Intramolecular Carbolithiation Reactions for the Preparation of Azabicyclo[2.2.1]heptanes

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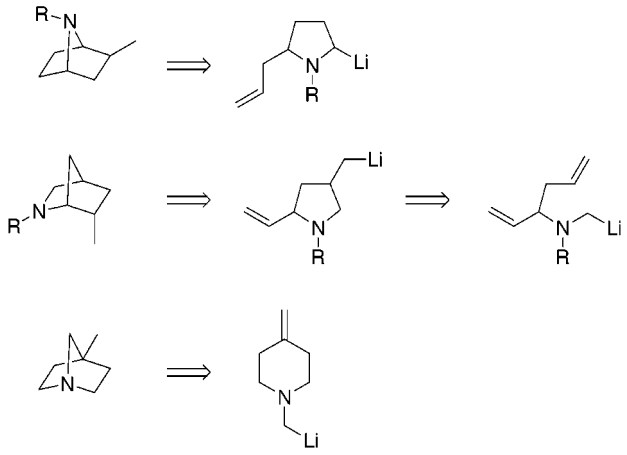
Tin−lithium exchange and intramolecular carbolithiation (anionic cyclization) have been used to construct the three nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system. The 7-azabicyclo[2.2.1]heptane ring system is accessed from either diastereomer of a 2,5-disubstituted pyrrolidine, via a chiral organolithium intermediate. The 2-azabicyclo[2.2.1]heptane ring system is formed stereoselectively in low yield by a tandem cyclization, together with the product from monocyclization. Better yields of the 2-aza ring system can be obtained using an alternative approach from a 2-tributylstannyl-4-allylpyrrolidine, despite the trans arrangement of the tin (and, hence, lithium) atom and the allyl unit. The 1-azabicyclo[2.2.1]heptane ring system is accessed in just three steps from 4-piperidone.

Introduction

The formation of a carbon−carbon bond by an intramolecular carbolithiation (anionic cyclization) reaction to give a cyclopentane ring system has been gaining increasing use for organic synthesis.[1] Anionic cyclization offers a valuable alternative to the related radical cyclization and indeed can be successful where the radical chemistry fails and can provide enhanced or complementary stereoselectivity. The extension of this chemistry to heterocyclic systems has proven possible using aryl- or vinyllithium species, normally generated by halogen−lithium exchange,[2] or using alkyllithium species generated by tin−lithium exchange[3] or by proton abstraction.[4] This chemistry has provided a convenient route to pyrrolidine, tetrahydrofuran, indoline, pyrrolizidine, and indolizidine ring systems. As a further development in this area, we wished to extend the range of products that can be accessed by such anionic cyclizations by applying this methodology to the preparation of the three types of nitrogen-positional isomers of the azabicyclo[2.2.1]-heptanes. These ring systems are present in a number of natural products and biologically active compounds.[5] The three isomers are shown in Scheme 1, together with one type of disconnection of a derivative (containing a methyl group β- to the nitrogen atom) for each substrate. In all cases, these disconnections allow the use of an α-amino-organolithium species (formed by tin−lithium exchange), followed by anionic cyclization onto an alkene.

Scheme 1



Results and Discussion

7-Azabicyclo[2.2.1]heptanes. Only one type of disconnection, as outlined in Scheme 1, is possible for the preparation of the 7-azabicyclo[2.2.1]heptane ring system using an anionic cyclization with an α-aminoorganolithium species.[6] A pyrrolidine substrate is required, in which the initial 2-lithio species, generated by tin−lithium exchange, is attached to a chiral carbon center. With an allyl group in the 5-position of the pyrrolidine ring, this gives rise to two diastereomeric organolithium species, one with the lithium atom cis to the allyl unit and one trans to it. Anionic cyclization reactions onto unactivated alkenes are thought to proceed by initial coordination of the lithium atom to the alkene π-bond, followed by insertion across the double bond (carbolithiation). Evidence for this comes from calculations,[7] NMR experiments,[8] the enhanced stability of organolithium species containing a suitably positioned π-bond,[9,10] and

(1) For an example, see: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.

(2) (a) Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, F. J. *J. Am. Chem. Soc.* **1998**, *120*, 4865. (b) Nishiyama, H.; Sakata, N.; Sugimoto, H.; Motoyama, Y.; Wakita, H.; Nagase, H. *Synlett* **1998**, 930. (c) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248. (d) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594. (e) Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596.

(3) (a) Coldham, I.; Hufton, R.; Rathmell, R. E. *Tetrahedron Lett.* **1997**, *38*, 7617. (b) Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541. (c) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954. (d) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.

(4) (a) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1764. (b) Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103. (c) Woltering, M. J.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **1998**, 797. (d) Tomooka, K.; Komine, N.; Sasaki, T.; Shimizu, H.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 9715.

(5) Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.

(6) Coldham, I.; Fernàndez, J.-C.; Snowden, D. J. *Tetrahedron Lett.* **1999**, *40*, 1819.

(7) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.

(8) Rölle, T.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1953.

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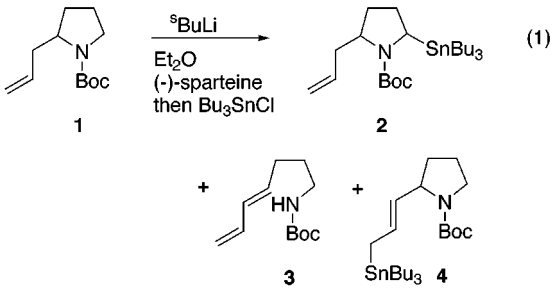
from the known stereoselectivity of the cyclization, which occurs with retention of configuration at the carbanion center.[10,11] It would seem apparent therefore, that only the diastereomer in which the lithium atom and allyl units are cis to one another would be aligned for cyclization. We therefore wished to test the ability of both the cis and the trans diastereomers to undergo cyclization.

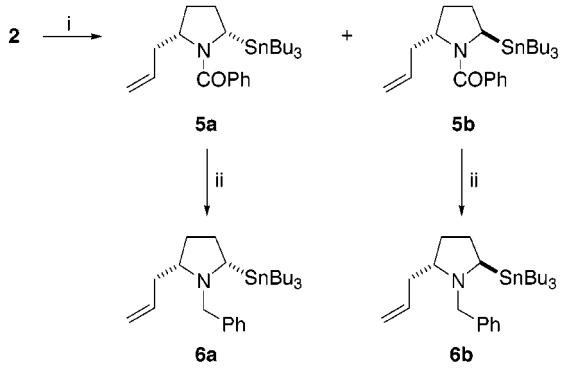
The 2-allylpyrrolidine **1** was prepared from *N*-Boc-pyrrolidine by proton abstraction with 1.2 equiv of *sec*-butyllithium (with TMEDA as external ligand) and trapping with allyl bromide.[12] At this stage, we needed to introduce the tin group on the other side of the nitrogen atom from the allyl group using similar methodology. Proton abstraction of *N*-Boc-2-alkylpyrrolidines with *sec*-butyllithium in Et_2O and TMEDA is a known process.[13] However, under these conditions, *N*-Boc-2-allylpyrrolidine **1** gave only a mixture of the recovered starting material and some of the diene **3**. Deprotonation at C-5 was successful using the ligand (−)-sparteine, rather than TMEDA. Treatment of the pyrrolidine **1** with *sec*-butyllithium and (−)-sparteine in Et_2O at −78 °C for 4 h, followed by addition of Bu_3SnCl and allowing the mixture to warm slowly to room temperature, gave an equal mixture of the two diastereomeric (cis and trans) racemic pyrrolidines **2** in 25% yield (eq 1). There was no asymmetric kinetic resolution in this process, and the recovered starting material **1** (10%) was racemic. Other products isolated from this reaction included the diene **3** (24%) and the stannane **4** (15%). Despite the poor yield of the pyrrolidines **2**, this represented a very short (two step) and convenient route to the desired 2,5-disubstituted pyrrolidine.



