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Diastereoselective Synthesis of Tetrahydrofurans from Aryl 3-Chloropropylsulfoxides and Aldehydes‡

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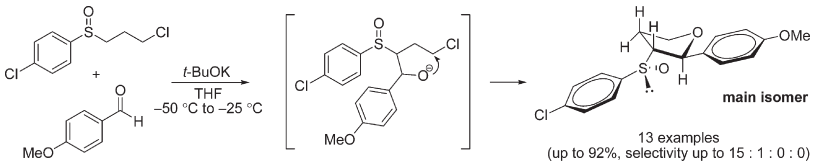

Carbanions of aryl 3-chloropropylsulfoxides react with nonenolizable aldehydes to give 2,3-disubstituted tetrahydrofurans. Deprotonation of the sulfoxides carried out in the presence of aldehydes results in the addition of the carbanions to the carbonyl group of the aldehydes, followed by 1,5-intramolecular substitution of the resulting aldol-type anion to produce the tetrahydrofuran ring. The 2-aryl and 3-arylsulfinyl substituents are always in *trans* relation, and the reaction proceeds with high diastereoselectivity also in respect to the chiral sulfur atom. The diastereoselectivity is attributed to the cyclic transition state of the aldol addition and increases when the aromatic ring of the sulfoxide contains electron-withdrawing substituents, whereas that of the aldehyde has electron-donating groups.

Introduction

γ-Halocarbanions are short-lived intermediates that enter rapid intramolecular substitution to produce three-membered rings. This reaction is a valuable process for the synthesis of cyclopropanes[1] and also a key step for such important processes as the Favorsky,[2] Ramberg−Bäcklund,[3] and related transformations.[4] Recently we have shown that despite the fast intramolecular 1,3-substitution, often called γ-elimination, γ-halocarbanions can be trapped by aldehydes, imines, and Michael acceptors to form tetrahydrofurans,[5−7] pyrrolidines,[8] and cyclopentanes,[9] respectively. These processes resemble to some extent the Darzens and aza-Darzens reactions, where α-halocarbanions add to electron-deficient C═O and C═N bonds to form aldol-type anion intermediates that subsequently undergo intramolecular substitution to produce three-membered rings. Similarity of these reactions is based on the fact that the carbanions containing leaving groups such as halogen, upon addition to the electron-deficient double bonds, form anions in which nucleophilic and electrophilic centers are separated by two more atoms. Thus, α-halocarbanions in which nucleophilic and electrophilic centers are at the same atom, upon addition to electron-deficient double bonds form anions with 1,3-relation to these centers, whereas γ-halocarbanions with 1,3-relation to nucleophilic and electrophilic centers form systems with 1,5-relation to such centers (Scheme 1).

Despite their similarities, γ-halocarbanions differ markedly from α-carbanions because of the fast intramolecular substitution, which competes with the intermolecular addition to electrophiles. While α-carbanions are relatively stable species and their potential side processes (such as dimerization or α-elimination to carbenes) are generally suppressed,

‡ Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday.

(1) (a) Zwanenburg, B.; De Kimpe, N. In *Carbocyclic Three-Membered Ring Compounds*, 4th ed.; de Meijere, A., Ed.; Georg Thieme Verlag: Stuttgart, 1996; Vol. E17a, pp 29−40. (b) Gronert, S.; Azizian, A.; Friedman, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3220. (c) Habusha, U.; Rozental, E.; Hoz, S. *J. Am. Chem. Soc.* **2002**, *124*, 15006.

(2) Guijarro, D.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1713 and references therein.

(3) Clough, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 861.

(4) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051.

(5) Shibata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 6909.

(6) (a) For a preliminary communication of the synthesis of tetrahydrofurans from 4-chlorobutyronitrile and aldehydes under basic phase transfer catalysis conditions, see: Mąkosza, M.; Przyborowski, J.; Klajn, R.; Kwast, A. *Synlett* **2000**, 1773. (b) For a review of reactions of γ-halocarbanions, see: Barbasiewicz, M.; Judka, M.; Mąkosza, M. *Russ. Chem. Bull., Int. Ed.* **2004**, *53*, 1846.

(7) Mąkosza, M.; Judka, M. *Chem.—Eur. J.* **2002**, *8*, 4234.

(8) Mąkosza, M.; Judka, M. *Helv. Chim. Acta* **2005**, *88*, 1676.

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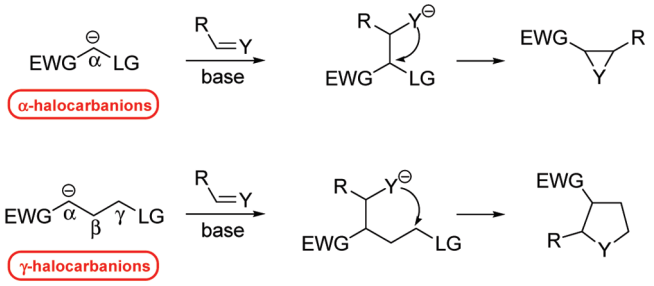
SCHEME 1. Reactions of α- and γ-Halocarbanions[a]



[a]Deprotonation of the precursors with base gives carbanions that in the presence of electrophile (aldehydes, imines, or Michael acceptors) can be trapped into aldol-type adducts and then cyclized to three- and five-membered rings, respectively. The mechanistic scheme is of general character and is similar for a few reactions, such as Darzens, Corey–Chaykovsky, etc.

γ-halocarbanions rapidly cyclize to cyclopropanes, and the competition between intra- and intermolecular reactions is controlled by numerous factors. In attempts to favor the bimolecular reaction nature of the leaving group,[7,10,11] the electron-withdrawing group,[8] substituents in the chain of the γ-halocarbanion precursor, various bases and solvents,[11,12] concentration of the reactants,[7] the temperature, and the reaction time[11,13] were studied. For a variety of structures the optimized conditions provided high yield and selectivity of the desired products resulting from the intermolecular reactions.

Manipulation of leaving groups,[10] for instance, exchanging a halogen for trimethylammonium and diphenylphosphinoxy groups, was partially successful. Nucleophilic replacement of the trimethyl ammonium group is known to proceed more slowly than replacement of the chlorine; however, carbanions of 3-(trimethylammonium)propyl phenyl sulfone and 4-trimethylammonium butyronitrile do not cyclize to cyclopropane derivatives. These carbanions add to benzaldehyde, but so-formed aldol-type adducts do not cyclize either.[10a] On the other hand the diphenylphosphinoxy group in carbanion of 3-diphenylphosphinoxypropyl phenyl sulfone behaved as expected.[10b] Cyclization of the carbanion was a slow process, so formation of tetrahydrofurans via its reaction with aldehydes proceeded smothly.

