Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1255–1257

TETRAHEDRON: *ASYMMETRY*

Synthesis of (*S*)-*N*-(diphenylphosphinyl)-*S*-methyl-*S*-phenyl sulfoximide: a new ligand for asymmetric catalysis

Taryn C. Kinahan and Heather Tye*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

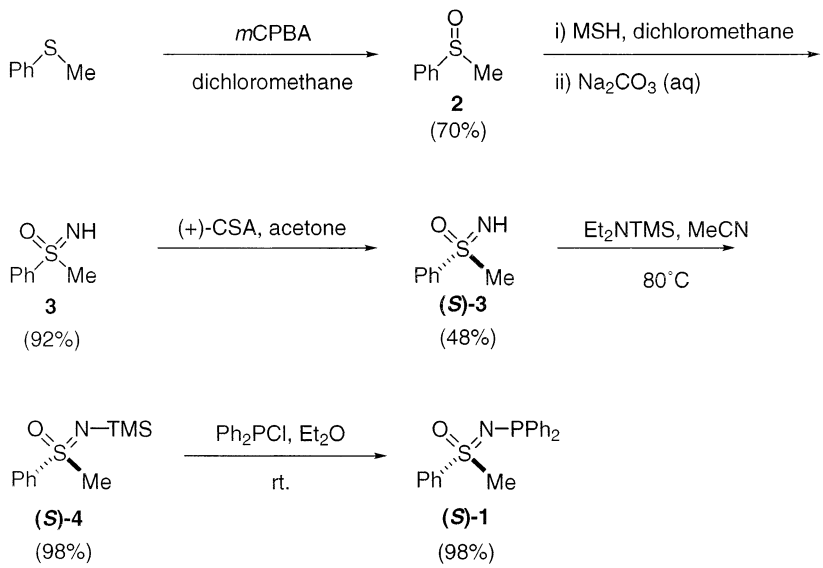
Received 4 April 2001; accepted 16 May 2001

Abstract—The synthesis of (*S*)-*N*-(diphenylphosphinyl)-*S*-methyl-*S*-phenyl sulfoximide is reported. Preliminary investigations into the use of this novel sulfoximide as a ligand for asymmetric conjugate addition reactions are also described.

1. Introduction

Sulfoximides were discovered in 1949 by Bently et al.[1] who identified methionine sulfoximide as the toxic component found in flour that had been treated with 'Agene'. Since then much research has been carried out on the synthesis and use of a wide range of sulfoximide-containing compounds.[2] One key feature of sulfoximides is the stereogenic centre at sulfur, which makes them suitable for use as auxiliaries and ligands in asymmetric synthesis.

An early application of a sulfoximide as a ligand for asymmetric catalysis was reported by Johnson and Stark in 1979 who demonstrated the use of a β-hydroxy sulfoximide in the borane mediated reduction of ketones to afford secondary alcohols with e.e.s of up to 82%.[3] More recently Bolm et al. have developed a number of β-hydroxy sulfoximide ligands for a range of asymmetric transformations including the reduction of ketones and imines,[4] the titanium catalysed hydrocyanation of aldehydes[5] and the nickel catalysed conjugate addition reactions.[6] A number of sulfoximide-contain-



Scheme 1.

* Corresponding author. Fax: +121 414 4403; e-mail: h.tye@bham.ac.uk

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00224-5

ing bidentate ligands have also been utilised in palladium catalysed asymmetric allylic alkylation reactions.[7]

As part of an ongoing program of research into potential ligands for catalytic asymmetric conjugate addition reactions, we decided to prepare a range of ligands incorporating both sulfoximide and phosphine moieties, our rationale for this being that the phosphine would act as a soft donor ligand and the sulfoximide would provide a chiral unit with the potential of acting as a hard donor ligand in certain cases.

To our knowledge no sulfoximide-containing ligands which also incorporate a phosphine moiety have yet been reported. Herein, we present the synthesis of (*S*)-*N*-(diphenylphosphinyl)-*S*-methyl-*S*-phenyl sulfoximide **1** (Scheme 1) and the results of preliminary investigations into its use as a ligand in copper-catalysed asymmetric conjugate addition reactions.