(1)

We have reported previously that an anionic cyclization of an *N*-Boc derivative was unsuccessful,[3b] and consistent with this, treatment of the pyrrolidines **2** with *n*-butyllithium gave no identifiable cyclized products. Transmetalation of **2** does occur, to give tetrabutyltin, but the only other products were very polar, indicating loss of the *N*-Boc group. Conversion of the *N*-Boc group to an *N*-alkyl group was carried out using either a one- or a two-step procedure. Addition of 2 equiv of *B*-bromocatecholborane,[14] followed by trapping the resulting N-unsubstituted pyrrolidine with benzoyl chloride, gave a mixture of the diastereomeric amides **5** in 80% yield

Scheme 2[a]

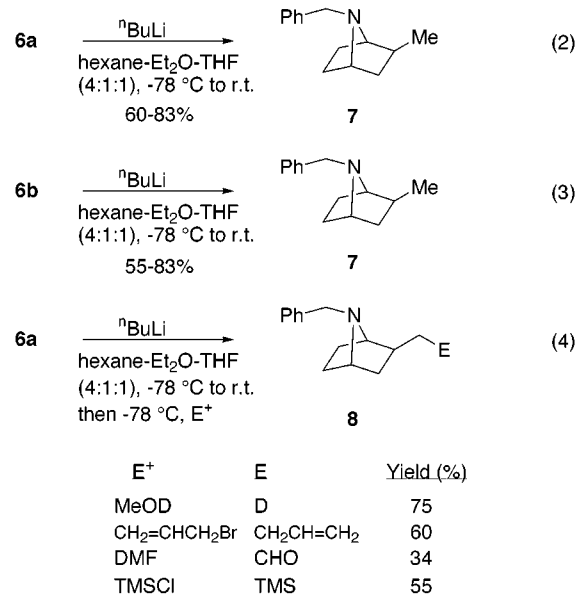


[a] Key: (i) *B*-bromocatechol borane, CH_2Cl_2, then NaOH, PhCOCl; (ii) AlH_3, Et_2O.

(Scheme 2). The amides **5a** and **5b** were separable by chromatography over silica gel. Reduction of each amide using alane[15] gave the *cis*- and *trans*-pyrrolidines **6a** and **6b** (79% and 71% yields, respectively). The stereochemistry of these amines was confirmed by ^1H NMR NOESY studies. Alternatively, the *N*-Boc-pyrrolidines **2** (mixture of cis and trans isomers) could be converted directly to the mixture of diastereomeric *N*-benzylpyrrolidines **6** (45%) using *B*-bromocatecholborane, followed by trapping with benzyl bromide.

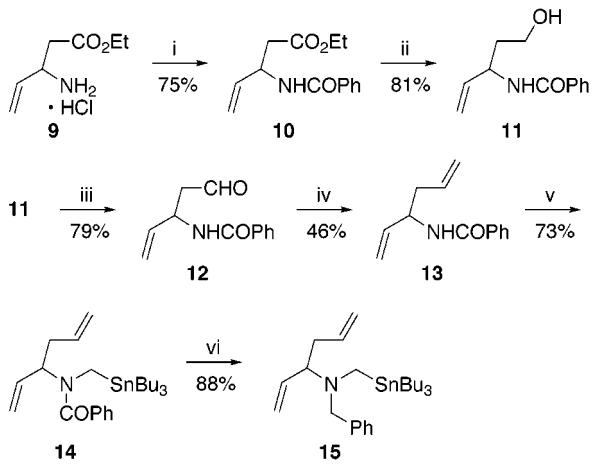
With the separated *N*-benzylpyrrolidines **6** in hand, we were ready to test whether the anionic cyclization would take place from either or both diastereomers. We were pleased to find that, on treatment of the cis isomer **6a** with *n*-butyllithium, the 7-azabicyclo[2.2.1]heptane **7** was formed in good yield and as a single diastereomer (eq 2). The stereochemistry of the product **7** (exo) was assigned by NOESY experiments and by analogy with the preference for a chairlike conformation in the transition state, as observed in other examples.[7,10] The transmetalation was most effective using the mixed solvent system hexanes−Et_2O−THF (4:1:1) with warming from −78 °C to room temperature (essentially no transmetalation takes place below 0 °C). Somewhat surprisingly, the use of THF alone did not promote transmetalation, even at room temperature. Treatment of the corresponding *trans*-pyrrolidine **6b** with *n*-butyllithium also gave the desired *exo*-2-methyl-7-azabicyclo[2.2.1]heptane **7** (eq 3). As tin−lithium exchange is expected to occur with retention of configuration,[16] this result suggests that the organolithium species derived from the trans isomer **6b** epimerizes[17] to the cis isomer before cyclization. Alternative explanations include an anionic cyclization with inversion of configuration at the organolithium center (although anionic cyclizations have been shown to proceed with retention of configuration[10]) or the formation of an ion pair, with cyclization from the carbanion.[18] The ability to form the same 7-azabicyclo[2.2.1]heptane ring from either diastereomer of the starting stannane is particularly noteworthy.

(9) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817.
(10) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322.
(11) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939.
(12) Beak, P.; Lee W. K. *J. Org. Chem.* **1993**, *58*, 1109.
(13) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(14) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.
(15) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Org. Chem.* **1996**, *61*, 7627.
(16) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. (c) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (d) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522.
(17) Amano, S.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1998**, 409.
(18) Hoffmann, R. W.; Koberstein, R.; Harms, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 183.



E^+	E	Yield (%)
MeOD	D	75
CH_2=$CHCH_2Br$	CH_2CH=CH_2	60
DMF	CHO	34
TMSCl	TMS	55

Scheme 3[a]



[a] Key: (i) PhCOCl, Et_3N, Et_2O; (ii) $LiAlH_4$, THF, 0 °C; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N; (iv) Ph_3PMeBr, ^tBuOK, THF; (v) NaH, ICH_2SnBu_3, THF, rt, 3 d; (vi) AlH_3, Et_2O, −78 °C to rt.

After anionic cyclization, it is possible to add an electrophile to the resulting organolithium species in order to prepare a variety of substituted cyclic amine products.[3b,6] The addition of electrophiles was investigated with the 7-azabicyclo[2.2.1]heptanes to give the 2-substituted products **8** (eq 4). The yields of the substituted products are modest to good, and care must be taken to purify the electrophile in order to avoid the formation of the protonated 2-methyl product **7**. This methodology therefore allows a rapid access to 2-substituted 7-azabicyclo[2.2.1]heptane derivatives with complete stereochemical control in favor of the exo diastereomer.

2-Azabicyclo[2.2.1]heptanes. There are two obvious disconnections to the 2-azabicyclo[2.2.1]heptane ring system that allow the use of an α-aminoorganolithium species (formed by tin−lithium exchange), followed by anionic cyclization onto an alkene. The first disconnection (shown in Scheme 1) was chosen in order to investigate the possibility of carrying out a cascade/tandem cyclization. Our previous work had demonstrated that it is possible to prepare 2,4-disubstituted pyrrolidines as predominantly (≥6:1) the cis isomer.[3a] We expected therefore that anionic cyclization of a 2-vinyl derivative would generate a *cis*-2-vinyl-4-lithiomethylpyrrolidine in which a second in situ cyclization would be possible. This procedure would provide a method for the preparation of a bicyclic product from an acyclic precursor with the formation of two carbon−carbon bonds in a single operation. If the organolithium species formed after the second cyclization could be trapped with carbon-based electrophiles, then three carbon−carbon bonds could be formed in one step.

The route to the substrate needed to test the cascade cyclization is shown in Scheme 3. The known *β*-amino ester **9** was prepared in two steps from butadiene, according to the literature.[19] N-Benzoylation gave the ester **10**, which was reduced to the alcohol **11** and oxidized under Swern conditions[20] to give the aldehyde **12**. Wittig olefination using Ph_3PMeBr and KO^tBu in THF gave the diene **13**. This substrate is a carboxylic amide rather than a secondary amine, so the alkylation on the nitrogen atom is best performed using sodium hydride and iodomethyltributyltin[21] (rather than the corresponding mesylate,[21b] used for the formation of amines). Reduction of the amide **14** with alane[15] gave access to the desired substrate **15**.

