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FULL PAPER

Systematic Evaluation of Sulfoxides as Catalysts in Nucleophilic Substitutions of Alcohols

Sebastian Motsch,[a] Christian Schütz,[a] and Peter H. Huy*[a]

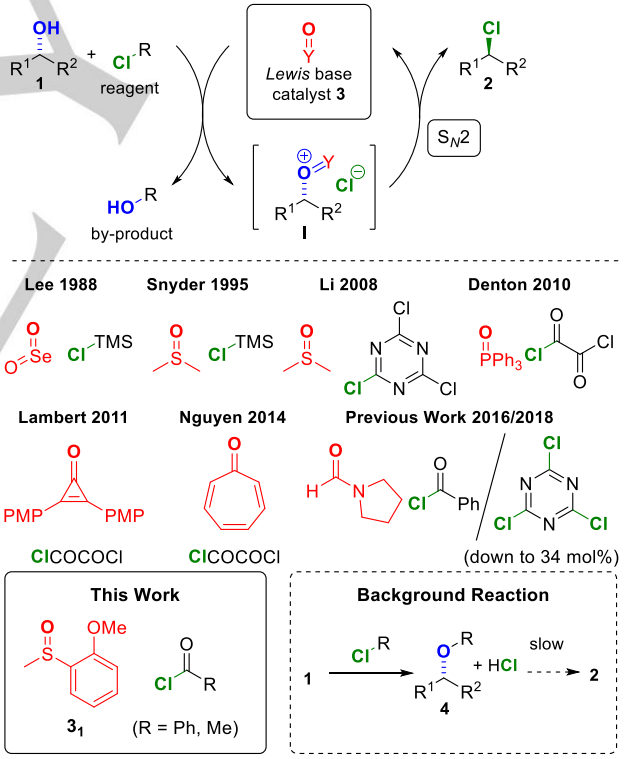
Abstract: Herein, a method for the nucleophilic substitution (S_N) of benzyl alcohols yielding chloro alkanes is introduced that relies on aromatic sulfoxides as Lewis base catalysts (down to 1.5 mol%) and benzoyl chloride (BzCl) as reagent. A systematic screening of various sulfoxides and other sulfinyl containing Lewis bases afforded methyl(2-methoxyphenyl)sulfoxide as optimal catalyst. In contrast to reported formamide catalysts, sulfoxides also enable the application of plain acetyl chloride (AcCl) as reagent. In addition, it was demonstrated that weakly electrophilic carboxylic acid chlorides like BzCl promote Pummerer rearrangement of sulfoxides already at room temperature. This side-reaction also provided the explanation, why sulfoxide catalyzed S_N-reactions of alcohols do not allow the effective production of aliphatic and electron deficient chloro alkanes. Comparison experiments provided further insight into the reaction mechanism.

Introduction

Sulfoxides account to the most versatile functional groups in chemistry and have consequently been exploited as directing groups, metal ligands, chiral auxiliaries and leaving groups in glycosylations, for instance.[1-3] Moreover, sulfinyl groups (S=O) can be found as key structural motif in many natural products and pharmaceuticals and therefore continue to inspire chemists to develop efficient strategies towards their synthesis.[4] Against this background, it is surprising that sulfoxides have rarely been employed as catalyst in nucleophilic substitutions (S_N), which belong to the most fundamental and widely-used chemical transformations.[5-8] In particular bimolecular nucleophilic substitutions (S_N2) are of paramount importance, as they enable the stereoselective construction of C-Cl, C-O, C-N and C-C bonds, for example.

So far, mainly phosphine oxides, cyclopropenone derivatives, tropone and formamides (by our group) have been applied as Lewis base catalysts **3** for the S_N-type conversion of alcohols **1** to chloro alkanes **2** (Scheme 1).[9,10] Earlier, SeO_2[11a] and dimethylsulfoxide (DMSO)[11b,c] have been also engaged as catalytic species, whereby either trimethylchlorosilane (TMSCl) or trichlorotriazine (TCT) were used as reagent.[12] In the case of DMSO procedures are either limited to primary and tertiary[11b] or certain benzylic alcohols.[11c] Additionally, in the contribution utilizing TCT only two examples were performed in the presence of catalytic amounts of DMSO (20 mol%), whereas the majority of the products was synthesized under application of DMSO as the solvent.[11c]

Indeed, the major challenge in Lewis base catalyzed S_N-methods is the minimization of condensation of the nucleophilic starting material **1** with the electrophilic reagent, which gives rise of oxalate and benzoate esters of type **4** (see Scheme 1). The formation of these undesired side-products has been reduced by (1) comparably high catalyst loadings (typically 10-20 mol%) and (2) either the slow addition of the reagent to a diluted solution of the substrate[9] or (3) the utilization of less electrophilic benzoyl chloride (BzCl) or TCT in substoichiometric amounts instead of highly reactive oxalyl chloride.[10] The weakly electrophilic nature of these bulk chemicals enables an improved chemoselectivity in favor for substitution product **2** (over side-product **4**).



