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Synthesis and Stereoselective Halogenolysis of Optically Pure Benzylstannanes

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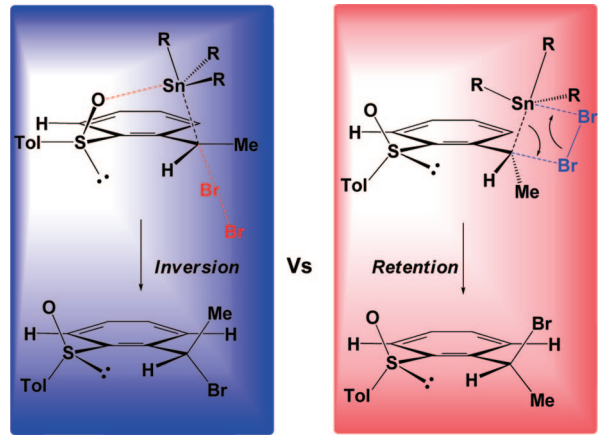

In this work we show that lithium *ortho*-sulfinyl benzylcarbanions are highly efficient reagents for the synthesis of optically pure benzylstannanes by reacting with halotriorganyl tin (up to >98:2 dr). The stereoselectivity of these reactions is opposite to those observed with carbon electrophiles. Bromolysis of the obtained *ortho*-sulfinylbenzylstannanes with Br_2 in the presence of CuBr takes place in a highly stereoselective way (up to 90:10 dr) with retention of the configuration, which allows the synthesis of optically pure 2-sulfinylated benzyl bromides. Different experiments support the proposed mechanistic rationalization for both processes.

Introduction

Optically pure benzyl-bromo derivatives are a versatile class of compounds widely used for resolution studies,[1] oxidative addition with palladium,[2] racemization processes,[3] and even as precursors of transition metals stabilized complexes.[4] Different strategies have been employed for the synthesis of benzyl bromides, such as inversion of optically pure alcohols,[5] enzymatic resolution of α-bromo-α-phenylacids,[6] opening of epoxides and aziridines with a nucleophilic bromine[7] and others.[8] Most of them lead to 1,2-difunctionalized compounds (bromoalcohols, bromoamines or α-haloacids), whereas methods affording optically pure benzyl bromides without additional α-functionalities are limited to the bromination of alcohols.[5] To our knowledge, methods allowing for stereocontrolled conversion of benzylic C−H into C−Br have not been reported.

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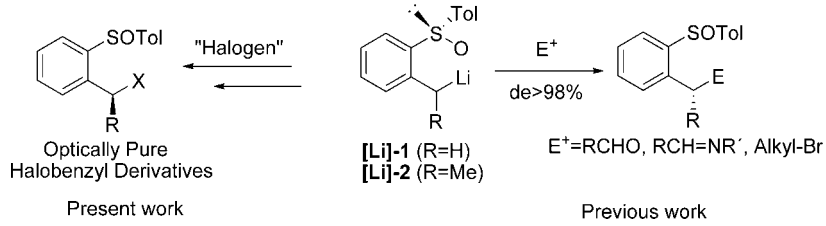
SCHEME 1. Reactions of *ortho*-Sulfinyl Benzyl Carbanions with Electrophiles



In the course of our studies dealing with stereoselective functionalization mediated by remote sulfoxides, we have found that reactions of lithium 2-*p*-tolylsulfinyl benzylcarbanions ([Li]-**1** and [Li]-**2**) with different electrophiles, such as carbonyl compounds,[9] imines,[10] alkyl halides,[11] and others,[12] proceed in a highly stereoselective manner, thus demonstrating the efficiency of the remote sulfinyl group for controlling the stereochemical evolution of the benzyl carbanions (right equation, Scheme 1). It prompted us to investigate the use of [Li]-**1** and [Li]-**2** as nucleophiles in the synthesis of the optically pure *ortho*-sulfinylated benzyl halides (left equation, Scheme 1). We considered that the electrophile may play an interesting role in determining the stereochemical outcome of the reaction given the ability of the sulfinyl group to behave as an anchimeric assistant.[13] Our efforts to develop an efficient and practical method for obtaining benzyl halides derivatives in a highly stereoselective manner are reported in this work.

Results and Discussion

The first strategy that we planned involved reactions of [Li]-**1** and [Li]-**2** with chemically different electrophilic halogen sources. Unfortunately, poor results were obtained from the reaction of the carbanions with Selectfluor,[14] NFSI,[15] or hexachloro-2,4-cyclohexadienone,[16] as well as with different brominating reagents.[17,18] At this point, we decided to obtain benzylic halo derivatives by an indirect way, involving the use of benzylstannanes as intermediates, which would be transformed into the desired halides by halogenolysis or via stanna-Pummerer transformation.[12a] This route involves developing a new strategy for the preparation of optically pure tin derivatives,[19] which is interesting because of the low number of strategies applied to this task. Thus, after the pioneering contributions from Podesta,[19a−e] most of the papers describing the synthesis of enantiopure tin compounds are based on the use of the (−)-sparteine.[19f−x]

The synthesis of 2-*p*-tolylsulfinyl benzylstannanes was achieved by the reaction of R_3SnCl with carbanions derived from **1** and **2** (Table 1). Thus, the addition of R_3SnCl to the [Li]-**1** solution afforded **3** in good yield (entry 1), whereas inverse addition of the reagent did not proceed well (entry 2). Starting from the prochiral carbanion [Li]-**2**, a 80:20 diastereomeric mixture of **4A** and **4B** was obtained, these compounds were epimers at the benzylic position (entry 3, Table 1). Interestingly, the stereoselectivity was increased with a higher number of equivalents of Bu_3SnCl (compare entries 3−5), increasing to a diastereomeric ratio of >98:2 when 3 equiv of the electrophile were used (entry 5).

