

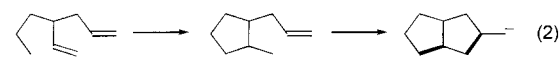
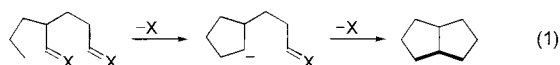
## Novel Anionic Cyclization of *N*-Aziridinylimines. An Efficient Route to Carbocycles via Consecutive Carbon–Carbon Bond Formation Approach

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Anionic cyclizations, widely utilized for the construction of carbocycles and heterocycles, primarily involve stabilized anionic intermediates,<sup>1</sup> although much attention has recently been devoted to the cyclization of reactive anionic intermediates onto unactivated alkenes.<sup>2</sup> Herein we report a conceptually novel anionic cyclization reaction of *N*-aziridinylimines, involving the formation of consecutive carbon–carbon bonds, which we believe has considerable synthetic potential for the construction of carbocycles (eq 1). Although we have demonstrated a similar approach via sequential radical cyclizations,<sup>3</sup> as far as we are aware, this anionic approach is unprecedented because all sequential ring forming reactions developed to date involve the formation of alternating carbon–carbon bonds using C=C bonds as acceptors (eq 2).<sup>4,5</sup>



Our initial studies evolve from the speculation that the *N*-aziridinylimino group would function as the vinyl anion equivalent<sup>6</sup> and as the anionic acceptor (Scheme 1).<sup>7,8</sup> When bis-aziridinylimine **1a** was treated with LDA (1.0 equiv) in THF at  $-78\text{ }^{\circ}\text{C}$  and the solution was warmed to room temperature,

(1) For recent reviews, see: (a) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, FL, 1994; p 169 (b) Ho, T.-L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992. (c) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467.

(2) (a) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742. (b) Pearson, W. H.; Walters, M. A.; Oswald, K. D. *J. Am. Chem. Soc.* **1986**, *108*, 2769. (c) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. (d) Chamberlin, A. R.; Bloom, S. H. *Tetrahedron Lett.* **1986**, *27*, 551. (e) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (f) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, *31*, 627. (g) 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. (h) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080. (i) Kim, S.; Kim, B. S.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1994**, *15*, 701. (j) Cooke, M. P., Jr. *J. Org. Chem.* **1994**, *59*, 2930. (k) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.

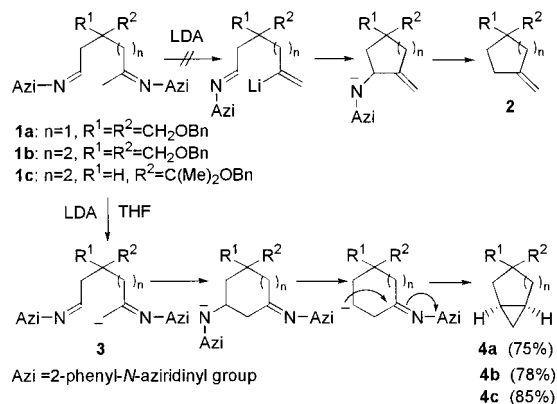
(3) (a) Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882. (b) Lee, H.-Y.; Kim, D.-I.; Kim, S. *Chem. Commun.* **1996**, 1539. (c) Kim, S.; Cheong, J. H. *Synlett* **1997**, 947. (d) Kim, S.; Cheong, J. H.; Yoo, J. *Synlett* **1998**, 981.

(4) For the sake of convenience, only anionic cyclization reactions are shown in eq 2. The formation of carbon–carbon bonds is indicated by solid lines. We thank Professor D. P. Curran for his suggestion in naming the formation of carbon–carbon bonds.

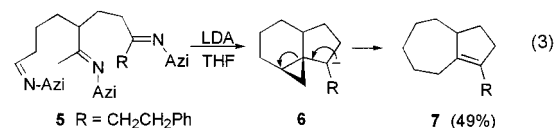
(5) For selected examples on polyene cyclizations, see: (a) Cationic: Johnson, W. S.; Chen, Y.-Q.; Kellogg, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 6653. Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (b) Carbopalladation: Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. Zhang, Y.; Wu, G.-z.; Agnel, G.; Negishi, E.-i. *J. Am. Chem. Soc.* **1990**, *112*, 8590. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701. (c) Radical: Begley, M. J.; Pattenden, G.; Smithies, A. J.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 2417. Chen, L.; Gill, G. B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.

(6) (a) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (b) Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 2289.

