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Sulfoxides in the allylation of aldehydes in the presence of silicon tetrachloride and allyltributylstannane

Research Article

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Abstract: $SiCl_4$ can be conveniently activated by catalytic amounts of dimethyl sulfoxide or other readily-available sulfoxides for the allylation of aromatic, hetero-aromatic and unsaturated aldehydes in the presence of allyltributyl stannane. Chiral aryl methyl sulfoxides have been used to develop asymmetric allylation methods, as well as probe the aldehyde substrate scope.

Keywords: *Allylation of aldehydes • Sulfoxides • Lewis base • Silicon tetrachloride • Allyltributylstannane*

1. Introduction

The allylation of aldehydes is one of the most important methods for C-C bond formation. Homoallylic alcohols are useful building blocks for the synthesis of complex molecules and natural products [1]. In recent years, a number of new methods based on allylating reagents such as allylboranes, allylsilanes and allylstannanes have been developed [2-4]. Particular attention has been devoted to the development of enantioselective versions utilizing chiral allylating reagents, chiral Lewis acids as catalysts and, more recently, chiral Lewis base organocatalysts [2-4]. The Lewis base strategy, pioneered by Kobayashi [5] and Denmark [6], has been successful in the allylation of aldehydes in the presence of allyltrichlorosilane. A wide variety of chiral Lewis bases derived from phosphoramides, N-oxides, sulfoxides, formamides, phosphine oxides, amines and ureas, has been demonstrated to be effective in enantioselective allylation [2a,3,4]. Moreover Lewis base catalytic activation of weak Lewis acids like $SiCl_4$ has proven to be a very versatile approach in a great number of aldol-type reactions with silylenolethers [7,8], the asymmetric opening of epoxides [9], Passerini reactions [10] and the allylation of aldehydes using allyltributylstannane [11]. In $SiCl_4$-mediated reactions, very good yields and enantioselectivities have been achieved by Denmark in the presence of the chiral bidentate phosphoramide [7,9a-c,10,11], while little attention has been paid to the use of different Lewis bases. Chiral N-oxides [9d,9e] and phosphine oxides [9f] have been used in asymmetric ring opening of epoxides with good results. Very recently chiral phosphine oxides have been used in the asymmetric phosphonylation of aldehydes with moderate asymmetric induction [12]. It is important to note that in the reported SiCl4-mediated transformations, none of the used Lewis bases are commercially available or easy to synthesize. This is an important limitation to be overcome to expand the scope of the system. However, despite the importance of enantiopure sulfinyl groups in many asymmetric transformations [13], this chiral controller has never been exploited as Lewis base in $SiCl_4$ mediated transformations. This is an important limitation to be overcome to expand the scope of the system. Moreover, despite the synthetic usefulness of homoallylic alcohols, only the chiral bidentate phosphoramide has been used in the allylation of aldehydes using allyltributylstannane and $SiCl_4$ [11]. For these reasons, in our continuous efforts to develop reactions catalyzed by new Lewis bases [7g,7h,8,14a,14c,14e], we report the first application of simple and readily-available sulfoxides in allylation of aldehydes using this system.

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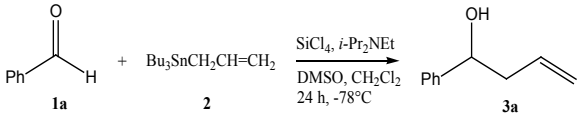
2. Experimental Procedure

All reactions were performed in oven-dried (140°C) or flame-dried glassware under dry N_2. Dichloromethane (reagent grade) was dried and distilled immediately from CaH_2 before use. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). Other reagents (Aldrich and Fluka) were used without further purification. The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ^{1}H; 100 MHz, 75 MHz, 62,5 MHz ^{13}C). Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. HPLC analyses were performed with Waters Associates equipment (Waters 2487 Dual λ absorbance Detector) and using a CHIRALPAK AD, a CHIRALCEL OD column with hexane/isopropyl alcohol mixtures and flow rates as indicated in [14] for chiral homoallylic alcohols 3 and [15] for chiral sulfoxides 4. The HPLC methods were calibrated with the corresponding racemic mixtures. GC analysis were performed using an Agilent Technologies equipment (mod. 6850) with the chiral column Supelco β-DEX 120. Optical rotations were measured with a JASCO DIP-1000 polarimeter. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole.

