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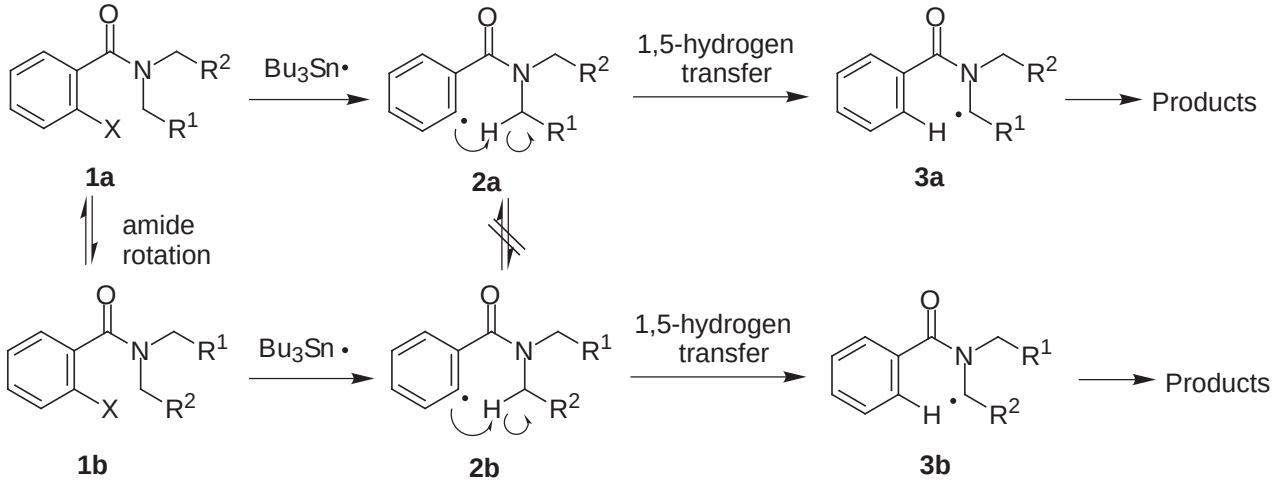
A GENERAL ROUTE TO BRIDGED AZABICYCLIC COMPOUNDS USING RADICAL TRANSLOCATION/ CYCLIZATION REACTIONS†

Tatsunori Sato and Masazumi Ikeda*
Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8414, Japan

Abstract - This review summarizes a general route to bridged azabicyclic compounds using tributyltin hydride-mediated radical translocation/cyclization reactions.

Introduction

α-Acylamino radicals ($RCONR'CH_2\bullet$) have been widely used for the syntheses of a variety of the nitrogen-containing heterocycles.[1-3] In general these radicals can be generated either by direct abstraction of X from acylamino derivatives functionalized at the α-position ($RCONR'CH_2X$)[2] or by radical translocation reaction of aryl radicals generated from the *N,N*-disubstituted *o*-halobenzamides (**1**)[3] and the related compounds.[4-6] In the latter reaction the initially formed aryl radicals (**2**) undergo rapid 1,5-hydrogen transfer reactions to form the α-acylamino radicals (**3**)[3] as shown in Scheme 1. Aryl radicals (**2**) are very reactive and their solution lifetimes are estimated to be *ca.* 10^{-5} sec,[7] while the interconversion of rotamers of the amides in solution is on the order of 10^{-1} to 10^{-2} sec.[8] Because these figures are well separated, the aryl radicals (**2a**) and (**2b**) cannot interconvert during their lifetime.[3b] Therefore, the 1,5-hydrogen-transfer reactions of the unsymmetrical disubstituted amides will depend on the rotamer population of the radical precursors (**1a**) and (**1b**).[3a,b]