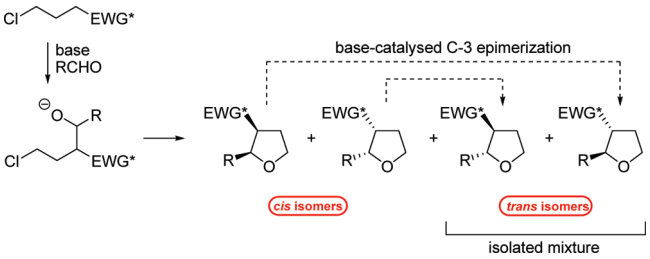
In further studies the methodology was extended to reactions of δ-halocarbanions[14,15] and anions of 2-haloalcohols[16] taking advantage of the same mechanistic scheme as presented for the reactions of γ-halocarbanions. δ-Halocarbanions are relatively long-lived species as a result of much slower competing intramolecular 1,4-substitution, and thus their facile addition to a carbonyl group is expected. In fact reactions of 4-bromobutyl phenyl sulfone, methyl 5-bromopentanoate, and δ-bromovalerophenone with aldehydes gave substituted tetrahydropyranes in good to excellent yields.[15] In turn, oxygen analogues of γ- and δ-halocarbanions, i.e., anions of 2-chloroethanol and 3-chloropropanol, react with aldehydes to form cyclic acetals (1,3-dioxolanes and 1,3-dioxanes) under kinetically controlled basic conditions; the method is complementary to an acid-catalyzed (equilibrated) acetalization of aldehydes with glycols.[16]

An important aspect of the discussed methodology is the stereochemistry of the products and methods of its control. In the model reactions of carbanions of 3-chloropropyl phenyl sulfone, alkyl 4-chlorobutyrates, and 4-chlorobutyronitrile with aldehydes, two new stereogenic centers are created. In most cases the predominant products of the reactions are *trans* isomers of 2,3-disubstituted tetrahydrofurans, and only when EWG is of a minimal steric demand is formation of the *cis* isomer observed.[7,12] This high stereoselectivity may be attributed to the selective, kinetically controlled formation of the predominant *trans* isomer or, alternatively, to thermodynamically controlled base-catalyzed epimerization of the *cis* product at the C-3 position, in the vicinity of the electron-withdrawing group. Although reliable mechanistic data is available for only a few systems,[7,12] the first possibility seems to be more plausible. A more complicated situation can be considered for systems where asymmetric induction is exerted by a nonenolizable stereogenic center present in the substrates;[17] as two new stereogenic centers are created at the five-membered ring, four diastereoisomeric products ($2^2 = 4$) are expected. In our case only the stereogenic center at C-2 position is irreversibly fixed in the cyclization step, while the second one, at C-3, is labile and prone to epimerization due to the presence of adjacent EWG group. Therefore in the general case, when one of the substrates possesses a nonenolizable stereogenic center, the product selectivity at C-2 derives from induction by this center, while the configuration at C-3 could be established by base-induced epimerization of the product (Scheme 2).[18]

Finally, we should consider that the mechanism of the process consists of two steps: the aldol-type addition and the subsequent cyclization via intramolecular nucleophilic substitution; both steps can control the stereochemistry of the products with respect to the nonlabile C-2 position. When the aldol-type addition is a stereoselective process, the intermediate adduct is formed as a predominant isomer that subsequently cyclizes (Scheme 3, path a). On the other hand, when the addition is faster than 1,5-substitution, then the composition of the diastereoisomeric products can be governed by the relation between rates of the cyclization of the isomeric adducts (providing that the addition step is reversible and the aldol-type adducts may quickly equilibrate)[19] (Scheme 3, path b).

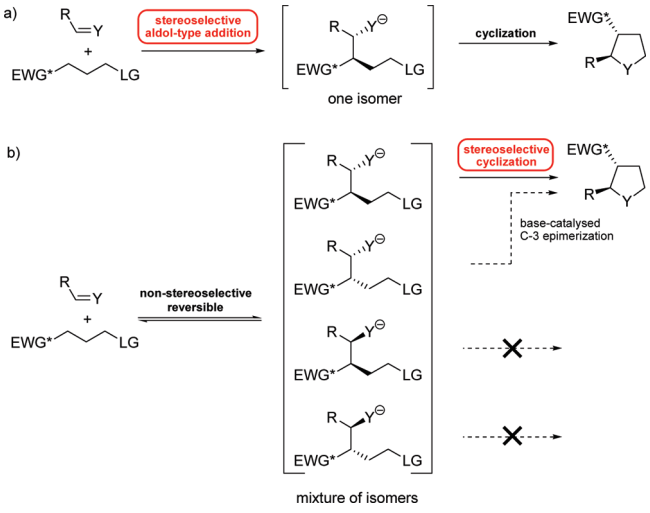
(10) (a) Mąkosza, M.; Judka, M. *Synthesis* **2003**, 820. (b) Mąkosza, M.; Wojtasiewicz, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2009**, *184*, 857.
(11) Mąkosza, M.; Barbasiewicz, M.; Krajewski, D. *Org. Lett.* **2005**, *7*, 2945.
(12) Barbasiewicz, M.; Mąkosza, M. *Synthesis* **2006**, 1190.
(13) Wojtasiewicz, A.; Barbasiewicz, M.; Mąkosza, M. *Eur. J. Org. Chem.* **2010**, 1885.
(14) Fleming, F. F.; Gudipati, V.; Steward., O. W. *J. Org. Chem.* **2003**, *68*, 3943.
(15) Barbasiewicz, M.; Brud, A.; Mąkosza, M. *Synthesis* **2007**, 1209.
(16) Barbasiewicz, M.; Mąkosza, M. *Org. Lett.* **2006**, *8*, 3745.
(17) For reactions of γ-halocarbanions with chiral imines, see: (a) Baricordi, N.; Benetti, S.; Biondini, G.; De Risi, C.; Pollini, G. P. *Tetrahedron Lett.* **2004**, *45*, 1373. (b) Hassner, A.; Usak, D.; Kumareswaran, R.; Friedman, O. *Eur. J. Org. Chem.* **2004**, 2421. For reactions of γ-halocarbanions with chiral Michael acceptors, see: (c) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp., D. *Pure Appl. Chem.* **2000**, *72*, 1671.
(18) The configurations at C-2 and C-3 of newly formed tetrahydrofurans depend on the selectivity of the aldol addition and cyclization process. However, in the end proportion of *trans* and *cis* isomers (relative C-2 to C-3 configuration) approaches the thermodynamic limit after the base-induced C-3 epimerization.
(19) Alternatively, aldol-type adducts may isomerize by epimerization. For some hint that it actually involves a dissociation–addition sequence see note 17 in ref 15.

SCHEME 2. Reaction of a Chiral Precursor of γ-Halocarbanion with an Aldehyde[a]



[a]This reaction may lead to four distereoisomers of the product. However, two of them are prone to epimerization and only *trans*-2,3-disubstituted tetrahydrofurans can be isolated from the reaction mixture.

SCHEME 3. Mechanistic Considerations of the Asymmetric Induction in a Two-Step Reaction[a]



[a]Selectivity is gained in the first (a) or in the second step, providing that the first step is reversible (b).

Recently we demonstrated that 2,3,5-trisubstituted tetrahydrofurans are produced in the aldol-type addition of γ,δ-epoxycarbanions to aldehydes and subsequent Lewis acid catalyzed intramolecular substitution via opening of the oxirane ring acting as a leaving group.[11] Diastereoselectivity of the reaction is controlled by the stereocenter present in the carbanion precursor; the first step is nonstereoselective but reversible, and what controls distribution of the stereoisomers (according to the Curtin−Hammett postulate) is the difference between rates of the subsequent irreversible cyclization of the diastereoisomeric adducts. Having in mind the results of the above-mentioned reaction, where the cyclization step determines the stereoselectivity, we took up the idea of the diastereoselective aldol-type reaction (Scheme 3, path b). In this report we present and discuss reactions of γ-halocarbanions containing chiral electron-withdrawing groups that act as "chiral auxiliaries"[20] at the first, irreversible step of the reaction, the aldol addition, and we therefore expect that this step shall control the overall stereochemistry of the product formation.

