A New Class of Chiral Lewis Basic Metal-Free Catalysts for Stereoselective Allylations of Aldehydes

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Abstract: A new class of amine *N*-oxides derived from *trans*-2,5diphenylpyrrolidine were synthesized in enantiomerically pure form and tested as metal-free catalysts in the reaction of aldehydes with allyl(trichloro)silane to afford homoallylic alcohols. The products were obtained in fair to good yields and up to 85% ee. The behavior of structurally different catalysts and the influence of a coordinating unit present in the organocatalyst on controlling the stereochemical efficiency of the reaction were also investigated. Noteworthy a catalyst capable of promoting the allylation of aliphatic aldehydes with an almost unprecedent and unusually high enantioselectivity, up to 85%, was identified.

Key words: *N*-oxides, allyltrichlorosilane, homoallylic alcohol, enantioselective catalysis, organocatalysis

The design and the synthesis of novel chiral Lewis bases which are able to act both as metal ligand as well as metalfree catalysts is a topic of paramount interest in the field of stereoselective catalysis.¹ Recently, special attention has been given to the development of an environmentally benign methodology that involves the use of nontoxic silicon-based reagents.² The coordination of a Lewis base to a tetracoordinated silicon atom leads to hypervalent silicate species of increased Lewis acidity at silicon center. As a consequence, such extracoordinated organosilicon compounds become very reactive carbon nucleophiles or hydride donors with a strong electrophilic character at silicon and an enhanced capability to transfer a formally negative-charged group to an acceptor.³

A paradigmatic example of successful chiral Lewis base catalyzed reaction is represented by the allylation of aldehydes with allyltrichlorosilanes to afford homoallylic alcohols with high enantioselectivity. Among the different classes of compounds which have been employed as chiral Lewis bases to catalyze the reaction,⁴ chiral phosphoramides,⁵ and less often diphosphine oxides⁶ have been employed with excellent results.

Among Lewis basic catalysts, one class of compounds that deserve a special attention are chiral *N*-oxides derived from tertiary amines and pyridines. The high nucleophilicity of the oxygen in *N*-oxides, coupled with a high affinity of silicon for oxygen represent ideal properties for the development of synthetic methodology based on nucleophilic activation of organosilicon reagents.⁷ A few efficient systems were developed, but the high level of stereocontrol achieved was the result of an extensive optimization of the stereochemical features of the catalysts, the synthesis of which required long and tedious procedures, sometimes involving also a resolution step. Furthermore a difficult-to-control stereogenic element such as a stereogenic axis in the catalyst is often required to achieve high levels of stereocontrol.

Even if systems of relatively easy synthesis were developed,⁸ including chiral bispyridine N,N'-dioxides,⁹ or simple pyridine N-oxides easily assembled from inexpensive aminoacids,¹⁰ the search of new, readily available, efficient chiral organocatalysts for the reaction of trichlorosilyl compounds is still very active.

In this field an element of novelty was brought by Hoveyda which developed an *N*-oxide prolinamide derivative, the only representative of aliphatic tertiary amine *N*-oxides so far reported, that presents a stereogenic center at the nitrogen.¹¹ We decided to synthesize a new family of rigid, aliphatic *N*-oxides bearing the stereocenters close to the catalytic site. To avoid the problem of the diastereoselective oxidation of the amine group, a cyclic structure was selected, where the nitrogen atom, although chirotopic, is not stereogenic. In this context, here we describe a new class of amine *N*-oxides derived from *trans*-2,5diphenylpyrrolidine as novel metal-free catalysts for the addition of allyltrichlorosilane to aldehydes.

According to a known procedure¹² starting from the commercially available 1,4-diphenyl-1,4-butandione the enantiomerically pure (1R,4R)-1,4-diphenyl-1,4-butandiol was obtained through reduction mediated by borane-(S)-diphenylprolinol complex. Conversion of the diol to the corresponding bismesylate derivative, followed by reaction with an excess of a proper amine afforded generally in good yields the *trans*-(2R,5R)-2,5-diphenylpyrrolidine derivative (Scheme 1).¹³ Finally, the oxidation of the tertiary amine to the corresponding *N*-oxide was accomplished by reaction with MCPBA at low temperature.¹⁴

The outlined general synthetic procedure allowed to prepare several molecules characterized by different structural features. Selected examples of the synthesized compounds are shown in Figure 1.

