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# The first approach to optically active 2,2′-bipyridine alkyl sulfoxides ☆

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**Abstract**

The synthesis of 6,6′-bis(alkylsulfanyl)-2,2′-bipyridines and their asymmetric oxidation to non-racemic 2,2′-bipyridine alkyl sulfoxides using either (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine or a modified Sharpless reagent is reported.


*Keywords:* Chiral 2,2′-bipyridine alkyl sulfoxides; 5,5′-Bi-1,2,4-triazine; Diels–Alder reaction

Recently, a number of chiral 2,2′-bipyridines have been prepared and tested in a variety of asymmetric reactions.[1] In addition to their applications as ligands in transition metal catalysis, chiral 2,2′-bipyridine bis N-oxides have been employed as selective organocatalysts in metal free reactions.[2] Most of the synthetic approaches to chiral 2,2′-bipyridines are based on the transition metal catalyzed heteroaryl homo-coupling and cross-coupling reactions of chiral halopyridines,[1–3] or Kröhnke-type synthesis from pyridinium salts and chiral α,β-unsaturated ketones,[4] which often require multistep procedures. In contrast, the introduction of chirality to the 2,2′-bipyridine framework by secondary functionalization of substituents directly attached to bipyridine rings has not received much attention. Examples in the literature refer mostly to the amidification of mono and dicarboxy 2,2′-bipyridines with amino acids[5,6] or non-racemic amines,[7] esterification with (−)-menthol,[8] and lipase-catalyzed enantioselective acetylation of 1-[(2,2′-bipyridyl)] ethanol.[9] The chirality could also be introduced into the 2,2′-bipyridine core via nucleophilic halide substitution or the modification of a carbonyl group as indicated by the preparation of ligands bearing camphor sultam moieties[10] or bis-oxazolidine substituents.[11] The limited use of these approaches for the preparation of chiral 2,2′-bipyridines may be due to the lack of suitable substituents on the 2,2′-bipyridine precursors or efficient methods for their synthesis.

We have recently developed a simple route to 2,2′-bipyridine alkyl sulfides[12] and now report their application to the synthesis of previously unknown chiral 2,2′-bipyridine mono- and bis(sulfoxide)s via direct asymmetric oxidation. Due to the presence of a good coordinating sulfinyl moiety,[13]6,6′-mono- and bis-sulfinyl 2,2′-bipyridines may constitute a new group of chiral catalysts in asymmetric reactions.

The synthesis of 2,2′-bipyridine alkyl sulfides **3a**–**c** is based on Diels–Alder/*retro* Diels–Alder reaction of easily accessible alkyl sulfides of 5,5′-bi-1,2,4-triazines **2a**–**c** with norbornadiene as outlined in Scheme 1.[14a–c] As an extension of this investigation the functionalized sulfides **6** and **7** could be conveniently prepared in high yields under non-basic conditions by heating methyl sulfide **3a** with ethyl haloacetates **4a**–**c** and benzyl halides **5a**–**b**, respectively.[15] Both S-transalkylation reactions proceed via reactive sulfonium salts, **6a** and **7a**, which undergo methyl group removal by the halides present in the reaction mixture.[16] Reactions of **3a** with ethyl iodoacetate **4a** or ethyl bromoacetate **4b** proceeded much faster than the analo-

