the use of redox reagents. Often, chemical initiators are used.[29] The first formed radical interacts with the radical precursor and this starts the chain. The amount of initiator needed depends upon the efficiency of the process (chain length). The most commonly used chemical initiator is probably AIBN (2,2'-azobisisobutyronitrile) which has a half-life of 1h at 80 ^{o}C. It can also be cleaved photochemically.

The propagation steps involve reactions such as atom/group transfer, addition/elimination, and redox reactions.

Homolytic substitution is involved in many radical processes (Scheme 10).[30]



Scheme 10. Homolytic substitution.

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[28] [a)]Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. [b)]Fischer, H. (ed.), 'Radical Reaction Rates in Liquids', Springer-Verlag, West Berlin, 1983-85; Landolt-Börnstein, new series, vols. II/13a-e. [c)]Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 193, 317. [d)]Fischer, H.; Paul, H. *Acc. Chem. Res.* **1987**, *20*, 200.

[29] [a)]Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.*, **1991**, *56*, 678. [b)]Pattenden, G. *Chem. Soc. Rev.*, **1988**, *17*, 361. B. B. Snider, *Chem. Rev.*, **1996**, *96*, 339. [c)]Molander, G. A.; Harris C. R. *Chem. Rev.*, **1996**, *96*, 307. [d)]Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *J. Chem. Soc., Perkin Trans. 1*, **2000**, *8*, 1187.

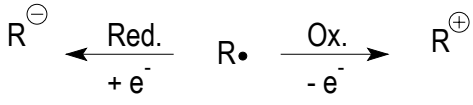
[30] [a)]Russel, G. A. in 'Free Radicals', Wiley, New York, 1973, vol. 1, 273. Dannen, W. C. in 'Methods in Free Radical Chemistry', ed. Huyser, E. L. S., Dekker, New York, 1974, vol. 5, 1. [b)]Poutsma, M. in 'Free Radicals', Wiley, New York, 1973, vol. 2, 113.

These reactions are often irreversible and polar effects can sometimes be important (e.g. chloride radicals avoid attacking hydrogens on polar carbons).[31]

Addition reactions are by far the most useful propagation reactions. Here the radical attacks a multiple bond to form a new σ-bond. Since a σ-bond is produced at the expense of a π-bond, the reaction will be exothermic. If a heteroatom centered radical adds to a double bond, the addition is often irreversible if the heteroatom is from the first row in the periodic table.

Radicals add to olefins with different rates depending on the nature of the olefin and the character of the radical. It has proven useful to distinguish between electrophilic, nucleophilic or ambiphilic radicals.[32] By considering Frontier Molecular Orbital (FMO) interactions, radicals are classified as nucleophilic if they have a high energy Singly Occupied Molecular Orbital (SOMO). This makes the interaction with the multiple bond Lowest Unoccupied Molecular Orbital (LUMO) the most important one. The reaction with unsaturated molecules with low energy LUMOs, i.e. electron deficient olefins and acetylenes, will be accelerated. A decelerating factor in radical reactions is large substituent groups at the carbon to be attacked by the radical. Radicals are sensitive to steric hindrance and often add more rapidly to the less substituted end of an olefin. The borderline between the electrophilic and ambiphilic radicals is obscure. Whereas radicals bearing two or more electron-withdrawing groups are safely electrophilic,[33] radicals carrying only one can be either electrophilic or ambiphilic. Additions of electrophilic radicals are accelerated by lowering of the SOMO and/or by raising of the olefin HOMO. For ambiphilic radicals addition is accelerated with both electron poor and electron rich olefins.[34] This happens because SOMO energies are intermediate to those of electrophilic and nucleophilic radicals.

Redox reactions[35] involve addition or removal of electrons to/from radicals by chemical or electrochemical methods. Whether reduction or oxidation occurs (Scheme 11), depends on the SOMO energy level. Redox reactions are rarely involved in propagation reactions.

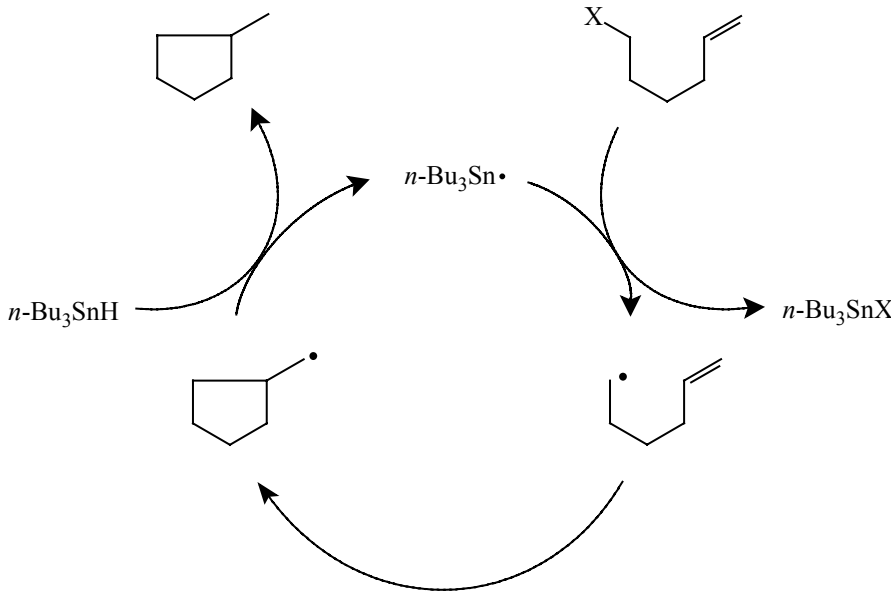


Scheme 11. Redox reactions.

[31] Tedder, J. M. *Angew. Chem.*, *Int. Ed. Engl.*, **1982**, *21*, 401.
[32] Giese, B. *Angew. Chem., Int. Ed. Engl.,* **1983**, 22, 753.
[33] Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, *36*, 701.
[34] [a)]Barnek I. and Fischer H. in 'Free Radicals in Synthesis and Biology', ed. F. Minisci, Kluwer, Dordrecht, 1989, 303. [b)]Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063.
[35] Eberson, L. E. 'Electron Transfer Reactions in Organic Chemistry', Springer-Verlag, Berlin, 1987.

There are some important non-chain methods for carrying out radical reactions. These will not be discussed here. The interested reader is directed to some nice comprehensive literature on the subject.[36]

1.2.2 The tin hydride method.[37]



Scheme 12. The tin hydride method for radical cyclization.

The tin hydride method relies on the ability of the tin radical to act as a mediator and the tin hydride to act as a hydrogen atom donor for the removal of the final product radical (Scheme 12). It has turned out to be the most powerful of all the radical chain methods and can be applied to both inter- and intramolecular radical reactions. Since our interest lies in intramolecular reactions, no attempt will be made to provide a comprehensive treatment of intermolecular reactions.

The rate constant for hydrogen abstraction from the tin hydride is ~$2x10^6$ M^{-1} s^{-1}, and the rate of cyclization for the 5-hexenyl radical is around $2x10^5$ M^{-1} s^{-1}. Thus, for successful radical cyclization to occur, the tin hydride concentration must be kept low. The lower the tin

[36] [a]Fossey, J.; Lefort, D.and Sorba, J. in 'Free Radicals in Organic Chemistry', Wiley, New York, 1995. [b]Curran, D. P. in 'Comprehensive Organic Synthesis', ed. Trost, B. M.; Fleming, I. Pergamon Press, Oxford, 1991, vol. 4, 715, 779, and references herein.

[37] [a]Neumann, W. P. *Synthesis* **1987**, 665. [b]Giese, B. *Angew. Chem.*, *Int. Ed. Engl.*, **1985**, *24*, 553. [c]Barluenga, J.; Yus, M. *Chem. Rev.* **1988**, 88, 487. [d]Pereyre, M.; Quintard, J-P. and Rahm, A. 'Tin in Organic Synthesis', Butterworths, London, 1987. [e]Davies, A. G. in 'Comprehensive Organometallic Chemistry', ed. Wilkins, G.; Stone F. G. A. and Abel, E. W. Pergamon Press, Oxford, 1982, vol. 2, 519.

hydride concentration, the longer is the time allowed for useful reactions to occur. The limitation is again competing reactions (*vide supra*). The radical precursors commonly used in combination with tin hydride are, in order of reactivity: iodides, phenyltellurides, bromides, phenylselenides, xanthate esters, nitro groups, chlorides and phenylsulphides. Iodine is abstracted at almost diffusion-controlled rate. To keep the tin hydride concentration low, syringe pump addition is often used.

In another approach, catalytic amounts of tin hydride or halide are employed together with a reducing agent such as $NaBH_4$ or $NaBH_3CN$.[38] Polymer supported tin reagents have been used in a few cases.[39] Sometimes it can be helpful to employ tins little sister, germanium, to control reactions. Germanes are poorer hydrogen donors than stannanes ($k_H \sim 10^5$ M^{-1} s^{-1}).[40] Therefore hydride donation is less competitive. However, germanium can cause other problems due to slow β-elimination after attack on unsaturated bonds. The silicon-hydrogen bond in trialkyl silanes is too strong for hydrogen donor applications. Also olefin addition will be a severe problem as β-elimination is even slower than for germanes. A new silicon reagent, tris(trimethylsilyl)silicon hydride, has come into use, though, much because of the toxicity of trialkyltin hydride.[41]

1.2.3 The 5-hexenyl radical.

The 5-hexenyl radical is a classic reactive intermediate. A lot of data relating to this particular radical have accumulated. It cyclizes with intermediate rate ($2x10^5$ s^{-1} for *5-exo-trig* and $4x10^4$ s^{-1} for *6-endo-trig* cyclization) (Scheme 13):[42]

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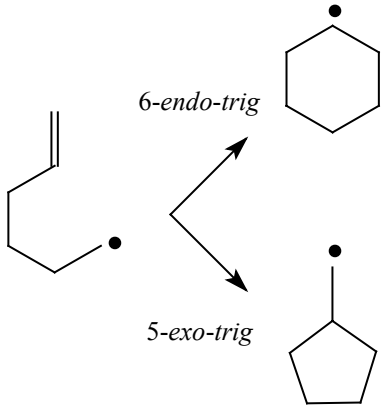
[38] [a)]Kuivila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165. [b)]Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. [c)]Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726. [d)]Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. [e)]Bergbreiter, D. E.; Blanton, J. R. *J. Org. Chem.* **1987**, *52*, 472.

[39] [a)]Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1351. [b)]Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. [c)]Weinshenker, N. M.; Crosby, G. A.; Wong, J. Y. *J. Org. Chem.* **1975**, *40*, 1966. [d)]Schumann, H.; Pachaly, B. *Angew. Chem.*, *Int. Ed. Engl.*, **1981**, *20*, 1043.

[40] [a)]Lusztyk, J.; Maillard, B.; Lindsay, D. A.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 3578. [b)]Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509.

[41] [a)]Baguley, P. A.; Walton, J. C. *Angew. Chem.*, *Int. Ed. Engl.*, **1998**, *37*, 3072. [b)]Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

[42] Beckwith, A. L. J.; Shiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.



Scheme 13. Two possibilities for cyclization of the 5-hexenyl radical.

The preferential formation of the less thermodynamically stable cyclopentyl methyl radical can be explained by the Beckwith – Houk model (*vide infra*). As stated above 5-hexenyl radicals cyclize with intermediate rate. However, cyclization can be accelerated in different ways (Figure 5):

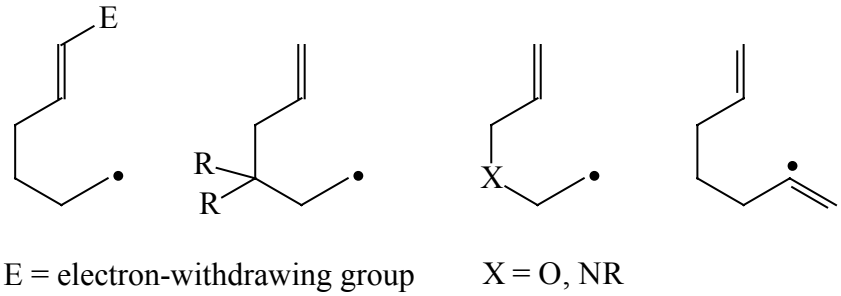


Figure 5. Four different ways to accelerate 5-hexenyl radical cyclization.

Electron-withdrawing groups on the olefin accelerate cyclization. Substituents on the chain raise the ground state energy relative to the transition state. Oxygen and nitrogen ring substituents in the 3-position also accelerate ring-closure. The C-N-C and C-O-C bond lengths and angles cause better overlap between the SOMO and the π-bond LUMO (k = 9.0×10^6 s^{-1} and 1.7×10^7 s^{-1} for X = O and N, respectively).[43]

[43] Della, E. W.; Knill, A. W. *Aust. J. Chem. Soc.* **1995**, *48*, 2047.

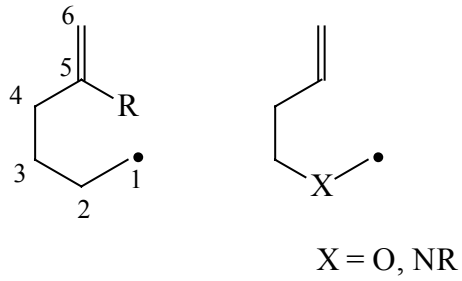


Figure 6. Two decelerating cases.

Substituents in the 5-position of 5-cyclohexenyl radicals slow down cyclization via the *5-exo* mode (Figure 6). This is because of the greater steric bulk that the attacking radical experiences. It is interesting that substitution at the attacking site (C-1) does not cause any deceleration. This means that primary, secondary and tertiary radicals cyclize with approximately the same rate.

