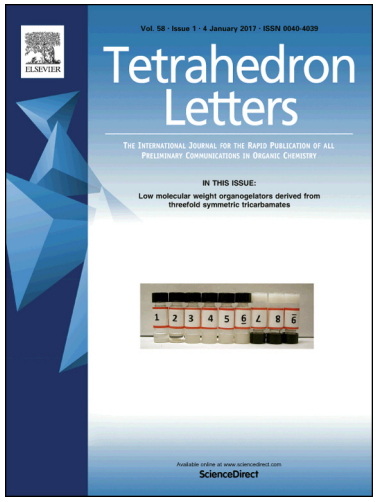


# Diastereoselective synthesis of *N*-sulfinyl α-aminophosphine sulfides and phosphines

Wei Zhang, Scott R. Gilbertson

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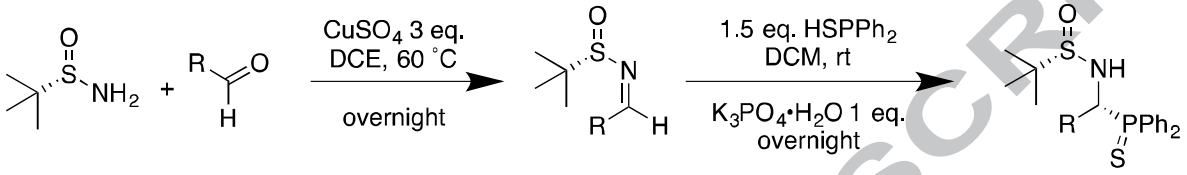

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# Diastereoselective synthesis of *N*-sulfinyl α-aminophosphine sulfides and phosphines

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ABSTRACT

The diastereoselective synthesis of *N*-sulfinyl α-aminophosphine sulfides and phosphines is reported. These molecules are synthesized by formation of sulfinyl imine followed by diastereoselective addition of a diphenylphosphine sulfide. The product *N*-sulfinyl α-aminophosphine sulfides can be converted to phosphines through removal of the sulfur by reaction with Raney nickel. Hydrolysis of the sulfinyl group provides an amine that can then be attached to other ligands or structural scaffolds.



Phosphines have been used in catalysis as ligands on transition metals for many years. In cases of asymmetric catalysis they have been used as monovalent and bivalant ligands on their own or with other metal ligands, such as oxazolines, alkenes and ether oxygens.[1-3] With very few exceptions, the chirality of the transition metal complex is present in the phosphine's partner or the tether connecting the two ligands. Recently, the sulfinyl group has been used in asymmetric catalysis as a bivalent ligand on its own, or in combination with other groups including phosphines or olefins (Figure 1).[4-12] The use of a sulfinyl group provides a chiral atom directly attached to the catalytic metal and maybe an excellent complement to the more traditional phosphine partners. In addition to transition metal catalysis, there have been reports where *N*-sulfinyl α-aminophosphines, related to α-aminophosphonates, have been used as nucleophilic catalysts in reactions such as the cross Rauhut-Currier reaction.[13] Sulfinamide phosphinates have also been used in organo-catalytic reduction of imines.[14] To date there have not been any reports of phosphine based *N*-sulfinyl α-aminophosphine sulfides and phosphines being used as ligands for transition metals in reactions catalyzed by the metal.

The stereoselective synthesis of various phosphine ligands has been an ongoing program for us. We have recently begun to explore the role of phosphines, phosphine oxides and phosphine sulfides as transition metal ligands.[15] *N*-sulfinyl α-aminophosphines have not been extensively studied and may offer ready access to a series of metal complexes useful in catalysis. This paper reports a route to the synthesis of a series of phosphine based *N*-sulfinyl α-aminophosphine sulfides, oxides and phosphines (Figure 2).

Since both enantiomers of the *tert*-butyl amino sulfinyl group are inexpensive and commercially available, a logical approach to the desired chiral *N*-sulfinyl α-aminophosphine derivatives was to synthesize the sulfinyl imine and then add a phosphide anion, or the equivalent, to the imine using the sulfur chirality to direct the addition. Such an approach has been used in the synthesis of amino phosphates, which are then used as amino acid mimics.[16]

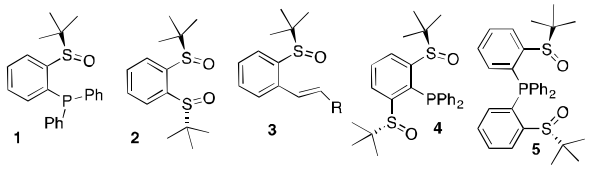

**Figure 1. Sulfinyl based ligands bidentate ligands**

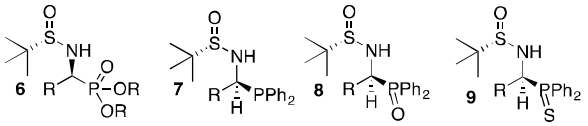

**Figure 2. N-sulfinyl aminophosphine based ligands**

Reaction of the sulfinyl amine to form the necessary imines is performed by the copper catalyzed addition of commercially available optically active 2-methyl-2-propanesulfinamide to a variety of aldehydes (Table 1).[17-18] Both aromatic and aliphatic aldehydes participate in the reaction at 60 ˚C in generally good yields (**12**-**24**).