### Scheme 1



somewhat surprisingly, bicyclo[3.1.0]hexane **4a** was isolated without the formation of **2a**. Apparently, lithiated aziridinylimine **3a** underwent tandem anionic cyclizations to result in **4a** via the formation of two consecutive carbon–carbon bonds. This reaction occurred very rapidly at  $-10\text{ }^{\circ}\text{C}$ , going to completion within 10 min. The use of a catalytic amount of LDA (0.1 equiv) under the similar conditions resulted in somewhat lower yield (65%) and longer reaction time (5 h). Similar results were obtained with **1b** and **1c**. Furthermore, in the case of tris-aziridinylimine **5**, it is noteworthy that tricyclic intermediate **6** underwent  $\beta$ -elimination to afford **7** (49%) apparently due to the relief of cyclopropane ring strain (eq 3).<sup>9</sup>



Our next studies involved initial attack of organometallic reagents on the *N*-aziridinylimino group and the subsequent successive elimination to generate the anionic intermediate **8**, which undergoes anionic cyclization reaction for ring formation (Scheme 2). Treatment of bis-aziridinylimine **1a** with vinylmagnesium bromide (3 equiv) in THF at  $60\text{ }^{\circ}\text{C}$  for 3 h resulted in **10** (72%).<sup>10</sup> It is noteworthy that the formation of **10** is highly stereoselective (*trans/cis* = 40/1).<sup>11</sup> However, when **1a** was treated with allylmagnesium bromide (3 equiv) in THF at room temperature, the reaction proceeded rapidly and was complete within 10 min, yielding a mixture of **11** (39%) and **12** (42%).<sup>12</sup> This result indicates that (i) allylmagnesium bromide was reactive enough, attacking the ketonic *N*-aziridinylimino group and (ii)

(7) For previous reports on anionic reactions of *N*-aziridinylimines, see: (a) Leone, C. L.; Chamberlin, A. R. *Tetrahedron Lett.* **1991**, *32*, 1691. (b) Kim, S.; Cho, C. M.; Yoon, J.-Y. *J. Org. Chem.* **1996**, *61*, 6018. (c) Oishi, M.; Yamamoto, H. *Synlett* **1997**, 191.

(8) For the use of tosylhydrazones as 1,1-dipoles, see: (a) Shapiro, R. H.; Gadek, T. *J. Org. Chem.* **1974**, *39*, 3418. (b) Vedejs, E.; Stolle, W. T. *Tetrahedron Lett.* **1977**, 135. (c) Bertz, S. H. *Tetrahedron Lett.* **1980**, *21*, 3151.

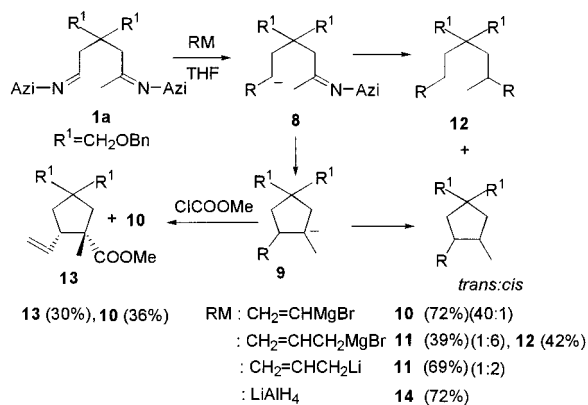
(9) (a) Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579. (b) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. (c) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855.

(10) 1,2-Vinyl rearrangement of tertiary to secondary alkylmagnesium bromide was not observed. Silver, M. S.; Shafer, P. R.; Nordlander, J. E.; Ruchardt, C.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 2646.

(11) The ratio was determined by GC–MS. The *cis*-isomer (**10b**) was prepared by the known procedure (Felkin, H.; Umpleby, J. D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* **1972**, 2285). Furthermore, **10b** was converted into **11b** to determine the ratio of **11a** and **11b** (see Supporting Information).

(12) The use of 1.0 equiv of allylmagnesium bromide under the similar conditions gave a mixture of **11** (42%) and **12** (10%) along with the protonated form of **8** (27%).