Transmetalation of the stannane **15** with *n*-butyllithium in hexanes−Et_2O (9:1) was very sluggish, and the substrate **15** was recovered in this nonpolar solvent mixture. Addition of THF allowed efficient transmetalation of the stannane **15** to the organolithium species, although no cyclization occurred at −78 °C. Warming to room temperature did, however, effect cyclization (eq 5). Two major products, the desired bicyclic amine **16** (22%) and the pyrrolidine **17** (32%), were isolated using these reaction conditions. The product **17** arises from monocyclization of the organolithium species to give the new organolithium species **18**. Protonation of this organolithium species could occur on quenching the reaction; however, extended reaction times did not enhance the yield of the bicyclic product **16**. Variation of the conditions (including the use of TMEDA) did not improve this result, and it appears that, although monocyclization to the pyrrolidine ring occurs easily, the second cyclization is slow. The mixture must be warmed to room temperature to effect the transmetalation−cyclization, and at this temperature organolithium species are known to abstract a proton from THF.[22] This proton abstraction seems to compete with the second cyclization, thereby diminishing the yield of the 2-azabicyclo[2.2.1]heptane product **16**. The product **16** was formed as a single stereoisomer with endo stereochemistry, as verified by ^{1}NMR NOESY studies (see Supporting Information) and is consistent

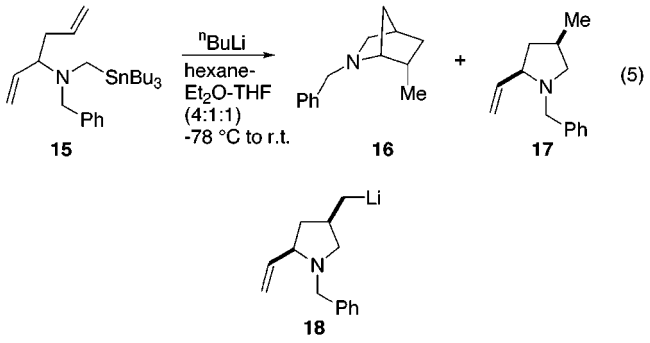
(19) Zablocki, J. A.; Rico, J. G.; Garland, R. B.; Rogers, T. E.; Williams, K.; Schretzman, L. A.; Rao, S. A.; Bovy, P. R.; Tjoeng, F. S.; Lindmark, R. J.; Toth, M. V.; Zupec, M. E.; McMacins, D. E.; Adams, S. P.; Markos, M. M. C. S.; Milton, M. N.; Paulson, S.; Herin, M.; Jacqmin, P.; Nicholson, N. S.; Panzer-Knodle, S. G.; Haas, N. F.; Page, J. D.; Szalony, J. A.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Faigen, L. P. *J. Med. Chem.* **1993**, *38*, 2378.

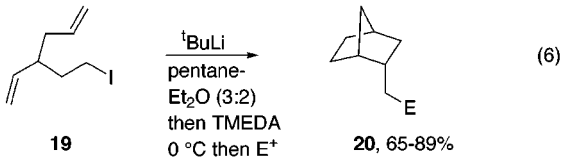
(20) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(21) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151. (b) Seitz, D. E.; Carroll, J. J.; Cartaya, C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129. (c) Ahman, J.; Somfai, P. *Synth. Commun.* **1994**, *24*, 1117.

(22) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791.

with cyclization in a chairlike conformation. On the basis of previous studies on the anionic cyclization to give 2,4-disubstituted pyrrolidine products,[3a] the product **17** was assigned cis stereochemistry. The organolithium species **18** generated by monocyclization would therefore be of the required stereochemistry to effect the second cascade/tandem cyclization to give the 2-azabicyclo[2.2.1]heptane product **16**.



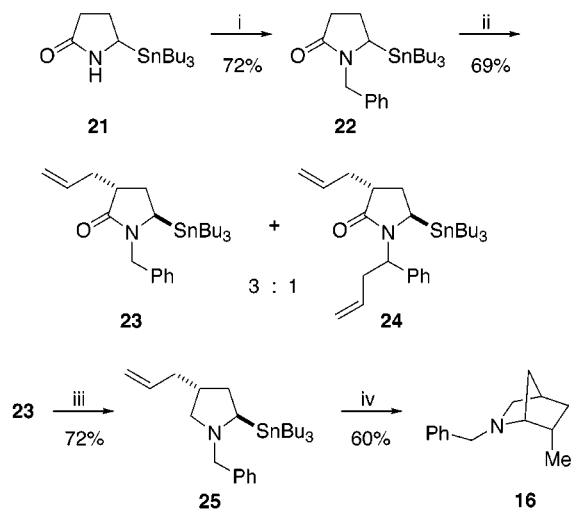


The related carbocyclic version of this cyclization has been reported by Bailey (eq 6).[23] Treatment of the iodide **19** with 2.2 equivalents of *tert*-butyllithium and TMEDA at 0 °C for 4 min resulted in the formation, after the addition of one of various electrophiles, of the bicyclo-[2.2.1]heptanes **20** in high yield. Some monocyclized product (~10%) as the trans isomer was formed, but no *cis*-1-ethenyl-3-methylcyclopentane was detected. It would appear, therefore, that a nitrogen atom within our substrate slows the intramolecular carbolithiation reaction, possibly by coordination of the nitrogen lone pair with the lithium atom. While monocyclization from an α-aminoorganolithium species is high yielding, a second cascade-type cyclization from a γ-aminoorganolithium species is slow.

After the poor yield achieved in the preparation of the 2-azabicyclo[2.2.1]heptane ring system by the cascade/tandem cyclization route, we studied an alternative route using a second obvious disconnection. To carry out this new synthetic approach, we needed to prepare the stannane **21** (Scheme 4). This compound has been reported;[24] however, in our hands the final displacement of the benzotriazole group for the tributyltin group using Bu_3SnH and LDA was very low yielding. We were pleased to find, however, that the use of Bu_3SnLi generated from Bu_6Sn_2 and BuLi gave satisfactory yields (up to 75%) of the stannane **21**.

N-Benzylation of the stannane **21** gave the stannane **22** (72%). Enolization of **22** followed by allylation gave the stannane **23** (51%) exclusively as the trans isomer (by ^{1}NMR NOESY studies). A small amount of the easily separable diallylated compound **24** (18%) was also produced, in which a second allylation had occurred at the benzylic position. Using LDA in the absence of HMPA

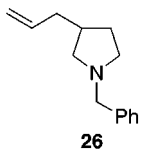
Scheme 4[a]



[a] Key: (i) NaH, DMF, $PhCH_2Br$; (ii) LDA, THF/HMPA, $CH_2{=}CHCH_2Br$; (iii) AlH_3, Et_2O, 0 °C; (iv) ^{n}BuLi, hexane−Et_2O (4:1), −78 °C to rt, 16 h, then MeOH.

resulted in lower yields of the stannane **23**. Reduction of **23** with alane gave the required pyrrolidine **25** (72%).

Tin−lithium exchange and anionic cyclization are known to occur with retention of configuration at the metal-bearing carbon center,[10] so it may be anticipated that the trans substrate **25** would be unsuitable for cyclization. However, epimerization of organolithium species is possible, and this would account for the successful cyclization using the substrate *trans*-**6b**. Such epimerization would generate the cis isomer, thereby allowing Li−π complexation and subsequent cyclization. We were pleased to find that treatment of the stannane **25** with *n*-butyllithium in hexanes−Et_2O (4:1) gave the desired 2-azabicyclo[2.2.1]heptane product **16** in reasonable yield (60%). Conducting the transmetalation−cyclization in the presence of THF gave a mixture of products predominantly (by NMR spectroscopy) with the allyl unit intact and only a trace of the desired bicyclic amine **16**. Some of the protodestannylated pyrrolidine **26** (16%) was also isolated. The reaction mixture must be warmed to room temperature to complete transmetalation−cyclization, and this result suggests that epimerization of the intermediate organolithium species can take place, thereby generating the isomer with the lithium and allyl units cis to one another, as required for cyclization.



To our surprise, the only isomer isolated from the anionic cyclization of the substrate **25** was the endo product **16** and it was not possible to observe (by NMR spectroscopy) any exo isomer. We had anticipated that the anionic cyclization from the substrate **25** would generate the exo isomer, based on a chair-shaped transition state (Figure 1). Anionic cyclization from the substrates **15** and **19** give the expected *endo*-bicyclo[2.2.1]-

(23) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053.
(24) Pearson, W. H.; Stevens E. P. *J. Org. Chem.* **1998**, *63*, 9812.

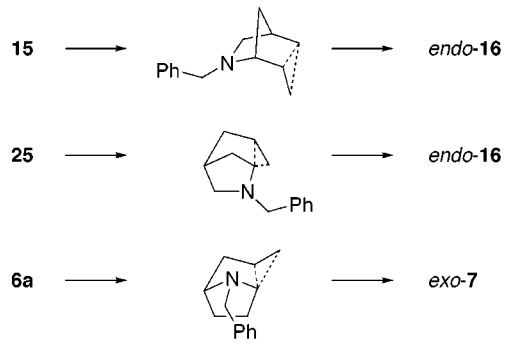
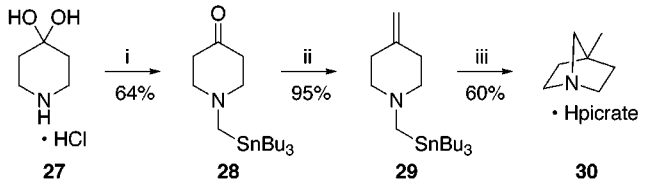


Figure 1.

heptane ring system, based on a chair-shaped transition state. The product resulting from the anionic cyclization of the stannane **25** was identical in every respect to that from the stannane **15**. It appears, therefore, that cyclization from the stannane **25** favors a boat-shaped transition state (Figure 1). A possible explanation for this lies in the expected coordination of the lithium atom to the nitrogen lone pair.[25] It is constructive to consider the difference between the two isomeric organolithium species generated from the stannanes **25** and **6a**. These two organolithium species differ only in the position of the nitrogen atom in the five-membered ring. In both cases, the observed product is that in which the transition state has the alkene π-bond aligned on the same side as the nitrogen atom. This backs up the evidence for lithium$-\pi$ complexation[7−11] *combined* with coordination of the lithium atom with the lone pair of the nitrogen atom.[25,26] The transition state from the stannane **6a** would favor the normal chair shape, as this places the alkene unit closer to the lithium atom coordinated to the nitrogen lone pair, whereas the boat-shape transition state is favored from the stannane **25**. Semiempirical molecular orbital calculations (MOPAC version 6.0, AM1 Hamiltonian) support this postulate (in the gas phase), as the lowest energy conformations of the organolithium species generated from *cis*-**25** and **6a** resemble those shown in Figure 1, with relatively short Li$-\pi$ (2.42 Å) and Li−N (2.39 or 2.87 Å respectively) distances.

