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Desulfurative Chlorination of Alkyl Phenyl Sulfides

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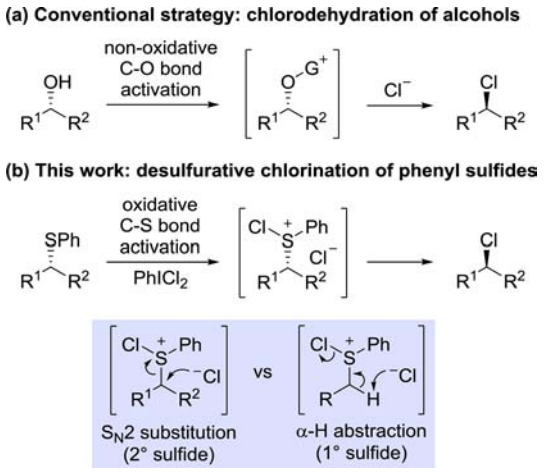
Supporting Information

ABSTRACT: The chlorination of readily available secondary and tertiary alkyl phenyl sulfides using (dichloroiodo)benzene ($PhICl_2$) is reported. This mild and rapid nucleophilic chlorination is extended to sulfa-Michael derived sulfides, affording elimination-sensitive β-chloro carbonyl and nitro compounds in good yields. The chlorination of enantioenriched benzylic sulfides to the corresponding inverted chlorides proceeds with high stereospecificity, thus providing a formal entry into enantioenriched chloro-Michael adducts. A mechanism implying the formation of a dichloro-λ^4-sulfurane intermediate is proposed.

Alkyl chlorides are fundamentally important synthetic intermediates and motifs found in halogenated natural products.[1] A general entry into this class of compounds is the S_N2 displacement of alkyl alcohols with chloride ion.[2] However, activation of the strong sp^3 hybridized C−O bond toward chloride ion attack is necessary and is achieved by conversion of alkyl alcohols, for instance, into the corresponding sulfonate esters.[3] Chlorodehydration of alcohols by in situ activation of the C−O bond has been studied extensively (Scheme 1a),[4] providing a range of transformations best exemplified by the Appel reaction.[2,5,6] Catalytic variants of the Appel reaction,[7] and other innovative catalytic chlorodehydrations, have recently been reported.[8] However, despite the progress made, limitations remain such as the formation of side products, narrow substrate scope, reactivity issues, and the use of multiple reagents.

Scheme 1. S_N2 Substitution Strategies to Alkyl Chlorides; G^+ = Activating Group



In this letter, we describe an alternative approach to nucleophilic chlorination starting from easily accessible alkyl phenyl sulfides (Scheme 1b) and disclose an extension to sulfa-Michael-derived substrates which can be chlorinated without the formation of significant elimination side products.

Sp^3 hybridized C−S bonds are generally weaker than the corresponding C−O bonds and can be activated toward nucleophiles by sulfur oxidation to sulfonium ions. This reaction manifold has been exploited in the desulfurative fluorination of thioacetals, dithioacetals, and trithioorthoesters[9] and, to a lesser extent, in the analogous chlorinations.[10] However, *direct* halogenative C−S bond cleavage without the anchimeric assistance of geminal heteroatoms has been the subject of few studies. In these cases, activation of the C−S bond toward substitution by a fluoride ion was promoted by oxidative *S*-methylation,[11] *S*-nitrosylation,[12] or *S*-halogenation.[9]

In contrast, reports on analogous chlorinations are rare.[13] The reaction of molecular chlorine (Cl_2) with propylene sulfide was shown to result in ring opening caused by a net addition of Cl_2 across the primary C−S bond.[14] Likewise, ring opening chlorinolysis of thiacyclobutane was reported to occur with sulfuryl chloride (SO_2Cl_2).[15] To the best of our knowledge, the only other examples stem from activated phenyl sulfides capable of generating stable carbenium ion intermediates. Thus, treatment of trityl phenyl sulfide or benzhydryl phenyl sulfide with $PhICl_2$ was reported to form the corresponding chlorides.[16]

