Asymmetric Cyclization of Achiral Olefinic Organolithiums Controlled by a Stereogenic Lithium: Intramolecular Carbolithiation in the Presence of (−)-Sparteine

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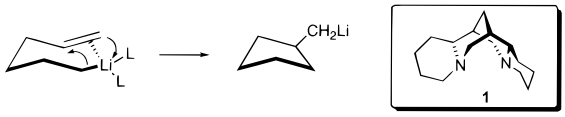
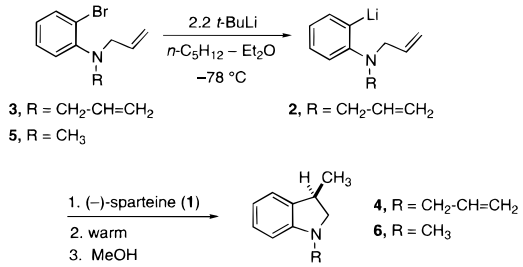
The cycloisomerization of olefinic organolithiums provides a regiospecific and highly diastereoselective route to functionalized carbocyclic and heterocyclic systems.[1−4] Molecular orbital calculations indicate the stereochemical course of these formally anionic cyclizations[5] is a consequence of a fairly rigid transition state for the process in which the lithium atom is coordinated to the remote π-bond.[3] Indeed, the ground-state structure of archetypal 5-hexenyllithium (shown below) resembles a chairlike arrangement in which the lithium atom at C(1) is coordinated to the C(5)−C(6) π-bond.[3,6] Calculations further suggest that the cycloisomerization of 5-hexenyllithium (and, by analogy, other unsaturated organolithiums) should proceed with complete retention of configuration at the lithium-bearing C(1) position by *syn*-addition to the π-bond.[3] This later prediction has been confirmed experimentally by the groups of Hoppe and Nakai[7] and the stereoselectivity of the ring closure has been exploited in several recent reports detailing the asymmetric cyclization of chiral 5-hexenyllithiums that possess a stereogenic carbanionic center.[2k,7,8]



On the assumption that the internally coordinated lithium atom of an unsaturated organolithium has two additional sites available for ligation, the lithium atom of an achiral substrate is rendered stereogenic upon complexation in an η_2-fashion with a chiral, bidentate ligand. It occurred to us that, on this basis, it might be possible to effect enantiofacially selective cycloisomerization of an *achiral* olefinic organolithium by simply conducting the isomerization of the achiral substrate in the presence of such a chiral ligand. In light of the elegant pioneering studies by Normant and Marek, demonstrating the ability of the lupine alkaloid (−)-sparteine (**1**) to promote enantioselective *inter*molecular carbolithiation,[9] this readily available, chiral diamine was chosen for exploratory investigation. As demonstrated by the results of model studies presented below, conducting the cyclization of achiral olefinic organolithiums in the presence of stoichiometric amounts of **1** renders the isomerization enantioselective.

The 2-(*N*,*N*-diallylamino)phenyllithium (**2**) substrate, which is known to afford high yields of 3-substituted indolines upon 5-exo cyclization and trapping with an electrophile,[4] was selected as a representative model to assess the possibility of effecting enantioselective ring closure of an achiral organolithium. Aryllithium **2** was prepared in virtually quantitative yield, as previously described,[4b] by treatment of 0.1 M solutions of *N*,*N*-diallyl-2-bromoaniline (**3**), typically (vide infra) in dry *n*-pentane−diethyl ether (9:1 by vol), with 2.2 molar equiv of *t*-BuLi at −78 °C.[10] Asymmetric cyclization of **2** was easily accomplished, as illustrated in Scheme 1, by addition of 2.2 equiv of dry, oxygen-

Scheme 1



free (−)-sparteine (**1**) to the −78 °C solution and allowing the resulting mixture to warm and stand at various temperatures for 1−1.5 h prior to quench with MeOH. The enantiomeric purity of the resulting (*R*)-(−)-1-allyl-3-methylindoline (**4**)[11] was assayed directly by CSP HPLC on a Chiralcel-OD column as detailed in the Supporting Information. The results of these experiments, summarized in Table 1, demonstrate that the (−)-sparteine-mediated cyclization of **2** is indeed highly enantioselective.

Several features of the data summarized in Table 1 are worthy of note. Not surprisingly, the cyclization is more enantioselective at lower temperatures (Table 1, cf. entries 1, 3, and 4); at temperatures below ∼−40 °C the isomerization is too slow to be of practical value (Table 1, entry 10). Solvent has a very dramatic effect on the enantioselectivity of the ring closure: while solvent systems composed of hydrocarbon−diethyl ether (Table 1, entries 3−5 and 7), pure hydrocarbon (Table 1, entry 2), or pure ether (Table 1, entry 8) are equally effective media for the cycloisomerization, the use of THF as solvent is to be avoided since it leads to virtually racemic product (Table 1, entry 9).[12] It should also be noted that at least 2 molar equiv of **1** must be

(1) For a review, see: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, Mechanisms of Importance in Synthesis, pp 251−273.

