Enantioselective Mukaiyama aldol and Sakurai allylation reactions catalysed by silver(I) complexes with chiral atropisomeric chelating ligands †.

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† *We are pleased to dedicate this work to Prof. Renato Ugo in the occasion of his 65th birthday.*

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Abstract

Sakurai and Mukaiyama aldol reactions have been studied using (tetraMeBITIOP)silver(I) and (BITIANP)silver(I) complexes as catalysts; these complexes show high and comparable activities despite the differences in the electron availability and Lewis acid character of the phosphorus atoms.

Keywords

Chiral Lewis acid, Mukaiyama reaction, Sakurai reaction, tetraMeBITIOP, BITIANP, chiral atropisomeric diphosphines.

1. Introduction

The reaction between a silyl enol ether or a ketene silyl acetal and aldehydes, ketones, acetals, ketals, ortoesthers, commonly referred as the Mukaiyama reaction, is a mild but powerful method of carbon-carbon bond formation (scheme 1, eqs. 1 and 2) [1][2]. The reaction is catalysed by Lewis

acids, the same Lewis acids that usually catalyse the Sakurai reaction, i.e. the condensation of aldehydes, ketones or acetals with allyl silanes or allyl stannanes (scheme 1, eq. 3)[3].

(Insert scheme 1)

When the Lewis acid is modified introducing a chiral ligand, the Mukaiyama and Sakurai reactions in their asymmetric version become an extremely versatile synthetic method. In recent years particular attention has been given to the chiral Lewis acids derived from the transition metals including a variety of rhodium(I) [4], iron(II) [5], palladium(II) [6], titanium (IV) [7] complexes which show good productivity and enantioselectivity, are often air stable and easier to handle and are less prone to hydrolysis or to react with protic solvents. In particular, many reports concern silver (I)-catalysed reactions such as the condensation between aldehydes and isocyanides with Ag(I)-BPPFA [8] or the asymmetric aldol reactions between aldehydes and trimethoxysilyl enol ethers [9], the reactions between aldehydes and tin enolates [10], or the allylation of aldehydes with allylbutyl tin [11]; these three reactions are catalysed by silver(I) complexes modified with the ubiquitous and successful Noyori's BINAP ligand. Recently we have developed a new class of chiral chelating atropisomeric diphosphines derived from the condensation of five-membered heteroaromatic rings such as 2,5-dimethylthiophene, benzo[b]thiophene, indole, benzimidazole; the Rh(I) and the Ru(II) complexes derived from the sulphur containing ligands (+)- or (-)-tetraMeBITIOP, [2,2',5,5'-tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene] and (+)- or (-)BITIANP, [2,2'-bis(diphenylphosphino)-bibenzo[b]thiophene] (scheme 2) are able to compete with those derived from the well known BINAP in the asymmetric hydrogenation of olefins and ketones [12][13][14][15].

(Insert scheme 2)

These ligands have a unique feature however: the type of heteroatom and/or its position in the heteroaromatic ring can tune the electronic availability of the phosphorus atoms decreasing or increasing the basicity of the diphenylphosphino groups which in turn should decrease or increase the Lewis acid character of the metal complex. The electron availability of the phosphorus atoms is strictly correlated to the electrochemical oxidative potentials which have been found to be 0.57 V for tetraMeBITIOP, 0.63 V for BINAP and 0.83 V for BITIANP; the oxidative potentials data coincide with the basicity of the diphosphine established by titrimetry in no aqueous media and correlate well with the variation of the ν-CO stretching frequencies in [(Phosphine)Ni$(CO)_2$] complexes [16]. Here we wish to describe the reactivity and the enantioselectivity of the (tetraMeBITIOP)silver(I) and (BITIANP)silver(I) complexes in the catalysed asymmetric Sakurai allylation reactions and Mukaiyama aldol reactions on some selected substrates; the analogous reactions with (BINAP)silver(I) complex are reported for comparison.

