Account

Recent Advances in Organic Reactions Catalyzed by Lanthanide(III) Complexes

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Lanthanide compounds have been attracting much attention in organic synthesis. Chiral Ln-substituted BINOL have been widely studied in several asymmetric organic reactions. $LnCl_3$ and $Ln(OTf)_3$ have been expected to serve as Lewis acids and have been applied to many important synthetic reactions in a one-pot manner. $Ln(O-i-Pr)_3$ exhibits some basic characters, which also can be utilized in some special organic transformation. This article deals with some lanthanides(III) complexes promoted organic reactions, which we have recently developed.

Keywords   lanthanide, chiral Ln-BINOL, $LnCl_3$, $Ln(OTf)_3$, organic reaction

Introduction

The name "rare earth" applies to the lanthanides, yttrium and scandium. The 15 elements of lanthanide from lanthanum to lutetium constitute a unique family of closely related elements (the difference lying in the number of 4f eletrons) from which regents or catalysts with "tunable" chemical properties can be expected. Lanthanide ions [Ln(III)] are usually considered as hard acids in the HSAB classification by Pearson, being located between Sr(II) and Ti(IV). Many of the applications of lanthanides to organic chemistry deal with trivalent lanthanides, which are considered to be the most common oxidation state. Ln(III) derivatives are Lewis acids as deduced from their chemical behavior, but their properties are closely related to the nature of the ligand around the metal centre. For example, $Ln(OTf)_3$ is the strongest

Lewis acid while $Ln(O-i-Pr)_3$ is a stronger base than the group 4 metal alkoxides due to the lower ionization potential (*ca.* 5.4—6.4 eV) and the lower electronegativity (1.1—1.3 eV) of rare earth elements.

Another characteristic feature of lanthanides is their strong affinity for oxygen. Oxophilicity is an important property, which can be helpful for the activation of oxygenated organic functions. Furthermore, Multiple coordination sites available to lanthanide salts might allow coordination of ancillary chiral ligands and the substrates.

This account, which covers the literatures published since 1997, intends to convey the heightened interest of us upon the discovery, exploration of the lanthanide compounds in some asymmetric reactions, as well as important synthetic reactions in a one-pot manner.

Asymmetric organic reactions catalyzed by chiral lanthanide(III) complexes

Recently, the great applications of lanthanide catalysts in organic synthesis have been found, particularly as a chiral catalyst for some asymmetric reactions, because of their strong Lewis acidity, high coordination numbers and fast coordination-dissociation equilibrium. Our group has recently explored some catalytic asymmetric organic reactions catalyzed by chiral lanthanide complexes and achieved good enantioselectivity.

Enantioselective trimethylsilylcyanation of aldehyde catalyzed by chiral lanthanide alkoxides [2]

We have reported the first example of enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral lanthanide alkoxides. An obvious effect of substituents at the 3,3'-positions of BINOL on the enantioselectivity was observed. The (S)-3,3'-bis(methoxyethyl)-BINOL which contains a donor group had the advantage over simple BINOL to give (S)-products in excellent yields and up to 73% ee.

Treatment of the chiral ligand with 1.5 equiv. of La-(OBu-t)$_3$ in dichloromethane gave a clear solution containing a catalytically active species for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde (Scheme 1). With the catalysts prepared above, we succeeded in carrying out the enantioselective trimethylsilylcyanation of aldehyde (Table 1).

A variety of aldehydes including aromatic and aliphatic aldehydes are silylcyanated in good to excellent yields with the moderate enantioselectivity. The highest enantiomeric excesss is 73% using cat. **4**. It was found that the substituents in the 3,3'-position of BINOL skeleton have a significant effect on the enantioselectivity of the asymmetric trimethylsilylcyanation of aldehyde, and chiral cat. **4** afforded the products in 48%—73% ee which was higher than that provided by simple BINOL (23%—58%). However, sterically hindered ligand such as (S)-3,3'-bis(trimethylsilyl)-BINOL and (S)-3,3'-diphenyl-BINOL produced α-hydroxy nitriles with lower enantioselectivity than simple BINOL.

Asymmetric nitroaldol reactions catalyzed by chiral lanthanide alkoxides [3]

With more effective chiral ligands in hand, we prepared 4 kinds of heterobimetallic catalysts [(S)-LLB] according to Shibasaki's method,[4] as described in Scheme 2. Then, we succeeded in applying these catalysts to the nitroaldol reaction. The nitroaldol (Henry) reaction is a powerful synthetic tool and is utilized for constructing numerous natural products and other useful compounds.

Just as in the case of asymmetric trimethylsilylcyanation, cat. **7** showed better enantioselectivity (62%—88%) than that obtained by simple BINOL (36%—73%).

Scheme 1

(S)-3,3'-bis(R)-BINOL

(S)-Chiral La catalyst
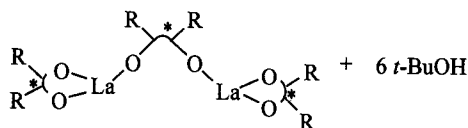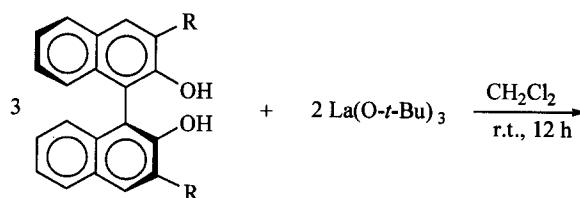
cat. **1**: R = H; cat. **2**: R = SiMe$_3$;
cat. **3**: R = Ph; cat. **4**: R = CH$_2$CH$_2$OCH$_3$.