The catalytic ability of such new trans-(2R,5R)-2,5- diphenylpyrrolidine-derived *N*-oxides was then studied in

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Scheme 1 General procedure for the synthesis of catalysts 1–9



Figure 1 trans-(2R,R)-2,5-Diphenylpyrrolidine derivatives 1–9

the test reaction of the addition of allyltrichlorosilane to benzaldehyde (Scheme 2). In a typical procedure 0.1 mol equivalents of catalyst, 1.2 mol equivalents of allyltrichlorosilane, and 3 mol equivalents of DIPEA in acetonitrile were reacted 48 hours at different temperatures.¹⁵ Isolated yields and ee, as determined by HPLC, are collected in Table 1; the *R* absolute configuration was assigned to the predominant isomer of **10a** on the basis of its optical rotation. A comparison of the results obtained with catalysts **1** and **2** (entries 1 and 2 of Table 1) clearly showed that the presence of a chelating element on the *N*-alkyl chain was necessary in order to have a chemically active catalyst. These findings are in accordance with the general proposed transition state for the reaction involving the coordination of the silicon atom by two binding units.¹⁶

Not only the nature of the ancillary coordinating element besides the aliphatic *N*-oxide but also the distance be-

tween the two chelating units may play a decisive role in determining the chemical and stereochemical efficiency of the catalyst. For this reason in this new family of metal-free catalysts different silicon-coordinating moieties were used, such as pyridine, pyridine *N*-oxides, formamide, and amide groups, located at variable distances from the pyrrolidine *N*-oxide. The results of entries 3-5 of Table 1 show that a distance of five atoms between the coordinating elements proved to afford a good balance of activity and stereocontrol. Catalyst **5**, bearing a formamide group as secondary binding unit with a five-atom distance between the two coordinating oxygen atoms, offered the best performance and was able to promote the reaction at 0 °C in decent yield and 81% ee (entry 5 of Table 1).

The substitution of the formamide with a benzamide (entry 6), as well as with other coordinating elements such as a diphenylphosphine oxide or another tertiary amine *N*-



Scheme 2 Addition of allyltrichlorosilane to different aldehydes promoted by catalysts 1–9.

Table 1Addition of Allyltrichlorosilane to Benzaldehyde Promoted by Catalysts $1-9^a$

Entry	Temp (°C)	Catalyst (10 mol%)	Yield (%) ^b	ee (%) ^c
1	0	1	n.r.	n.d.
2	0	2	45	11
3	25	3	55	17
4	25	4	24	21
5	0	5	51	81
6	0	6	11	23
7	0	7	33	33
8	0	8	24	11
9	0	9	n.r.	n.d.
10 ^d	0	5	45	61
11 ^e	25	5	65	61

^a Reaction conditions: DIPEA (0.9 mmol), allyltrichlorosilane (0.36 mmol), aldehyde (0.3 mmol), catalyst (0.03 mmol), 48 h in MeCN.
 ^b Yields determined after chromatographic purification.

^c The ee determined by HPLC (Chiracel OD).

^d Reaction run in CH_2Cl_2 .

^e Reaction run at 25 °C for 60 h.

oxide (entries 7 and 8) resulted in much less active catalysts. As further demonstration of the importance of the distance between the chelating units, compound 9 bearing a C₃ alkyl chain instead of a C₂ alkyl chain present in catalyst 5 was completely ineffective in promoting the addition of allyltrichlorosilane to benzaldehyde (entry 9). Among various tested solvents catalyst 5 performed better in dichloromethane and specially in acetonitrile;¹⁷ the chemical yield was not dramatically improved even for longer reaction times, while an increase of the reaction temperature up to 25 °C led to a decreased enantioselectivity of 61% (entries 8 and 9).

Having thus identified the *trans*-(2R,5R)-2,5-diphenylpyrrolidine derivative **5** as the more efficient catalyst, its use was extended to the allylation of other aldehydes to afford alcohols **10b**–**g** (Scheme 2 and Table 2). Interestingly, the chemical yield seemed to depend on the electronic nature of the aryl substituents in the aldehydes. Electron-

Table 2 Stereoselective Addition of Allyltrichlorosilane to Different Aldehydes Promoted by Catalysts 5^a