It is well established that the reaction of *primary* alkyl phenyl sulfides with chlorinating agents forms phenyl α-chloro-sulfides

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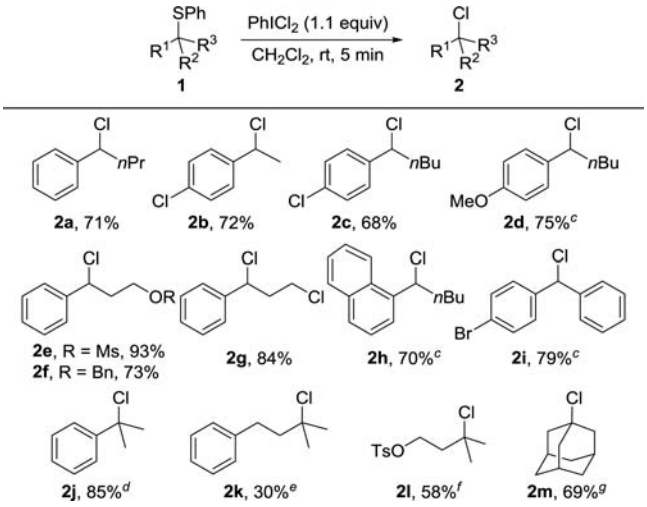
arising from a chloro-Pummerer rearrangement.[17] We reasoned that a combination of an activated *secondary* alkyl phenyl sulfide such as **1a** (Scheme 2) and $PhICl_2$, acting as both the oxidant

Scheme 2. Chlorination of Alkyl Phenyl Sulfides[a,b]



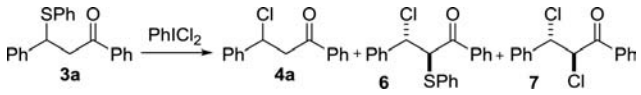
[a]Reactions performed on 0.5 mmol scale at 0.17 M (3 mL). [b]Isolated yield after SiO_2 chromatography. [c]Yield of corresponding trifluoroethyl ether derivative. [d]NMR Yield. [e]Styrene (1.1 equiv) was added after 5 min. [f]Time: 10 s. [g]1.0 mmol.

and the source of the weakly basic chloride ion, could allow for chloride ion displacement of the in situ generated chlorosulfonium ion intermediate to become competitive with chloride α-proton abstraction to the thionium ion (or Pummerer) intermediate (Scheme 1b).

After initial optimization, we discovered that by simply combining sulfide **1a** and $PhICl_2$ in dry dichloromethane at room temperature, a color change from yellow to orange occurred within 5 min accompanied by rapid consumption of sulfide **1a**. We were delighted to confirm the formation of chloride **2a** which was isolated in 71% yield after SiO_2 chromatography (Scheme 2). All subsequently tested substrates gave, under the same reaction conditions, complete conversion to the chlorinated products within 5 min as judged by ^1H NMR spectra of the crude products. Chlorides **2b**, **2c**, and **2e−g** were isolated in good yields after chromatography. However, crude chlorides **2d**, **2h**, and **2i** were sensitive toward purification by chromatography and were isolated in good yields as their corresponding trifluoroethyl ether derivatives **2da**, **2ha**, and **2ia** (Scheme 2).[18] Sulfide **1j** underwent desulfurative chlorination in 85% yield demonstrating that the reaction scope included activated tertiary phenyl sulfides. Moreover, nonactivated tertiary phenyl sulfides **1k−m** were also suitable substrates affording chlorides **2k−m** in moderate yields (Scheme 2). Secondary nonactivated phenyl sulfides, however, gave complex mixtures under the above conditions.