2.1. Typical experimental procedure for allylation reaction

In a flame-dried, 2-necked, round-bottom flask, allyl tributyl stannane (1.1 eq., 0.66 mmol) was added to a solution of sulfoxide, i-Pr_2EtN (1.0 eq., 0.60 mmol), $SiCl_4$ (1.1 eq., 0.66 mL of 1.0 M solution in CH_2Cl_2) and aldehyde (0.60 mmol) in dry dichloromethane (2.0 mL) under nitrogen at -78°C. At the end of the reaction, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), extracted with 15×3 mL of CH_2Cl_2 and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude oil was purified by flash chromatography with a hexane / AcOEt mixture from 9.5/0.5 to 8/2 to afford the pure products 3.

All the compounds 3 are known compounds and were characterised comparing the spectroscopic data with those reported in literature [14].



Scheme 1. Allylation of benzaldehyde in the presence of DMSO

Table 1. Allylation of benzaldehyde 1a under different reaction conditions.

Entries	Eq. DMSO	Time (h)	Yield 3a (%)[a]
1	0.1	5	62
2	0.2	5	70
3	0.2	24	87
4	2	5	60
5	3	5	57
6	--	5	No react.

[a] *Yields refer to chromatographically pure compounds*

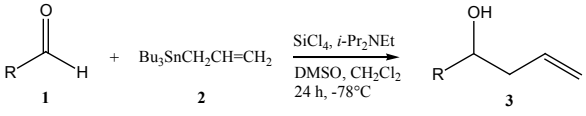
3. Results and Discussion

In preliminary experiments, we attempted the allylation of benzaldehyde 1a in the presence of dimethyl sulfoxide (DMSO) under the condition described in Scheme 1 and Table 1. Performing the reaction with varying equivalents of the Lewis base, we observed a higher reactivity when 0.2 eq. of DMSO were used (Table 1, entries 2, 3), while in the presence of 2 or 3 equivalents, the reaction was slower (Table 1, entries 4, 5). These results are in contrast with allylation of aldehydes in the presence of allyltrichlorosilane, where sulfoxides should be used in excess (≥ 2 eq.) to ensure high reactivity [14].

No reaction was observed in the absence of DMSO, supporting the importance of the Lewis base in the activation of the weak Lewis acid $SiCl_4$ [9-11].

Under the optimized reaction conditions (Table 1, entry 3), different aldehydes were reacted in order to probe the scope of the method (Scheme 2, Table 2). Good to high yields were observed for aromatic, hetero-aromatic and unsaturated aldehydes in the presence of both electron-withdrawing and electron-donating groups. In the presence of a substrate bearing a cyano group in the ortho- position, the reaction was significantly slower. 3-phenyl propionaldehyde [7] did not react at all.

Next we turned our attention to developing an asymmetric version of the reaction (Scheme 3, Tables 3 and 4). Using the commercially-available (R)-



Scheme 2. Allylation of aldehydes in the presence of DMSO

Table 2. Allylation of different aldehydes in the presence of 0.2 eq. of DMSO.

Entries	Aldehyde 1 (R)	Yield 3 %[a]
1	C_6H_5	87
2	p-$OMeC_6H_4$	68
3	p-$NO_2C_6H_4$	78
4	p-CNC_6H_4	82
5	o-CNC_6H_4	58
6	PhCH=CH	88
7	2-furyl	70
8	5-nitro-2-furyl	72
9	5-nitro-2-thiophenyl	79
10	$PhCH_2CH_2$	No react.

[a] *Yields refer to chromatographically pure compounds*

Table 3. Allylation of aldehydes in the presence of several chiral (R)-aryl methyl sulfoxides

