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Novel chiral sulfinamide phosphines: valuable precursors to chiral β-aminophosphines

Peng Chen [a], Xiao Su [a], Wei Zhou [a], Yuanjing Xiao [a,*], Junliang Zhang [a,b,*]

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, 200062, PR China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS. 345 Lingling Road, Shanghai, 200032, PR China

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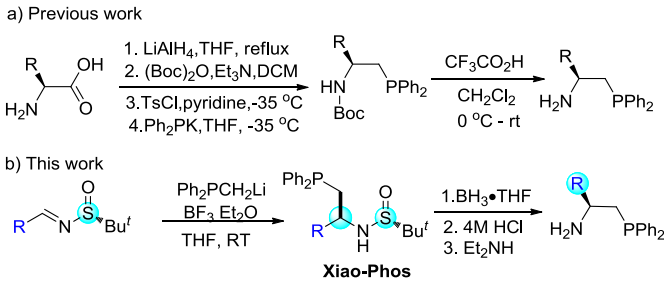
ABSTRACT

Starting from commercially available aldehyde and chiral *tert*-butanesulfinamide, a series of chiral sulfinamide phosphines (**Xiao-Phos**) were synthesized via a two-step condensation-nucleophilic addition procedure. In most cases, nucleophilic addition of the *N*-*tert*-butanesulfinyl imine with diphenyl methyl phosphonic lithium showed high diastereoselectivity (d.r>20:1) with BF_3 as additives. Following removal of the chiral auxilliary, an important class of ligands i.e chiral β-aminophosphines and its derivatives were obtained in high yields using this approach.

1. Introduction

In the past two decades, the asymmetric nucleophilic catalysis has been developed into one of the most powerful and efficient tool for the preparation of chiral organic molecules. Compared with similarly substituted amine catalysts, phosphines displayed unique catalytic activities because of their weaker basicity and stronger nucleophilicity.[1] Phosphine-promoted catalytic processes, particularly asymmetric reactions that are catalyzed by chiral phosphines have emerged as a powerful approach to structurally diverse and synthetically valuable optically active organic building blocks,[2] which has attracted enormous attention in recent years.

The development of novel chiral phosphine catalysts is one of the most attractive and practical aspects in organocatalysis. Very recently, our group has developed a new type of chiral sulfinamide monophosphine ligands (**Ming-Phos**), which performed well in the enantioselective gold-catalyzed cycloaddition reaction of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones. Both enantiomers of the products could be obtained in good yields and with excellent diastereo- and enantioselectivity by the use of gold complexes derived from two diastereomers of Ming-Phos. The Ming-Phos ligands could be easily prepared in good yields from inexpensive, commercially available chiral *tert*-butylsulfinamide via a two-step condensation-nucleophilic addition procedure.[3] It was well known that chiral β-aminophosphines represent one of the most attractive chiral phosphines, which have been widely utilized as nucleophilic catalysts[4] or chiral ligands[5] in a broad spectrum of useful organic transformations. However, only a few methods for the efficient synthesis of β-aminophosphines have been developed and the one from natural amino acids is the most commonly used one method (Scheme 1a).[6] Very recently, we designed a novel type of chiral β-sulfinamide phosphines, structured as **Xiao-Phos**, which could be obtained by using commercially available aldehyde and diphenyl methyl phosphonic lithium.[7] We envisaged that an important class of ligands i.e. chiral β-aminophosphines could be



Scheme 1. Synthesis of chiral β-aminophosphines.

* Corresponding authors. Tel.: +86 21 62233213; e-mail addresses: yjxiao@chem.ecnu.edu.cn (Y. Xiao), jlzhang@chem.ecnu.edu.cn (J. Zhang).