2. Experimental

General: The ligands are purchased (BINAP, Aldrich) or prepared as already described [13][15]; the catalysts are prepared under inert atmosphere (argon) using the standard Schlenk techniques. ^{1}H- and ^{31}P-NMR spectra are recorded on a Bruker AC300 equipped with a non-reverse probe and on a Bruker DRX300 Avance. Elemental analysis are performed on a Perkin-Elmer 2400 CHN; HPLC analysis are performed on a Merck-Hitachi L-7100 equipped with Detector UV6000LP and a chiral column Chiralcel OD (Daicel Chemical Ind.); GC-MS analysis are done on Finnigan MD800 equipped with a capillary column with a chiral stationary phase MEGA DAcTButSilBETA (25 m, internal diameter 0.35 mm); polarimetric analysis are performed on a Perkin-Elmer model 343 Plus.

Preparation of [((-)-tetra MeBITIOP)AgOTf]

AgOTf (28.1 mg, 0.1 mmol) and (-)-tetra MeBITIOP (67.5 mg, 0.11 mmol) are placed in a Schlenk tube under argon, dissolved in THF (3 ml) and stirred in darkness; portions of THF are added until

the solution becomes homogeneous, then the solution is stirred for an additional 15 minutes. Evaporation of the solvent produces a white solid; elemental analysis: calculated for $C_{37}H_{32}AgF_3O_3P_2S_3$, C, 52.42; H, 3.81, found C, 52.06, H, 4.19. MS (FAB^+, nitrobenzyl alcohol) 699, calculated for $[(-)\text{-tetra MeBITIOP})Ag]^+$ $(C_{36}H_{32}P_2S_2\ ^{109}Ag)^+$, 699. ^{31}P-NMR at –20°C (THF/$CDCl_3$ 1/1 v/v) δ 6.5 (dd, $J_{^{109}Ag\text{-}^{31}P}$ = 261 Hz, $J_{^{107}Ag\text{-}^{31}P}$ = 227 Hz).

Preparation of [((+)-BITIANP)AgOTf]

The preparation is analogous to that of [((-)-tetra MeBITIOP)AgOTf].

Elemental analysis: calculated for $C_{41}H_{28}AgF_3O_3P_2S_3$, C, 55.23; H, 3.17, found C, 52.08, H, 3.38. MS (FAB^+, nitrobenzyl alcohol) 743, calculated for $[(+)\text{-BITIANP})Ag]^+$ $(C_{40}H_{28}P_2S_2\ ^{109}Ag)^+$, 743. ^{31}P-NMR at –20°C (THF/$CDCl_3$ 1/1 v/v) 0.6 (dd, $J_{^{109}Ag\text{-}^{31}P}$ = 268 Hz, $J_{^{107}Ag\text{-}^{31}P}$ = 233 Hz).

Preparation of [((-)-tetra MeBITIOP)AgOAc]

The preparation is analogous to that of [((-)-tetra MeBITIOP)AgOTf].

The reaction mixture is characterized by the presence of three complexes a, b and c in the ratio 5.7 / 2 / 1. a: ^{31}P-NMR at –50°C (THF/$CDCl_3$ 1/1 v/v) 3.2 (dd, $J_{^{109}Ag\text{-}^{31}P}$ = 412 Hz, $J_{^{107}Ag\text{-}^{31}P}$ = 355 Hz), b : 6.5 (dd, $J_{^{109}Ag\text{-}^{31}P}$ = 263 Hz, $J_{^{107}Ag\text{-}^{31}P}$ = 225 Hz), c : -8.7 (dd, $J_{^{109}Ag\text{-}^{31}P}$ = 771 Hz, $J_{^{107}Ag\text{-}^{31}P}$ = 668 Hz). MS (FAB^+, nitrobenzyl alcohol): 1289, calculated for $[((-)\text{-tetra MeBITIOP})_2Ag]$ $(C_{72}H_{64}P_4S_4\ ^{109}Ag)$ 1289, 699, calculated for [((-)-tetra MeBITIOP)Ag] $(C_{36}H_{32}P_2S_2\ ^{109}Ag)$, 699.