Results and Discussion

Although for the aldol-type processes a wealth of chiral auxiliaries is available,[21] strong basic conditions and the presence of weakly coordinating potassium cations, as required for the one-pot synthesis of tetrahydrofurans, limit their number to few.[22] Taking into account our earlier observations of stereochemical course of the tetrahydrofuran synthesis[7,11] we have chosen 4-chlorobutyrates of chiral alcohols and aryl 3-chloropropyl sulfoxides as γ-halocarbanion precursors for the reaction with aldehydes. We believed that, in the same way as achiral *tert*-butyl 4-chlorobutyrate and 3-chloropropyl phenyl sulfone, also esters of the chiral alcohols and sulfoxides upon deprotonation in the presence of the aldehydes should give tetrahydrofurans with ring substituents in *trans* relation, and the stereogenic center present in the molecule will control the stereochemistry of the addition step.

Synthesis of Substrates. 4-Chlorobutyrates of (−)-menthol, (−)-8-phenylmenthol, and 1,2:5,6-diisopropylidene-D-glucofuranose were obtained in the reaction of the chiral alcohols with 4-chlorobutyric acid chloride. Aryl 3-chloropropyl sulfoxides were synthesized in two steps starting from commercially available thiophenols. Thiophenol and 4-chlorothiophenol were reacted with 1,3-dichloropropane under phase transfer catalysis conditions (NaOH and catalytic amount of NBu_4Cl) and purified by vacuum distillation. Under such conditions 2-mercaptopyridine reacted with 1,3-dichloropropane nonselectively and substantial amounts 1,3-bis(2-thiopyridyl)propane were formed. The reaction with 1-bromo-3-chloropropane in the presence of KOH in ethanol gave the desired sulfide, which was purified by column chromatography. Aryl 3-chloropropyl sulfides were subsequently oxidized to sulfoxides with bromine under a simple two-phase aqueous $KHCO_3/CH_2Cl_2$ system described by Mikołajczyk.[23] Again, the pyridine derivative gave under the above-mentioned conditions unsatisfactory yields and required periodate oxidation followed by column chromatography. In all cases, yields of the desired sulfoxides (**1**−**4**) were moderate to good and purity of the products was uncompromised.

Reactions of 4-Chlorobutyrates of Chiral Alcohols with Aldehydes. In the first attempts toward the asymmetric synthesis of tetrahydrofurans via the reaction of γ-halocarbanions with aldehydes, we used 4-chlorobutyrates of chiral alcohols: menthol, 8-phenylmenthol, and 1,2:5,6-diisopropylidene-D-glucofuranose. Treatment of a mixture of menthyl and 8-phenylmenthyl 4-chlorobutyrates and benzaldehyde

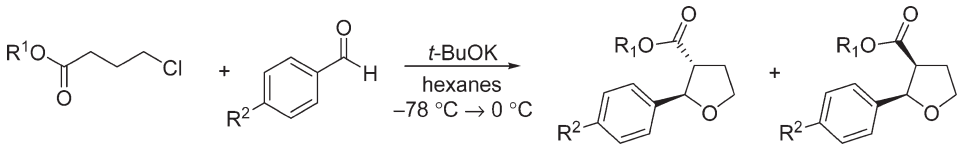
(20) By definition, a chiral auxiliary is a unit that is temporarily incorporated into the molecule, so that the synthesis can be carried out in an asymmetric manner. A chiral auxiliary is capable of being recycled, and therefore we refer to sulfoxides as formal chiral auxiliaries.[21] Our attempts to synthesize the pure enantiomer of **1** by oxidation of 3-chloropropyl phenyl sulfide (Brunel, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086) failed (ee < 15%).

(21) For a recent review, see: Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899.

(22) As lifetimes of typical γ-halocarbanions are on the order of only seconds or shorter at −78 °C, to avoid cyclization to cyclopropanes, base is added to a mixture of an aldehyde and γ-halocarbanion precursor (so-called Barbier conditions). Under these conditions many strong bases such as *n*-BuLi or LDA add preferentially to the carbonyl group (see, for example Commins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078) of non-enolizable aldehyde rather than deprotonate γ-halocarbanion precursor, and thus *t*-BuOK remains a reagent of choice for this one-pot process. See refs 7, 8, and Judka, M.; Wojtasiewicz, A.; Danikiewicz, W.; Mąkosza, M. *Tetrahedron* **2007**, *63*, 8902.

(23) Drabowicz, J.; Midura, W.; Mikołajczyk, M. *Synthesis* **1979**, 39.

TABLE 1. Reactions of Alkyl 4-Chlorobutyrates with Arylaldehydes in the Presence of *t*-BuOK in Hexanes Gives Tetrahydrofuran Derivatives in High Yields



R^1	R^2	isolated yield (%)	*trans*:*cis* isomer ratio[a]	yield (%) in THF
t-Bu	H	97	86:14	61[b]
t-Bu	Me	88	93:7	62[b]
t-Bu	MeO	91	88:12	[c]
t-Bu	Cl	86	88:12	44[b]
Me	H	46 (+18)[d]	50:50	31[b]
menthyl	H	96	*trans* only[e]	38
8-phenyl-menthyl	H	80	67[e]:33	50

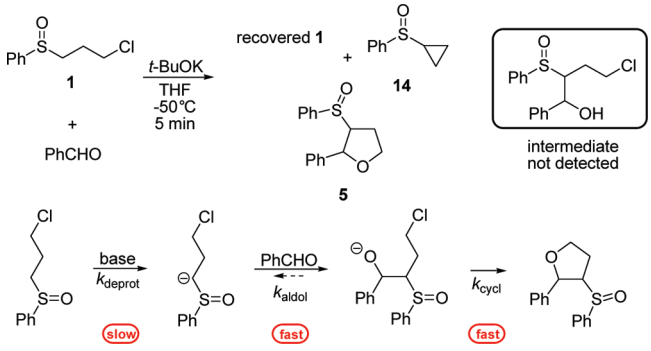
[a]According to ^{1}H NMR, *trans*-*cis* isomerization is limited in hexanes. [b]Data taken from ref 7. [c]No data available. [d]Transesterification product with *t*-BuOK. [e]As a 50:50 mixture of *trans* isomers.

with *t*-BuOK under various conditions gave the expected substituted tetrahydrofurans in moderate yields, but with low or negligible induction by stereogenic centers of the alcohols (however, good *trans*:*cis* selectivity was observed in most cases). The reaction of the ester of 1,2:5,6-diisopropylidene-D-glucofuranose under the identical conditions resulted in decomposition. The only interesting observation was a high yield of the tetrahydrofurans when reactions of ester 4-chlorobutyrates were performed in hexane (Table 1). For aromatic aldehydes yields of tetrahydrofurans reached 80−95%, much superior to those obtained in a *t*-BuOK/THF system.[7] (For broader comparison several reactions with achiral precursors of γ-halocarbanions with aldehydes were performed in hexane.) The detailed experimental results of the reactions are presented in Supporting Information.

