A catalytic asymmetric allylation of aldehydes with allyl trichlorosilane activated by a chiral tetradentate bis-sulfoxide

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ABSTRACT

Chiral homoallylic alcohols are easily accessible by asymmetric allylation of aldehydes with allyl trichlorosilane in the presence of catalytic amounts of a chiral tetradentate bis-sulfoxide, as organocatalyst, whose synthesis is reported.

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1. Introduction

Chiral homoallylic alcohols are among the most valuable building blocks for the synthesis of complex molecules.[1] The typical preparative approach is represented by the allylation of carbonyl compounds, and recently many stereoselective procedures have been reported.[2] In particular, allyl trichlorosilane has recently proven to be a very useful allylating agent: in fact, its activation by strong neutral Lewis bases, such as *N,N*-dimethyl formamide,[3] was found to result in the formation of a hypervalent silicon compound capable of reacting with suitable electrophiles. As regards the allylation of carbonyl compounds, the allyl group transfer through a cyclic six-membered transition state has been exploited in a variety of enantioselective procedures involving the use of chiral phosphoramides,[4] N-oxides,[5] formamides,[6] ureas,[7] and phosphine oxides.[8]

Sulfoxides have been widely exploited as chiral auxiliaries in many fundamental C–C bond-forming reactions.[9] Nevertheless, their use, as Lewis bases, in allylation reactions with allyl trichlorosilane has found rather modest applications. In fact, while the allylation of *N*-acylhydrazones proceeded with good yields and high enantioselectivities,[10] less satisfactory results were obtained in the allylation of aldehydes.[11] Furthermore, the main disadvantage of both the above reactions is represented by the use of the organocatalysts in high excess (3 equiv) to get the best levels of enantioselectivity. No significant improvement was observed by using bidentate mono-sulfoxides (1 equiv),[12] while the allylation of benzoyl hydrazones took place with high enantiomeric excesses in the presence of chiral sulfoxides[10] as well as C_2 symmetric bis-sulfoxides[13,14] although relevant organo-catalyst loading was again required (1–3 equiv).

Herein, we report a very simple approach to a chiral tetradentate bis-sulfoxide of type **4** and its application in a catalytic enan-

tioselective metal-free allylation of aldehydes by using allyl trichlorosilane as the allyl group transfer reagent.

2. Results and discussion

The key-step of the synthesis of bis-sulfoxide **4** is represented by the enantioselective sulfoxidation of the commercially available sulfide **1** (Scheme 1), performed through a suitable modification of Modena's protocol:[15] in fact, by treatment with cumyl hydroperoxide (CHP) in the presence of titanium tetraisopropoxide/(*R,R*)-diethyl tartrate (DET) complex at −20 °C, **1** was converted into the corresponding chiral sulfoxide **2** in 81% yield and 80% ee.
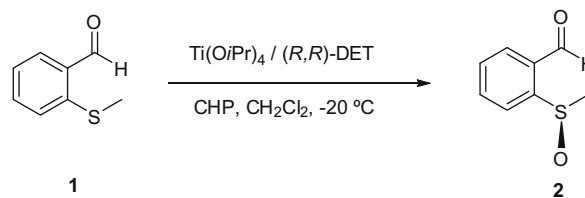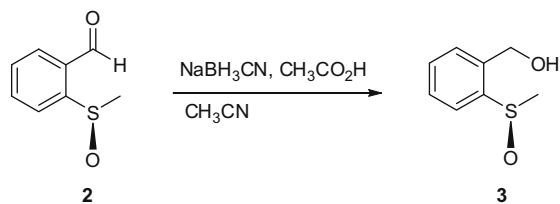

Scheme 1.

Only one crystallization from diethyl ether gave **2** in 71% yield (calculated on the starting material **1**) and 96% ee. The (*R*)-absolute configuration was assigned by reducing **2** with NaBH₃CN (49% yield) and comparing the sign of the specific rotation with the one of the known (*R*)-alcohol **3**[16] (Scheme 2).

Finally, bis-sulfoxide **4** was obtained through a modification of a known procedure[17] by reacting **2** with ethylenediamine in refluxing methanol (95% yield), Scheme 3. ¹H NMR analysis (400 MHz) of the purified product did not exhibit the typical signals of *meso*-**4**,[17] confirming that no significant change of the absolute configuration of the stereogenic centers had been caused by the above treatment.

