

Spiro[4,4]-1,6-Nonadiene-Based Diphosphine Oxides in Lewis Base Catalyzed Asymmetric Double-Aldol Reactions**

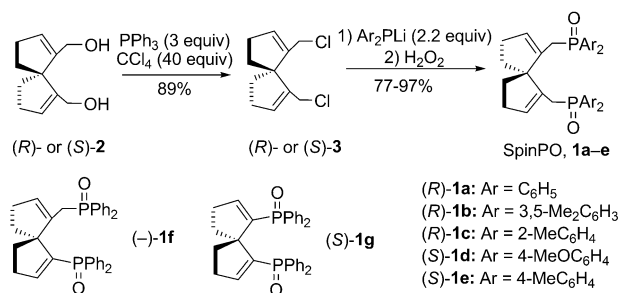
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Dedicated to Professor Teruaki Mukaiyama

The aldol reaction is one of the most fundamental processes in chemical and biological transformations, and plays an essential role for carbon–carbon bond formation in synthetic organic chemistry.^[1] Although the direct asymmetric aldol reaction has been well developed using various chiral organometallic catalysts^[2–4] or organocatalysts,^[5–11] very few examples are known for the synthesis of double-aldol products to date.^[12] In fact, the realization of the first asymmetric double-aldol reaction of an acyclic ketone with two aldehyde molecules to afford the corresponding optically active 1,3-diol derivatives was only recently reported by Nakajima et al.^[13a] in which a chiral diphosphine oxide catalyst, 2,2'-bis(diphenylphosphinoxy)-1,10-binaphthyl (BINAPO), turned out to be the catalyst of choice among various commonly used Lewis bases, and catalyzed the reaction with moderate to good activity and stereoselectivity, albeit with a limited substrate scope.^[13a] A spiro backbone has been recognized as one of the privileged scaffolds for the construction of chiral ligands and catalysts for various asymmetric transformations,^[14] since it was introduced by the pioneering work of Chan and co-workers on the development of SpirOP (Scheme 1),^[15] a diphosphine ligand with a spiro[4,4]nonane backbone. We have reported the development of spiro[4,4]-1,6-nonadiene-based chiral phosphine-oxazoline ligands (SpinPHOX),^[16a–e] for which the complexity associated with the stereochemistry and the separation of diastereomers in spiro[4,4]nonane-based scaffolds, can be avoided.^[16a] The Ir^I complexes of these species were found to

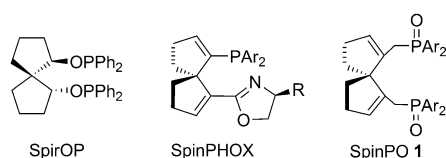
be highly efficient for the catalytic hydrogenation of a variety of imines and α,β -unsaturated carbonyl substrates.^[16a–e] As part of our ongoing efforts to explore new catalyst systems based on the spiro[4,4]-1,6-nonadiene skeleton, we herein report the development of a new type of Lewis base catalysts, SpinPO **1**, and their excellent performance in the catalysis of the direct asymmetric double-aldol reaction of ketones with aldehydes, as well as the potential applications of the resultant optically active double-aldol products.

The synthesis of the enantiopure SpinPO diphosphine oxides **1a–e** is shown in Scheme 2 (for detailed procedures



Scheme 2. Preparation of enantiopure phosphine oxides **1a–1e**, and the structures of **1f–g**.