A similar increase of the diastereomeric ratio was observed in reactions with Ph_3SnCl (entries 6−8); however, the stereo-

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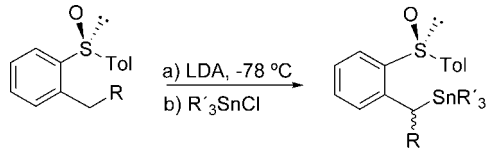
TABLE 1. Benzylstannanes Produced by Addition of [Li]-1 or [Li]-2 to R_3SnCl



1 (R=H)
2 (R=Me)

3 (R=H, R´= *n*-Bu)
4A : **4B** (R=Me, R´= *n*-Bu)
5A : **5B** (R=Me, R´= Ph)

entry	sulfoxide (mmol)	R	reagent (equiv)	product	yield (%)	dr (**A**:**B**)
1	0.041	H	Bu_3SnCl (2)	**3**	92	
2	0.041	Me	Bu_3SnCl (3)	**3**	*a,b*	
3	0.041	Me	Bu_3SnCl (1)	**4A**:**4B**	*c*	80:20
4	0.041	Me	Bu_3SnCl (1.5)	**4A**:**4B**	*c*	85:15
5	0.041	Me	Bu_3SnCl (3.0)	**4A**:**4B**	75[d]	>98:2
6	0.041	Me	Ph_3SnCl (1.5)	**5A**:**5B**	*c*	60:40
7	0.041	Me	Ph_3SnCl (3.0)	**5A**:**5B**	84[d]	86:14
8	0.041	Me	Ph_3SnCl (5.0)	**5A**:**5B**	81[d]	91:9
9[e]	0.041	Me	Ph_3SnCl (1.5)	**5A**:**5B**	*c*	45:55
10	0.082	Me	Bu_3SnCl (3.0)	**4A**:**4B**	82[d]	90:10
11	0.200	Me	Bu_3SnCl (3.0)	**4A**:**4B**	*c*	85:15
12	0.400	Me	Bu_3SnCl (3.0)	**4A**:**4B**	*c*	75:25

[a] Addition of the carbanion to a solution of Bu_3SnCl at −78 °C. [b] No reaction. [c] Yield not determined. [d] Combined yield for both diastereoisomers. [e] One equivalent of 12-crown-4 ether was added.

selectivity was lower compared with *n*-butyltin derivatives. Thus, using 3 equiv of the electrophile, the **5A**:**5B** ratio was only 86:14 (entry 7), which was increased to 91:9 when 5 equiv of the Ph_3SnCl was used (entry 8). The addition of 12-crown-4 ether decreased the stereoselectivity dramatically (entry 9). For synthetic purposes, we scaled up the reaction with *n*-Bu_3SnCl (entries 10−12). The stereoselectivity decreased when the amount of reagents became larger (compare entries 5 and 10−12), and the diastereomeric ratio was only 75:25 when the experiments were carried out with 0.4 mmol (entry 12), which is 10 times higher than the amount used in entry 5.

Unequivocal configurational assignment at the benzylic carbon of the epimers **A** and **B** (Scheme 2) was achieved by oxidation of **5A** into the sulfone **11**, whose absolute configuration was unequivocally established as *R* by X-ray analysis (see Scheme 6). Consequently, it allows us to assign the (S*S*,*R*) configuration to **5A** and therefore (S*S*,*S*) to **5B**. Interestingly, the configuration of the benzylic center at the major isomer is opposite to that obtained in the reactions of **2** with other electrophiles previously reported.[9,10] Surprisingly, all these facts suggest an unprecedented stereochemical evolution and demonstrate that the configurational assignment previously reported for **4A**[12a] was wrong, since we assumed that the stereochemical evolution was identical for $ClSnBu_3$ and other electrophiles.[9,10] We have obtained stereochemistry retention in the reaction with R_3SnCl; a comparison to other reported benzylic stannylation reactions[19u] reveals an observed inversion using (−)-sparteine as chiral external source.

These results could be explained as follows: [Li^+]-**2** must exhibit a boatlike chelated structure (Scheme 2), with the sulfinyl group stabilizing the metal atom via coordination, while the H and the lone electron pair are oriented toward the flagpoles of the boat, as we previously proposed on the basis of theoretical calculations.[10e] The high oxophilicity of the tin could explain that the addition of R_3SnCl causes the immediate attack of the sulfinyl oxygen at the metal, substituting the chloride (which will join the Li^+, forming LiCl) and favoring species like **I** (Scheme 2). The most hindered face in both species ([Li^+]-**2** and **I**) is completely different (see Scheme 2), and therefore, **A** epimers will be formed in the evolution of species **I**,[20] whereas the **B** epimers will be obtained by attack of the electrophiles at [Li^+]-**2**.[21] The **A**:**B** ratio obtained in each case will depend on the composition of the equilibrium between **I** and [Li^+]-**2**. The use of an excess of R_3SnCl will cause an increase in the proportion of **I** and, therefore, in the amount of isomer **A** formed (higher stereoselectivity). It is possible to prepare optically active benzylstannane using this methodology, because diastereomers **4A**−**5A** and **4B**−**5B** are chromatographically separable.