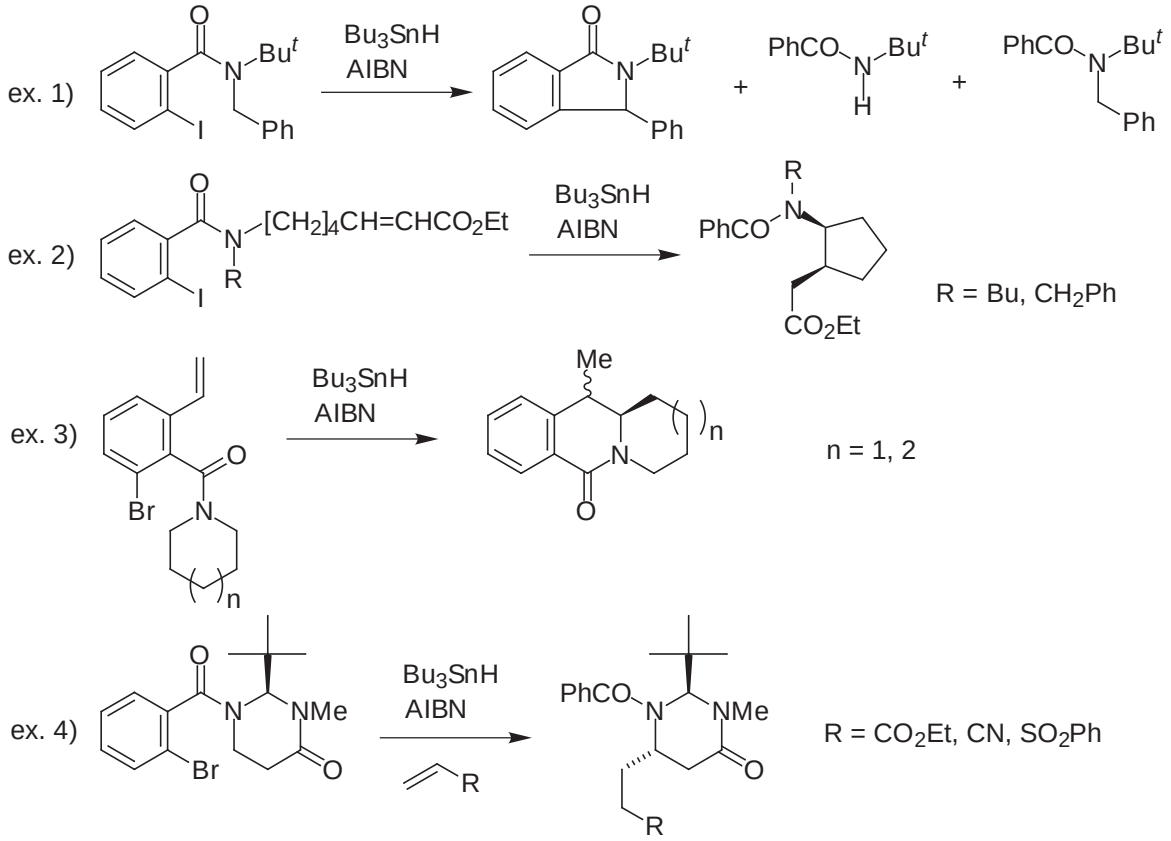
1a **2a** **3a**

1b **2b** **3b**

Scheme 1

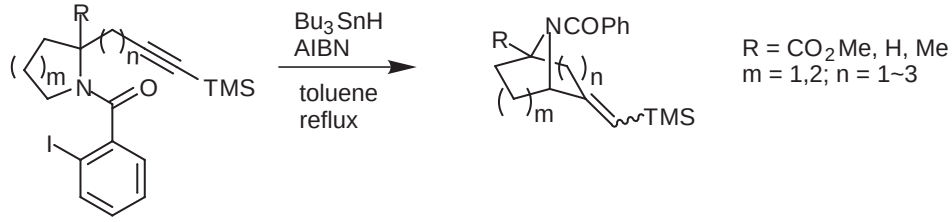
†This paper is dedicated to Professor Yuichi Kanaoka, Professor Emeritus of Hokkaido University on the occasion of his 75th birthday.

The reactions of the α-acylamino radicals (**3**) derived from the *o*-halobenzamides (**1**) include (i) a simple reduction by tributyltin hydride (Bu_3SnH) (ex. 1),[3a,b] (ii) oxidation to an acyliminium ion which produces a net *N*-dealkylation product after workup (ex. 1),[3a,b] (iii) cyclization onto the phenyl ring of the benzoyl group followed by aromatization (ex. 1),[3a,b] (iv) cyclization to an alkenyl double bond on the nitrogen substituents (ex. 2),[3a,b] (v) cyclization to an alkenyl double bond on the phenyl ring of the benzoyl group (ex. 3),[3a,b] and (vi) intermolecular addition to an alkene (ex. 4).[3c] Some of the typical examples are illustrated in Scheme 2.



Scheme 2

Because the bridged azabicyclic rings are widely found as the basic structural unit in the biologically active alkaloids such as epibatidine, tropane alkaloids (*i.e.*, cocaine, atropine, and scopolamine), euphococcinine, adaline, and anatoxin-a, a variety of the synthetic methods for such ring systems have been developed. This review summarizes a new general synthetic route to these bridged azabicyclic compounds using Bu_3SnH-mediated radical translocation/cyclization reactions (Scheme 3).

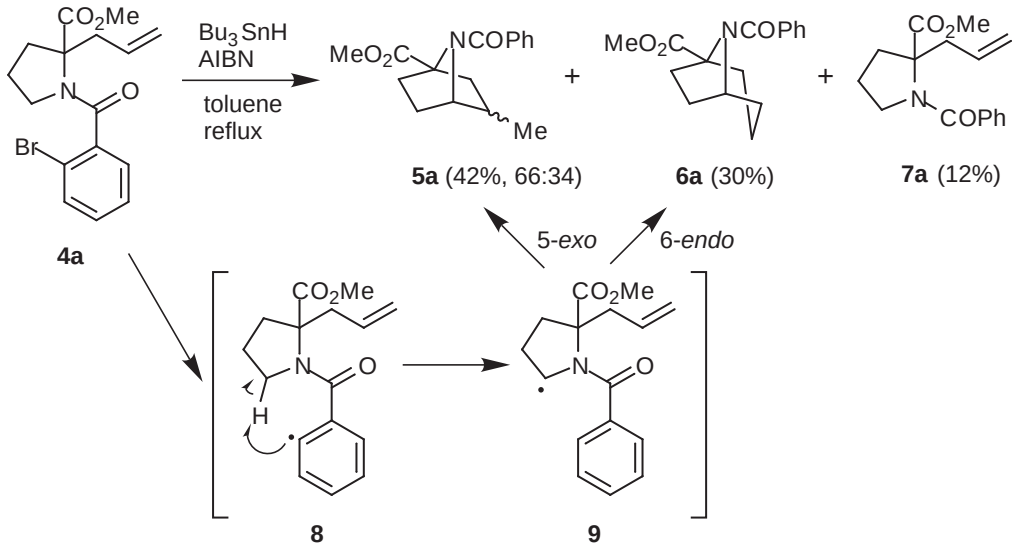


Scheme 3

1. Synthesis of 7-Azabicyclo[2.2.1]heptanes

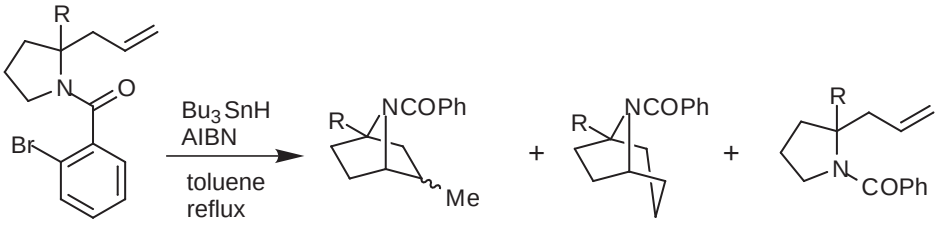
Treatment of the 2-(prop-2-enyl)pyrrolidine-2-carboxylate (**4a**) with Bu_3SnH in the presence of a catalytic amount of AIBN in boiling toluene gave the 7-azabicyclo[2.2.1]heptane (**5a**) (a 5-*exo* cyclization product) [42% yield as a diastereomeric mixture (66:34)] and the 8-azabicyclo[3.2.1]octane (**6a**) (a 6-*endo* cyclization product) (30%), together with the reduction product (**7a**) (12%).[9, 10]

A mechanistic rationalization for the formation of **5a** and **6a** would involve a 1,5-hydrogen transfer of the aryl radical (**8**) to form the α-acylamino radical (**9**). This step is then followed by either a 5-*exo-trig* or 6-*endo-trig* cyclization, leading to **5a** and **6a**, respectively (Scheme 4).



