Highly Stereoselective Preparation of Chiral α-Substituted Sulfides from α-Chloro Sulfides via 1,2-Asymmetric Induction

Preparation of Chiral α-Substituted Sulfides

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Abstract: A C–S stereogenic center is created with efficient stereocontrol by 1,2-asymmetric induction due to a vicinal C–O stereogenic center. Propargylic, allylic, and alkyl sulfides are readily prepared in good yield and stereoselectivity from α-chloro sulfides. The allylic sulfide have been converted to the corresponding sulfoxide/sulfilimine/sulfur ylide and subjected to [2,3]-sigmatropic rearrangement. The efficient 1,3-chirality transfer observed in this reaction eventually results in a net 1,4-chirality transfer.

Key words: α-chloro sulfide, rearrangement, sulfoxide, stereoselective synthesis, asymmetric induction

The development of new and highly selective carbon–carbon and carbon–heteroatom bond-forming processes are an important topic in organic synthesis. The creation of stereogenic centers in acyclic systems, as compared to cyclic systems, is particularly challenging due to the many available degrees of freedom. Chiral α-branched propargylic and allylic sulfides are versatile building blocks as a source of epoxy alkynes,[1] epoxydiynes,[2] allylic alcohols,[3] allylic amino derivatives,[4] and γ,δ-unsaturated acids.[5] However, the required substrates are not readily available and are prepared from the chiral-pool starting materials[6] thus making one enantiomer more available than the other while simultaneously limiting the products that can be prepared. An exception to this is the recent report by Armstrong and co-workers on the preparation of allylic sulfides by organocatalysis.[4] An alternative approach to chiral α-branched sulfides would therefore greatly expand the scope of the process. We disclose herein the results of our investigation on the stereoselective synthesis of chiral α-branched sulfides **2** by reacting α-chloro sulfides **1** with organometallic reagents, via 1,2-asymmetric induction by an adjacent stereogenic carbon bearing a protected hydroxy group (Scheme 1).

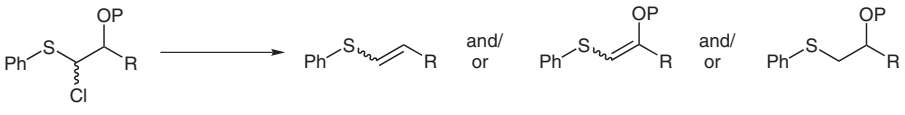
1 2

Scheme 1 Diastereoselective preparation of α-substituted sulfides

α-Chloro sulfides are valuable synthetic intermediates as reactive electrophiles,[7] nucleophiles in metal-promoted carbon–carbon bond-forming reactions[1,2,8] and as aldehyde or ketone equivalents.[9] The reaction of α-chloro sulfides with silyl enol ethers[10] constitutes an important method for the regioselective introduction of a thioalkyl substituent α to the carbonyl group. The reaction of α-chloromethyl methylsulfide with phenyl Grignard reagent reported first by Bohme[11] has been extended into a general method for introducing α-alkyl/aryl substituents. However, the reactions reported thus far have been carried out on simple cyclic and acyclic α-chloro sulfides only. There are no reports on the preparation of α-branched sulfides by the reaction of α-chloro sulfides with Grignard and other organometallic reagents.

The envisaged reaction of the α-chloro sulfide with a basic organometallic reagent was expected to pose difficulties because of the other competing reactions like metal–halogen exchange and subsequent β-elimination of the alkoxy substituent to furnish vinyl sulfide **3**, elimination of chlorine to yield enol ether **4** or reduction[12] to yield sulfide **5** (Scheme 2).

The study was initiated with racemic sulfide[13] **6**. On treatment of **6** with an equivalent amount of *N*-chlorosuccinimide (NCS) in benzene at ambient temperature α-chlorosulfide **7** was formed. The α-chlorosulfide **7** was used without isolation, being added to 1-octynylzinc bromide (**8a**), that was prepared from 1-octynylmagnesium chloride and anhydrous zinc bromide[14] in THF. Work up



1 3 4 5

Scheme 2 Possible side reactions

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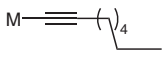
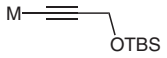
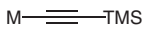
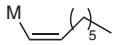
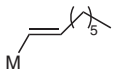
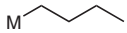
of this mixture afforded propargyl sulfide **9a** as a 9:1 mixture of diastereomers in 86% yield[15] (Table 1).

