Enantiomerically Pure Bithiophene Diphosphine Oxides as Catalysts for Direct Double Aldol Reactions

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ABSTRACT The direct aldol reaction between aryl methyl ketones with aromatic aldehydes in the presence of tetrachlorosilane and a catalytic amount of a chiral bithiophene diphosphine oxide was studied; the product of double aldol addition was isolated as diacetate in good diastereoselectivity (up to 95:5) and enantioselectivities up to 91%. The reaction with heteroaromatic aldehydes was also investigated leading to the corresponding 1,3 diols, in some cases with excellent stereoselectivities. *Chirality 00:000–000, 2013.*

KEY WORDS: aldol reaction; Lewis bases; organocatalysis; stereoselectivity; tetrachlorosilane

INTRODUCTION

The use of tetrachlorosilane in combination with catalytic amount of chiral Lewis bases to promote stereoselective reactions nowadays is a well-established methodology.[1–3] Seminal works by Denmark and colleagues[4–6] with chiral phosphoroamides have shown the versatility of the catalytic system that opened avenues to several different synthetic applications.[7] Soon after, Nakajima and colleagues[8–14] and we[15–17] demonstrated that phosphine oxides could also coordinate $SiCl_4$ and generate hypervalent cationic silicon species in situ as chiral Lewis acids able to promote stereoselective direct aldol reactions.

Recently, it was reported[18] that the binaphthyl-based phosphine oxide BINAPO catalyzed the double aldol reaction[19,20] of acetophenone with benzaldehyde, leading to the formation of the corresponding products as a mixture of two diastereoisomers and 60% e.e for the major isomer. By looking for the best experimental conditions it was found that a mixture of DCM and propionitrile as reaction solvent in combination with the use of dicyclohexylmethylamine allowed an increase in the stereoselectivity up to 70% enantiomeric excess (e.e.) Only with 2-furyl and 2-cyclopropyl methyl ketones was 90% of enantioselectivity reached.

We were interested in applying our catalytic methodologies to the transformation; in our previous studies of Lewis-based catalyzed reactions in the presence of silicon tetrachloride the use of biheteroaromatic diphosphine oxides, more electron-rich than the commonly used binaphthyl diphosphine derivatives, has often led to the formation of the desired products with enantioselectivities higher than those obtained with BINAPO[21]; therefore we decided to investigate the behavior of (*S*)-tetramethyl-bithiophene phosphine oxide, (*S*)-TetraMe-BITIOPO, in the direct double aldol reaction between aryl methyl ketones and aromatic aldehydes.

MATERIALS AND METHODS

General

TLC was performed on Merck silica gel 60 TLC plates F254 and visualized using UV or phosphomolibdic acid. Flash chromatography was carried out on silica gel (230–400 mesh). ^{1}H NMRs were recorded at 300 MHz (Bruker Fourier 300 or AMX 300) with the indicated solvent. ^{13}C NMRs were obtained at 75 MHz with complete proton decoupling. Chemical shifts were determined relative to tetramethylsilane (for hydrogen atoms) and residual solvent peaks (for carbon atoms). HPLC for e.e. determination was performed on an Agilent 1100 or 1200 instrument under the conditions reported below. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II and Xmass software (Bruker Daltonics).All reactants were freshly distilled (if liquid) or crystallized (if solid) before use.

Double Aldol Reaction: Typical Procedure

To a stirred solution of (*S*)-tetra-Me-BITIOPO (0.016 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL), DIPEA (diisopropylethylamine) (0.8 mmol, 5 equiv.) and the ketone (0.16 mmol, 1 equiv.) were added. The mixture was cooled to –40°C, then freshly distilled tetrachlorosilane (0.64 mmol, 4 equiv.) was added dropwise with a syringe. After 15 min, aldehyde (0.352 mmol, 2.2 equiv.) was added. The mixture was stirred for 20 h. After this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (2 mL). The mixture was allowed to warm to room temperature and stirred for 30 min, then CH_2Cl_2 (15 mL) was added. The two-layer mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature to give the crude 1,3-diols, as confirmed by ^{1}H-NMR.