Scheme 4

In this reaction, the presence of the substituent at the 2-position of the pyrrolidine ring is important. The 2-formyl (**4b**) and 2-hydroxymethyl derivatives (**4c**) gave the corresponding azabicyclic compounds (**5b,c**) and (**6b**,**c**), while the 2-unsubstituted congener (**4d**) afforded the reduction product (**7d**) as the major product (81%) and the 8-azabicyclo[3.2.1]octane (**6d**) as the minor product (17%) (Scheme 5).



Scheme 5

One possible explanation for the effect of the 2-substituent would involve a higher population of the reacting conformer in the 2-substituted derivatives. In order for the cyclization to take place, the alkenyl double bond and the radical center must be first brought together. The radicals derived from the 2-substituted derivatives (**4a-c**) can take the conformation required for the cyclization more readily than the

radical derived from the 2-unsubstituted derivative (**4d**). This is because the reacting conformer **A** derived from **4a-c** is almost energetically equivalent to the conformer **B** (although it depends on the sizes of the substituent at the 2-position), whereas the conformation of the reacting conformer **C** derived from **4d** is less stable than that of **D** (Figure 1). An alternative explanation is based on angle compression at the 2-position caused by the 2-substituent (geminal dialkyl effect[11]). This effect may lead to a decrease of the angle θ_A ($\theta_A<\theta_B$), which causes the prop-2-enyl group to be moved closer to the radical center. Probably both factors are responsible for the increase in rate of the cyclization in the 2-substituted derivatives.[10]

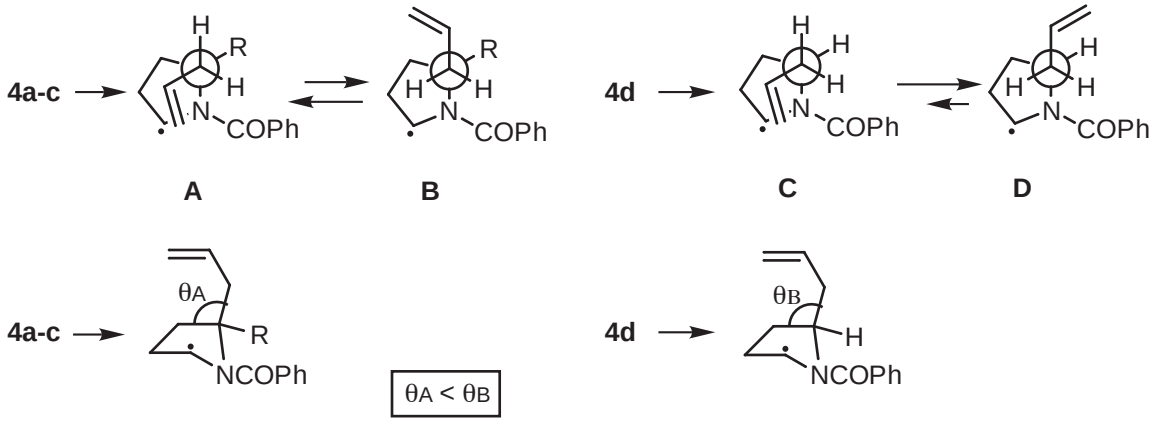
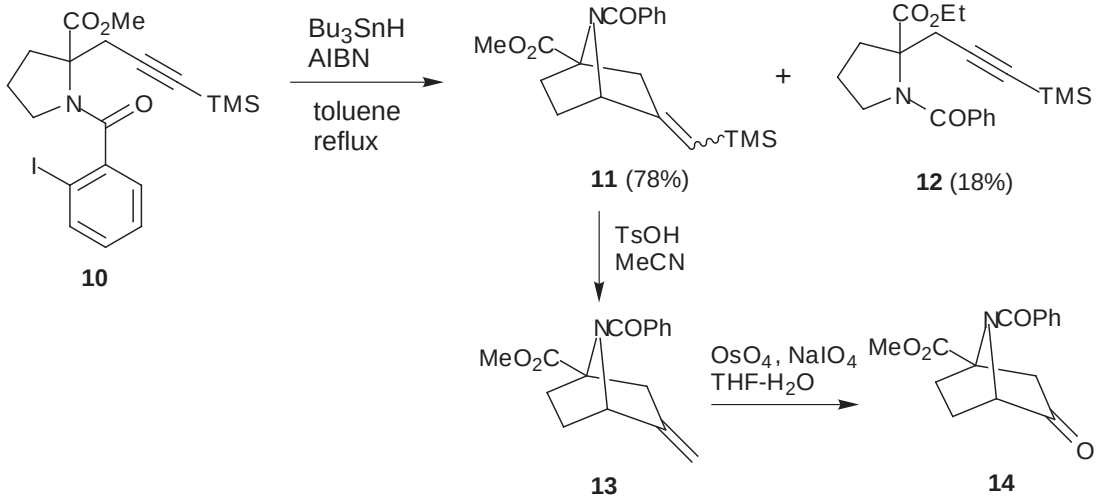