Reactions of Aryl 3-Chloropropyl Sulfoxides with Aldehydes. In the following studies a model reaction of 3-chloropropyl phenyl sulfoxide **1** with benzaldehyde was investigated. In the preliminary experiment 1 mmol of **1** and 1.5 mmol of benzaldehyde were dissolved in THF and cooled to −50 °C, and a solution of *t*-BuOK (2 mmol) was added slowly. In contrast to the results obtained with more acidic γ-chlorocarbanion precursors such as sulfones, esters and nitriles, which are deprotonated immediately upon treatment with potassium *t*-BuOK even at low temperatures,[7] the sulfoxide exhibited only moderate acidity. The reaction carried out for 1 h resulted in substantial substrate recovery. The same experiment repeated at −25 °C for 1 h gave the expected tetrahydrofuran derivative **5** in good yield of 77% (as a 6:1 mixture of diastereoisomers **5a**:**5b**, based on ^{1}H NMR), cyclopropyl phenyl sulfoxide **14** (10%), and small amounts of unchanged substrate **1**. Interestingly, when the mixtures of reaction performed at low temperatures were quenched after a short time, we were able to isolate only unreacted **1**, cyclopropane **14**, and the final product **5** (as a mixture of isomers), whereas intermediate aldol-type adducts could neither be isolated nor detected by ^{1}H NMR of the crude reaction mixtures (Scheme 4). All attempts to isolate the intermediate adducts when the reaction mixture was quenched with aqueous NH_4Cl after 1 min at −78 °C, −50, and −25 °C failed.

The experiment revealed that the deprotonation of **1** is a rate-determining step followed by fast aldol-type addition of the carbanion to the aldehyde and 1,5-intramolecular substitution of the produced aldol-type anion. Once the carbanion is generated, it reacts immediately with the aldehyde, and this addition process is much faster than the competing cyclization to the cyclopropane. In the next step the aldol-type anion cyclizes immediately, so its concentration in the reaction mixture is negligible, and hence acidic quenching of the mixture does not produce protonated aldol intermediates. This reasoning also gives a hint concerning the source of the diastereoselectivity observed in the reaction. Under these conditions equilibration of the addition is hardly possible, and the kinetic composition of the diastereoisomeric aldol adducts is probably fixed by the fast cyclization to tetrahydrofurans.

SCHEME 4. Unsuccessful Attempts To Isolate Protonated Intermediate Aldol Anions[a]

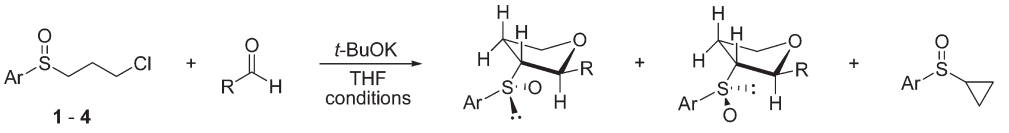


[a]The kinetic pattern of the process consists of a rate-determining deprotonation step, followed by fast aldol-type addition and subsequent cyclization.

In the course of optimization of the reaction conditions, manipulation with solvents appeared unsuccessful. Reaction of **1** with benzaldehyde in the presence of *t*-BuOK carried out at −25 °C in THF for 1 h gave only traces of **5** accompanied by large amounts of unreacted sulfoxide. In turn the reaction carried out in DMF gave **5** in moderate yield (46%), but stereoselectivity was negligible (**5a**:**5b** = 1:1.4), whereas cyclopropane **14** was produced as a main product (50%, see the next section for details).

To overcome the difficulties with the conversion and reduce the side reactions observed at the higher temperatures

TABLE 2. Reactions of Aryl 3-Chloropropyl Sulfoxides (1−4) with Aldehydes



two of four possible isomers are formed

Ar	R	Conditions	Isomer ratio[b)]	Yield %[c)]
Ph, (**1**)	Ph	−25 °C, 1 h	(**5**), 6 : 1	77
4-Cl-C_6H_4, (**2**)	Ph	−50 °C → −25 °C, 3 h	(**6**), 8 : 1	81
4-Cl-C_6H_4, (**2**)	4-CH_3O-C_6H_4	−50 °C → −25 °C, 3 h	(**7**), 10 : 1	86
4-Cl-C_6H_4, (**2**)	3-CH_3O-C_6H_4	-50 °C → −25 °C, 3 h	(**8**), 6 : 1	84
4-Cl-C_6H_4, (**2**)		−50 °C → −25 °C, 3 h	(**9**), 6 : 1	68
4-Cl-C_6H_4, (**2**)	*t*-Bu	−50 °C → −25 °C, 3 h	(**10**), one isomer[d)]	35
2-Py, (**3**)	Ph	−50 °C → −25 °C, 3 h	(**11**), 7 : 1	40
3,4-Cl_2-C_6H_3, (**4**)	Ph	−50 °C, 1 h	(**12**), 10 : 1	87
3,4-Cl_2-C_6H_3, (**4**)	4-CH_3O-C_6H_4	−50 °C, 1 h	(**13**), ~15 : 1	92

[a]Aryl cyclopropyl sulfoxides (≤10%) were not isolated in routine preparative experiments. [b]The ratio corresponds to proportion of isomers denoted in the text as "**a**" and "**b**" respectively. [c]2-Bromobenzaldehyde, 4-chlorobenzaldehyde, 2-pirydylaldehyde, and furfural failed to react (see the explanation below). [d]4-Chlorophenyl cyclopropyl sulfoxide **15** (25%) and two products of secondary transformations (23%) were observed in the reaction mixture (see Supporting Information for details).

when longer reaction times were necessary, we have tested sulfoxides that exhibit higher C−H acidity due to the presence of electron-withdrawing groups in the aromatic rings. Thus 3-chloropropyl 4-chlorophenyl (**2**), 2-pirydyl (**3**), and 3,4-dichlorophenyl (**4**) sulfoxides were subjected to reactions with aldehydes in the presence of *t*-BuOK in THF.[24]

In the routine experiments, crude reaction mixtures were analyzed with ^{1}H NMR to determine the ratio of isomers. The products were then isolated by chromatography as mixtures of isomers, whereas minor amounts of cyclopropane derivatives were not isolated in preparative experiments. From the mixtures of diastereoisomers analytical samples of only the main isomers ("**a**") were isolated. The pure main isomers were characterized with ^{1}H and ^{13}C NMR, MS, IR and elemental analysis. Only product **6** was fully resolved, and full analysis also of minor isomer **6b** was made. The results are presented in Table 2.

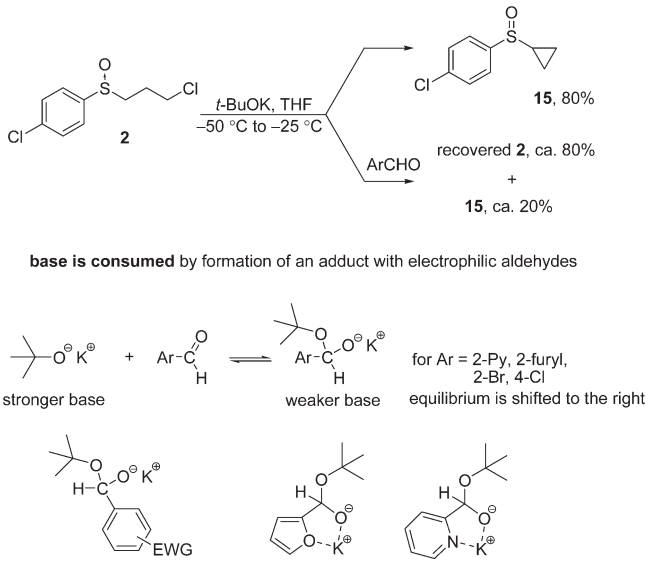
As expected, conversion of these more acidic sulfoxides at low temperatures was higher in comparison with **1**, and even the ratio of isomers was slightly improved.[25] Surprisingly the four aldehydes 2-bromobenzaldehyde, 4-chlorobenzaldehyde, 2-pirydylaldehyde, and furfural failed to react. When the sulfoxide **2** was subjected to the reaction with these aldehydes under standard conditions with an excess of *t*-BuOK, the only product was the cyclopropane **15** in moderate yield (< 20%), whereas a majority of **2** was recovered. The unexpected behavior can be rationalized by our earlier findings that nonenolizable aldehydes react with potassium alkoxides to form hemiacetal-type adducts. The addition is a reversible process and equilibrium of the addition depends on substituents present in the aromatic ring.[16] The electron acceptors and the coordinating sites of pyridine and furane stabilize adducts and force the equilibrium to the right (Scheme 5). In the investigated system *t*-$BuO^{\ominus}$ anion is presumably trapped in a form of the hemiacetal anion, the alkoxide of much lower basicity that cannot efficiently deprotonate the sulfoxide. Both the base and the aldehyde are consumed in a competitive but reversible process, and thus in the system there is a weaker base, whereas concentration of an electrophile is reduced. As a result only formation of minor amounts of the cyclopropane **15**, the product of an intramolecular process, is observed. After the reaction mixture is quenched with aqueous NH_4Cl, hemiacetal anion is decomposed into the alcohol and the aldehyde, whereas the sulfoxide is mostly recovered. Strong support for the hypothesis was derived from comparative experiments performed on the model sulfoxide (**2**) in the presence and absence of an aldehyde (Scheme 5).