If a radical stabilising group (O or NR) is located α to the radical, cyclization is also slowed down (Figure 6).[44]

1.2.4 The Beckwith-Houk model.

Although thermodynamics favour *6-endo* cyclization (more stable ring and radical), the 5-hexenyl radical cyclizes preferentially *5-exo*. This can be understood if one considers the transition state (TS) structure. The Beckwith-Houk TS model has developed from studies of the preferred TS for bimolecular radical addition and is based on conformational analysis.[45] Radicals attack olefins with an angle close to 109°. In this process the 5-hexenyl radical can adopt either of two conformations (Figure 7):

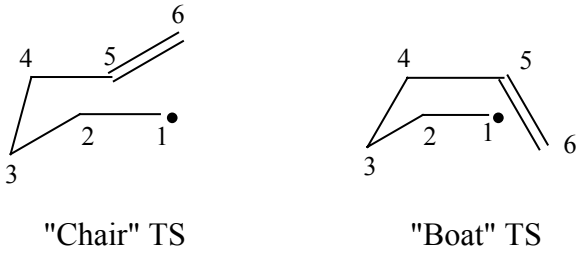


Figure 7. The two transition states in radical cyclization.

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[44] Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157.

[45] [a)]Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *Aust. J. Chem. Soc.* **1983**, *36*, 545. [b)]Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. [c)]Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. [d)]Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. [e)]Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

The preferred ring-size in this cyclization is dictated by the different angles of attack by the radical on carbons 5 and 6 (Figure 7). If the radical adopts the Beckwith-Houk TS, the angle of attack at C5 is 106^{o} and at C6 94^{o}. This means that the SOMO-LUMO overlap will be better at C5. The TS is early and therefore resembles the free radical. This makes the forming bond between C1 and C5 longer than usual (calculated to be 2.2-2.3 Å). This distance is close to the cyclohexane C1-C3 distance. As a result of this elongation, the TS does not experience the bond angel strain of the final five membered ring. It is important to realise, however, that the energy difference between these two TSs is only 1 kcal/mol. In contrast, the cyclohexane chair and boat conformers differ by 7 kcal/mol in energy. C1 and C5 are close to sp_2 hybridised. This means that only C2-C4 are cyclohexane-like. The difference in the chair and boat TS energies is a steric effect and it depends on the arrangement of the allylic group (compare with “skew” and “gauche” 1-butene) (Figure 8).

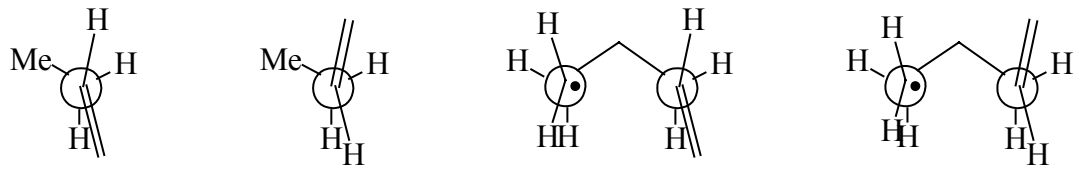

Figure 8. Newman projections for the chair and boat TS.

The strength of the Beckwith-Houk model is its predictive power with respect to diastereoselectivity in the ring-closure of hexenyl radicals bearing one or more substituents. Four TSs appear likely (Figure 9):

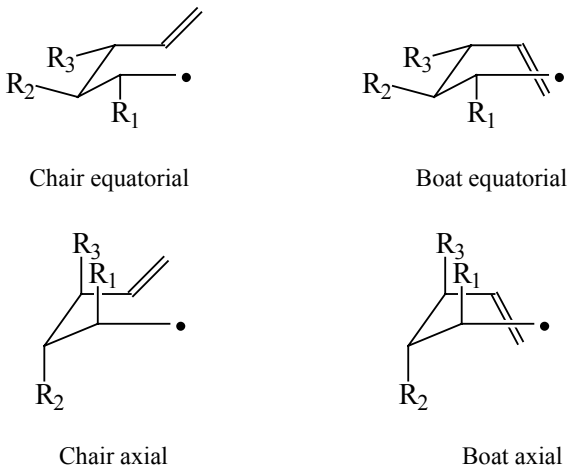

Figure 9. The four TSs for cyclization of substituted 5-hexenyl radicals.

The boat-axial TS is generally higher in energy than the other three. Beckwith and Houk have both developed advanced computational methods to predict diastereoselectivity in these types of cyclisation. The following paragraphs will briefly summarise the emerging pattern of diastereoselectivity for cyclization of 5-hexenyl radicals carrying one additional substituent:

1.2.4.1 1-substituted hexenyl radicals.

Selectivities vary over a wide range, but cyclization occurs in many cases to give predominantly the *cis*-diastereomer. This is in accordance with the Beckwith-Houk model assuming a chair-equatorial TS:

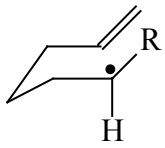

Figure 10. Cyclization of 1-substituted 5-hexenyl radicals.

Because of the elongated forming bond, the eclipsing interaction of the olefin and the substituent R is usually small (Figure 10), although selectivity is reversed (to *trans*) if the substituents are too bulky. Preferential formation of the *trans*-product is also observed if the radical centre is directly bonded to a heteroatom.[46,47,48,49,50]

1.2.4.2 2-substituted hexenyl radicals.

The Beckwith-Houk model predicts selective formation of *trans*-1,3-disubstituted cyclopentanes. Spelmeyer and Houk calculated the chair-equatorial TS to be lowest in energy.[51] Again the selectivity is somewhat dependent on the substituent.[52]

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[46] [a)]Arya, P.; Wayner, D. M. *Tetrahedron Lett.* **1991**, *32*, 6265. [b)]Aurrecoechea, J. M.; Fernandez-Acebes, A. *Tetrahedron Lett.* **1993**, *34*, 549. [c)]Tsai, Y. -M.; Chang, F.-C.; Huang, J.; Shiu, C. -L. *Tetrahedron Lett.* **1989**, *30*, 2121.

[47] [a)]Curran, D. P.; Kim, D.; Liu, T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. [b)]Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. [c)]Feldman, A. L.; Romanelli, R. E.; Ruckle, Jr., R. E.; Jean, G. *J. Org. Chem.* **1992**, *57*, 100.

[48] [a)]Cossy, J.; Madaci, A.; Pete, J. -P. *Tetrahedron Lett.* **1994**, *35*, 1541. [b)]Swartz, J. E.; Mahachi, T. J.; Kariv-Miller, E. *J. Am. Chem. Soc.* **1988**, *110*, 3622. [c)]Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.

[49] Swartz, J. E.; Kariv-Miller, E.; Harrold, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 1211.

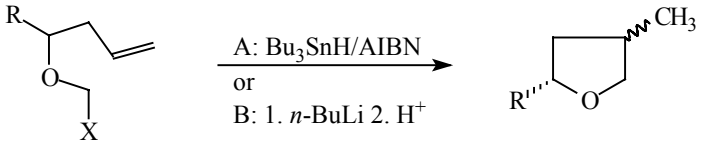
[50] [a)]Ueno, Y.; Khare, R. K.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2637. [b)]Renaud, P. *Tetrahedron Lett.* **1990**, *31*, 4601.

[51] See ref. 45e.

[52] [a)]Stork, R.; Mook, Jr., R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. [b)] Srikrishna, A.; Krishnan, K. *J. Org. Chem.* **1989**, *54*, 3981.

1.2.4.3 3-substituted hexenyl radicals.

Simple 3-substituted 5-hexenyl radicals are predicted to give predominantly 1,3-*cis*-disubstituted cyclopentanes. With a *tert*-butyl group in the side chain, the *cis*-selectivity is as high as 85:15. An example of the 2-oxa-analogue cyclization is shown in Figure 11:[53]



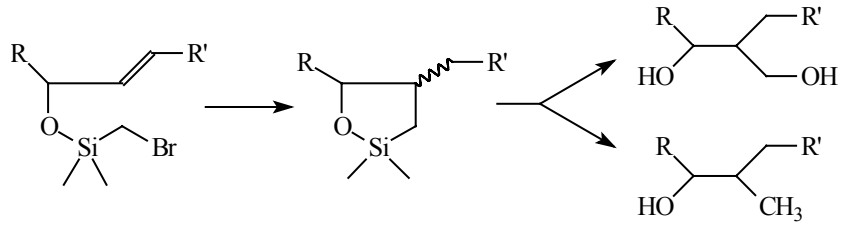
			Cis		*Trans*
A	R = Ph , X = SePh	-80°C	91	:	9
B	R = C_6H_{13}, X = Bu_3Sn	-80°C	91	:	9

Figure 11. Similarity in diastereoselectivity between radical and ionic ring-closure.

The radical pathway (A) and the ionic pathway (B) give almost identical product mixtures. Thus, the lithium aggregate does not seem to affect diastereolselectivity. The Beckwith-Houk model can actually provide a rationale for the ionic as well as the radical cyclization.

1.2.4.4 4-substituted hexenyl radicals.

These systems give the highest level of selectivity of the various monosubstituted 5-hexenyl radicals. Here the model predicts that allylic strain directs cyclization to occur in a *trans*-selective manner.[54] A nice example is the cyclization of silylmethyl radicals. The product can be further transformed into alcohols or diols (Scheme 14):[55]



Scheme 14. *5-Exo* radical cyclization for the stereocontrolled preparation of diols and alcohols.

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[53] [a)]Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1991**, *56*, 5245. [b)]Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 7718. [c)]Broka, C. A.; Shen, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.

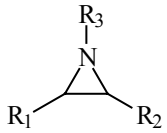
[54] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

[55] [a)]Nishayama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. [b)]Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. [c)]Kurek-Tyrlik, A.; Wicha, J.; Zarecki, A. *J. Org. Chem.* **1990**, *55*, 3484.

2. Aziridines - the Hassner reaction revisited.

2.1 Introduction.

Epoxides play a central role in organic synthesis. Their importance has grown even larger with the availability of several asymmetric synthetic methods for their preparation.[56] Their synthetic usefulness stems from their ability to be ring-opened under various conditions to give an alcohol with formation of a new carbon-carbon or carbon-heteroatom bond. Also, they can easily be constructed from olefins via the Prileschajew reaction using mCPBA. It is not hard to envision a similar role[57] for the nitrogen analogues - the aziridines. As shown in the latter parts of this thesis, aziridines can be used as precursors of pyrrolidines. It would therefore seem appropriate to discuss their synthesis in some detail.



R_3 = COR, COOR, SO_2R; "Activated aziridine"
= H, Alkyl, Aryl; "Unactivated aziridine"

Figure 12. The two classes of aziridines.

Unless activated by electron-withdrawing groups at nitrogen (Figure 12), aziridines are much less reactive than epoxides. They do not undergo ring-opening with nucleophiles unless the reaction is carried out in acidic media. Due to increased s character of the nitrogen lone pair, and/or the prevailing Jahn-Teller effect, protonated aziridines show a lower pK_a ($\approx$ 8) than protonated ammonia, mono-, di- or trisubstituted amines. The protonated aziridine is very unstable, and reacts even with poor nucleophiles. The mechanism for this type of ring-opening is not clear. In cases where a tertiary carbocation can be involved, the aziridine is ring-opened in a Markovnikov fashion (S_N1-like). This produces a sterically less crowded amine. Terminal aziridines, though, ring-open from the least crowded side (anti-Markovnikov, S_N2-like).

Activated aziridines, much like the epoxides, normally react via an S_N2 mechanism. These aziridines gain their activation by experiencing a stabilisation of the forming N-centred anion

[56] [a)]Elliott, M. C. *J. Chem. Soc, Perkin Trans. 1*, **2000**, 1291. [b)]Jorgensen, K. A. *Chem. Rev.* **1989**, *89*, 431.
[57] M^{c}Coull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347.

on ring-opening. The nitrogen can then be alkylated and finally deprotected to give a secondary amine.

Aziridine synthesis has been accomplished using widely different protocols.[58] Maybe the most attractive method (at least in the authors mind) is the controlled addition of nitrenes or nitrene analogues to olefins. The best reaction in this category so far is the Mansuy-Evans aziridination protocol which involves the use of a metal catalyst (iron, manganese or copper) and PhINTs - a hypervalent iodine nitrene precursor (Figure 13, Scheme 15).[59]

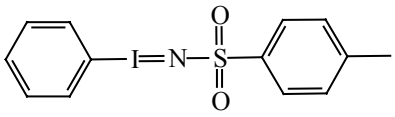
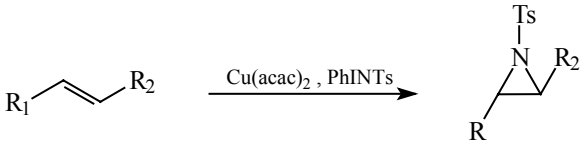


Figure 13. PhINTs.



Scheme 15. The Mansuy-Evans reaction.

The groups of Evans and Jacobsen have also shown that the copper catalysed aziridination reactions can be performed enantioselectively.[60] In spite of these exciting results, the reaction is still in its infancy, and has proven to be quite substrate dependent. The aziridines that result from the reaction are activated, and therefore unstable. This makes removal of the protecting group difficult. However, Andersson *et al* have shown that the tosyl protecting group can be removed with magnesium in an ultrasound-assisted reaction.[61]

Another indirect route to aziridines from olefins has proven very powerful in synthesis: the Blum reaction (Scheme 16).[62] This reaction takes advantage of the easy access to epoxides and their tendency to undergo ring-opening.