Scheme 1. Catalytic nucleophilic substitutions of alcohols. PMP = para-methoxyphenyl.

In light of (1) the strong Lewis basicity of sulfoxides in general and (2) the manifold opportunities to tune their electron and steric properties by the adjacent substitutions, we were intrigued to explore sulfinyl group based catalysts in S_N-reactions. From a systematic and extensive structure activity relationship study,

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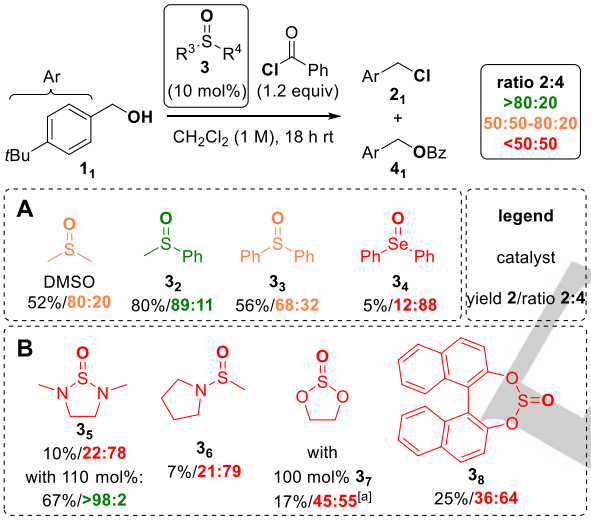
sulfoxide **3₁** arose as optimal catalyst for the transformation of benzylic alcohols **1** into alkyl chlorides of type **2** (Scheme 1).

Results and Discussion

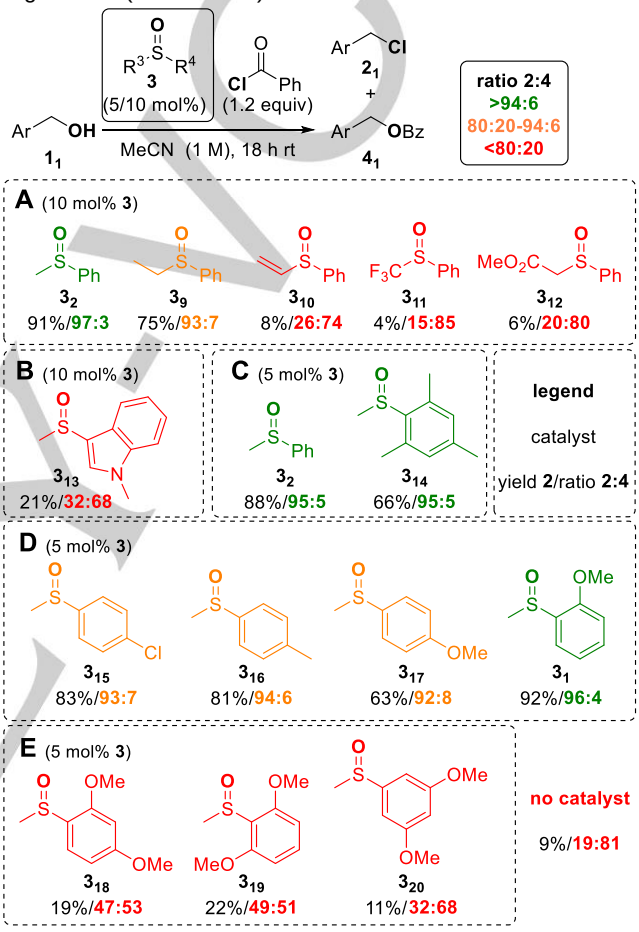
At the outset, a broad variety of sulfinyl group containing Lewis bases were tested on their ability to catalyze the reaction of benzylic alcohol **1₁** as a simplified model substrate with the reagent BzCl to chloro alkane **2₁** (Scheme 2). In the current study, the catalytic activity is reflected by the ratio of the desired substitution product **2₁** in respect to benzoate **4₁**, which is obtained as major product in the absence of a catalyst (ratio **2₁/4₁** 19:81). For the purpose of a clearer visualization of the selectivites, catalyst structures and ratios **2₁/4₁** are displayed in either green, orange or red colour in alignment to a traffic light. The best chemoselectivity in Scheme 2 was attained with methylphenylsulfoxide (**3₂**). Both, DMSO and diphenylsulfoxide (**3₃**) delivered mixtures of product **2₁** and **4₁** in poorer ratios (Scheme 2 **A**).



