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Enantioselective Synthesis of 2-Benzothiazolyl Oxiranes

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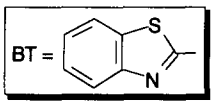
Abstract: Lithiation of 2-(chloroethyl)benzothiazole **1a** gives (benzothiazolylchloroethyl)lithium **1b**. The reaction of **1b** with ketones in the presence of (-)-sparteine leads to chlorohydrins **2a-c** that cyclize to epoxides **3a-c**, enantioselectively, the enantiomeric enrichment being dependent upon the solvent, the lithiating agent, the reaction time. The reaction with aldehydes furnishes chlorohydrins **2d-g** and then epoxides **3d-g** diastereo- and enantioselectively. © 1997 Elsevier Science Ltd.

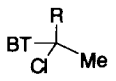
An emerging methodology of asymmetric synthesis is based on the reaction of an achiral electrophile with a carbanion or a carbanionic species generated by using a chiral base or in the presence of a chiral ligand. The stereochemistry of dipole-stabilized carbanions in the presence of chiral ligands has been extensively investigated,[1] as well as the chiral lithium amide-mediated enantioselective aldol reaction.[2] An enantioselective Darzens reaction of *t*-butyl chloroacetate mediated by a chiral lithium amide has been recently reported by Koga.[3]

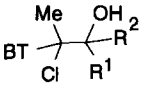
We have recently reported that certain heteroaryl α-chloromethyllithiums behave as Darzens reagents, adding smoothly to carbonyl compounds and imines to give stereoselectively heteroaryl epoxides[4-6] and aziridines,[7] respectively. Heteroaryl epoxides are of some interest in medicinal chemistry[8] and have a potential in synthetic organic chemistry for the functionalization in the side chain of the heterocyclic system. Therefore, we considered it worth developing an enantioselective synthesis of such compounds. In this paper, we report on the first enantioselective synthesis of 2-benzothiazolyl epoxides, based on the reaction of a benzothiazolylchloroalkyllithium with carbonyl compounds under the asymmetric conditions created by the presence of (-)-sparteine.

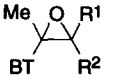
Treatment of 2-(chloroethyl)benzothiazole **1a** with lithium diisopropylamide (LDA) in THF at -100 °C gave benzothiazolylchloroethyllithium **1b**, which was proved to be stable and could be trapped, even after hours, by deuteromethanol to give **1c** (72% of deuteration) and by MeI to give the methylation product **1d**. Complexation of **1b** with (-)-sparteine, followed by addition of acetone after 1h and quenching with NH_4Cl, furnished the chlorohydrin **2a**, that was subsequently cyclized to the epoxide **3a**, in overall yields and enantiomeric enrichments which were remarkably dependent upon the experimental conditions in terms of reaction times, solvent and lithiating agent (Table). The best results (86% yield; ee: 67%)[9] were achieved when LDA was used as the lithiating agent and toluene as the solvent. Comparable results were obtained with cyclohexanone to give first the chlorohydrin **2b** and then the epoxide **3b** (ee 63%). In the case of adamantanone the chlorohydrin **2c** could not be isolated. The epoxide **3c** (ee 72%) was obtained directly.

Lithiation of **1a** with LDA in THF, followed by the addition of benzaldehyde furnished the chlorohydrins **2d** as a mixture of diastereomers (*syn/anti* : 3/7). Cyclisation of the diasteromeric halohydrins **2d** gave epoxides **3d** (*Z/E* : 3/7)[10] which could be separated by column chromatography. The configuration of the two diastereomers was assigned by ^{13}C NMR spectroscopy.[11] In the ^{13}C-H coupled spectrum (gated decoupling) the $^{3}J_{CH3\text{-}H}$ (1.78 Hz) of the *E* isomer (having the CH_3 and the ring hydrogen in a *cis* arrangement) was found to be larger than that of the *Z* isomer (~ 0 Hz). Such a configuration assignment was confirmed by a NOE difference experiment.[12] The same diastereomeric ratio (de) of the halohydrins **2d** (*syn/anti* : 3/7) and the epoxides **3d** (*Z/E*: 3/7) was observed when the reaction was performed in THF and the anion **1b** was pretreated with (-)-sparteine. Both the *E* and *Z* epoxides, however, were racemic. This lack of enantioselection is to be ascribed, as reported in other cases,[1k] to the coordinating ability of THF which prevents **1b** from complexing with (-)-sparteine.







