

## Disulfide catalyzed the highly regioselective conversion of epoxides to halohydrins with elemental halogens

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### ABSTRACT

The regioselective ring opening of styrene oxide using elemental iodine and bromine in the presence of disulfides as new catalysts was studied. The conductivity titration and UV spectroscopy were used to study the interaction of iodine with these catalysts. The results indicate that disulfide **11** is efficient in polyiodide formation, and can catalyze this reaction in excellent yield and high regioselectivity. The complex  $[(\mathbf{11}\text{-disulfide})\text{I}]^+\cdot\text{I}_3^-$  is considered to be formed initially which could be bulkier by addition of excess of iodine in the course of the reaction. These bulky nucleophiles have a fundamental role in the high regioselectivity by attacking the less sterically hindered epoxide carbon.

**Keywords:** Epoxides, Methimazole, Ring opening, Polyiodide, Halohydrins, Disulfide.

### 1. Introduction

Interactions of anti-thyroid drugs methimazole, and propylthiouracil with molecular iodine has been thoroughly studied in recent years [1-3]. These studies have aimed at drawing conclusions about their mechanism of action [4]. Recently, we showed that methimazole catalyzed regioselective ring opening of epoxides using elemental iodine and bromine. Recovery of the catalyst showed that methimazole converted to methimazole-disulfide which can also be catalyzed the ring opening of epoxide. These studies confirmed that iodine converted to oxidized iodonium ion which formed a stable complex with sulfur containing heterocycles and simultaneously realized the reduced iodide ion (or in the presence of excess iodine, polyiodide ions) which play a nucleophile rule in the ring opening of epoxides [5].

Moreover, the catalytic ring opening of epoxides with elemental halogens has been reported in the presence of thiourea and related crown ethers [6-8]. Herein, we decided to examine the capacities of different sulfur containing compounds in polyhalide complex formation and regioselective ring opening reactions of epoxides in the presence of elemental halogens (Scheme 1). Also, some aniline derivatives were examined for understanding amino group rule in this reaction.

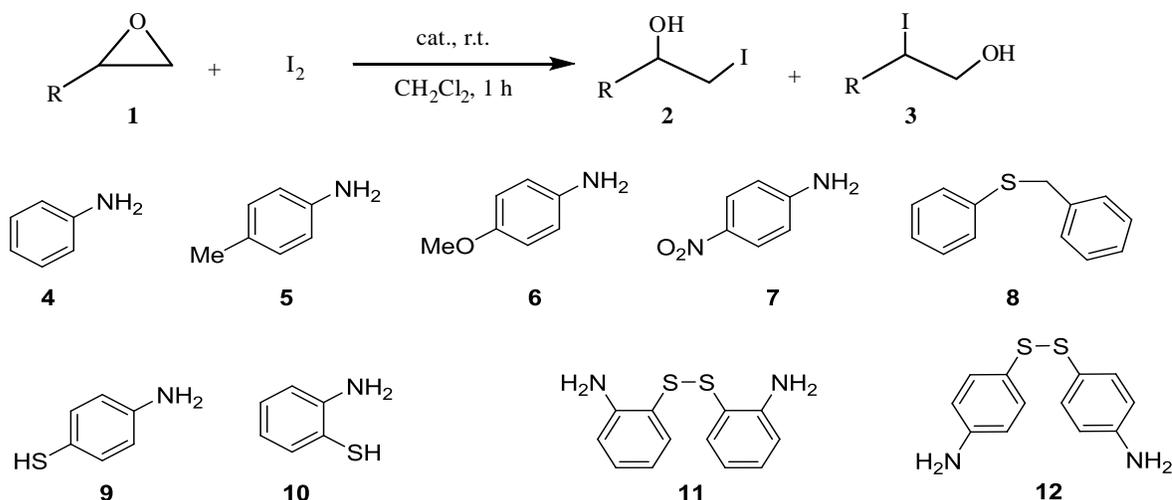
### 2. Experimental

All materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland). Melting points were determined in open capillary tubes in an Electrothermal IA 9700 melting point apparatus.  $^1\text{H-NMR}$  spectra were recorded on a Bruker-100 MHz instrument using *TMS* as an internal standard. UV-Vis spectra were obtained with a Shimadzu-AA 670 spectrometer. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. The purity determination of the substrates and reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument with a flame ionization detector using a column of 15% carbowax 20 M chromosorb W acid-washed 60-80 mesh. Column chromatography was carried out on short columns of silica gel 60 (230-400 mesh) in glass columns (2-3 cm diameter) using 15-30 g silica gel per 1 g of crude mixture. Catalyst **11** and **12** were prepared according to our previously reported method [9,10].