Scheme 2. Screening of various sulfinyl group containing Lewis bases. Yields and ratios were determined by means of the ^{1}H-NMR of the crude material with internal standard. [a] Conducted in MeCN.

Surprisingly, the more polar selenoxide **3₄** did not show any catalytic activity at all. Similar results were observed, when the sulfurous acid derived amide **3₅** and esters **3₇** and **3₈** and sulfinic acid amide **3₆**, respectively, were utilized as Lewis bases (Scheme 1 **B**, for more details see Table S2 in the Supporting Information = SI). However, in the presence of stoichiometric amounts of sulfinyl compound **3₅** benzylic halogenide **3₅** was generated in an excellent selectivity (**2₁/4₁** ≥98:2). This observation might be explained by decomposition of this Lewis base. In the following, a solvent screening applying methyl-phenylsulfoxide as catalyst revealed MeCN as optimal (see Table S8, SI). Therefore, MeCN was utilized as solvent instead of CH_2Cl_2 for the further catalyst refinement.

As the initial experiments uncovered alkyl aryl substituted sulfoxides as potent catalyst, subsequently various alkyl phenyl sulfoxides were probed (Scheme 3 **A**). While the application of ethylphenylsulfoxide **3₉** already resulted in a depleted selectivity, a vinyl substituted analog and two sulfoxides containing electron-withdrawing substituents showed basically no catalytic activity. Exchange of the phenyl group of methylphenylsulfoxide (**3₂**) through a more electron rich indole moiety caused significantly declined ratios of **2₁** to **4₁**, which could be rationalized by catalyst degradation (Scheme 3 **B**).



Scheme 3. Catalyst optimisation. Yields and ratios were determined by means of the ^{1}H-NMR of the crude material with internal standard. Ar = 4-*t*BuPh.

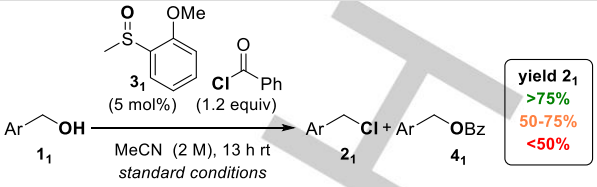
For the following test reactions, the catalyst loading was decreased from 10 to 5 mol% in order to more clearly identify the optimal structure. After having secured that the optimal sulfinyl based catalyst must contain a methyl and a phenyl group, substituents were introduced on the phenyl backbone. Although the mesityl group bearing sulfoxide **3₁₄** gave rise of an identical selectivity compared to methylphenylsulfoxide, the higher steric demand caused a lower conversion of substrate **1₁**, which is also reflected by a lower yield (Scheme 3 **C**). In order not to increase the steric shielding of the Lewis basic O-atom, we introduced various substituents in the *para*-position of the phenyl skeleton (Scheme 3 **D**). Neither an electron withdrawing Cl-atom nor

electron donating Me- and MeO-moieties allowed an improvement of the catalytic activity. This also accounted for substituents in the *ortho*-position (see Table S4 to S7, SI) with one single exception.

