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Asymmetric allylation of *N*-benzoylhydrazones promoted by novel C_2-symmetric bis-sulfoxide organocatalysts

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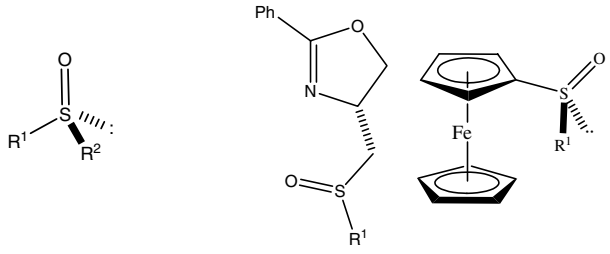
Abstract—Novel C_2-symmetric bis-sulfoxide/*N*-oxide (*R*,*R*)-**5** was prepared in good yield according to the Andersen protocol with (*S*)-menthyl *p*-tolyl sulfinate (2 equiv) and the dilithium derivate of 2,6-dimethylpyridine *N*-oxide. Reduction of (*R*,*R*)-**5** to pyridine/bis-sulfoxide (*R*,*R*)-**6** was accomplished by means of Katritzky's procedure (Fe^0/AcOH). Both bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** are efficient chiral organocatalysts in the asymmetric allylation of *N*-benzoyl hydrazones derived from both aldehydes and ketones.

1. Introduction

The development of practical enantioselective syntheses of chiral amines is of great relevance to synthetic organic chemistry. In particular, enantiopure homoallylic amines are useful intermediates for the preparation of nitrogen-containing compounds, which are biologically active.[1] In this regard, resonance-stabilized allyl organometallics have been used with success in imine addition reactions;[2] nevertheless, metal-free organic molecule-catalyzed allylation reactions are most attractive in terms of reagent stability and environmentally benign nature relative to metal complex-catalysts.[3]

A major problem encountered in the addition of allylmetals to imines is competitive α-deprotonation.[4] This complication can be solved at least in part, by the use of allylsilanes;[2,5] nevertheless, their relative low reactivity usually requires the use of catalysts. In particular, allyltrichorosilanes are essentially inert to the electrophilic imines in the absence of external promoters. Therefore, activation of the reaction has been achieved in two ways: (1) by the use of Lewis acid catalysis, including asymmetric variants using chiral Lewis acids, which activate the imine,[6] and (2) by means of a Lewis base, which activates the nucleophile via coordination to the silicon atom of the allyltrichlorosilanes to form hypervalent silicon intermediates. In particular, *N*,*N*-dimethylformamide (DMF),[7] hexamethylphosphoramide (HMPA),[7] *N*-oxides,[8] *P*-oxides,[9] and ureas,[10] including their optically active derivatives for asymmetric catalysis,[6b] promote the allylation of aldehydes.

Recently, the use of chiral sulfoxides **1**–**3** (Chart 1) as ligands in the enantioselective allylation of aldehydes and



1 (R^1, R^2) **2** (R^1) **3** (R^1)

(*R*)-**1a** (Me, *p*-tolyl)	**2a** (Ph)	**3a** (*p*-tolyl)
(*R*)-**1b** (Et, *p*-tolyl)	**2b** (*p*-$O_2NC_6H_4$)	**3b** (*t*-Bu)
(*R*)-**1c** (*i*-Pr, *p*-tolyl)	**2c** (2-$C_{10}H_7$)	**3c** (*i*-Pr)
(*S*)-**1d** (*o*-tolyl, Me)	**2d** (*p*-$MeOC_6H_4$)	
(*S*)-**1e** (*o*-$MeOC_6H_4$, Me)	**2e** (2,4,6-$Me_3C_6H_2$)	
(*S*)-**1f** (*p*-$MeOC_6H_4$, Me)	**2f** (Me_2CH)	

Chart 1.

Keywords: Organocatalysis; Chiral sulfoxide; Enantioselective allylation; Chiral sulfur reagents.
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hydrazones has been explored by several researchers,[11–13] with observed enantioselectivities that vary from poor to very good enantiomeric excesses.

Attracted by the wide applicability of enantiopure sulfoxides in asymmetric carbon–carbon bond formation,[14] and intrigued by the possibility of bidentate complex formation between the silicon moiety in allyltrichlorosilane and C_2-symmetric chiral ligands,[15] we undertook the synthesis of novel bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** and the examination of their potential as promoters in the asymmetric allylation of *N*-benzoyl hydrazones derived from aldehydes and ketones.

