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The sulfinyl moiety in Lewis base-promoted allylations

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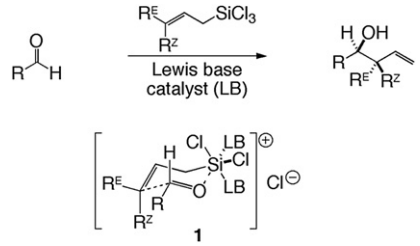
ABSTRACT

By employing Senanayake's oxathiazolidine-2-oxide reagent, a collection of sulfinamides was prepared and provided the first examples of sulfinamides promoting the allylation of benzaldehyde and *N*-benzoylhydrazones with allyltrichlorosilane. The optimum sulfinamide-derived Lewis base promoter displays comparable activity to the best sulfinyl-based Lewis bases reported. The use of bis-sulfoxides is also discussed.

1. Introduction

Lewis acid catalysis is still the dominant form of catalysis in organic chemistry; Lewis base-mediated processes are less comprehensively studied even though they offer catalysts with increased stability and the potential to catalyse a more diverse selection of reactions.[1,2] One aspect of Lewis base catalysis that has attracted appreciable attention is the allylation/crotylation of aldehydes and hydrazones with trichlorosilanes (Scheme 1).[3–7] A range of chiral Lewis bases have been introduced as catalysts for this transformation including phosphoramides,[3,5,6,8] phosphine oxides,[9] *N*-oxides[10] and formamides.[11] All these reagents are thought to interact with the silane to give a penta- or hexa-coordinate hypervalent silicate that enhances both the nucleophilicity of the allyl moiety and the electrophilicity of the silicon atom. The major attraction of this methodology is its high diastereospecificity in crotylations, which is postulated to arise due to the closed transition state **1**. The relative scarcity of Lewis base catalysts compared to the vast number of ligands for Lewis acid catalysis means there is a need to increase the repertoire of potential Lewis base catalysts.



Scheme 1. Lewis base-mediated crotylation.

The sulfinyl moiety has yet to be fully exploited in this arena even though it has good donor properties, is readily prepared and the chirality of sulfur is in close proximity to all the components of the reaction. We, along with two other groups, introduced chiral sulfoxides as Lewis basic organocatalysts for allylation[12–14] and subsequently, other groups have reported the use of sulfinyl derivatives in similar reactions.[15–18] Unfortunately, none of the sulfoxides investigated have proven entirely satisfactory; none show catalytic turnover,[19] and the allylation of aldehydes proceeds with only moderate enantioselectivity. In this paper we outline our preliminary attempts to ameliorate this situation with bis-sulfoxides and report the first use of monodentate sulfinamides as promoters for the Lewis base-mediated allylation of both aldehydes and *N*-benzoylhydrazones.

During detailed analysis of the mechanism of chiral phosphoramide-catalysed allylation, Denmark revealed that the reaction follows second order kinetics in the monodentate phosphoramide catalyst (such as **1**; Scheme 1) and hence proposed that bidentate promoters should be superior.[2,5,6,20] This drove us to investigate bidentate sulfinyl oxazoline promoters **2**

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(Fig. 1);[14] these were encouraging, giving homoallylic alcohols in good yield with moderate enantioselectivity but they were far from perfect. They displayed no catalytic turnover, requiring excess reagent to achieve acceptable yields and, more worryingly, decomposed under the reaction conditions. The results indicated that the enantioselectivity of the allylation was controlled by the sulfinyl moiety and that the oxazoline moiety was not only unnecessary but was detrimental to the promoter's stability. Therefore, we decided to replace it with a second sulfoxide group in order to maintain the bidentate nature of the promoters (**3**; Fig. 1). This research was undertaken before the publication of Fernández and Khiar's report on the activity of bis-sulfoxides in the allylation of hydrazones.[16,21]

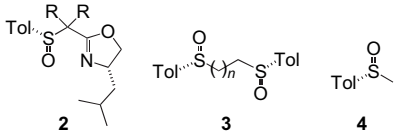


Figure 1. Sulfoxide-derived Lewis base promoters.

2. Results and discussion

2.1. Sulfoxide-derived Lewis base promoters

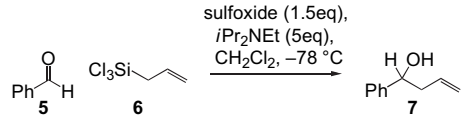
Our initial targets were the bis-sulfoxides **3** (n=1 to 3; Fig. 1).[21] The methyl-linked promoter (**3**; n=0) was not prepared as it was felt that the relatively acidic methylene position (pK_a approximately 18.2 in DMSO) would encourage deoxygenation by the Pummerer reaction. The ethyl-linked bis-sulfoxide (**3**; n=1) was prepared according to a literature procedure by copper(II)-mediated oxidative dimerisation of the (*R*)-methyl toluenesulfoxide **4**.[22] Bis-sulfoxides with a longer linker proved harder to synthesise; the most direct route, formation of a bis-Grignard reagent from a suitable dihalide and reaction with Andersen's sulfinate, (1*R*,2*S*,5*R*)-(+)-menthyl (*S*)-*p*-toluenesulfinate, failed. Reversal of the coupling partners with the anion of **4** displacing a suitable leaving group from the linker was also tried with equally unsatisfactory results.