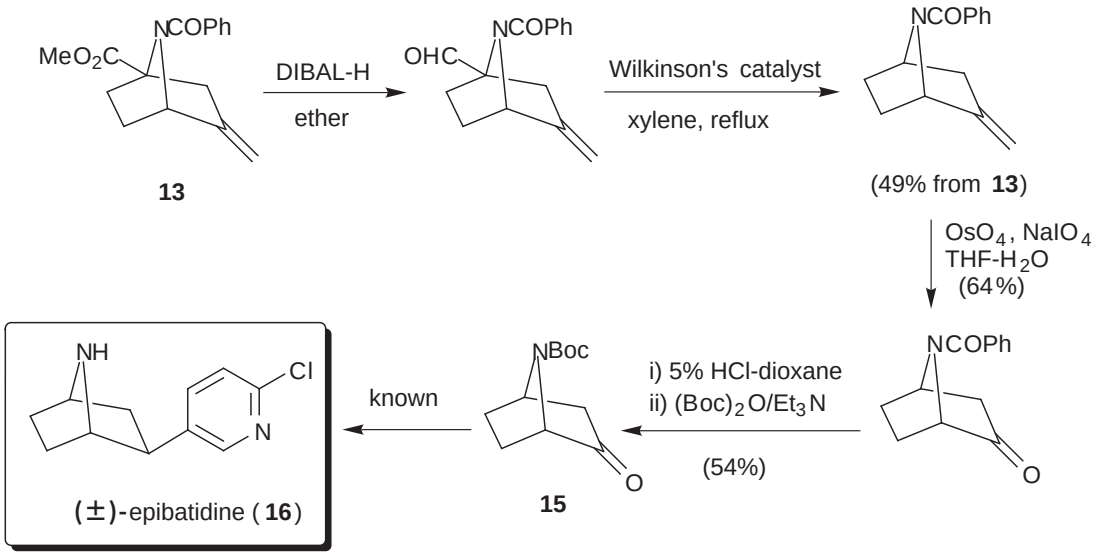
Figure 1

The main disadvantage of this reaction is the lack of the regio- and stereoselectivities. This problem was overcome by using an alkynyl group as the radical acceptor instead of the alkenyl group. Treatment of 2-[3-(trimethylsilyl)prop-2-ynyl]pyrrolidine (**10**) gave the 7-azabicyclo[2.2.1]heptane (**11**) (a 5-*exo* cyclization product) in a 78% combined yield as a diastereomeric mixture along with the reduction product (**12**) (18% yield). The compound (**11**) was transformed into the ketone (**14**) by treatment with *p*-toluenesulfonic acid in acetonitrile followed by oxidation of the resulting methylene derivative (**13**) with OsO_4 and $NaIO_4$ (Scheme 6).[12] The exclusive formation of the *exo* cyclization product (**11**) may reflect the closeness between the radical center formed at the 5-position of the pyrrolidine ring and the internal position of the alkynic bond.



Scheme 6

This method was then applied to the synthesis of the 7-azabicyclo[2.2.1]heptan-2-one (**15**), a key intermediate in the total synthesis of (±)-epibatidine (**16**),[13] which is the first alkaloid containing the 7-azabicyclo[2.2.1]heptane ring system. This is illustrated in Scheme 7.[12]



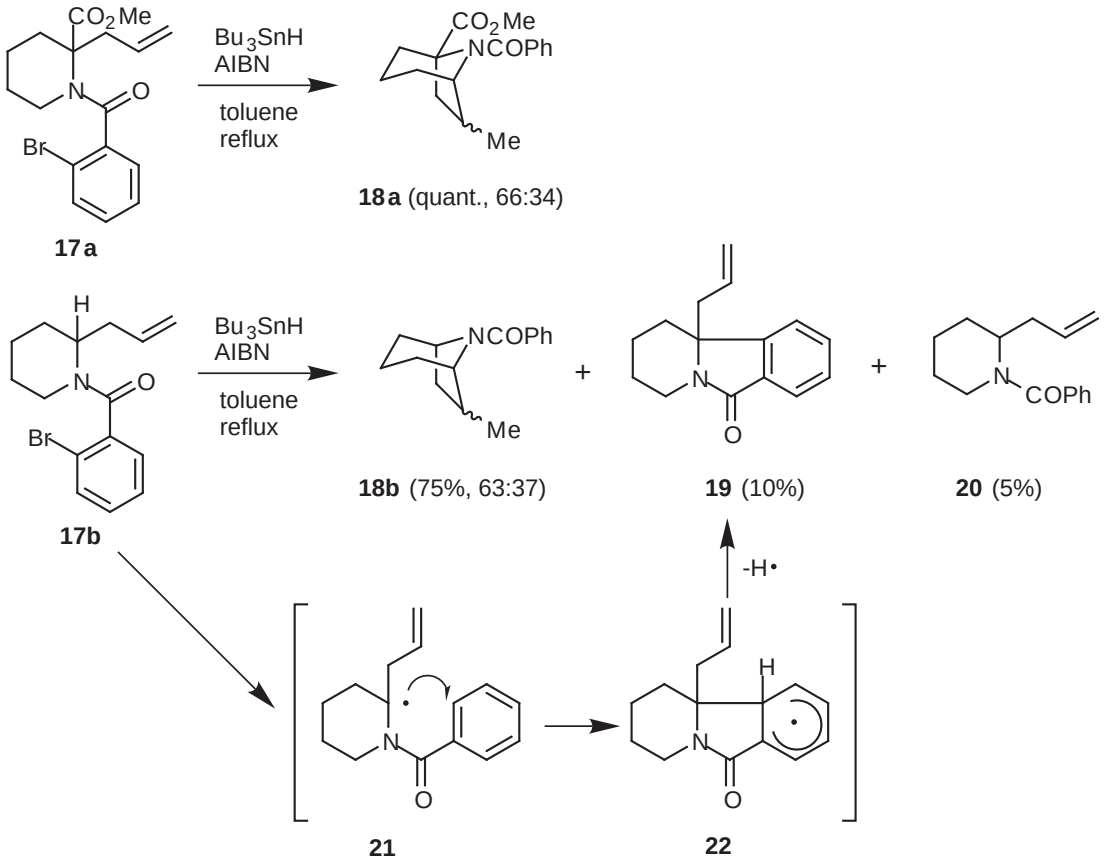
Scheme 7

2. Synthesis of 8-Azabicyclo[3.2.1]octanes

The synthesis of the 8-azabicyclo[3.2.1]octane (nortropane ring) system was achieved by two routes. One involves the cyclization of the piperidine derivatives, and the other includes the cyclization of the pyrrolidine derivative.