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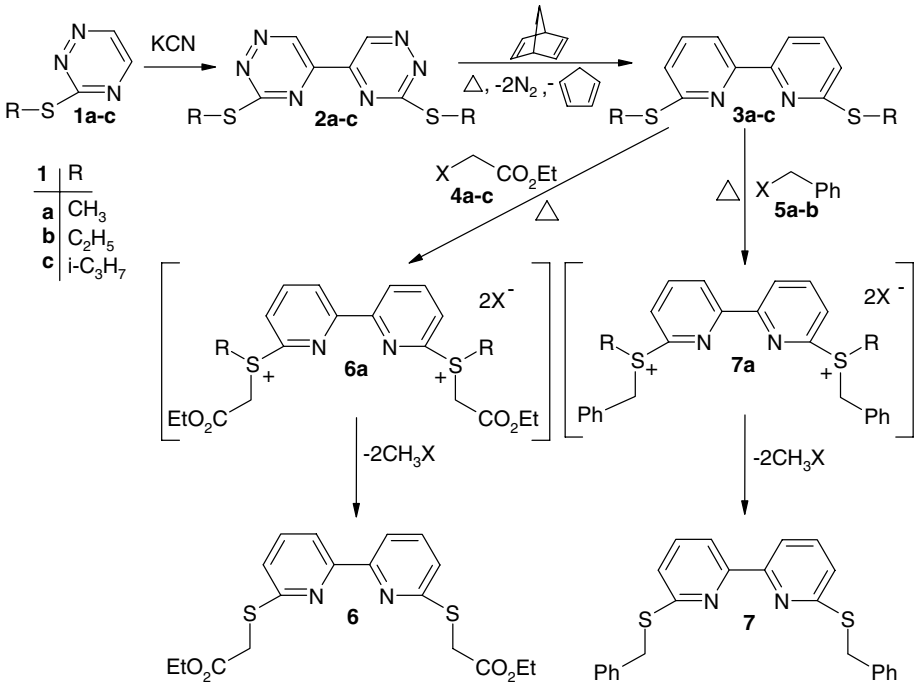



Scheme 1. Synthesis of sulfides **3a**–**c**, **6** and **7**.

gous reaction of **3a** with ethyl chloroacetate **4c**. Likewise, demethylation of **3a** with benzyl bromide **5a** gave compound **7** almost quantitatively, within 2 h. However, the formation of **7** by reaction of **3a** with benzyl chloride **5b** was less favourable and needed forty five hours for completion. As expected, a similar order of reactivity was observed on treatment of **3b** ($R = C_2H_5$) or **3c** ($R = i\text{-}C_3H_7$) with ethyl bromoacetate **4b** and benzyl bromide **5a** giving compounds **6** and **7** in reasonable yields (Scheme 1, Table 1).

With the 2,2′-bipyridine alkyl sulfides in hand we next evaluated their asymmetric sulfoxidation. Among the most convenient and efficient methods for achieving high enantioselectivity during oxidation of prochiral sulfides are the catalytic reactions described by Kagan and co-workers[17] who modified the Sharpless reagent, and with the chiral oxaziridine developed by Davis et al.[18] In addition, biological oxidants such as enzymes, yeasts and microorganisms can also be considered.[19] We report here the results obtained on the asymmetric oxidations of alkyl 2,2′-bipyridine sulfides **3a**–**c**, **6** and **7** using (+)-(8,8-dichlorocamphorylsulfonyl) oxaziridine[20] (Method A) or Kagan conditions[21] (Method B), consisting of formation of a complex between titanium(IV) isopropoxide, (*R*,*R*)-(+)-diethyl tartrate (D-DET), $H_2O$ and *tert*-butylhydroperoxide (TBHP). The reactions were performed in methylene chloride giving the corresponding mono-sulfoxides **8a**–**e**, accompanied by small amounts of bis oxidation products **9a**–**e** (Table 2).

Table 1
Synthesis of compounds **6** and **7**

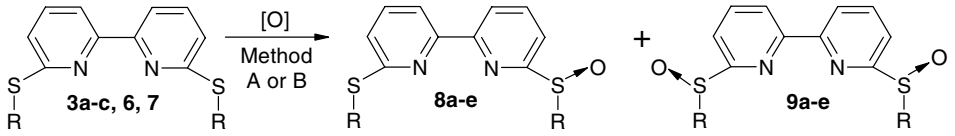
| Compound | Halide | X | Time [h] | Sulfide | Yield [%] |
|---|---|---|---|---|---|
| **3a** | **4a** | I | 1 | **6** | 91 |
| **3a** | **4b** | Br | 8 | **6** | 98 |
| **3a** | **4c** | Cl | 20 | **6** | 75 |
| **3a** | **5a** | Br | 2 | **7** | 95 |
| **3a** | **5b** | Cl | 45 | **7** | 60 |
| **3b** | **4b** | Br | 13 | **6** | 60 |
| **3c** | **5a** | Br | 8 | **7** | 76 |