The increase of stereoselectivity observed when the number of equivalents of the electrophile becomes larger supports this explanation (the equilibrium depicted in Scheme 2 will be shifted toward **A**).[22] Taking into account that THF is also able to stabilize the R_3SnCl by association with the metal, competing with the sulfinyl oxygen, and thereby reducing the amount of electrophile which is available to intervene in the equilibrium of Scheme 2, we have additionally performed experiments that use different amounts of solvent. When the conditions of entry 4 (Table 1) were repeated by using 5 times more solvent, the ratio of **4A**/**4B** was decreased (59:41), whereas when the amount of solvent was reduced to half, the diastereomeric ratio was increased (90:10); these experiments support the equilibrium proposed in Scheme 2. On the other hand, the lower stereoselectivity observed in the reactions with Ph_3SnCl could be a consequence of the decrease of the oxophilicity promoted by the phenyl group, although the role of the dilution[23] and the different reactivity[24] must not be ignored. Finally, the decrease of stereoselectivity when the reaction is performed at larger scale

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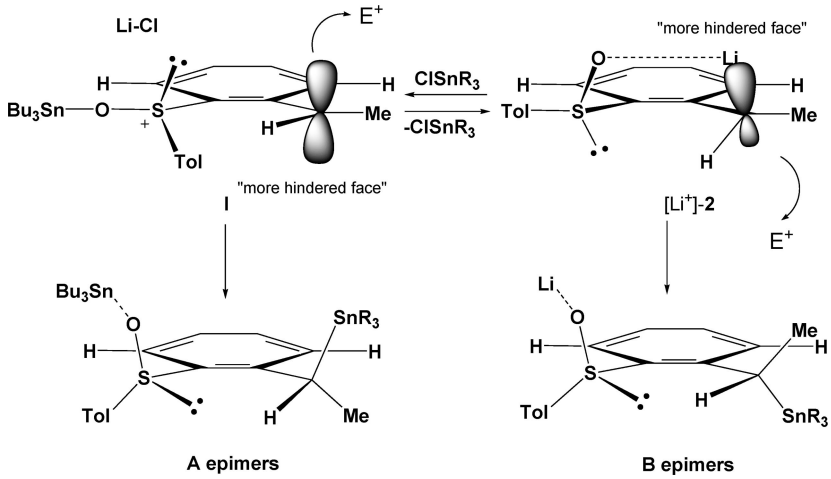
(20) This evolution could be less stereoselective for compounds with groups other than methyl joined to the benzylic carbon, because the conformational preferences around the C−C bond would alter the relative easiness of the electrophilic approach.

(21) **B** epimers are the major or exclusive isomers obtained in reactions with other electrophiles such as carbonyls or imines, because these reactions take place on the species [Li]-**2**. See also ref 10e.

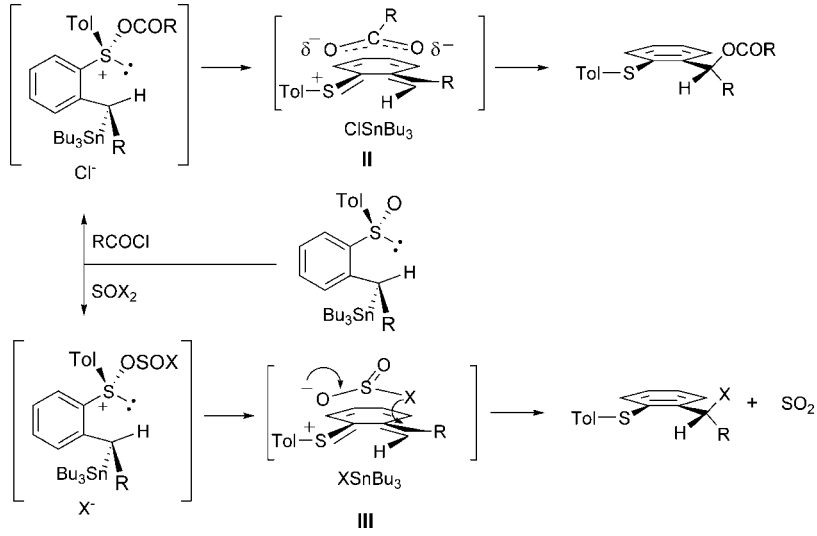
(22) The addition of LiCl to the reaction media induces a decrease of the stereoselectivity, but the scarce solubility of the salt precludes this effect.

(23) Reactions with solid Ph_3SnCl require more THF to be dissolved before the addition to the reaction media (whereas Bu_3SnCl is liquid).

SCHEME 2. Stereochemical Model To Explain the Results Obtained



SCHEME 3. Reactions of Benzylstannanes with Acid Chlorides

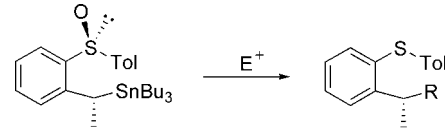


could be attributed to diffusion problems, determining that reaction of [Li^+]-**2** with the electrophile takes place to some extent before the equilibrium is completely reached.