1-Azabicyclo[2.2.1]heptanes. Of the three types of azabicyclo[2.2.1]heptanes, the 1-aza ring system proved easiest to access. Treatment of the commercially available hydrochloride salt of 4-piperidone monohydrate **27** with the alkylating agent *O*-methanesulfonyl tributylstannylmethanol ($MeSO_2OCH_2SnBu_3$)[21b] in MeCN and K_2CO_3 gave the ketone **28** (Scheme 5). Wittig olefination gave the substrate **29**. Tin−lithium exchange with *n*-butyllithium (2 equiv) in hexanes−Et_2O (9:1) at −78 °C, followed by addition of TMEDA (2 equiv) and warming to room temperature for 4 h, gave after quenching with methanol and isolation as the picrate salt 4-methyl-1-azabicyclo[2.2.1]heptane **30** (60%). This represents a short and efficient route to this bridged bicyclic amine. Transmetalation was successful in the absence of TMEDA, but no cyclized products were observed under these conditions. This is in contrast to the related carbocyclic

Scheme 5[a]



[a] Key: (i) $MsOCH_2SnBu_3$, MeCN, K_2CO_3, rt, 4 d; (ii) Ph_3PMeBr, ^{n}BuLi, THF, rt, 12 h; (iii) 2 equiv, ^{n}BuLi, hexane-Et_2O (9:1) then 2 equiv of TMEDA, −78 °C to rt, 4 h, then −78 °C MeOH, then picric acid.

analogue, which cyclizes within 1 h at room temperature, but within 11 min in the presence of TMEDA.[27] It appears therefore that the nitrogen atom slows the rate of cyclization, presumably by coordination to the lithium atom. Successful cyclization to the 1-azabicyclo[2.2.1]-heptane ring system requires a transition state with boat-shaped conformation for the six-membered ring.

Conclusion

Anionic cyclizations are a convenient method to access complex cyclic amine products with excellent stereoselectivity. All three nitrogen-positional isomers of the azabicyclo[2.2.1]heptane ring system can be prepared using this methodology. We are currently extending this chemistry to prepare other bicyclic amine products, with cyclizations onto alkene or carbonyl electrophiles[28] and their application to the synthesis of biologically active targets.

Experimental Section

(2*RS*,5*RS*)- and (2*RS*,5*SR*)-1-(*tert*-Butoxycarbonyl)-2-prop-2′-enyl-5-(tri-*n*-butylstannyl)pyrrolidine (2). *sec*-Butyllithium (1.3 M in cyclohexane, 8.5 mL, 11.1 mmol) was added to (−)-sparteine (2.6 g, 11.1 mmol) in dry Et_2O (40 mL) under argon at −78 °C. The mixture was allowed to stir for 2 h at −78 °C and was added to the pyrrolidine **1**[12] (2.0 g, 9.3 mmol) in Et_2O (80 mL) under argon at −78 °C. After 4 h at −78 °C, tri-*n*-butyltin chloride (4.7 mL, 16.9 mmol) was added. The mixture was allowed to warm to 25 °C for 12 h. Water was added, and the mixture was extracted with Et_2O. The combined extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel, eluting with light petroleum−EtOAc (95:5) to give the stannane **2** (1.2 g, 25%) as an oil: ratio of diastereomers 50:50 [determined by ^{1}H and ^{13}C NMR spectroscopy]; ν_{max} (film)/cm^{-1} 1675, 1640; δ_H (400 MHz, $CDCl_3$) 5.75 (1H, ddt, J = 17, 8, 7 Hz), 5.05 (1H, dd, J = 17, 2 Hz), 5.00 (1H, dd, J = 8, 2 Hz), 3.82−3.66 (1H, m), 3.37 (0.5H, dd, J = 8, 6 Hz), 3.25 (0.5H, dd, J = 9, 7 Hz), 2.53−2.37 (1H, m), 2.24−1.65 (5H, m), 1.63−1.37 (15H, m), 1.37−1.21 (6H, m), 1.00−0.68 (15H, m); δ_C (75 MHz, $CDCl_3$) 9.77 and 10.28, 13.68, 27.47, 27.85, 28.39, 28.54, 31.36, 39.12 and 39.26, 47.31 and 47.48, 57.05 and 57.34, 78.50 and 78.60, 116.57 and 116.77, 135.36 and 135.84, 154.02 (found M^+, 501.2640, $C_{24}H_{47}NO_2{}^{120}Sn$ requires M 501.2631) and the diene **3** (up to 24%) as an oil and the stannane **4** (up to 15%) as an oil (see the Supporting Information for spectroscopic data).

(2*RS*,5*SR*)- and (2*RS*,5*RS*)-1-Benzoyl-2-prop-2′-enyl-5-(tri-*n*-butylstannyl)pyrrolidine (5). *B*-Bromocatechol borane[14] (464 mg, 2.32 mmol) in CH_2Cl_2 (5.8 mL) was added dropwise to the carbamate **2** (604 mg, 1.16 mmol) in CH_2Cl_2 (10 mL) at room temperature under argon. After 5 min, benzoyl chloride (0.27 mL, 2.32 mmol) was added. After 4 h,

(25) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887.

(26) The 1-azabicyclo[2.2.1]heptane product **30** could not arise from combined lithium-π and lithium-n_N coordination, although this product is formed only in the presence of TMEDA, which may affect the extent of such coordination.

(27) Bailey, W. F.; Khanolkar, A. D. *Organometallics*, **1993**, *12*, 239.

(28) Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R. E.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621.

the mixture was extracted with aqueous NaOH. The organic phase was dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel, eluting with light petroleum−EtOAc (95:5) to give the amides *cis*-**5a** (220 mg, 38%) as an oil [ν_{max} (film)/cm^{-1} 1640, 1600, 1575; δ_H (300 MHz, $CDCl_3$) 7.45−7.26 (5H, m), 5.37 (1H, ddt, J = 17, 10, 7 Hz), 4.90 (1H, d, J = 10 Hz), 4.77 (1H, d, J = 17 Hz), 3.97−3.96 (1H, br m), 3.52 (1H, dd, J = 10, 7 Hz), 2.24−1.79 (6H, m), 1.68−1.45 (6H, m), 1.45−1.24 (6H, m), 1.05−0.79 (15H, m); δ_C (75 MHz, $CDCl_3$) 10.25, 13.73, 27.04, 27.64, 29.25, 31.37, 39.05, 47.54, 58.78, 117.43, 126.44, 128.31, 128.98, 134.37, 137.98, 168.19 (found M$^+$, 505.2370, $C_{26}H_{43}NO^{120}Sn$ requires M 505.2367)] and *trans*-**5b** (244 mg, 42%) as an oil: ν_{max} (film)/cm^{-1} 1640, 1610, 1575; δ_H (300 MHz, $CDCl_3$) 7.47−7.29 (5H, m), 5.42 (1H, ddt, J = 17, 10, 7 Hz), 4.91 (1H, dd, J = 10, 1 Hz), 4.79 (1H, dd, J = 17, 1 Hz), 4.00−3.89 (1H, br m), 3.61 (1H, dd, J = 8.5, 4.5 Hz), 2.39−2.21 (1H, m), 2.04−1.79 (5H, m), 1.65−1.45 (6H, m), 1.45−1.18 (6H, m), 1.05−0.84 (15H, m); δ_C (75 MHz, $CDCl_3$) 10.55, 13.71, 26.70, 27.61, 29.22, 31.04, 38.81, 47.17, 58.95, 117.73, 126.65, 128.36, 129.22, 133.87, 137.63, 168.36 (found M$^+$ 505.2370, $C_{26}H_{43}NO^{120}Sn$ requires M 505.2367).

