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The First Enantiomerically Pure Thiadiazol-3-one 1-oxide and Thiatriaza-indene 3-Oxide Systems Chiral at the Sulfur atom

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Abstract — The first synthesis of an enantiomerically pure C₂ symmetric benzothiadiazole 2-oxide is described along with the first synthesis of a enantiomerically thiadiazol-3-one 1-oxide and a thiatriaza-indene 3-Oxide system both chiral at the Sulfur atom. Excellent levels of diastereoselectivity were observed in the SO installation step, i.e. reaction of the prerequisite bis-amines with thionyl chloride at ambient temperature. © 2014 Elsevier Science. All rights reserved

1.0 Introduction

There are a wide number of reports utilizing a 1,3-dinitrogen skeleton as a basis for catalyst/ligand design; for example, N-heterocyclic carbenes 1, phosphoramides 2, and thioureas 3 (Figure 1). Indeed 1,3-amines and imines have themselves been reported as ligands and catalysts. However, there are very few reports regarding the synthesis of structurally related thiadiazolines 4 or thiadiazolidine oxides 5. The majority of reports regarding thiadiazolinediones 1,1-dioxides 6 relate to their pharmacological properties, the zwitterion 7 has been used in a Mitsunobu-type reaction 8 and 8 has been employed as a chiral auxiliary in reactions which have traditionally used the Oppolzer sultam.6 Thiadiazolidine 1,1-dioxides have also been reported as useful polar aprotic solvents 9 and as key intermediates for the synthesis of constrained peptides.8 We were particularly attracted to the thiadiazolidine oxides as we postulated that they may be interesting and useful ligands for phosphate free metal-catalysed reactions.

Figure 1. Various 1,3-dinitrogen containing compounds

To this end we were the first to report the highly active thiadiazoline 1-oxide 9 catalyst system in the Mizoroki–Heck reaction (Scheme 1).7 Excellent yields of stilbenes derived from aryl iodides and bromides have been achieved using as little as 0.00002 mol% catalyst. The ligand/palladium system can be stored as a stock solution open to air at room temperature with no observable loss of activity for a period of several months.

![Scheme 1](image)

Scheme 1. Application of the thiadiazoline 1-oxide system for the Mizoroki-Heck reaction.

The synthesis of the mesityl-derived thiadiazoline 1-oxide ligand 9 was easily achieved in two steps; mesityl amine and glyoxal were reacted neat, and upon formation of the bright yellow bis-imine, sodium borohydride/ethanol was added to furnish the bis-amine 10 in excellent yield (Scheme 2). Treatment of a solution of 10 in diethyl ether/triethylamine with thionyl chloride afforded the thiadiazolidine oxide 9 in good yield.

![Scheme 2](image)

Scheme 2. Synthesis of the thiadiazoline 1-oxide 9

Our strategy for the development of highly enantioselective catalysis revolves around the fact that if the substituents attached at the nitrogen atoms of a thiadiazolidine 1-oxide system are non-equivalent then the sulfur atom will be chiral. This means that the controlling chiral element for...
asymmetric catalysis will be directly attached to the metal atom and hence will be closer to the site of the reaction. This should then impart high levels of enantiomeric excess. The corresponding phosphine systems have been shown to impart high levels of enantiomeric excess, prominent examples of chiral phosphorus ligand systems are the C₂-symmetric non-functionalized bisphospholane ligands DuPHOS, and BPE and the o xo-functionalized bisphospholanes RoPHOS and BASPHOS, as well as several monophospholanes being part of mono- or bidentate ligands. However, the discovery of new, efficient P-chiral bisphosphanes has been slow, partly because of the difficulties in ligand synthesis, and their synthetic routes are characterized by several disadvantages, e.g. poor air stability, low variability, limited tolerance of functional groups and serious problems during up scaling due to extreme or hazardous reaction conditions. Hence, we believe our systems will add significant value to this highly topical area.

To the best of our knowledge, the synthesis and application of the enantiomerically pure C₂ symmetric benzothiadiazolone 1-oxide, and the thiadiazol-3-one 1-oxide and thatatriazole 1-oxide systems chiral at sulfur have not been reported. This communication details our efforts to synthesize the first such examples.

