Cyclizations of Aminyl Radicals Generated from Substoichiometric Stannane

Huimin Zhai, Jason G. Wickenden, Glenn M. Sammis*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, V6T 1Z1, Canada
Fax +1(604)8220614; E-mail: gsammis@chem.ubc.ca

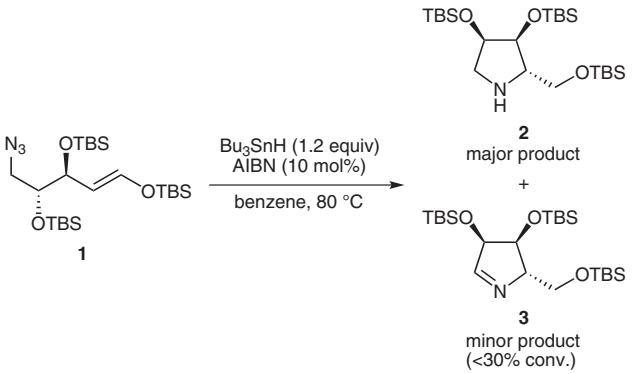
Received 16 September 2010

Abstract: Substoichiometric amounts of tributyltin hydride were utilized in nitrogen-centered radical cyclizations onto silyl enol ethers for the formation of substituted cyclic imines.

Key words: aminyl radical cyclization, substoichiometric tributyltin hydride, silyl enol ethers, cyclic imines

Aminyl radical cyclizations[1] are powerful synthetic methods for the construction of pyrrolidines and have been utilized in the syntheses of numerous natural products. Of the many methods that have been developed for the generation of nitrogen-centered radicals,[1] the formation of aminyl radicals from azides[2] is synthetically attractive as azides are readily incorporated into molecules and are stable under a variety of reaction conditions. Herein, we report a new methodology for the formation of versatile cyclic imines that utilizes aminyl radicals generated from azides and only a substoichiometric amount of tributyltin hydride.

We recently reported a new route to polyhydroxylated pyrrolidines using aminyl radical cyclizations onto silyl enol ethers.[3] These cyclizations required the addition of 1.2 equivalents of tributyltin hydride and 0.1 equivalents of azobisisobutyronitrile (AIBN) to effect clean cyclizations to the desired pyrrolidines. However, a sterically bulky cyclization precursor, azide **1**, cyclized to form both the desired pyrrolidine **2** as well as a minor amount of cyclic imine **3** (Scheme 1).



Scheme 1 Nitrogen-centered radical cyclization onto a silyl enol ether

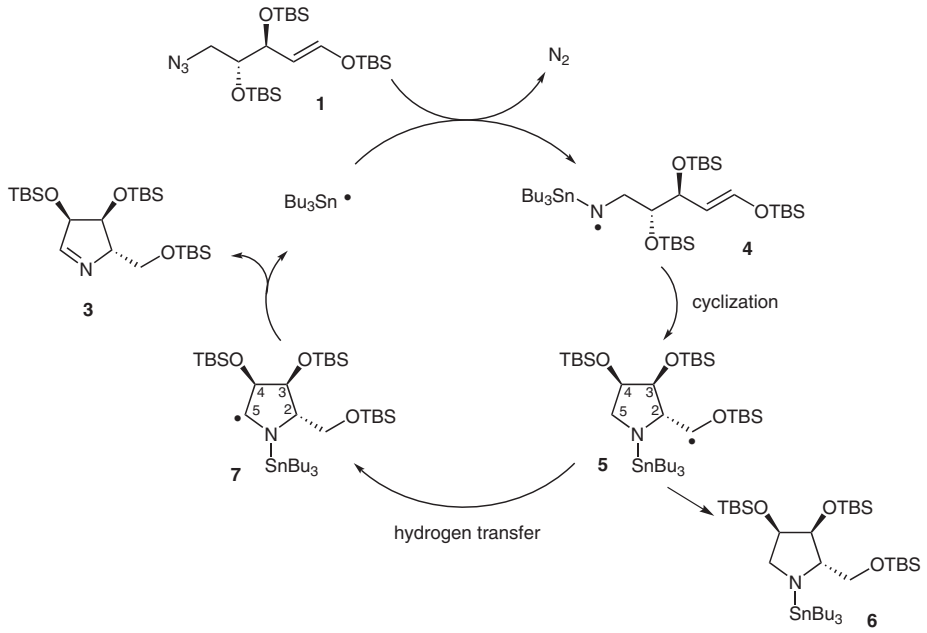
We hypothesized that the formation of imine **3** occurs through the mechanism illustrated in Scheme 2. Treatment of azide **1** with tributyltin radical results in the formation of tin-bound aminyl radical **4**, which rapidly cyclizes to form pyrrolidine **5**. Subsequent radical trapping with hydrogen provides pyrrolidine **6**. Protonolysis of the nitrogen–tin bond readily occurs in workup to provide **2**. The imine product may be formed through an intermolecular hydrogen transfer[4,5] between pyrrolidines **5** and **6** to form pyrrolidines **6** and **7**. Radical fragmentation of pyrrolidine **7**[6] results in the formation of the imine **3** and regeneration of tributyltin radical. This mechanism suggests the possibility of cyclizing an azide to the corresponding cyclic imine utilizing only a substoichiometric amout of tributyltin hydride.