Table 1 Enantioselective trimethylsilylcyanation of aldehyde

$$RCHO + Me_3SiCN \xrightarrow[CH_2Cl_2, -78\,^\circ C, 10\,h]{Chiral\ La\ cat.\ (10\ mol\%)}$$

| R	Cat.	Yield (%)	ee % (confign.)
Ph	**1**	81	49 (S)
	2	86	36 (S)
	3	84	32 (S)
	4	77	71 (S)
p-CH$_3$C$_6$H$_4$	**1**	79	58 (S)
	2	83	40 (S)
	3	82	34 (S)
	4	80	73 (S)
p-CH$_3$OC$_6$H$_4$	**4**	56	63 (S)
c-C$_6$H$_{11}$	**4**	76	54 (S)

Asymmetric hydrophosphonylation of aldehydes [5]

In order to explore the effect of substituents in the BINOL skeleton, we took advantage of a convenient and direct ortho-lithiation strategy and the Ni-catalyzed coupling reaction to synthesize two newly polysubstituted
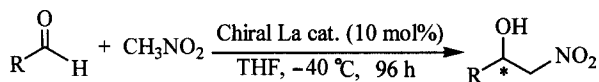
Scheme 2
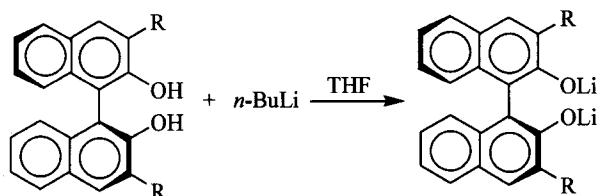
(S)-3,3'-bis(R)-BINOL
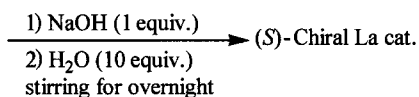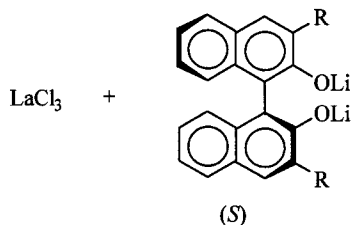
cat. **5**: R = SiMe₃; cat. **6**: R = Ph; cat. **7**: R = CH₂CH₂OCH₃;
cat. **8**: R = H.

BINOL-dervatives. One is (S)-6, 6'-diphenyl-BINOL which was obtained in 65% yield and > 99% *ee*. The other is (S)-3,3'-bis(2-methoxyethyl)-6,6'-diphenyl-1, 1'-bi-2-naphthol (49% yield, 99% *ee*.)

The chiral lanthanide catalysts were prepared according to Scheme 3 and succeeded in applying to the asymmetric hydrophosphonylation of aldehyde. The enantiomeric excesses of the hydrophosphonylation product are very different although the activities of all five chiral catalysts are good. This is exemplified by a comparison of cat. **11** and cat. **13**. By using cat. **11**, α-hydroxyphosphonate was obtained in 39% *ee* and 69% *ee* for benzaldehyde and *p*-tolualdehyde, respectively, while using cat. **13**, racemic products for both aldehydes were obtained. As expected, the substitutes on BINOL skeleton also have an obvious effect on the enantioselectivity of this reaction, however, it is the substituents at the 6,6'-position, not those of the 3,3'-position. (S)-6,6'-Diphenyl

BINOL was found to give the best results. In addition, there is almost no synergetic effects between (S)-3,3'-bis(methoxyethyl)-BINOL and (S)- 6, 6'-diphenyl-BINOL. The reaction of an aliphatic non-conjugated aldehyde afforded the corresponding α-hydroxyphosphonate without any optical induction in a good yield, while aromatic and conjugated aldehydes gave higher enantioselectivity (Table 2).

Scheme 3
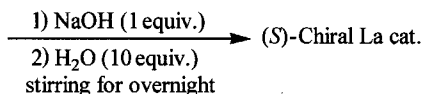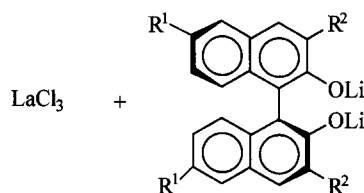
cat. **9**: R¹ = R² = H; cat. **10**: R¹ = H, R² = CH₂CH₂OCH₃;
cat. **11**: R¹ = Ph, R² = H; cat. **12**: R¹ = Ph, R² = CH₂CH₂-OCH₃; cat. **13**: R¹ = H, R² = SiMe₃.

Table 2   Catalytic asymmetric reaction of aldehydes with diethyl phosphite
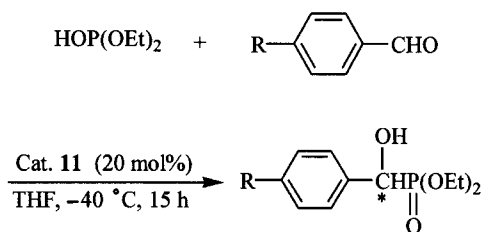
Entry	Aldehyde	Temp. (℃)	Yield (%)	*ee* (%)
1	PhCHO	−40	82	39
2	*p*-CH₃C₆H₄CHO	−40	93	69
3	*p*-CH₃OC₆H₄CHO	−78	89	74
4	*p*-ClC₆H₄CHO	−40	95	52
5	PhCH = CHCHO	−20	78	41
6	1-naphthylcarbaldehyde	−40	80	35
7	PhCH₂CH₂CHO	−40	75	0

Asymmetric epoxidation of (E)-enones[6]

The catalytic asymmetric epoxidation of α,β-unsaturated ketones has been received much attention during the last few years due to the fact that enantiomerically enriched epoxides can be converted into various useful optically active synthetic intermediates. Recently, we synthesized several derivatives of (S)-BINOL ligands with 6,6'-substituents and applied as chiral ligands in the Yb(O-i-Pr)$_3$ catalyzed asymmetric epoxidation of α,β-unsaturated ketones. Superior results were obtained with (S)-6,6'-diphnyl-BINOL ligand, as exemplified in the asymmetric epoxidation of (E)-1,3-diphenylprop-2-en-1-one in 91% yield and up to 97% ee at 0 ℃ (Scheme 4). Using simple (S)-BINOL as the ligand, the epoxy ketone was isolated in low ee (44%). It was found that the substituents aryl group in 6,6'-position of BINOL skeleton strongly influence the degree of enantiomeric excesses of epoxidation products. When the electron-withdrawing substituent in the phenyl ring, i. e., p-CF$_3$C$_6$H$_4$ was introduced into the 6,6'- position of the BINOL, the enantiomeric excess of epoxidation product was slightly increased compared with the results obtained with 6,6'-diphenyl-BINOL. On the contrary, the enantioselectivity of the epoxidation product was decreased when p-CH$_3$C$_6$H$_4$, p-MeOC$_6$H$_4$ and 1-naphthyl substituents at 6,6'-position of BINOL. In addition, excellent chemical yield and enantioselectivity have been achieved for several epoxides at room temperature by using 5 mol% of Gd(O-i-Pr)$_3$-(S)-6,6'-diphenyl-BINOL and La(O-i-Pr)$_3$-(S)-6, 6'-dibromo-BINOL, respectively. Up to 95% ee was obtained for e-poxychalcone with both Gd(O-i-Pr)$_3$-(S)-6,6'-diphenyl-BINOL and La (O-i-Pr)$_3$-(S)-6, 6'-dibromo-BINOL catalytic systems at room temperature. These catalysts are much cheaper than ytterbium system.