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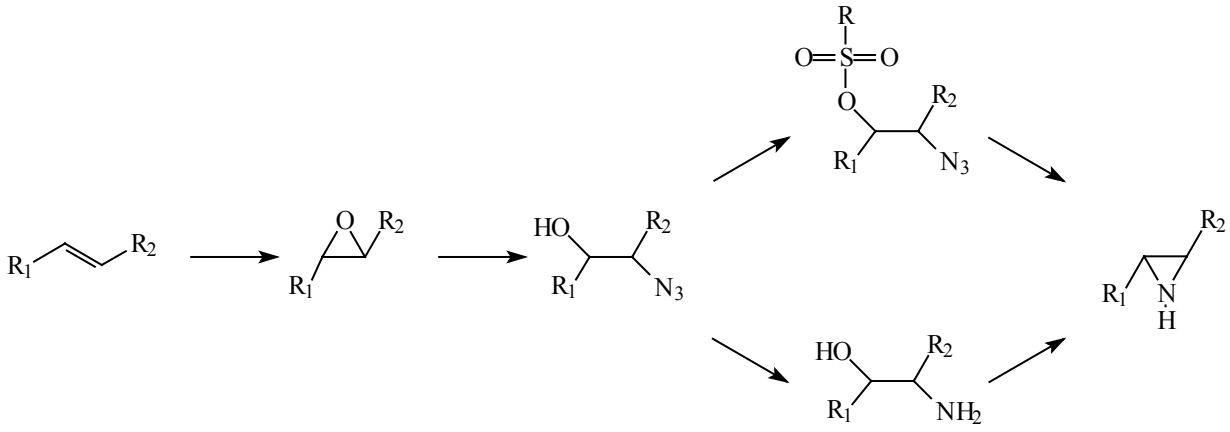
[58] [a)]Tanner, D. *Angew. Chem. Int. Ed.* **2002**, 33, 599. [b)]Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry*, **1997**, 11, 1693.

[59] [a)]Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, *17*, 1161. [b)]Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2* **1988**, *8*, 1517. [c)]Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. [d)]Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742.

[60] [a)]Evans, D.A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. [b)]Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

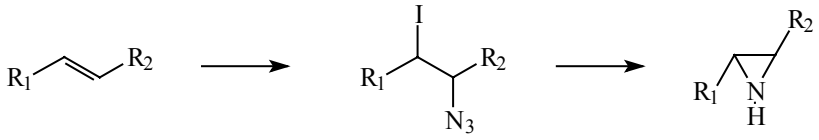
[61] Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455.

[62] [a)]Ittah, Y.; Shahak, I.; Blum, J. *J. Org. Chem.* **1978**, 43, 397. [b)]Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.



Scheme 16. The Blum reaction.

Since there are also well known methods for asymmetric epoxidations, this procedure can be used to construct enantiomerically pure aziridines. The ring-opening of the epoxide is frequently carried out with NaN_3 in water/methoxyethanol and gives high yields. The subsequent reduction/ring-closure or sulfonylation/reductive ring-closure are both well worked out. A similar but rarely used method for aziridine synthesis is the Hassner reaction (Scheme 17).[63]



Scheme 17. The Hassner aziridination.

The philosophy of Hassners aziridine synthesis is very similar to that of Blums reaction: To produce an aziridine in few steps from olefins. The required β-iodoazides are synthesised from olefins in almost quantitative yields by the addition of *in situ* formed iodoazide. The reduction/ring-closure is then carried out with LAH, borane or triphenylphosphine (TPP; the Staudinger reaction). However, all these reductions have drawbacks. LAH and borane are both strong reducing agents and thus attack other functional groups. In our hands, LAH was also found to reduce a substantial amount of the iodide to produce the corresponding primary amine. In comparison, TPP is mild. The triphenylphosphine oxide that forms when TPP is

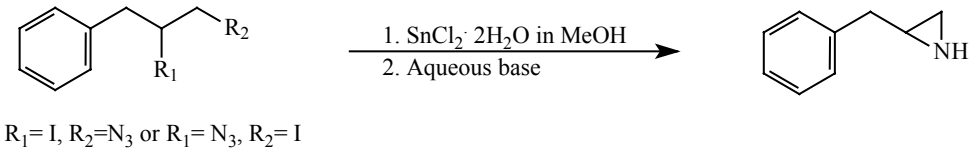
[63] [a)]Hassner, A.; Galle, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3733. [b)]Hassner, A.; Matthews, G. J.; Fowler, F. W. *J. Am. Chem. Soc.* **1969**, *91*, 5046. [c)]Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077.

used is often difficult to get rid of but in this case is not a major problem since the products are easily purified by steam distillation. The problem is that the reduction with TPP is notoriously low-yielding.

It is known that tin(II)chloride is a mild and selective reducing agent.[64] The material is compatible with a number of different functional groups and it has also been used for formation of nitrogen heterocycles. We thought the scope of the Hassner method for aziridine synthesis would be significantly widened if $SnCl_2$ could be used in the reduction step.

2.2 Results and discussion.

To begin with, we adopted the standard protocol for these types of reductions.[64] This involves adding the iodoazide to a methanolic solution of stannous chloride at room temperature. For the initial studies we employed a mixture of the iodoazidination products of allylbenzene-1-azido-2-iodo-3-phenylpropane and 2-azido-1-iodo-3-phenylpropane (Scheme 18). The reaction starts to liberate nitrogen soon after addition of the azide and the temperature is increased. After 15-30 minutes the gas-evolution ceases, indicating that reduction is finished. We thought that ring-closure would be so fast that it could be achieved in the work-up with aqueous NaOH. This also removes the tin salts formed during the reduction.



R_1= I, R_2=N_3 or R_1= N_3, R_2= I

Scheme 18. The first aziridination protocol.

Although several by-products were seen in the crude mixture, the first attempt looked promising. Next we tried different inorganic bases (K_2CO_3, $NaHCO_3$, KF) but no real improvement was seen. Distillation of crude aziridine was tried (with and without steam), but to our dismay we could isolate only very low yields of product. A lot of the material seemed to polymerise. If the aziridine was left at room temperature the product also polymerised. We hypothesised some sort of tin-containing by-product could act as a catalyst for the polymerisation. At lower temperature (0 ^oC) the reaction did not start at all. Also, attempts to run the reaction in other solvents (THF, toluene, MeCN, acetone, EtOH, *i*-PrOH, *t*-BuOH)

[64] a) Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett*. **1986**, *27*, 1423. b) Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587.

proved unfruitful. Since nitrogen containing organic molecules are highly polar, they are not well suited for silica gel chromatography unless the slightly acidic silanol groups are deactivated by silylation or by deprotonation by a component of the eluent (often Et_3N). However, it seemed that the column absorbed aziridine irreversibly even though the silica was deactivated. This was confirmed in a control experiment (silica deactivation with Et_3N). Basic alumina was also investigated, but, like silica, did not give full recovery of material loaded on the column.

Chromatography using cellulose as a stationary phase was also tried as was ion exchange chromatography, both without any success.

Disappointed, we also tried to modify the standard synthetic protocol. A reverse addition procedure was tried where an amine was added to the tin chloride before the iodoazide. This would neutralize any HCl formed in the reaction of $SnCl_2$ with the azide. Both ethylene diamine and DBU were tried. The former could form bidentate complexes with tin, thus preventing it from interacting with aziridine formed, and the latter is basic enough to cause immediate ring-closure of intermediate β-iodoamine. Surprisingly, the reaction seemed to be accelerated by the addition of amines. The white salts initially formed dissolved as reduction proceeded and gas-evolution progressed. Although by-products were still formed, both procedures gave cleaner product than seen before. Attempts to trap the aziridine with various reagents (TMS-Cl, Bz-Cl and Ts-Cl) gave 40-60 % yields of the respective *N*-protected aziridines after distillation/flash chromatography.

In the literature there are examples where both azides and halides were present when using stannous chloride reduction.[65] This is pointing against involvement of electron transfer in the mechanism for reduction.

The electronic configuration of $SnCl_2$ is a closed shell sp^2 singlet (Figure 14).

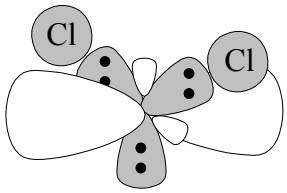
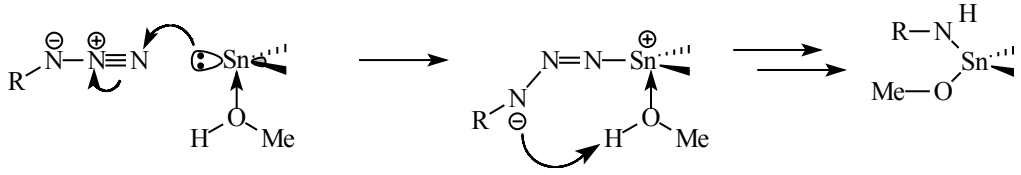


Figure 14. The electronic structure of stannous chloride (orbitals not drawn to any scale).

[65] Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6143.

The gap between the HOMO and LUMO is probably large, thus making the stannous chloride nucleophilic. The reduction mechanism (Scheme 19) is more likely to resemble that of the Staudinger reaction where the azide is attacked by the nucleophilic phosphorous.[66]



Scheme 19. Plausible mechanism for the stannous chloride reduction.

This mechanism could explain why methanol is crucial for the reaction and also why the amine bases accelerate the reduction. A potential problem in the reactions under basic conditions could be that the aziridine is quickly formed and that it suffers further reduction under the conditions used. To test this hypothesis, we synthesised the other haloazides. Both BrN_3 and ClN_3 add more slowly to olefins than IN_3. We found that the β-iodoazides shown in Scheme 18 were converted to the corresponding chlorides by heating (50 ^oC) in DMF with LiCl. The corresponding β-bromoazides were obtained by treatment with tetrabutylammonium bromide in MeCN at 50 ^oC in high yields. After stannous chloride/DBU treatment of β-bromoazides, aziridines of similar quality to those obtained from iodoazides were isolated. However, β-chloroazides were converted to the corresponding β-chloroamines. This gave an opportunity to purify by precipitation of an ammonium salt. The ammonium oxalate was easily formed. After thorough washing with ether, treatment with NaOH (aq.) regenerated the β-chloroamine. Ring-closure was then effected at elevated temperature in aqueous NaOH or in MeCN with DBU at reflux.

At this time a strange observation was made. Up to this point stannous chloride of 95% purity had been used. When an amine-free reduction was attempted using 98% stannous chloride, no reaction took place. Under basic conditions the reaction occurred but slower than before. The aziridine produced was almost void of by-products, though. However, when styrene was added as an internal standard the yield calculated by integration in the NMR spectrum was only 50%. At this point we decided to abandon the route based on direct ring-closure of β-iodoazides. If halide exchange and reduction could be effected in decent yields, the procedure could still be of some interest for aziridine synthesis.

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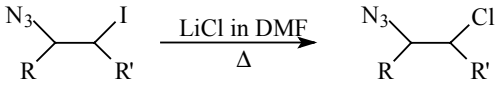
[66] Alajarin, M.; Conesa, C.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, *9*, 1811.



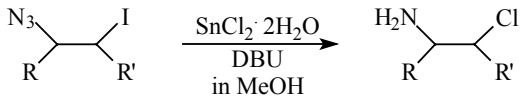
R	R'	Yield (%)[a]	R	R'	Yield (%)[a]
ferrocenyl	H	71	hexyl H	H hexyl	83
$(CH_2)_{10}OAc$ H	H $(CH_2)_{10}OAc$	92	—(CH_2)$_6$—		60
phenoxymethyl H	H phenoxymethyl	97	benzyl H	H benzyl	96
			phenyl	phenyl	——

[a] Isolated yield.

Table 1. β-Chloroazides prepared by halide exchange from the corresponding β-iodoazides.

Table 1 is a summary of the β-iodoazides that were tried in the substitution reaction. It should be pointed out that whenever there is a possibility for regioisomerism in the starting β-iodoazide, a mixture is often obtained. Thus, the β-chloroazides formed in the above manner are usually mixtures of regioisomers. Fair to good yields of β-chlorides were isolated. The main side reaction was elimination. However, the β-iodoazide from stilbene decomposed even at room temperature. The β-chloroazides attained were reduced with stannous chloride/DBU and purified as oxalates (Table 2). Again, fair to good yields were obtained.

The ring-closing step has not yet been worked out in any detail. Refluxing of the β-chloroamines in NaOH (aq.) induced cyclization. We also attempted to ring-close the amines in acetonitrile with DBU as a base.



R	R'	Yield (%)[a]	R	R'	Yield (%)[a]
ferrocenyl	H	86[b]	hexyl H	H hexyl	70
$(CH_2)_{10}OAc$ H	H $(CH_2)_{10}OAc$	92	—(CH_2)$_6$—		68
phenoxymethyl H	H phenoxymethyl	86	benzyl H	H benzyl	58

[a] Isolated yield.
[b] Crude yield, oxalate did not precipitate.

Table 2. β-Chloroamines prepared by $SnCl_2 \cdot 2H_2O$/DBU-reduction of the corresponding β-chloroazides.

2.3 Summary and outlook.

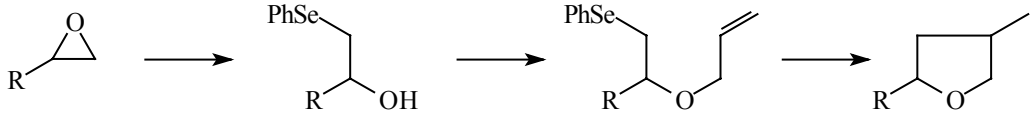
In summary, two protocols based on the Hassner reaction were tried for aziridine synthesis. In the quick procedure, β-iodoazides were reduced with $SnCl_2 \cdot 2H_2O$/DBU under conditions which effected ring-closure of the intermediate β-iodoamine. The main limitation to this protocol is still the difficulties associated with the purification of the aziridines from trace amounts of tin-containing waste. The halogen exchange was not as helpful as first anticipated. It adds two more steps and lowers the efficiency of the procedure. We imagine aziridines could be purified in pretty much the same manner as β-chloroamines after proper ring-opening, i.e., by precipitation of the corresponding ammonium compound. The candidate for ring-opening that has come to our mind is pyridinium hydrobromide. This salt has a sufficiently low pK_a to force open the ring, but is still weak enough acid not to be harmful to many functional groups. The ammonium bromide formed would then (hopefully) undergo ring-closure upon base treatment.