and for the preparation of enantiopure diol (R)-**2**, starting from either racemic^[16a,g–h] or enantiopure spiro[4,4]nonane-1,6-dione,^[16f] see the Supporting Information). The reaction of enantiopure diol (R)- or (S)-**2** with carbon tetrachloride and triphenylphosphine afforded the corresponding dichloride **3** in 89% yield.^[17] Treatment of the enantiopure dichloride **3** with Ar₂PLi^[18] furnished the corresponding bisphosphines, which were oxidized in situ with hydrogen peroxide to give the (R)- or (S)-diphosphine oxides **1a–e** in high yields (77–97%). The absolute configuration of (+)-**1a** was determined to be *S* by single-crystal X-ray diffraction analysis (Supporting Information, Figure S1),^[19] whereas those of the remaining phosphine oxides **1b–e** were deduced by comparison of their CD spectra with that of (S)-(+)-**1a** (Figure S2). To investigate the impact of structural rigidity of the backbone on the catalytic performance, diphosphine oxides **1f** and **1g**, which are close structural analogues of **1a**, but which contain only one or no flexible methylene linker between the spiro[4,4]-1,6-nonadiene scaffold and the diphenylphosphine oxide unit, were also synthesized (for details, see the Supporting Information).



Scheme 1. Structures of SpirOP, SpinPHOX, and SpinPO (**1**).

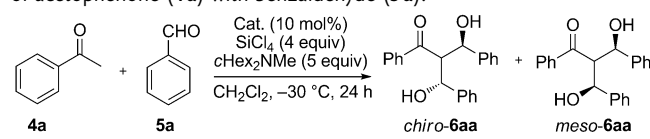
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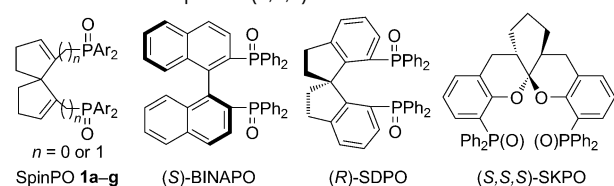
With catalysts SpinPO **1a–g** in hand, we then investigated their catalytic performance in the direct double-aldol reaction, choosing acetophenone (**4a**) and benzaldehyde (**5a**) as the standard substrates. After screening a variety of reaction parameters, including base, solvent, temperature, catalyst loading, and substrate concentration (Tables S1–S5), it was found that the reaction proceeded smoothly in CH₂Cl₂ (0.1 M) at –30 °C in the presence of catalyst (*R*)-**1a** (10 mol %) and dicyclohexylmethylamine (cHex₂NMe; 5 equiv) as the base, to give the corresponding 1,3-diol (–)-**6aa** in 84 % yield with a diastereomeric ratio (d.r.) of 91:9 (*chiro*/*meso*) and 94 % *ee* for *chiro*-**6aa** (Table 1, entry 1). Under the optimized reaction

Table 1: Catalyst optimization for the asymmetric double-aldol reaction of acetophenone (**4a**) with benzaldehyde (**5a**).^[a]



Entry	Catalyst	Yield ^[b] [%]	d.r. ^[c]	<i>ee</i> ^[d] [%]
1	(<i>R</i>)- 1a	84	91:9	94 (<i>S,S</i>)
2	(<i>R</i>)- 1b	76	86:14	84 (<i>S,S</i>)
3	(<i>R</i>)- 1c	60	72:28	74 (<i>S,S</i>)
4	(<i>S</i>)- 1d	82	92:8	88 (<i>R,R</i>)
5	(<i>S</i>)- 1e	84	91:9	94 (<i>R,R</i>)
6	(–)- 1f	45	50:50	66 (<i>R,R</i>)
7	(<i>S</i>)- 1g	83	92:8	57 (<i>R,R</i>)
8	(<i>S</i>)-BINAPO	62	75:25	54 (<i>R,R</i>)
9 ^[e]	(<i>S</i>)-BINAPO	86	78:22	70 (<i>R,R</i>)
10	(<i>R</i>)-SDPO	50	58:42	34 (<i>R,R</i>)
11	(<i>S,S,S</i>)-SKPO	38	52:48	58 (<i>S,S</i>)
12	(<i>S,S,S</i>)-SKPO ^[f]	12	38:62	46 (<i>S,S</i>)