(2*RS*,5*RS*)-1-Benzyl-2-prop-2′-enyl-5-(tri-*n*-butylstannyl)-pyrrolidine (6a). Aluminum chloride (65 mg, 0.49 mmol) and lithium aluminum hydride (56 mg, 1.47 mmol) in Et_2O (5 mL) were stirred at 0 °C for 15 min, and then amide **5a** (243 mg, 0.5 mmol) in Et_2O (5 mL) was added dropwise. After 2 h, MeOH (1 mL) was added, the solvent was evaporated, and the mixture was purified by column chromatography on silica, eluting with light petroleum−EtOAc (95:5) to give the amine **6a** (190 mg, 80%) as an oil: ν_{max} (film)/cm^{-1} 1635, 1605, 1490; δ_H (300 MHz, $CDCl_3$) 7.29−7.05 (5H, m), 5.81 (1H, ddt, J = 17, 10, 7 Hz), 5.03 (1H, dd, J = 10, 2 Hz), 4.97 (1H, dd, J = 17, 2 Hz), 3.99 (1H, d, J = 14 Hz), 3.56 (1H, d, J = 14 Hz), 2.80 (1H, t, J = 9 Hz), 2.60 (1H, ddt, J = 8, 5, 3.5 Hz), 2.16−2.06 (1H, m), 2.03−1.88 (3H, m), 1.88−1.55 (8H, m), 1.55−1.34 (6H, m), 1.16−0.95 (15H, m); δ_C (75 MHz, $CDCl_3$) 9.35, 14.02, 28.07, 29.70, 29.90, 32.14, 41.07, 58.34, 60.46, 64.91, 115.98, 127.27, 128.46, 129.36, 136.94, 140.67 (found M$^+$ 491.2568, $C_{26}H_{45}N^{120}Sn$ requires M 491.2574).

(2*RS*,5*SR*)-1-Benzyl-2-prop-2′-enyl-5-(tri-*n*-butylstannyl)-pyrrolidine (6b). In the same way as **6a**, aluminum chloride (45 mg, 0.3 mmol), lithium aluminum hydride (38 mg, 1.0 mmol), and the amide **5b** (168 mg, 0.3 mmol) gave the amine **6b** (105 mg, 71%) as an oil: ν_{max} (film)/cm^{-1} 1640, 1495; δ_H (300 MHz, $CDCl_3$) 7.26−7.05 (5H, m), 5.80 (1H, ddt, J = 16, 11, 7 Hz), 5.08 (1H, dd, J = 16, 2 Hz), 5.02 (1H, dd, J = 11, 2 Hz), 4.06 (1H, d, J = 14 Hz), 3.54 (1H, dd, J = 9.5, 1.5 Hz), 3.33 (1H, d, J = 14 Hz), 2.76−2.61 (1H, m), 2.39−2.11 (3H, m), 2.00−1.89 (2H, m), 1.82−1.68 (1H, m), 1.68−1.53 (6H, m), 1.53−1.34 (6H, m), 1.11−0.95 (15H, m); δ_C (75 MHz, $CDCl_3$) 11.00, 13.97, 28.10, 28.90, 30.01, 30.60, 37.82, 57.85, 58.01, 62.26, 116.42, 127.06, 128.40, 128.57, 136.50, 140.81 (found M$^+$ 491.2568, $C_{26}H_{45}N^{120}Sn$ requires M 491.2574).

(1*RS*,2*SR*,4*SR*)-7-Benzyl-2-methyl-7-azabicyclo[2.2.1]-heptane (7). *n*-Butyllithium (2.5 M in hexanes, 0.18 mL, 0.45 mmol) was added to the amine **6a** (42 mg, 0.09 mmol) in dry hexanes−Et_2O−THF (4:1:1) (1 mL) under argon at −78 °C. The mixture was stirred for 30 min and was allowed to warm slowly to 25 °C for 9 h. The mixture was quenched with MeOH (0.2 mL) at −78 °C and was allowed to warm to room temperature for 30 min. The solvent was evaporated, and the mixture was purified by column chromatography on alumina, eluting with light petroleum−EtOAc (50:1 then 9:1) to give the amine **7** (15 mg, 83%) as an oil: ν_{max} ($CHCl_3$)/cm^{-1} 1605, 1490; δ_H (400 MHz, $CDCl_3$) 7.44−7.24 (5H, m), 3.63 (1H, d, J = 14 Hz), 3.49 (1H, d, J = 14 Hz), 3.28−3.23 (1H, br m), 2.85−2.82 (1H, br m), 1.90−1.83 (2H, m), 1.64−1.55 (1H, m), 1.49 (1H, dd, J = 11, 8.5 Hz), 1.35−1.28 (2H, m), 1.28−1.20 (1H, m), 1.03 (3H, d, J = 7 Hz); δ_C (100 MHz, $CDCl_3$) 21.57, 26.07, 26.50, 37.58, 40.05, 51.62, 60.06, 64.75, 126.46, 128.06, 128.23, 140.97 (found M$^+$ 201.1510, $C_{14}H_{19}N$ requires M 201.1517).

In the same way, *n*-butyllithium (2.5 M in hexanes; 0.42 mL, 0.17 mmol) and the amine **6b** (102 mg, 0.21 mmol) in dry hexanes−Et_2O−THF (4:1:1) (3 mL) gave the amine **7** (35 mg, 83%) as an oil, data as above.

(1*RS*,2*SR*,4*SR*)-7-Benzyl-2-deuteriomethyl-7-azabicyclo-[2.2.1]heptane (8, E = D). In the same way as the amine **7**, *n*-butyllithium (2.5 M in hexanes, 0.3 mL, 0.82 mmol) and the amine **6a** (100 mg, 0.20 mmol) gave, after quenching with CD_3-OD (0.1 mL), the amine **8**, E = D (30 mg, 75%), as an oil: ν_{max} ($CHCl_3$)/cm^{-1} 1495; δ_H (400 MHz, $CDCl_3$) 7.42−7.22 (5H, m), 3.61 (1H, d, J = 14 Hz), 3.48 (1H, d, J = 14 Hz), 3.26−3.23 (1H, m), 2.83−2.80 (1H, m), 1.86−1.83 (2H, m), 1.62−1.59 (1H, m), 1.47 (1H, dd, J = 11, 8 Hz), 1.31−1.27 (2H, m), 1.27−1.24 (1H, m), 1.00−0.98 (2H, m); δ_C (100 MHz, $CDCl_3$) 21.06, 21.25, 21.44, 26.06, 26.48, 37.49, 40.00, 51.60, 60.03, 64.71, 126.43, 128.03, 128.20, 140.99 (found M$^+$ 202.1578, $C_{14}H_{18}DN$ requires M 202.1580).

(1*RS*,2*SR*,4*SR*)-7-Benzyl-2-but-3′-enyl-7-azabicyclo[2.2.1]-heptane (8, E = Allyl). In the same way as the amine **8**, E = D, *n*-butyllithium (2.5 M in hexanes, 0.4 mL, 1.05 mmol), the amine **6a** (129 mg, 0.26 mmol), and allyl bromide (0.09 mL, 1.05 mmol, distilled over CaH_2) gave the amine **8**, E = allyl (36 mg, 60%), as an oil: ν_{max} ($CHCl_3$)/cm^{-1} 1495; δ_H (400 MHz, $CDCl_3$) 7.41−7.23 (5H, m), 5.82−5.78 (1H, m), 5.01−4.92 (2H, m), 3.59 (1H, d, J = 14 Hz), 3.48 (1H, d, J = 14 Hz), 3.26−3.22 (1H, m), 2.97−2.94 (1H, m), 2.00−1.89 (2H, m), 1.88−1.84 (2H, m), 1.61−1.58 (1H, m), 1.47−1.43 (3H, m), 1.33−1.27 (3H, m); δ_C (100 MHz, $CDCl_3$) 26.21, 26.62, 31.97, 35.12, 38.26, 42.94, 51.59, 59.64, 63.01, 114.08, 126.48, 128.07, 128.16, 139.26, 141.00 (found M$^+$ 241.1832, $C_{17}H_{23}N$ requires M 241.1830).