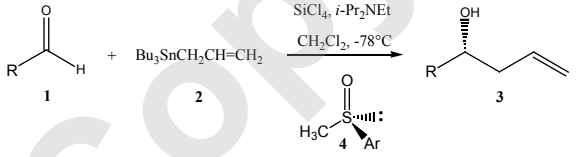
Entry	Aldehyde	Sulfoxide (Ar)[a,b]	Eq. sulfoxide	Time (h)	Yield (%)[c]	e.e. (%)[b]
1	Benzaldehyde	4a p-tolyl	0.1	5.5	55	7
2	Benzaldehyde	4a p-tolyl[d]	0.2	23	89	12
3	Benzaldehyde	4a p-tolyl	1	5	86	18
4	Benzaldehyde	4a p-tolyl	2	6	32	34
5	Benzaldehyde	4a p-tolyl[e]	2	23	70	33
6[f]	Benzaldehyde	4a p-tolyl[g]	2	23	49	7
7	Benzaldehyde	4a p-tolyl	3	23	No react.	--
8	Benzaldehyde	4b p-MeO-phenyl[e]	2	23	59	36
9	5-nitro-2-furyl	4a p-tolyl	2	23	67	57
10	5-nitro-2-furyl	4b p-MeO-phenyl[e]	2	23	76	60
11	5-nitro-2-furyl	4c 2-naphthyl[e]	2	23	48	40

[a] *Sulfoxide 4a is commercially available; 4b and 4c were synthesized according to the procedure described in [15] and were obtained respectively with 97 and 98% e.e.s*
[b] *Enantiomeric excesses were determined by chiral HPLC.*
[c] *Yields refer to chromatographically pure compounds*
[d] *The sulfoxide was recovered in quantitative yield and 50% e.e.*
[e] *The sulfoxide was recovered in quantitative yield and 96% e.e.*
[f] *Reaction performed without i-Pr$_2$EtN.*
[g] *The sulfoxide was recovered in 84% yield and 20% e.e.*

methyl p-tolyl sulfoxide 4a, we tried the enantioselective allylation of benzaldehyde in the presence of different amount of the Lewis base (Table 3, entries 1-6). Unfortunately, the enantioselectivity was low even in the presence of 2 equivalents of the sulfoxide (Table 3, entries 4 and 5). Sub-stoichiometric amounts of the Lewis base showed higher reactivity but lower e.e.s (Table 3, entries 1 and 2), while the trend was the opposite when 2 equivalents of the chiral sulfoxide were used (Table 3, entries 4 and 5). At the end of the reaction, the chiral sulfoxide was recovered in quantitative yield but in varying enantiomeric purities that depended on the number of equivalents of the sulfoxide. When 2 eq. were used, 4a was recovered in quantitative yield and 97% e.e. (Table 3, entries 4 and 5), while in the presence of 0.2 eq., 4a was recovered in quantitative yield but with 50% e.e. (Table 3, entries 1 and 2) [14,16]. When we used fewer equivalents of 4a, this effect was more evident in terms of percentage value on the e.e. of the recovered sulfoxide. These results can in part explain the lower enantioselectivity in the presence of catalytic amount of 4a (Table 3, entries 1 and 2).

Since the racemization of chiral sulfoxides has been reported to occur under acidic conditions [17], partial racemization of 4a can be due HCl, formed by the hydrolysis of $SiCl_4$ due to trace amounts of water. For this reason, it is important to use i-Pr$_2$EtN to neutralize excess HCl [14,16]. Performing the reaction in the same conditions of entry 5 (Table 3) but without i-Pr$_2$EtN, we recovered 4a in 84% yield and 20% e.e., while 3a was obtained in significantly lower yield and e.e. (Table 3, entry 6).

The observed reactivity reflects what we have described in the preliminary experiments using different amounts of DMSO (Table 1). In the presence of a large excess of 4a we did not observe the formation of the product presumably due to the saturation of the silicon



Scheme 3. Asymmetric allylation of aldehydes in the presence of chiral methyl aryl sulfoxides

center with the coordination of three Lewis bases (Table 3, entry 7).

We screened other chiral aryl methyl sulfoxides in order to analyze the effect of the substituent of the aromatic ring in the allylation of benzaldehyde and 5-nitro-2-furfural. Higher enantioselectivity was observed in the presence of 5-nitro-2-furfural with both 4a and 4b (Table 3 entries 9-11), suggesting the possibility of an important electronic effect of the substrate on the enantioselectivity. Among the sulfoxides screened, 4b with an electron-donating group on the aromatic ring, showed a slightly higher enantioselectivity (Table 3, entries 8 and 10), while the hindered naphthyl group in 4c gave poorer results (Table 3, entry 11). At the end of the reaction, all the sulfoxides were recovered in quantitative yields and with e.e.s > 96%.