The crude products were then treated with acetic anhydride (1.76 mmol, 11 equiv) in 2 mL of pyridine at room temperature (RT). After stirring for 20 h, the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum at RT. The diastereoisomeric ratio was calculated by ^{1}H-NMR spettroscopy. Yields were determined after chromatographic purification on silica gel with different hexane/ethyl acetate mixtures as eluent (see below). The e.e. was determined by high-performance liquid chromatography (HPLC) on a chiral stationary phase. Attributions were performed using racemic mixtures as references. (*S*)-tetra-Me-BITIOPO was quantitatively recovered by further elution with 10% MeOH in CH_2Cl_2 without any loss of optical purity.

(3-acetoxy-2-(1′-acetoxy(phenyl)methyl)-1,3-diphenylpropan-1-one (3). This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of chiral and meso adducts.

Additional Supporting Information may be found in the online version of this article.

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R_f = 0.24(8 : 2 hexane/ethyl acetate).

Data for *chiral* (**3a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, 2H, J = 9 Hz), 7.44 (d, 2H, J = 6 Hz), 7.35-7.11 (m, 11H), 6.37 (d, 1H, J = 6 Hz), 6.22 (d, 1H, J = 9 Hz), 4.55 (dd, 1H, J = 9 Hz, J = 6 Hz), 2.03 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.59, 169.47, 169.38, 138.47, 138.22, 137.64, 132.60, 128.50, 128.23, 128.08, 127.78, 127.65, 127.2, 74.90, 74.05, 55.91, 20.83, 20.65.
HRMS Mass (ESI+): m/z = calc for $C_{26}H_{24}O_5Na^+$ = 439.46, found 439.15 [M + Na].
Data for *meso* (**3b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, 2H, J = 9 Hz), 7.68 (d, 2H, J = 9 Hz), 7.35-7.11 (m, 11H), 5.95 (d, 2H, J = 6 Hz), 4.40 (t, 1H, J = 6 Hz), 1.78 (s, 6H).

The e.e. was determined by chiral HPLC with Daicel Chiralpak AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm, t_R 9.44 min (*chiral*, minor), t_R 12.51 min (*chiral*, major), t_R 17.63 min (*meso*). (Table 1)

3-acetoxy-2-(1′-acetoxy-1′-(4-chlorophenyl)methyl)-1-phenyl-3-(4-chlorophenyl)-propan-1-one (Table 2, entry 3). This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts. R_f = 0.25 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, 2H, J = 9 Hz, *meso*), 7.48 (d, 2H, J = 6 Hz, *chiral*), 7.45-7.06 (m, 11H *chiral* + 11H *meso*), 6.27 (d, 1H, J = 9 Hz, *chiral*), 6.14 (d, 1H, J = 9 Hz, *chiral*), 5.92 (d, 2H, J = 9 Hz, *meso*), 4.56 (dd, 1H, J = 9 Hz, J = 6 Hz, *chiral*), 4.42 (t, 1H, J = 9 Hz, *meso*), 1.93 (s, 3H, *chiral*), 1.80 (s, 6H, *meso*), 1.76 (s, 3H, *chiral*). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.59, 169.68, 138.47, 136.95, 136.43, 134.71, 133.48, 129.41, 129.02, 128.92, 128.75, 128.22, 74.0, 74.41, 73.66, 55.95, 21.14, 21.00. HRMS Mass (ESI+): m/z = calc for $C_{26}H_{22}Cl_2O_5Na^+$ = 507.07, found 507.20 [M + Na].

The e.e. was determined by chiral HPLC with a Daicel Chiralpak AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 242 nm, t_R 10.52 min (*chiral*, minor), t_R 14.81 min (*chiral*, major), t_R 26.10 min (*meso*).