Experimental procedure for the Sakurai reaction:

A typical procedure for the catalytic asymmetric allylation of benzaldehyde by allyltributyltin is: in darkness a solution of the complex [((-)-tetra MeBITIOP)AgOTf], (0.1 mmol in 3 ml THF) prepared as described above, is cooled to –20°C, benzaldehyde (2.0 mmol; 1.5 ml of a 1.35 M solution in THF) is added to the solution followed by allyltributyltin (2.25 mmol, 0.670 ml) drop by drop within one hour. After 24 hours at –20°C the solution is stirred for 15 minutes at room

temperature with 1.5 g of KF in 15 ml HCl (2M), extracted with ether (3 x 5 ml). The organic layer is dried, evaporated in a vacuum and the oily residue is purified by flash chromatography on silica gel (hexane/etylacetate 9/1 v/v) to afford the homoallylic alcohol (222 mg, 68.5 % yield as a colourless oil). The enantioselectivity is determined to be 70 % by HPLC with a chiral column (Chiralcel OD, Daicel Chemical Industries, hexane/2-propanol 95/5, flow rate 0.3 ml/min). The absolute configuration is determined to be R by comparison of the $[\alpha]_D$ = + 42° (c = 5.5, C_6H_6) with reported data [11][17].

Experimental procedure of Mukaiyama aldol reaction:

A representative experimental procedure for the catalytic asymmetric Mukaiyama aldol reaction of benzaldehyde and methyl propionate ketene silyl acetal is: in the absence of light benzaldehyde (2.5 mmol; 1.8 ml of a 1.35 M solution in THF) is added to a solution of the complex [((-)-tetra MeBITIOP) AgOTf], (0.1 mmol in 3 ml THF) prepared as described above followed by the methyl propionate ketene silyl acetal drop by drop. After 24 hours the solution is stirred for 1 hour with hydrofluoric acid (1 ml, 40%) and the solution is reduced to small volume by evaporation of most of THF. Water (10 ml) is added to the oily residue and the suspension is extracted with ether (3 x 5 ml). The organic layer is dried, evaporated in a vacuum and the residue is purified by flash chromatography on silica gel (hexane/ethyl acetate 75/25 v/v) to afford the mixture of syn and anti methyl 3-hydroxy-2-methyl-3-phenylproprionate (63 mg, 13 % yield as a colourless oil). The enantioselectivity is determined to be 51% for the anti diastereosisomer and 32% for the syn diastereosisomer by GC-MS equipped chiral capillary column.

3. Results and discussion

The (phosphine)silver(I) catalysts are rapidly prepared by stirring an equimolar mixture of the ligand and silver(I) triflate in dry THF at room temperature for ten minutes. The ^{31}P-NMR spectra at –20°C, the MS (Fab^+) and the elemental analysis indicate that the [(phosphine)AgOTf]

complexes are formed almost quantitatively. In the Sakurai reaction the solution is cooled at –20°C and the proper amount of aldehyde, dissolved in THF is added. After 30 minutes the allyltributylstannane is added dropwise wthin one hour. Table 1 summarizes the results obtained at –20°C after 24 hours.

(Insert table 1)

Neither catalyst [((+)-tetraMeBITIOP)AgOTf] nor [((+)-BITIANP)AgOTf] show remarkable differences in chemical yield or in the enantioselectivity which are rather high and comparable with those obtained with [(R)-(+)-BINAP)AgOTf] (entries 1, 3 and 5). The presence of an electron-withdrawing group at the *para*-position of benzaldehyde gives rise to opposite effects on the enantioselectivity. With both complexes the presence of bromo group in the aldehyde decreases to some extent the reaction rate of the allylation reaction but the less electron rich BITIANP increases the enantioselectivity up to 78% e.e. while the more electron rich tetraMeBITIOP gives the homoallylic alcohol with a lower e.e.% (entries 2 and 4). Under the same reaction conditions the enantioselectivity of [(R)-(+)-BINAP)AgOTf] is insensitive to the presence of the electron-withdrawing group; only the reactivity appears decreased to some extent (entries 5 and 6) [11].
Table 2 summarizes the results of the asymmetric Mukaiyama aldol reaction between benzaldehyde and the ketene silyl acetal derived from methyl propionate; we have chosen this nucleophile because it is easily prepared and almost chemically pure in the E form [18]. The (phosphine)silver(I) catalysts are prepared as for Sakurai reaction; benzaldehyde and the ketene silyl acetal are added in order at room temperature.