We began our investigations into the selective formation of cyclic imines using substoichiometric amounts of tributyltin hydride with a simple, unbiased cyclization precursor (**8**, Scheme 3). Using our optimized conditions developed for pyrrolidine formation, azide **8** cyclized to form exclusively pyrrolidine **10** with no detectable amounts of either cyclic imine **9** or starting material **8**. Decreasing the amount of tributyltin hydride to 50 mol% resulted in the formation of pyrrolidine **10**, unreacted azide **8**, and two imine products (**9** and **11**). Imine **9** was the expected imine product based upon the mechanism proposed in Scheme 2. Imine **11** is also likely formed through an intermolcular hydrogen transfer at C_2 followed by elimination. Despite the large amount of unreacted azide, the sum of all cyclized products is greater than the percentage of tin added to the reaction.

With the basic substoichiometric reactivity established, we sought to optimize the ratio of imine products **9** and **11** to the pyrrolidine **10**. Lowering the amount of tributyltin hydride to 30 mol% led to an increase in total imine formation relative to pyrrolidine and unreacted starting material (Table 1, entries 1). Slowing the addition rate to 0.4 mL/h and 0.2 mL/h (entries 2 and 3) resulted in complete conversion to cyclized products with no detectable amounts of starting azide **8** (entry 2).[7] Increasing the concentration provided a higher percentage of pyrrolidine **10** relative to imine products.

Decreasing tributyltin hydride from 30 mol% to 15 mol% using the new slow addition rate procedure (entry 4) afforded an increase in the ratio of imine products to pyrrolidine **10**. However, decreasing the tin to 10 mol% resulted in poor imine to pyrrolidine selectivities and a large amount of unreacted azide **8**. Changing the tin

SYNLETT 2010, No. 20, pp 3035–3038
Advanced online publication: 24.11.2010
DOI: 10.1055/s-0030-1259062; Art ID: S06210ST



Scheme 2 Proposed mechanism for the formation of imine **3**

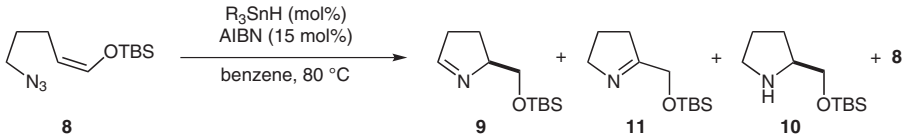
source to triphenyltin hydride did not significantly effect the product distribution compared to tributyltin hydride (entries 6 and 7). Initiation using in situ generated dichloroindium hydride[8] afforded poor yields of imine products.