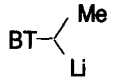


1a: R = H

1b: R = Li

1c: R = D

1d: R = Me

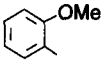
1e: 

2a: $R^1 = R^2 = Me$

2b: $R^1, R^2 =$ 

2c: $R^1, R^2 =$ 

2d: $R^1 = H$; $R^2 = Ph$

2e: $R^1 = H$; $R^2 =$ 

2f: $R^1 = H$; $R^2 = CH(CH_3)_3$

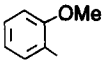
2g: $R^1 = H$; $R^2 = Me$

3a: $R^1 = R^2 = Me$

3b: $R^1, R^2 =$ 

3c: $R^1, R^2 =$ 

3d: $R^1 = H$; $R^2 = Ph$

3e: $R^1 = H$; $R^2 =$ 

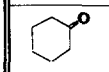
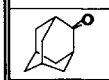
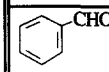
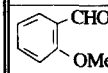
3f: $R^1 = H$; $R^2 = CH(CH_3)_3$

3g: $R^1 = H$; $R^2 = Me$

When the reaction of **1b**, pretreated with (-)-sparteine (1h), and benzaldehyde was carried out in toluene, the halohydrins **2d** formed in a high yield (*syn/anti* : 7/3). When treated with NaOH in isopropanol the halohydrins **2d** furnished, in a stereospecific manner,[13] the epoxides **3d** (*Z/E*: 7/3). It is worth noting that the de of both the chlorohydrins **2d** and the epoxides **3d** in toluene was opposite to that measured in THF. The HPLC inspection revealed that the *E* isomer was almost racemic (ee 3%) while a good ee (67%) was detected in the *Z* isomer. The ee, however, was time dependent in both the two diastereomers. Indeed, quenching of the reaction after 3h led to a mixture of the halohydrins **2d** which were cyclized to the epoxides **3d** as a mixture of *E* (ee 12%) and *Z* (ee 33%) in a 3 to 7 ratio.[14] Comparable results were obtained with *o*-anisaldehyde, isobutyraldehyde and acetaldehyde. It was interesting to note that the ee in the halohydrins **2e** was almost the same as in the corresponding epoxides **3e**. This seems to suggest that what keeps the ee under control is the halohydrin formation and not the successive cyclization to the epoxide.

To rationalize these results, we assume that it is the preformed (-)-sparteine/**1b** complex[15] that reacts with the carbonyl compound leading to the chlorohydrins, which subsequently cyclize to the corresponding epoxides. The halohydrin-epoxide conversion is supposed not to be the enantiodetermining step as in some cases we have proved that the ee in the epoxides is the same of the parent chlorohydrins.[16] Therefore, the enantioselectivity must be established in the deprotonation step of **1a** or in the C-C bond formation step of the reaction of (-)-sparteine/**1b** complex with the carbonyl compound to give the chlorohydrin. It is likely that the enantioselection is determined by the energy differences in the competitive diastereomeric transition states consequent to the nucleophilic attack of the **1b**/(-)-sparteine complex to the enantiotopic faces of the carbonyl compound. More work is in progress in our laboratory in order to rationalize the above diastereo and enantioselections.

Table: Lithiation of 2-(chloroethyl)benzothiazole **1a** and reactions with carbonyl compounds.