Indeed, the best selectivity in favor of chloride **2₁** was achieved utilizing (2-methoxyphenyl)methylsulfoxide (**3₁**). Unexpectedly, sulfoxides carrying two methoxy groups in 2,4-, 2,6- and 3,5-position turned out to be rather poor catalysts (Scheme 3 **E**). Apparently, the chemoselectivity **2₁/4₁** is especially influenced by the electron density in the aryl portion. The deteriorated Lewis basicity of arylmethyl-sulfoxides bearing electron poor aryl residues should reason the diminished ratios **2₁/4₁** in comparison to methylphenyl-sulfoxide (**3₂**) as expected (e.g., **3₁₅**). Although sulfinyl compounds containing electron-rich aryl moieties such as **3₁₇**, **3₁₈**, **3₁₉** and **3₂₀** are unquestionable stronger Lewis bases than **3₂**, they are less feasible as catalysts for the transformation of alcohol **1₁** into alkyl chloride **2₁**. Also in this instances, a low stability of the catalysts under the reaction conditions could provide a rationalization of the observed outcome. In the case of optimal sulfoxide **3₁**, however, the steric repulsion between the *ortho*-methoxy group and the sulfinyl moiety should effect a rotation of the S=O bond out of the orthogonal orientation in respect to the ring plan of the aryl group. Therefore, the conjugation between this adjacent groups is diminished in comparison to the para-methoxy substituted phenylsulfoxide **3₁₇**, which causes a lower Lewis basicity. As final conclusion, sulfur catalyst **3₁** seems to be the best compromise between Lewis base strength and chemical stability. Indeed, utilization of sulfoxide catalyst **3₁** (5 mol%) allowed to isolate benzylic chloride **2₁** in 86% yield (Table 1, entry 1).

Pleasingly, a high substrate concentration of 2 M was identified as optimal, which is a result of the utilization of weakly electro-philic BzCl (Table S9, SI). In the aforementioned experiment slightly deteriorated selectivities **2₁/4₁** were observed in comparison to the test reaction on a smaller scale (compare entries 1+2). Neither, a slow addition of BzCl by means of a syringe pump nor cooling of the reaction mixture to 0 °C during the reagent addition could improve the selectivity. A similar impact of the reaction scale on the ratio **2/4** was also obtained with other substrates. Nevertheless, an upscaling to gram quantities did not alter the ratio **2₁/4₁** further (see Scheme 4), which verifies a reasonable scalability of the current method. Moreover, the catalyst loading could be reduced to 2.5 mol% **3₁** (entry 3), which accords to a reasonable turn over number (TON) of 30 under consideration of 79% isolated yield. Worthy of note, the catalyst **3₁** could also be prepared *in situ* from *meta*-chloroperoxybenzoic acid (MCPBA) and commercial (2-methoxyphenyl)methylsulfide (entry 4), whereas *N*-chloro-succinimide proved to be a less adequate oxidant. Furthermore, MeCN could not be replaced by a more environment-friendly solvent (entry 5, see also Table S8 in the SI). The superior catalytic activity of sulfoxide **3₁** was highlighted through comparison experiments with 2.5 mol% of *N*-formyl pyrrolidine (FPyr)[10a] and DMSO, respectively, which provided substitution product **2₁** in moderate yields of 33-66% (entries 6+7).

Table 1. Method development.



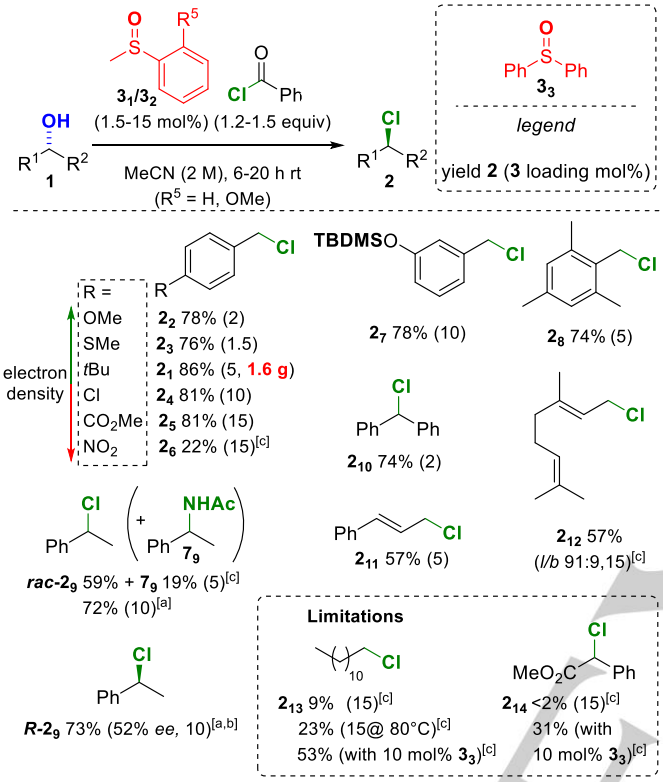
entry	changes from standard conditions[a]	ratio **2₁**:**4₁**[b]	yield **2₁** [%]
1	/	94:6	86[c]
2	/	97:3	93[d]
3	2.5 instead of 5 mol% **3₁**	89:11	79[c]
4	Ar´SMe (7 mol%) + MCPBA (5 mol%) instead of **3₁**	91:9	82[c]
5	EtOAc, MTBE or acetone instead of MeCN	≤94:6	≤46[d]
6	FPyr (2.5 mol%) in dioxane instead of **3₁** in MeCN	87:13	66[d]
7	DMSO (2.5 mol%) instead of **3₁**	62:38	33[d]
8	no **3₁**	15:85	4[d]