2. Results and discussion

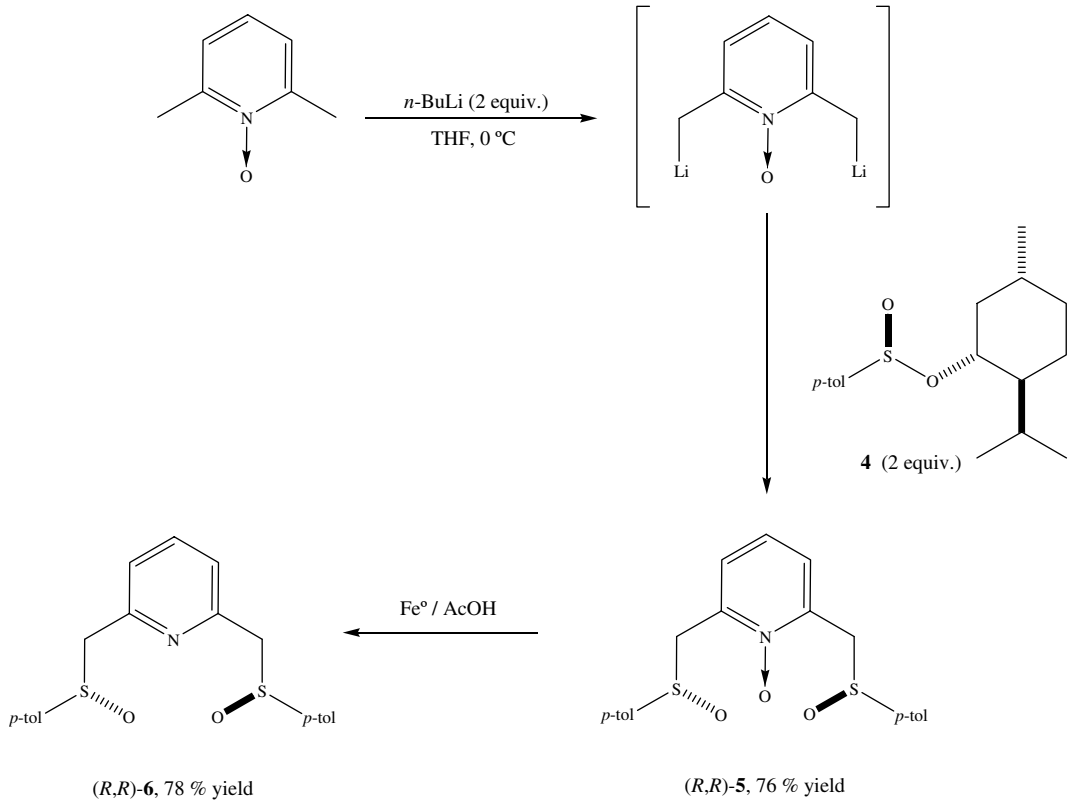
The synthesis of novel bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** was carried out following the general method developed by Andersen.[16] Thus, (*S*)-(−)-menthyl *p*-tolylsulfinate, **4**, was prepared according to the literature procedure[17] and was made to react with the dilithium derivate of 2,6-dimethylpyridine *N*-oxide.[18] The desired bis-sulfoxide/*N*-oxide (*R*,*R*)-**5**, arising from the inversion of configuration at the sulfinate's stereogenic sulfur,[19] was obtained as white solid in a good yield.[20] Bis-sulfoxide (*R*,*R*)-**6** was prepared from (*R*,*R*)-**5** by the reduction with Fe^0/CH_3CO_2H according to the general method of Katritzky and co-workers[21,22] (Scheme 1).

Table 1 summarizes the results obtained when allylation of the *N*-benzoyl hydrazone derived from benzaldehyde (**7**) was promoted by achiral dimethylsulfoxide (DMSO), by chiral monosulfoxide (*R*)-methyl *p*-tolyl sulfoxide (MTS), and by C_2-symmetric bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6**. The conditions employed by Kobayashi et al.[11] were followed, using 1.5 or 3.0 equiv of the sulfoxides.[23]

Analysis of the observations collected in Table 1 reveals that bis-sulfoxide/*N*-oxide (*R*,*R*)-**5** is quite efficient in promoting the enantioselective allylation of hydrazone **7a** with allyltrichlorosilane (er = 12:88, entry 3 in Table 1). By contrast, lower enantioinduction is observed with bis-sulfoxide (*R*,*R*)-**6**. Indeed, the er = 20:80 of the allylated hydrazide (entry 4 in Table 1) is essentially the same as the one achieved with (*R*)-methyl *p*-tolyl sulfoxide (er = 21:79, entry 2 in Table 1). Although the yield of the allylation reaction in the presence of (*R*,*R*)-**6** is lower than those achieved with monosulfoxide (*R*)-MTS, it should be mentioned that no allylation takes place in the absence of sulfoxide activator.