The final version of this quick and mild protocol for easy access to aziridines is still not written. What seemed to be an elementary reaction in the beginning proved to be a wolf in sheeps clothing and is further testimony that aziridines are primadonnas in chemistry. The outlook for this alternative aziridine protocol seems bleak, and if ever asked, I would not hesitate to recommend the Blum reaction for making an aziridine.

3. *N*-Tosylpyrrolidines from *N*-tosylated aziridines. The initial protocol.

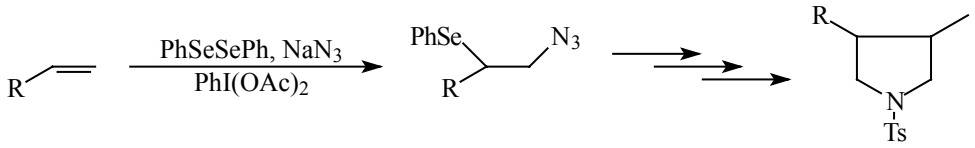
3.1 Introduction.

In previous work,[67] our group devised a synthetic scheme for making 2,4-disubstituted tetrahydrofurans from terminal epoxides via radical ring-closure (Scheme 20).



Scheme 20. The synthesis of 2,4-disubstituted tetrahydrofurans.

It appeared attractive to try to extend this protocol to pyrrolidine synthesis starting from aziridines. A similar approach to 3,4-disubstituted pyrrolidines was envisioned, taking advantage of the finding by Tingoli and coworkers that terminal alkenes undergo azidoselenenation as shown in Scheme 21.[68]



Scheme 21. The strategy for making 3,4-disubstituted pyrrolidines.

3.2 Results and discussion.

3.2.1 Conversion of tosyl aziridines to pyrrolidines.

The Mansuy-Evans synthesis provides a short route to activated aziridines from olefins (*vide supra*). Although this reaction is very substrate dependent and gives low yields in many cases (for example, allyl phenyl ether gave only a 10% yield of aziridine with tetra(acetonitrile)copper(I)perchlorate as a catalyst), we managed to produce a series of aziridines as shown in Figure 15.

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[67] Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157.
[68] Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809.

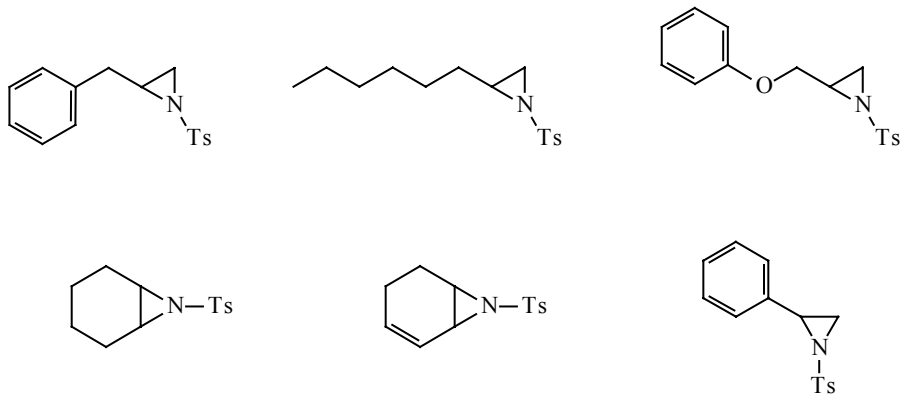
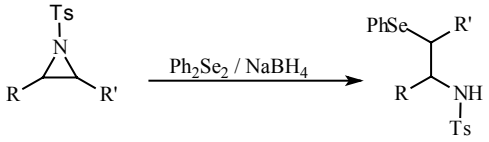


Figure 15. *N*-Tosyl aziridines studied in this work.

N-tosyl aziridines are activated aziridines in the sense that nucleophilic attack on the ring produces a stabilised amide anion. This means that introduction of selenium into the molecule can easily be effected by reacting the aziridine with the nucleophilic boron complex that is formed when diphenyl diselenide is reduced with sodium borohydride (Table 3).



Entry	Substituents	Yield (%)[a]	Entry	Substituents	Yield (%)[a]
1	R = phenyl R' = H	67 [b]	4	R = benzyl R' = H	81
2	R = hexyl R' = H	84	5	R and R' = - $(CH_2)_4$ -	77
3	R = phenoxymethyl R' =H	81	6	R' and R = -HC=CH-$(CH_2)_2$-	83

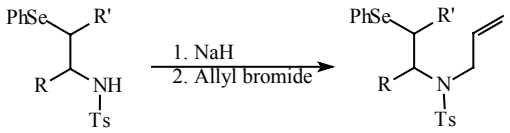
[a] Isolated yield.
[b] From styrene, Ph_2Se_2 and Chloramine-T

Table 3. Ring-opening of *N*-tosyl aziridines.

Fortunately, ring-opening is highly regioselective in most cases, favouring attack at the least substituted carbon. In fact, none of the other regioisomer could usually be found after workup and purification. However, the *N*-tosyl aziridine derived from styrene was an exception. It

showed poor selectivity in the ring-opening reaction. The problem with this aziridine is that the phenyl group stabilises positive charge on the non-terminal aziridine carbon. *N*-Tosyl-2-amino-2-phenylethyl phenyl selenide was therefore made from styrene and the reaction product of diphenyl diselenide and chloramine-T. Barton[69] has suggested that the reactive intermediate formed is the diselendiimide. This species could then fragment into nitrogen radicals or react via ions to form an episelenonium intermediate.

Allylation of *N*-tosyl-2-amino-2-alkyl phenyl selenides was a straightforward reaction (Table 4). Tosylamide anions are good nucleophiles and they are much less basic than amide ions. Thus, β-tosylaminoselenides were allylated simply by first treating them with sodium hydride and then with allyl bromide. These reactions gave good yields in all cases studied (Table 4).



Entry	Substituents	Yield (%)[a]	Entry	Substituents	Yield (%)[a]
1	R = phenyl R' = H	89	4	R = benzyl R' = H	87
2	R = hexyl R' = H	83	5	R and R' = - $(CH_2)_4$ -	84
3	R = phenoxymethyl R' =H	92	6	R' and R = -HC=CH-$(CH_2)_2$-	85

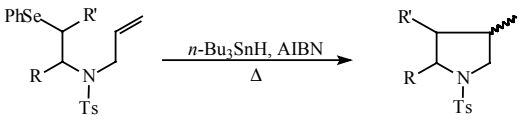
[a] Isolated yield.

Table 4. Preparation of *N*-allyl-*N*-tosyl-2-aminoalkyl phenyl selenides.

Radical cyclization was carried out using the metal hydride mediated radical chain method (*vide supra*). By refluxing in benzene with tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN), good yields of 2,4-substituted pyrrolidines were obtained (Table 5). The cyclization of the 5-hexenyl radical is very fast. Furthermore, the nitrogen in the 3-position accelerates it even more (85 times). These factors make the reaction highly selective for 5-*exo*-cyclisation. Essentially, no 6-*endo* cyclized products or reduced radical precursors could be found. In

[69] Barton, D. H. R.; Britten-Kelly, M. R.; Ferreira, D. *J. Chem. Soc.*, *Perkin Trans. 1*, **1978**, 1682.

some cases the chain process was difficult to initiate and only starting material was recovered after several hours at reflux. This problem was often eliminated if nitrogen or argon was bubbled through the reaction mixture for a few minutes before heating. It was also observed that the quality of tri-*n*-butyl tin hydride was critical to the outcome of the reaction (*vide supra*).



Entry	Substituents	*cis/trans*-ratio[b]	Yield (%)[a]	Entry	Substituents	*cis/trans*-ratio[b]	Yield (%)[a]
1	R = phenyl R' = H	3 / 1	67	4	R = benzyl R' = H	3 / 1	81
2	R = hexyl R' = H	3 / 1	84	5	R and R' = - $(CH_2)_4$ -	1 / 3 *endo*/*exo*	77
3	R = phenoxymethyl R' =H	2 / 1	81	6	R' and R = -HC=CH-$(CH_2)_2$-	1 / 2 *endo*/*exo*	83

[a] Isolated yield.
[b] According to NMR.

Table 5. Pyrrolidines made by cyclization of *N*-allyl-*N*-tosyl-2-amino-2-alkyl phenyl selenides.

The *N*-Tosyl-2,4-disubstituted pyrrolidines were obtained as mixtures of *cis* and *trans* isomers. Based on the Beckwith-Houk model (*vide supra*), we expected *cis*/*trans*-ratios close to 1:3. The assignment of *cis* and *trans* isomers was based on NOE difference and/or noesy experiments (Figure 16).

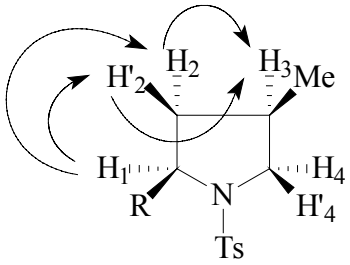


Figure 16. NOE studied in *N*-tosyl-2,4-disubstituted pyrrolidines.

It is simple to distinguish H_2 from H'_2 just by measuring the size of the NOE. The proton on the same side as H_1 gives a larger NOE than the proton sitting on the opposite side. This is also true for the NOE between H_3, H_2 and H'_2. Unfortunately, no long-range NOEs could be seen. According to Watanabe and co-workers,[70] a long-range NOE (13%) could be seen between H_1 and the 4-methyl (Figure 16, R = benzyl). This observation made them assign their radical cyclization product as a 2,4-*trans* compound. Since we could not see the "Watanabe NOE" in our samples of the *cis*/*trans*-diastereomers, we think the Watanabe group has made a false assignment in their work. Our NOE experiments are all consistent with the assignment of the major diastereomer as the *cis*-compound. Therefore, the isomer composition is opposite to the one predicted by Beckwith-Houk.[71] As a further proof, we found that ring closure of the unprotected radical precursor under the same conditions, followed by *N*-tosylation of the pyrrolidine formed, afforded a product enriched in the other (*trans*) diastereomer. *Endo*-*exo* selectivities were varying as one would expect if the conformation of the six-membered ring affect diastereoselectivity in radical cyclization.

We also noticed some interesting features in the ^{1}H NMR spectra of the 2,4-disubstituted pyrrolidines. The shift difference between H_2 and H'_2 (Figure 16) was larger for the *cis*-isomer. This is most prominent in the case of 2,4-dimethyl pyrrolidine (see Table 9, entry 1 on page 44). In the *trans*-isomer, H_2 and H'_2 have almost equal shifts, whereas in the *cis*-isomer the two protons are different by 1.22 ppm. There is also a small but visually noticeable long-range coupling between one of the H_2 protons and one of the H_4 protons in the *cis*-isomer. In the trans isomer the coupling becomes disappearingly small, and can only be seen as a broadening of the peaks in one of the H_2 multiplets.

3.2.2 Azidoselenation of olefins for the preparation of 3,4-disubstituted pyrrolidines.

Tingoli and coworkers[68] reported that azidoselenation of olefins occurred in an anti-Markovnikov fashion in the presence of diphenyl diselenide, sodium azide and iodobenzene diacetate. This reaction is claimed to be a radical addition process and forms the terminal azide exclusively. Five azidoselenation products were prepared in good yields (66-90%) in this manner for further transformation into pyrrolidines (Figure 17):

---

[70] Watanabe, W.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. *Tetrahedron Lett.* **1987**, *28*, 3953.
[71] For a similar result see Giovannini, R.; Petrini, M. *Synlett* **1998**, 90.

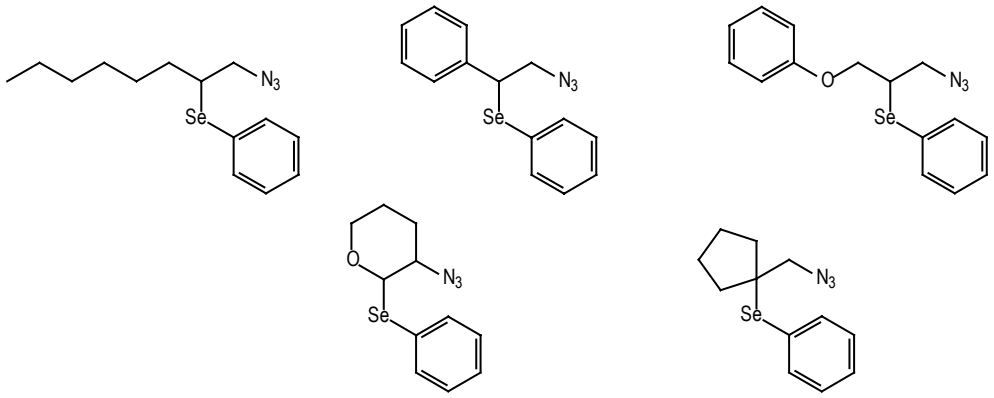


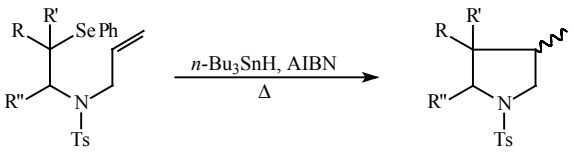
Figure 17. Azidoselenation products synthesised according to Tingolis method.

Azides can be reduced to amines in many different ways.[72] We used LAH or triphenylphosphine (the Staudinger reaction)[73] for the transformation. Both methods gave good results (yields in the range of 68 to 92%). The 2-aminoalkyl phenyl selenides thus formed were tosylated using Et_3N as a base and imidazole as a tosyl activating agent (60-84% yields).