Thus, the 2-(prop-2-enyl)piperidine-2-carboxylate (**17a**), upon treatment with Bu_3SnH/AIBN in boiling toluene, gave regioselectively the 8-azabicyclo[3.2.1]octane (**18a**) (a 5-*exo* cyclization product) in quantitative yield as a diastereomeric mixture in a ratio of 66:34. In contrast to the 2-unsubstituted pyrrolidine (**4d**), the 2-(prop-2-enyl)piperidine congener (**17b**) afforded the 8-azabicyclo[3.2.1]octane (**18b**) (75% yield as a diastereomeric mixture in a ratio of 63:37) as the major product. The other products were the isoindolone (**19**) (10%) and the simple reduction product (**20**) (5%). The formation of **19** from **17b** may proceed *via* the radical intermediate (**21**) which cyclizes to form the radical intermediate (**22**). This radical then loses hydrogen atom to give **19** (Scheme 8).[14]

The difference in behavior between the piperidine (**17b**) and the pyrrolidine (**4d**) may be rationalized by considering the preferred conformations of the radical intermediates (Figures 1 and 2). The prop-2-enyl group in the radical derived from **17b** may occupy an axial position [see the conformer (**E**)] in order to minimize allyic 1,3-strain ($A^{1,3}$-strain) with the C=N double bond in the amide.[15] This causes the 2-position of the prop-2-enyl group to be brought into the correct position to react in the 5-*exo*-*trig* manner. The same argument may be applied to the pyrrolidine case, but the 2-substituent adopts a quasi-axial position, so that the distance between either the 2- or 3-position of the prop-2-enyl group and the radical center becomes longer than in the piperidine case. Consequently the reduction competes favorably with the cyclization (since the 3-position of the two reactive sites is relatively closer to the radical center, the observed 6-*endo* cyclization is favored over the 5-*exo* cyclization).



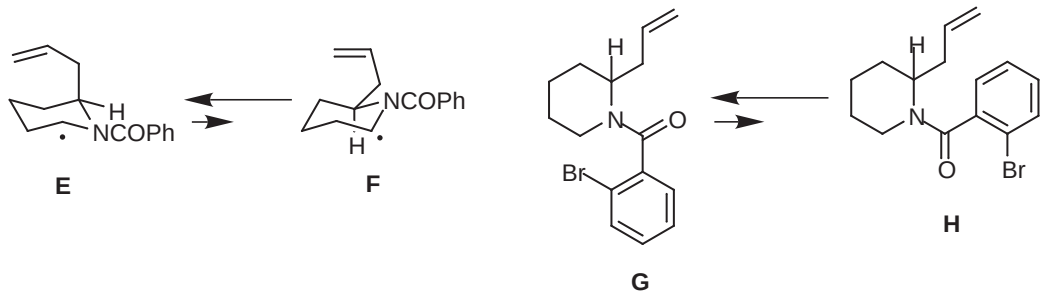
17a **18a** (quant., 66:34)

17b **18b** (75%, 63:37) **19** (10%) **20** (5%)

21 **22**

Scheme 8

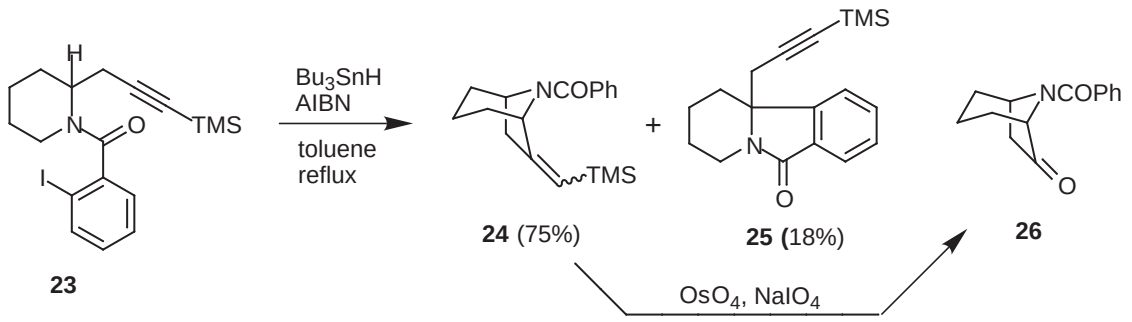
The product distribution of **18b** (75%) and **19** (10%) probably reflects the population of two conformers **G** and **H** of **17b**, which generate the α-acylamino radicals at the 6- (leading to **18b**) and 2-position of the piperidine ring (leading to **19**), respectively, through the corresponding short-lived aryl radicals. The conformer **G** is favored over the conformer **H** because the steric repulsion between the bulky *o*-bromophenyl and 2-(prop-2-enyl) groups may occur in the latter, in spite of the fact that the side chain at the 2-position mainly occupies an axial position in order to minimize $A^{1,3}$-strain with the N=C double bond in the amide.



E **F** **G** **H**

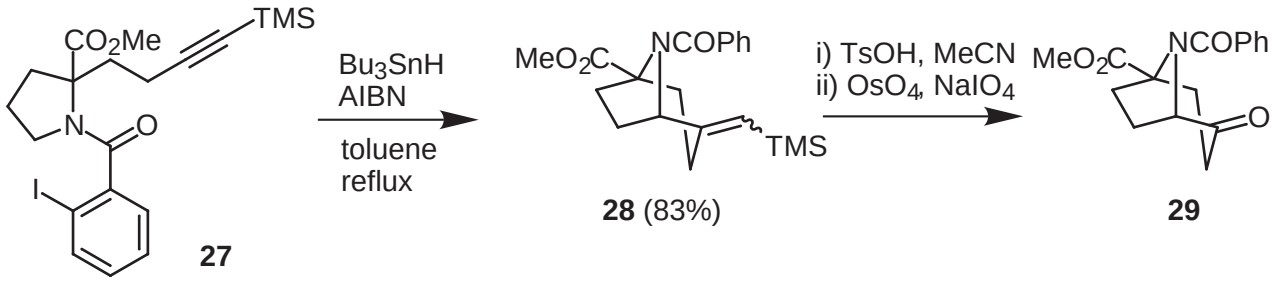
Figure 2

Since the translocation/cyclization reactions were found to proceed cleanly in the 2-unsubstituted piperidine (**17b**), the cyclization of the 2-[3-(trimethylsilyl)prop-2-ynyl]piperidine (**23**) was examined. Treatment of **23** with Bu_3SnH/AIBN in boiling toluene gave the 8-azabicyclo[3.2.1]octane (**24**) (75%) as a diastereomeric mixture along with the tricyclic compound (**25**) (18%). The compound (**24**) was transformed into the ketone (**26**).[14]