(Insert table 2)

The catalysts are inactive at –20°C; at room temperature the reactions proceed slowly and the syn diastereomer is always favoured. In contrast to [(R)-(+)-BINAP)AgOTf] which gives syn and anti diastereomers with almost the same enantioselectivity (entry 4), [(-)-tetra MeBITIOP)AgOTf] and [(+)-BITIANP)AgOTf] give the anti diastereomer with an almost double enantioselectivity in respect to the more abundant syn diastereomer (entries 1 and 2). According to its electronic properties the more electron rich [(-)-tetra MeBITIOP)AgOTf] complex is the less efficient catalyst but increasing the amount of complex up to 20 mol % the conversion is complete in 24 hours with the same diastereo- and enantiosectivities shown at 4 mol % catalyst (entries 1 and 3). The less electron rich BITIANP ligand produces a silver catalyst which shows a high diastereoselectivity towards the syn diastereoisomer (entry 2) but the diastereoselectivity and the productivity are coupled with a lower enantioselectivity.

When [((-)-tetraMeBITIOP)AgOAc] is used, the Mukaiyama reaction proceeds with the highest rate and with the higher diastereoisomeric ratio but both syn and anti distereoisomers are almost racemic (entry 5). Such a result is not unprecedented; in a recent and very detailed investigation of the mechanism of the Mukaiyama aldol reaction, the effect of the CH_3COO^- anion is well described and compared to that of PF_6^- anion. The cationic character of the complex and its enantioselectivity in the reaction between benzaldehyde and acetophenone sylil enol ether is enhanced by the PF_6^- anion; on the other hand the presence of the CH_3COO^- anion increases the activity of the catalyst but reduces dramatically the stereoselectivity. [19].

4. Conclusion

The atropisomeric chelating diphosphines (+)- or (-)-tetraMeBITIOP and (+)- or (-)BITIANP are characterised by a comparable and very high stereoselectivity when used as ligands in the asymmetric hydrogenation of prochiral olefins and ketones with rhodium(I) and ruthenium(II) complexes and parallel to those obtained with the well known BINAP ligand; the ligands however are noteably different in electron density at phosphorus atom and consequently in the basicity of the

diphenylphosphino groups. When these diphosphines are used as silver(I)OTf catalysts in the Mukaiyama and Sakurai reactions the NMR spectroscopy and the other analytical evidences indicate that the largely prevailing species in solution are the same with tetraMeBITIOP, BITIANP and BINAP; thus the results of the aldol cross-coupling reactions seem to indicate that the more or less Lewis acid character contained in the ligands plays a minor role in respect to other parameters such as the nature of the counter anion and, to a lesser extent, the solvent of the reaction.

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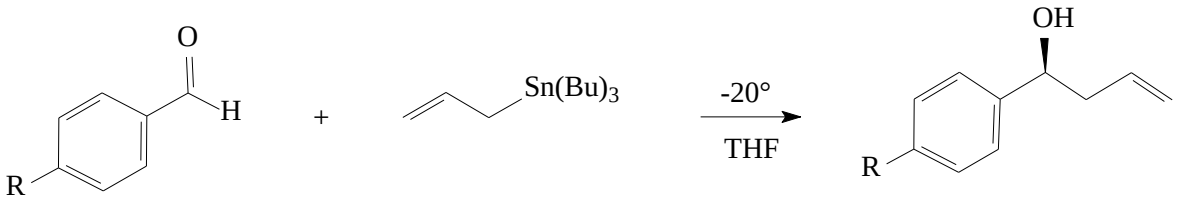
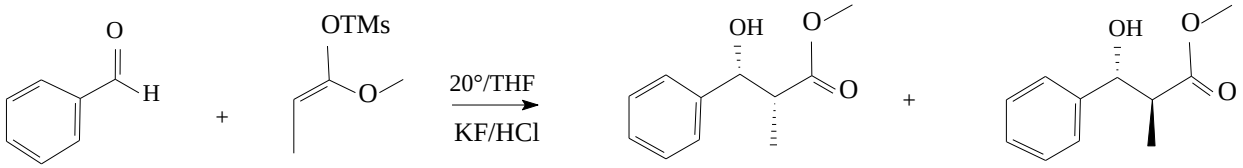
GRAPHICAL ABSTRACT