[a] Unless otherwise noted, the reactions were carried out by addition of silicon tetrachloride (0.8 mmol) to a solution of **4a** (0.2 mmol), **5a** (0.44 mmol), cHex₂NMe (1.0 mmol), and the catalyst (10 mmol %) in CH₂Cl₂ (2 mL) at –30 °C. [b] Yields of the isolated *chiro*-diastereomers. [c] Determined by ¹H NMR analysis of the crude reaction mixtures (*chiro*/*meso*). [d] Determined by HPLC analysis on a chiral stationary phase (AD-H column). The absolute configurations were assigned by comparing the optical rotation obtained with values reported in the literature.^[13a] [e] The data is cited from Ref. [13a]. [f] (*S,S,S*)-SKPO⁺ is the monooxide counterpart of (*S,S,S*)-SKPO.

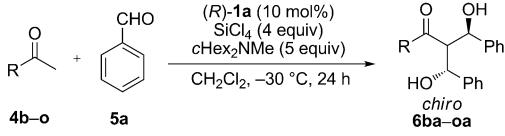


conditions, a variety of spiro[4,4]-1,6-nonadiene-based chiral phosphine oxides, including (*R*)- or (*S*)-**1b–e** with different aryl substituents at the P atoms, were then tested as catalysts for the double-aldol reaction between **4a** and **5a**. As shown in Table 1, the steric hindrance of the aryl groups on the P atoms has a significant impact on the asymmetric induction (entries 1 and 2). With catalysts (*R*)-**1b** and (*R*)-**1c** bearing 3,5-xylyl and 2-tolyl moieties, respectively, on the P atoms, the diastereo- and enantioselectivities decreased in comparison with the results obtained with their structural analogue **1a**

(entries 2 and 3 vs. 1). The introduction of electron-donating MeO groups on the aryl rings attached to the P atoms led to a slight decrease in the enantioselectivity of the reaction (88 % *ee*; entry 4). Catalyst (*S*)-**1e** with 4-tolyl groups on the P atoms performed comparably to the prototypical catalyst (*R*)-**1a** in terms of reactivity, diastereoselectivity, and enantioselectivity, affording the corresponding 1,3-diol product (+)-**6aa** in 84 % yield with a diastereoselectivity of 91:9 and 94 % *ee* (entry 5). The examination of diphosphine oxides **1f** and **1g** indicated that the presence of the methylene bridges between the spiro[4,4]-1,6-nonadiene skeleton and the diphenylphosphine oxide units of the catalyst is critically important for the stereoselectivity of the reaction (entries 6 and 7 vs. entry 1). The use of diphosphine oxides with privileged skeletons, such as (*R*)-BINAPO^[13] (entries 8 and 9) or (*R*)-SDPO^[14d] (entry 10), as well as our aromatic spiroketal-based diphosphine oxide (*S,S,S*)-SKPO^[16b] (entry 11), gave only inferior results (< 78:22 d.r. and < 70 % *ee*) to those obtained with SpinPO (entry 1). These results emphasize the advantageous features of the spiro[4,4]-1,6-nonadiene-1,6-bis-(methyl) skeleton of the bisphosphine oxides for this catalytic system. The reaction in the presence of a monooxide catalyst (SKPO⁺; entry 12), did give the expected product, but only in low yield (12 %), poor d.r. (38:62) and modest *ee* (46 %), in comparison with the results obtained with SKPO (entry 11). Although we are unable to clarify the underlying reason for the outstanding catalytic performance of (*R*)-**1a**, it is clear that fine-tuning of the steric and electronic environment of the phosphine oxide catalyst is critically important in achieving maximum asymmetric induction.