3-acetoxy-2-(1′-acetoxy-1′-(4-nitrohenyl)methyl)-1-phenyl-3-(4-nitrophenyl)-propan-1-one (Table 2, entry 4). This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts. R_f = 0.12 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09-8.01 (m, 4H *chiral* + 4H *meso*), 7.64-7.17 (m, 9H *chiral* + 9H *meso*), 6.44 (d, 1H, J = 6 Hz, *chiral*), 6.30 (d, 1H, J = 9 Hz, *chiral*), 6.01 (d, 2H, J = 6 Hz, *meso*), 4.58 (dd, 1H, J = 9 Hz, J = 6 Hz, *chiral*), 4.46 (t, 1H, J = 9 Hz, *meso*), 2.06 (s, 3H, *chiral*), 1.97 (s, 6H, *meso*), 1.89 (s, 3H, *chiral*). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 195.44, 169.98, 144.84, 140.30, 139.26, 136.96, 134.27, 133.39, 129.82, 129.59, 128.73, 127.09, 123.93, 123.70, 73.02, 71.64, 55.43, 20.74. HRMS Mass (ESI+): m/z = calc for $C_{26}H_{22}N_2O_9Na^+$ = 529.12, found 529.3 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate,

TABLE 1. Tetra-Me-BITIOPO-catalyzed condensation of acetophenone with benzaldehyde

Entry	R. time (h)	R. temp (°C)	Yield (%)[a]	Diast. ratio[b]	e.e major isomer[c] (%)
1[d]	20	-40	65	84/16	53
2[e]	24	-40	90	81/19	60
3[f]	20	-40	31	79/21	31
4[g]	20	-40	35	86/14	61
5[h]	20	-40	61	88/12	75
6[h]	20	-78	n.r.	—	—
7[h]	72	-78	35	75/25	69

[a]Reactions were run with 4 mol equiv. of $SiCl_4$, 1 mol equiv of ketone,2.2 mol equiv of aldehyde and 10 mol % amount of catalyst; yields were determined after chromatographic purification on the diacetate derivative;
[b]diastereoisomeric ratio was determined by ^{1}H-NMR and confirmed by HPLC;
[c]e.e. was determined by HPLC on chiral column (see Supporting Information);
[d](S)-BINAPO was used;
[e]Lit. data, Ref. 18; (S)-BINAPO was used;
[f](S)-BINAPO was used with Cl_3SiOTf;
[g]the reaction was quenched with $NaHCO_3$ sat. sol.
[h]the reaction was quenched with NH_4Cl sat. sol.

TABLE 2. Tetra-Me-BITIOPO-catalyzed condensation of acetophenone with differently substituted aldehydes

Entry	Ar	Yield (%)[a]	Diast. ratio[b]	e.e major isomer[c] (%)
1	Ph	61	88/12	75
2	4-CF_3Ph	63	90/10	41
3	4-ClPh	65	80/20	70
4	4-NO_2Ph	51	70/30	26
5	4-OMePh	40	73/27	91
6	4-MePh	43	89/11	80
7	1-Naphth	55	89/11	41
8	2-furyl	45	92/8	71
9	2-thienyl	25	90/10	90

[a]Reactions were run with 4 mol equiv. of $SiCl_4$, 1 mol equiv of ketone,2.2 mol equiv of aldehyde and 10 mol % amount of catalyst for 20 h at -40°C; yields were determined after chromatographic purification on the diacetate derivative;
[b]diastereoisomeric ratio was determined by ^{1}H-NMR;
[c]e.e. was determined by HPLC on chiral column (see Supporting Information).

detection: 254 nm, t_R 12.73 min (*chiral*, major), t_R 13.97 min (*chiral*, minor), t_R 15.9 min (*meso*).

