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Article (Special Issue on Catalysis in Organic Synthesis)

Highly enantio- and diastereoselective reductive aldol reactions catalyzed by chiral spiro bisphosphine oxides



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ARTICLE INFO

Article history:

Received 4 September 2014

Accepted 26 September 2014

Published 20 January 2015

Keywords:

Aldehyde

Asymmetric catalysis

Enone

Lewis base

Reductive aldol reaction

Spiro bisphosphine oxide

ABSTRACT

A spiro bisphosphine oxide (**SpinPO**) was found to be an efficient chiral Lewis base catalyst in asymmetric reductive aldol reaction of enones and aldehydes in the presence of trichlorosilane as the reductant, affording a variety of β -hydroxyketones in good yields with moderate to high levels of diastereo- and enantioselectivities.

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1. Introduction

The reductive aldol reaction between an α,β -unsaturated carbonyl compound and an aldehyde or ketone is a powerful method for stereocontrolled C–C bond formation [1]. These tandem reactions generally proceed via conjugate reduction of an enone or enoate followed by aldol reaction of the in-situ generated enolate with an aldehyde or ketone electrophile. By this way, the β -hydroxy carbonyl products with several contiguous stereocenters can be directly constructed in a one-pot fashion, thus providing an attractive alternative approach for stereocontrolled synthesis of aldols. Following the seminal studies by Revis and Hilty in 1987 [2], a variety of catalysts based on Rh [3], Co [4], Cu [5,6], Ni [7], In [8,9], Sn [10], etc. [11], have been developed for inter- or intramolecular reductive aldol reactions, wherein mostly silanes or molecular hy-

drogen [12], sometimes diethylzinc [13], or trialkylborane [7] were used as the stoichiometric reductants. The first example of the asymmetric reductive aldol reaction was reported by Morken et al. in 2000 [14], and since then a number of chiral metal–ligand complexes based on Ir [15], Rh [16–21], or Cu [22–29] have also been used as the catalysts to control the stereochemistry of the reactions, delivering various chiral aldol products with synthetically useful diastereo- and enantioselectivities. A notable progress in this area was made recently by Nakajima and coworkers [30–33], who have developed highly enantio- and diastereoselective asymmetric reductive aldol reactions using chiral bisphosphine oxides as Lewis base catalysts. It is also noteworthy that over the decades, Lewis base catalysis has been established as an attractive and highly competitive alternative to the methods employing metal complexes, providing elegant solutions to numerous challenging organic

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This work was supported by the National Basic Research Program of China (2010CB833300), the National Natural Science Foundation of China (21121062, 21232009), the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality.

The supporting information of this article is available from the corresponding author.

DOI: 10.1016/S1872-2067(14)60241-2 | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 36, No. 1, January 2015

transformations in general [34], and including the Mukaiyama aldol reactions in particular [35]. In this context, we recently reported the successful development of a class of spiro[4,4]-1,6-nonadiene-based phosphino-oxazoline ligands/catalysts [36–47] and bisphosphine oxides (**SpinPO**) [48], and the use of **SpinPO** as chiral Lewis base catalysts in the direct asymmetric double-aldol reaction of ketones with aldehydes. As an ongoing effort to develop efficient Lewis base catalyzed asymmetric synthesis, herein we report a highly enantio- and diastereoselective reductive aldol reaction of enones and aldehydes with **SpinPO** as the catalyst and trichlorosilane as the reductant.

2. Experimental

2.1. General methods

Unless otherwise noted, all reactions and manipulations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques or in a glovebox. All solvents were purified and dried using standard procedures. Melting points were measured on an RY-I apparatus and uncorrected. ^1H , ^{13}C , ^{31}P , and ^{19}F NMR spectra were recorded on Varian Mercury 300 MHz or 400 MHz spectrometers. Chemical shifts (δ values) were reported in ppm downfield from internal TMS (^1H NMR), internal CDCl_3 (^{13}C NMR), external 85% H_3PO_4 (^{31}P NMR), and external $\text{CF}_3\text{CO}_2\text{H}$ (^{19}F NMR), respectively. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. The IR spectra were measured on a Bruker Tensor 27 FT-IR spectrometer. ESI-MS and HRMS (ESI) spectra were taken on a Shimadzu LCMS-2010EV and an Agilent Technologies 6224 TOF LC/MS spectrometer, respectively. HPLC analyses were performed on a JASCO 2089 liquid chromatograph. Trichlorosilane, the α,β -unsaturated ketones, and aldehydes were purchased from commercial sources and used without further purification.