Table 1 Stereoselective Synthesis of Racemic α-Substituted Sulfides[a]

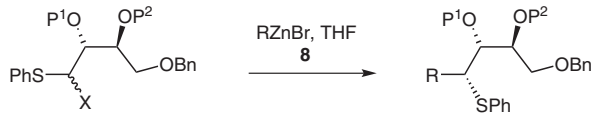
Entry	Organozinc reagent (RM)	Product, yield (%)[b] (ratio *syn*/*anti*)[c]
1	 **8a**	**9a**, 86 (9:1)
2	 **8b**	**9b**, 76 (9:1)
3	 **8c**	**9c**, 90 (>95:<5)
4	 **8d**	**9d**, 80 (>95:<5)
5	 **8e**	–[d]
6	 **8f**	**9f**, 90 (>95:<5)[e]
7	 **8g**	**9g**, 72 (>95:<5)[f]
8	 **8h**	**9h**, 76 (>95:<5)
9	 **8i**	**9i**, 60 (>95:<5)
10	 **8j**	**9j**, 60 (>95:<5)
11	 **8k**	**9k**, 64[g] (>95:<5)
12	 **8l**	**9l**, 60[g] (>95:<5)

[a] All reactions were carried out on a 0.5 mmol scale.
[b] Yield refers to isolated yield.
[c] Ratios determined by examination of crude ^{1}H NMR.
[d] Reagent polymerization during organozinc bromide preparation.
[e] 1.5:1 mixture of geometrical isomers.
[f] 5:1 ratio of geometrical isomers.
[g] 10% of vinyl sulfide of type **4** and sulfide observed.

Similarly reaction of **7** with the organozinc bromide **8b** prepared from propargyl silyl ether afforded a 9:1 mixture of diastereomers. A bulky TMS substituent in **8c**, however, led to the isolation of a single product in 90% yield. The alkenyl organozinc reagents were prepared from the corresponding Grignard reagents which were either commercially available or prepared.[16] The reaction of mono-, di-, and trisubstituted alkenylzinc bromides with **7** proceeded very stereoselectively to afford a single diastereomer in good yield (Table 1). Likewise the reaction of **7** with primary and secondary alkylzinc bromides proceeded very stereoselectively, to afford the products in moderate yield though, as a consequence of some reduction to sulfide **6** and elimination to afford vinyl sulfide of the type **4**.[17]

We next explored the preparation of optically active products. Acetonide **10**, prepared from L-tartaric acid in four steps, was converted to α-chloro sulfide **11** and reacted with a variety of organozinc bromides (Table 2). An in-

Table 2 Stereoselective Synthesis of Chiral α-Branched Sulfides[a]

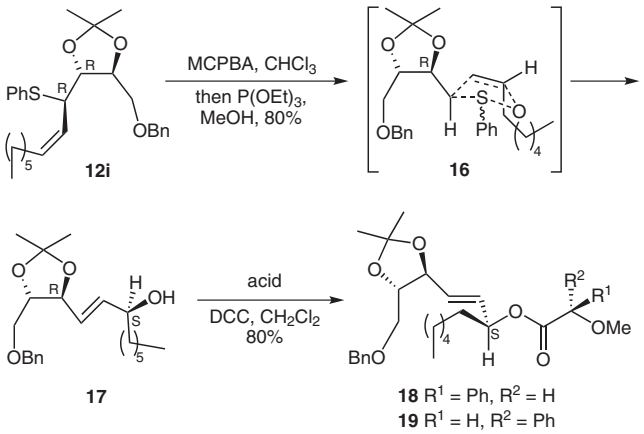


Entry	Organozinc reagent (RM)	Chlorosulfide	Product, Yield (%)[b] (ratio *syn*/*anti*)[c]
1	**8a**	**11**	**12a**, 76 (3:1)
2	**8d**	**11**	**12d**, 78 (>95:<5)
3	**8f**	**11**	**12f**, 80 (>95:<5)
4	**8h**	**11**	**12h**, 86 (>95:<5)
5	**8i**	**11**	**12i**, 66 (>95:<5)
6	**8k**	**11**	**12k**, 60[d] (>95:<5)
7	**8l**	**11**	**12l**, 60[d] (>95:<5)
8	**8a**	**14**	**15a**, 70 (98:2)
9	**8f**	**14**	**15f**, 80 (98:2)
10	**8k**	**14**	**12a**, 60[d] (98:2)