#### 2.1. General procedure for halogenative cleavage of epoxides

A solution of styrene oxide (**1**, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml) was added to a stirred solution of disulfide (**11**) (0.023 g, 0.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml) at room temperature. Next, a solution of 1 mmol elemental halogen in  $\text{CH}_2\text{Cl}_2$  (5 ml) was added dropwise during 40 min.

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**Scheme 1.** Regioselective ring opening reactions of epoxides in the presence of elemental halogens.

The progress of reaction was monitored by TLC and GLC. After complete disappearance of the starting material, the reaction mixture was washed with 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  ( $2 \times 10$  ml) and  $\text{H}_2\text{O}$  ( $2 \times 10$  ml). The aqueous layer was further extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  ml). The combined organic layer was dried over anhydrous  $\text{MgSO}_4$  and evaporated. The crude was purified by chromatography on a column of silica gel. For catalyst recovery, the reaction mixture was treated with  $\text{HCl}$  and catalyst precipitated as its hydrochloride salt. Neutralization with base gave pure catalyst for further reusability. The halohydrins obtained throughout this procedure was identified by comparison of their physical and spectral data with authentic samples prepared according to literature procedures [5-8].

*Selected spectral data for 1-Iodo-3-(3-methoxy-1-phenoxy)-propan-2-ol (Table 2, entry 10):*

IR (neat):  $\bar{\nu} = 3400$  (OH), 3050, 2920, 1590, 1490, 1420, 1030, 900, 815, 740, 500.  $^1\text{H NMR}$  (100 MHz;  $\text{CDCl}_3$ ):  $\delta = 2.2$  (1H, br, OH), 3.4-3.6 (2H, m,  $\text{CH}_2\text{I}$ ), 3.78 (s, 3H,  $\text{CH}_3$ ), 4.0 (1H, m, CH), 4.2 (2H, m,  $\text{CH}_2\text{O}$ ), 7.2-7.3 (2H, m, ArH), 6.4-6.6 (3H, m, ArH), 7.15 (t, 1H,  $J = 8$  Hz, ArH).

### 3. Results and Discussion

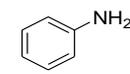
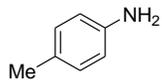
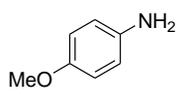
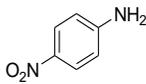
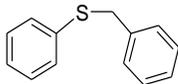
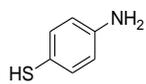
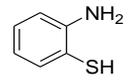
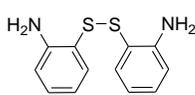
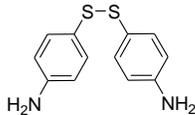
The results of the reactions of styrene oxide with elemental iodine in the presence of some selected catalysts are summarized in Table 1. As shown previously, iodination of styrene oxide with an excess of elemental iodine in the absence of catalyst did not occur even under reflux and extension of reaction time to several days, and unreacted styrene oxide was completely recovered [5,11]. As previously reported by Turos and reexamined by us, iodination cleavage of