2.2. Synthesis of the chiral spiro[4,4]-1,6-nonadiene-based bisphosphine oxides (**SpinPO**)

The chiral **SpinPO** (**S**)-**1a-c**, (**R**)-**1d-e**, (–)-**1f**, and (**S**)-**1g** (Fig. 1) were synthesized by following our previously reported procedures [48].

2.3. General procedure for the spiro phosphine oxides catalyzed asymmetric reductive aldol reactions

To a Schlenk tube containing a stirred solution of the enone

2 (0.25 mmol), chiral phosphine oxide (**S**)-**1c** (15.1 mg, 0.025 mmol), and the aldehyde **3** (0.30 mmol) in anhydrous THF (1.0 mL) was added dropwise trichlorosilane (0.17 mL, 0.5 mmol) at -78°C . The resultant yellowish emulsion was stirred at -78°C for 24 h, and the reaction was quenched by saturated aqueous sodium bicarbonate solution (5.0 mL). The mixture was stirred for 0.5 h at this temperature, warmed to r.t., and stirred for further 0.5 h, and the solids were removed by filtration through a pad of celite. The filtrate was extracted with ethyl acetate (20 mL \times 3), and the combined organic phases were washed sequentially with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, and filtered. After removal of the volatiles under reduced pressure, the residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (15/1–10/1) as the eluents, to give the aldol product **4** as a diastereomeric mixture. The diastereomeric ratio (dr, *syn/anti*) and the enantiomeric excess (ee) values of the optically enriched **4a–q** were determined by chiral HPLC, while the ^1H , ^{13}C , and ^{19}F NMR spectral data were recorded on the diastereomeric samples of **4a–q** obtained from the corresponding reductive aldol reactions catalyzed by racemic BINAP dioxide (BINAPO) or achiral triphenylphosphine oxide.

3. Results and discussion

3.1. **SpinPO** catalyzed asymmetric reductive aldol reaction of chalcone with benzaldehyde

3.1.1. Optimization of the reaction conditions

Nakajima et al. [30] have shown that trichlorosilane can be activated by an appropriate Lewis base to undergo conjugate reduction with an enone, and the in situ generated trichlorosilyl enolate may react with a coexisting aldehyde to give the reductive aldol product. Denmark et al. [49–52] have extensively investigated the aldol additions of trichlorosilyl enolates derived from various carbonyl compounds and demonstrated that the reactions proceeded via the catalysis of some hypervalent silicon species stabilized by a suitable Lewis base. Inspired by these pioneering studies, we initiated the study by examining the viability of **SpinPO** catalysts of asymmetric reductive aldol reaction, using substoichiometric (**S**)-**1a** in the reaction of chalcone (**2a**) and benzaldehyde (**3a**) with two equivalents of trichlorosilane as the reductant. As shown in Table 1, a large variation in reactivity and stereoselectivity was observed, depending on the temperature, solvent, and/or catalyst loading used in the reactions. For the

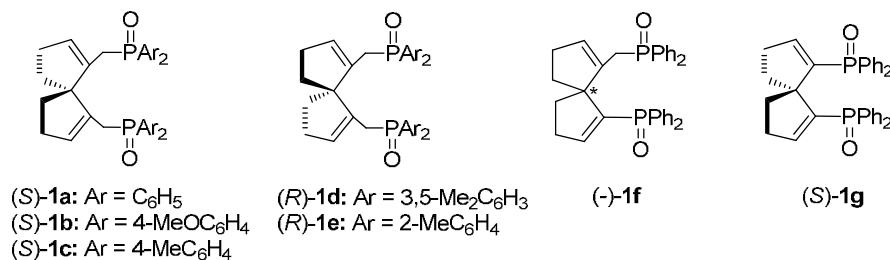


Fig. 1. Chiral spiro[4,4]-1,6-nonadiene-based bisphosphine oxides (**S**)-**1a-c**, (**R**)-**1d-e**, (–)-**1f**, and (**S**)-**1g**.

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