Treatment of 4-chlorophenyl 3-chloropropyl sulfoxide (**2**) with *t*-BuOK at low temperature resulted in formation of the substituted cyclopropane **15** (80%), while under the same conditions in the presence of 4-chlorobenzaldehyde mainly unreacted **2** and the aldehyde was recovered. Thus in the latter case the aldehyde consumed reversibly the base and

(24) Pentachlorophenyl 3-chloropropyl sulfoxide was synthesized but decomposed when subjected to reaction with benzaldehyde in the presence of *t*-BuOK at low temperature (see Supporting Information for details).

(25) We assume that the selectivity derives from decreased reactivity of more stabilized carbanions and less electrophilic aldehydes in agreement with common reactivity-selectivity principle. For some criticizm on reactivity-selectivity principle see: Mayr, H.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844.

SCHEME 5. Reaction of 2 with *t*-BuOK Gives Substituted Cyclopropane 15[a]



[a]The presence of electrophilic aldehydes results in substrate recovery. This discrepancy can be explained by formation of the hemiacetal anion, the process that consumes both the base and electrophile.

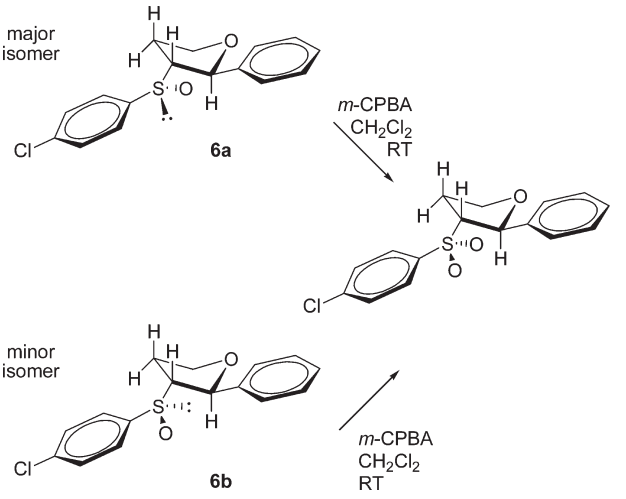
hence "protected" the substrate from deprotonation and subsequent reactions.[26]

Determination of the Stereochemistry of the Product. To verify the hypothesis that substituents at positions C-2 and C-3 in the obtained tetrahydrofurans are always in *trans* relation and the diastereoisomers differ only in configuration on the sulfur, both diasteroisomeric tetrahydrofurans **6a** and **6b** were oxidized with *m*-CPBA in CH_2Cl_2. In both of the experiments the same sulfone was formed, proving that diastereoisomers **a** and **b** differ only by configuration on the sulfur atom (Scheme 6).

Finally, to unambiguously determine a relative configuration of the stereogenic centers, the X-ray structure of the main crystalline isomer of tetrahydrofuran (**7a**) was obtained (Figure 1).

Discussion of Mechanism of the Reaction. Taking into account the results presented above, we analyzed the mechanism of the reaction from a viewpoint of stereochemistry. As we assumed previously, deprotonation of the sulfoxide with *t*-BuOK is a rate-determining step, and all subsequent steps are fast and generally irreversible. Thus, the very short lifetimes of the γ-halocarbanions and relatively high rate of the cyclization step of the aldol-type adducts suggested that there is no equilibration at the addition step. On the other hand, when the reaction was carried out in the more polar

SCHEME 6. Oxidation of Diastereoisomeric Tetrahydrofurans (6a and 6b) Leads to the Same Product



solvent dimethylformamide (DMF), the two diastereoisomers were formed in almost equal quantities, with a slight preference for the minor isomer that was produced earlier in THF (Scheme 7).[28]

On the basis of the literature data,[29] we assumed that the transition state of the addition process has a cyclic structure, where potassium cation chelates the oxygen atoms of the sulfoxide and aldehyde and forms a six-membered, chair-like transition state. Potassium cations are generally more weakly coordinating than, e.g., Li^+; however, the disparate distributions of isomeric products produced in reactions carried out in THF and DMF suggest that in the latter case donor solvent associates with potassium cations and the transition state has no longer organized structure. To confirm this assumption, we retracted the structure of the transition state of the aldol addition in THF, which after cyclization should give the characterized main isomer of the product (Scheme 8).

The geometry was perfectly consistent with expectations that sterically demanding aryl groups should occupy the equatorial positions, giving preference to the observed configurations at the sulfur atom and nonepimerizable C-2 position. In turn, the configuration at C-3 may still arise from direct cyclization of the *anti* adduct or cyclization of the *syn* isomer followed by base-catalyzed isomerization; both possibilities are in agreement with the observed data (Scheme 8).[11] However, the first structure of the transition state has all substituents in a favored equatorial orientation, and the second possibility, where the 2-chloroethyl group is oriented axially, must not be disregarded. In contrary to the bulky aryl groups, which may suffer from considerable 1,3-diaxial repulsive forces with hydrogen atom and solvent molecules coordinated to potassium cation, a 2-chloroethyl group located axially is influenced only slightly by the

(26) The situation can be alternatively explained by the formation of intermediate aldol-type adducts that decompose when quenched with aqueous NH_4Cl to release the substrate (when their cyclization is a rate-determining step). The possibility is less plausible because under the similar conditions (1) adducts with less electrophilic aldehydes cyclize to tetrahydrofurans in high yield, (2) average rates of cyclization of adducts of sulfones, esters, and nitriles under similar conditions range from seconds to minutes (see Supporting Information for details), and (3) cyclization of the sulfoxide **2** in the absence of an aldehyde is a slow process in contrast to the behavior of more acidic precursors such as sulfones, nitriles, and esters.

(27) We wish to acknowledge the use of a free version of Ortep-3 for Windows program: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

(28) The same observation was made when **2** was reacted with benzaldehyde in DMF to give tetrahydrofurans (**6**, 45%; **6a**:**6b** = 1:1.4) and cyclopropane (**15**, 51%).

(29) (a) Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, C. *Tetrahedron Lett.* **1992**, *33*, 2733. (b) Sato, T.; Itoh, T.; Fujisawa, T. *Tetrahedron Lett.* **1987**, *28*, 5677. (c) Casey, M.; Mukherjee, I.; Trabsa, H. *Tetrahedron Lett.* **1992**, *33*, 127. (d) Kingsbury, C. A. *J. Org. Chem.* **1972**, *37*, 102.

