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Novel Chiral Biheteroaromatic Diphosphine Oxides for Lewis Base Activation of Lewis Acids in Enantioselective Allylation and Epoxide Opening

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Abstract: Enantiomerically pure biheteroaromatic diphosphine oxides were synthesised and tested as organocatalysts in two different reactions involving trichlorosilyl compounds. The allylation of aldehydes with allyl(trichloro)silane afforded homoallylic alcohols in fair to good yields and up to 95% *ee*. Preliminary experiments showed that this new class of metal-free catalysts was able also to promote the stilbene oxide opening by addition of tetrachlorosilane with enantioselectivity higher than 80%. The interesting results in terms of chemical and stereochemical efficiency open the way to further studies towards the development of new chiral heteroaromatic Lewis bases as efficient metal-free catalysts.

Keywords: allylation; biheteroaromatic diphosphine oxides; chiral Lewis bases; organic catalysts

The chemistry of penta- and/or hexavalent silicon compounds has recently attracted much attention because it offers the possibility to develop organocatalyzed enantioselective reactions which employ cheap, low toxic and environmental friendly compounds.[1] The hypervalent silicon species involved in synthetically useful processes are generally formed *in situ* by reaction between a four-coordinated silicon atom and a Lewis base in what is often called the "activation step".[2] The so formed five- or six-coordinated silicon species is able to promote the desired reaction in a catalytic process where the base dissociates from silicon after the product is formed and can start a new catalytic cycle.

In this context, the enantioselective addition of allyl(trichloro)silane to aldehydes represents a clear example of how metal-based enantioselective catalysts may be effectively replaced with simple organic molecules while maintaining high levels of chemical and stereochemical efficiency.[3] Among the different classes of compounds which have been employed as chiral Lewis bases to catalyze the reaction,[4] chiral phosphoramides[5] and pyridine *N*-oxides[6] have been widely employed with excellent results. Even if systems with relatively easy syntheses were developed,[7] including chiral bispyridine *N,N'*-dioxides,[8] or simple pyridine *N*-oxides that are easily assembled from inexpensive amino acids,[9] the search for new, readily available, efficient chiral organocatalysts for the reaction of trichlorosilyl compounds is still a true necessity.

Quite surprisingly diphosphine oxides, which are also able to coordinate trichlorosilyl derivatives and generate hypervalent silicates, have been scarcely considered as Lewis bases in such organocatalysed reactions.[10] So far, only BINAPO **1a**, the corresponding bis-phosphine oxide of the very popular diphosphine ligand BINAP, was employed by Nakajima's group in the allylation of aldehydes and the aldol reaction of trichlorosilyl enol ethers.[11] However, modest results were obtained in the addition of allyl(trichloro)silane to aldehydes ($<44\%$ *ee*) and only when working with additives and substitued allylsilanes were the enantioselectivties improved to a typical range of 50–70% *ee*.[11]

Since in the past years a wide and homogeneous series of electronically tunable C_2 symmetric diphosphines characterized by a biheteroaromatic atropisomeric backbone has been synthesized by us,[12] we decided to test the corresponding diphosphine oxides as organic catalysts in the reaction of trichlorosilyl compounds. The advantages offered by the biheteroaryldiphosphine oxides, with respect to carbocyclic aromatic derivatives, reside in their greater synthetic accessibility and in the possibility of testing a series of catalysts displaying different electronic properties. The influence of not only the electronic availability of the heterocyclic system but also the position of the phosphorus atoms on the latter on the kinetics and stereoselection has been demonstrated for the biheteroaromatic diphosphines.[13a] Since similar effects could be

observed also in the case of the corresponding diphosphine oxides, we selected tetraMe-BITIOPO **2**[13b] and N-Me-2-BINPO **3**,[13a] which are based on electron-rich 3-thiophenyl and 3-indolyl scaffolds, and the electron-poorer BITIANPO **4**[13c] where the sulfur atom exerts electron-withdrawing effects on the adjacent phosphorus function. These diphosphine oxides can be easily resolved through fractional crystallization of the diastereomeric adducts with optically active acids and recovered in an enantiopure state after alkaline decomplexation.