Considering that phenyl sulfides **1** were readily chlorinated under mild reaction conditions with $PhICl_2$, we turned our attention to easily accessible sulfa-Michael derived phenyl sulfides to probe the suitability of this reaction for the preparation of elimination sensitive β-chloro carbonyl compounds.[19] Chalcone (**5**) derived sulfide **3a** was chosen as the test substrate and was allowed to react with $PhICl_2$ under the same reaction conditions to those used in Scheme 2. Chloride **4a** was obtained as the major product accompanied by *anti*-chloro sulfide **6** and small amounts of *anti*-dichloride **7** (Table 1, entry 1).[20] Lowering the temperature to 0 °C resulted in a

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp	time (min)	ratio (**4a**:**6**:**7**)[b]
1	CH_2Cl_2	rt	5	81:16:3
2	CH_2Cl_2	0 °C	30	72:27:1
3[c]	CH_2Cl_2	rt	5	80:0:20
4[d]	CH_2Cl_2	rt	5	95:2:3 (84)[e]
5[d]	THF	rt	5	91:9:0

[a]Conditions: **3a** (0.5 mmol), $PhICl_2$ (0.55 mmol), solvent (3 mL, 0.17 M); all reactions proceeded to complete conversion (≥98%). [b]Determined by ^1H NMR of crude product. [c]2.0 equiv of $PhICl_2$. [d]Freshly prepared $PhICl_2$. [e]Yield of isolated **4a**.

slower reaction and in shifting of the product ratio toward chloro sulfide **6** (Table 1, entry 2). Interestingly, doubling the amount of $PhICl_2$ gave chloride **4a** in a comparable ratio, but with *anti*-dichloride **7** as the sole side product.[21] The reaction worked also without precautions in nonpurified solvents but gave higher amounts of side products (see the Supporting Information (SI) for details).

We assumed that side products **6** and **7** were the result of stereoselective *anti*-addition of in situ formed phenylsulfenyl chloride (PhSCl) to chalcone (**5**) generated during the reaction by dehydrochlorination of **4a**,[22] presumably due to traces of HCl present in $PhICl_2$. Indeed, the quality of $PhICl_2$ was found to be crucial for reproducibility in experiments with sulfides **3**.[23] We found that $PhICl_2$ generated from $PhI/NaClO_2/HCl$[24] gave consistently better chloride to side product ratios compared with $PhICl_2$ prepared by other methods.[25] Repeating the reaction with freshly prepared $PhICl_2$ with strict exclusion of moisture in dry dichloromethane or THF gave significantly improved chloride **4a** to side product ratios (entries 4 and 5). In contrast to $PhICl_2$, use of NCS[26] or SO_2Cl_2[14] as the chlorinating agents proved to be far less selective,[27] giving rise to complex mixtures with chloride **4a** to side product ratios of 32:68 and 57:43, respectively.[28]

Having studied the chlorination of sulfide **3a**, we proceeded to examine other β-sulfido carbonyl compounds according to the conditions of entry 4 in Table 1, ensuring that $PhICl_2$ was either freshly prepared or used within 3 weeks of preparation. Generally, these substrates underwent rapid conversion to the corresponding β-chloro derivatives in good yields (Scheme 3). Scope included β-sulfido ketones **3a−c**, β-sulfido esters **3d−j**, and β-sulfido amides **3l** and **3m**. Interestingly, thioester **3k** having two electronically modified phenylsulfenyl groups also underwent the chlorination resulting in a 78% yield. β-Aryl-β-chloro nitro compounds such as **4n** are known to be prone to dehydrochlorination.[29] However, using our method, we were able to obtain **4n** as an inseparable mixture with *trans*-β-nitrostyrene and nitro chloride **4o** in pure form in 55% yield after recrystallization. Finally, and in order to demonstrate the scalability of this reaction, the chlorination was carried out with 5.0 mmol of sulfide **3i** affording chloride **4i** in an excellent 90% yield (Scheme 3).