2. Results and discussion

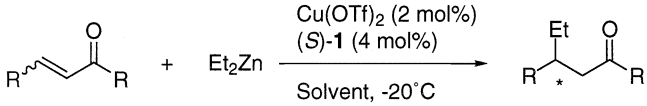
In general the best approach to an enantiomerically pure sulfoximide is via the corresponding sulfoxide, since imination can be achieved with retention of configuration at sulfur. Thus, oxidation of commercially available thioanisole using either *m*-CPBA in dichloromethane or sodium periodate in methanol/water gave the corresponding racemic sulfoxide **2** in good yield. Imination of **2** was then achieved using the electrophilic aminating agent *O*-(mesitylenesulfonyl)hydroxylamine (MSH) giving sulfoximide **3** in up to 92% yield.[8] Resolution of (±)-**3** was carried out using (+)-camphorsulfonic acid (CSA) according to the procedure developed by Gais et al.,[9] which resulted in the isolation of enantiomerically pure (*S*)-**3** in 48% yield.[10]

At this point in the synthesis a number of methods for the introduction of the *N*-phosphinyl group were explored. Initial attempts at the reaction of (*S*)-**3** with chlorodiphenylphosphine in the presence of triethylamine proved unsuccessful due to difficulties encountered with the removal of triethylamine hydrochloride from the product. An alternative approach was to employ *N*,*N*-(dimethylamino)diphenylphosphine as the phosphorus source. This involved heating a 1:1 mixture of (*S*)-**3** and the amino-phosphine in refluxing toluene or benzene until evolution of the volatile dimethylamine (as monitored by the pH of the gas outlet) ceased. Unfortunately a mixture of phosphorus-containing products was obtained, as determined by ^{31}P NMR. A solution to the problem proved to be utilisation of a procedure developed by Roesky et al.,[11] who reported the synthesis of a similar *N*-phosphinyl sulfoximide from dimethyl sulfoxide. The target sulfoximide (*S*)-**1** was successfully prepared by reacting freshly prepared *N*-TMS protected derivative (*S*)-**4**[12] with chlorodiphenylphosphine in dry diethyl ether. This resulted in the formation of (*S*)-**1** as a white precipitate, which could be isolated from the reaction mixture by filtration under an inert atmosphere. In our experience this compound is moisture sensitive but can be stored in a refrigerator under an inert atmosphere for several months.

Spectroscopic characterisation of (*S*)-**1** served to confirm the structure,[†] however, a slight anomaly in the ^{1}H NMR data should be noted: two signals (unequal in intensity) relating to the *S*-methyl group were observed. At first this was thought to be due to a rotameric effect (possibly resulting from slow rotation about the N–P bond). However, variable temperature NMR studies seemed to disprove this hypothesis since no variation in signal intensity or coalescence was observed upon heating. A second hypothesis was that (*S*)-**1** might exist as a mixture of *cis*- and *trans*-isomers about the S=N bond. Attempts at separation of the two forms were unsuccessful due to the instability of the compound to column chromatographic purification and difficulties with recrystallisation. Despite this we thought it useful to assess the capability of this novel sulfoximide (even as a possible mixture of isomers) to act as a ligand in asymmetric transformations. The reaction chosen for investigation was the copper-catalysed addition of an organometallic reagent to an α,β-unsaturated ketone.

There has been considerable interest, over the past decade, in the addition of organometallic reagents to α,β-unsaturated ketones using chiral ligands to enhance the enantioselectivity in the reaction.[13] We chose to adopt the reaction conditions of Feringa et al.,[13b] in which diethylzinc is employed as the organometallic reagent along with $Cu(OTf)_2$ (converted to Cu(I) in situ) as the copper source (Scheme 2). The results of our preliminary studies using a range of enones as substrates are shown in Table 1.

Reactions were carried out in either toluene or dichloromethane at −20°C, giving exclusive formation of the 1,4-adduct in all cases. The rate of the reaction was considerably reduced in the case of 4,4-disubstituted substrates probably due to increased steric hindrance at the 4-position. The enantioselectivities achieved were also much lower in these cases. The best results were obtained upon reaction of cylohex-2-enone (23% e.e.) and cyclohept-2-enone (44% e.e.), demonstrating that the ligand performs best with unhindered



Scheme 2.