Comparison of the two methods showed that better ees were obtained using Kagan's conditions. High enantiomeric excesses were never obtained for sulfoxides **8d** and **9d** bearing an electron-withdrawing group on the sulfur, whatever the method used. The highest enantioselectivity was obtained for bis sulfoxide **9a** (99% ee). The absolute configuration at both sulfur atoms in **9a** was confirmed by X-ray analysis.[22]

To investigate the catalytic properties of chiral monosulfoxide **8a** and bis-sulfoxides **9c** and **9d** obtained here, the asymmetric addition of diethylzinc to benzaldehyde **10** was carried out in benzene or toluene.[23] The results on the catalyst efficiencies and the enantiomeric excess of the resulting 1-phenyl-1-propanol **11** are presented in Table 3. Although the catalytic efficiency of ligand **8a** was poor, those of ligands **9c** and **9d** possessing a bis-sulfinyl functionality were promising. Ligand **9d** which has only 17% ee provided the chiral product **11** with 11% ee. This enantioselectivity is probably due to the presence of two sulfinyl groups in **9d** which better coordinate the metal ion. These results may thus provide impetus for further development of more selective catalysts in this series. Work in this direction is underway in our laboratories.

In summary, the synthetic protocol described herein provides an expedient access to a novel family of optically

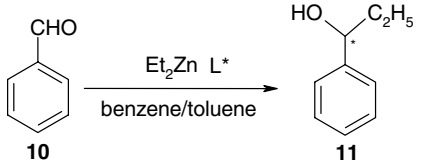
Table 2
Asymmetric oxidation of sulfides by the Davis and Kagan methods




| Substrate | R | Product | Method | Yield [%] | ee [%] | Product | Yield [%] | ee [%] |
|---|---|---|---|---|---|---|---|---|
| **3a** | $-CH_3$ | **8a** | A[a] | 54 | 47[c] | **9a** | 8 | 42[c] |
| | | | B[b] | 40 | 70 | | 13 | >99[c] |
| **3b** | $-C_2H_5$ | **8b** | A[a] | 52 | 76[d] | **9b**[e] | | |
| | | | B[b] | 41 | 82[d] | | | |
| **3c** | $-CH(CH_3)_2$ | **8c** | A[a] | 36 | 51[c] | **9c** | 11 | 22[d] |
| | | | B[b] | 42 | 54[d] | | 9 | 27[d] |
| **6** | $-CH_2CO_2C_2H_5$ | **8d** | A[a] | 41 | 5[d] | **9d** | 12 | 17[d] |
| | | | B[b] | 45 | 14[d] | | 26 | 12[d] |
| **7** | $-CH_2Ph$ | **8e** | A[a] | 61 | 15[d] | **9e** | 23 | 40[d] |
| | | | B | 35 | 62[d] | | 17 | 5[d] |

[a] Davis method.
[b] Kagan method.
[c] ee was determined by $^1H$ NMR using the CSA method.[24]
[d] ee was determined by HPLC analysis using a chiral stationary phase column (Chirobiotic T).
[e] Bis sulfoxide **9b** was not isolated.