For sake of comparison also *p*-Tol-BINAPO (*S*)-**1b**, obtained by oxidation of (*S*)-Tol-BINAP, was tested (Figure 1).

The catalytic activity of the phosphine oxides was established using the allylation of benzaldehyde to afford homoallylic alcohol **5a** as the model reaction (Scheme 1). A typical experiment involved the use of 0.1 mol equiv. of catalyst, 1.2 mol equiv. of allyl(trichloro)silane, and 3 mol equiv. of DIPEA in acetonitrile for 48 h at 0 °C. Isolated yields and *ee*s, as determined by HPLC, are collected in Table 1; the absolute configuration was assigned to the predominant isomer of **5a** by comparison of its optical rotation.

From the preliminary experiments it was immediately clear that the compounds **1**–**4** behaved very differently as organocatalysts for the allylation of benzaldehyde. The most electron-deficient diphosphine oxide **4** was not able to promote the reaction in appreciable yields, while the electron-rich compounds **2** and **3** showed a significant catalytic activity, promoting the addition of allyl(trichloro)silane at 0 °C in 85% and 83% yield, respectively. Interestingly, the reaction catalysed by the medium electron-rich diphosphine oxide **1b** afforded the product in 55% yield, an intermediate value between those obtained with **2** and **4**. (entries 2–5 of Table 1). Biheteroaromatic diphosphine oxides showed not only a high chemical activity but also an extraordinary ability in determining the stereochemical outcome of the reaction. With (*S*)-*N*-Me-2-BINPO **3** the homoallylic alcohol was isolated in 81% *ee*, a result clearly higher than 51% of enantioselectivity obtained with catalyst **1b**. It is worth mentioning that BINAPO was shown to promote the reaction at 25 °C in only 37% *ee* (entry 1, Table 1).[11] Best results were obtained with (*S*)-tetraMe-BITIOPO **2** which catalysed the allylation in 93% *ee*, a very high level of enantioselectivity, comparable to those obtained with the best known catalysts.[4,7]

A few experimental parameters of the reaction promoted by (*S*)-**2** were investigated; among the different solvents tested in the reaction, such as toluene, tetrahydrouran, hexane and dichloromethane, only the last one led to good reasults and it allowed to us obtain the product in 87% *ee* even if in lower yield (entry 6 *vs.* entry 2, Table 1). Upon further lowering the reaction temperature the product was not isolated in an appreciable yield, while it was possible to decrease the catalyst loading amount: by running the reaction with 5% of the catalyst it was still possible to

Table 1. Enantioselective addition of allyltrichlorosilane to benzaldehyde.[a]

Entry	Catalyst	T [°C]	Solvent	Yield [%][b]	*ee* [%][c]
1[11]	**1a**	25	DCM	79	37
2	**2**	0	CH_3CN	85	93
3	**3**	0	CH_3CN	83	81
4	**4**	0	CH_3CN	<5	n.d.
5	**1b**	0	CH_3CN	55	51
6	**2**	0	DCM	67	87
7	**2**	−20	CH_3CN	<5	n.d.
8[d]	**2**	0	CH_3CN	65	93
9[e]	**2**	0	CH_3CN	83	77

[a] *Typical experimental conditions:* 0.1 mol equiv. of catalyst, 1.2 mol equiv. of allyl(trichloro)silane, and 3 mol equiv. of DIPEA, 40 h reaction time.
[b] Yields of isolated products.
[c] As determined by HPLC on a chiral stationary phase; yields and *ee* are average of duplicate experiments.
[d] Reaction run in the presence of 1 mol equiv of $SiCl_4$.
[e] Reaction run with 0.05 mol equiv of catalyst.