Given that the catalytic asymmetric sulfa-Michael addition has been studied extensively leading to the development of methods that deliver aryl sulfides with high enantiopurity,[30] we

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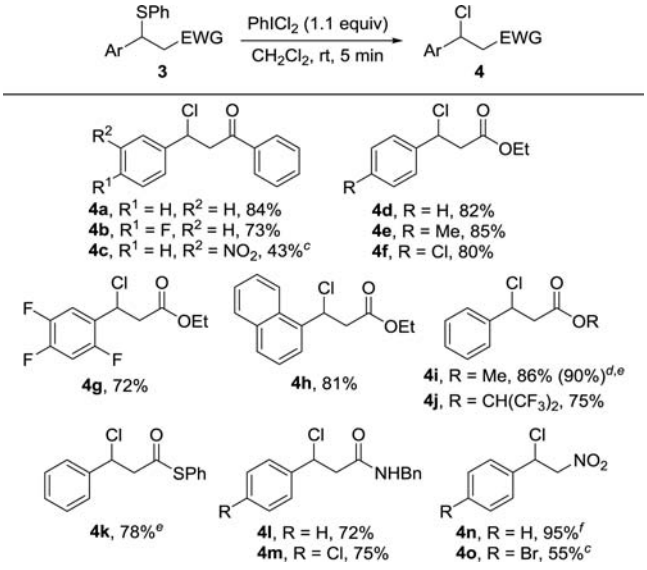
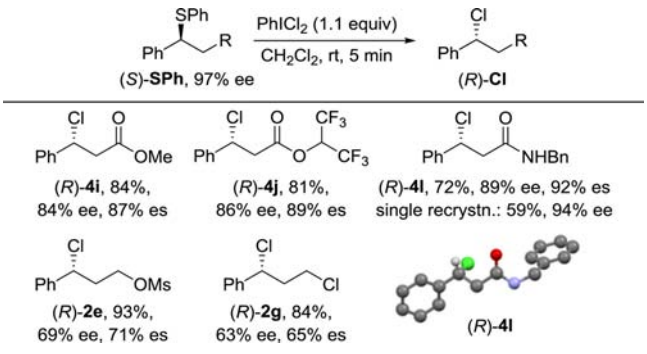
Scheme 3. Sulfa-Michael-Derived Sulfides[a,b]



[a]Reactions performed on 0.5 mmol scale at 0.17 M (3 mL). [b]Isolated yield after chromatography. [c]Isolated yield after recrystallization. [d]Reaction performed on 5.0 mmol scale with 1.04 equiv of $PhICl_2$. [e]Styrene (1.1 equiv) was added after 5 min. [f]Contains 25% *trans*-β-nitrostyrene.

embarked on a preliminary investigation to uncover the stereochemical course and thus to gain insight into the mechanism operating in our chlorination. Treatment of β-sulfido esters (*S*)-**3i** and (*S*)-**3j** of 97% ee[31] with $PhICl_2$ gave the corresponding inverted chloride (*R*)-**4i** and (*R*)-**4j** in good yields and in 84% and 86% ee, respectively, establishing that the reaction proceeded with high stereospecificity (es) (Scheme 4).

Scheme 4. Enantioenriched Sulfides[a,b]

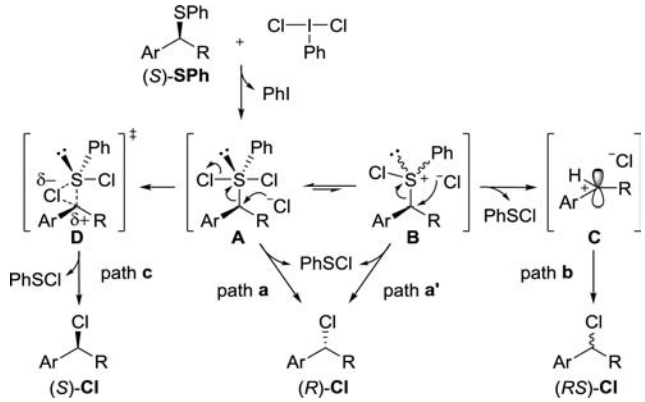


[a]Reactions performed on 0.5 mmol scale at 0.085 M (6 mL). [b]Isolated yield after chromatography. [c]Ee's were determined by HPLC analysis on chiral stationary phase.