Table 3
Enantioselective diethylzinc addition to benzaldehyde **10**




| L* | ee [%] | Amount of ligand (mol %) | Time [days] | Solvent | Yield [%] | ee [%] |
|---|---|---|---|---|---|---|
| **8a** | 54 | 2.5 | 6 | Toluene | 40 | 14 (26)[a] |
| **9c** | 22 | 2.5 | 5 | Benzene | 41 | 14 (64)[a] |
| **9d** | 17 | 3 | 5 | Benzene | 35 | 11 (68)[a] |

L*: Ligands **8a**, **9c**,**d**.
[a] Calculated ee based on pure catalyst.

active 2,2′-bipyridine alkyl sulfoxides from readily accessible 2,2′-bipyridine alkyl sulfides.

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14. (a) Typical three step procedure for the preparation of 2,2′-bipyridine alkyl sulfides **3a**,**b**; (a) Synthesis of compound **1b**. A solution of 5 g (55 mmol) of thiosemicarbazide and 8.58 (55 mmol) of iodoethane in 40 ml of absolute ethanol was refluxed for 5 h. After that time ethanol was evaporated in vacuo. A solution of 7.95 g (55 mmol) of 40% glyoxal and 4.62 g (55 mmol) of sodium bicarbonate in 100 ml of water was added to the brown residue. The mixture was stirred at 5 °C for 3 h and for an additional 12 h at room temperature. The resulting precipitate was filtered and the filtrate was extracted with chloroform (5 × 100 ml). After evaporation of the combined organic extracts the remaining oily residue was purified by chromatography ($SiO_2$, methylene chloride) to give 3-(ethylsulfanyl)-1,2,4-triazine **1b** (7.04 g, 91% yield) as an orange oil. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ (ppm): 1.37 (t, $J = 7.2$, 3H, $CH_3$), 3.20 (q, $J = 7.2$, 1H, $CH_2$), 8.33 (d,

1H, $J = 2.4$ triazine hydrogen), 8.88 (d, 1H, $J = 2.4$ triazine hydrogen). HRMS (EI): calcd for $C_5H_7N_3S$ ($M^+$): 141.0364; found: 141.0360; (b) Synthesis of compound **2b**. A solution of 3-(ethylsulfanyl)-1,2,4-triazine **1b** (6.5 g, 46.1 mmol) in water (170 ml) was stirred until complete dissolution. Excess potassium cyanide (4.8 g, 73.8 mmol) was added in five portions. The mixture was stirred at room temperature for 2 h, after which the reaction mixture was extracted with ethyl acetate ($10 \times 100$ ml). The combined organic extracts were dried over magnesium sulfate, then filtered and concentrated in vacuo. The crude product was purified by chromatography ($SiO_2$, $CH_2Cl_2$), to give pure 3,3′-bis(ethylsulfanyl)-5,5′-1,2,4-triazine (**2b**) (5.28 g, 81% yield) as a yellow solid. Mp 129–130 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm) 1.50 (t, 6H, $J = 7$ Hz, $CH_3$), 2.35 (q, 4H, $J = 7$ Hz, $CH_2$), 9.85 (s, 2H, triazine hydrogen). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 13.9 ($CH_3$), 25.4 ($CH_2$), 141.8, 149.9, 174.1 (triazine carbon atoms). Anal. Calcd for $C_{10}H_{12}N_6S_2$: C, 42.86; H, 4.29; N, 30.00. Found: C, 42.90; H, 4.32; N, 29.89; (c) Synthesis of compound **3b**. A solution of **2b** (1.5 g, 5.35 mmol) in *p*-cymene (10 ml) and norbornadiene (3.6 ml, 25.7 mmol) was heated at 150 °C for 30 h. *p*-Cymene was evaporated in vacuo. The crude product was purified by chromatography ($SiO_2$, $CH_2Cl_2$–hexane 10:3) to give pure 6,6′-bis(ethylsulfanyl)-2,2′-bipyridine (**3b**)(0.85 g, 58% yield) as an orange solid. Mp 68–70 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 1.45 (t, 6H, $J = 7.4$ Hz, $CH_3$), 3.28 (q, 4H, $J = 7.2$ Hz, $CH_2$), 7.14 (d, 2H, $J = 7$ Hz, pyridine hydrogen), 7.58 (d, 2H, $J = 7.8$ Hz, pyridine hydrogen), 8.11 (d, 2H, $J = 1.68$ Hz, pyridine hydrogen); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 14.6 ($CH_3$), 24.4 ($CH_2$), 116, 122, 136, 155 and 158 (pyridine carbon atoms). Anal. Calcd for $C_{14}H_{16}N_2S_2$: C, 60.86; H, 5.79; N, 10.14. Found C, 60,63; H, 5.76; N, 10.05. Compounds **2a**, **c** and **3a**, **c** were obtained as indicated (in Ref. 12c).