N-allylation was performed as before, using sodium hydride and allyl bromide (53-98% yields).

Radical cyclization was performed as described in Table 6. The radicals that form are more stable since they are secondary. Because of this they are more easily formed than primary radicals. The *cis/trans*-ratios obtained in these reactions were as predicted by the Beckwith-Houk model. In most cases the *cis*-isomer was the major product formed. This can be allotted to the chair-equatorial TS (Figure 18). The chair TS is known to be lowest in energy, but only by 1 kcal/mol as compared with the boat TS. When the 3-substituent becomes too bulky as with phenyl, the steric interaction between the olefin and the substituent raises the chair-equatorial TS energy above that for the boat-equatorial or the chair-axial TS. In these cases the trans-isomer becomes predominating. This effect is known from the literature (*vide supra*).

[72] R. C. Larock, 'Comprehensive Organic Transformations - 2nd ed', p 815, Wiley-VCH, 1999. ISBN 0-471-19031-4



Entry	Substituents	*cis*/*trans*-ratio[a]	Yield (%)[b]	Entry	Substituents	*cis*/*trans*-ratio[a]	Yield (%)[b]
1	R = phenyl R' = H R'' = H	1 / 2	82	4	R = - $O(CH_2)_3$ - = R'' R' = H	10 / 1 *endo*/*exo*	89
2	R = hexyl R' = H R'' = H	2 / 1	85	5	R = - $(CH_2)_4$ - = R' R'' = H		85
3	R = phenoxymethyl R' = H R'' = H	2 / 1	90				

[a] According to NMR..
[b] Isolated yield.

Table 6. Pyrrolidines prepared from azidoselenation products.

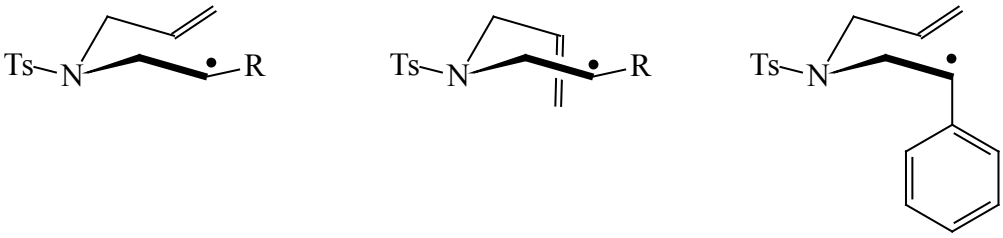


Figure 18. Three transition states for radical cyclization. The chair-equatorial is the only one giving a cis-3,4-disubstituted pyrrolidine.

3.2.3 Preparation of 4-methylene pyrrolidines.

Some attempts were made to prepare 4-methylene pyrrolidines from organoselenium radical precursors by 5-*exo*-*dig* cyclizations. In these reactions the radical adds to an acetylene rather than to an olefin, giving fair yields (50-70%, Table 7). The radical precursors were simply made by substituting allyl bromide for propargyl bromide in the alkylation of *N*-tosyl-2-aminoalkyl phenyl selenides. This could offer an alternative route to the pyrrolidines described in Table 5 provided the double bond could be hydrogenated with some selectivity.

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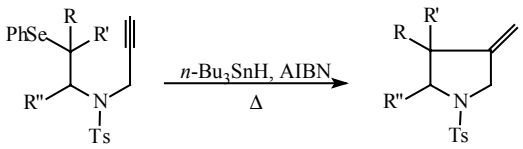
[73] Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.



Entry	Substituents	Yield (%)[a]	Entry	Substituents	Yield (%)[a]
1	R = phenyl R' = H R'' = H	56	4	R = - $O(CH_2)_3$ - = R'' R' = H	54
2	R = H R' = H R'' = hexyl	58	5	R = - $(CH_2)_4$ - = R' R'' = H	70
3	R = phenoxymethyl R' = H R'' = H	50			

[a] Isolated yield.

Table 7. 4-Methylene pyrrolidines prepared via 5-*exo*-*dig* cyclization.

3.3 Summary.

We have described two strategies for making tosyl-protected 2,4- and 3,4-disubstituted pyrrolidines from olefins employing a radical ring-closure in the key step. The methodologies are both high yielding and could find use in synthesis. The diastereoselectivity of 2,4-disubstituted pyrrolidines prepared could not be predicted from the Beckwith-Houk theory. It was also shown that 2-substituted-4-methylene pyrrolidines could be prepared in moderate yields via 5-*exo*-*dig* cyclization.

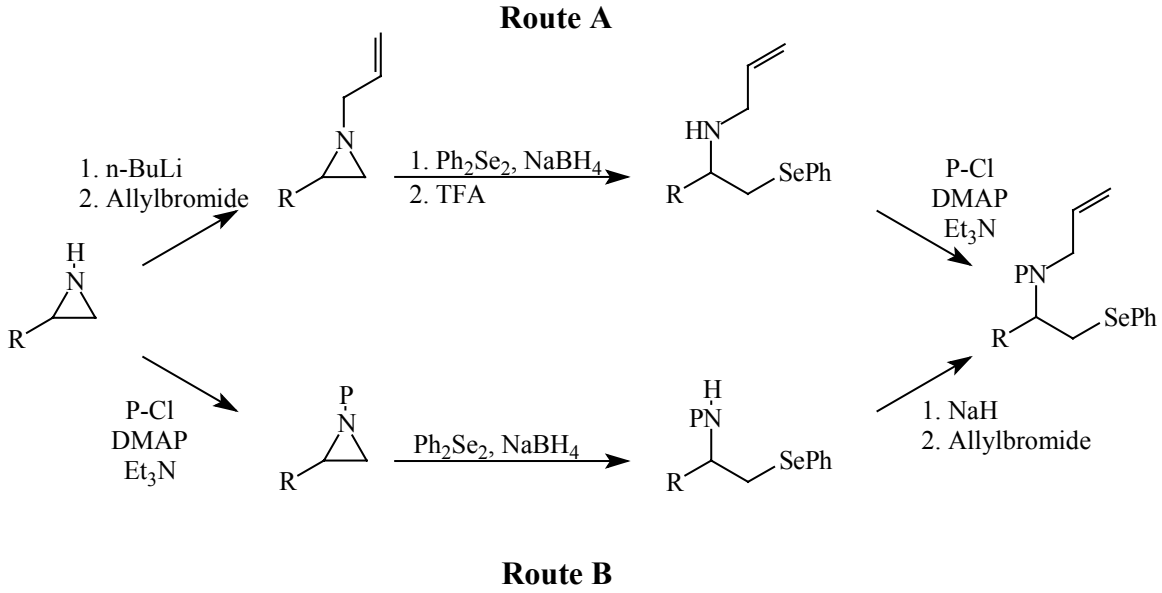
4. Diastereoselectivity control by the N-substituent.

4.1 Introduction.

According to Beckwith-Houk theory, 2,4-disubstituted pyrrolidines produced via radical ring-closure of 3-aza-5-hexenyl radicals would produce the *trans*-compound as the major diastereomer. Since the tosyl protecting group seemed to direct cyclization to occur in a *cis*-selective fashion, we thought it would be a good idea to probe the effect of other N-protecting groups in this reaction. Also, selectivity would probably increase if one could make the radical cyclization work at temperatures lower than 80 ^{o}C. Our initial pyrrolidine synthesis had to be slightly modified in order to allow for these variations in the *N*-protecting group of the radical precursors.

4.2 Results and discussion.

Unprotected aziridines prepared as described above or by other routes[74] were transformed into N-protected radical precursors according to the two protocols shown in Scheme 22.



Scheme 22. Two routes for aziridine ring-opening.

There are *pros* and *cons* with both methods: Allylated aziridines were low boiling in some cases (Route A). This made them difficult to purify and called for further *in situ*

[74] Brois, S. J. *J. Org. Chem.* **1962**, *27*, 3532.

manipulation. The moderate yields were another problem with the allylation of aziridines. A procedure reported by Somfai *et al*,[75] involving treatment of the aziridine with allyl bromide, potassium carbonate and 18-crown-6 did not result in any improvement. Deprotonation of the aziridine with *n*-BuLi at low temperature in diethyl ether or THF, followed by addition of allyl bromide and warming of the mixture to room temperature (or in some cases further heating) also gave only moderate product yields. We also attempted to make use of the Tsuji-Trost allylation reaction[76] to improve yields. In this reaction, a flask was charged with palladium (0) tetrakis[triphenylphosphine], allyl chloride, bromide or iodide, and sodium hydride as a base (Et_3N was allylated under these conditions and DBU worked poorly). However, after workup the reaction did not give satisfactory product yields, and was abandoned due to the costly catalyst. Since allylated aziridines were ring opened much more efficiently than many N-protected ones, route A seemed to be the best method for making our radical precursors. Whereas the N-protected aziridines were ring opened with benzeneselenoate, allylated aziridines were untouched under these conditions. Instead, benzeneselenol prepared *in situ* under acidic conditions (TFA), was found to regioselectively open the aziridines from the sterically least hindered side (Scheme 22; Route A).[77] N-protected radical precursors were then prepared in good yields from acid chlorides (P-Cl) with DMAP as an activating agent and triethylamine serving as a base. However, when the aziridine 2-substituent was *t*-butyl, the allylated and ring-opened product could not be phosphinoylated, probably because the secondary amine is too sterically hindered.

For some of the radical precursors, α-phenylselenenyl ketones were used as substrates. These compounds are efficiently synthesised,[78] and can be transformed into *N*-allyl imines by treatment with allylamine and $TiCl_4$ as a dehydrating agent (Scheme 23).[79] The imine can then be reduced with $NaBH_3CN$[80] at pH 4 and –78 °C to the *N*-allyl-2-aminoalkyl phenyl selenide.

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[75] Åhman, J.; Jarevang, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148.

[76] [a)]Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. [b)]Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144. [c)]Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

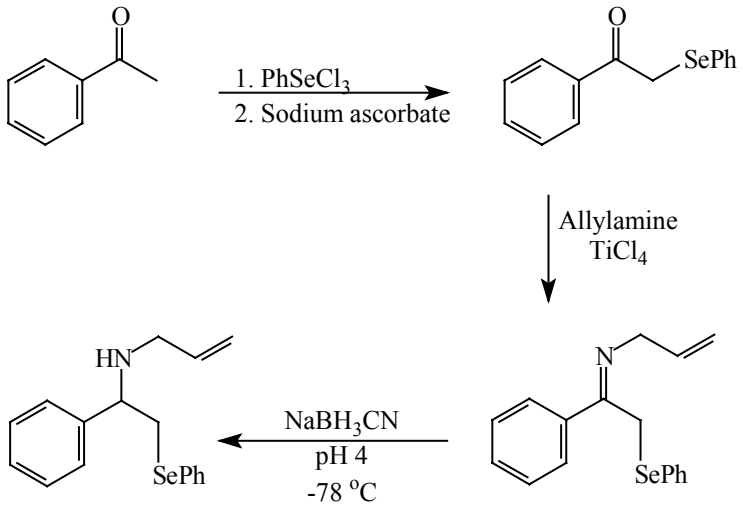
[77] For the thiol opening see: [a)]Lin, P-Y.; Bellos, K.; Stamm, H.; Onistschenko, A. *Tetrahedron.* **1992**, *48*, 2359. [b)]Wehrmeister, H. L. *J. Org. Chem.* **1963**, *28*, 2587. [c)]Hata, Y.; Watanabe, M. *Tetrahedron* **1987**, *43*, 3881. [d)]Dureault, A.; Tranchepain, I.; Depezay, J-C. *J. Org. Chem.* **1989**, *54*, 5324. For selenol opening see: Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323.

[78] Engman, L. *Tetrahedron Lett.* **1985**, *26*, 6385. Engman, L. *J. Org. Chem.* **1987**, *52*, 4086. Engman, L. *J. Org. Chem.* **1988**, *53*, 4031.

[79] [a)]Van, T. N.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7299. [b)]Aelterman, W.; Tehrani, K. A.; Coppens, W.; Huybrechts, T.; De Kimpe, N.; Tourwe, D.; Declercq, J-P. *Eur. J. Org. Chem*. **1999**, 239.

[80] Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Amer. Chem. Soc.* **1971**, *93*, 2897.

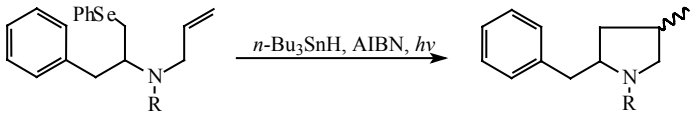
Since the α-phenylselanyl imines are sensitive to C-Se bond cleavage, the latter reaction calls for a mild reducing agent.



Scheme 23. An alternative procedure for the preparation of *N*-allyl-2-aminoalkyl phenyl selenides.

N-Allyl-2-amino-3-phenylpropyl phenyl selenide was selected as a model compound for studying the influence of the protecting groups on diastereoselectivity in the radical cyclization. Six different protecting groups, all electron-withdrawing but with different steric requirements, were tried (Table 8).

Radical cyclizations were performed at two different temperatures, 80 °C and 17 °C. AIBN can be homolytically cleaved either by heat or by ultraviolet light. For radical cyclization at 80 °C, the standard reaction conditions described previously (*n*-Bu_3SnH, AIBN, benzene) were used. Cyclization at 17 °C was carried out in a photoreactor from Aldrich (see supplementary material). With a filter cutting wavelengths lower than 300 nm, undesired photochemical reactions could be prevented. Photoinitiation turned out to be highly satisfactory for radical cyclizations near room temperature. We also found that pre-bubbling of the solution with argon for 5-10 minutes (to remove dissolved oxygen), and the use of freshly distilled (tin hydrides are air sensitive) tri-*n*-butyltin hydride increased reproducibility and facilitated workup. Some attempts were also made to initiate reactions at lower temperatures (-78 °C) using triethyl borane and O_2 as radical initiators. We were disappointed to find that this did not work.