(1*RS*,2*RS*,4*SR*)-7-Benzyl-7-azabicyclo[2.2.1]heptan-2-ylacetaldehyde (8, E = CHO). In the same way as the amine **8**, E = D, *n*-butyllithium (2.5 M in hexanes, 0.4 mL, 0.92 mmol), the amine **6a** (115 mg, 0.20 mmol), and DMF (0.07 mL, 0.92 mmol, distilled over CaH_2) gave the amine **8**, E = CHO (18 mg, 34%) as an oil: ν_{max} ($CHCl_3$)/cm^{-1} 1720, 1495; δ_H (400 MHz, $CDCl_3$) 9.71 (1H, s), 7.35−7.22 (5H, m), 3.53 (1H, d, J = 13 Hz), 3.47 (1H, d, J = 13 Hz), 3.25−3.24 (1H, m), 2.95−2.94 (1H, m), 2.57−2.50 (2H, m), 1.99−1.87 (2H, m), 1.57−1.24 (5H, m); δ_C (100 MHz, $CDCl_3$) 26.04, 26.19, 37.52, 37.80, 50.4, 51.53, 59.42, 63.34, 126.70, 128.14, 128.32, 143.94, 202.62 (found M$^+$ 229.1466, $C_{15}H_{19}NO$ requires M 229.1466).

(1*RS*,2*SR*,4*SR*)-7-Benzyl-2-trimethylsilylmethyl-7-azabicyclo[2.2.1]heptane (8, E = TMS). In the same way as the amine **8**, E = D, *n*-butyllithium (2.5 M in hexanes, 0.3 mL, 0.82 mmol), the amine **6a** (100 mg, 0.20 mmol) and TMSCl (0.06 mL, 0.82 mmol, distilled over CaH_2) gave the amine **8**, E = TMS (30 mg, 55%) as an oil: ν_{max} ($CHCl_3$)/cm^{-1} 1495; δ_H (400 MHz, $CDCl_3$) 7.41−7.23 (5H, m), 3.64 (1H, d, J = 14 Hz), 3.47 (1H, d, J = 14 Hz), 3.26−3.23 (1H, m), 2.84−2.81 (1H, m), 1.85−1.82 (2H, m), 1.60−1.55 (1H, m), 1.51 (1H, dd, J = 11, 8 Hz), 1.30−1.27 (3H, m), 0.80−0.78 (2H, m), −0.30 (9H, s); δ_C (100 MHz, $CDCl_3$) −0.72, 24.89, 26.00, 26.58, 39.36, 41.56, 51.69, 60.14, 66.14, 126.45, 128.04, 128.23, 140.88 (found M$^+$ 273.1913, $C_{17}H_{27}NSi$ requires M 273.1913).

Ethyl 3-(*N*-Benzoylamino)pent-4-enoate (10). Benzoyl chloride (9.9 g, 70 mmol) was added to a mixture of triethylamine (11.8 g, 117 mmol) and the hydrochloride salt of the ester **9**[19] (10.5 g, 58 mmol) in Et_2O (100 mL) at 0 °C. After 18 h, water (100 mL) was added, and the mixture was extracted with Et_2O. The combined Et_2O extracts were washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with light petroleum−EtOAc (4:1) to give the ester **10** (10.87 g, 75%) as an oil: ν_{max} (film)/cm^{-1} 3315, 1735, 1640, 1535; δ_H(400 MHz, $CDCl_3$) 7.79−7.34 (5H, m), 5.89 (1H, ddd, J = 17, 10, 5 Hz), 5.23 (1H, dd, J = 17, 1 Hz), 5.13 (1H, dd, J = 10, 1 Hz), 5.08−5.00 (1H, m), 4.11 (2H, q, J = 7 Hz), 2.69 (2H, d, J = 5 Hz), 1.21 (3H, t, J = 7 Hz); δ_C (100 MHz, $CDCl_3$) 14.2, 38.3, 48.0, 60.9, 116.0, 127.0, 128.6, 131.5, 134.3, 136.5, 166.5, 171.8 (found M$^+$ 247.1213, $C_{14}H_{17}NO_3$ requires M 247.1208).

3-(*N*-Benzoylamino)pent-4-en-1-ol (11). The ester **10** (3.37 g, 13.6 mmol) in THF (20 mL) was added to a suspension of lithium aluminum hydride (517 mg, 13.6 mmol) in THF (50 mL) at 0 °C. After 15 min at room temperature, water was added at 0 °C until the precipitated inorganic salts became granular. The mixture was filtered through Celite and washed

with THF, evaporated, and purified by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH (95:5) to give the alcohol **11** as an oil (2.26 g, 81%): ν_{max} (film)/cm^{-1} 3295, 1635, 1525; δ_H (400 MHz, $CDCl_3$) 7.81−7.43 (5H, m), 6.55−6.45 (1H, m), 5.94 (1H, ddd, J = 17, 10, 2 Hz), 5.30 (1H, dd, J = 17, 2 Hz), 5.23 (1H, dd, J = 10, 2 Hz), 4.95−4.85 (1H, m), 3.77−3.71 (2H, m), 3.18 (1H, br s), 2.09−2.04 (1H, m), 1.66−1.60 (1H, m); δ_C (100 MHz, $CDCl_3$) 37.31, 48.87, 58.85, 115.54, 126.95, 128.67, 131.75, 134.03, 137.79, 167.85 (found M$^+$ 205.1100, $C_{12}H_{15}NO_2$ requires M 205.1103).

3-(*N*-Benzoylamino)pent-4-enal (12). Dimethyl sulfoxide (1.07 g, 13.7 mmol) in CH_2Cl_2 (3.2 mL) was added to oxalyl chloride (0.87 g, 6.8 mmol) in CH_2Cl_2 (16 mL) at −50 °C. After 2 min, the alcohol **11** (1.28 g, 6.2 mmol) in CH_2Cl_2 (3 mL) was added. After 15 min, Et_3N (3.1 g, 31 mmol) was added, and the mixture was allowed to warm to room temperature. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with aqueous HCl, saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with CH_2Cl_2−MeOH (95:5) to give the aldehyde **12** (997 mg, 79%) as an oil: ν_{max} (film)/cm^{-1} 3315, 1725, 1635, 1540; δ_H (400 MHz, $CDCl_3$) 9.85 (1H, s), 7.78−7.41 (5H, m), 6.70−6.60 (1H, m), 5.98 (1H, ddd, J = 18, 10, 2 Hz), 5.28 (1H, dd, J = 18, 2 Hz), 5.22 (1H, dd, J = 10, 2 Hz), 5.15−5.06 (1H, m), 2.93−2.90 (2H, m); δ_C (100 MHz, $CDCl_3$) 47.41, 47.70, 116.41, 126.93, 128.62, 131.70, 134.10, 136.51, 166.73, 200.66 (found M$^+$ 203.0944, $C_{12}H_{13}NO_2$ requires M 203.0946).

3-(*N*-Benzoylamino)hexa-1,5-diene (13). Methyltriphenylphosphonium bromide (0.97 g, 2.73 mmol) was added to potassium *tert*-butoxide (0.26 g, 2.37 mmol) in THF (5 mL) under nitrogen at 0 °C. The yellow suspension was stirred for 30 min at room temperature prior to the addition of the aldehyde **12** (370 mg, 1.82 mmol) in THF (5 mL). After 18 h, saturated $NH_4Cl_{(aq)}$ was added, and the mixture was extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with light petroleum−EtOAc (4:1) to give the diene **13** (167 mg, 46%) as needles: mp 49−51 °C; ν_{max} (film)/cm^{-1} 3310, 1635, 1545; δ_H (400 MHz, $CDCl_3$) 7.78−7.41 (5H, m), 6.20−6.05 (1H, m), 5.95−5.78 (2H, m), 5.27−5.13 (4H, m), 4.85−4.75 (1H, m), 2.52−2.39 (2H, m); δ_C (100 MHz, $CDCl_3$) 39.06, 50.56, 115.17, 118.48, 126.84, 128.57, 131.44, 133.78, 134.70, 137.64, 166.73 (found M$^+$ 201.1156, $C_{13}H_{15}NO$ requires M 201.1154). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.57; H, 7.52; N, 6.96. Found: C, 77.19; H, 7.42; N, 6.79.

3-[*N*-Benzoyl-*N*-(tributylstannylmethyl)amino]hexa-1,5-diene 14. Sodium hydride (0.16 g, 3.9 mmol, 60% dispersion in mineral oil) was added to the amide **13** (0.26 g, 1.3 mmol) in THF (5 mL) under nitrogen at room temperature. After 2 h, iodomethyltributyltin (0.83 g, 1.9 mmol) was added. After 70 h, water was added, and the mixture was extracted into CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with light petroleum−EtOAc (99:1) to give the stannane **14** (478 mg, 73%) as an oil: ν_{max} (film)/cm^{-1} 1640, 1635, 1545; δ_H (400 MHz, $CDCl_3$) 7.38−7.31 (5H, m), 5.85−5.75 (1H, m), 5.60−5.50 (1H, m), 5.26−5.04 (4H, m), 4.38−4.32 (1H, m), 2.72−2.63 (2H, m), 2.50−2.40 (1H, m), 2.35−2.25 (1H, m), 1.60−1.45 (6H, m), 1.35−1.29 (6H, m), 0.95−0.88 (15H, m); δ_C (100 MHz, $CDCl_3$) 11.04, 13.71, 27.07, 27.50, 29.25, 36.13, 61.34, 116.95, 118.05, 126.68, 128.38, 129.07, 133.77, 136.23, 136.84, 171.46 (found M$^+$ 505.2370, $C_{26}H_{43}NO^{120}Sn$ requires M 505.2367). Anal. Calcd for $C_{26}H_{43}NOSn$: C, 61.75; H, 8.58; N, 2.77. Found: C, 61.58; H, 8.56; N, 3.11.