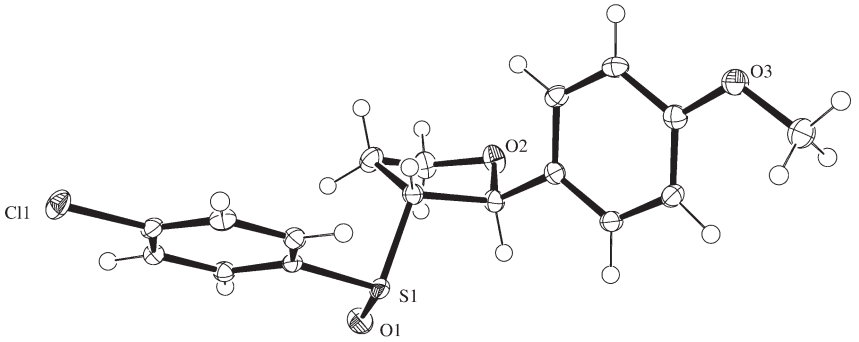
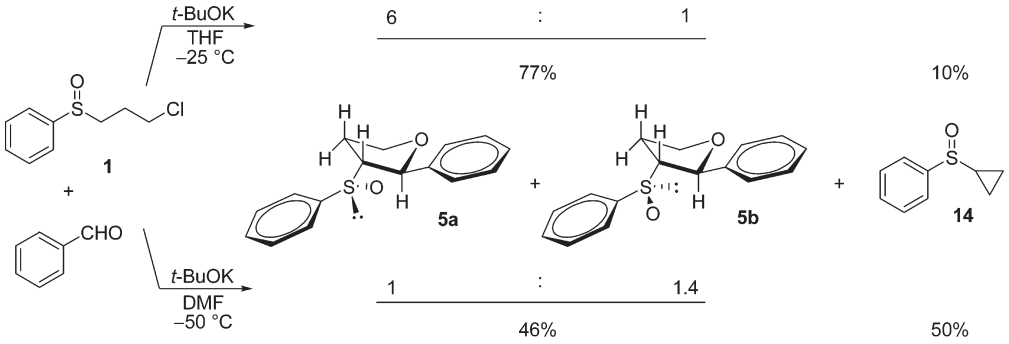
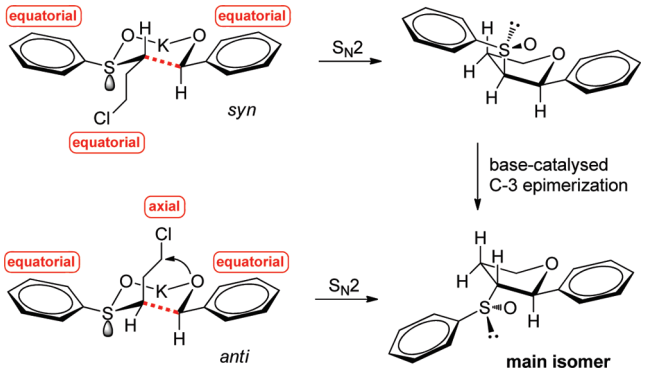


FIGURE 1. ORTEP representation of X-ray structure of **7a** (the main isomer).[27]

SCHEME 7. Distribution of Diastereoisomeric Tetrahydrofurans 5a and 5b and Cyclopropane 14 for the Reaction Carried out in THF and DMF[27]



SCHEME 8. Proposed Geometry of the Transition State Leading to the Main Isomer of the Product



presence of the oxygen lone pairs. The same phenomena demonstrated in 5-substituted-1,3-dioxanes[30] is attributed to the reduced bulkiness of the lone electron pairs of the oxygen as compared to the hydrogen atoms present in the parent cyclohexane system that expel substituents from axial positions by repulsive 1,3-interactions. Thus energetic preference for equatorial orientation of the 2-chloroethyl group is expectedly limited. However, the key argument for the *anti* transition state stems from the ability of the isomeric aldol-type anions to undergo 1,5-intramolecular substitution of chlorine atom. Both *anti* and *syn* aldol-type adducts are stabilized in the form of cyclic structures, where the potassium cation is chelated by oxygen atoms and sterically demanding aryl groups occupy favorable equatorial positions.

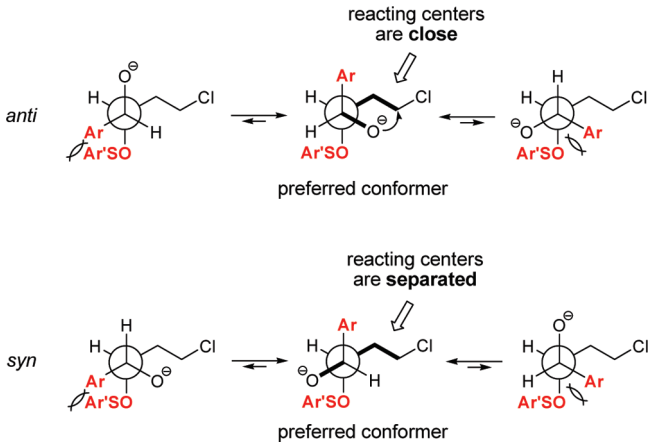
(30) Eliel, E. L.; Knoeber, M. C., Sr. *J. Am. Chem. Soc.* **1968**, *90*, 3444.

At the same time, the bulky groups are located in the preferred antiperiplanar orientation around the newly formed carbon−carbon bond. Thus the conformations of the isomeric adducts are not only stabilized by chelation with the potassium cation arranged in the transition state of the addition but also biased against unfavorable *gauche* orientation of the substituents after the addition is completed.

In turn *anti* orientation of the aryl and arylsulfinyl groups forces the reacting centers of the alkoxide and β-chloroethyl group to 60° and 180° angles for *anti* and *syn* isomers, respectively, and the latter situation strongly disfavores cyclization to the tetrahydrofurane ring (Scheme 9). As was demonstrated by us[11,15] and Hassner[17b] for five-membered rings and supported by data for Darzens[31] and Corey−Chaykovsky[32] cyclizations to oxiranes, only *anti*-configured intermediates may feasibly cyclize and *syn* isomers are much less prone to cyclize or do not cyclize at all. The phenomena is common to the "*gem*-dimethyl effect" and applicable for systems where bulky substituents located on a cyclizing chain alter the energy of its conformers[33] and thus control orientation of the reacting centers. The conformational origin of the effect[34] is still supported by observation that the rate of the 1,5-intramolecular substitution in the model reactions of

(31) Zimmerman, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1960**, *82*, 5459.
(32) (a) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964. (b) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105.
(33) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.
(34) The modern explanation of the *gem*-dimethyl effect for increased rates of cyclizations of medium size rings is based on the "reactive rotamer" idea, associated with changes in conformer populations as clarified in the text.[33] The alternative concept of a valence distortion posed by substituents, the so-called Thorpe−Ingold effect, would be too small to rationalize the observed differences.

SCHEME 9. Conformational Equilibria of the Intermediate Aldol-Type Adducts



γ-halocarbanions with aldehydes varies greatly with the size of the electron-withdrawing group: sulfones rapidly cyclize to tetrahydrofurans and only aldol-type adducts of esters and nitriles can be isolated in high yields after the reaction mixtures are quenched with aqueous NH_4Cl at low temperature (see Supporting Information for details).