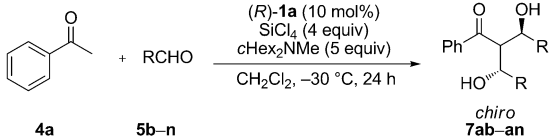
Having established (*R*)-**1a** as the most effective catalyst, we subsequently investigated the double-aldol reaction of various ketones with benzaldehyde (**5a**) under the optimized conditions. As shown in Table 2, the reaction of **5a** with aromatic (**4b–k**), heteroaromatic (**4l** and **4m**), olefinic (**4n**) or aliphatic (**4o** and **4p**) ketones proceeded smoothly, giving the corresponding double-aldol adducts in high yields with good to excellent diastereo- and enantioselectivities. The reaction tolerates both electron-withdrawing and electron-donating substituents on the aromatic ring of the ketones; however, a slightly negative effect was observed in the case of a sterically demanding 2-methyl (entry 3) or a strongly electron-withdrawing 4-NO₂ group (entry 7). In the reaction of 4-bromoacetophenone with benzaldehyde, the *chiro* product (–)-**6ga** was obtained with an *ee* value of > 99 %. With ketones **4l** and **4m**, which contain heteroaromatic rings, remarkable reactivities (87 % and 91 % yield, respectively) and enantioselectivities (96 % *ee*) were observed for the reaction with **5a** (entries 11 and 12). Similarly, the reactions of olefinic and aliphatic ketones afforded the corresponding adducts in high yields and stereoselectivities (entries 13 and 14). In the double-aldol reaction of butanone **4p**, a sterically less-hindered ketone with two enolizable α-carbon positions, the two aldol reactions occurred at the two different α-carbons of the carbonyl group. Thus adduct **6pa** was obtained in good yield with excellent diastereo- and enantioselectivity (Scheme 3a), results comparable to those achieved by Nakajima and co-workers using BINAPO as the catalyst.^[13b]

Table 2: Asymmetric double-aldol reaction of various ketones (**4b–4o**) with benzaldehyde (**5a**).^[a]

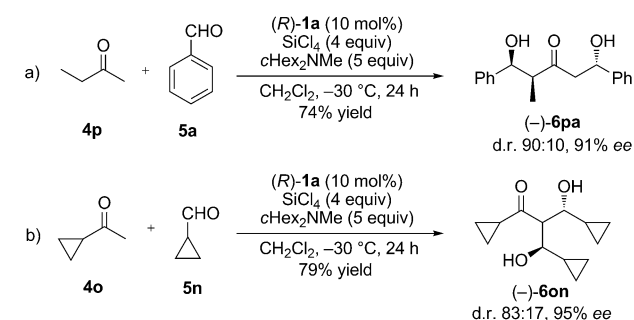
					
Entry	Ketone	R	Yield ^[b] [%]	d.r. ^[c]	ee ^[d] [%]
1	4b	4-MeC ₆ H ₄	82	90:10	94 (–)
2	4c	3-MeC ₆ H ₄	83	88:12	94 (–)
3	4d	2-MeC ₆ H ₄	80	86:14	81 (–)
4 ^[e]	4e	4-MeOC ₆ H ₄	76	93:7	91 (–)
5 ^[f]	4f	2-MeOC ₆ H ₄	93	85:15	92 (+)
6	4g	4-BrC ₆ H ₄	78	84:16	> 99 (–)
7 ^[f]	4h	4-NO ₂ C ₆ H ₄	86	74:26	90 (–)
8	4i	4-FC ₆ H ₄	79	88:12	95 (–)
9	4j	4-CF ₃ C ₆ H ₄	76	78:22	90 (–)
10	4k	2-naphthyl	81	87:13	94 (–)
11	4l	2-thienyl	87	91:9	96 (–)
12 ^[f]	4m	2-furyl	91	88:12	96 (+)
13	4n	C ₆ H ₅ CH=CH	76	80:20	95 (–)
14	4o	cyclopropyl	87	93:7	90 (–)

[a] Unless otherwise noted, the reactions were carried out by addition of silicon tetrachloride (0.8 mmol) to a solution of **4** (0.2 mmol), **5a** (0.44 mmol), cHex₂NMe (1.0 mmol), and the catalyst (10 mmol%) in CH₂Cl₂ (2 mL) at –30 °C. [b] The yield of the isolated *chiro*-diastereomer. [c] Determined by ¹H NMR analysis of the crude reaction mixtures (*chiro*/*meso*). [d] Determined by HPLC analysis on a chiral stationary phase (AD-H or AS-H column). [e] Reaction temperature: –60 °C. [f] The yield of *chiro*- and *meso*- diastereomers.

