Lithiation and Reactions of Stilbene Oxides: Synthetic Utility

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ABSTRACT



The lithiation of *trans*- and *cis*-stilbene oxides (\pm)-1 and 8 has been investigated. While with 8, lithiation occurred exclusively at the benzylic position, with the trans isomer (\pm)-1, ortho-lithiation competed with α -lithiation depending upon the experimental conditions. The configurational stability of the α -lithiated *cis*- and *trans*-stilbene oxides (\pm)-2 and (\pm)-9, respectively, was proved as well as that of scalemic stilbene oxide (*R*,*R*)-2.

Polysubstituted epoxides are often key intermediates in the construction of structurally complex molecules,¹ and as such their synthesis has been intensively studied.^{2a-g} Among the numerous routes that have been developed to this end, the oxiranylanion-based methodology has been exploited in only a few cases.^{2h} The related enantioselective version has been pursued even less.^{2k,3,4}

Quite recently, we developed a new stereospecific synthesis of styrene oxide derivatives, which was based on the oxiranyllithium methodology. Starting from (S)- or (R)styrene oxide, it was possible to obtain α -substituted styrene oxides in high yields and excellent enantiomeric purity.³ The stereospecificity of the lithiation-trapping sequence of phenylpropylene oxides has also been shown.⁴

In continuation of our work on the chemistry of arylstabilized oxiranyllithiums, and to evaluate the substituent effect on their reactivity and stability, we conducted a detailed exploration of the lithiation of stilbene oxides and successive trapping with electrophiles.

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Lithiation of racemic *trans*-stilbene oxide **1** followed by quenching with MeI gave a mixture of the expected epoxide *trans*-**4a** and the ortho-methylated epoxide **5a**, the **4a**:**5a** ratio being dependent upon the experimental conditions (Scheme 1 and Table 1). *s*-BuLi (1.5 equiv), TMEDA (1.5 equiv),

Table 1. Lithiation—Methylation of (\pm) -1: Effect of the Lithiating System and Experimental Conditions on the Regioselectivity^{*a*}

		T	t		conversion of 1
entry	base $(equiv)^b$	(°C)	(min)	4a:5a ^{c,d,e}	$(\%)^c$
1	s -BuLi (2) f	-78	45	70:30	98
2	s -BuLi (2) f,g	-78	45	66:34	98
3	s -BuLi (2) f	-50	30	85:15	98
4	s-BuLi (2)	-78	30	50:50	90
5	s -BuLi $(1.5)^h$	-60	60	74:26	82
6	s -BuLi $(1.5)^h$	-98	60	36:64	67
7	<i>s</i> -BuLi (1.1)	-98	30	37:63	48
8	<i>s</i> -BuLi (1.5)	-98	10	36:64	36
9	<i>n</i> -BuLi (3)	-60	120	92:8	88
10	<i>n</i> -BuLi (1.5)	-60	180	90:10	85
11	n -BuLi $(1.5)^{h,i}$	-55	35	85:15	85
12	<i>n</i> -BuLi (1.5)	-60	120	90:10	81
13	<i>n</i> -BuLi (1.5)	-60	60	90:10	55
14	n-BuLi (3) ^f	-60	120	>98:2	40
15	n -BuLi $(1.5)^{h,j}$	-55	35	85:15	34
16	<i>t</i> -BuLi (1.2) ^{<i>f</i>}	-78	60	>98:2	22
17	MeLi (1.5) ^f	-55	35	_	-
18	LDA (1.5) ^f	-98	15	_	_

^{*a*} Reactions performed in THF/TMEDA (3 equiv). ^{*b*} Equivalents with respect to **1**. ^{*c*} Determined by ¹H NMR analysis. ^{*d*} For spectroscopic data of **4a** and **5a**, see ref 8. ^{*e*} Inseparable mixture. ^{*f*} Reaction without TMEDA. ^{*g*} Reaction in 2/1 hexane/THF. ^{*h*} Reaction performed with 1.5 equiv of TMEDA. ^{*i*} Reaction in toluene. ^{*j*} Reaction in DME.