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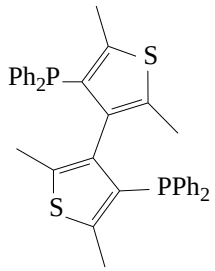
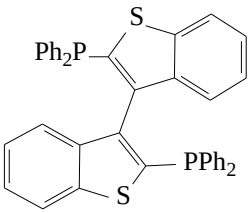
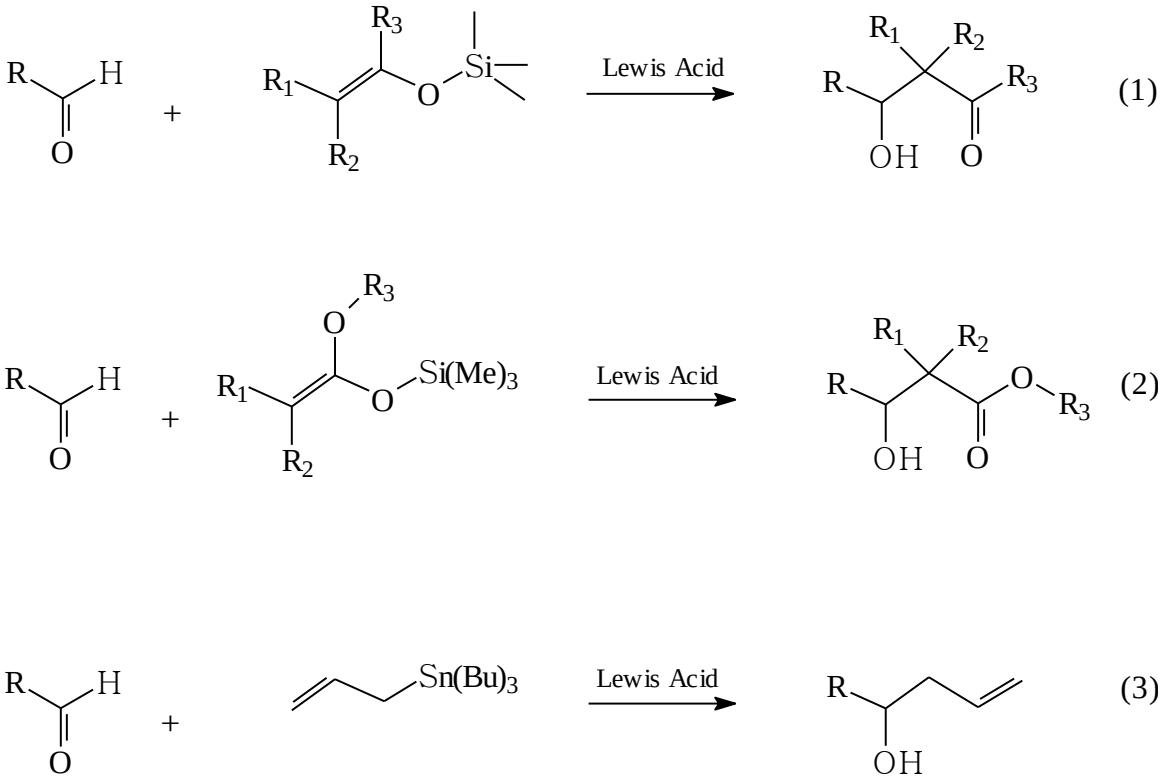