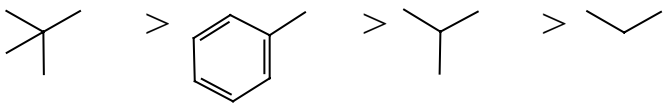


Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]	Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]
1	H	A: 60 B: 92	1 / 3 1 / 4	5	PhC(=O)	A: 72 B: 89	4 / 1 7 / 1
2	EtC(=O)	A: 88 B: 82	2 / 1 3 / 1	6	4-$MeC_6H_4SO_2$	A: 77 B: 78	3 / 1 4 / 1
3	*i*-PrC(=O)	A: 79 B: 82	3 / 1 3 / 1	7	Ph_2P(=O)	A: 79 B: 81	10 / 1 24 / 1
4	*t*-BuC(=O)	A: 93 B: 87	2 / 1 2 / 1				

[a] Isolated yield. Method A: at 80 °C; Method B: at 17 °C
[b] According to NMR.

Table 8. Diastereoselectivities in the radical cyclization of *N*-protected *N*-allyl-2-amino-3-phenylpropyl phenyl selenide.

The results of the model radical cyclization study is shown in Table 8. Good yields were obtained with all protecting groups tried. Assuming that the free energy difference between an axial and an equatorial cyclohexane alkyl substituent could be used for comparison of the corresponding acyl groups, the bulkiness of the acyl protecting groups used decreases in the following order (Figure 19):[81]



$-\Delta G^o$ (kcal/mol)	4.9	2.7	2.15	1.75

Figure 19. Free energy difference between an axial and an equatorial alkyl substituent in cyclohexane.

[81] J. March, 'Advanced organic chemistry – Reactions, Mechanisms, and Structure', 4th Ed., Wiley, New York, 1992, p 145.

If steric interactions in the transition state are important, this relative order could be expected to be roughly reflected in the observed *cis/trans*-ratios. Except for the 2,2-dimethyl propanoyl group, this is the case. A strange phenomenon was observed in the ^{1}H NMR spectra of the radical precursor and the product pyrrolidine carrying this group. The mixture of rotamers seen with the other three acyl protected compounds was absent in the case of the 2,2-dimethylpropanoyl protected compound.

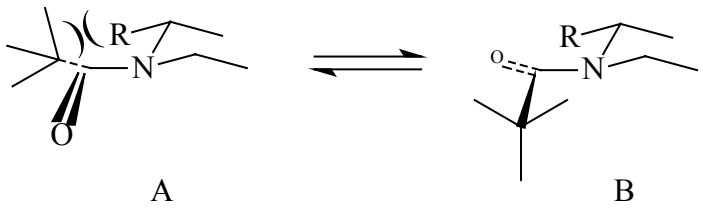


Figure 20. Two rotamers of the radical precursor.

One explanation could be that the bulkiness of the *tert*-butyl group prevents free rotation around the amide bond, thus favouring one of the rotamers (B in Figure 20). The bulk may actually be so large that the nitrogen lone-pair can no longer be conjugated with the carbonyl group (Figure 20). The other three protecting groups could probably rotate more freely around this bond, and therefore interact with the side-chain substituent R more efficiently. According to Beckwith and Houk's transition state model (*vide supra*), the hexenyl radical assumes a "chair-like" transition state with the "boat-like" transition state not much higher in energy (ca 1 kcal/mol). In the chair-equatorial conformation (Figure 21) the substituent R is equatorial. This explains why the 2,4-*trans* diastereomer is the major product in the N-unsubstituted compound. Since our reactions with N-protected compounds are *cis*-selective, either the boat-equatorial or the chair-axial transition states are likely to be involved in product formation. It is tempting to think that the latter transition state becomes more and more important as the bulk of the N-protecting group P and the side-chain substituent R increases.

Sulfonyl and phosphinoyl amides are probably less resonance stabilized than carboxamides. Thus, rotation around the N-heteroatom bond could occur more easily in these compounds. The longer N-S and N-P bonds would also make steric interactions less severe.

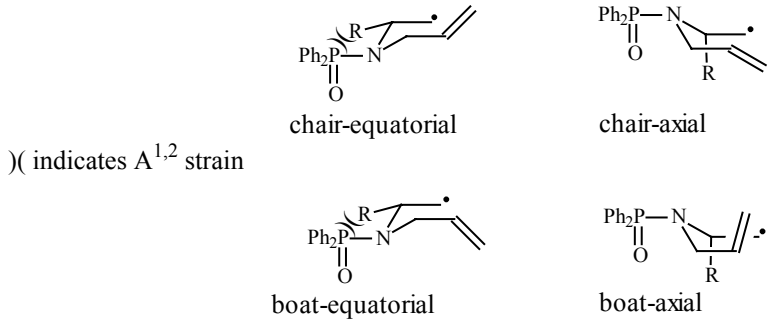
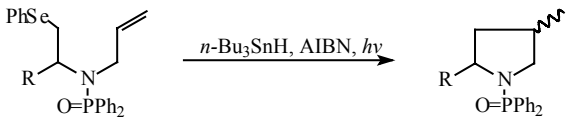


Figure 21. Transition states for formation of N-protected 2,4-disubstituted pyrrolidines.

The diphenyl phosphinoyl group is more three-dimensional (propeller-like) than acyl or tosyl groups. This could be the reason for its stronger *cis*-directing effect. As can be seen in Table 8, the diphenyl phosphinoyl group is very much better than the other groups in directing cyclization to occur in a *cis*-selective fashion. Therefore, we decided to investigate the generality of this protecting group effect. The results of this investigation are summarised in Table 9.



Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]	Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]
1	methyl	A: 59 B: 78	1 / 4 18 / 1	5	phenoxymethyl	A: 75 B: 72	1 / 14 21 / 1
2	2-methylpropyl	A: 91 B: 84	1 / 3 17 / 1	6	*t*-butyl	A: 59 B: -[c]	>1 / 20
3	hexyl	A: 86 B: 85	1 / 4 20 / 1	7	phenyl	A: 61 B: 88	1 / 10 10 / 1
4	benzyl	A: 92 B: 81	1 / 4 24 / 1				

[a] Isolated yield. Method A: Cyclization of unprotected precursor followed by *N*-protection.
Method B: Cyclization of protected precursor.

[b] According to NMR.

[c] Radical precursor could not be prepared.

Table 9. Diastereoselectivity in the radical cyclization of *N*-diphenylphosphinoyl protected radical precursors.

The unprotected β-aminoalkyl phenyl selenides (Method A) and their corresponding diphenylphosphinoylated derivatives (Method B) were subjected to radical cyclization at 17 ^{o}C in benzene with photochemical initiation. As seen in Table 9, unprotected compounds afforded *trans*-2,4-disubstituted compounds with fair to high selectivity (*cis*/*trans* = 1/4 - 1/20). The yields reported in Table 9 are those obtained after radical cyclization and *N*-diphenylphosphinoylation. *N*-Diphenylphosphinoylated compounds gave the corresponding *cis*-2,4-disubstituted pyrrolidines with high selectivity (*cis*/*trans* = 10/1 - 20/1). There is some evidence in the literature that $A^{1,2}$ strain can raise the energy for a chair-equatorial conformation in piperidine systems above that for the chair-axial conformation.[82] Itoh and coworkers[83] also reported similar N-protecting group effects in radical cyclizations related to ours.

Whatever the reasons, one would expect the *cis/trans*-ratio to increase as $A^{1,2}$ strain becomes larger. Bearing this in mind, it is somewhat surprising that the ratios do not differ very much. The exception is the case with a phenyl in the side-chain, where the bulk of the substituent is brought very close to the ring to be formed. In this case axial crowding is probably much more severe than in the other cases. This is already apparent in the cyclization of the unprotected compound where a much larger than expected trans selectivity was found.

The directing effects of $A^{1,2}$ strain (equatorial substituent) and diaxial interactions (axial substituent) are always counteracting as far as the diastereoselectivity is concerned. π–stacking between N-protecting group phenyls and a phenyl side chain could also be a determining factor. The *cis*-selectivity could probably be increased even further using bulkier N-protecting groups.

Another intriguing observation was the higher than expected *trans*-selectivity obtained in the cyclization of the unprotected radical precursor carrying a phenoxymethyl substituent β to nitrogen (Table 9; entry 5). This case will be discussed in some detail in the next chapter (*vide infra*).

[82] Craig, D.; Meadows, J. D.; Pécheux, M. *Tetrahedron Lett.* **1998**, *39*, 147. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. Hopman, J. C. P.; van den Berg, E.; Ollero Ollero, L.; Heimstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315.

4.3 Summary and outlook.

It has been shown that stereoselectivities in the formation of 2,4-disubstituted pyrrolidines by radical cyclization are highly dependent on the N-protecting group. High *cis*-selectivities were seen when diphenylphosphinoyl was used and the radical ring-closure was performed at 17 ^{o}C. We believe that the selectivities could be increased even further if the phosphinoyl phenyls could be replaced by bulkier groups. Selectivity would probably also increase if one could induce cyclization to occur at a lower temperature. It would also be of interest to study the effect of the N-protecting group in the radical formation of 3,4-disubstituted pyrrolidines.

[83] Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464.

5. Use of a hydroxyl auxiliary in the synthesis of *trans*-2,4-disubstituted pyrrolidines via radical cyclization.

5.1 Introduction.

The aforementioned radical ring-closure to form 4-methyl-2-phenoxymethylpyrrolidine occurred with unexpectedly high *trans*-selectivity. This finding stimulated us to try to develop a more general methodology for the preparation of *trans*-2,4-disubstituted pyrrolidines. It occurred to us that a hydroxyl group situated in close proximity to the nitrogen could be used as a handle in the ring-closure. The radical species giving rise to 4-methyl-2-phenoxymethylpyrrolidine (Figure 22) has got an ether group β to the nitrogen. Since side-chains of similar steric demand directed cyclization to occur in a far less *trans*-selective manner, we hypothesised that the effect may be due to an intramolecular hydrogen bond (Figure 22).[84]

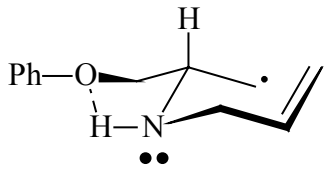


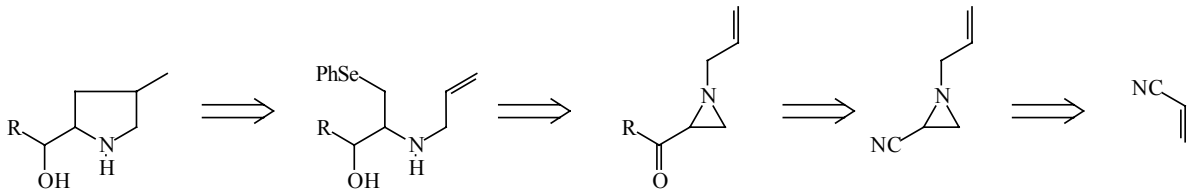
Figure 22. Intramolecular hydrogen bond in the radical species.

The hydrogen bond may conceivably increase the energy difference between the chair-equatorial and chair-axial transition states, thus increasing the diastereoselectivity. We decided to test this hypothesis by synthesising radical precursors carrying an α-hydroxyl group on the 2-substituent of the ring to be formed. To achieve this, we had to develop some novel synthetic methodology.

5.2 Results and discussion.

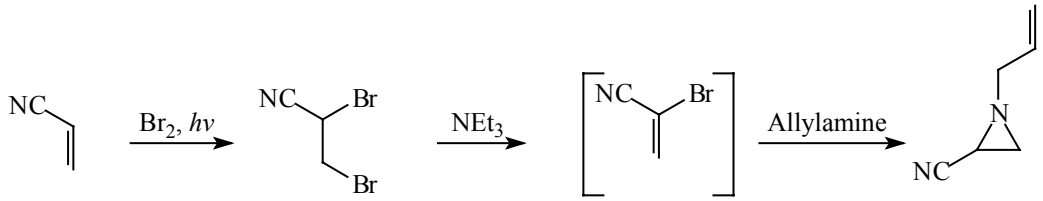
5.2.1 Synthesis of radical precursors.

The idea of starting from an aziridine and ring-opening it with selenol appeared attractive. The retrosynthetic analysis that emerged, starting from 1-allyl-2-cyanoaziridine, is shown in Scheme 24.



Scheme 24. Retrosynthetic scheme for synthesis of pyrrolidines carrying a hydroxyl auxiliary in the side-chain.

The synthesis of 1-allyl-2-cyano aziridine is described in the literature and is shown in Scheme 25.[85]



Scheme 25. Synthesis of 1-allyl-2-cyano aziridine.

Bromine was added to an excess of neat acrylonitrile and the reaction mixture was irradiated with a sun lamp. The addition was highly exothermic and very fast under these conditions. Excess acrylonitrile was distilled off under water aspirator vacuum. The crude dibromide was treated with NEt_3 in ethanol to form α-bromoacrylonitrile *in situ* before allylamine was added. The amine attacks the α-bromoacrylonitrile in a Michael-fashion and ring-closes intramolecularly to give an aziridine.

2-Cyanoaziridines can be reacted both with Grignard and organolithium reagents.[86] The addition of phenylmagnesium bromide proceeded smoothly in THF using TMEDA as co-solvent to give a high yield of the corresponding imine. Hydrolysis was conveniently effected by warming in MeOH/water containing LiOH.