Cyclization with 15 mol% tributyltin hydride favored the formation of cyclic imine **9** to cyclic imine **11** in 2.1:1 ratio. For this radical methodology to be synthetically useful, it must provide higher selectivity for the formation of one of the cyclic imines. Our original cyclization studies (Scheme 1) indicated a possible solution as cyclization of azide **1** resulted in the formation of only one imine product. We postulated that the other cyclic imine does not form because the steric bulk at C_3 slows the rate of hydrogen abstraction from C_2.

To test this hypothesis we examined substrates with varying steric bulk at C_3 (Schemes 4 and 5). Using the previously developed conditions (Scheme 4), cyclization of azide **12** exclusively afforded pyrrolidine **13** in high yield. Similarly, cyclization of phenyl-substituted substrate **14** provided pyrrolidine **15** in excellent yield and selectivity. Using newly developed procedure with 30 mol% of tributyltin hydride (Scheme 5),[9] azide **12** cyclized to afford imines **16** and **17** in 67% yield as a 3.3:1 mixture. Cyclization of phenyl-substituted substrate **14** afforded only one imine product (**18**).

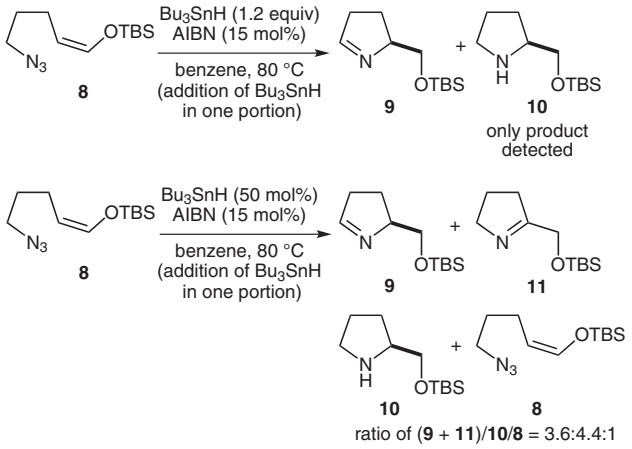
Another method for increasing the selectivity of one of the two cyclic imines is to stabilize the radical at C_5 through substitition (Scheme 2, **7**). Cyclization of alkyl-substitut-

Table 1 Optimization Studies for Total Imine Product **9** and **10**

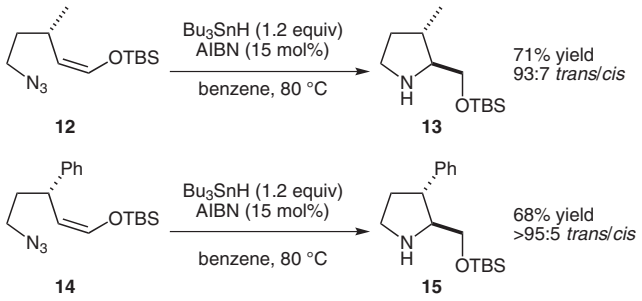


Entry[a]	Addition rate (mL/h)	Metal hydride	R_3SnH (mol%)	Product ratio[b] (**9** + **11**)/**10**/**8**
1	1 portion	Bu_3SnH	30	1.3:1.4:1
2	0.4	Bu_3SnH	30	1.5:1:0
3	0.2	Bu_3SnH	30	1.9:1:0
4	0.2	Bu_3SnH	15	2.5:1:0
5	0.2	Bu_3SnH	10	1.3:1:2.3
6	0.2	Ph_3SnH	40	1.8:1:0
7	0.2	Ph_3SnH	20	1.8:1:0

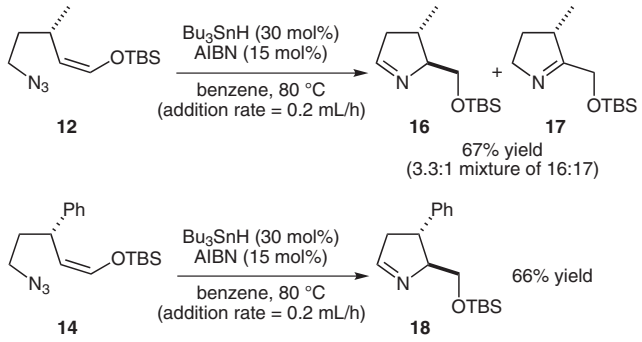
[a] Reactions were carried out on a 0.31 mmol scale and were 0.03 M in benzene.
[b] Product ratios were determined by ^1H NMR spectroscopic analyses of crude reaction mixtures.