Once we solved the problem of stereoselective synthesis of benzyl stannanes, we studied their conversion into the corresponding halo derivatives. Our first approach consisted of reacting benzylstannanes with X_2SO (X = Cl or Br), based on the previous results obtained in reactions of benzylstannanes with acid chlorides (stanna-Pummerer rearrangement[12a]), to provide benzylic acetates in high enantiomeric excess (ee). The key intermediate justifying the high stereoselectivity of these reactions was the intimate ion pair **II** (Scheme 3), resulting from the acyl-oxysulfonium derivative formed by attack of the acyl chloride on the sulfinyl group (Scheme 3). According to this observation, the use of X_2SO instead of the acyl chloride could allow for the stereoselective introduction of the halogen at the benzylic position, by formation of the species **III**.

The results obtained in the reaction of **4A** with $SOCl_2$ and $SOBr_2$ under different conditions are collected in Table 2.

TABLE 2. Halo Derivatives Produced As Illustrated in Scheme 3



4A **6** (R= Cl) **7** (R= Br)

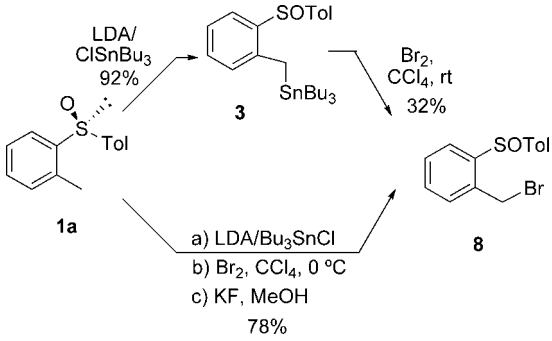
entry	solvent/T (°C)	reagent	yield (%)	er[a]
1	CH_2Cl_2/rt	$SOCl_2$	65	49:51
2	acetone/−78 to rt	$SOCl_2$	67	54:46
3	CH_2Cl_2/rt	$(COCl)_2$	72	55:45
4	CH_2Cl_2/−20 to rt	$(COCl)_2$	42	52:48
5	CH_2Cl_2/rt	PCl_3	35	52:48
6	CH_2Cl_2/rt	$SOCl_2$/Py	69	55:45
7	CH_2Cl_2/−40 to rt	$SOCl_2$/Py	71	23:77
8	DMF/-20	$SOCl_2$/Py	66	28:72
9	CCl_4/−78 to rt	$SOCl_2$/Py	68	42:58
10	CH_2Cl_2/−78 to rt	$(COCl)_2$/Py	65	21:79
11	CH_2Cl_2/−20	$SOBr_2$	42	51:49

[a] Enantiomeric ratio determined by HPLC.

Reaction with $SOCl_2$ in CH_2Cl_2 at room temperature afforded **6** in good yield but with very low enantiomeric excess (entry 1) which could not be significantly improved by changing the

(24) The influence of the reactivity on the selectivity was indicated by studying the reaction with Me_3SnCl under conditions of entry 4. A 66:33 mixture of diastereoisomers was instantaneously produced, suggesting that the attack of Li-**2** to this electrophile is faster than the establishment of the equilibrium depicted in Scheme 2.

SCHEME 4. Synthesis of the Simplest Benzylbromide 8



solvent (acetone at −78 °C, entry 2) or using other chloride sources such as $(COCl)_2$ or PCl_3 (entries 3−5). Better stereoselectivities were obtained by using pyridine as an additive (entry 6−10), which also inverted the selectivity. The reaction with $SOBr_2$ also afforded **7** with very low stereoselectivity (entry 11).

The lower stability of the intimate ion pair **III** (Scheme 3), evolving into a separated ionic pair, and/or the easy elimination of SO_2 from X−SO−O− to yield X^-, which would attack from any of the two faces of the planar benzylic carbocation, would explain the low ee observed in these reactions.

The second and definitive approach to obtain optically enriched benzyl halides involves the halogenolysis of tin derivatives. It is well-known that the C−Sn bond can be cleaved by using halogens, where the reactivity depends on the halogen used ($Cl_2 > Br_2 > I_2$) and the group attached to the metal,[25] with benzyl derivatives among the most reactive substrates. The stereochemistry of the cleavage of C−Sn bonds by halogens depends on the temperature, the structure of the substrate, and mainly the solvent,[26] usually taking place with retention of configuration in apolar solvents such as CCl_4 but with a large degree of inversion in more polar solvents.

According to the known ability of the sulfinyl group as an anchimeric assistant in halogenolysis of C−Sn bonds,[27] 2-*p*-tolylsulfinyl benzylstannanes should be appropriate substrates for an easy Sn−C cleavage with halogens. When the simple benzylstannane **3** reacted with bromine in CCl_4, a complete conversion into **8** was observed at room temperature (Scheme 4). Chromatographic separation of **8** from Bu_3SnCl was a tedious task that required the use of low polarity solvents and therefore long periods of time. Thus a low isolated yield was observed (32%) for compound **8** which was barely stable in light. By modifying the reaction conditions, by performing the bromination in the absence of light, and by reducing the time of the purification process by addition of KF/MeOH[28] to the crude reaction mixture, the reaction formed insoluble Bu_3SnF that precipitated and allowed for separation of **8** by filtration. The isolated yield of **8** from **1a** was increased to 78% (Scheme 5).