THF, -98 °C, and 1 h as the reaction time represented the best conditions for the formation of epoxide **5a** (**4a**:**5a** = 36:64, entry 6). To account for formation of **5a** we believe that there is coordinative assistance of the epoxide oxygen to the H–Li exchange on the phenyl ring (intermediate **3**). In other words, the epoxide is acting as an ortho-directing group (DoM methodology).⁵ This behavior is quite surprising since benzylic ethers, unlike the related benzylic amines, usually undergo exclusive α -lithiation rather than ortholithiation.⁶

(5) Organolithiums: Selectivity for Synthesis; Clayden, J., Ed.; Pergamon: Oxford, 2002; Tetrahedron Organic Chemistry Series, Vol. 23, pp 28–73.

We made several attempts to increase the regioselectivity in favor of the ortho-lithiation by using different bases, lower temperatures (-110 to -98 °C), and different solvents: all were unsuccessful. The percentage of *trans*-**4a**, which was the minor product at -98 °C when using *s*-BuLi, increased with temperature until it became the main product at -60 °C (**4a**:**5a** = 74:26, entry 5). The conversion of starting material also increased with the temperature. When *trans*-**1** was lithiated (*s*-BuLi/TMEDA, -98 °C) and then allowed to warm to rt, PhCH₂COPh formed (75% yield) after acidic quenching. Such an isomerization of **1** has been already reported.⁷

We subsequently focused on finding conditions that favored α -deprotonation. Lithiation of **1** with either 3 or 1.5 equiv of *n*-BuLi and 3 equiv of TMEDA in THF at -60 °C for 2 h gave the best conversion of **1** to **2** with high regioselectivity. Quenching with MeI gave the α -substituted product **4a** in very good yields (81 and 73%) and high regioselectivity: the **4a**:**5a** ratio ranged from 92:8 to 90:10 (Table 1, entries 9 and 12).

An increase in regioselectivity was also observed (4a:5a > 98:2) when the deprotonation was performed without TMEDA, but the conversion of **1** was poor (40%) (Table 1, entry 14). Good yield and regioselectivity were also noted in toluene (entry 11). In all cases, the conversion of **1** to **4a** proceeded with complete retention of configuration.

We suspected that the observed temperature dependence in the regioselective lithiation of **1** could be the result of an equilibration of the α - and ortho-lithiated species ("anion translocation").⁹ However, three experiments ruled out such a possibility. In the first, we subjected the *o*-bromo-*trans*stilbene oxide **6**¹⁰ to a lithiation—methylation sequence under a variety of experimental conditions. In no case did we observe α -methylation: only *trans*-**1** and the ortho-methylated compound **5a** were obtained (Table 2). The formation

Table 2. Reaction of Lithiated (\pm) -6 in THF with MeI

Br O, (*)-6	,Ph <u>i) RLi</u> ii) Mel),,,Ph ,, + 5a	Ph (<u>+</u>)-1
RLi	time (h)	temp (°C)	5a (%) ^a	$1 \ (\%)^a$
t-BuLi	1.5	-98	68	32
n-BuLi	1.5	-78	77	23
n-BuLi	$0.5^{b,c}$	-78	72	10

^{*a*} Yield by ¹H NMR analysis on the crude mixture. ^{*b*} Formation of **1** is lowered by shorter reaction times. ^{*c*} ¹H NMR analysis on the crude mixture showed 18% of unreacted (\pm) -**6**.

of **1** and **5a** can be ascribed to Li-Br exchange and hydrogen trapping by any proton source in the reaction medium and methylation with MeI, respectively.

