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# $C_2$-Symmetric Bissulfoxides as Organocatalysts in the Allylation of Benzoyl Hydrazones: Spacer and Concentration Effects

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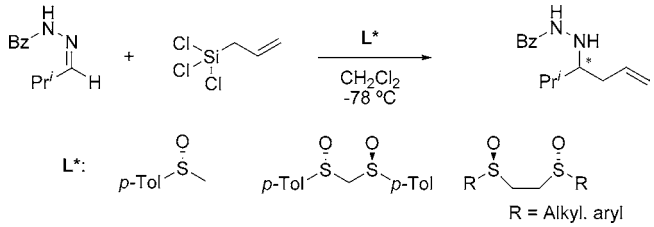
## ABSTRACT




**A comparative study on the allylation of a benzoyl hydrazone with allyl trichlorosilane using monosulfoxides, methylene-bridged $C_2$-symmetric bissulfoxides, and ethylene-bridged $C_2$-symmetric bissulfoxides shows that the enantioselectivity of the process is highly dependent on the spacer between the two sulfinyl sulfurs and the concentration of the reaction.**

The last decades have witnessed an increased interest toward the preparation of chiral sulfinyl derivatives in relation with their application in asymmetric synthesis.[1] This interest was mainly directed toward the preparation of chiral sulfoxides as a consequence of their high efficiency and wide applicability as chiral controllers in asymmetric carbon−carbon and carbon−heteroatom bonds formation.[2] Recent interesting applications of chiral sulfoxides include inter alia their utilization as chiral ligands or ligand precursors in metal-catalyzed asymmetric reactions,[1] in coordination chemistry,[1,3] and as a Lewis base in organocatalysis.[4,5] On the other hand, due to the importance of chiral amines which account for 75% of the total of drugs or drug candidates, their preparation has been a standing area of interest in the last decades.[6] While chiral sulfinamides have demonstrated themselves as universal intermediates in the stechiometric asymmetric synthesis of chiral amines, efficient catalytic approximations are still lacking.[7] Among the methods developed recently, the

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use of chiral Lewis base to promote the allylation of electrophilic imines presents the advantages of higher stability to aerobic conditions, the ability to be anchored on a solid support, and less environmental impact than their metal-based catalytic processes.[8] Following the pioneering work of Kobayashi,[5] we and others have recently shown that chiral sulfoxides are excellent organocatalysts in the allylation of aldehyde and hydrazones with trichloroallyl silane.[4] Accordingly, excellent enantioselectivities were obtained in the allylation of benzoyl hydrazones by using simple sulfoxides, though up to 3 equiv of the organocatalysts was necessary. Since the exact mechanism of the reaction is still missing, the only manner to enhance the enantioselectivity and to reduce the catalyst loading relies on the empirical modification of the promoter. Nevertheless, Denmark's group has recently reported that the allylation of aldehydes using phosphoramides as organocatalysts takes place by activation of the allylsilane by two phosphoramide molecules.[9] On the basis of these findings, in the present study we report our results on the allylation of benzoyl hydrazone **1** with trichloroallyl silane **2**, using enantiomerically pure methylene- and ethylene-bridged $C_2$-symmetric bissulfoxides as chiral promoters (Figure 1, Table 1).

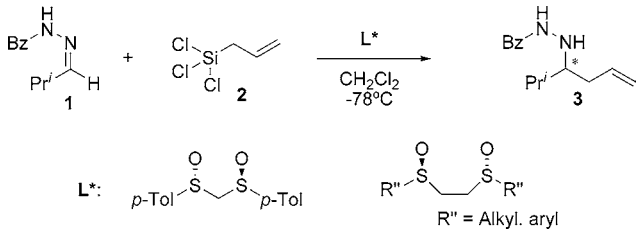
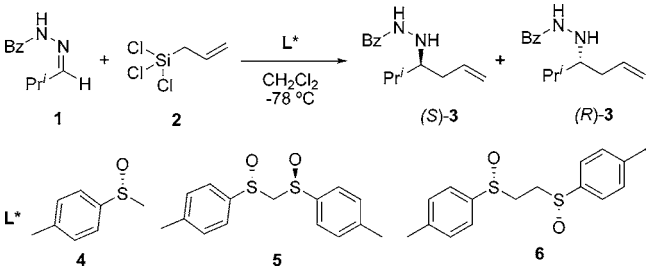