The reason for the excellent enantioselectivity produced by (S)-6, 6'-dibromo-BINOL and (S)-6, 6'-diphenyl-BINOL may be ascribed to the electronic effect of Br and Ph groups on the 6,6'-position of BINOL, which produces a more favorable coordination environment between the ligand and lanthanide, and leads to the improvement of asymmetric induction. As a comparison, ligand (S)-6, 6'-dimethyl-BINOL was further synthesized and applied to this epoxidation. Just as expected, it gave lower ee values than two ligands mentioned above due to the lower inductive effect.

Scheme 4

(S)-6,6'-Diphenyl-BINOL
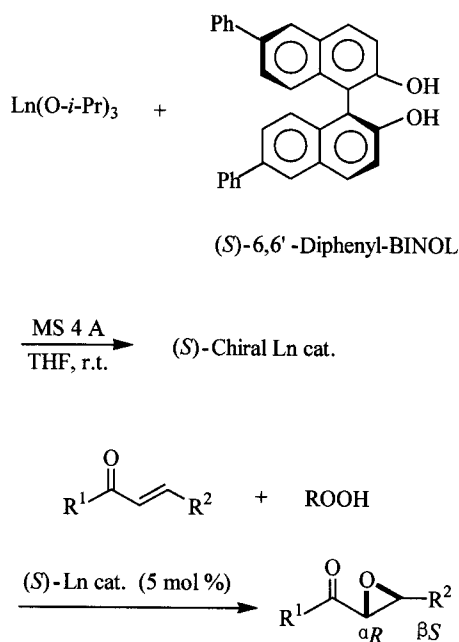
Asymmetric glyoxylate-ene reaction catalyzed by C_2-symmetric chiral bis(oxazoline)-lanthanide complexes [7]

In recent years, C_2-symmetric chiral bis(oxazoline)-metal complex has received a great deal of attention due to their successful use in various catalytic asymmetric processes. But there are few reports with the use of these ligands in lanthanide catalysts. We have developed the Ph-pybox-Yb(OTf)$_3$ catalytic system for the asymmetric glyoxylate-ene reaction [Eq. (1)]. The 2-aryl-1-alkene reacted with alkyl glyoxylate to afford unsaturated α-hydroxy esters in a reasonable yields and moderate enantioselectivities (46%—54%).


                                              (1)

Ph-pybox, R = Ph
i-Pr-pybox, R = i-Pr
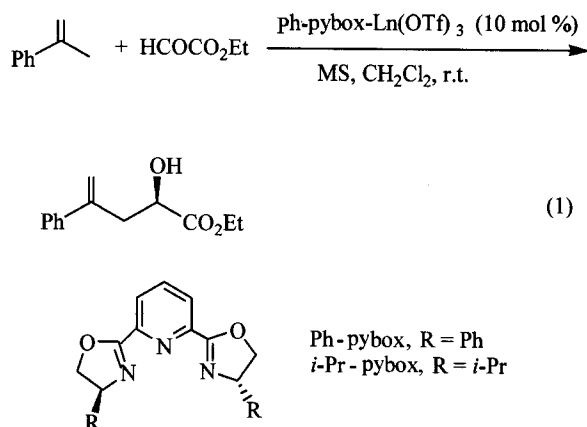
The glyoxylate-ene reaction between menthyl glyoxylate and alkenes catalyzed by Ph-pybox-Yb(OTf)$_3$ complex was further investigated. An enhanced level of diastereoselectivity (81% *de*) was obtained. We found that the reaction of menthyl glyoxylate with alkenes has higher diastereoselectivity than that of alkyl glyoxylate and the corresponding alkene. Evidently, the substrate and asymmetric catalyst have the same effect of induction.

Asymmetric hetero-Diels-Alder reaction of glyoxylate eaters and Danishefsky's diene catalyzed by chiral bis (oxazoline)-lanthanide complexes [8]

Using the chiral Yb(OTf)$_3$-*i*-Pr-pybox as the asymmetric catalyst, an enantioselectivity of 77% for hetero-Diels-Alder reaction of methyl glyoxylate with Danishesky's diene was achieved (Scheme 5), which is better than those with cationic bis(oxazoline)-Cu,[9] other lanthanide complex[10] and the (+)-BINOL-Ti activator system,[11] and is even comparable to the (*R*)-BINOL-Ti activator system.[12] Moreover, the chiral ligand can be recovered in 80%—90% isolated yield.
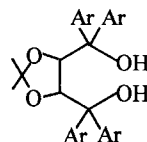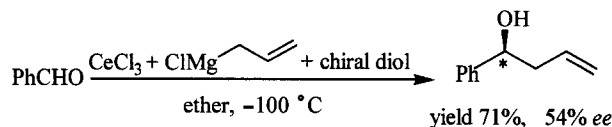
Scheme 5
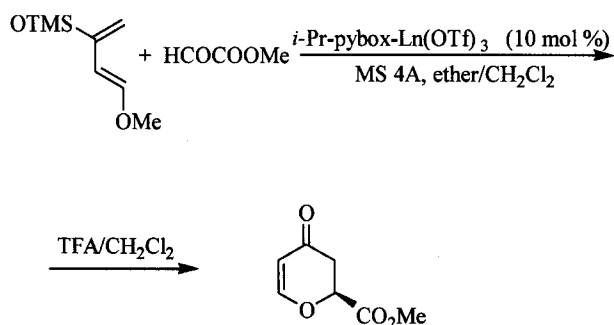
The first example of enantioselective allylation of aldehyde with chiral allyl organolanthanide reagents has been achieved in high chemical yield and moderate optical purity (up to 54% *ee*, Scheme 6).[13]