15. Compounds **6** and **7** were prepared by refluxing **3a** in the presence of six molar excess of the corresponding alkylating agent **4a**–**c** or **5a**,**b** for the time indicated in Table 1. After that time the reaction was cooled and diethyl ether was added. The precipitates **6** and **7** were filtered off and the crude products were purified by column chromatography using $CH_2Cl_2$ as eluent. The mp and spectroscopic data of **6** and **7** were in good agreement with those reported earlier. For **6** see reference (a), and for **7** see reference (b): (a) Branowska, D.; Rykowski, A.; Wysocki, W. *Tetrahedron Lett.* **2005**, *46*, 6223; (b) Branowska, D.; Buczek, I.; Kalińska, K.; Nowaczyk, J.; Rykowski, A. *Tetrahedron Lett.* **2005**, *46*, 8539.
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20. General procedure for asymmetric sulfoxidations of sulfides **3a**–**c**, **6**, **7** using (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine. To a solution of 1 mmol of the sulfide in anhydrous methylene chloride (30 ml), 0.75 mmol of oxaziridine was added and the reaction stirred at room temperature for 24 h. Afterwards, the solvent was evaporated and the residue was purified by flash chromatography ($SiO_2$, methylene chloride–acetone 10:1.5) to yield pure mono-sulfoxides **8a**–**e** and bis-sulfoxides **9a**, **c**–**e**.
21. General procedure for asymmetric sulfoxidations of sulfides **3a**–**c**, **6** and **7** using Kagan conditions: 3 mmol of titanium tetraisopropoxide (0.9 ml) and 6 mmol (0.51 ml) of D-DET were introduced by a syringe to a mixture of methylene chloride (10 ml) and water (1 ml). The resulting mixture was stirred for 20 min at room temperature. Then the sulfide (1 mmol) was added and the mixture was cooled to −20 °C. Finally, 0.8 mmol of TBHP (2 M solution in toluene) was added. After 16 h at this temperature, water (10 ml) was added and stirring was continued for an additional 1 h. After that time, $Al_2O_3$ (20 mg) was added and the mixture was filtered and the residue was washed with methylene chloride. The organic layer was stirred with 5% sodium hydroxide and brine. After decantation, the organic phase was dried with magnesium sulfate and the solvent was evaporated. Flash chromatography of the crude product ($SiO_2$, methylene chloride) yielded pure mono-sulfoxides **8a**–**e** and bis-sulfoxides **9a**, **c**–**e**.
22. The results of the X-ray analysis will be published elsewhere.
23. General procedure for the asymmetric addition of diethylzinc to benzaldehyde: To a solution of **8a**, **9c** (2.5 mol %) or **9d** (3 mol %) in anhydrous benzene was added diethylzinc (3 mmol, 1.0 M solution in hexane) under argon and the reaction stirred for 10 min at room temperature. The solution was cooled to 0 °C, and benzaldehyde (1 mmol) was added slowly. After being stirred for 2 h at 0 °C, and 12 h at room temperature, the reaction was quenched with 1 M aqueous HCl (20 ml). The mixture was extracted with $Et_2O$, and the combined organic layer dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography ($SiO_2$, hexane–ethyl acetate 10:1) to afford 1-phenyl-1-propanol as a colourless liquid.
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