3-acetoxy-2-(1′-acetoxy-1′-(4-methoxyphenyl)methyl)-1-phenyl-3-(4-methoxyphenyl)-propan-1-one (Table 2, entry 5). This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

$R_f = 0.13$(8 : 2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, 2H, J = 9 Hz, *meso*), 7.59 (d, 2H, J = 6 Hz, *chiral*), 7.53-7.28 (m, 5H *chiral* + 5H *meso*), 7.18-7.10 (m, 2H *chiral* + 2H *meso*), 6.85-6.68 (m, 4H *chiral* + 4H *meso*) 6.26 (d, 1H, J = 6 Hz, *chiral*), 6.16 (d, 1H, J = 9 Hz, *chiral*), 5.96 (d, 2H, J = 9 Hz, *meso*), 4.69 (dd, 1H, J = 9 Hz, 10.5Hz, *chiral*) 4.49 (t, 1H, J = 9 Hz, *meso*), 3.79 (s, 3H, *chiral*), 3.76 (s, 6H, *meso*), 3.71 (s, 3H, *chiral*), 1.92 (s, 3H, *chiral*), 1.73 (s, 3H, *chiral*), 1.66 (s, 6H, *meso*). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 195.84, 169.53, 159.55, 138.62, 132.63, 130.22, 129.56, 129.06, 128.76, 128.30, 128.17, 128.11, 127.87, 113.86, 113.59, 74.82, 73.86, 56.33, 55.29, 55.13, 20.89. HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_7Na^+$ = 499.17, found 499.3 [M + Na].

The e.e was determined by chiral HPLC with a Daicel Chiralpak AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm, t_R 13.86 min (*chiral*, minor), t_R 20.59 min (*chiral*, major), t_R 30.22 min (*meso*).

3-acetoxy-2-(1′-acetoxy-1′-(4-methylphenyl)methyl)-1-phenyl-3-(4-methylphenyl)-propan-1-one (Table 2, entry 6). This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

$R_f = 0.4$(8 : 2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, 2H, J = 6 Hz, *meso*), 7.51 (d, 2H, J = 9 Hz, *chiral*), 7.46-7.21 (m, 5H *chiral* + 5H *meso*), 7.11-6.92 (m, 6H, *chiral* + 6H *meso*), 6.24 (d, 1H, J = 9 Hz, *chiral*), 6.14 (d, 1H, J = 9 Hz, *chiral*), 5.92 (d, 2H, J = 6 Hz, *meso*) 4.65 (dd, 1H, J = 10.5Hz, J = 9 Hz, *chiral*), 4.44 (t, 1H, J = 6 Hz, *meso*), 2.26 (s, 3H, *chiral*), 2.25 (s, 6H, *meso*), 2.18 (s, 3H, *chiral*), 1.90 (s, 3H, *chiral*), 1.69 (s, 3H, *chiral*), 1.26 (s, 6H, *meso*).
^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.70, 169.48, 169.37, 138.63, 138.08, 135.15, 134.53, 132.51, 129.07, 128.88, 128.08, 127.90, 127.65, 127.31, 126.83, 74.97, 74.02, 55.65, 21.05, 20.89. HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_5Na^+$ = 467.18, found 467.18 [M + Na].

The e.e. was determined by chiral HPLC with a Daicel Chiralpak AD column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm, t_R 18.62 min (*chiral*, minor), t_R 44.06 min (*chiral*, major), t_R 50.69 min (*meso*).

3-acetoxy-2-(1′-acetoxy-1′-(1-naphthyl)methyl)-1-phenyl-3-(1-naphthyl)-propan-1-one (Table 2, entry 7). This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

$R_f = 0.4$(8 : 2 hexane/ethyl acetate).