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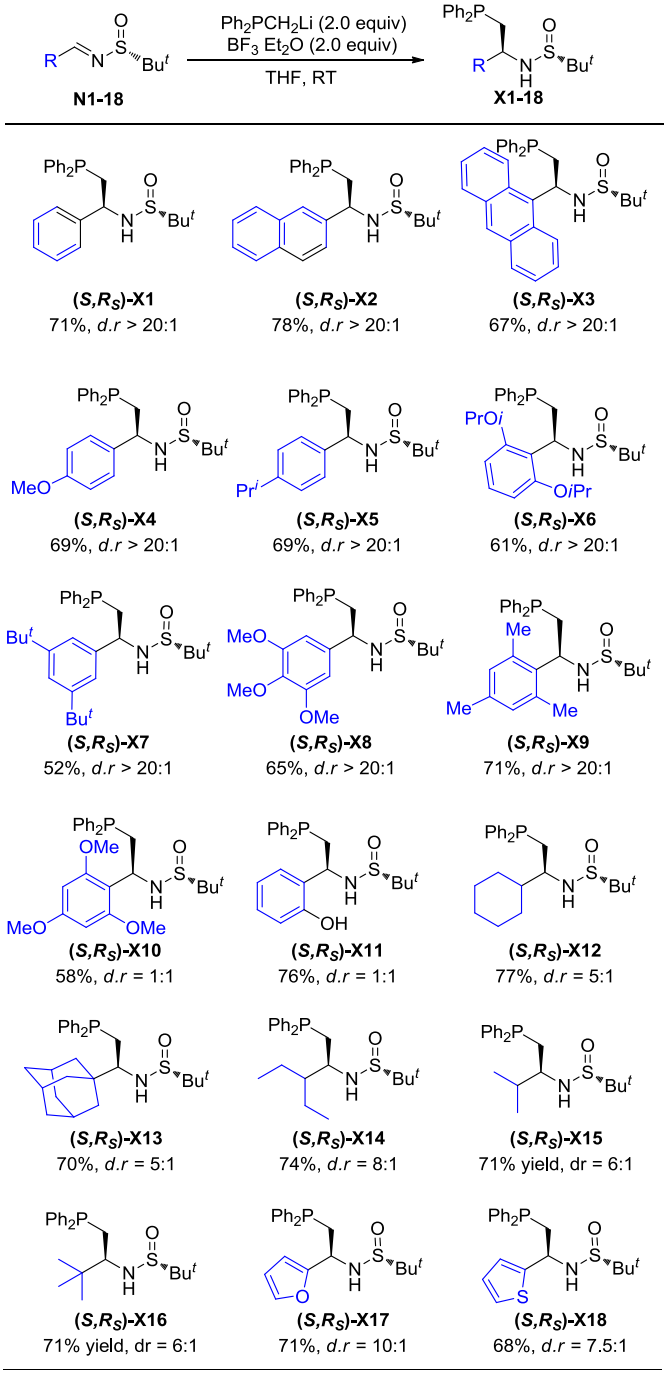
obtained via the removal of the chiral auxilliary (Scheme 1b). Herein, we report our efforts for the synthesis of Xiao-Phos and the success of removal of the ^{t}BuSO auxilliary group.

2. Results and discussion

Our initial attempts for the preparation of Xiao-Phos started from readily available benzaldehyde and chiral *tert*-butanesulfinamide (Scheme 2). The corresponding imine **N1** was obtained in excellent yield when the reaction was performed at 60 °C in the presence of titanium tetraisopropanolate as Lewis acid.[8] Treatment of Ph_2PMe with *n*-BuLi in the presence of TMEDA at room temperature would produce a solution of Ph_2PCH_2Li in THF according to reported procedure,[9] which would undergo nucleophilic addition to chiral (R_S)-sulfinimine **N1** at −78 °C, furnishing the desired product **X1** in 71% yield with 5:1 dr (Table 1, entry 1). The absolute configurations of **(*S, R*$_S$)-X1** was established by single-crystal X-ray diffraction analysis.[10] Solvent screening was subsequently performed and THF was found to be the best solvent. Other solvents such as Et_2O, toluene, DME and dioxane didn't bring significant improvement in diastereoselectivity. When the reaction was carried out at room temperature, the corresponding product could be obtained in 70% yields with 10:1 dr (Table 1 entry 6). Notably, the addition of $BF_3\cdot Et_2O$ (2.0 equiv) to the reaction system could remarkably improve the diastereoselectivity to >20:1 dr (Table 1 entry 7).