## Scheme 2



intermolecular addition of allylmagnesium bromide onto the *N*-aziridinylimino group would be slightly faster than the cyclization, presenting a striking contrast to those obtained in radical reactions.<sup>13</sup> This problem was solved by the use of reactive allyllithium. Reaction of **1a** with allyllithium in THF at  $-20^\circ C$  for 10 min afforded **11** in 69% yield without the formation of **12**. Somewhat surprisingly, the anionic cyclizations of **1a** with allylmagnesium bromide and allyllithium did not exhibit high stereoselectivities.<sup>14</sup> With allylmagnesium bromide, a 1:6 mixture of *trans*- (**11a**) and *cis*-isomer (**11b**) was obtained, whereas a 1:2 mixture of **11a** and **11b** was realized with allyllithium. Trapping anion **9** with methyl chloroformate was not efficient, yielding **13** in 30% yield along with **10** (36%).<sup>15</sup> Furthermore, reductive cyclization was achieved by treatment with lithium aluminum hydride in THF at room temperature for 5 h, in which the resulting anion could be successfully quenched with  $O_2$  and NBS (Table 1).<sup>7a</sup>

The synthetic usefulness of these anionic cyclizations was explored with several structurally different bis- and tris-aziridinylimines, and the synthetic potential of this approach is clearly evident in the carbocyclic ring formation processes as summarized in Table 1. The attractiveness of this approach is apparent from the efficiency of the formation of three consecutive carbon-carbon bonds in a single step to yield tricyclic compound **25** bearing a quadron skeleton with two alkenyl groups for further manipulation.<sup>16,17</sup> As compared with the previously reported methods involving reactive anionic intermediates, the present approach suggests several exciting directions. First, the initiation by the addition of organometallic reagents bearing functional groups to the substrates would be feasible. Second, sequential anionic cyclizations to accomplish multiple transformations in a single step could be utilized.<sup>18</sup> Finally, of synthetic significance is the use of this approach for the formation of consecutive carbon-carbon bonds.

(13) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 4.2.

(14) We have no clear answer why organometallic reagents would influence the stereochemical outcome of the cyclized products. Stereochemistry of the anionic cyclizations will be investigated in the near future.

(15) The reason for the low efficiency of trapping the resulting anions is unclear at the present. Furthermore, we failed to trap allyllithium **9** in THF with several electrophiles. Probably, allyllithium **9** would destroy THF rapidly. Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514.

(16) Wender, P. A.; Wolanin, D. J. *J. Org. Chem.* **1985**, *50*, 4418 and references therein.

**Table 1.** Carbocycles via Anionic Cyclizations of *N*-Aziridinylimines

substrate	RM <sup>a</sup>	product	yield, %
	A		<b>15</b> (76%)
	C		<b>16</b> (71%)
	D		E=H <b>17</b> (76%)
	D		=OH <b>18</b> (66%) <sup>b</sup>
	D		=Br <b>19</b> (65%) <sup>b</sup>
	A		<b>20</b> (72%) <sup>c</sup>
	C		<b>21</b> (70%) <sup>c</sup>
	C		<b>22</b> (63%) <sup>c</sup>
	C		<b>23</b> (57%) <sup>d</sup>
	C		<b>24</b> (69%) <sup>d</sup>
	B		<b>25</b> (65%) <sup>e</sup>

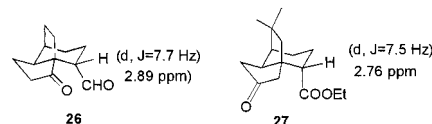
<sup>a</sup> A:  $CH_2=CHMgBr$ , THF,  $60^\circ C$ , 3 h; B:  $CH_2=CHLi$ , THF,  $0^\circ C$ , 0.1 h; C:  $CH_2=CHCH_2Li$ , THF,  $0^\circ C$ , 0.1 h; D:  $LiAlH_4$ , THF,  $20^\circ C$ , 3 h. <sup>b</sup> Quenching with  $O_2$  and NBS, respectively. <sup>c</sup> *trans*-/*cis*-Isomer by  $^1H$  NMR: **20** 4.3/1, **21** 3.2/1, **22** 1/3.4. <sup>d</sup> The ratio of isomers were determined by GC-MS: **23** 1/1, **24** 3/1. <sup>e</sup> Reference 17.

In conclusion, we have demonstrated (i) novel anionic cyclizations using *N*-aziridinylimines as 1,1-dipole, in which the formation of consecutive carbon-carbon bonds has been achieved for the first time, and (ii) its application to construct bicyclic and tricyclic carbocycles, providing efficient routes to natural product synthesis. Further studies on the application of this approach to natural product synthesis and the use of unactivated olefins as anionic acceptors are in progress.

**Supporting Information Available:** Experimental procedures as well as spectral data for the reaction products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) The stereochemistry of the vinyl group in **25** has tentatively been determined by comparison of *J* values ( $^1H$  NMR) of CH in **26** and **27**. Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.



(18) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765.