Data for *chiral* product: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, 1H, J = 6 Hz), 8.40 (d, 1H, J = 6 Hz), 7.83 (d, 1H, J = 9 Hz), 7.74-7.68 (m, 2H), 7.67-7.45 (m, 6H), 7.40-7.20 (m, 4H), 7.18-7.12 (m, 2H), 6.99 (d, 2H, J = 6 Hz), 6.87 (d, 2H, J = 6 Hz), 5.27 (dd, 1H, J = 9 Hz, J = 3Hz), 2.15 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.53, 168.51, 138.40, 133.85, 133.10, 132.48, 130.24, 129.09, 127.90, 127.52, 126.41, 125.69, 125.25, 124.89, 122.90, 53.32, 20.90.
HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_5Na^+$ = 467.18, found 467.18 [M + Na].The e.e. was determined by chiral HPLC with a Daicel Chiralpak AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 225.8 nm, t_R 12.71 min (*chiral*, minor), t_R 54.14 min (*chiral*, major).
Data for *meso* product: 7.82 (d, 2H, J = 6 Hz), 7.66 (d, 2H, J = 6 Hz), 7.51-7.18 (m, 13H), 7.04 (t, 2H, J = 9 Hz), 6.61 (d, 2H, J = 6 Hz), 5.11 (br, 1H), 2.00 (s, 6H).

RESULTS AND DISCUSSION

The reaction between 1 mol/eq. of acetophenone and 2.2 mol/eq. of benzaldehyde was first investigated in the presence of stoichiometric amounts of $SiCl_4$ and a catalytic amount of enantiomerically pure (*S*)-Tetra-Me-BITIOPO (0.1 mol/eq.) (Scheme 1). At the end of reaction the quenching and the work up with NH_4Cl sat.sol. allowed isolating the product as a mixture of diastereoisomers, as clearly indicated by ^{1}H NMR of the crude reaction mixture; however, any attempt to purify the 1,3 diol led to decomposition and low isolation yields.[22] Therefore, the crude products were reacted with acetic anhydride to afford the corresponding diacetate derivatives, which were obtained as pure compounds and properly analysed and characterized.[23]

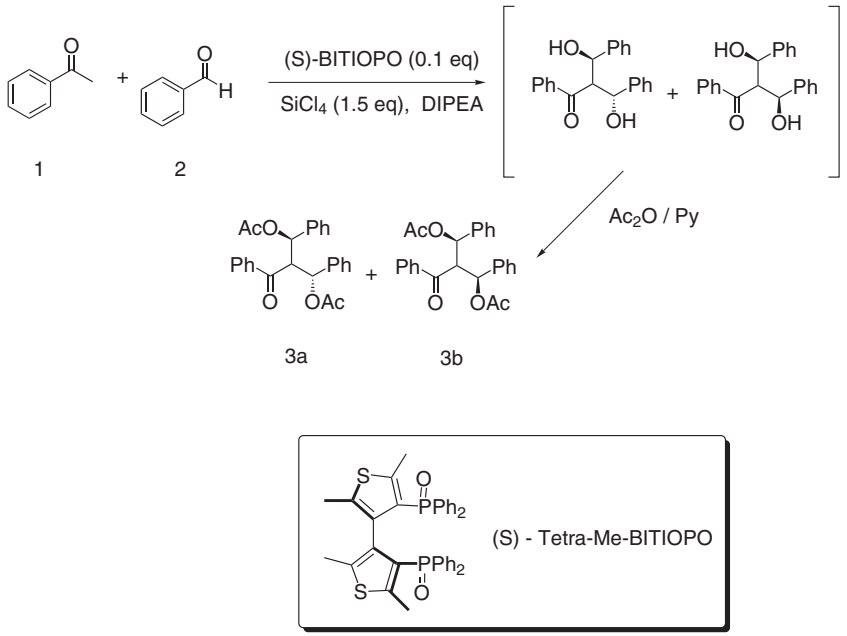
Different experimental conditions of solvent, temperature, and stoichiometric ratios were screened in order to optimize the performance of the Lewis base; a few selected results are shown in Table 1. At –40°C in DCM the reaction was found to proceed after 20 h in 35% yield, 86/14 ratio between the chiral isomer **3a** and the achiral species **3b**, with 55% e.e. for the major isomer (it must be noted that **3b** is an achiral molecule that may exist in two diastereoisomers because carbon in α to carbonyl group is an achirotopic stereogenic center; however, NMR showed one set of signals only and by HPLC analysis one peak was detected under many attempted conditions). For sake of comparison the reaction was performed under the same experimental conditions with (*S*)-BINAPO as a chiral catalyst: the product was obtained in comparable yields and stereoselectivities. The use of trichlorosilyl triflate did not bring any improvement to the process. It was also observed that the experimental conditions of the reaction work up strongly influenced the level of the enantioselectivity of the isolated products: it was found that quenching with ammonium chloride gave best results and it allowed to obtain the 1,3 diacetate **3a** as major product in good yield, 88/12 diastereoisomeric ratio and higher enantioselectivities, up to 75% e.e. (entry 5 of Table 1).