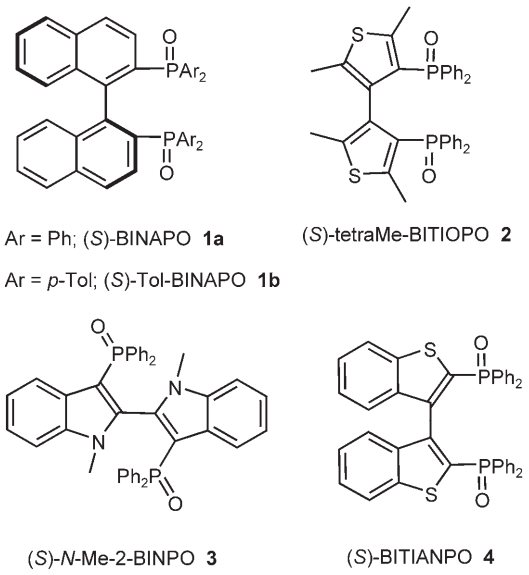
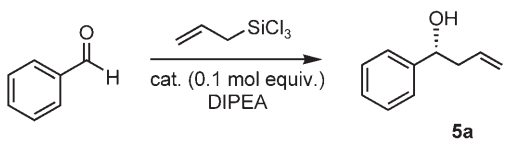
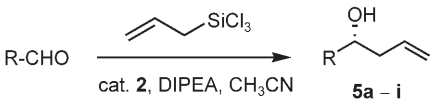


Figure 1. Structures of chiral diphosphine oxides.

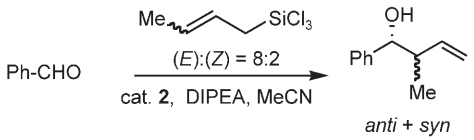


Scheme 1. Addition of allyl(trichloro)silane to benzaldehyde.



R = **5a**, Ph; **5b**, 4-$NO_2C_6H_4$; **5c**, 4-ClC_6H_4; **5d**, 4-$OMeC_6H_4$; **5e**, 2-$OMeC_6H_4$; **5f**, 3-$OMeC_6H_4$; **5g**, 1-naphthyl; **5h**, (*E*)-Ph-CH=CH **5i**, Ph-CH_2CH_2

Scheme 2. Addition of allyl(trichloro)silane to different aldehydes.

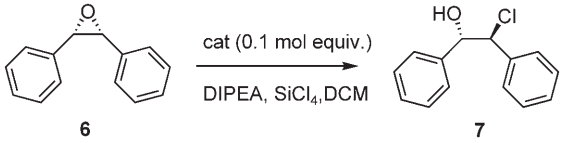


Scheme 3. Addition of (*Z*)-crotyltrichlorosilane to benzaldehyde promoted by catalysts **2.**

Table 2. Addition of allyltrichlorosilane to different aldehydes promoted by catalyst **2**.[a]

Entry	R group	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**5a**	85	93
2	4-$NO_2C_6H_4$	**5b**	51	93
3	4-ClC_6H_4	**5c**	55	95
4	4-$OMeC_6H_4$	**5d**	95	91
5	2-$OMeC_6H_4$	**5e**	95	83
6	3-$OMeC_6H_4$	**5f**	83	87
7	1-naphthyl	**5g**	98	81
8	Ph-CH=CH	**5h**	55	55
9	Ph-CH_2CH_2	**5i**	98	23[d]

[a] *Typical experimental conditions:* 0.1 mol equiv. of catalyst, 1.2 mol equiv. of allyl(trichloro)silane, and 3 mol equiv of DIPEA, 40 h reaction time at 0 °C in CH_3CN.
[b] Yields of isolated products.
[c] As determined by HPLC on a chiral stationary phase; yields and *ee* are average of duplicate experiments.
[d] The enantiomer with opposite configuration was obtained.



