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

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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.

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 hydrogen [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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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. ^{1}H, ^{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 (^{1}H NMR), internal $CDCl_3$ (^{13}C NMR), external 85% H_3PO_4 (^{31}P NMR), and external CF_3CO_2H (^{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 × 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 ^{1}H, ^{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

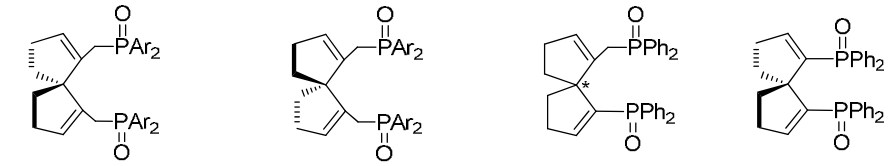
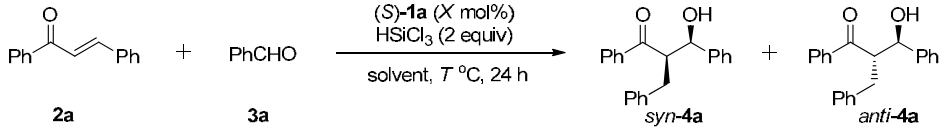


Fig. 1. Chiral spiro[4,4]-1,6-nonadiene-based bisphosphine oxides (*S*)-**1a-c**, (*R*)-**1d-e**, (–)-**1f**, and (*S*)-**1g**.

Table 1
(*S*)-**1a** catalyzed asymmetric reductive aldol reaction of chalcone (**2a**) with benzaldehyde (**3a**).



Entry	*X* (mol%)	*T* (°C)	Solvent	Yield [a] (%)	dr [b,c]	ee (*syn*) [c] (%)	ee (*anti*) [c] (%)
1	10	–78	CH_2Cl_2	48	45:55	90	0
2	10	–60	CH_2Cl_2	82	36:64	80	4
3	10	–40	CH_2Cl_2	89	50:50	76	4
4	10	–78	DCE	45	9:91	64	0
5	10	–78	$CHCl_3$	20	10:90	37	6
6	10	–78	CH_3CN	52	22:78	76	10
7	10	–78	Toluene	38	44:56	72	54
8	10	–78	THF	72	93:7	93	7
9	10	–78	Et_2O	6	82:18	89	15
10	10	–78	TBME	5	92:8	86	15
11	10	–78	DME	63	92:8	89	6
12	5	–78	THF	29	89:11	81	4
13	1	–78	THF	14	87:13	75	5

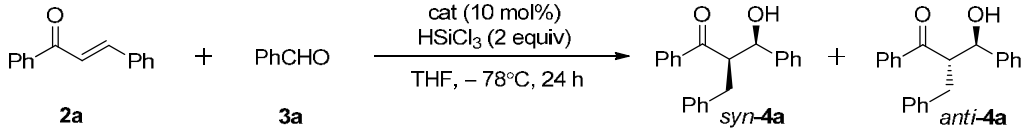
Reaction conditions: **2a** (0.25 mmol), **3a** (0.30 mmol), $HSiCl_3$ (0.50 mmol), 24 h.
[a] Yield of the isolated product **4a**. [b] dr = *syn*:*anti*. [c] Determined by chiral HPLC analyses.

reactions performed in dichloromethane in the presence of 10 mol% of (*S*)-**1a**, varying the temperatures from –78 to –40 °C raised the yield of the aldol adduct **4a**, but the diastereoselectivities (dr) were only modest (entries 1–3). Replacing dichloromethane with other types of aprotic polar or nonpolar solvents (entries 4–11) has been found to improve the dr values in most cases, but sometimes at a cost of poor conversion (entries 5, 9, and 10) or moderate ee values (entries 4 and 6). The coordinating ether THF and DME turned out to be the most favorable solvents for the reaction, affording preferentially *syn*-**4a** in good yields and high levels of diastereo- and enantioselectivities (entries 8 and 11). Further attempts to optimize the reaction by reducing the catalyst loadings of (*S*)-**1a** from 10 to 5 or 1 mol% were unsuccessful, resulting in poor yields and decreased dr and ee values (entries 12 and 13 vs 8). Thus, the optimized conditions as in entry 8 were used in subsequent catalyst survey studies.