[a] Standard conditions: BzCl (1.2 equiv), **3₁** (5 mol%), MeCN (2 M), 13 h rt. [b] Determined from ^{1}H-NMR of the crude material. [c] Isolated yield. [d] Yield determined by internal NMR-standard. Ar = 4-*t*BuPh, Ar´= 2-MeOPh.

After the establishment of the optimized reaction conditions, we set out to explore the substrate scope of the current protocol (Scheme 4). While model substrate **1₁** was produced on a gram scale with 5 mol% of catalyst **3₁**, the electron rich benzylic chlorides **2₂** and **2₃** were synthesized in good yields employing just 1.5-2 mol% **3₁** (TON up to 50). However, in the case of electron poor benzylic alcohols the sulfoxide quantity had to be increased (examples **2₄** to **2₆**). Albeit 4-(methoxycarbonyl)benzyl chloride (**2₅**) was isolated in a reasonable yield of 81%, even in the presence of 15 mol% **3₁** no full conversion was achieved within 24 h of reaction time. 4-Nitrobenzyl chloride (**2₆**) on the other hand could not be accessed in a useful yield anymore.

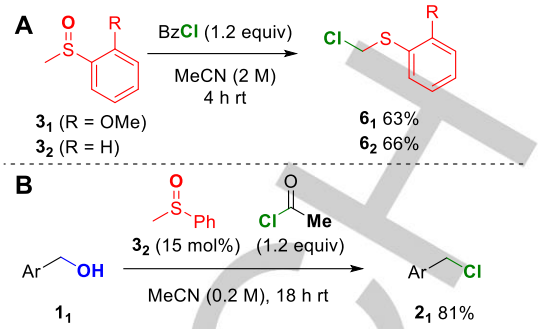
Example **2₇** demonstrated that acid sensitive functional groups such as silylethers are tolerated under the optimized reaction conditions, which is explained by the formation of weakly acidic benzoic acid as by-product instead of hydrogenchloride. In the instance of phenylethyl chloride **2₉** CH_2Cl_2 had to be employed as solvent, because reaction in MeCN afforded significant amounts of Ritter type acetamide **7₉** as side product. Transformation of enantioenriched *R*-phenyl ethanol **1₉** (96% *ee*) furnished *S*-phenylethyl chloride **2₉** under overall inversion in a diminished *ee* of 52%, which is a selectivity comparable to chlorinations with conventional reagents such as $SOCl_2$.[5,10a] In addition, the allylic chlorides **2₁₁** and **2₁₂** could be prepared in moderate yields. In the case of geraniol **1₁₂** a 91:9 mixture of regioisomeric linear and branched allylic chlorides was obtained, which is a better result than common reagents like $SOCl_2$ allow for.[10a] Finally we must note that aliphatic alcohols and α-hydroxyesters are non-suitable substrates. Even under variation

of the reaction temperature, 1-dodecyl chloride **2**$_{13}$ was generated in yields ≤23%, whereas in the case of methyl mandelate **1**$_{14}$ no chlorinated product **2**$_{14}$ could be detected. Worthy of note, in the absence of a feasible catalyst the majority of the alkyl chlorides **2** presented in Scheme 4 were formed in yields ≤25%, which highlights the crucial role of sulfoxides **3**$_1$ and **3**$_2$ (see Scheme S3, SI).



Scheme 4. Substrate scope and limitations. Yields refer to isolated material if not otherwise mentioned. [a] *ee* determined by chiral GC. [b] Prepared from the corresponding *R*-configured alcohol in 96%*ee*. [c] Yield determined by internal NMR-standard.