Five amino-TADDOL derivatives (Scheme 7) have been used as catalysts for the enantioselective addition of diethylzinc to aromatic aldehyde, and excellent chemical yield and good enantioselectivities were obtained (up to 88 % *ee*). It was found that the substituents on the nitrogen atom play an important role in the stereochemistry, or even reverse the configuration of the products. The effects of Li salts of aminoalcohols on the reaction depend on aminoalcohol character.[14]
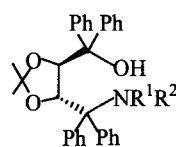
Scheme 6

Chiral diol = (+)- $\alpha,\alpha,\alpha',\alpha'$ -tetra (*o*-methoxylphenyl)- dioxalane-4,5-dimethylnol

Ar = *o*-CH$_3$OC$_6$H$_4$

Scheme 7

1) R^1 = R^2 = H
2) R^1 = H, R^2 = Me
3) R^1 = R^2 = Me
4) R^1 = H, R^2 = Bn
5) R^1 = H, R^2 = Et

Important organic reaction catalyzed by Lewis acids Ln(OTf)$_3$ and LnCl$_3$

Lewis acids catalyzed carbon-carbon bond forming reactions are now of great interest in organic synthesis. These reactions must be carried out under strictly anhydrous conditions, because most Lewis acids immediately react with water rather than the substrates and are decomposed or deactivated. Recent discoveries indicate that rare earth trifluoromethanesulfonate complexes are excellent water tolerants and reusable catalysts, and have unique properties as compared with traditional Lewis acids in several important carbon-carbon bond forming reactions.[15] Hydrated forms of the lanthanide(III) trifluoromethanesulfonates (triflates) are prepared from the reaction of the corresponding oxide with aqueous trifluromethanesulfonic acid (TfOH) solution in water. Typically, the crude product contains eight or nine molecules of water. Extensive heating under vacuum is required to produce a compound that is water free. In addition, Ln(OTf)$_3$ effectively activated carbonyl and related compounds as Lewis acids in water or several organic solvents. They have been

used for the activation of nitrogen-containing compounds which deactivate most Lewis acid. Herein, we will discuss the use of these reagents in some carbon-carbon formation processes such as glyoxylate-ene reactions, and in some carbon-heteroatom bond forming processes including asymmetric hetero Diels-Alder reaction, 1,3-dipolar cycloaddition of nitrones with electron-rich alkenes, and a one-pot synthesis of α-amino phosphonates, tetrahydroquinolines and dihydropyrimidinones.

Glyoxylate-ene Reaction [16]

Glyoxylate-ene reactions produce unsaturated α-hydroxyl esters, which are a class of compounds of synthetic and biological importance. The reactions take place at high temperature or are catalyzed by Lewis acids. Since Ln(OTf)$_3$ could activate the C = O bond of the glyoxylate, it was used to catalyze the Glyoxylate-ene reaction. The reactions proceed smoothly in the presence of a catalytic amount of ytterbium triflate (20 mol%) at room temperature in acetonitrile to give the corresponding α-hydroxy esters in good yields [Eq. (2)]. Yb(OTf)$_3$ could be recovered and reused, and the catalytic activity did not decrease at all. This reaction is the first example of the lanthanide-catalyzed ene reaction of glyoxylates with alkenes.

(2)
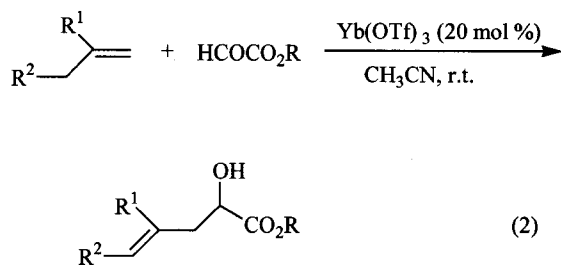
The reaction between a diene, such as isoprene, and an glyoxylate can lead to the formation of both the hetero Diels-Alder (DA) product and the Ene product [Eq. (3)]. In such cases, solvents controlled the mode of addition, and the ratio of Ene and DA products strongly depends on the solvents used. Acetonitrile led to a high degree of DA selectivity. In sharp contrast, dichloromethane brought about a great degree of Ene selectivity. Here, it seems that a high degree of DA selectivity was first realized in the reaction of glyoxylates with isoprene
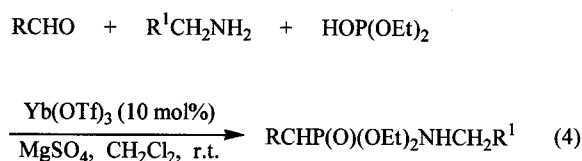
by using Yb(OTf)$_3$ catalyst in acetonitrile.

(3)
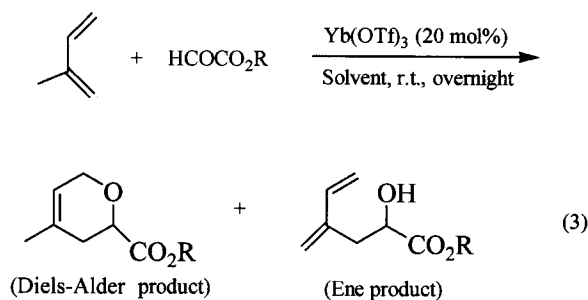
This new addition reaction provides several reactive functions in the products that can be successful manipulated for the synthesis of biologically important complex molecules.

One-pot synthesis of α-amino phosphonates from aldehydes, amine and diethyl phosphite [17]

Since rare earth metal triflates are stable in water and can be recovered after the reaction and reused without loss of activity. It was found that the one-pot reaction of benzaldehyde, benzylamine and diethyl phosphite took place smoothly in the presence of Yb(OTf)$_3$ (10 mol%) and MgSO$_4$ [Eq. (4)].

$$RCHO + R^1CH_2NH_2 + HOP(OEt)_2$$

$$\xrightarrow[\text{MgSO}_4, \text{ CH}_2\text{Cl}_2, \text{ r.t.}]{\text{Yb(OTf)}_3 \text{ (10 mol\%)}} RCHP(O)(OEt)_2NHCH_2R^1 \quad (4)$$

It is worth mentioning that the yield of the α-aminophosphate was only 21% when promoted by 100 mol% SnCl$_4$, but can be improved to 89% in the presence of 10 mol% Yb(OTf)$_3$, which demonstrates that the imines were much more effectively activated by Yb(OTf)$_3$ than that by other Lewis acids such as SnCl$_2$, SnCl$_4$ and BF$_3 \cdot$ Et$_2$O. In all cases, the three-component reaction proceeded smoothly to afford the corresponding phosphonates. Aromatic aldehydes provided excellent yields of products, while aliphatic aldehydes afforded phosphonates in moderate yields, due to the fact that aromatic aldehydes have higher reactivity than aliphatic aldehydes. Our modification of the hydrophosphonylation reaction can be

consider as a convenient variant Kabachnik-Field reaction. Therefore this reaction has a big potential.