3.1.2. Catalyst optimization

To further optimize the reaction results, the family of **SpinPO** catalysts **1a**–**g** was screened against reductive aldol reaction of chalcone (**2a**) and benzaldehyde (**3a**) using trichlorosilane as the reductant. The reactions were allowed to proceed in THF for 24 h at –78 °C in the presence of 10 mol% of **1a**–**g**, and the relevant results are summarized in Table 2. Generally moderate to high yields (41%–86%) were obtained for the β-hydroxyketone **4a**, whereas the sense and level of stereoselection fluctuated to some degree depending upon the **SpinPO** structure (entries 1–7). Both the steric effects and the skeleton flexibility in **SpinPO** structure appeared to be important for the diastereo- and enantioselectivity. While high diastereoselectivities (*syn*/*anti* ca 96/4) and excellent

Table 2
Screening of the **SpinPO 1a-g** for the catalytic asymmetric reductive aldol reaction.



Entry	Catalyst	Yield [a] (%)	dr [b,c]	ee (*syn*) [c] (%)	ee (*anti*) [c] (%)
1	(*S*)-**1a**	72	93:7	93 (*R*, *R*)	7
2	(*S*)-**1b**	78	96:4	92 (*R*, *R*)	14
3	(*S*)-**1c**	86	96:4	94 (*R*, *R*)	13
4	(*R*)-**1d**	59	82:18	81 (*S*, *S*)	4
5	(*R*)-**1e**	41	20:80	0 (*S*, *S*)	14
6	(–)-**1f**	82	97:3	68 (*S*, *S*)	6
7	(*S*)-**1g**	78	94:6	15 (*R*, *R*)	1

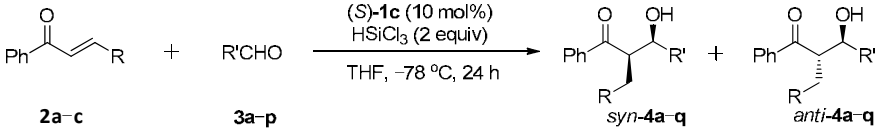
Reaction conditions: **2a** (0.25 mmol), **3a** (0.30 mmol), $HSiCl_3$ (0.50 mmol), **1** (0.025 mmol), THF (1.0 mL), –78 °C, 24 h.
[a] Yield of the isolated product **4a**. [b] dr = *syn*:*anti*. [c] Determined by chiral HPLC analyses. The absolute configurations of the *syn*-**4a** were assigned by comparison of the specific rotations with that reported in Ref. [31].

enantioselectivities (92%–94% ee) for *syn*-**4a** were reached in the cases of (*S*)-**1a–c** (entries 1–3), considerable losses in stereoselectivities were observed for the reactions catalyzed by (*R*)-**1d–e** with bulkier aryl substituents (entries 4 and 5). In contrast to flexible **1a–c** with two methylene moieties between the spiro scaffold and the Ar_2PO units, their structurally more rigid analogs **1f–g** bearing only one or no flexible methylene group led to a substantial decline in enantioselectivities (entries 6 and 7 vs 1). Among the **SpinPO** family, (*S*)-**1c** was identified as the optimal Lewis base catalyst for the reaction, affording preferentially *syn*-**4a** in high levels of diastereo- and enantioselectivities (dr 96/4, 94% ee, entry 3).