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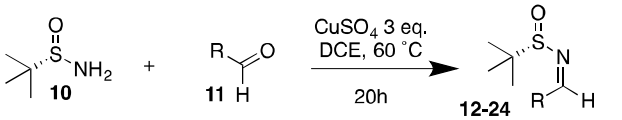
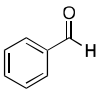
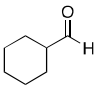
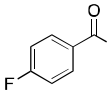
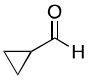
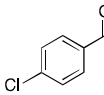
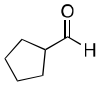
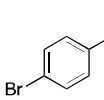
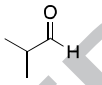
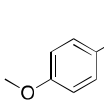
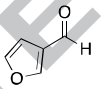
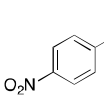
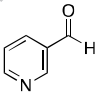
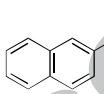
The isolated N-*tert*-butanesulfinyl imines were then reacted with diphenylphosphine sulfide in the presence of potassium phosphate at room temperature. In most cases the products were obtained in greater than 95:5 diastereomeric ratio. The stereochemistry was established by x-ray crystal structure of **27**. The stereochemistry of the other products from the reaction were assigned by correlation to the x-ray structure. In the case of the major product, the coupling constant between the NH and the H on the carbon bearing phosphorus is smaller (approx. 2.5 -3.0 Hz) than in the minor product (approx. 10-11 Hz). The reaction proceeded with both aliphatic and aromatic sulfinyl imines. The reaction tolerates a variety of different substitutions on the aromatic ring with only electron withdrawing groups in the para position reducing the selectivity (**26, 27** and **29**). In all cases the diastereomers are easily separated by silica gel chromatography.

**Table 1. Synthesis of tert-butylsulfinyl imines.**




| Cpd | Aldehyde | Yield | Cpd | Aldehyde | Yield |
|---|---|---|---|---|---|
| **12** |  | 81% | **19** |  | 99% |
| **13** |  | 81% | **20** |  | 99% |
| **14** |  | 83% | **21** |  | 56% |
| **15** |  | 69% | **22** |  | 93% |
| **16** |  | 92% | **23** |  | 82% |
| **17** |  | 96% | **24** |  | 80% |
| **18** |  | 91% | | | |

A number of transformations have been performed on the *N*-sulfinyl α-aminophosphine sulfides. The *N*-sulfinyl group can be hydrolyzed to the amine by reaction with HCl (**38**, **40**). The free amine can then be converted to a carbamoyl group by reaction with Boc anhydride in the presence of triethylamine (**41**). Reaction with acetyl chloride provides the N-acetyl protected phosphine sulfide. The phosphine sulfide can be converted to the free phosphine by reaction with Raney nickel (**44**, **45**). We have a long-standing program of using amino acid building blocks as potential chiral templates for asymmetric catalysts. With the correct ligand building blocks they allow for the ready construction of chiral ligands by amide coupling reactions. With this use in mind, it was demonstrated that the free amine after removal of the sulfinyl group could be coupled to amino acids (**47**).