Scheme 3 Investigating substoichiometric generation of aminyl radicals



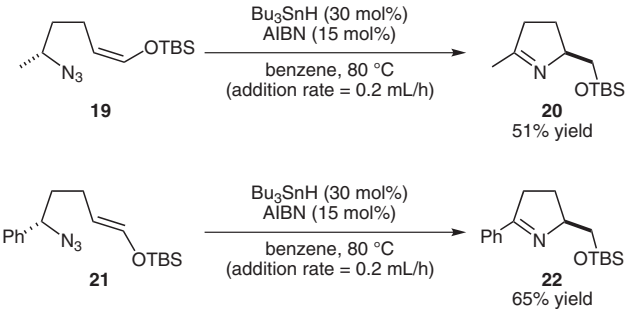
Scheme 4 Cyclizations using stoichiometric tributyltin hydride



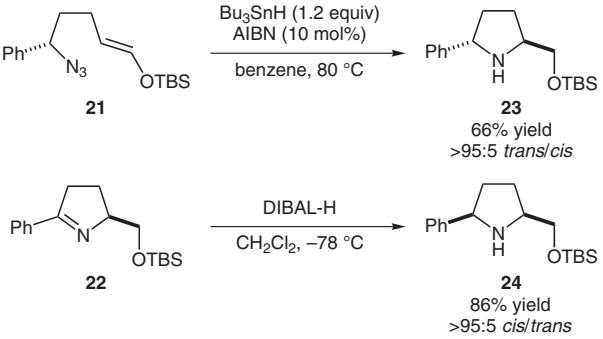
Scheme 5 Cyclizations using substoichiometric tributyltin hydride

ed azide (**19**, Scheme 6) provided cyclic imine **20** in good yield, with the remainder of the mass balance corresponding to the undesired cyclic imine (24%) and the corresponding pyrrolidine (8% yield). While the methyl provided some selectivity towards the formation of imine **20**, phenyl substitution (**21**) provided only one of the two imine products (**22**) along with 11% yield of the corresponding pyrrolidine. The high selectivity for imine **22** is presumably due to the enhanced stability of the benzylic radical at C_5. Changing the silyl enol ether geometry had no effect on the product distribution.

Using both our previously developed nitrogen-centered radical cyclizations and this new method, we can now access both *trans*- and *cis*-2,5-disubstituted pyrrolidines from a common intermediate (Scheme 7). Treatment of



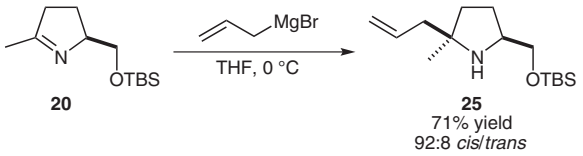
Scheme 6 Cyclization of secondary azides **19** and **21**



Scheme 7 Synthesis of both *trans*- and *cis*-2,5-disubstituted pyrrolidines

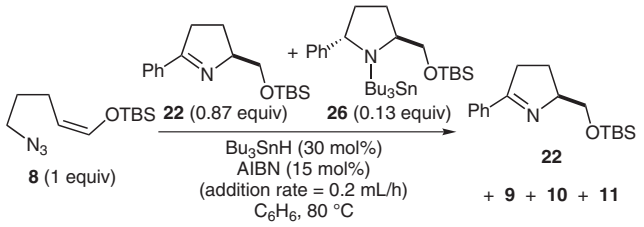
azide **21** with stoichiometric tributyltin hydride provided *trans*-pyrrolidine **23** in 66% yield.[10] The corresponding *cis*-isomer **24** can readily be accessed from DIBAL-H reduction of imine **22**.[11]