Indeed, exposure of sulfoxides **3**$_1$ and **3**$_2$ towards BzCl delivered α-chlorosulfides of type **6** through a Pummerer rearrangement (Scheme 5 **A**).[13] Thus in the case of less reactive alcohols (e.g., **1**$_6$, **1**$_{13}$ and **1**$_{14}$) catalysts of type **3** are consumed by this side-reaction before the starting material is fully converted. In fact, chlorosulfides of type **6** were found in all ^{1}H-NMR spectra of crude chlorides **2**. This also explains a similar limitation of the substrate scope in related chlorinations utilizing DMSO.[11c] Since chloride products of type **2** were occasionally challenging to separate from sulfide **6**$_1$ by means of chromatography, in some examples in Scheme 4 methylphenylsulfoxide (**3**$_1$) was engaged. Interestingly, utilization of diphenylsulfoxide (**3**$_3$), which cannot undergo Pummerer reaction, allowed to increase the yield in the case of aliphatic chloride **2**$_{13}$ and chloroester **2**$_{14}$ to 53% and 31%, respectively (Scheme 4). Other sulfinyl compounds that are incapable of or less prone to Pummerer rearrangement were ruled out earlier due to inactivity (Scheme 2 **B** and Scheme 3 **A**).

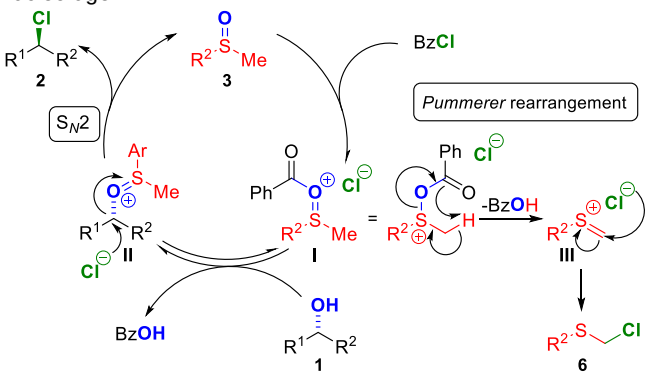


Scheme 5. A Pummerer rearrangement as side reaction and **B** chlorination with acetyl chloride (Ar = 4-*t*BuPh).

In contrast to FPyr,[10a] sulfoxide catalyst **3**$_2$ also enabled the utilization of plain acetyl chloride (AcCl) as reagent (Scheme 5 **B**).[15] The higher reactivity of AcCl in comparison to BzCl requested deviations from the optimized reaction conditions such as a lower substrate **1** concentration (see Table S10 + S11, SI).

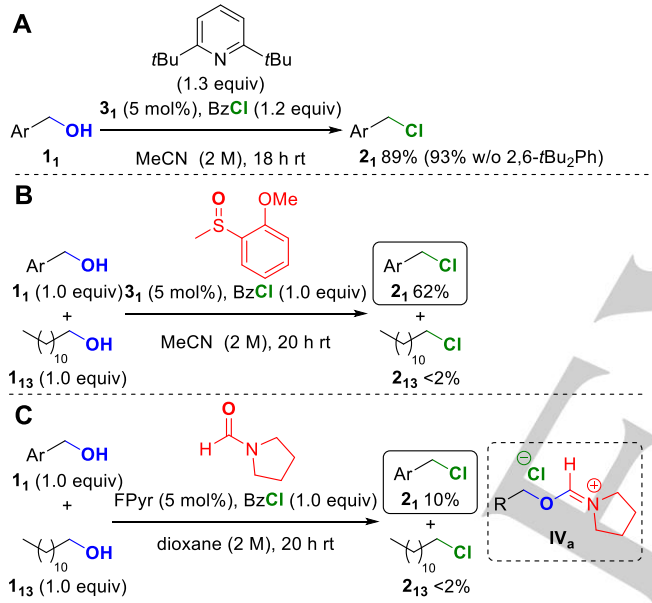
Recently we established a cyclopropenone catalyzed protocol for the dehydroxybromination and -iodination of alcohols using BzCl and sodium bromide and iodide, respectively, as halogen source.[14] However, the application of sulfoxides of type **3** instead of cyclopropenone derivatives under elsewise identical conditions allowed the synthesis of alkyl bromides and iodides only in moderate yields (see Table S12, SI).). For instance, 4-*tert*-butylbenzyl bromide (**11**$_1$) was formed in the presence sulfoxide **3**$_1$ in a moderate yield of 56% beside benzoate **4**$_1$ (32%), while in the absence of a catalytic species **11**$_1$ was already obtained in 41% yield.