Table 3: SpinPO-catalyzed asymmetric double-aldol reaction of acetophenone (**4a**) with various aldehydes (**5b–n**).^[a]

					
Entry	Aldehyde	R	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	5b	4-MeC ₆ H ₄	81	83:17	95 (–)
2	5c	3-MeC ₆ H ₄	82	91:9	97 (–)
3	5d	2-MeC ₆ H ₄	92	97:3	91 (–)
4	5e	4-MeOC ₆ H ₄	71	77:23	94 (–)
5 ^[e]	5f	2-MeOC ₆ H ₄	90	91:9	93 (–)
6	5g	4-BrC ₆ H ₄	80	83:17	94 (–)
7	5h	4-FC ₆ H ₄	80	83:17	93 (–)
8	5i	4-CF ₃ C ₆ H ₄	82	85:15	95 (–)
9	5j	2-naphthyl	78	86:14	95 (+)
10 ^[e]	5k	2-thienyl	88	87:13	96 (+)
11 ^[e]	5l	2-furyl	87	94:6	96 (+)
12 ^[e]	5m	C ₆ H ₅ CH=CH	91	55:45	88 (+)
13 ^[e]	5n	cyclopropyl	90	74:26	90 (+)

[a] Unless otherwise noted, the reactions were carried out by addition of silicon tetrachloride (0.8 mmol) to a solution of **4a** (0.2 mmol), **5** (0.44 mmol), cHex₂NMe (1.0 mmol), and the catalyst (10 mmol%) in CH₂Cl₂ (2 mL) at –30 °C. [b] The yield of isolated *chiro*-diastereomer. [c] Determined by ¹H NMR analysis of crude reaction mixtures (*chiro*/*meso*). [d] Determined by HPLC analysis on a chiral stationary phase (AD-H or AS-H column). [e] The yield of *chiro*- and *meso*-diastereomers.

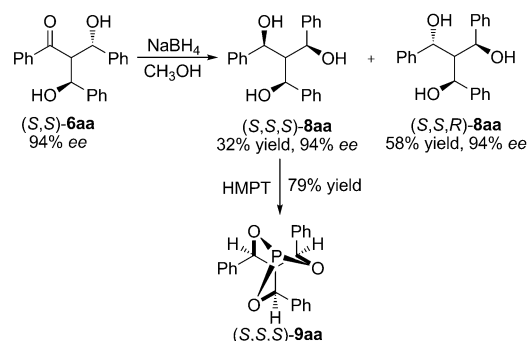


Scheme 3. Aldol reactions of aliphatic ketones **4p** and **4o** with the aromatic aldehyde **5a** and the aliphatic aldehyde **5n**, respectively, catalyzed by (*R*)-**1a**.

The substrate scope of aldehydes was also found to be quite general. As shown in Table 3, the reaction of acetophenone (**4a**) proceeded well with a number of aldehydes. Those with aromatic (**5b–j**), heteroaromatic (**5k** and **5l**), olefinic (**5m**) or aliphatic (**5n**) substituents afforded the corresponding products in 71–92% yield with 88–97% *ee*. Neither the electronic properties nor the steric hindrance of the aromatic aldehydes had a major influence on the enantioselectivity (entries 1–11), but some drops in diastereoselectivity were observed in the reactions of olefinic and aliphatic aldehydes (entries 12 and 13). For the reaction of two aliphatic substrates, sterically hindered 1-cyclopropylethanone (**4o**) and cyclopropanecarbaldehyde (**5n**), the general pattern of

the double-aldol reaction was observed, to give (–)-**6on** in 79% yield with 83:17 d.r. and 95% *ee* (Scheme 3b).