Lanthanide triflate catalyzed Biginelli reaction[18,19]

The Biginelli reaction,[20] first described more than a century ago, is a one-pot but low yield (usually 20%—50%) condensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of a catalytic amount of an acid. We disclosed a novel lanthanide triflate catalyzed Biginelli reaction applied to the one-pot syntheses of dihydropyrimidinones under solvent-free conditions, which not only is very simple and high yield (81%—99%), but also greatly decreases environmental pollution (Table 3).

Compared to the classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variation in all the three components. Besides the β-ketone ester, the aromatic β-diketone and heterocyclic β-diketone can also be employed. Most importantly, aromatic aldehydes carrying either electorn-donating or electron-withdrawing substitutuents reacted very well, giving the products in excellent yields, and many of the pharmacological relevant substitution patterns on the 4-aryl ring can thus be introduced with high efficiency.[21]

One-pot synthesis of tetrahydroquinolines catalyzed by Dy-(OTf)$_3$ in an aqueous solution[22]

We have found a very simple and highly efficient three-component condensation reaction of *N*-methylaniline, commercially avaliable formaldehyde solution and electron-rich alkenes for the one-pot synthesis of 1,4-disubstituted-1,2,3,4-tetrahydroquinolines in good yields (above 80 %) using 1 mol% Dy(OTf)$_3$ as the catalyst and in the absence of any organic solvents at ambient temperature [Eq. (5)]. The aqueous solution reaction can reduce hazardous pollution and achieve environmental benign synthetic organic process.

Syntheis of furo[3,2-c] and pyrano[3,2-c]quinoline by lanthanide triflate catalyzed imino-Diels-Alder reaction[23]

Tetrahydroquinoline derivatives are an important class of natural products and exhibit biological activities in various fields. Aza-Diels-Alder reaction between *N*-

**Table 3** Synthesis of dihydropyrimidinones catalyzed by Ln(OTf)$_3$ under solventless conditions

X = O, catalyst = Yb(OTf)$_3$(5 mol%)
X = S, catalyst = La(OTf)$_3$(3 mol%)
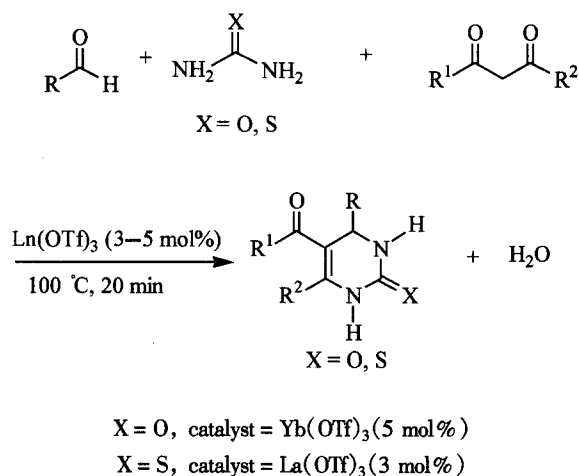
Entry	X	R	R^1	R^2	Yield (%)
1	O	C$_6$H$_5$	C$_2$H$_5$O	CH$_3$	96, 95, 97 ^{a}
2	O	4-CH$_3$OC$_6$H$_4$	C$_2$H$_5$O	CH$_3$	96
3	O	4-NO$_2$C$_6$H$_4$	C$_2$H$_5$O	CH$_3$	94
4	O	4-FC$_6$H$_4$	C$_2$H$_5$O	CH$_3$	94
5	O	2,4-Cl$_2$C$_6$H$_3$	C$_2$H$_5$O	CH$_3$	89
6	O	4-CF$_3$C$_6$H$_4$	C$_2$H$_5$O	CH$_3$	87
7	O	C$_6$H$_5$CH=CH	C$_2$H$_5$O	CH$_3$	81
8	O	*i*-Pr	C$_2$H$_5$O	CH$_3$	83
9	O	C$_6$H$_5$	CH$_3$	CH$_3$	94
10	O	4-CH$_3$OC$_6$H$_4$	CH$_3$	CH$_3$	91
12	O	C$_6$H$_5$	C$_6$H$_5$	CF$_3$	96
13	O	C$_6$H$_5$	2-thienyl	CF$_3$	94
15	O	4-CH$_3$OC$_6$H$_4$	CH$_3$O	CH$_3$	99
16	O	4-NO$_2$C$_6$H$_4$	CH$_3$O	CH$_3$	91
17	O	4-FC$_6$H$_4$	CH$_3$O	CH$_3$	81
18	S	C$_6$H$_5$	C$_2$H$_5$O	CH$_3$	98
19	S	3-CH$_3$C$_6$H$_4$	C$_2$H$_5$O	CH$_3$	96
20	S	4-CH$_3$OC$_6$H$_4$	C$_2$H$_5$O	CH$_3$	93
21	S	C$_6$H$_5$	C$_6$H$_5$	CH$_3$	96

^{a} Catalyst was reused for 3 times.
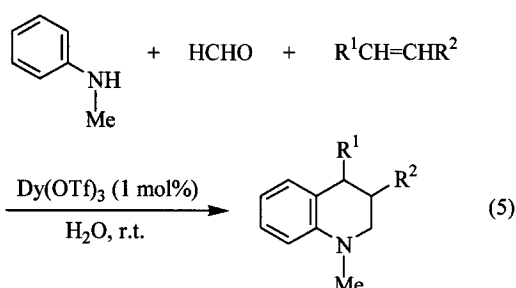
arylimines and nucleophilic olefins is one of the most powerful synthetic tools for constructing N-containing six-membered heterocyclic compounds. Takai[24] reported the catalytic reaction of N-arylaldimines with vinyl ethers, but the amount of catalyst was not screened in detail and afforded products in low yields together with by-products. We improved this reaction and found that the amount of lanthanide triflate catalyst affects strongly the yields of products and chemical selectivity. In the presence of Yb-$(OTf)_3$(0.5 mol%), the reaction of imines with 2,3-dihydrofuran or 3,4-dihydro-2-H-pyran proceeded smoothly