In alignment to the contribution of Li´s[11c] and our work[10] a tentative mechanism is proposed in Scheme 6. Initially, the sulfoxide is anticipated to be acylated by either BzCl or AcCl to give sulfonium intermediate **I**, in which the sulfinyl O atom is activated as a decent leaving group. Nucleophilic substitution of the carboxy moiety by the alcohol **1** then most probably delivers intermediate **II**, in which the hydroxyl group is converted to a good nucleofuge.[15]



Scheme 6. Proposed mechanism.

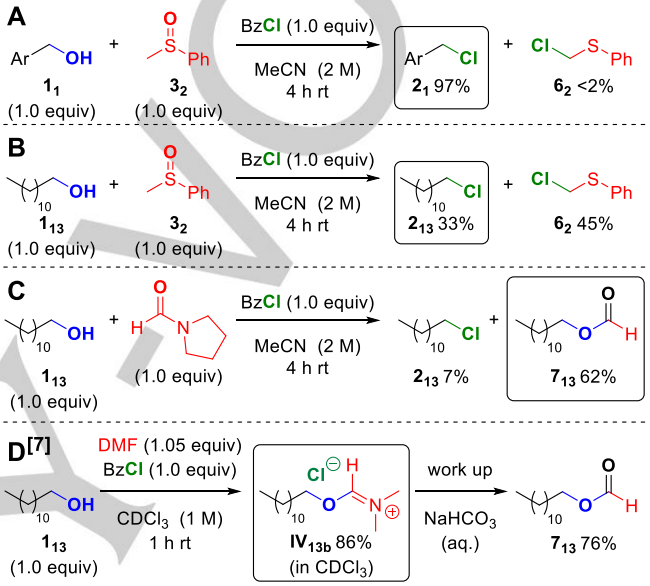
Eventually, the catalyst residue is replaced by the chloride counterion to deliver alkyl chloride **2**. If the plausible intermediate **I** is redrawn as illustrated in Scheme 6, the opportunity of an intermolecular *syn*-elimination becomes evident. The resulting sulfenium ion **III** should undergo an electrophilic addition to the chloride counterion to furnish α-chlorosulfide **6**, which corresponds to a Pummerer reaction. Finally, a couple of comparison experiments allowed for a further insight into the reaction mechanism. Brønsted acid cocatalysis can be ruled out, since the addition of an excess of 2,6-bis-*tert*-butylpyridine had no significant influence on our model reaction (Scheme 7 **A**). A competition experiment between a primary benzylic and aliphatic alcohol in the presence of catalyst $\mathbf{3_1}$ favored generation of benzylic chloride $\mathbf{2_1}$, albeit the yield of $\mathbf{2_1}$ was lower than in the absence of substrate $\mathbf{1_{13}}$ (Scheme 7 **B**). Interestingly, the same experiment with FPyr instead of sulfoxide $\mathbf{3_1}$ provided substitution product $\mathbf{2_1}$ in only 10% yield instead of 62% (Scheme 7 **C**).



Scheme 7. Comparison experiments I. Ar = 4-*t*BuPh.

The difference between the catalysts $\mathbf{3_1}$ and FPyr could be reasoned by a reversible formation of sulfonium intermediate **II**. Thus intermediate $\mathbf{II_{13}}$ derived from aliphatic substrate $\mathbf{1_{13}}$ would redeliver sulfoxide $\mathbf{3_1}$ or intermediate **I**, which could both react with benzylic starting material $\mathbf{1_1}$. In the case of formamide FPyr the related intermediate **IV** seems to be generated irreversibly (see Scheme 8 **C** + **D**).

Moreover, reaction of benzylic model substrate $\mathbf{1_1}$ and methylphenylsulfoxide in equimolar amounts with BzCl gave rise of substitution product $\mathbf{2_1}$, while α-chlorosulfide $\mathbf{6_2}$ was not obtained (Scheme 8 **A**). In a similar comparison experiment, in which dodecanol ($\mathbf{1_{13}}$) was utilized instead of benzylic alcohol $\mathbf{1_1}$, mainly chlorosulfide $\mathbf{6_2}$ was generated (Scheme 8 **B**). The latter test unveils that even an excess of sulfoxide catalyst does not facilitate the preparation of aliphatic chlorides. Interestingly, reaction of dodecanol with stoichiometric amounts of FPyr mainly gave dodecyl formate $\mathbf{7_{13}}$ after aqueous work up (Scheme 8 **C**). Ester $\mathbf{7_{13}}$ is most likely obtained from iminium intermediate $\mathbf{IV_{13a}}$ (see Scheme 8 **C**) through hydrolysis. Hence, the catalytic cycle seems to be interrupted at room temperature at the stage of intermediate $\mathbf{IV_{13b}}$. The comparably high stability of iminium intermediates of type **IV** derived from aliphatic alcohols at ambient temperature was already proven in our previous work (Scheme 8 **D**).[7a] Sulfonium intermediates of type **II** could not be identified by the same approach, which supports the assumption of a reversible generation of **II**.