Scheme 9

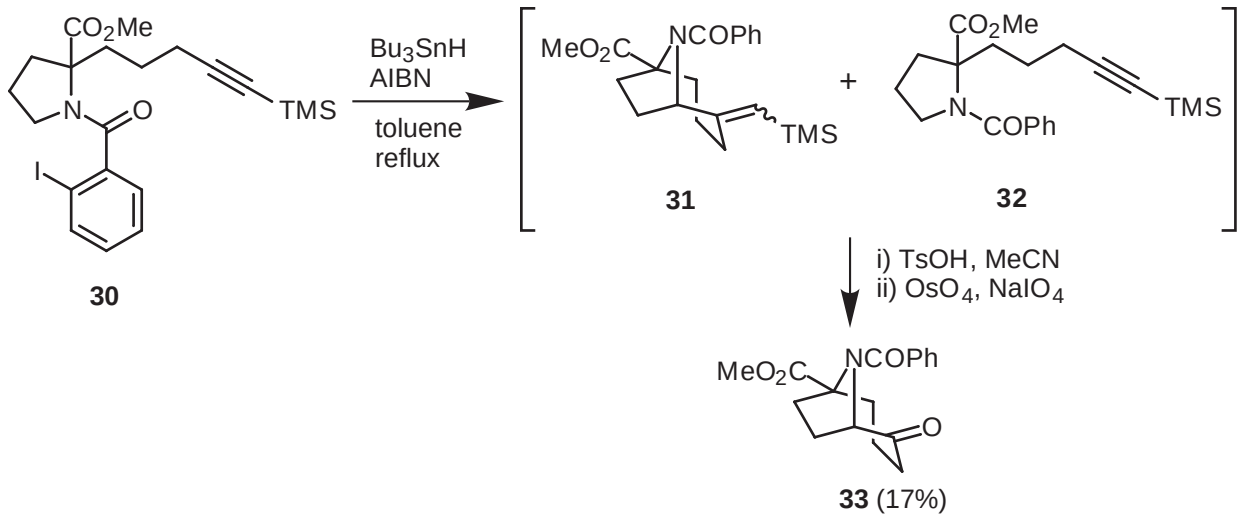
On the other hand, the 2-[4-(trimethylsilyl)but-3-ynyl]pyrrolidine (**27**) gave regioselectively the 8-azabicyclo[3.2.1]octane (**28**) in 83% combined yield as a diastereomeric mixture, which was again transformed into the ketone (**29**).[12]



Scheme 10

3. Synthesis of 9-Azabicyclo[4.2.1]nonanes

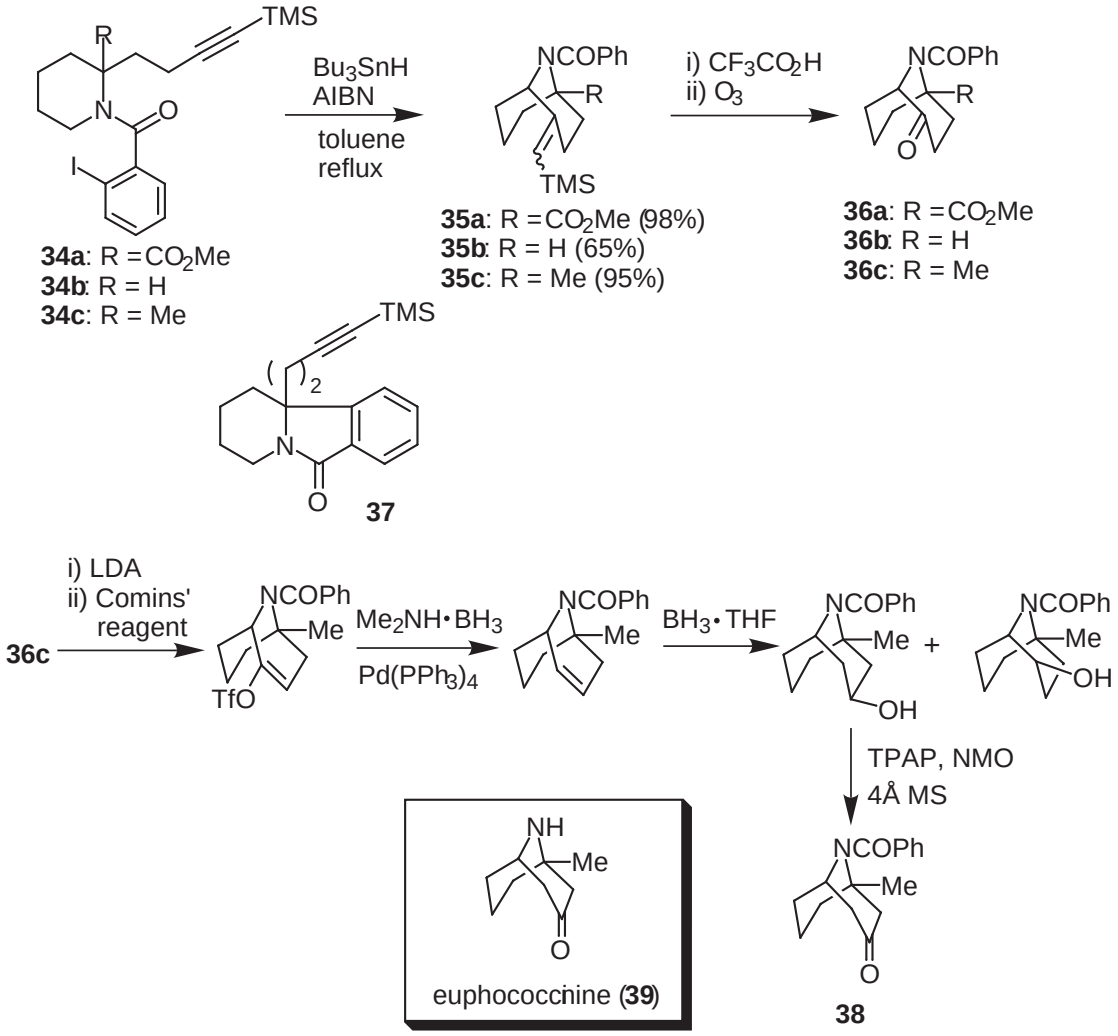
The 2-[5-(trimethylsilyl)pent-4-ynyl]pyrrolidine (**30**), upon treatment with Bu_3SnH/AIBN in boiling toluene, gave an inseparable mixture of the 9-azabicyclo[4.2.1]nonane (**31**) (as a diastereomeric mixture) and the reduction product (**32**) in 86% total yield and in a ratio of 48:52 (the ratio was determined by HPLC). The yield of **31** was estimated to be approximately 40%. The mixture was treated with *p*-toluenesulfonic acid followed by oxidation with OsO_4 and $NaIO_4$ to give the ketone (**33**) in 17% overall yield.[12]