[a] All reactions were carried out on a 0.5 mmol scale.
[b] Yield refer to isolated yield.
[c] Ratios determined by examination of crude ^{1}H NMR.
[d] 10% of sulfide and vinylsulfide of type **4** observed.

spection of Table 2 reveals that the reaction of **11** with alkynylzinc bromide proceeded with modest stereocontrol (entry 1). The reaction with alkenylzinc bromides, however, proceeded with excellent stereoselectivity to afford a single product in good yield. As with **7**, the yield of the products in the reaction of **11** with alkylzinc reagents were less due to side reactions. It is worthwhile to note that the reaction of **8a** with the chloro sulfide **14**, prepared from di-OTBS ether **13**,[18] proceeded with excellent stereoselectivity (Table 2, entry 8).

The configuration of the new stereogenic centre in sulfides **9** were assigned based on the *J* value of the methine proton. The observed coupling constant for the benzylic methine proton of the major isomer (6.6 Hz) and minor isomer (5.1 Hz) in **9a** is in full agreement[1] of a *syn* relationship between OR and SPh substituents in the major isomer. Since the earlier study[1] pertained to hydroxy sulfides, and conformational preferences could be different for the hydroxy sulfides and the corresponding silyl ethers, **9a** was desilylated to afford an inseparable mixture of hydroxy sulfides. The *J* value of the methine proton was 8.7 and 3.9 Hz, respectively, for the major and minor isomers thus unambiguously confirming the structural assignment. The structure was assigned to compounds **9b–l** based on analogy. The configuration at the newly created center in **12i** was assigned by conversion to mandelate esters **18** and **19**. Thus **12i** was oxidized with MCPBA to the corresponding sulfoxide **16** which underwent a [2,3]-sigmatropic rearrangement upon warming to furnish the allylic alcohol **17**. Reaction with (*R*)- and (*S*)-methoxy mandelic acid afforded esters **18** and **19**, respectively (Scheme 3). A comparison of the chemical shifts[19] led to an unambiguous assignment of *S*-configuration[20] to the carbinol and therefore *R*-configuration at sulfur-bearing carbon in **12i** since it is well precedented that the rearrangement proceeds with excellent transfer of chirality.[21] The structure of other products were assigned based on analogy.



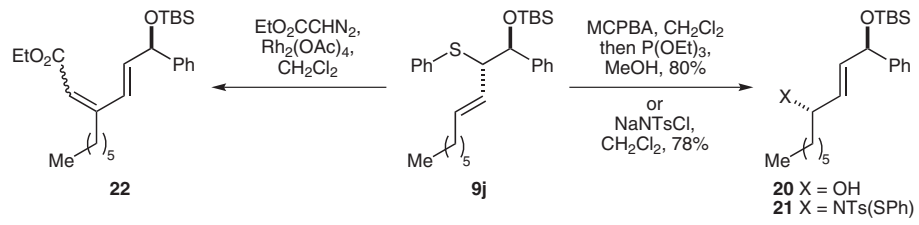
Scheme 3 Assignment of configuration

Scheme 4 Model to rationalize the stereoselectivity

The observed stereoselectivity can be rationalized by invoking a model depicted in Scheme 4 wherein the nucleophile attacks the sulfenium ion from the side opposite to the phenyl group.

The products are versatile synthons with many applications in organic synthesis. A recent report details the use of propargylic sulfides for the enantioselective preparation of allenamides.[22] Also they can be partially reduced to stereoselectively yield either the *cis*- or the *trans*-allylic sulfides or completely reduced to the alkyl sulfides. An added advantage is that the sp-hybridized nucleophiles are less basic compared to others, thereby side reactions are minimized and the reagent used in excess can be recovered and reused. The usefulness of allylic sulfide was demonstrated in the stereoselective preparation of the 1,4-diol derivative **17**, a subunit present in annonaceous acetogenins,[23a] oxylipins,[23b] etc. In a similar fashion, **9j** on treatment with MCPBA in dichloromethane followed by addition of triethylphosphite and warming the reaction mixture furnished allyl alcohol **20** in excellent yield. Treatment with anhydrous chloramine-T afforded the allyl amino derivative **21**.[24] Thus a hydroxy/amino substituent can be introduced stereoselectively at C4 relative to the alkoxy substituent via consequtive 1,2- followed by 1,3-aymmetric induction resulting in a net 1,4-induction. Also the double bond in **17**, **20**, and **21** further provides a useful handle for functionalization. It is noteworthy that from an appropriate trisubstituted alkenyl zinc reagent, quaternary stereogenic centers could in principle be created by the [2,3]-sigmatropic rearrangement. The in situ formation of sulfur ylide by treatment of **9j** with ethyl diazoacetate in the presence of catalytic amounts of $Rh_2(OAc)_4$[25] and subsequent rearrangement yielded a mixture of isomeric dienes[26] **22** instead of the desired product (Scheme 5).