Scheme 8
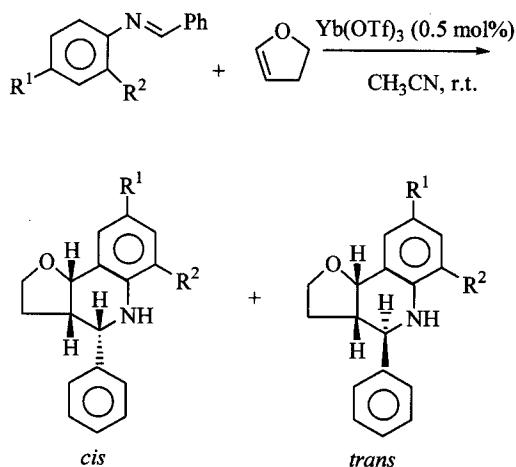
to afford furo[3,2-c] and pyrano[3,2-c]quinolines with an overyield of 74%—94% (Scheme 8).

Addition of silyl ketene acetals to nitrones catalyzed by lanthanum triflate [25]

Nitrones offer interesting advantages with respect to imines, hydrazones and other nitrogen derivatives of aldehydes in the reactions with nucleophiles. They possess the highest polarized C = N bond and a reactive oxygen atom which can react with allyltrimethylsilane, silylenolethers, silylketene acetals[26] and vinylketene acetals in the presence of a Lewis acid such as TMSOTf or ZnI_2. We reported the development of lanthanum triflate as efficient catalyst for the reaction of α-aryl-N-phenyl nitrones and silyl ketene acetals. Traditional Lewis acids such as $BF_3 \cdot Et_2$-O, $AlCl_3$, $ZnCl_2$ and $TiCl_4$ furnish adducts in an extremely low yield. However, α-aryl-N-tert-butyl nitrone reacted with ethyl trimethylsilylacetate to yield the unexpected α,β-unsaturated ester in a 100% E-form. The plausible mechanism is illustrated in Scheme 9.

The intermediate **II** that has more basic nitrogen after combining with a proton favors elimination, as compared with the intermediate **I**. Thus the β-elimination of **II** affords the more stabilized α, β-unsaturate esters, whereas **I** in which the nitrogen lone pair electron is stabilized by the phenyl group renders the addition product.

Scheme 9   A plausible mechanism
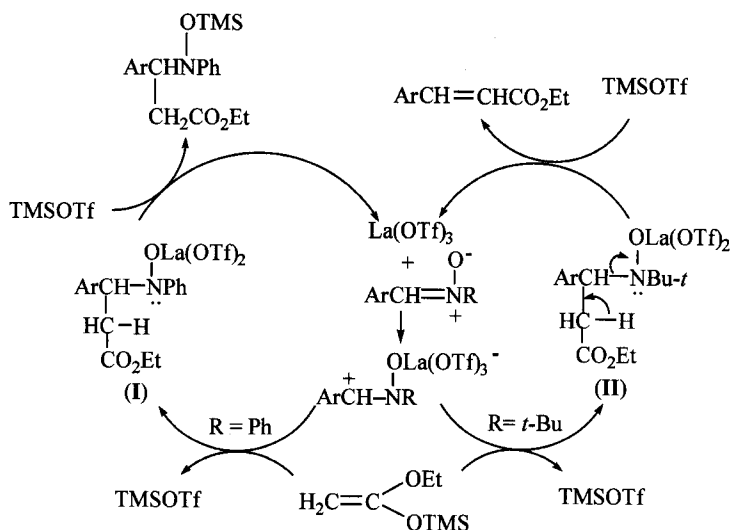
1, 3-Dipolar cycloaddition of nitrones with electro-rich alkenes catalyzed by Yb(OTf)$_3$[27]

The 1,3-dipolar cycloaddition (DC) of nitrones with alkenes involves a dominant interaction of the LUMO$_{nitrone}$ and the HOMO$_{alkene}$. Lanthanide compounds have strong affinity to nitrones, which could significantly decrease the LUMO$_{nitrone}$, therefore, accelerate the 1,3-DC. The 1,3-DC of the various nitrones proceeds well with the different aryl substituents on the nitrone carbon atom. We found that the reaction of different *N*-phenyl nitrones with ethyl vinyl ether (5 equiv.) was effectively catalyzed by Yb-(OTf)$_3$(10 mol%) in THF at room temperature giving the corresponding desired product in good yields after 30 min (Scheme 10). The ratio of stereoisomers varied with different nitrones examined, however, *trans*-isoxazolidines were obtained as the major isomer in all cases.

Scheme 10
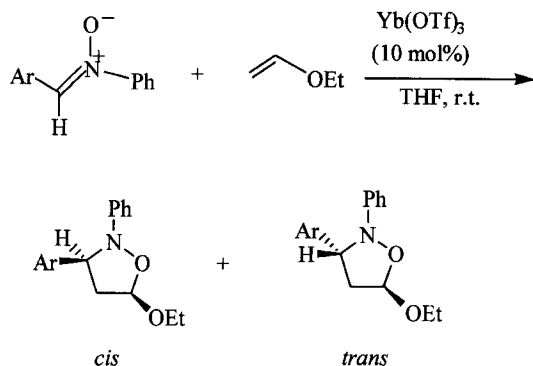
Ar = 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, C$_6$H$_5$, furyl,
4-NO$_2$C$_6$H$_4$.

At the same time ytterbium triflate (10 mol%) is also an efficient catalyst in the reaction of nitrones with 2,3-dihydrofurans to afford the bicyclic isoxazolidines in good yields.

Asymmetric hetero Diels-Alder reactions of chiral imines and Danishefsky's diene catalyzed by Yb(OTf)$_3$[28]

Yb(OTf)$_3$ can catalyze the hetero Diels-Alder reaction of chiral imines with Danishefsky's diene to afford the corresponding piperidine ring, which is one of the most abundant molecular fragments in both natural products and synthetic compounds with biological activities. In all cases, the reaction proceeded smoothly in dichlorome-

thane at -78 ℃ to give the corresponding adducts with high diastereoselectivity and moderate isolated yields (scheme 11).