Entry	Temp (°C)	Product	R	Yield (%) ^b	ee (%) ^c
1	0	10a	Ph	51	81
2	0	10b	$4-NO_2C_6H_4$	35	55
3	0	10c	$4-ClC_6H_4$	50	60
4	0	10d	2-OMeC ₆ H ₄	71	67
5	0	10e	(E)-PhCH=CH	33	63
6	0	10f	PhCH ₂ CH ₂	23	81
7 ^d	0	10f	PhCH ₂ CH ₂	67	85
8 ^e	25	10f	PhCH ₂ CH ₂	17	67
9 ^d	0	10g	Me(CH ₂) ₁₀	47	81

^a Reaction conditions: DIPEA (0.9 mmol), allyltrichlorosilane (0.36 mmol), aldehyde (0.3 mmol), catalyst (0.03 mmol), 48 h in MeCN.

^b Yields determined after chromatographic purification.

^c The ee determined by HPLC (Chiracel OD).

^d Reaction run with 30% cat mol.

^e Reaction run at 25 °C for 60 h.

poor aldehydes reacted slower than benzaldehyde, which reacted in lower yield than the electron-rich 2-methoxy benzaldehyde (entries 2 and 3 vs. entry 1, entry 1 vs. entry 4).

The **5**-catalyzed allylations of cinnamaldehyde and 3phenylpropanal were also attempted. While the former gave adduct **10e** in low yield (33%) and fair ee (63%), surprisingly the latter proved to be poorly reactive, but the product **10f** was isolated in high enantioselectivity (23% yield, 81% ee, entry 6). It must be noted that this result represents an element of novelty, compared to all the other known catalytic systems, which usually afforded the aliphatic homoallylic alcohol **10f** in low stereoselectivities.¹⁸

By increasing the catalyst loading the product **10f** was obtained in 67% yield and a very interesting 85% ee (entry 8 of Table 2). The use of catalyst **5** with other aliphatic aldehydes was also attempted; while the reaction with cyclohexanecarboxaldehyde did not lead to the product in appreciable yields, the addition of allyltrichlorosilane to dodecanaldehyde afforded the homoallylic alcohol **10g** in 47% yield and 81% ee. The result suggests that the presence of an aryl group in the aldehydic substrate does not play a decisive role in determining the stereochemical outcome of the reaction.

Finally, the use of catalyst **5** was extended to the reaction of benzaldehyde with a 81:19 mixture of (E)- and (Z)-cro-tyltrichlorosilane. A mixture of diastereoisomeric alcohols *anti*-**11** and *syn*-**11** in 78:22 ratio was obtained in 37% yield, the *anti* isomer having a 85% ee (Scheme 3). The fact that the *anti/syn* diastereoisomeric ratio reflected the E/Z ratio of the starting silane is generally considered¹⁹ a strong indication that a six-membered cyclic chair-like



Scheme 3 Addition of (Z)-crotyltrichlorosilane to benzaldehyde promoted by catalysts 5

transition structure is involved in the allylation. According to this model, the hypervalent silicon atom (commonly believed to be involved in this type of reactions) would be coordinated by the *N*-oxide oxygen and the formamide group in an even-membered chelate ring.^{9,10}

In conclusion a new class of Lewis bases to be used as metal-free catalysts in the addition of allyltrichlorosilane to aldehydes has been developed.

The proximity of the catalytically active *N*-oxide group to the stereocenters, the possibility to modulate the distance and the nature of a second silicon-binding unit, and the easy preparation in enantiomerically pure form in only three or maximum four steps from commercially available reagents are all positive features of the new catalytic system. Interestingly, a member of this new class of organocatalysts has shown an unusual ability to promote the allylation of aliphatic aldehydes with high enantioselectivity. Further studies directed to the development of new members of this new class of Lewis bases are under way in order to improve their stereochemical and specially their chemical activity.

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- (13) Reaction of (1*R*,4*R*)-1,4-Bis-(methansulfonyl)-1,4diphenylbutan with Ethylene Diamine and Formylation Reaction