Similarly, β-sulfido amide (*S*)-**3l** could be converted to the β-chloro amide (*R*)-**4l** in 89% ee and 92% es, with further enantioenrichment to 94% ee achieved after a single recrystallization. The absolute configuration of chloro amide **4l** was confirmed as being *R* by X-ray analysis, establishing that the chlorination proceeded with inversion of configuration. Interestingly, the chlorination of sulfides (*S*)-**1e** and (*S*)-**1g** gave the corresponding chlorides in lower stereospecificities to those obtained from the β-sulfido carbonyl series, hinting at a possible interaction of the carbonyl lone pairs with a sulfide-derived intermediate.

Our rationale for the presented desulfurative chlorination is outlined in Scheme 5. The capacity of aryl-λ^3-iodanes to oxidize

Scheme 5. Mechanistic Hypothesis Taking into Account the Observed Stereochemistry



organoelement compounds of groups 15 and 16 with concomitant transfer of one[32] or both[33] heteroatom ligands is well established,[34] with the latter being favored when both ligands are the same and of moderate *trans*-influence.[35] The latter also applies for reactions with $PhICl_2$.[36] For instance, treatment of diphenyl selenide or diphenyl sulfide with $PhICl_2$ was reported to form dichloro-λ^4-selane or -sulfurane, respectively.[37] Given the known oxidative dichlorination of aryl sulfides with Cl_2,[38] together with its similarities in reactivity and oxidation power to $PhICl_2$, we propose the generation of highly reactive dichloro-λ^4-sulfurane **A** in equilibrium with its diastereomeric chlorosulfonium salt **B**[39] as key intermediates. Due to the absence of Lewis acids capable of binding a chloride ion,[37,38c,40] this equilibrium is likely to favor the side of sulfurane **A**. Chloride ion displacement of PhSCl from intermediates **A** or **B** by an S_N2 mechanism furnishes the desired inverted chloride (*R*)-**Cl** (path **a** or **a'**). Alternative pathways arising from carbenium ion **C** (path **b**), or concerted ligand coupling (1,2-chloride shift) from sulfurane **A** via **D** (path **c**), which is expected to proceed with retention of configuration,[21a,b] would generate the undesired chloro-enantiomer (*S*)-**Cl**.

In conclusion, a novel chlorination reaction from alkyl phenyl sulfides has been developed. This rapid transformation enables the preparation of alkyl chlorides under mild reaction conditions, allowing the isolation of elimination sensitive benzylic β-chloro carbonyl and nitro compounds. Moreover, it proceeds with high stereospecificity thus providing an access to enantioenriched benzylic chlorides. We believe that the herein outlined chlorination of phenyl sulfides represents a viable alternative to the chlorodehydration of alcohols with the potential to serve as a platform for the development of related C–halogen and other C–X bond forming reactions.

■ ASSOCIATED CONTENT

Supporting Information

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Experiment details, spectral data, copies of ^{1}H and ^{13}C NMR spectra (PDF)
X-ray crystallographic data for (*R*)-**4l** (CIF)
X-ray crystallographic data for *syn*-chloro sulfide **6b** (CIF)

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Notes

The authors declare no competing financial interest.

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(20) Chloro sulfide **6** was prepared independently by addition of PhSCl to chalcone. See the SI for more details.
(21) We propose that the additional $PhICl_2$ equivalent rapidly oxidizes the in situ generated PhSCl to $PhSCl_3$ which undergoes stereoselective *anti*-addition to chalcone. The resulting *anti*-β-chlorophenylsulfonium dichloride intermediate collapses stereospecifically to *anti*-dichloride **7**. For similar reactivity of $PhSeCl_3$ with alkenes, see: (a) Garratt, D. G.; Schmid, G. H. *Can. J. Chem.* **1974**, *52*, 3599. (b) Engman, L. *J. Org. Chem.* **1987**, *52*, 4086.
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