Carbonyl Comp.	Base	Solv.	Chiral ligand[a,b]	React. time[b]	Chlorohydrin (% yield)	syn/anti ratio	ee% syn	ee% anti	Epoxide (% yield)	Epoxide ee%	
Me_2CO	LDA[c]	THF	(-)-sparteine	20 min	**2a** (94)	/	/	/	**3a** (>95)	6	
"	s-BuLi[c]	Toluene	"	"	" (27)	/	/	/	"	76	
"	"[c]	TBME	"	"	" (40)	/	/	/	"	70	
"	LDA[c]	Toluene	"	"	" (86)	/	/	/	"	67	
	"[c]	"	"	30 min	**2b** (75)	/	/	/	**3b** (>95)	63	
	"[c,d]	"	"	35 min	**2c**[e]	/	/	/	**3c** (70)	72	
										Z	E
	LDA[c]	THF	/	30 min	**2d** (60)	3 : 7	/	/	**3d** (>95)	/	/
"	"[c]	"	(-)-sparteine	30 min	" (57)	"	/	/	"	0	0
"	"[c]	Toluene	"	"	" (68)	7 : 3	/	/	"	67	3
"	"[c]	"	"	3 h	" (60)	"	/	/	"	33	12
	"[c]	THF	/	30 min	**2e** (69)	5.5 : 4.5	/	/	**3e** (>95)	/	/
"	"[c]	Toluene	(-)-sparteine	"	" (69)	7 : 3	75	37	"	77	39
Me_2CHCHO	"[c]	"	"	20 min	**2f** (63)[f]	3 : 2	51	79	**3f** (>95)	48	78
MeCHO	"[c]	"	"	10 min	**2g** (57)	5.6 : 4.4	/	/	**3g** (>95)	43	51

[a]Molar ratio of 2-(chloroethyl)benzothiazole: base: (-)-sparteine 1 : 2 : 2. [b]Complexation time and temperature always were 1h and -100 °C, respectively, except in the case of the reaction with adamantanone (see note *d*). [c]Lithiating agent was added to the complex **1a**/(-)-sparteine. [d]The time of complexation of **1b** with (-)-sparteine was in this case 2h. [e]Not isolated. [f]After 20 min it was also isolated a mixture of diastereomeric epoxides **3f** (23%) with ee 45% in the *E* isomer and ee 24% in the *Z* isomer.

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9. The ee values were determined by HPLC using a chiral column (Chiracel OD, Daicel Co., Tokyo, Japan) with hexane-isopropanol (90-99.5: 10-0.5, flow rate= 0.35-1 mL/min, monitored at 254 nm).
10. The same results were obtained when the reaction was quenched with NH_4Cl after 3h.
11. Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, *43*, 4696.
12. The methynic ring proton of the *E* isomer displays dipolar interaction with the vicinal methyl group; the saturation of the latter gives 7.0 enhancement of the ring proton resonance against no detectable enhancement in the case of the other isomer.
13. An example of stereospecific transformation of *syn* and *anti* chlorohydrins has recently been reported for 2-halogeno-3-hydroxy esters: Cabon, O.; Buisson, D.; Larcheveque, M.; Azerad, R. *Tetrahedron Asymmetry* **1995**, *6*, 2211.
14. The variation in the ee of **3d** could be ascribed to the equilibration of the parent halohydrins which may interconvert through a retroaldol-aldol reaction or an enolization reaction considering that **1b** has to be seen as an aza-enolate. See: Calò, V.; Lopez, L.; Fiandanese, V.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1978**, 4693; Zimmermann, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1960**, *82*, 5459. Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. See also ref. 13.
15. This kind of complex, between an organolithium and (-)-sparteine, has been used recently for the successful enantioselective deprotonation of carbamate protected alcohol (Hoppe, D.; Hintze, F.; Tebben, P.; Paelov, M.; Ahrens, H.; Schverdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure & Appl. Chem.* **1994**, *66*, 1479) and N-t-Boc-protected pyrrolidine (see Ref. 2e).
16. Diastereomeric chlorohydrins from the reaction of **1b** with aldehydes do not interconvert under the reaction conditions. Indeed, the *syn* chlorohydrin **2e** was recovered unchanged after treatment with LDA in the presence of (-)-sparteine.

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