Table 2 compiles the results of the allylation reaction (allyltrichlorosilane) of various prochiral *N*-benzoylhydrazones **7a**–**f** in the presence of chiral bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6**.

The configuration of the major enantiomeric *N*-benzoyl hydrazide **8b** was assigned as (*S*) by comparison of its optical rotation with that already assigned in the literature.[11a] Because of the similitude in optical rotation and chromatographic (chiral HPLC) retention times,[24] the predominant enantiomeric products **8a** and **8c** were also

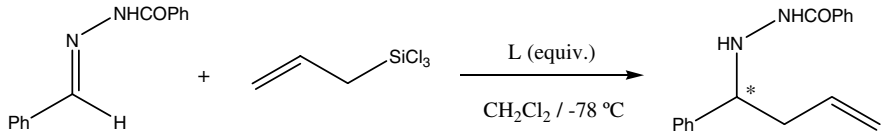


(*R*,*R*)-**6**, 78 % yield

(*R*,*R*)-**5**, 76 % yield

Scheme 1.

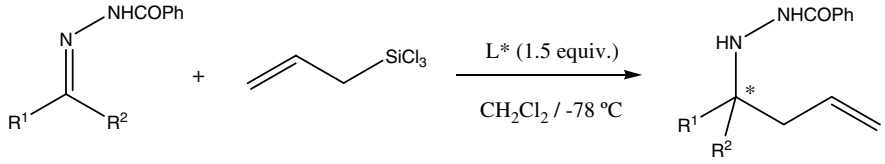
Table 1. Allylation of *N*-benzoyl-*N*′-benzyledene-hydrazone with allyltrichlorosilane using various sulfoxides (L) as promoters[a]



Entry	L	(equiv)	Yield	Enantiomeric ratio (*R*:*S*)[b]
1	DMSO	3	98	(50:50)
2	(*R*)-MTS[c]	3	94	(21:79)
3	(*R*,*R*)-**5**	1.5	89	(12:88)
4	(*R*,*R*)-**6**	1.5	73	(20:80)

[a] Half equivalent of 2-methyl-2-butene was added to suppress the racemization of the chiral sulfoxides.[11]
[b] Determined by chiral HPLC.[24]
[c] (*R*)-Methyl-*p*-tolyl sulfoxide.

Table 2. Allylation of various *N*-benzoyl-hydrazones **7a**–**f** with allyltrichlorosilane under catalysis by C_2-symmetric organocatalysts (*R*,*R*)-**5** and (*R*,*R*)-**6**[a]



7a-f **8a-f**

Entry	Substrate (R^1/R^2)	L*	Yield of **8**	Enantiomeric ratio (*R*:*S*)[b]
1	**7a** (Ph/H)	(*R*,*R*)-**5**	89	12:88
2	**7a**	(*R*,*R*)-**6**	73	21:79
3	**7b** (*p*-$MeOC_6H_4$/H)	(*R*,*R*)-**5**	80	14:86
4	**7b**	(*R*,*R*)-**6**	72	30:70
5	**7c** (*m*-$MeOC_6H_4$/H)	(*R*,*R*)-**5**	93	18:82
6	**7c**	(*R*,*R*)-**6**	68	30:70
7	**7d** (2-Furyl/H)	(*R*,*R*)-**5**	84	16:84[c]
8	**7d**	(*R*,*R*)-**6**	54	45:55[c]
9	**7e** (Me_2CHCH_2/H)	(*R*,*R*)-**5**	81	74:26[c]
10	**7e**	(*R*,*R*)-**6**	56	50:50
11	**7f** (Ph/Me)	(*R*,*R*)-**5**	82	20:80
12	**7f**	(*R*,*R*)-**6**	30	87:13

[a] Half equivalent of 2-methyl-2-butene was added to suppress the racemization of the chiral sulfoxides.[11]
[b] Determined by chiral HPLC.[24]
[c] This configurational assignment is tentative (see text).

assigned as (*S*). The absolute configuration in hydrazide (*R*)-(+)-**8f** was determined by Leighton et al.[5b] Interestingly, organocatalysts (*R*,*R*)-**5** and (*R*,*R*)-**6** induce the formation of enantiomeric products of opposite configuration, suggesting that coordination to the N → O group is operative and determinant. The configurational assignments of hydrazides **8d** and **8e** are tentatively assigned in Table 2 on the basis of optical rotation and chromatographic behavior.

Salient observations from the results compiled in Table 2 are (1) the ability of both bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** to catalyze the allylation of *N*-benzoyl hydrazones derived from both aliphatic and aromatic aldehydes and ketones; (2) the efficiency of *N*-oxide/bis-sulfoxide (*R*,*R*)-**5** is generally higher relative to the exhibited by pyridine/bis-sulfoxide (*R*,*R*)-**6**. This finding might suggest an effective coordination by the N → O group.