The addition of PhLi was more complicated. It was not until the order of addition of the reagents was reversed that any improvement was seen. By this protocol, butyl- and 2-thienyllithium were also successfully added to 1-allyl-2-cyano aziridine. Table 10 shows the keto aziridines prepared by addition of various organometallic reagents to 1-allyl-2-cyano aziridines and hydrolysis of the corresponding imines.

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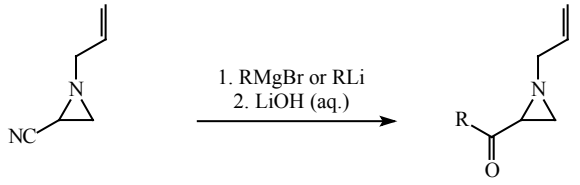
[84] For an example see Gelas-Mialhe, Y.; Touraud, E.; Vessiere, R. *Can. J. Chem.* **1982**, *60*, 2830.

[85] [a)] US Pat. 4,321,197 (1983). [b)] Gundermann, K. D.; Burzin, K.; Sprenger, F. J.; Schulze, H. *Chem. Ber.* **1972**, *105*, 312. [c)] Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. *J. Org. Chem.* **1985**, *50*, 4114.



Entry	R	Yield (%)[a]	Entry	R	Yield (%)[a]
1	phenyl	92	4	*i*-propyl	52
2	1-pentyl	60	5	2-(1,3-dioxolan-2-yl) -ethyl	73
3	2-thienyl	68			

[a] Isolated yield.

Table 10. Addition of organometallics to 1-allyl-2-cyano aziridine

Keto aziridines can act as bidentate ligands to metals. This offers an opportunity for stereoselective reduction of the carbonyl moiety. A procedure was found in the literature where $Zn(BH_4)_2$ had been used for this type of reduction. As shown in Figure 23, zinc chelates to the keto aziridine.[87]

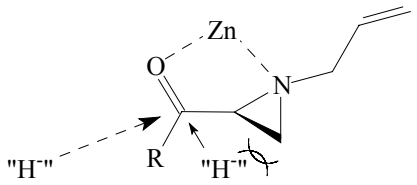
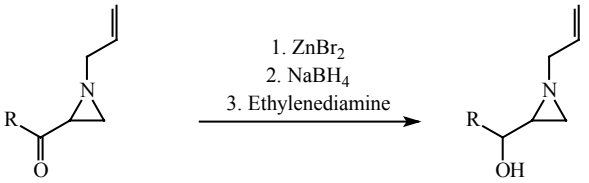


Figure 23. Borohydride delivers hydride from the least hindered side.

In the zinc complex, the carbonyl *Si* and *Re* faces can be distinguished by the hydride. The side pointing towards the aziridine methylene is less accessible. We found that the best procedure involved pre-treatment of the keto aziridine with $ZnBr_2$ in methanol followed by addition of $NaBH_4$ at reflux temperature. $NaBH_4$ itself does not give very high selectivity. Assuming complexation as shown in Figure 23, our aziridine alcohols have the *erythro*

[86] See refs. 85c and 87a. De Kimpe, N.; Sulmon, P.; Schamp, N. *Bull. Soc. Chim. Belg.* **1986**, *95*, 567.

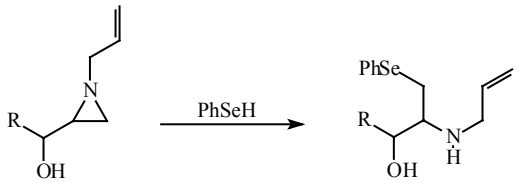
configuration. The best procedure for zinc decomplexation after reduction involved treatment with ethylene diamine (Table 11).



Entry	R	Yield (%)[a]	Entry	R	Yield (%)[a]
1	phenyl	84	4	*i*-propyl	43[b]
2	1-pentyl	88	5	2-(1,3-dioxolan-2-yl) -ethyl	66
3	2-thienyl	85			

[a] Isolated yield.
[b] Decomplexation with NaOH (aq.).

Table 11. Zinc mediated ketone reduction.



Entry	R	Yield (%)[a]	Entry	R	Yield (%)[a]
1	phenyl	79	4	*i*-propyl	65
2	1-pentyl	89	5	2-(1,3-dioxolan-2-yl) -ethyl	94
3	2-thienyl	96			

[a] Isolated yield.

Table 12. Aziridine ring-opening with benzeneselenol.

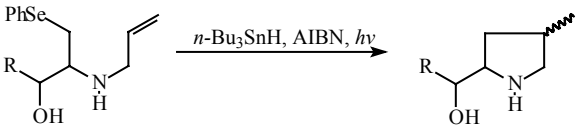
---

[87] [a)]Bartnik, R.; Laurent, A.; Lesniak, S. *J. Chem. Research (M)* **1982**, 2701-2717. [b)]Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1981**, *22*, 4723. [c)]Aoyama, Y.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 6731.

As before, the benzeneselenol ring-opening proceeded regiospecifically without complications to give the desired radical precursors (Table 12).

5.2.2 Radical ring closure.

Ring-closures were performed in a similar way as described before (*vide supra*). The results are shown in Table 13. In benzene, the *cis*/*trans*-ratios were 1/9 - 1/12. This is slightly higher than was obtained with 2-phenoxymethyl-4-methyl pyrrolidine (*cis*/*trans* 1/14; Table 9 entry 5).



Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]	Entry	R	Yield (%)[a]	*cis*/*trans*-ratio[b]
1	phenyl	82	1 / 9	4	*i*-propyl	79	1 /12
2	1-pentyl	96	1 / 10	5	2-(1,3-dioxolan-2-yl) -ethyl	84	1 / 9
3	2-thienyl	80	1 / 9				

[a] Isolated yield.
[b] According to NMR.

Table 13. Radical ring-closure.

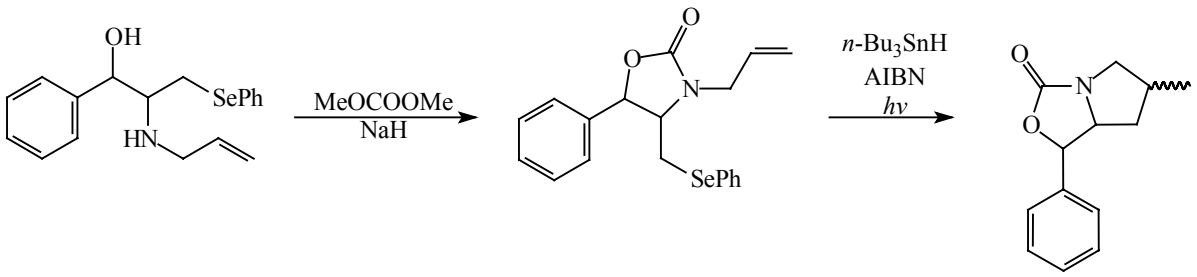
As an extra bonus the pyrrolidines carrying the hydroxyl auxiliary were highly crystalline. Thus, recrystallisation of the product shown in Table 13, entry 1, from cyclohexane, produced material highly enriched in the *trans* isomer (*cis*/*trans* < 1/25).

The ring-closure shown in Table 13, entry 1, was also tried in a protic solvent (*tert*-BuOH). However, no difference could be seen in the diastereoselectivity of the reaction. This could indicate that intramolecular hydrogen bonding does not serve to preorganize the carbon centered radical prior to cyclization. Also, ^{1}H NMR studies of the radical precursor did not

provide any evidence for a hydrogen bond. The signals from hydrogen bonded H normally appear well resolved at high shifts (δ 10-16) in non-polar solvents (e.g. in deuterated benzene). IR spectra run in CCl_4 were also inconclusive as to the existence of an intramolecular hydrogen bond.

In the light of the above results and the experiments that follow (*vide infra*), it seems more likely that the *trans*-directing effect of the hydroxyl auxiliary is in fact caused by the increased bulk of the side-chain.

We were also curious to investigate the effect of Lewis acids on ring-closure. Our group has recently shown dramatic effects of trialkylaluminums on the diastereoselectivity of 2,4-disubstituted tetrahydrofurans formed by radical ring-closure.[88] $ZnBr_2$ and four different aluminum species were tried: Me_3Al, *i*-Bu_3Al, (*t*-BuO)$_2$MeAl and MAD.[89] Unfortunately, none of the Lewis acids significantly affected the diastereoselectivity of cyclization. We also decided to lock the alcohol and amine functional groups into an oxazolidin-2-one structure and see how this would affect diastereoselectivity. The compound was synthesised by heating of the amino alcohol in dimethylcarbonate with NaH as base (Scheme 26).



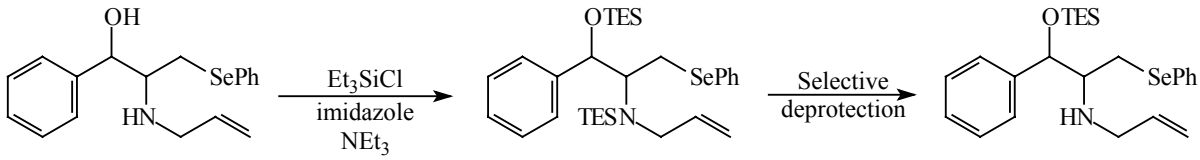
Scheme 26. Synthesis and radical ring-closure of an oxazolidin-2-one.

However, ring-closure proved to be less selective than cyclization of the corresponding amino alcohols (*endo*/*exo* = 1/6). This could be due to the rigidity of the system which brings the radical and olefin moieties away from each other.

If the *trans*-selectivity is an effect of increasing steric bulk in the side chain, the selectivity would increase if the one could attach a bulky protective group to the OH group. A few attempts to introduce a TES group were made (Scheme 27), but none of the approaches produced material that was useful for evaluating the concept.

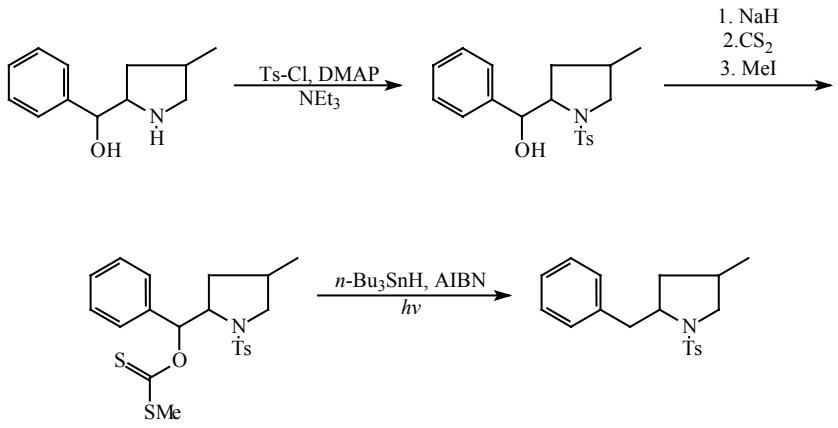
---

[88] Ericsson, C.; Engman, L. *Org. Lett.* **2001**, *3*, 3459.
[89] Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.



Scheme 27. Attempted preparation of a TES-protected radical precursor.

As a proof of principle and to verify our stereochemical assignment, we thought it would be appropriate to remove the hydroxyl auxiliary from one of our pyrrolidines. Hydroxyl groups can easily be removed by Barton-McCombie deoxygenation (Scheme 28).[90]



Scheme 28. Barton – McCombie deoxygenation.

All three steps are straightforward reactions that proceed in moderate to good yields. The stereochemistry of the deoxygenated product was in accordance with earlier work (*vide supra*).

5.3 Summary and outlook.

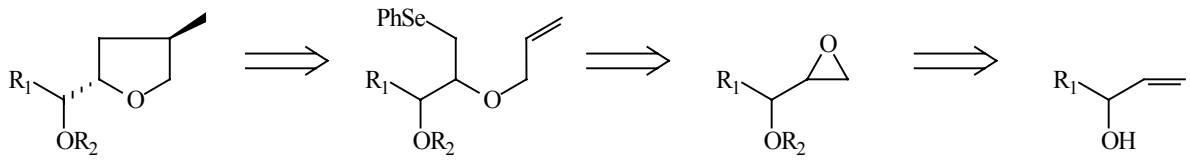
We have shown that it is possible to cyclize β-amino selenide radical precursors with higher *trans*-selectivity if a hydroxyl group is present in the 2-substituent of the pyrrolidine to be formed. We have still not been able to show if this is due to an intramolecular hydrogen bond or if the effect is just a steric one, although evidence point at the latter. If bulk is the main driving force for lowering the *cis*/*trans* ratio, it would be interesting to further explore the possibility of using a bulky O-protecting group as an auxiliary. In spite of the failure to

[90] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans.1* **1975**, 1574.

selectively protect amino selenides, we have succeeded in protecting the hydroxyaziridine with a TES group. The only question remaining is whether the TES group can withstand the acidic ring-opening conditions before the protected radical precursor is within reach.

The hydroxyl auxiliary can be removed by Barton-McCombie deoxygenation to form the kind of 2,4-disubstituted pyrrolidines that previously were made highly enriched in the *cis*-diastereomer employing the N-substituent as a control element (*vide supra*). Thus, the two methods are complementary.

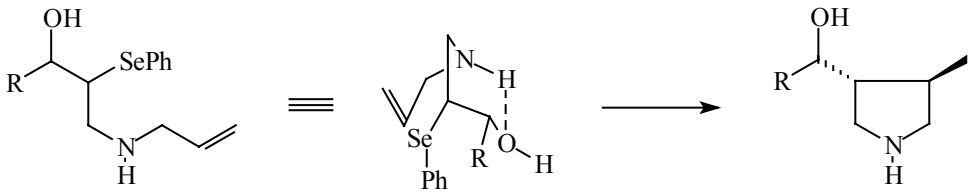
The hydroxyl auxiliary could also prove useful for controlling diastereoselectivity in the analogous oxygen containing systems (Scheme 29).