Scheme 11

4. Synthesis of 9-Azabicyclo[3.3.1]nonanes

The 2-[4-(trimethylsilyl)but-3-ynyl]piperidines (**34a-c**), upon treatment with Bu_3SnH/AIBN in boiling toluene, gave the 9-azabicyclo[3.3.1]nonanes (**35a-c**) in high yields, which were transformed into the corresponding ketones (**36a-c**).[16] In the case of **34b** the isoindolone (**37**)(23%) was also obtained. The compound (**36c**) was subjected to a 1,2-transposition reaction of the carbonyl group to give 9-benzoyl-1-methyl-9-azabicyclo[3.3.1]nonan-3-one (**38**),[16] a potential precursor for the synthesis of (±)-euphococcinine (**39**) (Scheme 12).[17]

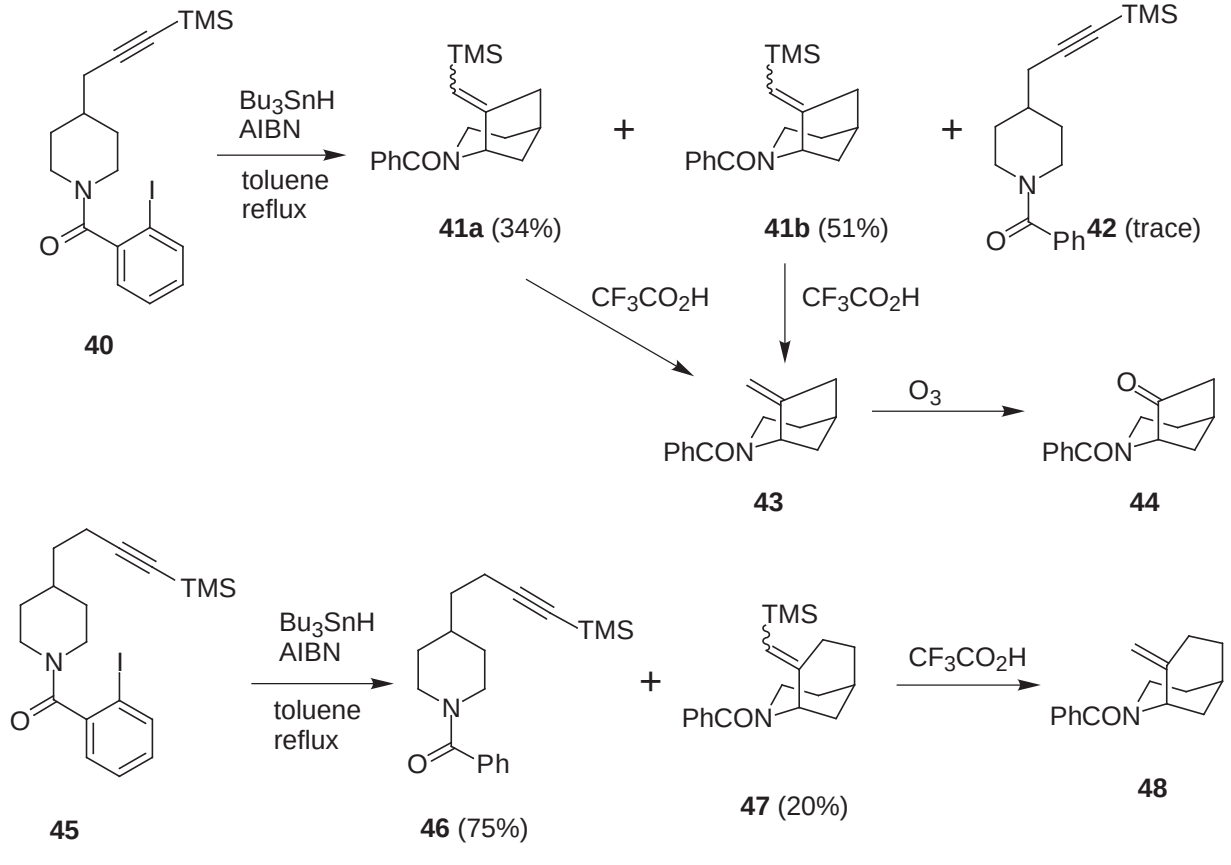


Scheme12

5. Synthesis of 2-Azabicyclo[3.2.1]octanes and 2-Azabicyclo[3.3.1]nonanes

Treatment of the 4-[3-(trimethylsilyl)prop-2-ynyl]piperidine (**40**) with Bu_3SnH/AIBN in boiling toluene gave the isomeric 2-azabicyclo[3.2.1]octanes (**41a**) (the less polar isomer) and (**41b**) (the polar one) in 34 and 51% yields, respectively, along with a trace amount of the reduction product (**42**). Both the compounds (**41a**) and (**41b**) were transformed into the ketone (**44**) *via* the methylene derivative (**43**).[18] Cyclization of **45** proceeded more slowly to give the 2-azabicyclo[3.3.1]nonane (**47**) in 20% yield as a diastereomeric mixture, which was transformed into the methylene derivative (**48**). In this case, the reduction product (**46**) was obtained as a major product in 75% yield. The low yield of **47** may be