Scheme 4. Enantioselective opening of *cis*-stilbene oxide.

obtain **5a** in 83% yield, even if with decreased enantioselectivity (entry 8 *vs.* entry 2, Table 1). Yields were not improved by using some additives, such as tetrachlorosilane, but the enantioselectivity was not influenced either (entry 9 *vs.* entry 2, Table 1)

Having thus identified (*S*)-tetraMe-BITIOPO **2** as the more efficient catalyst, its use was extended to the allylation of other aromatic aldehydes to afford alcohols **5b**–**g** (Scheme 2 and Table 2).

The reported data show that *ee*s equal to or greater than 80% could be obtained, with a maximum value of 95% *ee* observed in the case of the 4-chlorophenyl-substituted alcohol **5c** (entry 3). Catalyst (*S*)-**2** efficiently promoted the addition of allyltrichlorosilane both to aromatic aldehydes bearing electron-withdrawing groups (entries 2 and 3) as well as electron-donating groups (entry 4) always with enantioselectivities higher than 90%. Interestingly the chemical yield seems to depend on the electronic nature of the aryl substituents in the aldehydes. Electron-poor aldehydes react slower than electron-rich aldehydes which give the product constantly in yields higher than 90% (entries 4, 5, 7 *vs.* entries 2 and 3).[14] The **2**-catalyzed allylation of cinnamaldehyde and 3-phenylpropanal was also attempted. While the former gave adduct **5h** in fair yield (55%) and *ee* (55%), surprisingly the latter proved to be highly reactive, even if the product **5i** was isolated in low enantioselectivity (98% yield, 23% *ee*, entry 9).[15]

The use of catalyst **2** was extended to the reaction of benzaldehyde with an 80:20 mixture of (*E*)- and (*Z*)-crotyltrichlorosilane (Scheme 3). A mixture of diastereoisomeric alcohols *anti* and *syn* in 83/17 ratio was obtained in 47% yield, the *anti* isomer having 85% *ee*. The fact that the *anti*:*syn* diastereoisomeric ratio reflected the (*E*):(*Z*) ratio of the starting silane, is generally considered a strong indication that a six-membered cyclic chair-like transition structure is involved in the allylation.

(*S*)-TetraMe-BITIOPO **2** efficiently promoted also the ring opening of *cis*-stilbene oxide by addition of tetrachlorosilane in DCM.[16] (Scheme 4) By performing the reaction a −78 °C (0.1 mol equiv. of **2**, 12 h, 1.2 mol equiv. of DIPEA, −78 °C, DCM)[17] the corresponding chlorohydrin **7** was isolated in quantitative yield and 81% *ee*, which favourably compares with the 82% *ee* obtained with catalyst **1b**.[18]

In conclusion, the biheteroaromatic diphosphine oxide tetraMe-BITIOPO easily available in both the enantiomerically pure forms in large amounts, being the precursor of the industrially produced tetra-Me-BITIOP,[19] was shown to be a really chemically and stereochemically efficient catalyst for the reaction of trichlorosilyl compounds. In particular the allylation of aldehydes afforded the products in very high yields and *ee*s up to 95%, providing novel insights in the design and synthesis of new chiral Lewis bases as effcient organocatalysts.

Experimental Section

Allylation Reaction; Typical Procedure

To a stirred solution of catalyst (0.03 mmol) in acetonitrile (2 mL) kept under nitrogen, an aldehyde (0.3 mmol) and diisopropylethylamine (DIPEA, 0.154 mL, 0.9 mmol) were added in this order. The mixture was then cooled to 0 °C and allyl(trichloro)silane (0.054 mL, 0.36 mmol) was added dropwise by means of a syringe. After 48 h stirring at 0 °C the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and EtOAc (5 mL) were added. The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature to afford the crude products. These were purified by flash chromatography with different hexane:AcOEt mixtures as eluant. Yield and *ee* for each reaction are indicated in the Tables.

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