[†] Key data for (*S*)-**1**: $[\alpha]_D = +48.0$ ($c = 1.0$ in $CHCl_3$); mp 59–60°C; ν_{max} cm^{-1} (DCM) 3154, 2984, 1285 (N=S=O), 1095 (N=S=O); δ_H (300 MHz; $CDCl_3$), 3.17 (0.5H, s, S-C$\underline{H}_3$), 3.3 (2.5H, s, S-C$\underline{H}_3$), 7.2–8.1 (15H, Ar-$\underline{H}$); δ_c (75.5 MHz; $CDCl_3$) 133.8 (C), 132.5 (d, C, $J_{c\text{-}p}$ 3.8), 130.6 (d, CH, $J_{c\text{-}p}$ 11.5), 129.5 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 127.9 (CH), 45.4 (CH_3); δ_P (120 MHz; $CDCl_3$) 21.8; *m*/*z* (EI); 339 (M^+, 28%), 324 (100), 277 (5), 262 (5), 201 (15), 183 (9), 122 (15), 77 (15), 51 (6); HRMS (EI). Found: (M^+ 339.0831), $C_{19}H_{18}NOPS$ requires 339.0846.

Table 1.

Entry	Substrate	Solvent	Time	Yield (%)	E.e. (%)
1	Cyclohex-2-enone	Toluene	20 min	98	22[a]
2	Cyclohex-2-enone	Dichloromethane	40 min	95	23[a]
3	Cyclohept-2-enone	Toluene	6 h	60	44[a]
4	4,4-Dimethyl cyclohex-2-enone	Toluene	20 h	95	4[a]
5	4,4-Diphenyl cyclohex-2-enone	Toluene	20 h	82	3[a]
6	1,3-Diphenyl propenone	Toluene	4 h	89	0[b]
7	1,3-Diphenyl propenone	Dichloromethane	3 h	86	0[b]

[a] E.e. determined according to the method described by Alexakis et al.[14]
[b] E.e. determined by HPLC using Chiralcel OD column eluted with 0.5% *iso*-propanol in hexane at a flow rate of 0.75 mL/min.

cyclic substrates. The reaction of 1,3-diphenylpropenone gave racemic product suggesting that the ligand is not effective with hindered acyclic substrates.

3. Conclusion

Whilst the enantioselectivities achieved in these preliminary studies are relatively low, the results suggest that sulfoximide-containing ligands of this type may have potential as ligands for use in asymmetric conjugate addition reactions. Further investigations into the synthesis and use of related ligands incorporating a sulfoximide and a phosphine moiety are underway and the results of these studies will be reported in due course.

Acknowledgements

We thank the EPSRC (Quota award to T.C.K.), The University of Birmingham, Astra Zeneca and Pfizer (UK) for financial support.

References

1. Bently, H. R.; Booth, R. G.; Greer, E. N.; Heathcote, J. G.; Hutchinson, J. B.; Moran, T. *Nature* **1949**, *161*, 126.
2. Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.
3. Johnson, C. R.; Stark, C. J. *Tetrahedron Lett*. **1979**, *49*, 4713.
4. (a) Bolm, C.; Felder, M. *Tetrahedron Lett*. **1993**, *34*, 6041; (b) Bolm, C.; Seger, A.; Felder, M. *Tetrahedron Lett*. **1993**, *34*, 8079; (c) Bolm, C.; Felder, M. *Synlett* **1994**, 655.
5. Bolm, C.; Muller, P. *Tetrahedron Lett*. **1995**, *36*, 1625.
6. Bolm, C.; Felder, M.; Muller, J. *Synlett* **1992**, 439.
7. Bolm, C.; Kaufmann, D.; Zehnder, M.; Neuburger, M. *Tetrahedron Lett*. **1996**, *37*, 3985.
8. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
9. Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.
10. As determined by optical rotation.
11. Roesky, H. W.; Schrumpf, F.; Noltemyer, M. Z. *Naturforsch., B: Chem. Sci.* **1989**, *44*, 35.
12. Hwang, K.-J. *J. Org. Chem*. **1986**, *51*, 99.
13. (a) Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427; (b) de Vries, A. H. M.; Meetsma, A.; Feringa, B. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2374; (c) Knobel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, *8*, 1429; (d) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3193; (e) Yan, M.; Yang, L.-W.; Wong, K.-Y.; Chan, A. S. C. *Chem. Commun*. **1998**, 11; (f) Yan, M.; Chan, A. S. C. *Tetrahedron Lett*. **1999**, *40*, 6645.
14. Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.