A solution of ethylene diamine (8.45 g. 8.45 mmol) in CH₂Cl₂ (3 mL) was added under dry atmosphere at 0 °C to (1R,4R)-1,4-bis-(methansulfonyl)-1,4-diphenylbutan (0.587 g, 1.47 mmol). The reaction mixture was allowed to react at 0 °C for 16 h, then ethylene diamine and the solvent were evaporated under reduced pressure. The crude product was purified by a short column on silica gel (CH_2Cl_2 -MeOH = 8:2 as eluent mixture). A white waxy solid was obtained and used as such in the step (>98% yield). To a solution of the amine (0.428 g, 1.6 mmol) in formic acid (2.9 g, 63.4 mmol) cooled to 0 °C, Ac₂O (1.15 g, 11.2 mmol) was added dropwise. The reaction mixture was allowed to stir at r.t. for 20 h, then it was quenched with H_2O and solid K_2CO_3 to make the solution alkaline. The aqueous phase was extracted 3 times with CH₂Cl₂, the organic phase was then dried over Na₂SO₄ and evaporated under reduced pressure. The purification by flash chromatography (CH_2Cl_2 -EtOAc = 7:3 as eluent mixture) afforded the diol as colorless oil (53% yield). ¹H NMR (300 MHz, CDCl₃): δ = 8.01 (s, 1 H), 7.39– 7.21 (m, 10 H), 5.68 (br s, 1 H), 3.07 (m, 2 H), 2.57 (m, 2 H), 2.46 (m, 2 H), 1.96 (m, 2 H). MS (ESI⁺): *m*/*z* = 317.5 [M + Na]⁺. [α]²³ –131.0 (*c* 0.41, CHCl₃). IR (CH₂Cl₂): $v_{C=0} = 1685.5 \text{ cm}^{-1}$.

(14) N-Oxidation

To a solution of the N-formyl pyrrolidine (0.11 g, 0.35 mmol) in CH₂Cl₂ (7 mL) at -78 °C under nitrogen atmosphere K₂CO₃ (0.10 g, 0.76 mmol) and MCPBA 70% (0.092 g, 037 mmol) were added; the reaction mixture was stirred at -78 °C, followed by TLC and stopped after 6 h by filtering the mixture onto Celite cake. The organic phase was washed 3 times with K2CO3 sat. soln, dried over Na2SO4 and evaporated under reduced pressure. The purification by flash chromatography (CH_2Cl_2 -MeOH = 95:5 as eluent mixture) afforded catalyst 5 as white solid (73% yield); mp 139-141 °C; $[\alpha]^{23}$ –229.3 (*c* 0.48 in CHCl₃). IR: $v_{C=0}$ = 1669.09 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 8.65 (br s, 1 H), 7.91 (s, 1 H), 7.65 (m, 4 H), 7.50 (m, 5 H), 7.40 (m, 3 H), 5.00 (dd, 1 H), 4.55 (dd, 1 H), 3.45 (m, 1 H), 3.15 (m, 1 H), 3.00 (m, 1 H), 2.85 (m, 1 H), 2.65 (m, 1 H), 2.5 (m, 1 H), 2.25 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 160.8, 137.1, 132.4, 131.7, 129.8, 129.7, 129.5, 129.4, 128.2, 86.1, 76.8, 59.0, 34.2, 29.6, 28.2. MS (ESI⁺): *m/z* 333.5 [M + Na]⁺. Anal. Calcd for C₁₉H₂₂N₂O₂: C, 72.52; H, 7.14; N, 9.03. Found: C, 72.45; H, 7.18; N, 9.08.

(15) Allylation Reaction – Typical Procedure

To a stirred solution of catalyst (0.03 mmol) in MeCN (2 mL) kept under nitrogen, an aldehyde (0.3 mmol) and 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 NaHCO₃ (1 mL). The mixture was allowed to warm up to r.t. and H₂O (2 mL) and EtOAc (5 mL) were added. The organic phase was separated and the aqueous phase was extracted 3 times with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under vacuum at r.t. to afford the crude products. These were purified by flash

chromatography with different hexanes–ethyl acetate mixture as eluents. Yields and ee for each reaction are indicated in Tables 1 and 2. The assignment of the R absolute configuration to the predominant isomer formed in each reaction rests on comparison of sign of optical rotation with those reported in the literature, or on the reasonable assumption that the absolute configuration of the alcohols obtained by the reaction with a given catalyst is independent on the structure of the aldehyde.

- (16) For a discussion on the proposed transition states for these reactions, see ref. 2, 5, and 7.
- (17) The reaction performed in other solvents such as toluene, hexane, or THF afforded the product with lower stereoselectivity.
- (18) Enantioselectivities reported for product 10f were very often lower than 50%. For the only notable exception, see: Chai, Q.; Song, C.; Sun, Z.; Ma, Y.; Ma, C.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* 2006, 47, 8611.
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