In the presence of 2 eq. of the commercially-available (R)-methyl p-tolyl sulfoxide 4a, we examined the reactivity of a series of aldehydes (Scheme 3, Table 4). As previously observed with 5-nitro-2-furfural, aldehydes bearing electron-withdrawing groups showed a significantly higher enantioselectivities (Table 4, entries 5-9), while the other aldehydes gave the final products 3 with rather low e.e.s (Table 4, entries 2-4 and 10-12), comparable to benzaldehyde (Table 4, entry 1). Moreover, the presence of a group in the ortho position further decreased the enantioselectivity (Table 4, entries 10 and 12). According to the measured optical rotation, all the homoallylic alcohols were obtained with an excess of the (R)-enantiomer. This

is in contrast to the allylation of aldehydes using allyltrichlorosilane, in which (R)-methyl p-tolyl sulfoxide 4a produced products with opposite configuration [14]. This difference could be due to the different pathways occurring in the two transformations. In the presence of allyltrichlorosilane, the observed stereochemistry is well-described by a closed, chair-like transition state [14], while $SiCl_4$-mediated transformations proceed via an open transition state [9 -11,18].

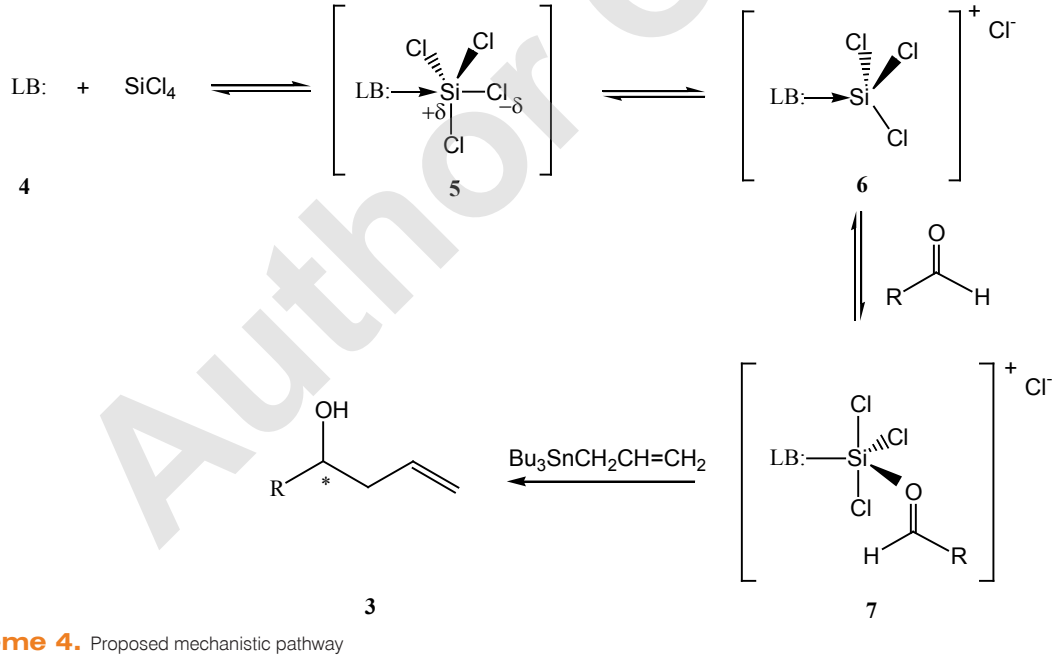
Table 4. Allylation of aldehydes in the presence of (R)-methyl p-tolyl sulfoxide 4a.

Entry	Aldehyde (R)	Yield 3 (%)[a,b]	e.e. 3 (%)[c]
1	C_6H_5	70	33
2	p-$MeOC_6H_4$	52	14
3	PhCH=CH	86	29
4	2-furyl	72	22
5	5-nitro-2-furyl	67	57
6	5-nitro-2-thiophenyl	79	52
7	p-$CF_3C_6H_4$	63	45
8	p-$NO_2C_6H_4$	57	45[d]
9	p-CNC_6H_4	54	50
10	o-CNC_6H_4	30	4
11	p-ClC_6H_4	58	37
12	o-ClC_6H_4	52	4
13	$PhCH_2CH_2$	No react.	