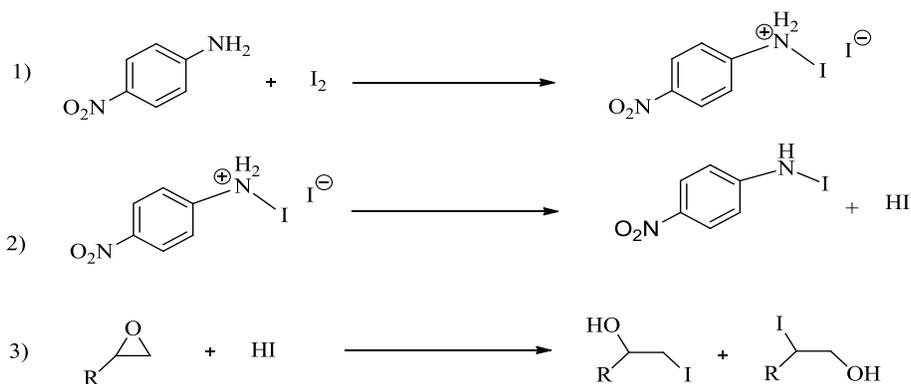
styrene oxide with iodine in the absence of a catalyst, in THF solvent, proceed to only about 30% conversion with low regioselectivity. Also, reaction in acetone gave a major by-product [5,11]. So, we select the  $\text{CH}_2\text{Cl}_2$  as an inert solvent. Whereas, 2-aminothiophenol (**10**) and 4-aminothiophenol (**9**) (10 mole %) can be catalyzed this reaction, but regioselectivity is not sufficient. Interestingly, we observed that the yields and regioselectivities are improved by reaction in the presence of the recovered catalysts (not shown). Spectral analysis showed that the catalysts were converted to disulfides (**11**) and (**12**).

However, it is well known that the thiols can be converted to disulfide in the presence of bromine or iodine [12]. So, we prepared [9] disulfides (**11**) and (**12**) easily from 2-aminothiophenol (**10**) and 4-aminothiophenol (**9**) in 98 and 96 % yield respectively, and were examined as catalysts in the ring opening reactions. The results of the reactions of styrene oxide with elemental iodine in the presence of disulfides (**11**) and (**12**), showed that yield and regioselectivity of the ring opening reaction were increased and catalyst **11** is the most effective one (Table 1, entry 8). Generally, the optimum amounts of the catalysts were found to be 10 mole % of epoxide and halogen. As it can be seen in Table 1, the catalyst could be reused without significant loss of its catalytic activity until at least 5 times. Disulfide **11** is the best selection because it is inexpensive and readily prepared with high conversion yield in short reaction times.

We suggested the low reverse regioselectivities of these reactions in the presence of other catalysts (Table 1, entries 3 and 4) are due to the formation of hydroiodic acid and interference in the reaction mechanism course (Scheme 2).

**Table 1.** Ring opening of styrene oxide (1 mmol) with elemental iodine (1 mmol) in the presence of different catalysts.<sup>a</sup>

Entry	Catalyst	Conditions	Products <sup>b</sup>	Conversion %
1		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	No reaction	-
2		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	No reaction	-
3		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  2 : 1	30
4		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  3 : 1	40
5		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	No reaction	-
6		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  1 : 8	88
7		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  1 : 9	>98
8 <sup>c-g</sup>		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  2 : 98	>98, (98), (95), (94), (92), (90)
9		I <sub>2</sub> , r.t/ CH <sub>2</sub> Cl <sub>2</sub>	 +  5 : 95	>98