**Figure 1.** Structure of $C_2$-symmetric bissulfoxides used as chiral promoters in allylation of benzoyl hydrazone.

Among the best sulfoxides found so far for the enantioselective allylation of benzoylhydrazones with allyl trichlorosilane was the Andersen−Solladié reagent (*R*)-methyl *p*-tolyl sulfoxide, which afforded the allylated product with up to 97% ee and 98% yield.[5] So, as a first comparative study we conducted the allylation of hydrazone **1** with trichloroallylsilane **2** using sulfoxide **4**, together with (*R*,*R*)-bis-(*p*-tolylsulfinyl)methane **5** and (*R*,*R*)-bis-(*p*-tolylsulfinyl)-ethane **6**. Bissulfoxide **5** was obtained by condensation of lithiomethyl *p*-tolyl sulfoxide with ($S_S$)-menthyl *p*-toluenesulfinate, as pioneered by Kuneida.[10] On the other hand, bissulfoxide **6** was obtained by Cu(I)-catalyzed dimerization

**Table 1.** Enantioselective Allylation of **1** with Use of Sulfoxides **4**−**6**[3]




| entry[a] | ligand | equiv | [L*] (M) | reaction time (h) | yield (%)[b] | (*R*)-**3**:(*S*)-**3**[c] |
|---|---|---|---|---|---|---|
| 1 | **4** | 3.0 | 0.46 | 0.5 | 95 | 96:4 |
| 2 | **4** | 2.0 | 0.46 | 18 | 60 | 97:3 |
| 3 | **4** | 2.0 | 0.16 | 18 | 59 | 91:7 |
| 4 | **4** | 1.0 | 0.46 | 18 | 60 | 88:12 |
| 5 | **5** | 3.0 | 0.46 | 18 | 30 | 65:35 |
| 6 | **5** | 1.0 | 0.2 | 18 | 10 | 61:39 |
| 7 | **5** | 1.5 | 0.08 | 18 | 60 | 58:42 |
| 8 | **6** | 1.5 | 0.46 | 0.25 | 81 | 91:9 |
| 9 | **6** | 1.0 | 0.46 | 1.5 | 60 | 92:8 |
| 10 | **6** | 0.5 | 0.46 | 18 | 52 | 80:20 |
| 11 | **6** | 0.5 | 0.15 | 18 | 45 | 72:28 |
| 12 | **6** | 0.5 | 0.05 | 18 | 45 | 59:41 |

[a] Reactions were conducted in the presence of 0.5 equiv of 2-methyl-2-butene to suppress ligand racemization. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis, using Daicel chiralpack AD-column.

of lithiomethyl *p*-tolyl sulfoxide, following a method developed some 30 years ago by Mislow.[11] As already observed by Kobayashi and by us the concentration of the ligand in the reaction is very important, the use of 2 equiv of **4** in a 0.46 M solution being the best concentration for a good enantioselectivity. Any change in this concentration led to a drop of the enantioselectivity (Table 1, entries 2 and 3). Significantly, using the methylene-bridged bissulfoxide **5** in these optimal conditions afforded the desired product **3**, in only 30% yield and 30% ee. Using fewer equivalents of the ligands leads to a lower ee, while the dilution of the solution afforded a mostly racemic allylated product.

On the other hand, the use of enantiomerically pure ethylene-bridged bissulfoxide **6** afforded the allylated product in excellent yield and excellent enantioselectivity (Table 1, entry 8). The enantioselectivity is maintained when only 1 mol equiv of **6** is used (Table 1, entry 9). Significantly, the allylated product **3** is still obtained with an interesting 60% ee, when only 0.5 mol equiv of the ligand is used. Nevertheless, upon diluting the reaction mixture, the enantioselectivity drops to 48% ee at 0.15 M and to 18% ee when the reaction is conducted at 0.05 M concentration.