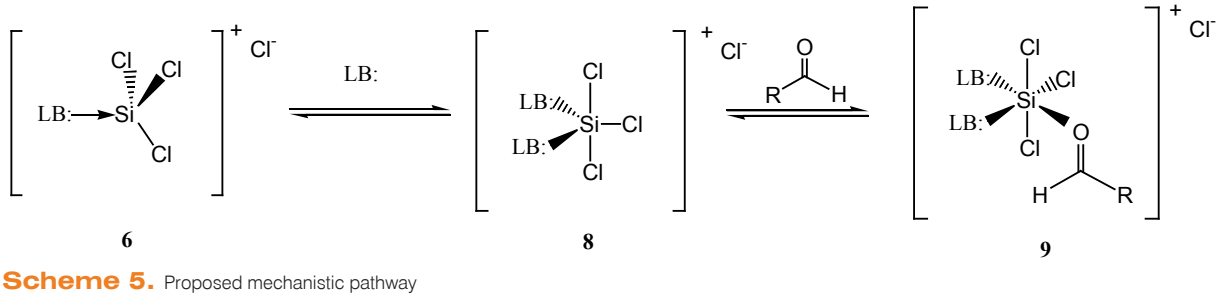
[a] *Yields refer to chromatographically pure compounds*
[b] *Reaction time = 23 h*
[c] *Enantiomeric excesses were determined by chiral HPLC.*
[d] *E.e. was determined by chiral GC using Supelco β-dex column.*

Since the yields vary from moderate to high independently of the aldehyde, the reactivity cannot be related to the electronic properties of the substrates. As observed with DMSO as the Lewis base (see Table 2, entry 5), the reaction of 2-cyano-benzaldehyde was even slower, probably due to a combination of steric and electronic effects (Table 4, entry 10). Also in the presence of the chiral sulfoxide, the aliphatic aldehyde did not react (Table 4, entry 13).

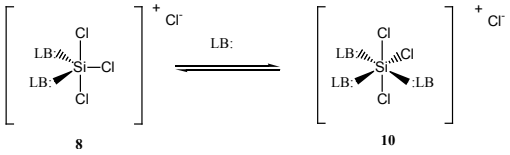
As widely accepted in the literature [9 -11,18], the coordination of the weak Lewis acid $SiCl_4$ by a strong Lewis base polarizes the silicon-chlorine bonds, leading to ionization of a chloride and formation of a catalytically active, five-coordinate trichlorosilyl cation 6 (Scheme 4). The generation of a cationic species results in a significant increase in the Lewis acidity of the central atom. The activated Lewis acid allows for the coordination and activation of the aldehyde in a hypervalent silicon centre transition state 7. The attack of the nucleophile yields the homoallylic alcohol 3.



Scheme 4. Proposed mechanistic pathway



Scheme 5. Proposed mechanistic pathway



Scheme 6. Proposed mechanistic pathway

The use of two equivalents of the sulfoxide can lead to a six-coordinated transition state 9 (Scheme 5). This species probably displays lower reactivity than the five-coordinate transition state 7 due to increased steric hindrance. However, the coordination of two chiral Lewis bases leads to a species that exhibits higher asymmetric induction.

In the presence of three equivalents of methyl p-tolyl sulfoxide, we did not observe any reaction. The excess of the sulfoxide could produce a six-coordinate, inactive complex in which three Lewis bases are bound to the silicon center (Scheme 6). In this octahedral complex, there is no possibility for the coordination and activation of the aldehyde.

Other mechanistic studies are necessary in order to determine the order of the sulfoxide and describe the equilibria between the possible silicon complexes. This could be useful for a better description of the enantio-determining step of the reaction and allow for a more rational design of effective sulfoxide-based Lewis bases. The strong dependence of the observed e.e.s on the substrate structure should be included in a more detailed kinetic model.

4. Conclusions

In conclusion, readily available chiral or achiral sulfoxides can be conveniently used as Lewis bases for the activation of $SiCl_4$ in the allylation of aldehydes using allyltributyl stannane. Good to high yields have been observed in the presence of aromatic, hetero-aromatic and unsaturated aldehydes using catalytic amount of sulfoxides. However in the presence of an excess of commercially available (R)-methyl p-tolyl sulfoxide 4a, moderate enantioselectivity was observed with aldehydes bearing an electron-withdrawing groups, while all other aldehydes showed rather low e.e.s. Due to the novelty of this application, further studies are currently underway to design more effective chiral sulfoxides and to develop other sulfoxide-$SiCl_4$ mediated reactions.

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