3.2. Substrate scope for the asymmetric reductive aldol reaction

The substrate adaptability of the protocol was evaluated with the reductive aldol reactions of chalcones (**2a** and **2c**) or (*E*)-1-phenylbut-2-en-1-one (**2b**) and various aromatic, aliphatic, α,β-unsaturated, and heteroaromatic aldehydes (**3a–p**) using trichlorosilane as the hydride source. The reactions were performed in THF at −78 °C for 24 h using 10 mol% of (*S*)-**1c** as the catalyst, and the representative results were presented in Table 3. The β-hydroxyketone products **4a–r** were obtained in 45%–88% yields, generally good to excellent diastereo- and enantioselectivities (dr 8/92–100/0, up to 95% ee for the *syn*-isomers). For the reactions of chalcone (**2a**) with the aromatic aldehydes **3a–j**, steric properties of the aldehyde component seem to be less significant, as aldehydes **3a–f** and **3j** afforded the corresponding aldol products **4a–f** and **4j** with comparable stereoselectivities (dr 90/10–97/3, 78%–94% ee for the major *syn*-diastereomers), regardless of the *o*-, *m*-, or *p*-locations of the electron-donating substituent on their phenyl rings (entries 1–6 and 10). On the other hand, the electronic nature of the aldehydes appears to play a major role in determining the stereoselectivities. Compared to their electron-rich homologues, aldehydes **3g** and **3i** bearing strongly electron-withdrawing *p*-nitro or *p*-trifluomethyl groups, respectively, gave the products **4g** and **4i** in drastically reduced stereoselectivities (*syn*/*anti* 46/54 and 53/47, 15%, and 44% ee for the *syn*- and racemic for *anti*-isomers, respectively) (entries 7 and 9), probably as a result of less favorable interaction with the hypervalent silicon species. The reaction of **2a** and **3h** is an exception, therein a high level of diastereo- and enantioselectivity was attained (dr 95/5, 94% ee for *syn*-**4h**) despite the presence of electron-withdrawing F atom on the aldehyde reactant (entry 8). Aldehydes **3k–m** containing heteroaromatic or naphthyl groups also reacted smoothly with **2a** (entries 11–13), to deliver β-hydroxyketone products **4k–m**

Table 3
(*S*)-**1c** catalyzed asymmetric reductive aldol reaction of enones (**2a–b**) with aldehydes (**3a–o**).



4a: R = Ph, R' = Ph
4b: R = Ph, R' = 2-MeC_6H_4
4c: R = Ph, R' = 3-MeC_6H_4
4d: R = Ph, R' = 4-MeC_6H_4
4e: R = Ph, R' = 4-$MeOC_6H_4$
4f: R = Ph, R' = 4-BrC_6H_4
4g: R = Ph, R' = 4-$O_2NC_6H_4$
4h: R = Ph, R' = 4-FC_6H_4
4i: R = Ph, R' = 4-$CF_3C_6H_4$
4j: R = Ph, R' = 2-$MeOC_6H_4$
4k: R = Ph, R' = 2-thienyl
4l: R = Ph, R' = 2-naphthyl
4m: R = Ph, R' = 2-furyl
4n: R = Ph, R' = (*E*)-PhCH=CMe
4o: R = Ph, R' = (*E*)-PhCH=CH
4p: R = Ph, R' = cyclopropyl
4q: R = Me, R' = Ph
4r: R = 4-MeC_6H_4, R' = Ph

Entry	Enone	R	Aldehyde	R'	Product	Yield[a] (%)	dr[b,c]	ee (*syn*)[c] (%)	ee (*anti*)[c] (%)
1	**2a**	Ph	**3a**	Ph	(*R,R*)-**4a**	86	96:4	94	13
2	**2a**	Ph	**3b**	2-$CH_3C_6H_4$	(–)-**4b**	78	95:5	92	1
3	**2a**	Ph	**3c**	3-$CH_3C_6H_4$	(–)-**4c**	81	92:8	94	7
4	**2a**	Ph	**3d**	4-$CH_3C_6H_4$	(–)-**4d**	75	97:3	94	0
5	**2a**	Ph	**3e**	4-$MeOC_6H_4$	(*R,R*)-**4e**	85	97:3	86	4
6	**2a**	Ph	**3f**	4-BrC_6H_4	(*R,R*)-**4f**	78	95:5	78	3
7	**2a**	Ph	**3g**	4-$O_2NC_6H_4$	(+)-**4g**	83	46:54	15	0
8	**2a**	Ph	**3h**	4-FC_6H_4	(–)-**4h**	86	95:5	94	0
9	**2a**	Ph	**3i**	4-$CF_3C_6H_4$	(–)-**4i**	87	53:47	44	0
10	**2a**	Ph	**3j**	2-$MeOC_6H_4$	(–)-**4j**	75	90:10	93	6
11	**2a**	Ph	**3k**	2-Thienyl	(–)-**4k**	86	98:2	88	18
12	**2a**	Ph	**3l**	2-Naphthyl	(+)-**4l**	73	92:8	93	5
13	**2a**	Ph	**3m**	2-Furyl	(*R,R*)-**4m**	80	99:1	84	1
14	**2a**	Ph	**3n**	(*E*)-PhCH=CMe	(–)-**4n**	45	8:92	1	54
15	**2a**	Ph	**3o**	(*E*)-PhCH=CH	(+)-**4o**	88	96:4	94	0
16	**2a**	Ph	**3p**	Cyclopropyl	(–)-**4p**	76	100:0	23	—
17	**2b**	Me	**3a**	Ph	(+)-**4q**	75	87:13	95	5
18	**2c**	*p*-tolyl	**3a**	Ph	(+)-**4r**	87	94:6	88	11