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In the second experiment, *trans*-1 was first lithiated with *s*-BuLi/TMEDA at -98 °C, kept there for 1.5 h, then warmed to -60 °C for 1 h and quenched with MeI. The **4a:5a** ratio was 57:43, which lies between the **4a:5a** ratio of 36:64 measured at -98 °C and 74:26 recorded at -60 °C. This result confirms that ortho-lithiation is favored at low temperature and α -lithiation at high temperature.¹¹

In the third experiment, dideutero stilbene oxide $1-d_2^{12a}$ was first deprotonated with *s*-BuLi/TMEDA at -98 °C, warmed to -60 °C for 1.5 h, and then quenched with MeI to give *o*-methyl stilbene oxide **5a**- d_2 , *o*,*o*'-dimethyl stilbene oxide **7**- d_2^{12b} and α -methyl stilbene oxide **4a**- d_1 (Scheme 2).



None of these products were ortho-deuterated, thus demonstrating the absence of ortho-lithiation followed by anion translocation to the α -lithio species. Interestingly, the regioselectivity (highly shifted toward ortho-lithiation) of the deprotonation—methylation sequence was highly dependent on the H/D substituent, thus demonstrating a remarkable kinetic isotopic effect. The deprotonation—methylation sequence carried out on the "light" stilbene oxide **1** led to a **4a:5a** ratio = 57:43, and the *o,o'*-dimethylated stilbene oxide **7** did not form at all.

Lithiation of **1**, carried out under conditions that favor α -deprotonation, followed by trapping with EtI and allylBr, afforded epoxides **4b** and **4c**, respectively, with high regioselectivity and complete retention of configuration, together with small amounts of epoxides **5b** and **5c**. Trapping with benzaldehyde, however, furnished epoxy alcohol **4d** (almost 1:1 diastereomeric mixture, dr = 60:40) together with epoxide **5d** (mixture of diastereoisomers, dr = 60:40) (Table 3).

The configuration of the two diastereoisomers of **4d** $(1R^*, 2S^*, 3R^* \text{ and } 1R^*, 2R^*, 3S^*)$ was deduced by 500 MHz ¹H NMR analysis.^{13a} The configuration of **4d***-syn* was also confirmed by X-ray analysis.^{13b} Lithiation of **1** followed by quenching with PhCONMe₂ produced exclusively epoxide

Ph (<u>+</u>)-'	1) <i>n</i> - THF, 2) E ⁴	BuLi/TMEDA 60°C, 2h	E,,,,,,,,,,,Ph Ph (<u>+</u>)- 4b-e	+ E	
entry	product	electrophile	E	4 (%) ^a	$4:5^{b}$
1	$4\mathbf{b}^c$	EtI	Et	57	97:3
2	$4\mathbf{c}^{c}$	AllylBr	Allyl	55	93:7
3	$4d^e$	PhCHO	PhCHOH	56^d	90:10
4	$4\mathbf{e}^{e,f}$	$PhCONMe_2$	PhCO	56	>99:1

^{*a*} Isolated yields. ^{*b*} Regioisomeric ratio by ¹H NMR analysis on the crude mixture. ^{*c*} For spectroscopic data of **4b** and **4c**, see refs 8 and 14, respectively. ^{*d*} Overall yield in both diastereomers (dr = 60/40). ^{*e*} For spectroscopic data, see Supporting Information. ^{*f*} *s*-BuLi was used instead of *n*-BuLi to avoid the formation of PhCOBu by the reaction of *n*-BuLi with PhCONMe₂.

4e (Table 3, entry 4). These results provide further evidence of the configurational stability of the parent lithiated oxirane when held at -60 °C for 2 h.