In the attempt to improve the stereoselectivity the reaction temperature was further lowered to –78°C; as expected, the condensation was promoted in lower yield but without any appreciable increase of the enantioselectivity. Therefore, it was decided to further explore the general scope of the methodology by performing the reaction at –40°C for 20 hours in the presence of 10% mol amount of (S)-BITIOPO.

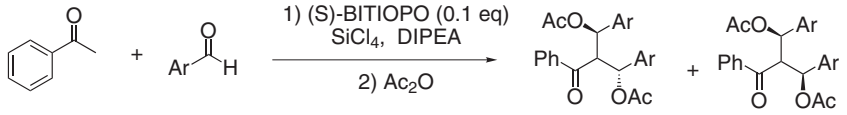
At first the acetophenone reaction with differently substituted aromatic aldehydes was investigated (see Scheme 2): the results are collected in Table 2.

Generally speaking, aldehydes bearing electron-withdrawing groups reacted with acetophenone in higher yields than benzaldehyde, while electron-rich aldehydes were less reactive; however, the opposite trend was observed for the enantioselectivity.

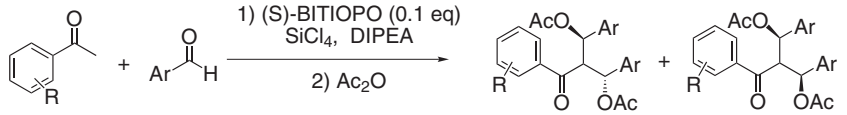
Indeed, while the diastereoselectivity seems not to be influenced by electronic characteristics of the substrates, enantioselectivities ranging from 80–91% were obtained



Scheme 1. Double aldol reaction between benzaldehyde and acetophenone.



Scheme 2. Double aldol reaction between acetophenone and different aromatic aldehydes.



Scheme 3. Double aldol reaction between differently substituted aryl methyl ketones and different aromatic aldehydes.

TABLE 3. Tetra-Me-BITIOPO-catalyzed condensation of aryl methyl ketones with differently substituted aldehydes

Entry	Ar	R	Yield (%)[a]	Diast. ratio[b]	e.e major isomer(%)[c]
1	Ph	4-OMe	45	85/15	43
2	4-CF_3Ph	4-OMe	71	85/15	25
3	4-OMePh	4-OMe	51	86/14	27
4	3,4-di-OMePh	4-OMe	70	95/5	15
5	2-furyl	4-OMe	71	84/16	11
6	2-thienyl	4-OMe	45	77/23	51
7	Ph	4-NO_2	30	70/30	83
8	4-CF_3Ph	4-NO_2	35	88/12	55
9	4-OMePh	4-NO_2	25	55/45	80
10	2-furyl	4-NO_2	40	83/17	90
11	2-thienyl	4-NO_2	35	61/39	90

[a]Reactions were run with 3 mol equiv. of $SiCl_4$, 1 mol equiv of ketone,2.2 mol equiv of aldehyde and 10 mol % amount of catalyst for 20 h at -40°C; yields were determined after chromatographic purification on the diacetate derivative;
[b]diastereoisomeric ratio was determined by ^{1}H-NMR;
[c]e.e. was determined by HPLC on chiral column (see Supporting Information).

for the reaction of 4-tolualdehyde, 4-anisaldehyde, and 2-thiophene caboxyaldehyde.