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Scheme 2.

Preliminary experiments were devoted to verify the possibility of employment of bis-sulfoxide **4** as an organocatalyst in an allylation reaction. Benzaldehyde **5a** and 5-nitro-2-formyl-furan **5b** were chosen as representative substrates and were reacted with allyl trichlorosilane in the presence of catalytic amounts (0.2 equiv) of the compound **4**.

Under the conditions reported in Scheme 4 and Table 1, the formation of the corresponding chiral homoallylic alcohols **6a** and **6b** was found to occur albeit in moderate yields and enantiomeric excesses (Table 1, entries 1 and 2). Nevertheless, the enhancement of the organocatalyst loading up to 0.3 equiv resulted in an appreciable increase in efficiency and enantioselectivity (entries 3 and 4). The extension of the procedure with results comparable to other aromatic (entry 6), heteroaromatic (entry 5) and, more interestingly, aliphatic aldehydes (entry 7) foresees a wide field of applicability.
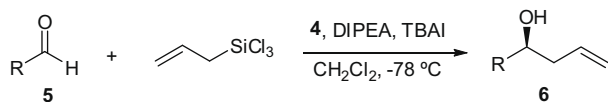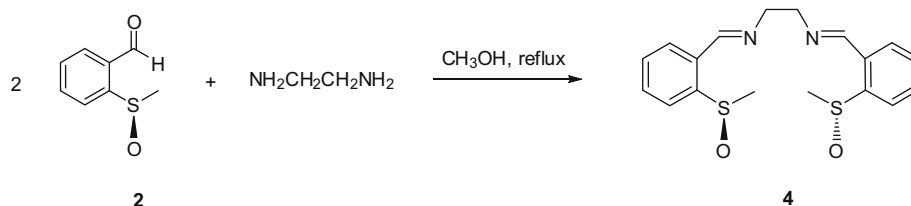

Scheme 4.

Table 1
Asymmetric allylation of aldehydes **5**

Entry	Cat. **4** (equiv)	R	6	Yield[a] (%)	ee (%)
1	0.2	Ph	**6a**	43	47
2	0.2	5-NO$_2$-2-Furyl	**6b**	61	63
3	0.3	Ph	**6a**	57	53
4	0.3	5-NO$_2$-2-Furyl	**6b**	69	66
5	0.3	5-NO$_2$-2-Thienyl	**6c**	65	70
6	0.3	p-CNC$_6$H$_4$	**6d**	60	61
7	0.3	C$_6$H$_5$CH$_2$CH$_2$	**6e**	60	62

[a] All the yields refer to isolated, chromatographically pure compounds whose structures were confirmed by analytical and spectroscopic data. Enantiomeric excesses were determined by chiral HPLC analysis. Absolute configurations were assigned to compounds **6a** (S),[4k] **6d** (S),[4k] and **6e** (R)[5e] by comparison of the specific rotations with the literature data. (S)-Absolute configuration was assigned to **6b** and **6c** by ^{1}H NMR analysis of the corresponding (R)-(−)- and (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid derivatives.

3. Conclusion

In conclusion, the chiral tetradentate imino-sulfoxide **4** proved to be available through a rapid sequence involving the

enantioselective oxidation of 2-(methylthio)benzaldehyde in the key-step. Furthermore, the achievement of a new asymmetric procedure for the allylation of aldehydes with allyl trichlorosilane, involving catalytic amounts of a chiral bis-sulfoxide, can be considered a notable improvement with respect to the known procedures, which required strong excesses of mono-sulfoxides as activators.