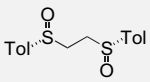
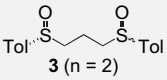
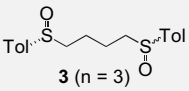
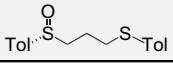
Finally, a convoluted, stepwise synthesis permitted a limited number of sulfoxides **3** to be prepared. The synthesis was based on the elaboration of **4**, thus one stereocentre was fixed. Unfortunately, the second was introduced by non-selective oxidation giving rise to a mixture of the desired enantiomer and the achiral *meso* diastereoisomer. Although separation of the diastereoisomers was impossible, we believed that the mixture would provide satisfactory preliminary results, as the unwanted diastereoisomer would only promote non-selective allylation and not preferential formation of the opposite enantiomer of homoallylic alcohol.

Since Kobayashi's[7] and Denmark's[3] seminal work in the early 1990s, the addition of allyltrichlorosilane to benzaldehyde has been extensively studied and is now considered as a benchmark reaction for understanding the potential of new Lewis base promoters. In order to ascertain the efficacy of the new sulfoxides **3** their activity was compared with methyl derivative **4**, the optimum sulfoxide for the allylation of benzaldehyde **5** with allyltrichlorosilane **6** (Table 1).[13]

All reactions were performed under identical conditions; 1 equiv of sulfoxide and 5 equiv of ethyldiisopropylamine in dichloromethane at −78 °C. Initial studies required the development of a method to evaluate the efficiency of the promoters simply and rapidly that did not rely on chiral chromatography or derivatisation; the yields were determined from the NMR spectra of the crude reaction mixture using 2,3,5,6-tetrachloronitrobenzene as an internal standard whilst the enantiomeric excess was ascertained using chiral solvating agent, (*S*)-*tert*-butylphenylphosphinothioic acid (TBPTA).[23] The spectra of a 1:2 mixture of (*S*)-TBPTA/alcohol **7** collected at −10 °C with proton decoupling displays a separate singlet for the benzylic proton of each enantiomer; (*R*)-**7** is at δ 4.76 ppm and (*S*)-**7** is at δ 4.74 ppm.

Table 1
Bis-sulfoxide-mediated allylation of benzaldehyde



Entry	Sulfoxide	Yield (%)	(*S*)-**7**/(*R*)-**7**
1	 **4**	27	77:23
2	 **3** (n = 1)	0	—
3	 **3** (n = 2)	3	70:30
4	 **3** (n = 3)	2	—
5		17	73:27

The results of the allylation are displayed in Table 1 and are disappointing with none of the novel sulfoxides competing with **4** (Table 1; Entry 1). The mixed sulfoxide sulfide gave the best results forming (*S*)-**7** in 46% ee (Table 1; Entry 5). This is comparable with the selectivity of **4** under the same reaction conditions. The bis-sulfoxide **3** (n=2) gave comparable enantioselectivity to both **4** and the mixed sulfoxide sulfide but was considerably less reactive (Table 1; Entry 3). Surprisingly, ethyl bis-sulfoxide **3** (n=1) gave pitiful results; this in stark contrast to the results of Fernández, who showed that **3** (n=1) was a competent promoter for the allylation of *N*-benzoylhydrazones.[16] The activity of the mixed sulfoxide sulfide (Table 1; Entry 5) compared to the bis-sulfoxides is far more intriguing; it appears that under our reaction conditions the second sulfoxide moiety impedes allylation, with all the bis-sulfoxides giving poor results. Ultimately, whilst these results are far from comprehensive they suggest that bis-sulfoxides show no substantial improvements over mono-sulfoxides; they show no catalytic turnover, reduced reactivity and, at best, comparable enantioselectivity.

Whilst more research needs to be performed in order to understand these systems, we felt that the sulfoxides did not offer sufficient potential to continue their pursuit; we had not improved enantioselectivity over existing sulfoxide promoters and we were still no closer to obtaining catalytic turnover. Therefore, we turned our attention to the study of sulfinamides as potential Lewis base catalysts.

2.2. Sulfinamide-derived Lewis base promoters

Sulfinamides proffer several advantages over sulfoxides; firstly, their synthesis is simpler, permitting facile access to greater structural diversity and secondly, the amine moiety increases their donor ability and hence their reactivity. Earlier observations had confirmed this latter supposition, with simple sulfinamides reacting faster than the sulfoxides.[14,24] The studies reported here represent the first examples of sulfinamides being employed as Lewis base promoters for the allylation of aldehydes and hydrazones.