4-Chloro benzaldehyde afforded the 1,3-diacetate in good yield and enantioselectivity comparable to that observed with benzaldehyde; reaction with 4-trifluoromethyl benzaldehyde gave the product even in 41% e.e., while the analogous 4-nitro derivative was isolated with 26% e.e. only (entries 2 and 4), probably due to the interference in the reaction mechanism of the nitro group, able to coordinate tetrachlorosilane.

The behavior of electronically different aryl methyl ketones was then studied (Scheme 3); 4-methoxyphenyl methyl ketone was reacted with two equivalents of different aromatic aldehydes (entries 1–6 of Table 3).

The reaction generally afforded the double aldol reaction products in good yields, with aldehydes functionalized both with electron-withdrawing or electron-donating groups; diastereoselectivities vary from 77/23 up to 95/5. Unfortunately, the reaction with the aryl ketone substituted with the electron-donating group as the methoxy group afforded the products generally with lower enantioselectivities than those with acetophenone. With benzaldehyde and 2-thiophencarboxyaldehyde, e.e. up to 43% and 51%, respectively, for the major isomer were obtained.

On the other hand, as expected, 4-nitrophenyl methyl ketone was shown to be less reactive than acetophenone and did not afford the desired product in appreciable yields with the poorly reactive electronrich aldehydes; however, the reaction with p-anisaldehyde led to the formation of the desired product in 80% e.e., although in low yields and diastereoselectivity. It must be mentioned that the heteroaromatic substrates like 2-furyl carboxyaldehyde and 2-thienyl carboxyaldehyde also reacted and afforded the corresponding 1,3-diacetate, in modest yields but with 90% of enantioselectivity.

CONCLUSIONS

In conclusion, the double aldol reaction of aryl methyl ketones with aromatic aldehydes was studied in the presence of catalytic amounts of diheteroromatic diphosphine oxide as chiral Lewis base; the reaction products were isolated as 1,3-diacetate derivatives in yields depending on the electronic characteristics of the reactive substrates: from the chemical activity point of view the best results were obtained by employing an electron-rich aryl methyl ketone and electron-poor aromatic aldehydes.

However, while the diastereoisomeric ratio seems to be quite independent from the substrate variation, ranging typically from 70/30 to 90/10, the highest enantioselectivities were observed in the reaction with aldehydes bearing electron-donating groups and heteroaromatic aldehydes: in those cases, e.e. up to 91% was obtained, showing that (*S*)-TetraMe-BITIOPO favorably compares with the BINAPO-derived ligand, leading with different substrates to the products in higher enantioselectivities. Further studies are needed in order to better address the diastereoselectivity of the process and the chemical activation of the less-reactive substrates.