4. Experimental

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry nitrogen. All the solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride, diethyl ether from lithium aluminium hydride). Column chromatographic purification of products was carried out using Silica Gel 60 (70–230 mesh, Merck). The reagents (Aldrich and Fluka) were used without further purification. The NMR spectra were recorded on a Bruker DRX 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C). Spectra were referenced to residual chloroform (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintept), m (multiplet) and by br (broad). Coupling constants, J, are reported in Hertz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. IR spectra were recorded on a Bruker Vector 22 (frequencies 400–4000 cm^{-1}, resolution 2 cm^{-1}). Mass spectrometry analysis was carried out using an electrospray spectrometer Waters 4 micro quadrupole. HPLC analyses were performed with Waters Associates equipment (Waters 2487 Dual l absorbance Detector) and using a CHIRALPAK AD. CHIRALCEL OD, CHIRALCEL OB, CHIRALCEL AS column with hexane/isopropyl alcohol mixtures and flow rates as indicated. Chiral GC (Supelco β-DEX 120 analyses were performed with FOCUS GC/FID Thermo Scientific. The HPLC and GC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.1. (R)-(+)-2-(Methylsulfinyl)benzaldehyde 2

In a flame-dried, two-necked, round-bottomed flask, a solution of cumene hydroperoxide (1.2 mL, 6.0 mmol) in dichloromethane dry (11.1 mL) was added to a solution of (R,R)-diethyl tartrate (346 μL, 4.0 mmol), Ti(OiPr)$_4$ (257 μL, 0.99 mmol), and 2-(methylthio)benzaldehyde (390 μL, 3.0 mmol) in dry dichloromethane (11.1 mL) under nitrogen at −18 °C. At the end of the reaction, the reaction was quenched with saturated aqueous Na$_2$SO$_3$ 1 M (22.0 mL), extracted with (25 × 3 mL) of CH$_2$Cl$_2$, and dried over anhydrous Na$_2$SO$_4$. After removing the solvent under reduced pressure, the crude oil was purified by silica gel chromatography with ethyl acetate. ^{1}H NMR δ 2.76 (s, 3H), 7.67 (dt, 1H, J = 7.2 Hz, J = 1.2 Hz), 7.83 (dt, 1H, J = 7.7 Hz, J = 1.5 Hz), 7.94 (dd, 1H, J = 7.3 Hz, J = 1.4 Hz), 8.25 (dd, 1H, J = 7.1 Hz, J = 1.5 Hz), 9.98 (s, 1H). ^{13}C NMR δ 42.3, 123.4, 129.6, 133.6, 134.2, 191.0. ESI-MS m/z 169 [MH]$^+$. [α]$_D$ = +145.8 (c 1.0, CHCl$_3$). Ee 96% (after crystallization

Scheme 3.

from Et$_2$O at 0 °C). The enantiomeric excess was determined by chiral HPLC (Chiralcel OB, hexane/2-propanol 1:1, 0.6 mL/min, 254 nm, t_S = 10.53 min for minor enantiomer, t_R = 14.62 min for major enantiomer). Anal. Calcd for C$_8$H$_8$O$_2$S: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.35; H, 4.68; S, 19.27. Mp 67–69 °C.

4.2. (*R,R*)-(+)-*N*$_1$,*N*$_2$-Bis-(2-(Methylsulfinyl)-benzylidene)-ethane-1,2-diamine 4

To a solution of (*R*)-(+)-2-(methylsulfinyl)benzaldehyde (150.0 mg, 0.89 mmol) in MeOH (7.3 mL) was added ethylenediamine (30.1 µL, 0.45 mmol) at room temperature. Then the mixture was heated at reflux for 22 h. After removing the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography with THF/Et$_2$O 2:1. ^{1}H NMR δ 2.69 (s, 6H), 3.87–3.90 (m, 2H), 4.02–4.06 (m, 2H), 7.46–7.61 (m, 6H), 8.20 (d, 2H, *J* = 8.32 Hz), 8.32 (s, 2H). ^{13}C NMR δ 42.9, 60.6, 122.9, 129.2, 130.2, 130.4, 131.5, 146.3, 159.6. ESI-MS *m/z* 361 [MH]$^+$. [α]$_D$ = +329.0 (*c* 0.4, CHCl$_3$). Ee 96%. Anal. Calcd for C$_{18}$H$_{20}$N$_2$O$_2$S$_2$: C, 59.97; H, 5.59; N, 7.77; S, 17.79. Found: C, 59.79; H, 5.77; N, 7.62; S, 17.96. Mp 71–73 °C.