To evaluate the effect of the substituents at the sulfinyl sulfur on the enantioselectivity of the process, various aryl and alkyl ethylene-bridged $C_2$-symmetric bissulfoxides were

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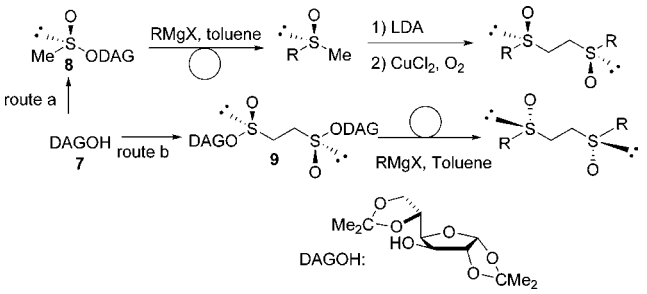
tested in the same reaction. For the synthesis of the required bissulfoxides, we have applied our methodology based on the dynamic kinetic resolution of sulfinyl chlorides, Scheme 1. The method named DAG-methodology is able to give both

**Scheme 1**

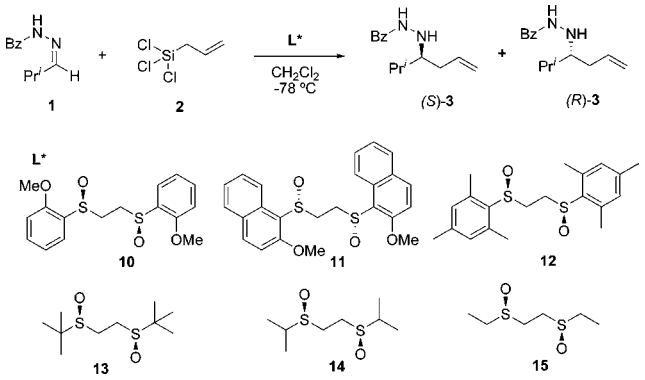



enantiomers of the final bissulfoxides with use of diacetone-D-glucose **7** as a single chiral auxiliary following two different pathways. The first approach (route a, Scheme 1) is based on the use of DAG methanesulfinate **8** as the common intermediate for the synthesis of various optically pure methyl sulfoxides,[1,12] followed by a copper catalyzed oxidative coupling of the corresponding lithium anions.[13] The second approach (route b, Scheme 1) is based on the condensation of Grignard reagents on diastereomerically pure $C_2$-symmetric DAG bissulfinate ester **9**, obtained by dynamic kinetic resolution of 1,2-ethane bissulfinyl chloride.[14] While both routes are able to give both enantiomers of the final sulfoxides with high ee, the former one is preferred when the R groups of bissulfoxides have no acidic proton, as in the case of bissulfoxides **6** and **10**−**13**. The later approach, which is more convergent and general, is the only approximation able to give simple dialkyl bissulfoxides, such as **14** and **15**.

The results obtained in the allylation of **1** with $C_2$-symmetric bissulfoxides **10**−**15** are summarized in Table 2. Bisaryl sulfoxides **10** and **11** give the allylated product in good yields and lower ee values than bis(*p*-tolylsulfinyl)-ethane **6** (Table 2, entries 1−3), even though an interesting 68% ee was obtained with only 0.5 equiv of **11**. On the other hand, the steric hindrance of the sulfinyl sulfur has a prominent influence on the enantioselectivity and the reactivity of the process. Very hindered sulfoxides such as bis-(mesitylsulfinyl)ethane **12** and bis(*tert*-butylsulfinyl)ethane **13** afforded the allylated product **3** in low yield and low ee. Significantly, the product is obtained in only 26% yield in racemic form, though 1.5 equiv of bis(*tert*-butylsulfinyl)-ethane **13** was used in the optimal conditions determined before (Table 2, entry 5).

Relieving the steric hindrance of the sulfoxide has a beneficial effect, as is shown from the results obtained, when

**Table 2.** Enantioselective Allylation of **1** with Use of Sulfoxides **10**−**15**[3]




| entry[a] | ligand | equiv | [L*] (M) | reaction time (h) | yield (%)[b] | (*R*)**3**:(*S*)**3**[c] |
|---|---|---|---|---|---|---|
| 1 | **10** | 3.0 | 0.46 | 0.25 | 89 | 16:84 |
| 2 | **10** | 1.0 | 0.46 | 18 | 96 | 47:53 |
| 3 | **11** | 0.5 | 0.02 | 18 | 30 | 84:16 |
| 4 | **12** | 0.5 | 0.14 | 18 | 58 | 35:65 |
| 5 | **13** | 1.5 | 0.46 | 0.25 | 26 | 50:50 |
| 6 | **14** | 1.5 | 0.46 | 0.25 | 81 | 65:35 |
| 7 | **15** | 1.5 | 0.06 | 18 | 60 | 86:14 |
| 8 | **15** | 1.0 | 0.16 | 6 | 76 | 90:10 |