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LITERATURE CITED

1. Reviews: Denmark SE, Beutner GL. Lewis base catalysis in organic synthesis. Angew Chem Int Ed 2008;47:1560–638.
2. Benaglia M, Guizzetti S, Pignataro L. Steroselective reactions involving hypervalent silicate complexes. Coord Chem Rev 2008;252:492–512.
3. Benaglia M, Guizzetti S, Rossi S. Silicate-mediated stereoselective reactions catalyzed by chiral Lewis bases. In: Catalytic methods in asymmetric synthesis. Hoboken, NJ: John Wiley & Sons; 2011. p 579–624.
4. Denmark SE, Stavenger RA. Asymmetric catalysis of aldol reactions with chiral Lewis bases. Acc Chem Res 2000;33:432–440.
5. For more recent contributions see ref. 3 and Denmark SE, Eklov BM, Yao PJ, Eastgate MD. On the mechanism of Lewis base catalyzed aldol addition reactions: kinetic and spectroscopic investigations using rapid-injection NMR. J Am Chem Soc 2009;131:11770–11787 and references cited.
6. See also: Massa A, Roscigno A, De Caprariis P, Filosa R, Di Mola A. Trimethylchlorosilane and silicon tetrachloride in two novel methodologies for the efficient and mild aldol addition of β-keto esters and malonates to aldehydes. Adv Synth Catal 2010;352:3348–3354 and references cited.
7. Rossi S, Benaglia M. Chiral phosphine oxides in present-day organocatalysis. Org Biomol Chem 2010;8:3824–3830.
8. Kotani S, Hashimoto S, Nakajima M. Chiral phosphine oxide BINAPO as a Lewis base catalyst for asymmetric allylation and aldol reaction of trichlorosilyl compounds. Tetrahedron 2007;63:3122–3132.
9. Sugiura M, Sato N, Kotani S, Nakajima M. Lewis base-catalyzed conjugate reduction and reductive aldol reaction of α,β-unsaturated ketones using trichlorosilane. Chem Commun 2008;0:4309–4311.
10. Sugiura M, Kumahara M, Nakajima M. Asymmetric synthesis of 4*H*-1,3-oxazines: enantioselective reductive cyclization of *N*-acylated β-amino enones with trichlorosilane catalyzed by chiral Lewis bases. Chem Commun 2009;0:3585–3587.
11. Kotani S, Shimoda Y, Sugiura M, Nakajima M. Novel enantioselective direct aldol-type reaction promoted by a chiral phosphine oxide as an organocatalyst. Tetrahedron Lett 2009;50:4602–4605.
12. Sugiura M, Sato N, Sonoda Y, Kotani S, Nakajima M. Diastereo- and enantioselective reductive aldol reaction with trichlorosilane using chiral Lewis bases as organocatalysts. Chem Asian J 2010;5:478–481.
13. Osakama K, Sugiura M, Nakajima, M, Kotani S. Enantioselective reductive aldol reaction using tertiary amine as hydride donor. Tetrahedron Lett 2012;53:4199–4201.
14. Aoki S, Kotani S, Sugiura M, Nakajima M. Trichlorosilyl triflate-mediated enantioselective directed cross-aldol reaction between ketones using a chiral phosphine oxide as an organocatalyst. Chem Commun 2012;48:5524–5526.
15. Rossi S, Benaglia M, Cozzi F, Genoni A, Benincori T. Organocatalytic stereoselective direct aldol reaction of trifluoroethyl thioesters. Adv Synth Catal 2011;353:848–854.
16. Rossi S, Benaglia M, Genoni A, Benincori T, Celentano G. Biheteroaromatic diphosphine oxides-catalyzed stereoselective direct aldol reactions. Tetrahedron 2011;67:158–166.
17. Bonsignore M, Benaglia M, Cozzi F, Genoni A, Rossi S, Raimondi L. Readily available (S)-proline-derived organocatalysts for the Lewis acid-mediated Lewis base-catalyzed stereoselective aldol reactions of activated thioesters. Tetrahedron 2012;68:8251–8255.
18. Shimoda Y, Kotani S, Sugiura M, Nakajima M. Enantioselective double aldol reaction catalyzed by chiral phosphine oxide. Chem Eur J 2011;17:7992–7995.
19. For recent review on direct aldol reactions see: Mukherjee S, Yang JW, Hoffmann S, List B. Asymmetric enamine catalysis. Chem Rev 2007;107:5471–5569.
20. For a recent review on domino reactions see: Pellisier H. Recent developments in asymmetric organocatalytic domino reactions. Adv Synth Catal 2012;354:237–294.
21. See ref. 15–17 and Simonini V, Benaglia M, Benincori T. Novel chiral biheteroaromatic diphosphine oxides for Lewis base activation of Lewis acids in enantioselective allylation and epoxide opening. Adv Synth Catal 2008;350:561–564.
22. From NMR analysis of the crude reaction mixture only minor amounts (<10%) of the mono-aldol product were typically detected.
23. See Supporting Information for detailed experimental procedures and product characterization.