2.0 Results and Discussion

For simplicity we initially chose to prepare a C₂ symmetric ligand. Diver has reported the use of C₂ symmetric carbenes based on a benzimidazole structure, and this prompts us to describe our own results in this area. Such a design of ligand is attractive because both of the enantiomers are, in principle, available, and because the ligands can be readily accessed through a short synthetic sequence; for example, the 1,2-bis-α-methylbenzylaniline 11 was easily prepared as shown in Scheme 3. The use of two sequential Buchwald-Hartwig couplings nevertheless proved frustrating as the second reaction consistently gave a lower yield than expected: reaction of the amine with 1,2-dibromobenzene gave the monosubstituted product in an excellent 87% yield, but attempts to introduce the second amine gave the desired product in no more than a respectable 60% yield in our hands.

Treatment of 1,2-bis-α-methylbenzylaniline 11 with thiouyl chloride in diethyl ether/triethylamine afforded the C₂ symmetric benzothiadiazole 2-oxido 12 in a disappointing 30% yield (Scheme 4).

We have also attempted the synthesis of a related C₂ symmetric system outlined in Scheme 5. Unfortunately cyclization to incorporate the SO moiety proved unsuccessful perhaps due to the steric crowding of the two nitrogen atoms.

Thiadiazole-indene 3-oxide 13 was synthesized using the following protocol (Scheme 6): coupling of ethyl chloroacetate and phenylglycinol under basic conditions afforded the amide 14 in 61% yield. The amide moiety was then converted to the imino ether 15 using trimethylxonium tetrafluoroborate. Addition of
phenylhydrazine hydrochloride afforded the a bis-amine precursor 16 which was suitable for treatment with thionyl chloride under the standard conditions to afford the intended target molecule 13 as a single diastereoisomer (as determined by $^1$H and $^{13}$C NMR spectroscopy) in 71% yield. Compound 13 was found to be crystalline and the X-ray crystal structure$^{18}$ is shown in Figure 2. It is interesting to note that the oxygen at sulfur is on the opposite face to that of the phenyl group in the morpholine ring system.

We next turned our attention to preparing a thiadiazol-3-one 1-oxide and this was achieved initially by the esterification of phenylalanine 17, followed by conversion of the ester moiety to the secondary amide 18 using methyleneamine. The primary amine was then protected with a p-methoxybenzyl group and subsequent treatment of the bis-amine 19 with thionyl chloride resulted in the final product 20 in four simple steps (Scheme 6). Unfortunately compound 20 was an oil and we have as yet been unsuccessful in determining the absolute stereochemistry at sulfur. By $^1$H and $^{13}$C NMR spectroscopy compound 20 appears to be a single diastereoisomer.

![Scheme 7. Synthesis of the thiadiazol-3-one 1-oxide 20.$^{11}$](image)

### 3.0 Conclusion

We have successfully synthesized the first example of an enantiomerically pure C$_2$ symmetric benzothiadiazole 2-oxide. We have also prepared the first thiatriaza-indene 3-oxide and thiadiazol-3-one 1-oxide systems chiral at the sulfur atom in high diastereoselectivity. We shall now endeavor to apply these and related systems in asymmetric catalysis.

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### References


11. All novel compounds were characterized by melting point, optical rotation, infra red, combustion analysis, $^1$H and $^{13}$C NMR spectroscopy, mass spectrometry, and accurate mass analysis.

18 Crystal data for enantiopure 13: C16H15N3O2S, M = 313.37, monoclinic, P2₁, a = 7.3744(4), b = 8.8835(5), c = 12.0593(7) Å, β = 105.7428(8)°, V = 760.38(7) Å³, Z = 2, D₀ = 1.369 g cm⁻³, μ(Mo-Kα) = 0.223 mm⁻¹, T = 150(2) K, colourless plate, 1.05×0.61×0.06 mm³; 8881 reflections measured as above; 4509 independent, data corrected as above (min. and max. transmission factors: 0.800, 0.987), R₁ = 0.0168, structure solved by direct methods, F² refinement, R₁ = 0.0323 for 4266 data with F² > 2σ(F²), wR₂ = 0.0826 for all data; 199 parameters; absolute structure parameter x = −0.01(5). CCDC 783758 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.