rationalized by considering the preferred conformation of the α-acylamino radical intermediates (**I**) and (**J**) derived from the 4-alkynyl-1-(*o*-iodobenzoyl)piperidines. The 4-alkynyl group adopts a more stable equatorial position, so that for the cyclization to take place the conformation of the 4-substituent must invert from the equatorial to the axial position (Figure 3). The distance of the 3-position of the 4-(but-3-ynyl) group and the radical center is still larger than that in the case of the 4-(prop-2-ynyl) group. Consequently, the reduction competes favorably with the cyclization.



Scheme 13

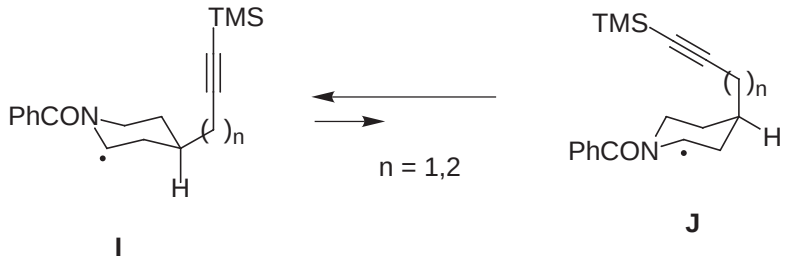
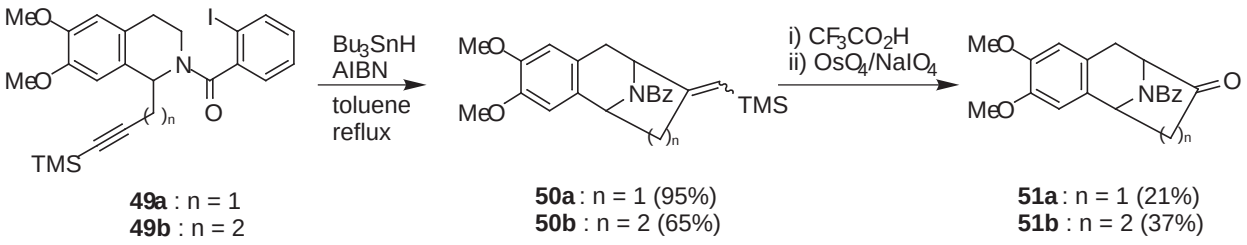


Figure 3

6. Synthesis of Tetrahydro-5*H*-benzocyclohepten-5,8-imine and Hexahydrobenzocycloocten-5,9-imine

Treatment of the 1-[3-(trimethylsilyl)prop-2-ynyl]tetrahydroisoquinoline (**49a**) with Bu_3SnH/AIBN in boiling toluene gave the tetrahydro-5*H*-benzocyclohepten-5,8-imine (**50a**) in 87% combined yield as a diastereomeric mixture. A similar treatment of the 1-[4-(trimethylsilyl)but-3-ynyl] congener (**49b**) with Bu_3SnH/AIBN yielded exclusively the hexahydrobenzocycloocten-5,9-imine (**50b**) in 65% yield as a

diastereomeric mixture. Both the compounds (**50a**,**b**) were converted into the corresponding ketones (**51a**,**b**).[19]



49a : n = 1
49b : n = 2

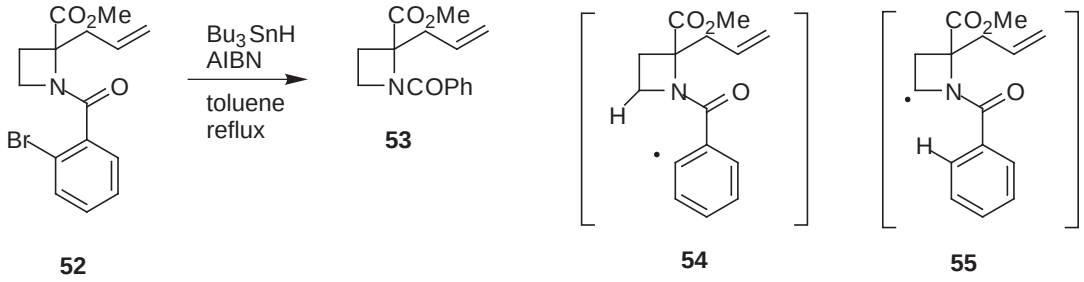
50a : n = 1 (95%)
50b : n = 2 (65%)

51a : n = 1 (21%)
51b : n = 2 (37%)

Scheme 14

Epilogue

The radical translocation and cyclization reactions of 2-alkynylpyrrolidines and 2- and 4-alkynylpiperidines provide a new general route to a variety of azabicyclic compounds. We hope to extend these reactions to the synthesis of the optically active compounds. For comparison, the behavior of the azetidine congener (**52**) was also investigated.[14] When **52** was treated with Bu_3SnH/AIBN in boiling toluene, only the reduction product (**53**) was obtained in 63% yield. A deuterium labeling experiment indicated that both the 1,5-hydrogen transfer and cyclization steps were retarded. Examination of Dreiding models reveals that the distance between the radical center formed on the phenyl ring and 4-hydrogen atom in **54** is slightly longer than that in the pyrrolidine case and the radical center in **55** formed after the 1,5-hydrogen transfer is too far away from the alkenic double bond to permit the cyclization.



52

53

54

55

Scheme 15

ACKNOWLEDGEMENTS

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