On the basis of results collected in Tables 1-3, the following conclusions can be drawn. First, the base used controls the regioselectivity of the deprotonation reaction, s-BuLi promoting ortho-lithiation, *n*-BuLi favoring α -lithiation. In all cases, addition of TMEDA promotes ortholithiation but to different extents depending on the base employed. Second, attempts to lithiate 1 with t-BuLi or LDA at -78 °C or lower temperature failed. In fact, just traces of 4a and 5a could be observed in the crude reaction mixture by ¹H NMR analysis after quenching with MeI (Table 1), although it had been reported that lithiated stilbene oxide 2, generated upon treatment of 1 with *t*-BuLi (or LDA), could be trapped with Me₃SiCl (internal quenching).¹⁵ Third, the regioselectivity depends also upon the electrophile, the addition of PhCONMe2 to a mixture of n-BuLi, TMEDA, and 1 (Table 3, entry 4) furnishing the α -acyl stilbene oxide 4e in a highly regioselective manner. NMR analysis of the crude reaction product did not show any trace of the acylated epoxide on the ortho position. This behavior may be due to a higher kinetic nucleophilicity of the oxiranyllithium 2 compared with the aryllithium 3. Moreover, under the experimental conditions that favor the α -lithiation [*n*-BuLi (1.5 equiv), TMEDA (3 equiv), PhCONMe₂ (1.5 equiv) at -60 °C], 1-phenylpentanone (formed by addition of the excess *n*-BuLi to PhCONMe₂) might protonate the lithiated

⁽⁹⁾ As an example of "anion translocation", see: Ahmed, A.; Clayden, J.; Rowley, M. *Tetrahedron Lett.* **1998**, *39*, 6103.

⁽¹⁰⁾ For the preparation of **6**, see: Akgun, E.; Glinski, M. B.; Dawan, K. L.; Durst, T. *J. Org. Chem.* **1981**, *46*, 2730.

⁽¹¹⁾ Lithiation at -98 °C was not complete. Therefore, as the mixture is warmed from -98 to -60 °C, the remaining strarting material is deprotonated at the higher temperature, which favors α -lithiation.

^{(12) (}a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. J. Am. Chem. Soc. **2003**, 125, 10926. (b) The presence of **7**- d_2 (not isolated) was ascertained by ¹H NMR, GC-MS analysis on the crude mixture, and comparison with the light compound **7** (see Supporting Information).

^{(13) (}a) According to previous observations on many diastereomeric epoxy alcohols (See ref 3 and: Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. J. Am. Chem. Soc. **1989**, 111, 203), the carbinol proton of the syn isomer (in our case corresponding to $(1R^*, 2S^*, 3R^*)$ -**4d**) absorbs at a lower field than the corresponding proton of the anti isomer (δ 4.81 vs 4.60 for **4d**-syn and **4d**-anti). (b) CCDC 246147 contains the supplementary crystallographic data for compound $(1R^*, 2S^*, 3R^*)$ -**4d**. These data can be obtained free of charge via the Internet at www.ccdc.ac.uk/ conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (int) +44-1223/336-033; e-mail: deposit@ccdc.an.ac.uk.

⁽¹⁴⁾ Yano, K.; Hatta, Y.; Baba, A.; Matsuda, H. *Synthesis* **1992**, 693. (15) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835–4840 and refs cited therein.

species 2 and 3: in fact, only 10% of 4e was observed. In that case, the use of *sec*-BuLi was necessary to obtain 4e in 56% yield.

We next studied the lithiation of *cis*-stilbene oxide **8**. It was interesting to observe that, in this case, the α -lithiation *versus* ortho-lithiation competition does not take place. Indeed, when MeI was added to the lithiated *cis*-stilbene oxide **9** [generated by deprotonation of **8** (*n*-BuLi (1.5 equiv)/TMEDA (3.0 equiv), THF, -98 °C, 30 min)], the α -methylated compound **10a** was formed exclusively. The absence of ortho-lithiation may reflect the reduced steric hindrance associated with α -lithiation of *cis*-stilbene oxide compared to the trans isomer. The higher reactivity of *cis*-epoxides toward deprotonation with respect to the trans isomers is well documented.¹⁶ Similarly, treatment of **9** with other electrophiles (Table 4) produced exclusively the α -functionalized

