



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 C_2 symmetric benzothiadiazole 2-oxide is described along with the first synthesis of an 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, that is, the reaction of the prerequisite bis-amines with thionyl chloride at ambient temperature.

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1. Introduction

There are a wide number of reports utilizing a 1,3-dinitrogen skeleton as the basis for catalyst/ligand design; for example, N-heterocyclic carbenes **1**,¹ phosphoramides **2**,² and thioureas **3** (Fig. 1).³ 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 thiadiazolidines **4** or thiadiazolidine oxides **5**. The majority of reports regarding thiadiazolidine-1,1-dioxides **6** relate to their pharmacological properties;⁴ the zwitterion **7** has been used in a Mitsunobu-type reaction⁵ 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 solvents⁷ 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 phosphine-free metal-catalyzed reactions.

To this end we were the first to report the highly active thiadiazolidine 1-oxide **9** catalyst system in the Mizoroki–Heck reaction (Scheme 1).⁹ 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.

The synthesis of the mesityl-derived thiadiazolidine 1-oxide ligand **9** was easily achieved in two steps; mesityl amine and glyoxal were reacted neat, and upon the 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 diethylether/triethylamine with thionyl chloride afforded the thiadiazolidine oxide **9** in good yield.

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 C_2 -symmetric non-functionalized bisphospholane ligands DuPHOS, and BPE and the oxyfunctionalized 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, for example, poor air stability, low variability, limited tolerance of the functional groups, and serious problems during the up-scaling due to extreme or hazardous reaction conditions. Hence, we believe that 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 C_2 symmetric benzothiadiazoline 1-oxide and the thiadiazol-3-one 1-oxide and thiatriazoline 1-oxide systems chiral at sulfur have not been reported. Herein we report our efforts to synthesize the first such examples.

2. Results and discussion

For the sake of simplicity, we initially chose to prepare a C_2 symmetric ligand. Diver has reported the use of C_2 symmetric carbenes based on a benzimidazole structure,¹⁰ and this prompts us to

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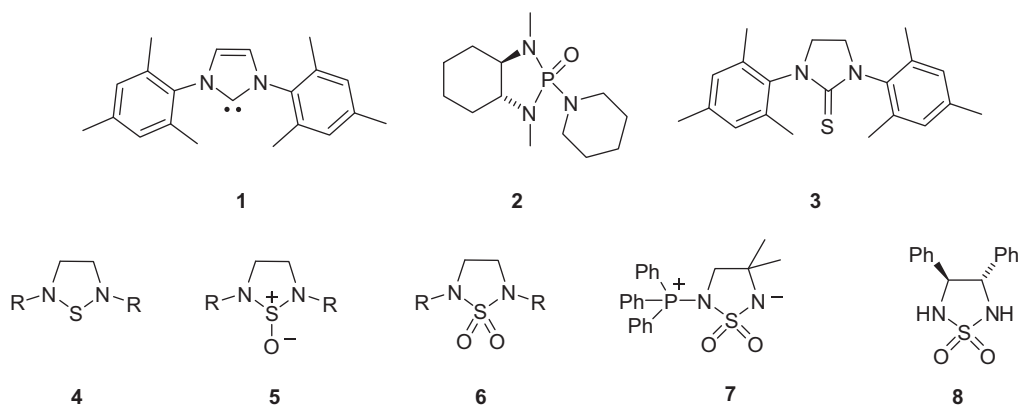
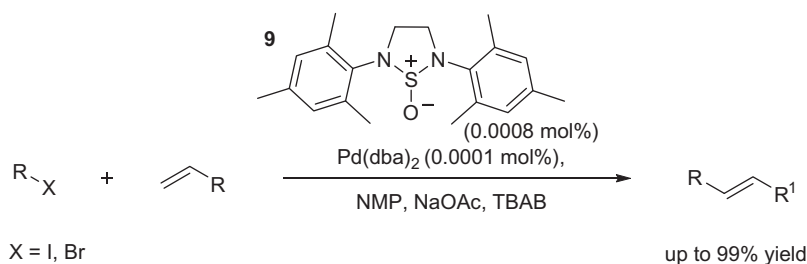
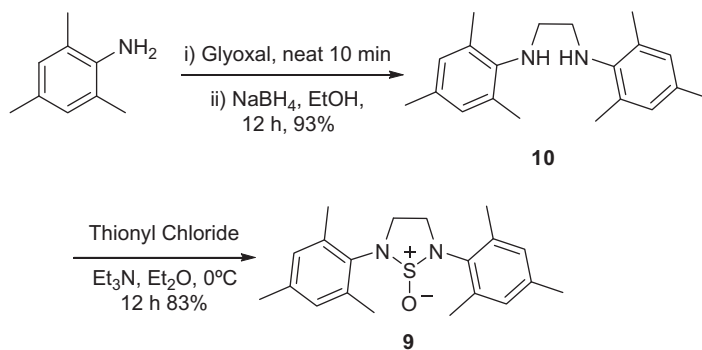


Figure 1. Various 1,3-dinitrogen containing compounds.