In summary, novel C_2-symmetric bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** are efficient organocatalysts in the enantioselective allylation of *N*-benzoyl hydrazones derived from both aldehydes and ketones. The potential application of these chiral Lewis bases in other asymmetric C–C bond forming reactions is being explored.

Acknowledgments

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20. *Preparation of (R,R)-2,6-bis(p-toluen-4-sulfenylmethyl)-pyridine-1-oxide* (*R*,*R*)-**5**. To a solution of 2,6-dimethylpyridine *N*-oxide (0.166 g, 1.35 mmol) in 5 mL of THF at 0 °C was added dropwise a solution of *n*-BuLi in hexane (2.5 M, 1.0 mL, 2.70 mmol). The resulting mixture was stirred at 0 °C for 1 h and then transferred via cannula to a flask containing (*S*)-(−)-menthyl *p*-tolylsulfinate (1.0 g, 3.34 mmol) in 5.0 mL of THF at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before quenching with aqueous saturated ammonium chloride solution. The product was extracted with methylene chloride, dried over anhyd sodium sulfate, concentrated at reduced pressure, and purified by silica gel column chromatography (EtOAc–$CHCl_3$–*i*-PrOH, 8:2:1). Bis-sulfoxide (*R*,*R*)-**5** crystallized from hexane–EtOAc (1:1) to afford 0.40 g (76% yield) of product, mp 175–176 °C. $[\alpha]_D^{24}$ +313.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 6H), 4.08 (d, $J = 12.1$ Hz, 2H), 4.49 (d, $J = 12.1$ Hz, 2H), 7.16–7.18 (m, 1H), 7.31–7.34 (m, 6H), 7.57–7.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 60.8, 123.9, 124.7, 128.2, 130.1, 140.6, 142.1, 142.9. MS *m*/*z* 399 (M^+). Anal. Calcd for $C_{21}H_{21}NO_3S_2$: C, 63.13; H, 5.30; N, 3.51; S, 16.05. Found: C, 63.07; H, 5.36; N, 3.55; S, 16.19.
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22. *Preparation of (R,R)-2,6-bis(p-toluen-4-sulfenylmethyl)-pyridine* (*R*,*R*)-**6**. To a solution of *N*-oxide (*R*,*R*)-**5** (399 mg, 1.0 mmol) in 1.0 mL of acetic acid was added reduced iron (168 mg, 3.0 mmol) at 0 °C. The resulting mixture was stirred at rt for 30 min and then neutralized by the addition of satd aq $NaHCO_3$, keeping the temperature at 0–5 °C. The reaction product was extracted with CH_2Cl_2 (3×100 mL), dried over anhyd Na_2SO_4, and concentrated at reduced pressure. The reduced product was purified by silica gel column chromatography (EtOAc–$CHCl_3$–*i*-PrOH, 8:2:1) followed by crystallization from hexane–EtOAc (1:1) to give 0.30 g (78% yield) of (*R*,*R*)-**6**, mp 159–160 °C. $[\alpha]_D^{24}$ +217.0 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 6H), 4.09 (d, $J = 12.1$, 2H), 4.13 (d, $J = 12.4$ Hz, 2H), 7.08 (d, $J = 7.7$ Hz, 2H), 7.26–7.42 (m, 8H), 7.55 (t, $J = 7.6$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 65.7, 124.3, 124.7, 129.9, 137.0, 140.1, 141.9, 151.2. MS *m*/*z* 383 (M^+). Anal. Calcd for $C_{21}H_{21}NO_2S_2$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.89; H, 5.76; N, 3.68.
23. Bis-sulfoxides (*R*,*R*)-**5** and (*R*,*R*)-**6** may be recovered by silica gel column chromatography: following the elution of the allylated hydrazides, the bis-sulfoxides are eluted with CH_2Cl_2–EtOAc (2:1) in 72–87% yields.
24. HPLC: Chiralcel OD, 0.46 cm × 25 cm, hexane–2-propanol (90:10), flow 1.0 mL/min, UV detector at 230 nm. Elution times: (*R*)-**8a**, 8.8 min; (*S*)-**8a**, 9.8 min. (*R*)-**8b**, 12.7 min; (*S*)-**8b**, 14.6 min. (*R*)-**8c**, 16.5 min; (*S*)-**8c**, 21.2 min. (*R*)-**8d**, 11.1 min; (*S*)-**8d**, 16.2 min. (*R*)-**8e**, 12.0 min; (*S*)-**8e**, 10.0 min. (*S*)-**8f**, 10.8 min; (*R*)-**8f**, 13.6 min.