To demonstrate potential applications of this method, the optically active double-aldol adduct (*S,S*)-(–)-**6aa** (94% *ee*) was then reduced with NaBH₄ in methanol, to afford the corresponding optically active triols, (*S,S,S*)-(+)-**8aa** and (*S,S,R*)-(–)-**8aa**, in 1:2 d.r. with excellent *ee* values (94%) for both diastereomers (Scheme 4). Both (*S,S,S*)-(+)-**8aa** and (*S,S,R*)-(+)-**8aa** can be readily isolated by flash column chromatography, thus providing a facile approach to C₃- and pseudo-C₃-symmetric triols.^[20] As shown in Figure 1, the molecular structure of (*S,S,S*)-(+)-**8aa** is C₃ symmetric, with a suprafacial orientation for all three hydroxy groups in the molecule. The reaction of (*S,S,S*)-(+)-**8aa** with P(NMe₂)₃ (HMPT) afforded an optically pure cage-like phosphite



Scheme 4. Synthetic application of double-aldol adduct (*S,S*)-(–)-**6aa** for the preparation of optically active triol compounds and phosphite derivative (*S,S,S*)-(+)-**9aa**.

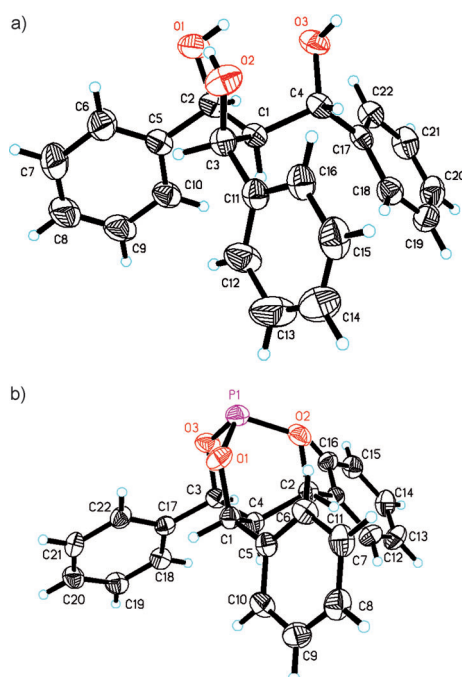


Figure 1. X-ray crystal structures of (S,S,S)-(+)-**8aa** (a) and its phosphite derivative (S,S,S)-(+)-**9aa** (b). Thermal ellipsoids set at 30% probability.^[22]

ligand (S,S,S)-(+)-**9aa** with perfect C_3 symmetry (Figure 1b) in 79% yield. Its application in the Rh-catalyzed asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide led to excellent enantiocontrol (92% *ee*; for details, see the Supporting Information). These results clearly indicate that this method can provide ready access to molecules that might be of interest for asymmetric catalysis or chiral recognition.^[21]

In summary, a new class of chiral spiro phosphine oxides based on the spiro[4.4]-1,6-nonadiene backbone (SpinPO) has been developed and successfully applied as Lewis base catalysts in the direct double-aldol reactions of a ketone with two molecules of an aldehyde, affording the corresponding double-aldol adducts in high yields (71–93%) and excellent stereoselectivities (up to 97:3 d.r. and 99% *ee*). The resulting optically active aldol adduct can be readily reduced by NaBH_4 to provide optically active C_3 -chiral and pseudo- C_3 -chiral triol molecules. These results might stimulate future work on the use of SpinPO catalysts and C_3 -chiral triols in the areas of asymmetric catalysis or molecular recognition.

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