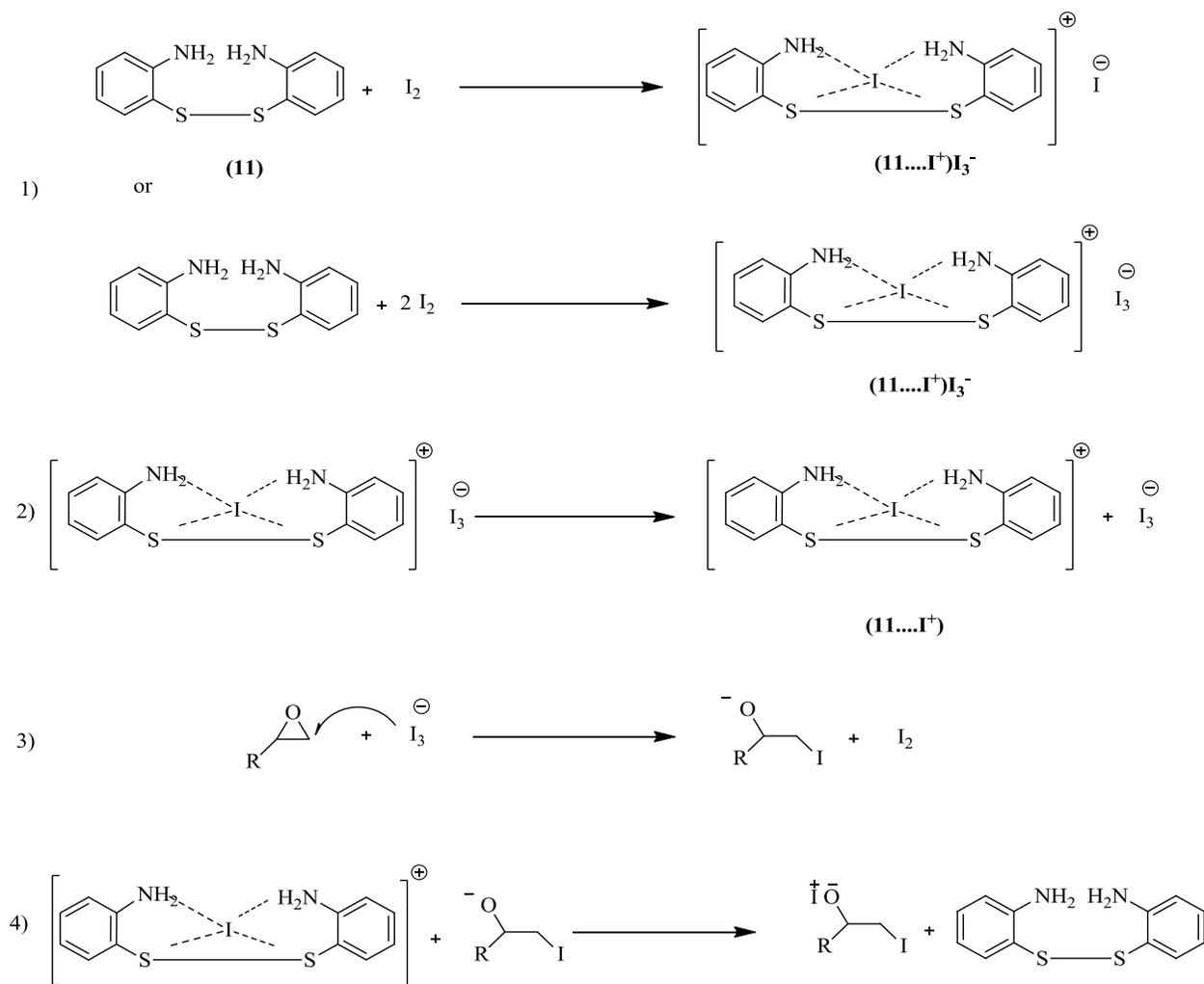
<sup>a</sup>Reaction conditions: styrene oxide (1 mmol), iodine (1 mmol) in the presence of different catalysts (0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) for 1h.<sup>b</sup>Relative yield by GC (c-g). Yields in parenthesis refer to reusability of the recovered catalyst in the new runs (five reused runs).**Scheme 2.** Formation of hydroiodic acid and interference in the reaction mechanism course.

The regioselectivity and rate of cleaving epoxides by elemental iodine in the presence of a catalyst can be satisfactory rationalized in terms of the suggested mechanisms [5,6]. Accordingly it is supported that the halogenative cleavage of epoxides occurs by the following four-step mechanism (Scheme 3).

In support of this mechanism, the UV spectra of iodine, and complex formation between iodine and catalysts **6**, **7** and **9-12** are shown in Fig. 1. None of the initial reactants show any measurable absorption in the 320-440 nm region, whereas the addition of the catalysts **11** and **12** to iodine results in a strong absorption band at 360 nm, presumably due to the complex formation of iodine with catalysts. The intensity of the band at 360 nm, as evidence for the ease of formation of polyiodide ion, decreased in the case of other catalysts. However, in the case of disulfide **11** this band appeared immediately and corroborated the much faster complexation of iodine with this catalyst. Also, the electron donor properties and powerful antioxidant behavior of catalyst **11** towards the steel have already received attention [10].