Table 4. Reaction of Lithiated 8 with Electrophiles

Ph	<i>n-</i> BuLi/ [−] THF, -9 ●Ph	ſMEDA 8°C, 0.5h Li∞ Ph		E., O Ph
8		(<u>+</u>)-9	(<u>+</u>)-10а-е
entry	product	electrophile	Е	yield (%) ^a
1	$10a^b$	MeI	Me	89^c
2	$10b^b$	EtI	\mathbf{Et}	76
3	$\mathbf{10c}^d$	AllylBr	Allyl	55^e
4	$\mathbf{10d}^{f,g,h}$	PhCHO	PhCHOH	91^i
5	10e ^f	$PhCONMe_2$	PhCO	88

^{*a*} Isolated yields. ^{*b*} For spectroscopic data of **10a** and **10b** see ref 8. ^{*c*} Yield by ¹H NMR analysis. ^{*d*} For spectroscopic data of **10c**, see ref 14. ^{*e*} 1,2-Diphenyl ethanone was isolated in 40% yield (oxiranyllithium isomerization product). ^{*f*} For spectroscopic data, see Supporting Information. ^{*s*} Inseparable mixture of diastereoisomers; the separation and subsequent full characterization was possible only on the *O*-acetyl derivatives. ^{*h*} Relative configuration of the two diastereoisomers (syn and anti, respectively, (1*R**,2*S**,3*S**)-**10d** and (1*R**,2*R**,3*R**)-**10d**) was assigned by ¹H NMR.^{13a} ^{*i*} Overall yield in both diastereomers (dr = 70:30).

stilbene oxides 10a-e again with complete retention of configuration. To understand the fate of lithiated *cis*-stilbene oxide 9 at temperatures higher than -98 °C, we deprotonated 8 with *n*-BuLi/TMEDA in THF at -98 °C and allowed the reaction mixture to reach room temperature. The major product was PhCH₂COPh (62% yield).

We also studied the lithiation of scalemic (R,R)-transstilbene oxide 1 (ee = 98%)¹² (Scheme 3). Treatment of

Scheme 3.	Lithiation-Ethylation of (A	R,R)- 1
Ph (<i>R</i> , <i>R</i>)-1	MEDA <u>1°C, 2h</u> Li _{x,0} , Ph Etl Ph (<i>R,R</i>)- 2	Et , , O , , Ph Ph (<i>R,R</i>)- 4b

(*R*,*R*)-1 with *n*-BuLi at -60 °C gave the lithiated derivative (*R*,*R*)-2, which proved to be quite stable and could be kept for at least 2 h at that temperature. Quenching with EtI furnished (*R*,*R*)-*trans*-stilbene oxide (+)-4b ([α]_D = + 22 (*c* 0.93, CHCl₃) (45% yield) together with the starting epoxide (*R*,*R*)-1 (27%). The ¹H NMR analysis of (+)-4b showed no signal of the cis epimer.

In conclusion, α -lithiated stilbene oxides **2** and **9** proved to be chemically much more stable than lithiated styrene oxide.³ Indeed, **2** and (*R*,*R*)-**2** can be kept at -60 °C for at least 2 h and **9** at -98 °C for 30 min. Moreover, due to their configurational stability, it is possible to trap the α -lithiated stilbene oxides, in a stereospecific manner, by alkylation, hydroxyalkylation, or acylation of the benzylic position. We have also observed, for the first time to our knowledge, the ortho-directing capability of the oxirane moiety in lithiation of the phenyl ring. Finding experimental conditions that favor the ortho-lithiation is at present being pursued in our labs. Further studies are under way to exploit the configurational stability of lithiated stilbene oxides.

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Supporting Information Available: Full experimental details and characterization data (¹H and ¹³C NMR, physical data) for compounds **4b**, **4d**–**e**, **7**, and **10a**–**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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