Reaction conditions: **2** (0.25 mmol), **3** (0.30 mmol), $HSiCl_3$ (0.50 mmol), (*S*)-**1c** (0.025 mmol), THF (1.0 mL), −78 °C, 24 h.
[a] Yield of the isolated products **4a–r**. [b] dr = *syn*:*anti*. [c] Determined by chiral HPLC analyses. Where appropriate, the absolute configurations were assigned by comparison of the specific rotations with those reported in Ref. [31].

in good yields (73%–86%) with a strong preference for the *syn*-diastereomers (dr 92/8–99/1) and high enantioselectivities (84%–93% ee). High levels of diastereoselectivity were also observed in the reactions involving α,β-unsaturated aldehydes **3n** and **3o** (entries 14 and 15), but only the reaction of cinnamaldehyde **3o** gave the corresponding adduct *syn*-**4o** with excellent enantioselectivity as well (94% ee, entry 15). The reaction of **2a** with alkyl aldehyde was examined using **3p** as a substrate, to result in the exclusive formation of *syn*-**4o** albeit with a modest ee value (entry 16). Enone **2b** with an aliphatic vinyl substituent (Me) was also used as the nucleophilic partner in the reductive aldol reaction with **3a**, giving the high levels of stereoselectivity (dr 87/13, 95% ee) for the *syn*-aldol product **4q** (entry 17). Finally, the chalcone derivative **2c** also underwent a smooth reductive aldol reaction with **3a** under the standard conditions, affording the corresponding aldol product **4r** in good yield (87%) with high diastereo- and enantioselectivities (*syn*/*anti* = 94:6, 88% ee for *syn*, entry 18).

4. Conclusions

We have developed a highly diastereo- and enantioselective synthesis of optically enriched β-hydroxyketones. Using the spiro bisphosphine oxides **SpinPO** as chiral Lewis base catalysts, the asymmetric reductive aldol reactions of enones and a range of aldehydes proceeded smoothly with trichlorosilane reductant, to afford the corresponding aldol adducts **4a**–**r** in 45%–88% yields, generally high *syn*-diastereoselectivity, and good to excellent enantioselectivity (up to 95% ee). Substrates with diverse stereoelectronic natures were tolerated, generally affording good yields and high stereoselectivities.

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Graphical Abstract

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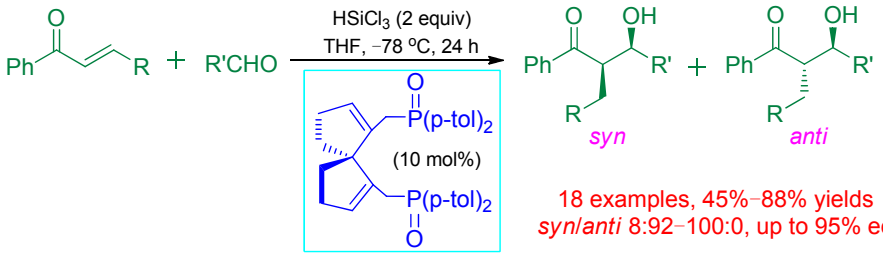

A spiro bisphosphine oxide (**SpinPO**) was found to be a highly enantio- and diastereoselective Lewis base catalyst in reductive aldol reactions of enones and aldehydes in the presence of trichlorosilane as the stoichiometric reductant.

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