Scheme 11
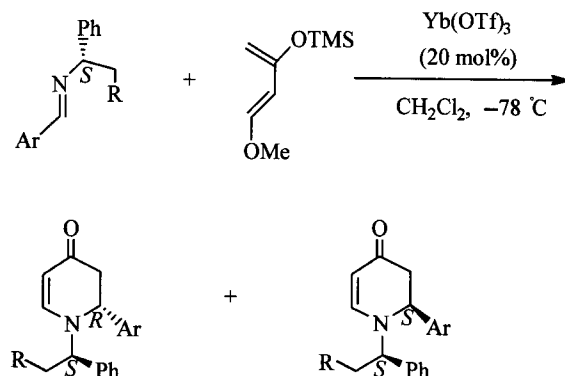
[2 + 2] Cycloaddition of imines with alkynyl selenides catalyzed by scandium triflate[29]

We found that imines can react with 1-alkynyl selenides in the presence of a catalytic amount of Sc(OTf)$_3$ to afford the α,β-unsaturated selenylimidates in moderate yields (Scheme 12). These reactions are assumed to proceed via a [2 + 2] cycloaddition of the imines to the alkynyl selenides to form azetine intermediates, which are unstable and immediately rearrange to afford the corresponding α,β-unsaturated selenylimidates.

This is another successful example of to activate imines by Ln(OTf)$_3$. We attempted to employ BF$_3$·OEt$_2$, ZnCl$_2$, MgBr$_2$ and ScCl$_3$ as the catalyst to catalyze our reaction, but failed.

Scheme 12
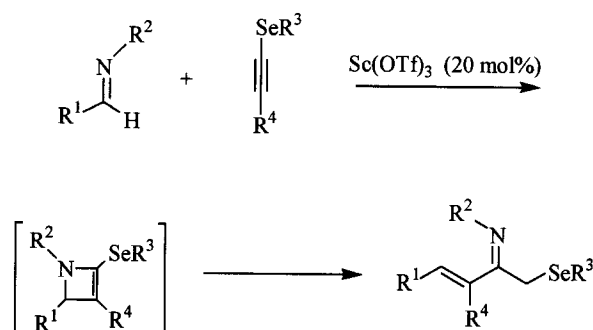
One pot synthesis of pyrano[3,2-c]*quinolines and furo-*[3,2-c]*quinolines catalyzed by* LnCl₃[30]

Pyranoquinoline derivatives are used as potential pharmaceuticals. Therefore, developing simple and efficient synthetic methods for preparing this type of compound becomes more and more important. $LnCl_3$(III) is a cheap and easily available Lewis acid, which is weaker than Ln (OTf)₃.[31-33] In the presence of GdCl₃ (20 mol%), a series of amines can react with benzaldehyde and 3,4-dihydropyran in a one-pot way to afford the corresponding pyrano[3,2-c]quinolines in high yields in the form of two stereoisomers, which could be separated by column chromatography. In all cases, this reaction could proceed smoothly and fast under mild reaction conditions (Table 4). In the same way, the reactivity of 2,3-dihydrofurans with aldehydes and anilines is also very high in the presence of GaCl₃(20 mol%).

A real advantage of procedures mentioned above is the very simple and robustness. The catalysts are water stable, recoverable, reusable with no loss of yield and environmental friendly. It is noteworthy that lanthanide triflates are expected to solve some severe environmental problems induced by Lewis acids promoted reactions in chemical industry.

Rare earth metal alkoxide-catalyzed organic reactions

Yb(O-*i*-Pr)₃ *catalyzed nitro-Mannich reaction* [34]

It was envisioned that the rare earth metal alkoxides would be stronger bases than group 4 metal alkoxides due to the lower ionization potentials (about 5.4—6.4 eV) and lower electronegativities (1.1—1.3 eV) of rare-earth elements. This enhanced basicity would then increase the utility of rare earth metal alkoxides with respect to catalytic organic synthesis. We found that Yb(O-*i*-Pr)₃ is suitable for use as a base in the nitro-Mannich reaction. As expected, Yb(O-*i*-Pr)₃ is an excellent and practical catalyst for the nitro-Mannich reaction of sulfonylimine, the corresponding adducts of different kinds of sulfonylimines with nitromethane can be isolated in excellent yields at room temperature in THF with Yb(O-*i*-Pr)₃(5 mol%) after 5 h (Table 5).

Table 4 One-pot synthesis of pyrano[3.2-c]quinolines from aldehydes catalyzed by GdCl₃
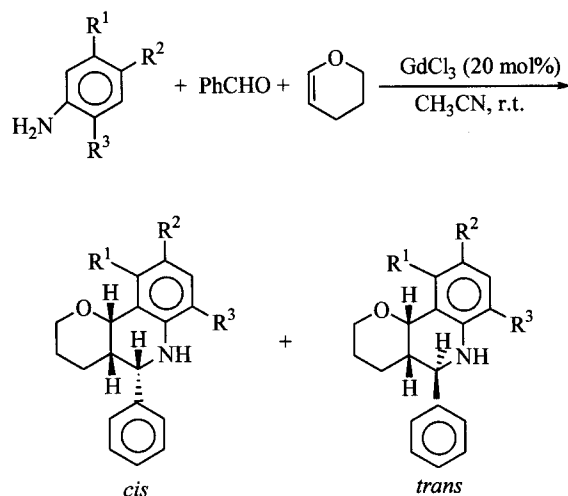
Entry	R¹	R²	R³	Time (min)	Ratio of cis : trans	Overall yield (%)
1	H	H	H	30	33:67	86
2	H	H	Cl	45	42:58	70
3	H	Cl	H	30	47:53	75
4	H	H	CH₃	45	39:61	80
5	H	H	OH	90	35:65	60
6	H	OCH₃	H	30	23:77	81
7	Cl	H	H	45	–	78
8	Cl	Cl	H	45	–	68