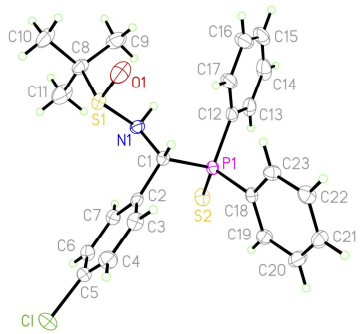
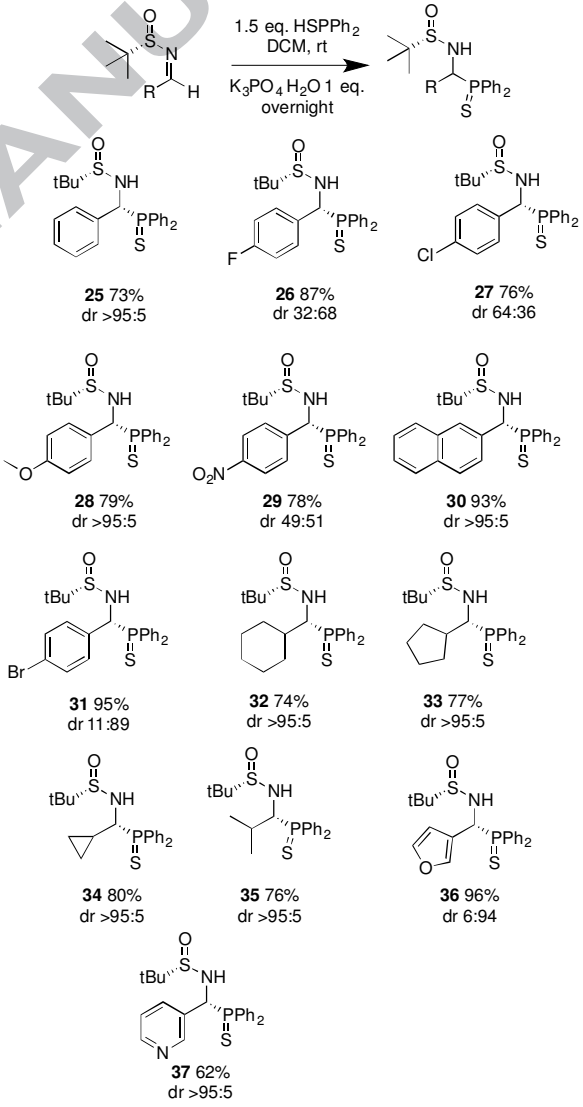
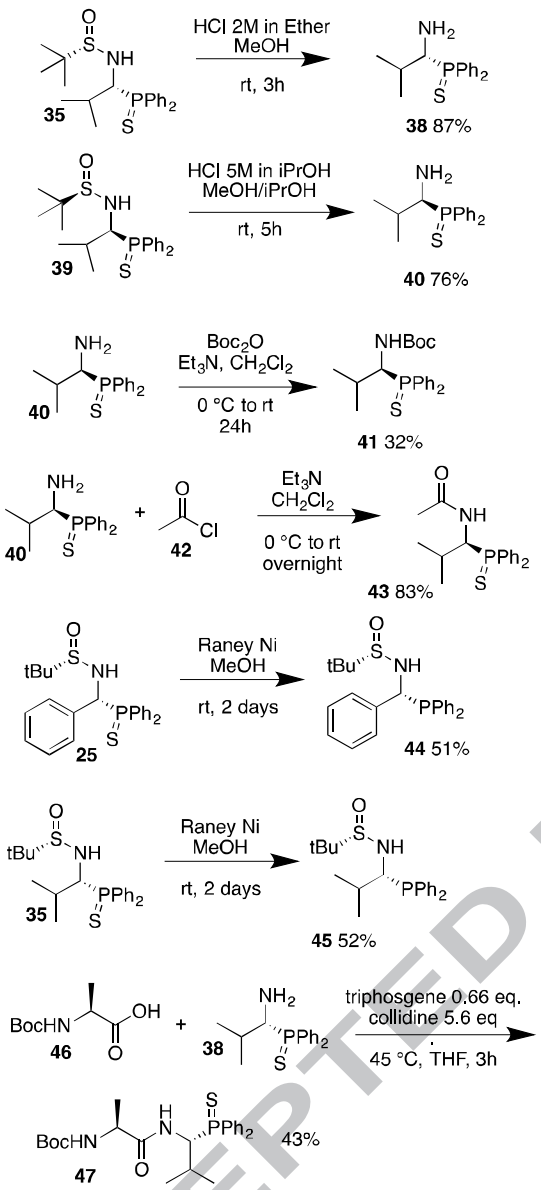



**Figure 3. X-ray structure of 27 major diastereomer**

**Scheme 1. Phosphine sulfide addition**



**Scheme 2. Modification of the *N*-sulfinyl α-aminophosphine sulfides products**




The approach presented here provides a route to molecules possessing a number of potential applications. We are currently investigating the use of *N*-sulfinyl α-aminophosphines and phosphine sulfides as ligands for transition metals. These types of molecules have potential as nucleophilic catalysts. After removal of sulfur these types of these molecules can be used to incorporate phosphine groups into any number of structures by amide formation.

**Acknowledgments**

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**Supplementary Material**

Supplementary material associated with this article can be found in the online version, at

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**Highlights**

Simple approach to N-sulfinyl α-aminophosphine sulfides and phosphines.

Access to chiral ligands from readily available starting materials,

A number of potential uses;

Transition metal ligands

Nucleolophilic catalysts

Amino acid surrogates.