Finally, the cyclic structure of the transition state of the aldol addition offers a simple explanation for the observed correlation between activity of the reactants and selectivity of the formation of the isomeric tetrahydrofurans.[25] On the basis of the assumption that reactions of more stabilized carbanions and less electrophilic aldehydes are characterized by higher energy barriers, the transition state of the reaction is reached later and has a more compact structure, in which 1,3-diaxial interactions of bulky substituents disfavoring formation of the minor isomers of tetrahydrofurans are more pronounced if compared with the loose, early variant in the case of the more reactive substrates. Thus difference between energy barriers leading to diasteroisomers is larger and manifests itself in an increased ratio of the isomers. The same phenomena was observed earlier for aldol reactions of nitriles[35] and other systems described in the literature.[36,37] Thus the distribution of the diastereoisomeric tetrahydrofurans suggests again that the addition step is responsible for the observed selectivity.

Conclusions

We have found that carbanions of aryl 3-chloropropyl sulfoxides react with nonenolizable aldehydes to give 2,3-disubstituted tetrahydrofurans. The products are formed as mixtures of two diastereoisomers (one predominant) that differ in the configuration at the sulfur atom, whereas substituents in the ring are always in the *trans* relation. The observed stereochemistry stems from the organized cyclic transition state of the aldol-type addition of the sulfoxide carbanions to aldehydes and correlates with their electronic properties, i.e., more stabilized carbanions and less electrophilic aldehydes react more selectively. In turn, the electrophilic aldehydes fail to react with precursors of carbanions, because base is consumed in the reaction with the carbonyl group of the aldehyde in a form of hemiacetal anion. In the one-pot synthesis of substituted tetrahydrofurans deprotonation with *t*-BuOK is a rate-determining step followed by diastereoselective aldol-type addition and subsequent cyclization of the adducts. We postulate that the latter step consists of *anti* aldol-type adducts that are prone to cyclize to the tetrahydrofurane ring.

Experimental Section

General. All reactions were carried out under an atmosphere of argon in dried glassware using standard Schlenck techniques. THF was distilled from K/benzophenone ketyl, and hexanes, toluene, and EtOAc were distilled. Benzaldehyde was distilled and stored under argon, while other aldehydes for preparative reactions were used as freshly obtained from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on 200, 400, and 500 MHz spectrometers. Chemical shifts are reported in ppm from the solvent resonance ($CDCl_3$ as 7.26 ppm). Data are reported as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. All crude reaction mixtures were analyzed with ^{1}H NMR. Isomer ratio was determined by integration of signals of characteristic doublets of protons present at position 2 of the tetrahydrofuran ring. Peak assignments of **5**−**13** are based on ^{1}H, (^{1}H−^{1}H) COSY, and NOE NMR spectra of *trans* and *cis* isomers of analogous 2-phenyl-3-tetrahydrofurancarboxylic acid *tert*-butyl ester (see page S-82 and spectra reproductions on pages S-84 to S-98 in Supporting Information). Melting points are uncorrected.

General Procedure for the Synthesis of Sulfoxides 5−13. A Schlenk flask was charged with sulfoxide (**1**−**4**, 1 mmol), aldehyde (1.5 mmol), and THF (4 mL) and cooled to low temperature under argon. A solution of potassium *tert*-butoxide (2 mL, 2 mmol, 1 M in THF) was added slowly with stirring. After 3 h the cooling bath was removed, and an aqueous solution of NH_4Cl was added. The mixture was extracted with ethyl acetate (3 × 60 mL), and the combined organic phases were washed with brine and dried with Na_2SO_4. Solvent was evaporated, and the residue was analyzed with ^{1}H NMR and then separated with column chromatography on silica gel with hexanes/ethyl acetate or toluene/ethyl acetate. Minor amounts of aldehydes, cyclopropane derivatives, and unreacted sulfoxides were observed in each case but were rejected in routine preparative experiments. See Supporting Information for details.

Characterization data for 5a. Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58−7.63 (m, 2H, H_{arom}), 7.50−7.55 (m, 3H, H_{arom}), 7.27−7.38 (m, 5H, H_{arom}), 5.09 (d, $^3J_{HH}$ = 6.7 Hz, 1H, H-2), 4.16−4.21 (m, 1H, H-5), 3.97−4.03 (m, 1H, H-5), 3.18−3.23 (m, 1H, H-3), 2.59−2.66 (m, 1H, H-2), 1.91−2.00 (m, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 140.2, 131.2, 129.2, 128.6, 128.0, 125.7, 124.3, 80.3, 71.9, 68.2, 24.1. IR (neat): 3059, 2874, 1603, 1582, 1494, 1477, 1443, 1307, 1086, 1047, 912, 751, 698, 522, 471 cm^{-1}. MS (ESI) calcd for $C_{16}H_{16}O_2SNa$ 295.1, found 295.1. Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.50; H, 5.95; S, 11.63.

Characterization data for 6a. Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.50 (m, 4H, H_{arom}), 7.23−7.36 (m, 5H, H_{arom}), 5.02 (d, $^3J_{HH}$ = 6.9 Hz, 1H, H-2), 4.08−4.16 (m, 1H, H-5), 3.87−3.95 (m, 1H, H-5), 3.07−3.17 (m, 1H, H-3), 2.45−2.56 (m, 1H, H-4), 1.81−1.93 (m, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 139.8, 137.2, 129.4, 128.6, 128.0, 125.6, 125.5, 80.1, 71.6, 68.1, 23.7. IR (neat): 3061, 2946, 2874, 1576, 1475, 1454, 1391, 1081, 1054, 1011, 824, 760, 742, 700, 518,

(35) Carlier, P. R.; Lo, K. M.; Lo, M. M.-C.; Lo, P. C.-K.; Lo, C. W.-S. *J. Org. Chem.* **1997**, *62*, 6316.
(36) Młynarski, J.; Rakiel, B.; Stodulski, M.; Suszczyńska, A.; Frelek, J. *Chem.—Eur. J.* **2006**, *12*, 8158.
(37) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783.

431 cm^{-1}. MS (ESI) calcd for $C_{16}H_{15}ClO_2SNa$ 329.0, found 329.0. Anal. Calcd for $C_{16}H_{15}ClO_2S$: C, 62.64; H, 4.93; Cl, 11.56; S, 10.45. Found: C, 62.71; H, 5.02; Cl, 11.44; S, 10.27.

Characterization data for 6b. Mp: 126−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.56 (m, 2H, H_{arom}), 7.41−7.45 (m, 2H, H_{arom}), 7.16−7.24 (m, 3H, H_{arom}), 6.99−7.03 (m, 2H, H_{arom}), 5.23 (d, $^3J_{HH}$ = 4.6 Hz, 1H, H-2), 4.12−4.18 (m, 1H, H-5), 3.94−4.02 (m, 1H, H-5), 3.29−3.35 (m, 1H, H-3), 2.24−2.38 (m, 2H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.8, 137.6, 129.5, 128.4, 127.6, 126.1, 125.7, 78.5, 70.3, 68.3, 28.9. IR (in CH_2Cl_2): 2955, 2878, 1452, 1390, 1048, 1034, 954, 818, 768, 716, 698, 505, 428 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{15}{}^{35}ClO_2SNa$ 329.03735, found 329.03764. Anal. Calcd for $C_{16}H_{15}ClO_2S$: C, 62.64; H, 4.93. Found: C, 62.63; H, 4.93.