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



Scheme 2. Synthesis of the thiadiazolidine 1-oxide **9**.

describe our own results in this area. Such a design of the ligand is attractive because both 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 -methylbenzylamine **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.

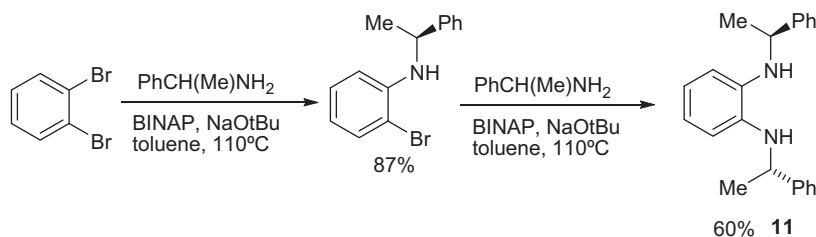
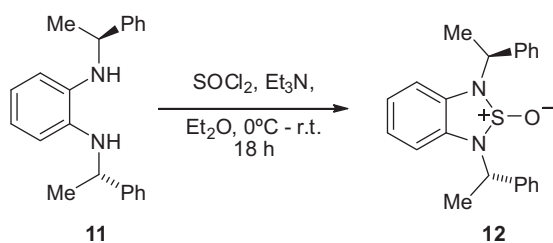
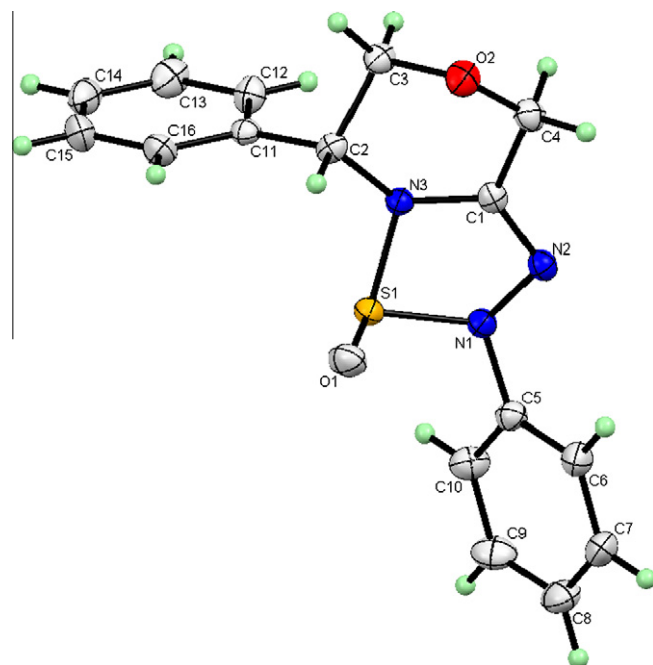
Treatment of 1,2-bis- α -methylbenzylamine **11** with thionyl chloride in diethylether/triethylamine afforded the C_2 symmetric benzothiadiazole 2-oxide **12** in a disappointing 30% yield (Scheme 4).

We also attempted the synthesis of a related C_2 symmetric system outlined in Scheme 5.¹² Unfortunately cyclization to incorpo-

rate the SO moiety proved unsuccessful perhaps due to the steric crowding of the two nitrogen atoms.