Scheme 29. Retrosynthetic analysis of *trans*-2,4-disubstituted tetrahydrofurans.

If the imines from the addition of organometallics to nitriles could be reduced with equally good diastereoselectivity as the ketones, β-amino pyrrolidines could be made in a similar way.

The idea of using a hydroxyl handle to control diastereoselectivity could also be applied to the preparation of 3,4-disubstituted pyrrolidines. In these systems hydrogen bonding is even more likely to be involved since the interaction occurs via a six-membered ring (Scheme 30).

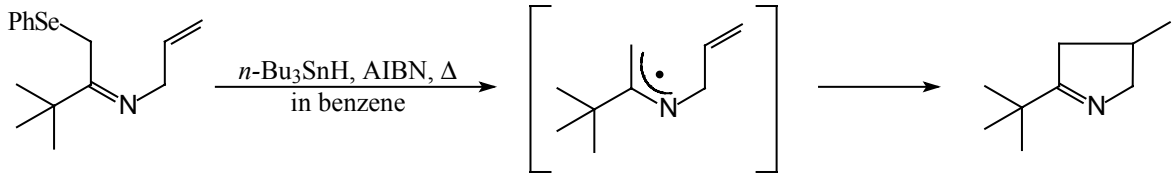


Scheme 30. The use of a hydroxyl auxiliary in the preparation of 3,4-disubstituted pyrrolidines.

6. Miscellaneous.

6.1 A radical cyclization approach to pyrrolines.

Two other projects were started but not finished. We investigated synthesis of pyrrolines via radical ring-closure of the iminoselenides used in chapter 4. Cyclization of *N*-allyl-2-imino-3,3-dimethyl-butyl phenyl selenide was tried as shown in Scheme 31.



Scheme 31. Attempted pyrroline synthesis.

This reaction is interesting since the pyrroline that forms can be hydrogenated to the corresponding *cis* 2,4-disubstituted pyrrolidine. It is also of interest to see how the resonance stabilized β-imino radical behaves under radical conditions. The synthesis of the radical precursor is described in chapter 4. It was noticed that the imine had to be purified by distillation to get any conversion of starting material during radical cyclization. Initial cyclization experiments afforded only hydrodeselenated product. This was in accord with our expectations that cyclization would be substantially slowed down due to resonance stabilization of the radical. Even with slow (syringe pump) addition of tin hydride, much reduced material was produced according to NMR analysis. We could suppress reduction even further by using $(TMS)_3SiH$ as a source of hydrogen atoms ($(TMS)_3SiH$ reacts about 10 times slower than *n*-Bu_3SnH).[91] During these studies a new side product started to appear. After some investigation we concluded that it was the group-transfer cyclization product shown in Figure 24.

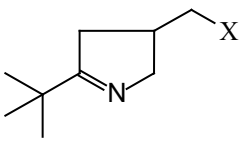


Figure 24. The group-transfer cyclization (X = SePh) and reduced cyclization (X = H) products.

It is well established that tellurides undergo group transfer under mild conditions, but selenide group transfer in radical reactions is rarely seen.[92] We tried to suppress reductive cyclization by using hexabutyldistannane as a source of tributyltin radicals. This reagent can be homolytically cleaved with heat or photons because of its weak tin-tin bond and is often used in group transfer reactions. The product mixture obtained from concentrated solutions of the reactants was a 1:1 mixture of group transfer and reduced pyrroline. It seemed that the solvent acted as a source of hydrogen atoms. In order to quantify pyrroline formation using $(TMS)_3SiH$ and syringe pump addition, all group transfer product was reduced by added *n*-Bu_3SnH and AIBN. By this procedure we could isolate 3-methyl-5-*tert*-butyl-3,4-dihydro-*2H*-pyrrole (Figure 24) in 57 % yield. This project has not been pursued any further. However, the procedure is potentially useful for pyrroline synthesis if group transfer could be controlled.

6.2 Homolytic substitution. A radical cyclization approach to thiazolines.

Radical cyclizations frequently involve addition of a carbon centred radical to an unsaturation, often a carbon-carbon double or triple bond, but sometimes also a carbon-heteroatom multiple bond.[93,94] In contrast, cyclization via intramolecular homolytic substitution at carbon is rarely seen.[95] This is probably because of difficulties in forming carbon-carbon bonds with this type of methodology. Heteroatoms are better suited for this type of chemistry, and our group has recently taken advantage of homolytic intramolecular substitution for making novel selenium-based antioxidants.[96] We thought that homolytic substitution could also be useful for the preparation of thiazolines – again using an aziridine as a starting material (Schemes 32 and 33).

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[91] See ref. 41b.

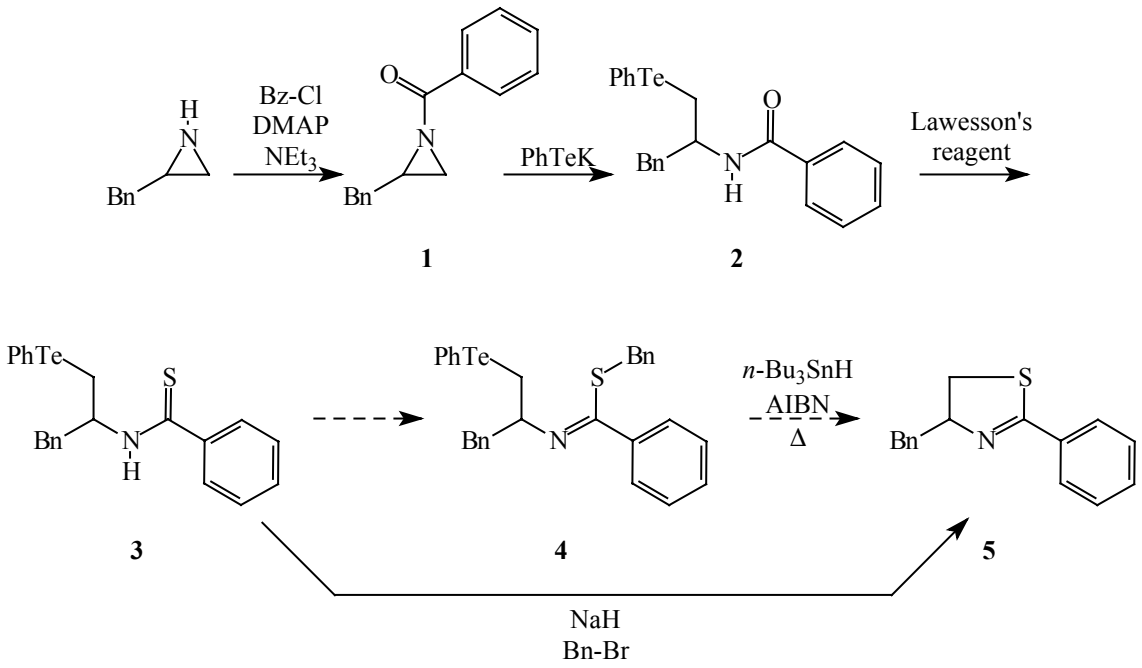
[92] Pandey, G.; Rao, K. S. S. P.; Rao, K. V. N. *J. Org.Chem.* **2000**, *65*, 4309.

[93] N=C : [a)]Grove, J. J. C.; Holzapfel, C. W. Tetrahedron Lett. **1997**, *38*, 7429. [b)]Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. [c)]Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447. [d)]Bartlett, P.A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.

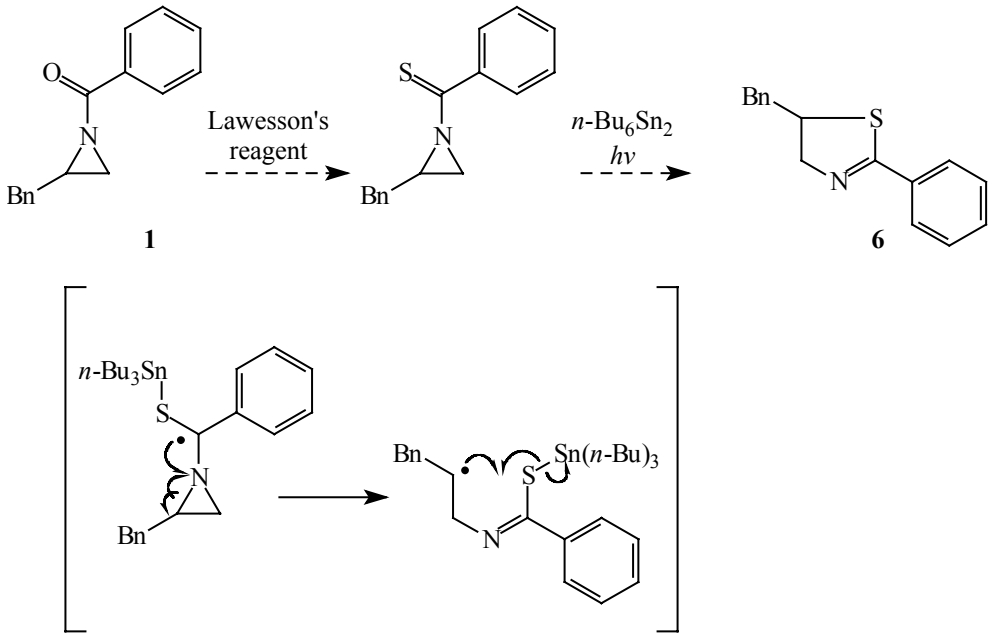
[94] O=C : [a)]Devin, P.; Fensterbank, L.; Malacria, M. Tetrahedron Lett. **1999**, *40*, 5511. [b)]Jiaang, W.-T.; Lin, H.-C.; Tang, K.-H.; Chang, L.-B.; Tsai, Y.-M. *J. Org. Chem.* 1999, *64*, 618. [c)]Chang, S.-Y.; Jiaang, W.-T.; Cherng, C.-D.; Tang, K.-H.; Huang, C.-H.; Tsai, Y.-M. *J. Org. Chem.* **1997**, *62*, 9089.

[95] Walton, J. C. *Acc. Chem. Res.* **1998**, *31*, 99.

[96] [a)]Al-Maharik, N.; Engman, L.; Malmström, J.; Schiesser, C. H. *J. Org. Chem.* **2001**, *66*, 6286. [b)]Engman, L.; Laws, M. J.; Malmström, J.; Schiesser, C. H.; Zugaro, L. M. *J. Org. Chem.* **1999**, *64*, 6764.



Scheme 32. Attempted synthesis of 4,5-dihydro-4-benzyl-2-phenyl thiazole.



Scheme 33. Attempted synthesis of 4,5-dihydro-5-benzyl-2-phenyl thiazole and mechanism for ring closure.

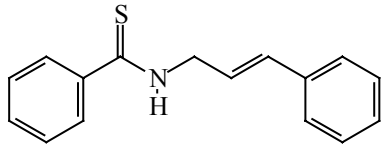
In the proposed synthesis of 4,5-dihydro-4-benzyl-2-phenyl thiazole (**5**) (Scheme 32) we thought it would be wise to use a telluride as a radical precursor. The reaction of a tin radical with tellurium is much faster than its reaction with selenium or sulphur. The aziridine **1** was

synthesised as previously described (*vide supra*). The following benzoylation worked well.[97] The benzoylated aziridine is activated and can therefore be ring-opened with nucleophiles. Heating of Ph_2Te_2 in THF with KH caused reduction of the tellurium-tellurium bond with formation of potassium benzenetellurolate.[98] When added to KTePh in THF/DMI at room temperature aziridine ring-opening proceeded efficiently to give a β-amido telluride **2** in 80% yield.

Lawesson's reagent is especially effective for converting amides to thioamides.[99] The telluride was therefore refluxed with Lawesson's reagent in THF and the product passed through a silica column. The corresponding thioamide **3** was isolated in 86 % yield. In order to install a good radical leaving group on sulphur, the thioamide was deprotonated with NaH and benzyl bromide was added. Strangely enough, no alkylation at sulphur was observed. The product was a 1:1–mixture of unreacted starting material and thiazoline **5**. It seems that benzyl bromide reacts at tellurium, transforming it into a good leaving group. Ring-closure then follows via an ionic mechanism.

We also looked into the synthesis of 4,5-dihydro-5-benzyl-2-phenyl thiazole as described in Scheme 33. The idea was to add tin radicals to a thioamide, thereby transferring the radical to the α-position of an aziridine nitrogen (Scheme 33; within brackets). The aziridine would then ring-open instantaneously to give the more stable secondary radical. This radical in turn can undergo intramolecular homolytic substitution at sulphur, with formation of a thiazoline. The tin radical can then react further. If the cycle can be kept alive, only a catalytic amount of hexabutyldistannane is required. The precursor seemed to be readily available using the Lawessons reagent. However, when aziridine **1** was refluxed with Lawesson's reagent in THF, and the reaction worked up by passing the crude through a short silica column, only a ring-opened product, *N*- (3-phenyl-2-propenyl)-thiobenzamide (**7**), was isolated.

Although uncompleted, this project still holds some potential. An alternative synthesis of the radical precursor has to be worked out. Nothing further can be added at this point except good luck to whoever bothers to pick these projects up!



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[97] Bates, G. S.; Varelas, M. A. *Can. J. Chem.* **1980**, *58*, 2562.
[98] Krief, A.; Trabelsi, M.; Dumont, W. *Synthesis* **1992**, 933.
[99] Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

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Past and present members of the Department. I will remember you all – in some way or another.

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My Friends, who stood by me all these years, although I wasn't around much.

My Family: my mother Gunilla Beşev Hellsing, Cecilia Beşev, Per Beşev and Miranda Beşev – I love you of all my heart.

Finally posthumously to my father, Cengiz Beşev, who was, and still is, my guiding light. I remember that day when you took me to see the DNA statue outside BMC. That was the day it all began.