Once we found the appropriate conditions for efficient bromolysis of these stannanes, we studied the behavior of **4A** and **5A** (Table 3), which would provide relevant information

SCHEME 5. Conversion of 9A and 9B into Enantiomeric Sulfones 10

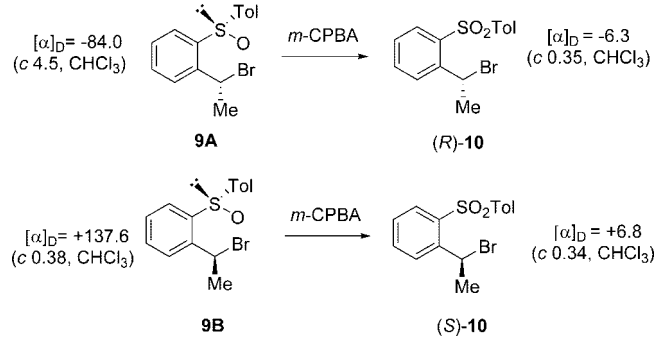
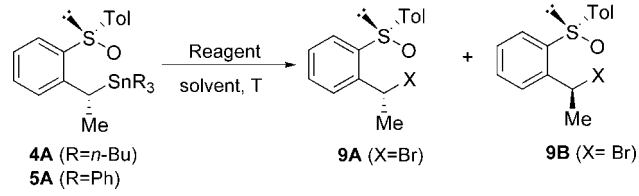


TABLE 3. Halogenolysis of Methyl 2-*p*-Tolylsulfinylbenzyl Stannanes



entry	reagent	R	solvent	*T* (°C)	yield (%)	dr[a] (**A**:**B**)
1	Br_2	*n*-Bu	CCl_4	0	45	57:43
2	Br_2	*n*-Bu	CCl_4	−20	60	60:40
3	Br_2	*n*-Bu	CH_2Cl_2	−78	55	42:58
4	Br_2	*n*-Bu	toluene	−78		NR[b]
5	Br_2	*n*-Bu	DMF	−40		NR[b]
6	NBS	*n*-Bu	CCl_4	−20		NR[b]
7	$PhNMe_3Br_2Br$	*n*-Bu	CH_2Cl_2	−78		NR[b]
8	Br_2/CuBr (10%)	*n*-Bu	CCl_4	−20	78	70:30
9	Br_2/CuBr (1 equiv)	*n*-Bu	CCl_4	−20	>99	80:20
10	Br_2/CuBr (2 equiv)	*n*-Bu	CCl_4	−20	90	90:10
11	Br_2	Ph	CCl_4	−20	nd	60:40
12	Br_2/CuBr (2 equiv)	Ph	CCl_4	−20	81	85:15
13	Br_2/CuBr (3 equiv)	Ph	CCl_4	−20	76	86:14

[a] Diastereomeric ratio measured by ^{1}H-NMR. [b] No reaction.

about the stereochemical aspects of the process. The reaction of enantiopure **4A** with Br_2 afforded a 57:43 mixture of **9A** and **9B** that was epimeric at the benzylic position (entry 1, Table 3) in a moderate yield. By decreasing the temperature to −20 °C (at lower temperatures the solvent was frozen), the stereoselectivity was scarcely improved (entry 2). Experiments carried out at −78 °C required change of the solvent. Thus, in CH_2Cl_2, we observed a similarly low diastereoselectivity, but the ratio was inverted to favor **9B** (entry 3, Table 3). Since an influence on stereoselectivity by solvent-polarity was suggested, we studied the reaction in other solvents, but unfortunately the reactions did not work in toluene or DMF (entries 4 and 5, Table 3). No expected products were obtained by using NBS or $PhNMe_3Br_2Br$ as brominating agents (entries 6 and 7, Table 2). All of these reactions were conducted in the absence of light and with the addition of KF/MeOH to the resulting reaction mixture in order to make the purification of the final products easier.

Taking into account the possible anchimeric assistance of the sulfinyl group, the low stereoselectivity observed in these reactions could be the result of a competition between the assisted and the unassisted process. In such a case, additives could be able to neutralize the participation of the sulfinyl group by association to the sulfinyl oxygen, and thus modify the

(25) (a) Davies, A. G.; Hawari, J. A. *J. Organomet. Chem.* **1983**, *251*, 1. (b) Davies, G. A. *Organotin Chemistry*; VCH: Germany, 1997.
(26) (a) Jensen, F. R.; Davis, D. D. *J. Am. Chem. Soc.* **1971**, *93*, 4048. (b) Rahm, A.; Pereyre, M. *J. Am. Chem. Soc.* **1977**, *99*, 1672. (c) McGahey, L. F.; Jensen, F. R. *J. Am. Chem. Soc.* **1979**, *101*, 4397. (d) Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* **1985**, *286*, 305. (e) Chopa, A. B.; Koll, L. C.; Podesta, J. C.; Mitchell, T. N. *J. Organomet. Chem.* **1989**, *376*, 283.
(27) Kuivila, H. G.; Karol, T. J.; Swami, K. *Organometallics* **1983**, *2*, 909.
(28) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