In summary we have disclosed a very versatile method for the synthesis of chiral α-branched propargylic, allylic, and



Scheme 5 Preparation of allyl alcohols/amines by [2,3] sigmatropic rearrangement

alkyl sulfides. The methodology would be useful for the synthesis of natural products possessing a 1,4-diol, 1,4-amino alcohol subunits, tetrahydrofuran, pyrrolidine, pyran, and piperidine rings from appropriate starting materials. The application of this methodology for the synthesis of bioactive target molecules is under investigation and the results would be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) For the preparation of the acetate corresponding to sulfide **6**, see: Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874; the resulting acetate was hydrolyzed and the hydroxy group protected as its silyl ether.
(14) Anhydrous zinc bromide was prepared as a 1.5 M solution in dry THF by heating at reflux for 2 h a 1.5 M solution of DCE containing excess acid washed zinc, see: Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.
(15) The reaction of chloro sulfide **7** with 1-octynylmagnesium chloride proceeded to afford the product in lower yield (50%), while reaction with 1-lithio octyne did not yield any desired product.
(16) (*Z*)-1-Octenylmagnesium bromide was prepared from (*Z*)-1-bromo octene and Mg turnings while (*E*)-1-octenylmagnesium chloride was prepared from (*E*)-1-iodo octene by halogen–metal exchange, see: Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.
(17) **General Experimental Procedure**
To a solution of 1-octyne (165 mg, 1.5 mmol) in dry THF (0.8 mL) cooled at –10 °C was added *i*-PrMgCl·LiCl (1 mL, 1.5 mmol, 1.5 M in THF) and stirred for 30 min at the same temperature. To the so generated Grignard reagent, $ZnBr_2$ (1.1 mL, 1.65 mmol, 1.5 M in THF) was added at 0 °C and stirred for 30 min. To the organozinc reagent maintained at 0 °C was added a solution of chloro sulfide (0.5 mmol) in benzene (5 mL), the reaction mixture stirred gradually allowing it to attain r.t., and stirred further for a period of 7 h when TLC examination indicated complete consumption of the chloro sulfide. The reaction mixture was cooled to 0 °C and quenched by the addition of an aq sat. NH_4Cl solution. It was allowed to warm to r.t. and diluted with Et_2O (5 mL), the layers were separated and aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product **9a** (192 mg, 0.43 mmol) in 86% yield as a liquid. TLC: R_f = 0.34 (hexanes). IR (KBr): 3445, 3063, 2954, 2928, 1586, 1463, 1384, 1253, 1094, 827, 837, 777, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.30 (m, 10 H), 4.91 (d, *J* = 6.8 Hz, 1 H), 4.16 (td, *J* = 2.3, 6.8 Hz, 1 H), 2.16 (dt, *J* = 2.3, 6.8 Hz, 2 H), 1.50–1.15 (m, 8 H), 1.00–0.90 (m, 12 H), 0.20 (s, 3 H), 0.0 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.00, 135.62, 132.11, 128.58, 127.82, 127.69, 127.36, 126.89, 87.32, 77.45, 48.91, 31.45, 28.51, 28.47, 25.89, 22.62, 18.35, 14.20, –4.55, –4.83. ESI-MS: *m/z* 469 $[M + NH_4]^+$. ESI-HRMS: *m/z* calcd for $C_{28}H_{40}ONaSiS$: 475.2467; found: 475.2466.
(18) Substrate **13** was prepared by deprotection of acetonide moiety in **10** followed by protection of the resulting diol, see Supporting Information.
(19) The signals for the olefinic, methine protons of the acetonide and C*H*$_2$OBn appear downfield in ester **18** compared to the corresponding protons of ester **19**, see Supporting Information.
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