Table 5 Nitro-Mannich reaction of sulfonylimine catalyzed by Yb-(O-*i*-Pr)₃(5 mol%)
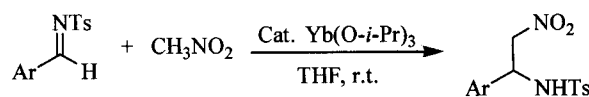
Entry	Ar	Adduct	Yield (%)
1	C₆H₅	C₆H₅	100
2	2-MeOC₆H₄	2-MeOC₆H₄	95
3	4-MeOC₆H₄	4-MeOC₆H₄	95
4	4-MeC₆H₄	4-MeC₆H₄	91
5	1-C₁₀H₇	1-C₁₀H₇	81
6	4-ClC₆H₄	4-ClC₆H₄	92
7	4-NO₂C₆H₄	4-NO₂C₆H₄	92

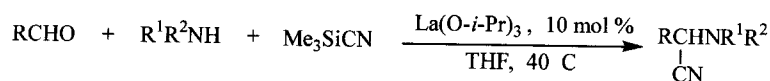La(O-i-Pr)$_3$ *catalyzed three-component condensation reaction: synthesis of α-amino nitriles* [35]

It is noticed that bifunctional α-amino nitriles are not only versatile intermediate in organic synthesis but also exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications. We have found a novel and convenient method for the synthesis of N, N-dialkyl substituted α-cyanoamines by La(O-i-Pr)$_3$ catalyzed three component condensation reaction of aldehyde, secondary amine and trimethylcyanide in a one-pot way (Table 6).

For most of the substrates we used the reaction can be completed in 8—15 h and gave the products in good yields. But the reaction of aliphatic aldehyde was rather difficult. It should be noted that for α,β-unsaturated aldehyde, the reaction took place perfectly in the 1,2-position, and the carbon-carbon double bond was not affected.

Summary

In conclusion, three kinds of applications of lanthanide(III) compounds have been developed. The first one is asymmetric reactions catalyzed by lanthanide complexes coordinated by several newly modified BINOL chiral ligands. Moderate to excellent enantioselectivity was achieved in most cases. Secondly, Ln(OTf)$_3$ as well as Sc(OTf)$_3$, which are stable in water, have been employed in a number of important and useful synthetic reactions as versatile Lewis acid catalysts. A catalytic amount of GdCl$_3$ was used in a one-pot synthesis of pyrano[3,2-c]quinolines and furo[3,2-c]quinolines. At last, Yb(O-i-Pr)$_3$ and La(O-i-Pr)$_3$ were successfully applied to catalyze the nitro-Mannich reaction and a three-component condensation reaction of aldehyde, secondary amine and trimethylsilylcyanide, respectively.

**Table 6** Results of the condensation reaction catalyzed by La (O-i-Pr)$_3$

$$\text{RCHO} + \text{R}^1\text{R}^2\text{NH} + \text{Me}_3\text{SiCN} \xrightarrow[\text{THF, 40 C}]{\text{La(O-}i\text{-Pr)}_3,\ 10\ \text{mol \%}} \underset{\underset{\text{CN}}{|}}{\text{RCHNR}^1\text{R}^2}$$

| Entry	R	R^1	R^2	Time (h)^a	Yields (%)^b
1	Ph	PhCH$_2$	PhCH$_2$	10	78
2	PhCH = CH	PhCH$_2$	PhCH$_2$	10	81
3	p-CH$_3$OC$_6$H$_4$	PhCH$_2$	PhCH$_2$	15	72
4	p-O$_2$NC$_6$H$_4$	PhCH$_2$	PhCH$_2$	8	75
5	p-BrC$_6$H$_4$	PhCH$_2$	PhCH$_2$	8	82
6	2-pyridyl	PhCH$_2$	PhCH$_2$	8	65
7	2,4-Cl$_2$C$_6$H$_3$	PhCH$_2$	PhCH$_2$	8	80
8	Ph	(CH$_3$)$_2$CH	(CH$_3$)$_2$CH	15	45
9	Ph	CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$		12	78
10	PhCH = CH	CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$		10$^-$	72
11	p-BrC$_6$H$_4$	CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$		10	64
12	(CH$_3$)$_2$CH	PhCH$_2$	PhCH$_2$	15	trace
13	Ph	PhCH$_2$	CH$_3$	10	71
14	p-BrC$_4$H$_6$	PhCH$_2$	CH$_3$	10	76

^{a}10 mol% catalyst, 40 ℃, in THF. ^{b} Isolated yields.

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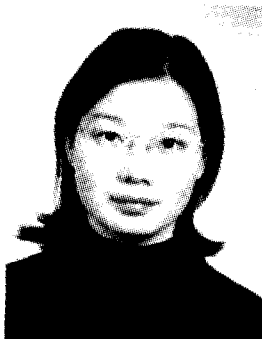
Dr. Ruifang Chen was born in, Zhejiang Province in 1971, and received her B.S. degree on analytical chemistry at Metallury Institute of East China in 1993. Then she moved to Zhejiang University as a graduate student, and obtained her M.S. degree in 1996. She received her Ph.D. degree in organic chemistry under the guidance of prof. Zhilin Jin at Dalian University of Science and Technology in 1998 and awarded the excellent Ph.D. thesis of Liaoning Province. After finishing two years postdoctoral research work in prof. Changtao Qian's group in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, she was recommended to Nagoya University (Japan) as a visiting scholar in prof. Kazuyuki Tasumi's group for three months. She is currently a postdoctoral researcher at Institute of Homogenous Catalysis, University of Amsterdam, the Netherlands. She won the First Prize for the Education Foundation of Qubochum awarded by Dalian University of Science and Techonology in 1998. She has published more than 30 articles and applied three patents. Her main interests are lanthanide compounds promoted organic reactions and homogenous catalysis.
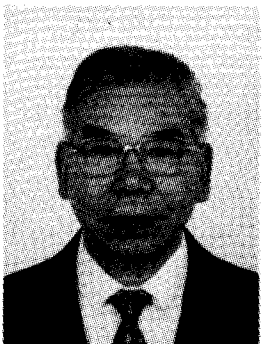
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He was the member of the International Organization Committee of the First and Second International Conference on the Basic and Applied Chemistry of f-Transition (at Venice 1983 and at Lisbon 1987). He has been the member of International Advisory Board of XVI, XVII, XVIII, XIX and XXth International Conference on Organometallic Chemistry (IUPAC series Conferences) at Brighton 1994, Brisbane 1996, Munich 1998, Shanghai 2000 and Corfu Island 2002, respectively, and he was the Cochairman of XIXth International Conference on Orgaometallic Chemistry (July 2000, Shanghai).

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