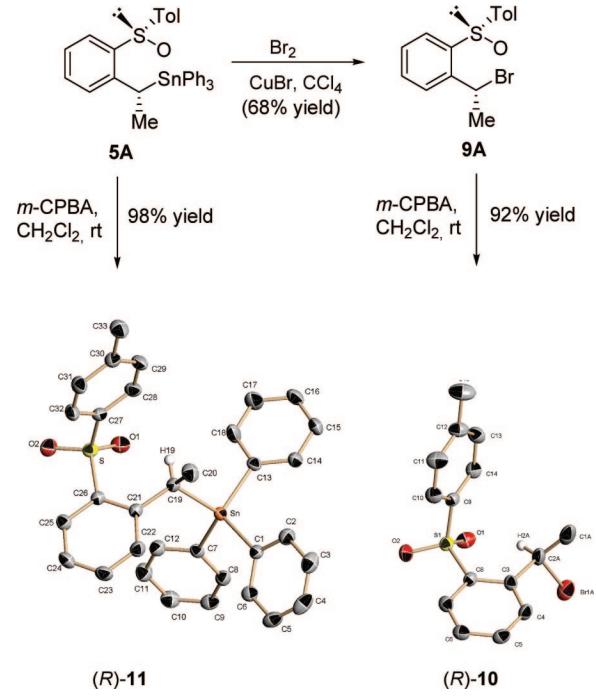
stereoselectivity. With this in mind, we investigated the influence of CuBr on the course of the reaction (entries 8−10, Table 3). To our delight, yield and stereoselectivity were significantly improved in the presence of this reagent, depending on the concentration. A quantitative yield was obtained by using 1 equiv of CuBr (entry 9), but the best stereoselectivity was observed using 2 equiv of this additive (80% de, entry 10). Because **9A** and **9B** are chromatographically separable, it is possible to prepare the optically pure halo benzyl derivatives we set out to obtain (as shown in Scheme 1). We have also investigated the bromolysis of triphenylstannane **5A** (entries 11−13). In this case, the reaction is barely stereoselective in the absence of CuBr, whereas its addition induces a substantial increase of the stereoselectivity. Thus, when 2 equiv of copper salt was used, the reaction afforded an 85:15 mixture of diastereoisomers, whereas the result was scarcely improved by the use of 3 equiv of additive (entry 13).

As the configurational instability of the sulfinyl groups in the presence of halogens has been reported as well as that of the benzyl bromides under light,[29] the stereochemistry of **9A** and **9B** had to be investigated. Once separated by chromatography, the independent *m*-CPBA oxidation of **9A** and **9B** provided enantiomeric sulfones [(*R*)-**10** and (*S*)-**10**], which clearly indicated that their precursors were epimers at the benzylic carbon (Scheme 5), and therefore, the sulfinyl configuration had not been affected under the reaction conditions. Additionally, by standing in solution, pure **9A** was spontaneously converted into a 55:45 mixture of **9A** and **9B**. The same result was obtained from **9B**, providing evidence of the low configurational stability of these benzyl bromides in solution in the presence of light.

The absolute configuration of the sulfones (*R*)-**10** and (*R*)-**11**, respectively, obtained by *m*-CPBA oxidation of the sulfoxides **5A** and **9A**, were unambiguously established by crystallization and X-ray analysis (Scheme 6).[30] As shown in Scheme 6, the configuration at the benzyl carbon is *R* for both substrates, which means that halogenolysis has taken place with retention of configuration.

The last issues to answer are the stereochemical course of the bromolysis and the role played by CuBr. According to the preceding stereochemical studies on halogenolysis, inversion of the configuration can be explained by assuming that the substrate is forming through an S_E2 (closed) mechanism.[25b] Starting from the presumably most stable conformation of the isomers **4A** or **5A** (**C** at Scheme 7), this mechanism would involve one of the bromine atoms of the Br_2 joining to the Sn, simultaneously enhancing the nucleophilic character of the carbon attached to the tin and the electrophilic character of the second bromine atom. The formation of the bromo derivative would be obtained with the same configuration as the starting stannane (bold line, Scheme 7). However, when the activation of the Sn would take place by another nucleophile, before the attack of the bromine, the reaction took place via inversion of the configuration of the carbon according to an S_E2 (assisted) mechanism.[25b] The presence of the sulfinyl group in our substrates, with the sulfinyl oxygen being able to act as an internal activator for the tin by formation of species **D**, suggests that the reaction proceeds through this mechanism (thinner line, Scheme 7). By assuming a similar rate for the formation of species **C** and **D**, the observed stereoselectivity would be related to the relative proportions of **C** and **D** in the equilibrium. The low diastereomeric ratio obtained in reactions of compounds **4A** or **5A** with Br_2 suggests that **C** and **D** are present in equal amounts in the equilibrium.[31] The addition of CuBr would favor the association of the sulfinyl oxygen to the copper, precluding the internal activation. Under these conditions, species **C′** would be formed which should react in a manner similar to that for **C** with retention of configuration through an S_E2 (closed) mechanism. When the amount of CuBr was increased, the proportion of **C′** becomes larger, and the observed results can be explained.

SCHEME 6. Synthesis and X-ray Analysis of Compounds (*R*)-11 and (*R*)-10



In order to support this mechanistic proposal, we studied the reaction of Br_2 with **4B**, the minor diastereoisomer obtained in reactions at Table 1. For this compound, the formation of species **D′** (Scheme 8; similar to **D** depicted in Scheme 7) would not be expected because of the strong steric destabilization produced by the methyl group occupying one of the flagpole positions of the boat. As a consequence, **4B** would mainly form through conformation **C′** which should increase the stereoselectivity in the reaction with Br_2 and simultaneously decrease the influence of the CuBr.