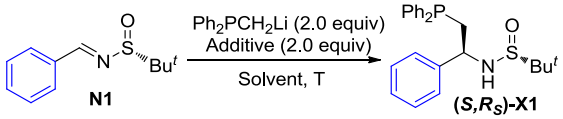


Scheme 2. Synthesis of chiral β-sulfinamide phosphines **X1**–**X18**.

Having established the optimal reaction conditions for the synthesis of chiral sulfinamide phosphines **(*S, R*$_S$)-X1**, we next focused on the substrate scope of this transformation. Chiral sulfinyl imines **N2**–**N18** were easily prepared by the condensation of *tert*-butanesulfinamide with the corresponding aldehydes according to the reported procedure. With these imines in hand, the scope of nucleophilic addition of Ph_2PCH_2Li to these substrates was subsequently investigated under identified reaction conditions and the results are outlined in Scheme 2. As demonstrated in Scheme 2, the nucleophilic addition of Ph_2PCH_2Li with chiral sulfinyl imines **N1**–**N18** is pretty general and practically useful method for the preparation of a range of functionalized chiral sulfonamide phosphine **X1**–**X18**. Chiral sulfinyl imines derived from aromatic aldehydes with various substituents at different position of phenyl ring generally exhibited high diastereoselectivities (d.r>20) with moderate isolated yields (***S, Rs*)-X1**–**X9** except the sulfinyl imines **N10**–**N11**, which give the corresponding **X10**–**X11** with a 1: 1 ratio of two diastereoisomers. The additions to chiral sulfinyl imines derived from aliphatic aldehydes as well as heteroaromatic aldehyde such as furan-2-carbaldehyde and thiophene-2-carbaldehyde showed acceptable diastereoselectivities (d.r=5: 1–10:1), delivered the corresponding (***S, Rs*)-X12**–**X18** in good yields, albeit that in some cases two diastereomers are not easily separated by the flash column chromatography.

Synthetic applications of our novel designed chiral β-sulfinamide phosphines (**Xiao-Phos**) for synthesis of various types of chiral β-aminophosphines and its derivatives have been showcased by the selective transformations of the representative Xiao-Phoses **X1**, **X14**, **X15** and **X16** (Scheme 3). The attempts to direct removal of the ^{t}BuSO auxilliary group under acid conditions (4M HCl/MeOH) failed, which led to the oxidation of the phosphine. Thus, we then decided to protect the phosphine with the use of borane in THF. The structure of BH_3-protected intermediate was confirmed after isolating representative **(*S, R*$_S$)-X1-BH$_3$** through column chromatography on silica gel (hexane/ethyl acetate=3:1, quantitative yield). H

Table 1
Solvent and additive effect on the yield and diastereomeric ratios



Entry[a]	T (°C)	Additive (2.0 equiv)	Solvent	Yield[b]	d.r.[c]
1	−78	—	THF	71%	5:1
2	−78	—	Et_2O	65%	5:1
3	−78	—	Toluene	67%	4.2:1
4	−78	—	DME	46%	4.4:1
5	−78	—	Dioxane	58%	3:1
6	RT	—	THF	72%	10:1
7	RT	$BF_3\cdot Et_2O$	THF	71%	20:1

[a] The reaction was conducted using **N1**(1.5 mmol), Ph_2PCH_2Li(3.0 mmol).
[b] Isolated yield.
[c] The d.r was determined by the ^{1}H NMR analysis.