Characterization data for 7a. Mp: 88−91 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48−7.64 (m, 4H, H_{arom}), 7.24−7.36 (m, 2H, H_{arom}), 6.89−6.99 (m, 2H, H_{arom}), 5.03 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H-2), 4.12−4.27 (m, 1H, H-5), 3.90−4.06 (m, 1H, H-5), 3.86 (s, 3H, OCH_3), 3.08−3.25 (m, 1H, H-3), 2.50−2.70 (m, 1H, H-4), 1.86−2.12 (m, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.5, 140.9, 137.3, 131.5, 129.4, 127.2, 125.6, 114.0, 80.1, 71.7, 68.0, 55.2, 23.8. IR (KBr): 3050, 2929, 2877, 2838, 1611, 1511, 1391, 1306, 1246, 1064, 1027, 845, 830, 816, 742, 537, 512, 423 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{17}{}^{35}ClO_3SNa$ 359.04791, found 359.04963. Anal. Calcd for $C_{17}H_{17}ClO_3S$: C, 60.62; H, 5.09; Cl, 10.53; S, 9.52. Found: C, 60.67; H, 5.17; Cl, 10.65; S, 9.57.

Characterization data for 8a. Mp: 66−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.54 (m, 2H, H_{arom}), 7.46−7.50 (m, 2H, H_{arom}), 7.24−7.29 (m, 1H, H_{arom}), 6.80−6.88 (m, 3H, H_{arom}), 5.02 (d, $^3J_{HH}$ = 6.7 Hz, 1H, H-2), 4.13−4.19 (m, 1H, H-5), 3.92−4.00 (m, 1H, H-5), 3.79 (s, 3H, OCH_3), 3.10−3.17 (m, 1H, H-3), 2.50−2.59 (m, 1H, H-4), 1.86−1.97 (m, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 141.6, 140.9, 137.5, 129.9, 129.6, 125.7, 117.9, 113.7, 111.1, 80.1, 71.9, 68.3, 55.2, 23.9. IR (in CH_2Cl_2): 2942, 1724, 1602, 1475, 1391, 1264, 1157, 1080, 1048, 1011, 825, 781, 742, 697, 518 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{17}{}^{35}ClO_3SNa$ 359.04791, found 359.04932. Anal. Calcd for $C_{17}H_{17}ClO_3S$: C, 60.62; H, 5.09; Cl, 10.53; S, 9.52. Found: C, 60.36; H, 4.94; Cl, 10.40; S, 9.38.

Characterization data for 9a. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.51 (m, 4H, H_{arom}), 6.75−6.79 (m, 3H, H_{arom}), 5.93−5.96 (m, 2H, H_{arom}), 4.92 (d, $^3J_{HH}$ = 7.3 Hz, 1H, H-2), 4.08−4.15 (m, 1H, H-5), 3.87−3.94 (m, 1H, H-5), 3.02−3.09 (m, 1H, H-3), 2.47−2.56 (m, 1H, H-4), 1.82−1.93 (m, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.5, 140.9, 137.4, 133.4, 129.5, 125.6, 119.6, 108.3, 106.1, 101.1, 80.3, 71.7, 68.1, 23.7. IR (in CH_2Cl_2): 2926, 1724, 1577, 1504, 1489, 1476, 1445, 1391, 1249, 1079, 1038, 1011, 932, 821, 742, 516, 433 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{15}{}^{35}ClO_4SNa$ 373.02718, found 373.02902.

Characterization data for 10. Mp: 102−105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.47 (m, 2H, H_{arom}), 7.48−7.42 (m, 2H, H_{arom}), 3.80−3.86 (m, 1H, H-5), 3.76 (d, $^3J_{HH}$ = 5.8 Hz, 1H, H-2), 3.61−3.68 (m, 1H, H-5), 2.88−2.91 (m, 1H, H-3), 2.31−2.38 (m, 1H, H-4), 1.59−1.69 (m, 1H, H-4), 0.80 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 137.1, 129.3, 125.5, 86.6, 68.1, 65.3, 34.3, 25.6, 24.7. IR (KBr): 2956, 1575, 1474, 1392, 1364, 1083, 1036, 1010, 826, 740, 508 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{19}{}^{35}ClO_2SNa$ 309.06865, found 309.06952. Anal. Calcd for $C_{14}H_{19}ClO_2S$: C 58.63; H, 6.68; Cl, 12.36; S, 11.18. Found: C, 58.89; H, 6.84; Cl, 12.12; S, 10.93.

Characterization data for 11a. Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.51−8.60 (m, 1H, H_{arom}), 7.87−8.02 (m, 2H, H_{arom}), 7.26−7.48 (m, 6H, H_{arom}), 5.26 (d, $^3J_{HH}$ = 7.3 Hz, 1H, H-2), 4.06−4.18 (m, 1H, H-5), 3.88−4.01 (m, 1H, H-5), 3.56−3.68 (m, 1H, H-3), 2.38−2.55 (m, 1H, H-4), 1.67−1.87 (m, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.7, 149.6, 139.9, 137.9, 128.6, 128.1, 126.0, 124.6, 120.3, 80.5, 68.9, 68.3, 23.6. IR (neat): 3490, 3059, 2978, 2876, 1576, 1562, 1494, 1452, 1423, 1054, 769, 700, 470 cm^{-1}. MS (ESI) calcd for $C_{15}H_{15}NO_2SNa$ 296.1, found 296.2.

Characterization data for 12a. Oil (87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, $^4J_{HH}$ = 2.0 Hz, 1H, H_{arom}), 7.55 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H_{arom}), 7.29−7.39 (m, 6H, H_{arom}), 5.05 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H-2), 4.13−4.18 (m, 1H, H-5), 3.92−3.98 (m, 1H, H-5), 3.09−3.15 (m, 1H, H-3), 2.49−2.56 (m, 1H, H-4), 1.86−1.95 (m, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 139.6, 135.7, 134.2, 131.3, 128.8, 128.4, 126.2, 125.9, 123.3, 80.5, 71.8, 68.3, 23.6. IR (neat): 3059, 2875, 1455, 1368, 1139, 1058, 1030, 809, 760, 699, 673, 581, 459 cm^{-1}. MS (ESI) calcd for $C_{16}H_{14}{}^{35}Cl_2O_2SNa$ 363.0 found 363.3. Anal. Calcd for $C_{16}H_{14}Cl_2O_2S$: C, 56.31; H, 4.14; Cl, 20.78; S, 9.40. Found: C, 56.99; H, 4.07; Cl, 19.92; S, 8.96.

Characterization data for 13a. Oil (92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, $^4J_{HH}$ = 2.0 Hz, 1H, H_{arom}), 7.55 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H_{arom}), 7.35 (dd, J_{HH} = 8.3, 2.1 Hz, 1H, H_{arom}), 7.23−7.28 (m, 2H, H_{arom}), 6.88−6.92 (m, 2H, H_{arom}), 4.97 (d, $^3J_{HH}$ = 7.5 Hz, 1H, H-2), 4.12−4.17 (m, 1H, H-5), 3.89−3.96 (m, 1H, H-5), 3.81 (s, 3H, OCH_3), 3.07−3.13 (m, 1H, H-3), 2.49−2.57 (m, 1H, H-4), 1.87−1.97 (m, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 142.8, 135.6, 134.2, 131.2, 127.4, 126.2, 123.3, 114.2, 80.4, 71.7, 68.0, 55.3, 23.8. IR (neat): 3077, 2948, 2868, 1612, 1512, 1458, 1366, 1305, 1243, 1048, 922, 829, 814, 673, 576, 449 cm^{-1}. MS (ESI) calcd for $C_{17}H_{16}{}^{35}Cl_2O_3SNa$ 393.0, found 393.7.

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Supporting Information Available: Lengthy experimental procedures, analytical and spectral characterization data, crystallographic information, and peripheral findings. This material is available free of charge via the Internet at http://pubs.acs.org.