(2) For leading references, see: (a) Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999. (b) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 9, 2442. (c) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. (d) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc*. **1989**, *111*, 765. (e) Bailey, W. F.; Khanolkar, A. D. *J. Org. Chem.* **1990**, *55*, 6058. (f) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc*. **1992**, *114*, 8053. (g) Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495 and references therein. (h) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc*. **1995**, *117*, 1954. (i) Bailey, W. F.; Jiang, X.-L.; McLeod, C. E. *J. Org. Chem.* **1995**, *60*, 7791. (j) Krief, A.; Kenda, B.; Remacle, B. *Tetrahedron* **1996**, *52*, 7435 and references therein. (k) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc*. **1996**, *118*, 5322.

(3) 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.

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(5) It is important to note that the lithium atom is intimately involved in the cycloisomerization of unsaturated organolithiums: 5-hexenyllithium is unique among the 5-hexenylalkalis in it ability to undergo facile cyclization. See: Bailey, W. F.; Punzalan, E. R. *J. Am. Chem. Soc.* **1994**, *116*, 6577.

(6) Intramolecular coordination of the lithium atom with the remote π-bond in the ground state of 5-hexenyllithium has been experimentally confirmed. See: Rölle, T.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1953.

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(8) (a) Krief, A.; Bousbaa, J. *Synlett* **1996**, 1007. (b) Tomooka, K.; Komine, N.; Sasaki, H.; Shimizu, T.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 9715. (c) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem.* **1999**, *64*, 8616. (d) Hoppe, D.; Woltering, M. J.; Oestreich, M.; Fröhlich, R. *Helv. Chim. Acta* **1999**, *82*, 1860.

(9) (a) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (b) Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. J. *Org. Chem.* **1997**, *62*, 4898. (c) For a review of enantioselective intermolecular carbolithiation of alkenes, see: Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535. (d) For reviews of the use of (−)-sparteine to effect asymmetric organolithium chemistry, see: Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552 and Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2282.

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(11) Determination of the absolute configuration of (*R*)-(−)-1-allyl-3-methylindoline (**4**) has been described: see, Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Phys. Chem. A* **1999**, *103*, 6603.

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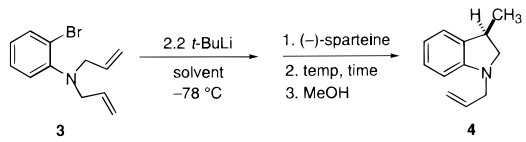
Table 1. Enantioselective Preparation of 1-Allyl-3-methylindoline (4)[a]

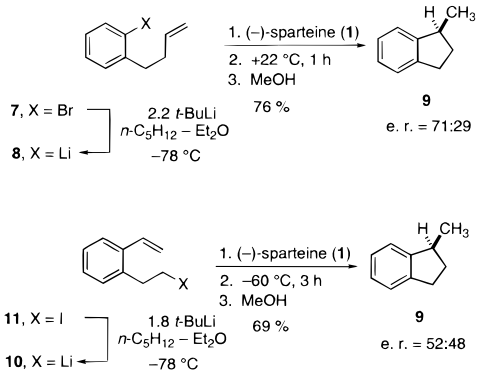


3 4

entry	solvent [b]	sparteine, molar equiv	temp, °C	time, h	yield,[c] %	e.r.[d]
1	n-C_5H_{12}−Et_2O	2.1	0	1.0	78	88:12
2	n-C_5H_{12}	2.2	0	1.0	80[e]	86:14
3	n-C_5H_{12}−Et_2O	2.5	−20	1.0	96[e]	89:11
4	n-C_5H_{12}−Et_2O	2.1	−40	1.5	69	93:7
5	n-C_5H_{12}−Et_2O	4.4	−40	1.5	68	92:8
6	n-C_5H_{12}−Et_2O	1.1	−40	1.5	4[e]	
7	cumene−Et_2O	2.3	−40	1.5	50	91:9
8	Et_2O	2.2	−40	1.5	91[e]	89:11
9	THF	2.3	−40	1.5	86[e]	51:49
10	n-C_5H_{12}−Et_2O	1.7	−60	1.0	<4[e]	

[a] See text. [b] The relative proportions of *n*-pentane−diethyl ether and cumene−diethyl ether were 9:1 by vol. [c] Isolated yields of chromatographically pure product unless otherwise noted. [d] Enantiomeric ratio determined by CSP HPLC. [e] Yield was determined by GC analysis.