4.3. (*R*)-(+)-2-(Hydroxymethyl)phenyl-methyl-sulfoxide 3

To a solution of (*R*)-(+)-2-(methylsulfinyl)benzaldehyde (30.0 mg, 0.18 mmol) in CH$_3$CN (3.8 mL), CH$_3$COOH (15.0 µL, 0.27 mmol) and NaBH$_3$CN (45.2 mg, 0.72 mmol) were added at room temperature. After stirring overnight, the reaction was quenched with saturated aqueous NaHCO$_3$ (4.0 mL), extracted with 5 × 3 mL of CH$_2$Cl$_2$, and dried over anhydrous Na$_2$SO$_4$. After removing the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography with ethyl acetate. Yield 49%. NMR data were in agreement with those reported in the literature. [α]$_D$ = +14.8 (*c* 4.0, acetone), {lit. [α]$_D$ = +12.2 (*c* 4.0, acetone)}.[2]

4.4. General procedure of allylation

In a flame-dried, two-necked, round-bottomed flask, allyltrichlorosilane (19 µL, 0.13 mmol) was added to a solution of sulfoxide (0.03 mmol), diisopropylethylamine (20 µL, 0.13 mmol), and N(Bu)$_4$I (44.3 mg, 0.12 mmol) in dry dichloromethane (0.6 mL) under nitrogen at −78 °C. After 5 min of stirring at that temperature, aldehyde was added (0.10 mmol). At the end of the reaction, the reaction was quenched with saturated aqueous NaHCO$_3$ (1.0 mL), extracted with 10 × 3 mL of CH$_2$Cl$_2$, and dried over anhydrous Na$_2$SO$_4$. After removing the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography.

4.5. (*S*)-(−)-1-[(5-Nitro)-2-furyl]-but-3-en-1-ol 6b

This product was purified by silica gel flash chromatography with petroleum ether to petroleum ether/Et$_2$O 60:40 mixture as eluant. ^{1}H NMR δ 2.56 (br s, 1H), 2.58–2.74 (m, 2H), 4.83 (t, 1H, *J* = 5.5 Hz), 5.19–5.24 (m, 2H), 5.75–5.81 (m, 1H), 6.52 (d, 1H, *J* = 3.6 Hz), 7.27 (d, 1H, *J* = 3.6 Hz). ^{13}C NMR δ 39.9, 66.7, 109.4, 112.4, 119.9, 132.0, 150.6, 159.7. ESI-MS *m/z* 184 [MH]$^+$. [α]$_D$ −62 (*c* 1.0, CHCl$_3$). Ee 66%. The enantiomeric excess was determined by chiral HPLC (Chiralcel AD, hexane/2-propanol 95:5, 0.8 mL/min, 254 nm, t_S = 18.04 min for major enantiomer, t_R = 20.97 min for minor enantiomer). Anal. Calcd for C$_8$H$_9$NO$_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.25; H, 4.77; N, 7.81.

4.6. (*S*)-(−)-1-[(5-Nitro-2-thienyl]but-3-ene-1-ol 6c

This product was purified by silica gel flash chromatography with petroleum ether to petroleum ether/Et$_2$O 60:40 mixture as eluant. ^{1}H NMR δ 2.51–2.68 (m, 2H), 2.82 (br s, 1H), 4.97–5.02 (dd, 1H, *J* = 5.1, 7.3 Hz), 5.19–5.30 (m, 2H), 5.72–5.89 (m, 1H), 6.89–6.91 (dd, 1H, *J* = 0.9, 4.2 Hz), 7.80 (d, 1H, *J* = 4.2). ^{13}C NMR δ 43.1, 68.8, 119.9, 122.0, 128.3, 131.8, 145.9, 156.8. ESI-MS *m/z* 200 [MH]$^+$. [α]$_D$ = −6 (*c* 3.0, CHCl$_3$). Ee 70%. The enantiomeric excess was determined by chiral HPLC (Chiralcel AD, hexane/2-propanol 95:5, 0.8 mL/min, 254 nm, t_S = 18.38 min for minor enantiomer, t_R = 20.29 min for major enantiomer). Anal. Calcd for C$_8$H$_9$NO$_3$S: C, 48.23; H, 4.55; N, 7.03; S, 16.09. Found: C, 48.42; H, 4.64; N, 7.23; S, 16.29.

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