The addition of carbon nucleophiles to imines **20** and **22** can also readily provide fully substituted carbon centers. Treatment of imine **20** with allyl magnesium bromide results in the formation of pyrrolidine **25** in excellent yield as a 92:8 ratio of *cis*/*trans* isomers (Scheme 8).[12]



Scheme 8 Addition of allyl magnesium bromide to cyclic imines

In the proposed mechanism depicted in Scheme 2, the only step which remained to be examined was the hydrogen transfer step (**5** to **7**). This transfer step may either occur through an intramolecular hydrogen transfer or through an intermolecular pathway. To probe these two possibilities, we explored whether a tin-bound pyrrolidine, such as **26**, could serve as a hydrogen-transfer agent. Indeed cyclization of azide **8** in the presence of a mixture of imine **22** and pyrrolidine **26** led to the complete conversion of tin-bound pyrrolidine to imine **22** along with cyclization products **9**, **10**, and **11** (Scheme 9). This result, coupled with the geometrical constraints of an intramolecular transfer within the ring system, strongly suggest that



Scheme 9 Mechanistic investigations into radical transfer reaction

the hydrogen transfer most likely proceeds through an intermolecular pathway.

We have developed a new method for the synthesis of cyclic imines using substoichiometric amounts of tributyltin hydride. The selectivity for formation of the desired cyclic imine product can be influenced by either altering the steric bulk of the substituents at C_3 or by increasing the substiution at C_5. This new methodology is complementary to our existing aminyl radical cyclizations onto silyl enol ethers as we can now access both *trans*- and *cis*-1,5-disubstituted pyrrolidines. Addition of carbon nucleophiles to the cyclic imines also provides the corresponding highly substituted pyrrolidine in excellent yield. We are currently exploring the efficacy of this cyclization in the context of complex natural product synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the University of British Columbia and the Natural Sciences and Engineering Research Council of Canada (NSERC).

References and Notes

(1) For reviews on nitrogen-centered radicals, see: (a) Neale, R. S. *Synthesis* **1971**, 1. (b) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241. (c) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. (d) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1. (e) Zard, S. Z. *Synlett* **1996**, 1148. (f) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (g) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (h) Curran, D. P. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 811. (i) Stella, L. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, 407.

(2) For initial studies, see: (a) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328. (b) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. (c) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem. Eur. J.* **2009**, *15*, 7830.

(3) Zhai, H.; Zlotorzynska, M.; Sammis, G. M. *Chem. Commun.* **2009**, 5716.

(4) For a review of radical hydrogen transfer reactions, see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

(5) For representative examples of hydrogen abstraction α to amines, see: (a) Routaboul, L.; Vanthuyne, N.; Gastaldi, S.; Gil, G.; Bertrand, M. *J. Org. Chem.* **2008**, *73*, 364. (b) El Blidi, L.; Nechab, M.; Vanthuyne, N.; Gastildi, S.; Bertrand, M.; Gil, G. *J. Org. Chem.* **2009**, *74*, 2901.

(6) For an example of an elimination of tributyltin radical from a carbon-centered radical α to a tin-bound amine, see ref. 2b.

(7) We did not explore addition rates slower than 0.2 mL/h as the reaction times became prohibitively long.

(8) Benati, L.; Bencivenni, G.; Leardini, R.; Nanni, D.; Minozzi, M.; Spagnolo, P.; Scialpi, R.; Zanardi, G. *Org. Lett.* **2006**, *8*, 2499.

(9) While cyclization of azide **8** using 15 mol% of tributyltin hydride provided good conversion to the cyclized products, these conditions proved not to be robust for other substitution patterns. Cyclizations using 30 mol% tributyltin hydride proved to be general and reliable for all substrates examined.

(10) We were also able to isolate 12% of the *cis*-isomer.

(11) Marco, J. L. *J. Heterocycl. Chem.* **1986**, 1059.

(12) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921.