Scheme 2

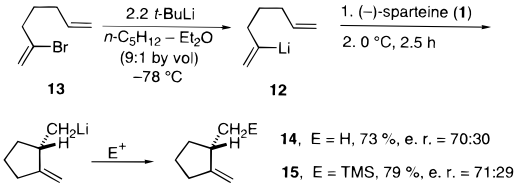


added to reaction mixtures to effect rapid enantioselective cyclization of the aryllithium (Table 1, cf. entries 4−6): the generation of **2** by lithium−bromine exchange is accompanied by the formation of a full equiv of LiBr, and this salt effectively removes a full equiv of the diamine ligand via preferential complexation with **1** (a precipitate forms at low temperature).

It is of interest to note that the (−)-sparteine-mediated cyclization of the aryllithium derived from *N*-allyl-*N*-methyl-2-bromoaniline (**5**) is somewhat less enantioselective than is the cyclization of the analogous diallyl substrate discussed above (Scheme 1). Cycloisomerization of the aryllithium generated from **5** afforded an 88% yield of (−)-1,3-dimethylindoline (**6**) with an ee of 70%. In light of the fact that cyclization of **2** under identical conditions (Table 1, entry 4) leads to product with an ee of 86%, it would appear that the presence of the two enantiotopic allyl units in **2** contributes to the high enantioselectivity of the process.

The results of a less extensive investigation of the (−)-sparteine-mediated isomerization of the achiral aryllithium (**8**) derived from 2-bromo-1-(3-butenyl)benzene (**7**) are summarized in Scheme 2. The cyclization of **8**, which was reported some time ago by

Scheme 3



Woolsey and co-workers,[13] is considerably less facile than are the ring closures discussed above. For this reason, it was necessary to allow solutions of **8** in *n*-pentane−diethyl ether containing 2.2 equiv of (−)-sparteine to stand for 1 h at +22 °C to effect cyclization. Nonetheless, even at this relatively high temperature, the cycloisomerization of **8** in the presence of **1** is fairly enantioselective: as illustrated in Scheme 2, trapping of the (1-indanyl)methyllithium product by protonation gave a 76% yield of the known[14] (*S*)-(−)-1-methylindan (**9**) in 76% yield with an ee of 42%.

An alternative route to (1-indanyl)methyllithium, involving cyclization of the styrene-tethered primary alkyllithium (**10**) generated from 1-(2-iodoethyl)-2-vinylbenzene (**11**), was also investigated. Not surprisingly, isomerization of **10** in *n*-pentane−diethyl ether containing 2 equiv of **1** is a very rapid 5-exo process. However, as shown in Scheme 2, the cycloisomerization, which proceeds to completion in 3 h at −60 °C, affords essentially racemic (ee ∼4%) 1-methylindan (**9**) in 69% yield. While it is tempting to attribute the formation of racemic **9** to a competing, rapid cyclization in the absence of ligated sparteine, control experiments demonstrate that less than 10% of **9** is formed when solutions of **10** are allowed to stand for 3 h at −60 °C in the absence of **1**. It would appear that the ability of (−)-sparteine to facilitate the cyclization of an achiral organolithium such as **10** is not always sufficient to render such a process enantioselective.

Be that as it may, the cyclization of very simple substrates may be conducted in an enantioselective fashion in the presence of (−)-sparteine. As illustrated in Scheme 3, the unadorned vinyllithium (**12**), derived from 2-bromo-1,6-heptadiene (**13**) by low-temperature lithium−bromine exchange in *n*-pentane − diethyl ether, undergoes a moderately enantioselective cyclization when stirred at 0 °C in the presence of 2.2 molar equiv of **1** to give, inter alia, (*S*)-(+)-(**14**) in ∼40% ee. Trapping of the organolithium product with TMS-Cl gave (*S*)-(+)-**15** of known absolute configuration[15] in 79% yield.

The chemistry described in this preliminary report, summarized in Schemes 1−3, demonstrates for the first time that a chiral ligand may confer enantiofacial selectivity in cyclizations of achiral olefinic organolithiums. This ability to discriminate between the enantiotopic faces of an unactivated carbon−carbon π-bond tethered to a formally carbanionic center considerably extends the synthetic utility of anionic cyclization as a route to carbocyclic and heterocyclic systems.

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Supporting Information Available: Detailed experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Apparently, as noted elsewhere by Collum, THF (but evidently not diethyl ether) saturates the coordination sphere of lithium to the exclusion of a bidentate diamine ligand such as **1**: see, Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

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(14) Brewster, J. H. *Helv. Chim. Acta* **1982**, *65*, 317.

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