3-[*N*-Benzyl-*N*-(tributylstannylmethyl)amino]hexa-1,5-diene (15). In the same way as the amine **6a**, lithium aluminum hydride (72 mg, 1.9 mmol), aluminum chloride (85 mg, 0.64 mmol), and the amide **14** (478 mg, 0.95 mmol) gave, after purification by column chromatography on alumina, the stannane **15** (410 mg, 88%) as an oil: ν_{max} (film)/cm^{-1} 1640; δ_H (400 MHz, $CDCl_3$) 7.22−7.22 (5H, m), 5.85−5.77 (2H, m), 5.24−4.99 (4H, m), 3.71 (1H, d, J = 14 Hz), 3.37 (1H, d, J = 14 Hz), 3.02−2.95 (1H, m), 2.65−2.55 (1H, m), 2.46−2.42 (2H, m), 2.27−2.24 (1H, m), 1.50−1.43 (6H, m), 1.32−1.27 (6H, m), 0.90−0.85 (15H, m); δ_C (100 MHz, $CDCl_3$) 9.65, 13.65, 27.43, 29.19, 36.43, 37.60, 58.10, 64.82, 115.66, 117.23, 126.57, 128.07, 128.59, 136.61, 136.69, 140.44 (found M$^+$ 491.2588, $C_{26}H_{45}N^{120}Sn$ requires M 491.2574).

(1*RS*,4*RS*,6*SR*)-2-Benzyl-6-methyl-2-azabicyclo[2.2.1]-heptane (16). In the same way as the amine **7**, *n*-butyllithium (2.5 M in hexanes, 0.25 mL, 0.6 mmol) and the stannane **15** (100 mg, 0.2 mmol) in hexanes−Et_2O−THF (2.5 mL, 4:1:1) gave, after purification by column chromatography eluting with CH_2Cl_2−EtOH−NH_3 (50:1:0.5), the amine **16** (9 mg, 22%) as an oil [ν_{max} (film)/cm^{-1} 2960, 2865; δ_H (400 MHz, $CDCl_3$) 7.40−7.19 (5H, m), 3.71 (1H, d, J = 13 Hz), 3.57 (1H, d, J = 13 Hz), 2.83 (1H, s), 2.65 (1H, d, J = 9 Hz), 2.30 (2H, m), 1.85 (1H, m), 1.75 (1H, m), 1.63 (1H, dd, J = 10, 1 Hz), 1.23 (1H, d, J = 10 Hz), 1.07 (3H, d, J = 7 Hz), 0.69 (1H, m); δ_C (100 MHz, $CDCl_3$) 16.56, 34.55, 36.24, 37.17, 39.31, 61.55, 61.92, 65.26, 126.40, 127.95, 128.41, 141.27 (found M$^+$ 201.1510, $C_{14}H_{19}N$ requires M 201.1517)] and the pyrrolidine **17** (13 mg, 32%) as an oil: ν_{max} (film)/cm^{-1} 2955, 2870; δ_H (400 MHz, $CDCl_3$) 7.32−7.21 (5H, m), 5.79 (1H, ddd, J = 17, 10, 8 Hz), 5.19 (1H, dd, J = 17, 2 Hz), 5.08 (1H, dd, J = 10, 2 Hz), 3.99 (1H, d, J = 13 Hz), 3.12 (1H, d, J = 13 Hz), 2.92 (1H, m), 2.57 (1H, dd, J = 9, 4 Hz), 2.38 (1H, t, J = 9 Hz), 2.14 (2H, m), 1.22 (1H, m), 0.95 (3H, d, J = 6 Hz); δ_C (100 MHz, $CDCl_3$) 21.57, 30.38, 41.35, 57.80, 60.46, 69.14, 116.09, 126.53, 128.03, 128.67, 140.00, 141.40 (found M$^+$ 201.1524, $C_{14}H_{19}N$ requires M 201.1517).

5-(Tri-*n*-butylstannyl)-2-pyrrolidinone (21). *n*-Butyllithium (0.4 mL, 0.94 mmol, 2.5 M in hexanes) was added to hexa-*n*-butylditin (0.59 mL, 1.19 mmol) in THF (2 mL) at −20 °C under nitrogen. After 15 min, 5-(benzotriazol-1-yl)-2-pyrrolidinone (120 mg, 0.59 mmol) in THF (5 mL) was added at 0 °C. After 2 h, NaOH (2 M) was added, and the organic layer was washed with NaOH (2 M) and brine and then dried (Na_2SO_4) and evaporated. Purification by chromatography eluting with light petroleum−EtOAc (100:1 to 1:100) gave the stannane **21** (168 mg, 75%) as an oil, data as reported.[24]

1-Benzyl- 5-(tri-*n*-butylstannyl)-2-pyrrolidinone (22). The pyrrolidinone **21** (0.33 g, 0.89 mmol) in DMF (5 mL) was added to sodium hydride (0.11 g, 2.6 mmol, 60% dispersion in mineral oil) in DMF (5 mL) under nitrogen at room temperature. After 15 min, benzyl bromide (0.21 mL, 1.78 mmol) in DMF (2.5 mL) was added. After 16 h, water was added, and the mixture was extracted into EtOAc. The organic extracts were combined, dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel eluting with light petroleum−EtOAc (99:1 to 5:1) to give the stannane **22** (300 mg, 72%) as an oil: ν_{max} (film)/cm^{-1} 1685; δ_H (400 MHz, $CDCl_3$) 7.37−7.24 (3H, m), 7.18 (2H, d, J = 7 Hz), 5.22 (1H, d, J = 15 Hz), 4.70 (1H, d, J = 15 Hz), 3.54 (1H, dd, J = 9, 5 Hz), 2.49−2.47 (1H, m), 2.40−2.32 (2H, m) 2.29−2.27 (1H, m), 1.48−1.41 (6H, m), 1.33−1.24 (6H, m), 0.94−0.86 (15H, m); δ_C (75 MHz, $CDCl_3$) 9.42, 13.57, 24.07, 27.43, 29.07, 31.97, 46.77, 47.83, 127.38, 127.46, 128.61, 136.67, 174.41 (found M$^+$ 465.2056, $C_{23}H_{39}NO^{120}Sn$ requires M 465.2054). Anal. Calcd for $C_{23}H_{39}NOSn$: C, 59.50; H, 8.47; N, 3.02. Found: C, 59.48; H, 8.51; N, 2.83.

***trans*-1-Benzyl- 3-prop-2′-enyl-5-(tri-*n*-butylstannyl)-2-pyrrolidinone (23).** The pyrrolidinone **22** (210 mg, 0.45 mmol) in THF (1.5 mL) was added to LDA [0.54 mmol, prepared from *n*-BuLi (0.22 mL, 0.54 mmol) and diisopropylamine (0.09 mL, 0.63 mmol] in THF (3 mL) and HMPA (0.1 mL) at −78 °C. After 1 h, allyl bromide (0.05 mL, 0.54 mmol) was added, and the mixture was warmed to −40 °C over 2 h. Water was added, and the mixture was extracted into EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography on silica gel eluting with light petroleum−EtOAc (99:1 to 4:1) to give the stannane **23** (118 mg, 51%) as an oil: ν_{max} (film)/cm^{-1} 1685, 1650; δ_H(400 MHz, $CDCl_3$) 7.34−7.26 (3H, m), 7.16 (2H, d, J = 7 Hz), 5.83−5.79 (1H, m), 5.24 (1H, d, J = 15 Hz), 5.13−5.04 (2H, m), 3.60 (1H, d, J = 15 Hz), 3.43 (1H, dd, J = 9, 3 Hz), 2.75−2.67 (1H, m), 2.47−2.40 (1H, m), 2.25−2.19 (2H, m), 2.01−1.99 (1H, m), 1.46−1.42 (6H, m), 1.32−1.27 (6H, m), 0.92−0.86 (15H, m); δ_C (75 MHz, $CDCl_3$) 9.56, 13.57, 27.43, 29.08, 30.23, 35.11, 42.20, 45.72, 46.77, 116.65, 127.40, 127.51,