Scheme 8. Comparison experiments II. Ar = 4-*t*BuPh.

Conclusions

In summary, nucleophilic substitutions of benzylic alcohols to furnish chloro alkanes with BzCl and AcCl, respectively, that are catalyzed by aromatic sulfoxides have been developed. The high Lewis basicity facilitates catalyst loadings below 2 mol% and consequently TONs of up to 50 in the case of selected examples. A systematic screening of manifold sulfoxides and sulfinyl group containing compounds allowed to establish a thorough structure activity relationship. As conclusions the optimal catalyst contains (1) a small methyl group and (2) an aromatic substituent, which is neither electron rich nor electron poor. These criteria were best met by (2-methoxyphenyl)methyl-sulfoxide ($\mathbf{3_1}$). Alongside it was demonstrated that weak acid chlorides such as BzCl also allow Pummerer rearrangement of sulfoxides. This observation rationalizes, why less reactive aliphatic and electron poor alcohols are less feasible for the present protocol.

Experimental Section

Experimental procedures for the synthesis of alkyl chlorides and new sulfoxides, analytical data, copy of ^{1}H- and ^{13}C-NMR-data and further

background information can be found in the Supporting Information. The following procedure may serve as representative example.

Gram scale synthesis of 4-*tert*-butylbenzyl chloride (2$_1$)

At room temperature a solution of (2-methoxyphenyl)methylsulfoxide (**3$_1$**, 84.1 mg, 0.50 mmol, 5 mol%) and 4-*tert*-butylbenzyl alcohol (**1$_1$**, 1.66 g, 10.0 mmol, 1.0 equiv) in MeCN (5 mL, 2 M) was treated with BzCl (1.41 mL, 12.0 mmol, 1.2 equiv) over 15 min by means of a syringe pump. Afterwards the reaction solution was allowed to stir until TLC control revealed full conversion of **1$_1$** after 12.5 h. In order to quench the remaining excess of BzCl, 2-ethanolamine (370 µL, 6.0 mmol, 0.6 equiv) was added dropwise under vigorous stirring at ambient temperature and the resulting suspension was allowed to stir for further 30 min. Then the mixture was diluted with Et_2O (20 mL) and 1 N NaOH solution (aq., 10 mL), the organic phase was washed with 1 N NaOH solution (aq., 10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude material (1.984 g, 109%) was subjected to column chromatographic purification on silica gel (17.3 g) with Et_2O/*n*Pen 1:99. After drying at 20 mbar at the rotatory evaporator the title compound was obtained as colourless oil in 86% yield (1.565 g, 8.57 mmol).

Acknowledgements

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Keywords: nucleophilic substitutions • homogenous catalysis • sulfoxides • organocatalysis • halogenation

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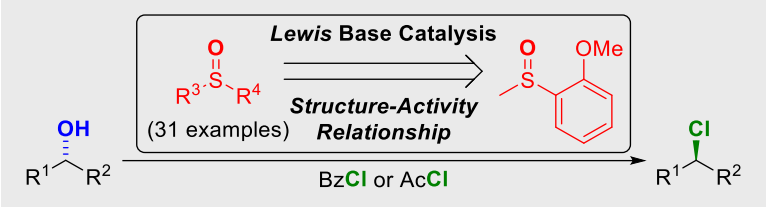

Out of a in-depth study of a range of sulfinyl compounds in the transformation of alcohols into chloro alkanes emerged (2-methoxyphenyl)methylsulfoxide as optimal *Lewis* base catalyst. While this catalyst allowed the synthesis of benzylic chlorides in turn-over numbers up to 50, aliphatic alcohols are non-suitable substrates due to competing Pummerer rearrangement .

Organocatalysis, Sulfoxides*

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Systematic Evaluation of Sulfoxides as Catalysts in Nucleophilic Substitutions of Alcohols