TetraMeBITIOP



BITIANP

SCHEME 1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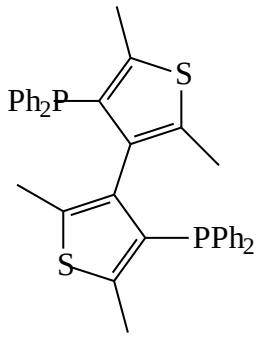

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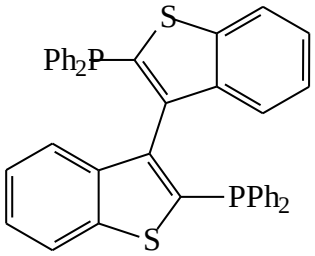


BITIANP

TABLE 1 : Allylation reaction of benzaldehydes with allyl tributyl tin catalysed by phosphine-silver(I)OTf complexes.
(Insert reaction formula)

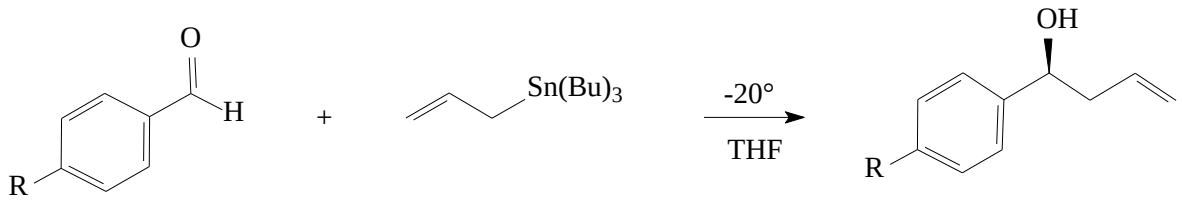
Entry	Phosphine	Substrate	Yield %	e.e.%	Conf.
1	(+)-tetraMeBITIOP	R = H	69	70	(S)-(-)
2	(-)-tetraMeBITIOP	R = Br	61	51	(+)
3	(+)-BITIANP	R = H	73	70	(R)-(+)
4	(+)-BITIANP	R = Br	55	78	(+)
5	(R)-(+)-BINAP	R = H	74	85	(R)-(+)
6	(R)-(+)-BINAP	R = Br	67	85	(+)

TABLE 2: Mukaiyama aldol reaction catalysed by phosphine-silver(I)OTf complexes.
(Insert reaction formula)

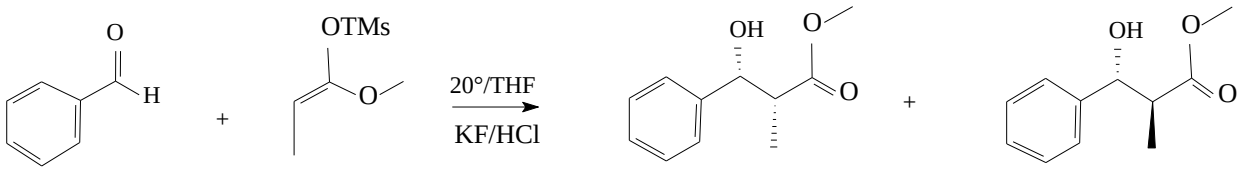
Entry	Catalyst	Yield%	Syn/Anti	e.e.%Syn	e.e.%Anti
1	(-)-tetraMeBITIOPAgOTf	13	1.2:1	32	51
2	(+)-BITIANPAgOTf	29	2.5:1	12	22
3	(-)-tetraMeBITIOP[(a)]AgOTf	98	1.7:1	30	48
4	(+)-BINAPAgOTf	33	1.4:1	21	18
5	((-)-tetraMeBITIOP)AgOAc	53	4.9:1	2	1

(a) 20 mol% catalyst is used.

Reaction formula of TABLE 1



Reaction formula of TABLE 2



syn anti