It should be noted that the bands at 292 and 364 nm are characteristic for the formation of polyiodide ions such as  $I_3^-$  and  $I_5^-$ , in the process of complex formation between iodine and electron-pair-donating atoms [13-16]. It is well known that both ions absorb in the same region around 360 and 290 nm with little deviation in their absorbivities [17,18].

The conductivity titration of the disulfide **11** with iodine which showed complex formation in a 1:2 molar ratio are shown in Fig. 2. According to the mechanism (Scheme 3) two equivalents of iodine consumed for generation of  $(11...I^+)I_3^-$  complex and excess of iodine in the presence of this *in situ*-formed complex can be converted to  $I_5^-$  and higher polyiodides which showed a lower slope rather than initial complex formation. Thus we suggest that the major nucleophile at the first of the reaction is  $I_3^-$ , and this nucleophile is converted to higher bulky polyiodides such as  $I_5^-$  and  $I_7^-$  in the course of the reaction. These bulky nucleophiles have a fundamental role in the high regioselectivity observed attacking on the less sterically hindered epoxide carbon.



Scheme 3. Four-step mechanism of halogenative cleavage of epoxide ring.

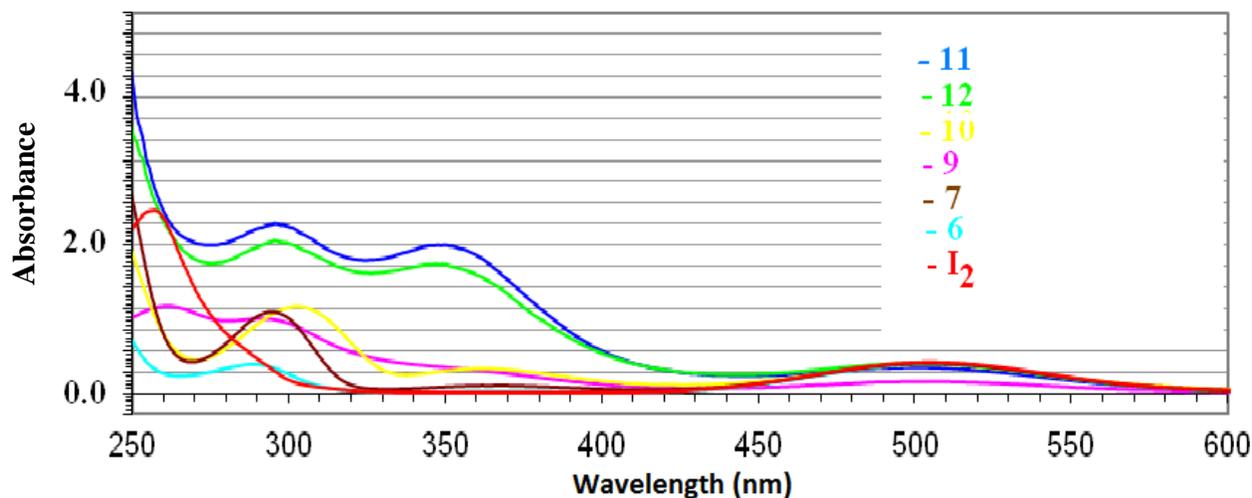


Fig. 1. Absorption spectra of iodine, and its complex formations with catalysts **6**, **7** and **9-12** in dichloromethane solution.

The results obtained with some representative epoxides in the presence of disulfide **11** as catalyst are summarized in Table 2. When epoxides were allowed to react in the presence of **11**, increases in yield and regioselectivities were observed in all of the reactions. However, bromination is faster than iodination cleavage with similar high yields and regioselectivity.

#### 4. Conclusions

In conclusion, we have found that disulfide catalyst **11** can be catalyze the regioselective ring opening of

styrene oxide by elemental iodine and bromine under neutral conditions. UV-Vis and conductivity titration indicated that the complex  $(\mathbf{11} \dots \text{I})^+ \text{I}_3^-$  is formed.

Accordingly, we suggest that the major nucleophile in the first of the reaction is the triiodide ion,  $\text{I}_3^-$  and can be bulkier in the presence of excess of iodine to  $\text{I}_5^-$  and  $\text{I}_7^-$ .