128.61, 135.82, 136.71, 174.73 (found M^+ 505.2443, $C_{26}H_{43}NO^{120}Sn$ requires M 505.2445). Anal. Calcd for $C_{26}H_{43}NOSn$: C, 61.75; H, 8.58; N, 2.77. Found: C, 61.82; H, 8.69; N, 2.66.the pyrrolidinone **24** (45 mg, 18%) was also obtained as a mixture of diastereomers (3:1): ν_{max} (film)/cm^{-1} 1680, 1640; δ_H (400 MHz, $CDCl_3$) 7.34−7.26 (5H, m), 5.80−5.71 (2H, m), 5.14−5.01 (4H, m), 4.94 (0.75H, dd, J = 8, 7 Hz), 4.86 (0.25H, t, J = 7 Hz), 3.47 (0.75H, dd, J = 9, 2 Hz), 3.27 (0.25H, dd, J = 9, 2 Hz), 2.94−2.88 (2H, m), 2.63−2.61 (1H, m), 2.46−2.36 (1H, m), 2.17−2.13 (2H, m), 2.02−1.92 (1H, m), 1.38−1.22 (12H, m), 0.89−0.61 (15H, m); δ_C (75 MHz, $CDCl_3$, major isomer) 9.68, 13.55, 27.36, 29.06, 31.85, 34.90, 35.72, 43.15, 44.53, 57.16, 116.37, 117.30, 127.68, 127.87, 128.61, 135.17, 136.01, 140.03, 175.44 (found M + H 546.2751, $C_{29}H_{47}NO^{120}Sn$ requires M + H 546.2758). Anal. Calcd for $C_{29}H_{47}NOSn$: C, 63.82; H, 8.69; N, 2.57. Found: C, 63.81; H, 8.86; N, 2.43.

***trans*-1-Benzyl-4-prop-2′-enyl-2-(tri-*n*-butylstannyl)-pyrrolidine (25).** In the same way as the amine **6a**, the pyrrolidinone **23** (111 mg, 0.22 mmol) and alane [0.22 mmol, prepared from $LiAlH_4$ (25 mg, 0.66 mmol) and $AlCl_3$ (29 mg, 0.22 mmol) in Et_2O (3 mL)] gave, after purification by chromatography over alumina eluting with light petroleum−EtOAc (98:2), the stannane **25** (77 mg, 72%) as an oil: ν_{max} (film)/cm^{-1} 1650; δ_H (400 MHz, $CDCl_3$) 7.32−7.24 (5H, m), 5.77−5.67 (1H, m), 5.02−4.91 (2H, m), 4.00 (1H, d, J = 12 Hz), 3.02 (1H, d, J = 12 Hz), 2.93−2.91 (1H, m), 2.60−2.56 (1H, m), 2.19−2.07 (4H, m), 1.65−1.49 (7H, m), 1.37−1.30 (7H, m), 0.94−0.75 (15H, m); δ_C (75 MHz, $CDCl_3$) 9.05, 13.66, 27.51, 29.32, 35.88, 38.19, 39.46, 56.72, 61.22, 115.12, 126.71, 128.13, 128.59, 137.58, 140.06 (found M^+ 492.2649, $C_{26}H_{45}N^{120}Sn$ requires M 492.2652).

(1*RS*,4*RS*,6*SR*)-2-Benzyl-6-methyl-2-azabicyclo[2.2.1]-heptane (16). *n*-Butyllithium (2.5 M in hexanes, 0.25 mL, 0.6 mmol) was added to the stannane **25** (60 mg, 0.12 mmol) in hexanes−Et_2O (1 mL, 4:1) at room temperature under argon. After 16 h, the mixture was quenched with MeOH (0.1 mL), evaporated, and purified by column chromatography on alumina, eluting with light petroleum−EtOAc (98:2) to give the amine **16** (14 mg, 60%) as an oil, data as above.

1-(Tri-*n*-butylstannylmethyl)-4-piperidone (28). *O*-Methanesulfonyltributylstannylmethanol[21b] (1.3 g, 3.3 mmol) in MeCN (5 mL) was added dropwise to 4-piperidone monohydrate hydrochloride (500 mg, 3.3 mmol) and K_2CO_3 (1.8 g, 13.2 mmol) in MeCN (30 mL) at room temperature. After 4 d, the mixture was filtered, evaporated, and purified by column chromatography on silica gel, eluting with light petroleum−EtOAc (95:5) to give the amine **28** (795 mg, 64%) as an oil: ν_{max} (film)/cm^{-1} 1725; δ_H (400 MHz, $CDCl_3$) 2.68 (4H, t, J = 6 Hz), 2.62 (2H, s), 2.40 (4H, t, J = 6 Hz), 1.63−1.42 (6H, m), 1.42−1.18 (6H, m), 1.00−0.79 (15H, m); δ_C (100 MHz, $CDCl_3$) 9.86, 13.65, 27.34, 29.16, 41.34, 45.60, 57.18, 209.04 (found M^+ 403.1885, $C_{18}H_{37}NO^{120}Sn$ requires M 403.1897).

1-(Tri-*n*-butylstannylmethyl)-4-methylenepiperidine (29). *n*-Butyllithium (2.4 M in hexanes, 1.32 mL, 3.15 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (1.5 g, 4.2 mmol) in THF (15 mL) at 25 °C. After 20 min, the ketone **28** (759 mg, 2.1 mmol) in THF (5 mL) was added. After 12 h, the mixture was quenched with MeOH, evaporated, and purified by column chromatography on silica gel, eluting with light petroleum−EtOAc (95:5) to give the amine **29** (706 mg, 95%) as an oil: ν_{max} (film)/cm^{-1} 1655; δ_H (400 MHz, $CDCl_3$) 4.68 (2H, s), 2.55 (2H, s), 2.35 (4H, t, J = 6 Hz), 2.25 (4H, t, J = 6 Hz), 1.60−1.42 (6H, m), 1.42−1.24 (6H, m), 1.00−0.78 (15H, m); δ_C (100 MHz, $CDCl_3$) 10.13, 13.65, 27.38, 29.20, 34.82, 46.70, 58.86, 107.62, 146.08 (found M^+ 401.2111, $C_{19}H_{39}N^{120}Sn$ requires M 401.2104).

4-Methyl-1-azabicyclo[2.2.1]heptane (30). *n*-Butyllithium (2.4 M in hexanes, 0.47 mL, 1.13 mmol) was added to the amine **29** (200 mg, 0.57 mmol) in dry hexanes−Et_2O (9:1) (2.5 mL) under argon at −78 °C. The mixture was allowed to stir for 15 min, and TMEDA (0.17 mL, 1.13 mmol) was added. The mixture was allowed to warm slowly to room temperature for 4 h and was quenched with MeOH at −78 °C. The mixture was allowed to warm slowly to room temperature, and picric acid (0.2 M in EtOH, 2.85 mL, 0.57 mmol) was added. After 15 min, the solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with light petroleum, then 2% MeOH in CH_2Cl_2 to give the picrate salt of the amine **30** (117 mg, 60%) as needles: mp 251−252 °C (picrate salt); ν_{max} (picrate salt, $CHCl_3$)/cm^{-1} 1610, 1570, 1495, 1550, 1365; δ_H (400 MHz, $CDCl_3$, picrate salt) 8.81 (2H, s), 3.65 (2H, dddd, J = 12, 10, 5, 2.5 Hz), 3.32 (2H, ddd, J = 12, 7.5, 5 Hz), 3.05 (2H, s), 1.97 (2H, dddd, J = 13, 10, 5, 2.5 Hz), 1.85 (2H, ddd, J = 13, 7.5, 5 Hz), 1.44 (3H, s); δ_C (100 MHz, $CDCl_3$, picrate salt) 16.42, 34.31, 44.40, 54.07, 63.47, 126.48, 128.13, 141.69, 162.23 (found M^+ − picric acid 111.1045, $C_7H_{13}N$ requires M − picric acid, 111.1048).

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Supporting Information Available: Full experimental details and data for all novel compounds, including ^{1}H and ^{13}C NMR spectra of compounds **2**, **5**, **6a**,**b**, **7**, **8**, **10**−**12**, **15**−**17**, **25**, and **28**−**30**. NOESY spectra of the amines **6a**,**b**, **7**, and **16**. In addition, an unsuccessful route to the 1-azabicyclo[2.2.1]-heptane ring system using *N*-lithiomethyl-3-vinylpyrrolidine is described. This material is available free of charge via the Internet at http://pubs.acs.org.

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