[a] Reactions were conducted in the presence of 0.5 equiv of 2-methyl-2-butene to suppress ligand racemization. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis, using Daicel chiralpack AD-column.

moving from a *tert*-butyl group to an isopropyl or an ethyl group (Table 2, entries 5−8). Bis(isopropylsulfinyl)ethane **14** afforded the allylated product with excellent yield but only a 30% ee (Table 2, entry 6), confirming our previous results that in terms of steric hindrance, the isopropyl sulfinyl group is a good compromise between the *tert*-butyl and the *p*-tolyl sulfinyl groups. Interestingly, the use of the smaller bissulfoxide, bis(ethylsulfinyl)ethane **15**, afforded the best results in terms of enantioselectivity (Table 2, entries 7 and 8). An interesting 90:10 enantiomeric ratio of **3**-(*R*):**3**-(*S*) was obtained, using only 1 equiv of the neutral ligand in a 0.16 M solution (Table 2, entry 8).

Taken all together, the results obtained so far can give some insights on the mechanism of the organocatalytic allylation of hydrazones with neutral sulfoxides, unknown for the moment. First, the erosion of the enantioselectivity upon reducing the catalyst loading and upon diluting the reaction medium suggests the possibility that the reaction could proceed through two operating pathways.

The first one is an effective and highly enantioselective pathway involving two sulfoxide molecules bound to the chlorosilane (transition state B, Figure 2), along with a less selective pathway involving only one catalyst molecule (transition state A, Figure 2). The proposition of a dual pathway permits the explanation of the results obtained with mono- and bissulfoxides. The good results obtained with 1 equiv of (*R*,*R*)-bis(*p*-tolylsulfinyl)ethane **6**, and which are equivalent to those obtained with 2 mol equiv of the

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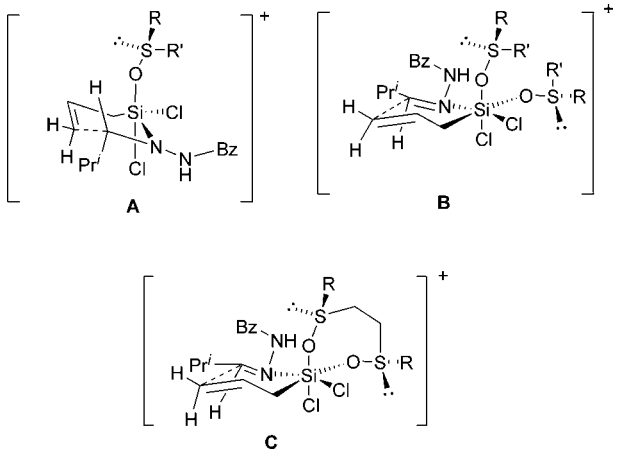


**Figure 2.** Possible transition states for the organocatalytic allylation of hydrazones with sulfoxides.

monosulfoxide **4**, can be ascribed to an increase of the effective catalysts through space approximation (Figure 2, transition state C). On the other hand, the low ee obtained with bis(*p*-tolylsulfinyl)methane **5** is a consequence of the short tether link between the two sulfinyl oxygens, forcing the ligand to actuate as sterically hindered monosulfoxides, which are known to be less selective catalysts.

In summary, we have demonstrated that ethylene-bridged bissulfoxides are effective organocatalysts for the allylation of benzoyl hydrazone with allyl trichlorosilane. Studies on the exact mechanism in order to rationally design chiral bissulfoxides to further enhance the enantioselectivity and lower the catalyst loading are already in progress.

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**Supporting Information Available:** Representative experimental procedures for the synthesis of compounds **3**, **6**, and **10**−**15**, and HPLC data for the determination of the enantiomeric excess of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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