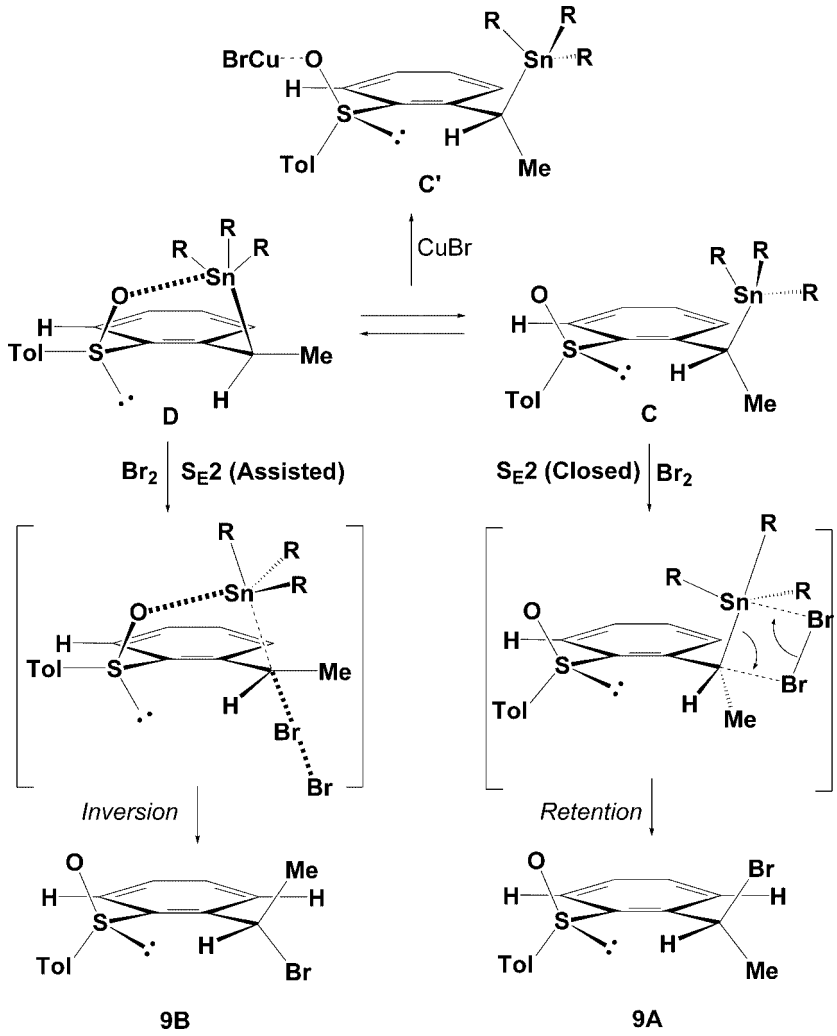
The reaction of **4B** with Br_2, under the conditions of the entry 2 (Table 3) provides a 82:18 mixture of **9B** and **9A** (much higher stereoselectivity than that observed for **4A** under similar conditions). The results were almost identical when **4B** reacted under conditions of the entry 10 at Table 3, which reveals the low importance of the addition of CuBr on the reaction course. These results can be explained by assuming that the preferred

(29) Buckles, R. E.; Steinmetz, W. E.; Wheeler, N. G. *J. Am. Chem. Soc.* **1950**, *72*, 2496.

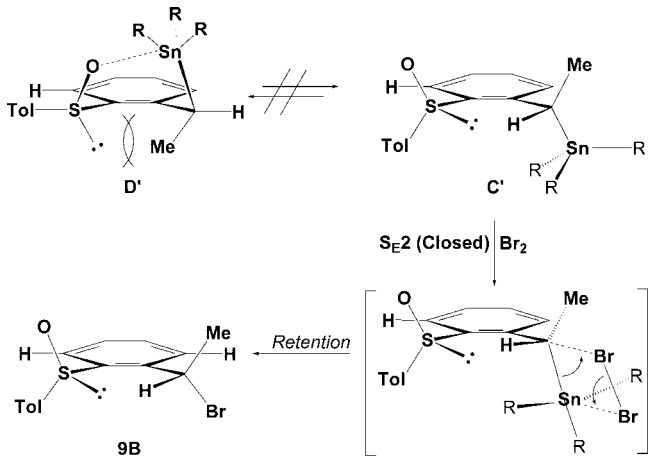
(30) CCDC 701382 [(*R*)-**10**] and 701383 [(*R*)-**11**] contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax: (internat.) +44(1223)336-033.

(31) This oversimplification, considering that the reaction rates of the S_E2 (closed) and S_E2 (assisted) processes are similar, could not be true for compounds bearing groups different from Me joined to the benzylic position, because the significance of the steric effects in the transitions states resulting in the evolution from **C** and **D** are clearly different.

SCHEME 7. Stereochemical Model Proposed To Explain the Obtained Results from 4a or 5a



SCHEME 8. Stereochemical Evolution of 4B



conformation of **4B** is indeed **C′**, which evolves through an S_E2 mechanism to produce **9B** constituting the principal route for the evolution of **4B** (Scheme 8).

Conclusions

In conclusion, we have shown that the lithium *ortho*-sulfinyl benzylcarbanions are highly efficient in the synthesis of optically pure benzylstannanes by reaction with halotriorganyl tin. The preferred stereoselectivity of these reactions is opposite to that observed with carbon based electrophiles, and we have discussed a possible mechanistic rationalization. Moreover, bromolysis of the *ortho*-sulfinylbenzylstannanes with Br_2 in the presence of CuBr takes place in a highly stereoselective manner with retention of configuration starting from **4A**, allowing the synthesis of optically pure 2-sulfinylated benzyl bromides following chromatographic separation. Different experiments supported the proposed mechanistic rationalization for both processes. We are now involved in studying the behavior of these compounds in their reactions with different nucleophiles, as well as in the synthesis of other benzyl halides supporting groups different to Me at the benzylic position. Results obtained in these studies will be reported in due course.