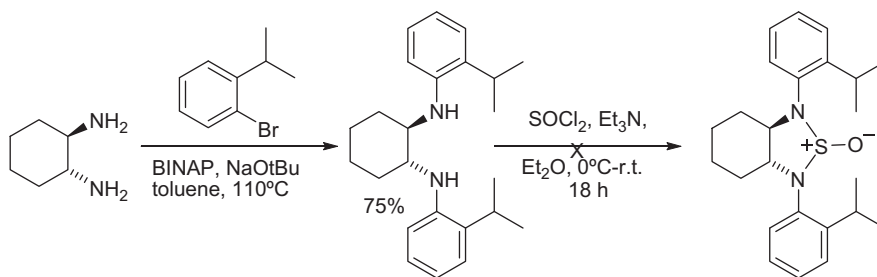
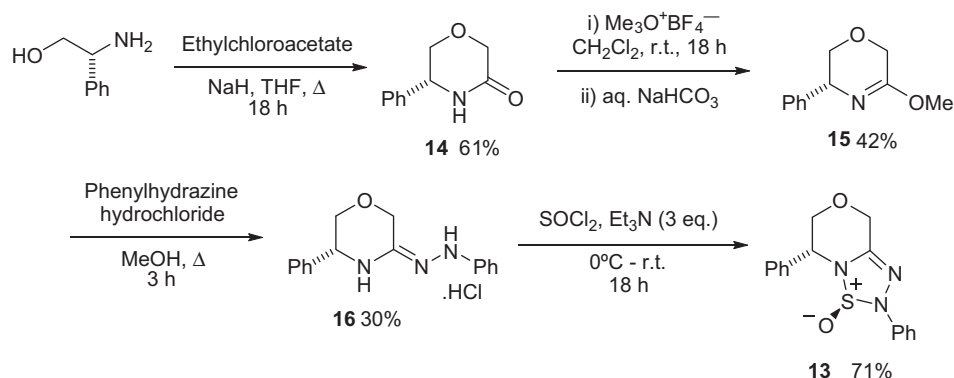
In order to develop the synthesis of a system chiral at sulfur we chose to prepare a thiatiazoline 1-oxide as the synthesis of enantiomerically pure unsymmetrical 1,3-diamines has been reported to be non-trivial.¹³ Leeper,¹⁴ Enders,¹⁵ Rovis,¹⁶ and others¹⁷ have shown that the NHC triazolium systems are capable of delivering high enantioselectivities in a variety of transformations, hence we chose a similar route to prepare the thiatriaza-indene 3-oxide **13**.

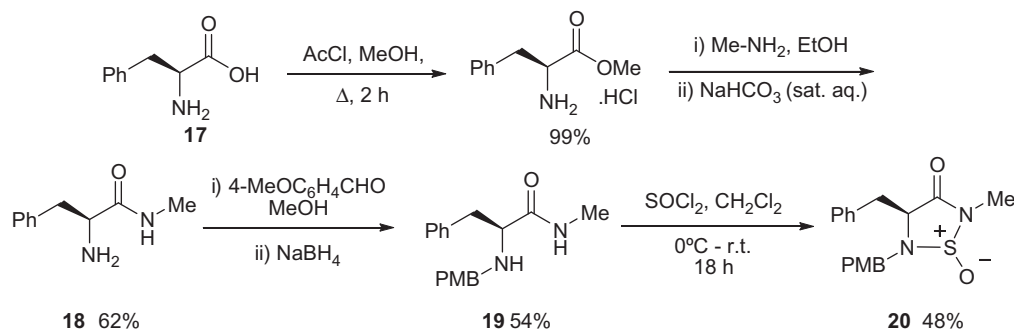
Thiatriaza-indene 3-oxide **13** was synthesized using the following protocol (Scheme 6): coupling of ethylchloroacetate and phenylglycinol under basic conditions afforded amide **14** in 61% yield. The amide moiety was then converted to the imino ether **15** using trimethyloxonium tetrafluoroborate. The addition of phenylhydrazine hydrochloride afforded bis-amine precursor **16**, which was suitable for treatment with thionyl chloride under the

Scheme 3. Synthesis of the 1,2-bis- α -methylbenzylaniline **11**.¹¹Scheme 4. Synthesis of the benzothiadiazole 2-oxide **12**.¹¹Figure 2. X-ray crystal structure of **13**.

standard conditions to afford the intended target molecule **13** as a single diastereoisomer (as determined by ^1H and ^{13}C NMR spectroscopy) in 71% yield. Compound **13** was found to be crystalline and the X-ray crystal structure¹⁸ is shown in Figure 2. It is interesting to note that the oxygen at the 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 initially achieved by the esterification of phenylalanine **17**, followed by conversion of the ester moiety to the secondary amide **18** using methylamine. 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 7). Unfortunately,

Scheme 5. Attempted synthesis of a cyclohexyldiamine derivative.¹¹Scheme 6. Synthesis of the thiatriaza-indene 3-oxide **13**.¹¹

Scheme 7. Synthesis of the thiadiazol-3-one 1-oxide **20**.¹¹

compound **20** was an oil and we have as yet been unsuccessful in determining the absolute stereochemistry at the sulfur. By ¹H and ¹³C NMR spectroscopy, compound **20** appears to be a single diastereoisomer.

3. Conclusion

We have successfully synthesized the first example of an enantiomerically pure C₂ 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 the related systems in asymmetric catalysis.

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