These bulky nucleophiles play a fundamental role in the high regioselectivity observed. It is due to an attack on the less sterically hindered epoxide carbon.

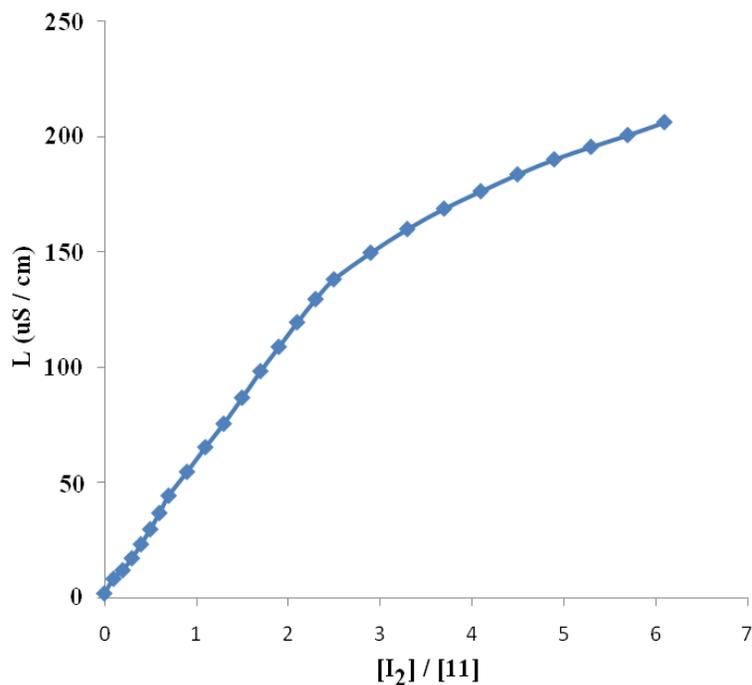
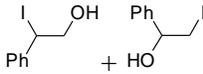
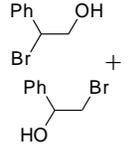
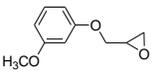
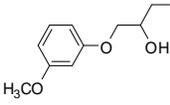
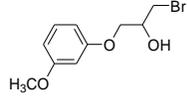
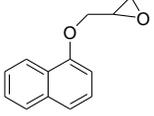
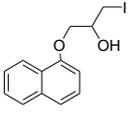
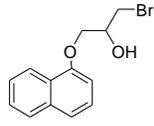


Fig. 2. The conductivity titration of the disulfide **11** with iodine in  $\text{CH}_2\text{Cl}_2$  ( $T = 273 \text{ K}$ ).

**Table 2.** Reaction of epoxides with elemental bromine and iodine in the presence of disulfide (**11**) as the catalyst.<sup>a</sup>

Entry	Epoxide	Catalyst	Reaction conditions	Time / h	Yield / % <sup>b</sup>	Product (s)	Ref.
1		-	LiI, AcOH, THF, rt	1.3	87(2:1)		[2]
2	"	-	HI, rt, CHCl <sub>3</sub>	0.25	>99		[19]
3	"	<b>11</b>	I <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	1	>98		
4	"	<b>11</b>	Br <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	0.5	>98		
5	"	-	Br <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	1	31		[11]
6	"	-	nBu <sub>4</sub> N <sup>+</sup> Br <sup>-</sup> / Mg(NO <sub>3</sub> ) <sub>2</sub> , CHCl <sub>3</sub> , rt	5	78(1:5)		[20]
7	"	-	HBr, rt, CHCl <sub>3</sub>	0.25	>99		[19]
8		<b>11</b>	I <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	6	92		
9	"	<b>11</b>	Br <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	4	90		
10		<b>11</b>	I <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	5	90		
11	"	<b>11</b>	Br <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	4	93		
12		<b>11</b>	I <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	3	95		
13	"	<b>11</b>	Br <sub>2</sub> , rt, CH <sub>2</sub> Cl <sub>2</sub>	1.5	95		

<sup>a</sup>Reaction conditions: styrene oxide (1 mmol), iodine (1 mmol) in the presence of disulfide **11** (0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml).<sup>b</sup>Isolated yield.

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