Experimental Section

General Procedure for Synthesis of Compounds of Table 1. A solution of *n*-BuLi (0.6 mmol, 2.3 M in hexane) was added to iPr_2NH (0.9 mmol) in THF (3 mL) at 0 °C. After stirring for 20 min, the mixture was cooled to −78 °C. A solution of the corresponding (*S*)-sulfoxide **1** or **2** (0.5 mmol) in THF (2 mL) was added. After stirring for 30 min, the corresponding tin chloride (1.5 mmol) was added at −78 °C. When the reaction was completed (20−30 min), the mixture was hydrolyzed (saturated NH_4Cl), extracted (3 × 10 mL of Et_2O), washed (2 × 10 mL of NH_4Cl

saturated), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Compounds were purified by flash silica gel column chromatography (eluent and yield were indicated in every case).

(S*S*)-Tributyl[2-(*p*-tolylsulfinyl)benzyl]stannane (3). The reaction was carried out using (*S*)-sulfoxide **1** and tributyltin chloride. The residue was purified by flash chromatography (15:1 *n*-hexanes/EtOAc) giving a colorless oil. Yield = 92%. IR (NaCl): 2923, 1588, 1492, 1464, 1084, 1034 cm^{-1}. ^1H NMR (200 MHz): δ 7.84 (dd, J = 6.8, 1.2 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.30−7.10 (m, 4H), 6.95 (d, J = 6.8 Hz, 1H), 2.35 (s, 3H), 2.29 (d, J = 12.0 Hz, 1H), 2.20 (d, J = 12.0 Hz, 1H), 1.44−1.30 (m, 6H), 1.29−1.10 (m, 12H), 0.88–0.80 (m, 9H). ^{13}C NMR (50 MHz): δ 142.4, 141.5, 141.4, 138.9, 130.7, 129.9, 128.6, 126.2, 124.6, 124.0, 28.8, 27.7, 27.2, 13.6, 13.5, 10.1. $[\alpha]_D^{20}$: −269.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{28}H_{27}NOS$: C, 79.02; H, 6.39; N, 3.29; S, 7.53. Found: C, 78.56; H, 6.39; N, 3.29; S, 7.53.

General Procedure for Synthesis of Compounds of Table 2. To a solution of the sulfoxide **4A** (0.2 mmol) in CH_2Cl_2 was added the corresponding halogenated compound (0.9 mmol) at the indicated temperature (for conditions, see Table 2). When the reaction was completed (20−30 min), the solvent was removed under reduced pressure. Compounds were purified by flash silica gel column chromatography (eluent and yield were indicated in every case).

[2-(1-Chloroethyl)phenyl](*p*-tolyl)sulfane (6). The residue was purified by flash chromatography (50:1 *n*-hexanes/EtOAc) giving a colorless oil. Yield = 72%. The enantiomeric ratio was determined by HPLC using a Chiralpak AD column [*n*-hexane/*i*-PrOH (100:0)]; flow rate 0.1 mL/min; τ_R = 35.0 min (major enantiomer), τ_R = 44.5 min (minor enantiomer). IR (NaCl): 1491, 1467, 1437, 1043 cm^{-1}. ^1H NMR (300 MHz): δ 7.66 (d, J = 8.0 Hz, 1H), 7.32 (td, J = 7.2, 1.2 Hz, 1H), 7.27−7.14 (m, 4H), 7.10 (d, J = 8.8 Hz, 2H), 5.78 (q, J = 6.8 Hz, 1H), 2.31 (s, 3H), 1.77 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz): δ 143.5, 137.1, 133.6, 132.8, 130.8, 130.1 (2C), 128.7, 128.1, 127.2, 55.3, 26.2, 21.1. Anal. Calcd for $C_{15}H_{15}ClS$: C, 68.55; H, 5.75. Found: C, 68.78, H, 5.41.

General Procedure for Synthesis of Bromide Compounds of Scheme 4 and Table 3. To a solution of the sulfoxide **3**, **4**, or **5** (0.2 mmol) in CCl_4 in the absence of light was added the corresponding halogenated compound (0.9 mmol) at the indicated temperature (see Scheme 4 and Table 3). When the reaction was completed (20−30 min), MeOH and KF (1000 mg) were added. A white precipitate appeared which was filtered through celite. The solvent was removed under reduced pressure. Compounds were purified by flash silica gel column chromatography (eluent and yield were indicated in every case).

(S*S*)-1-[(*R*)-1-Bromoethyl]-2-(*p*-tolylsulfinyl)benzene (9A). The residue was purified by flash-column chromatography (6:1 *n*-hexanes/EtOAc) giving a colorless oil. Yield = 50−90%. IR (NaCl): 2920, 1587, 1490, 1435, 809 cm^{-1}. ^1H NMR (300 MHz): δ 7.88 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.50−7.35 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 5.45 (q, J = 6.6 Hz, 1H), 2.28 (s, 3H). 1.70 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz): 141.9, 141.7, 141.4, 141.2, 131.8, 131.2, 129.2, 128.7, 125.9, 125.0, 41.9, 26.6, 21.2. $[\alpha]_D^{20}$: −137.4 (*c* 1.0, $HCCl_3$). EM (FAB) *m*/*z*: 325 (M + 1, 31), 245 (50), 244 (51), 243 (100), 225 (41),132 (29).

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Supporting Information Available: Complete experimental procedures, characterization for the all of the compounds (PDF) and CIF files are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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