Chiral–achiral ligand synergy: activation of a zirconium–BINOL Lewis acid complex by the addition of 4-*tert*-butylcalix[4]arene

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4-*tert*-Butylcalix[4]arene activates the enantioselective allylation of aldehydes catalyzed by a new zirconium–BINOL Lewis acid system allowing the use of less than 2% of the catalyst.

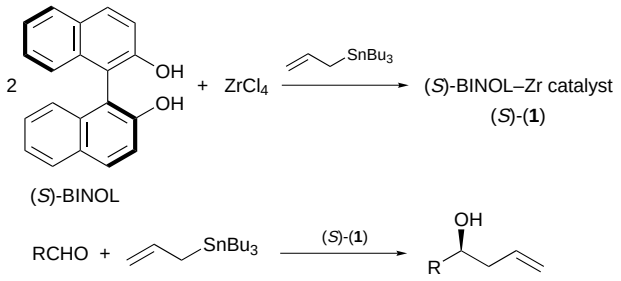
Enantioselective allylation reaction is becoming an important methodology in the total synthesis of complex chiral molecules. In order to enhance the broad applicability and the efficiency of this process for catalytic applications, a large number of groups have published different allylation methodologies which have been realized through the use of different metal–BINOL complexes.[1] The major drawback in all the reported methods is the high loading of the catalyst employed in the reaction (10–20%) which reduces the interest of this simple methodology.

Recently, an acceleration effect on the catalytic cycle of the allylation reaction was discovered whereby an additive, R_2MSR (where M = Al, B), was introduced *in stoichiometric amount* into the reaction mixture.[2]

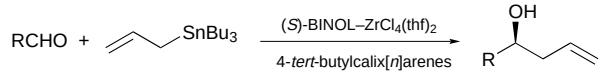
In searching for more active and efficient catalysts, we discovered that zirconium–BINOL Lewis acid **1** can be prepared by dissolving the $ZrCl_4$ in MeCN in the presence of BINOL, followed by the addition of allyltributyltin in CH_2Cl_2 (Scheme 1).[3]† After stirring the reaction mixture for 1–2 h at room temperature, the aldehyde was successively added at lower temperature (Scheme 1). The resulting data from this reaction are collected in Table 1. The drawback of this method is that two equivalents of BINOL (with respect to the zirconium) are needed to obtain high enantiomeric excesses (ees). Furthermore good reproducibility was difficult to obtain. We realized that another catalyst which could be prepared from commercially available $ZrCl_4(thf)_2$[4] could considerably enhance the applicability and the reproducibility of the procedure. Moreover, the higher solubility of $ZrCl_4(thf)_2$ in organic solvent, as compared to $ZrCl_4$, simplifies the procedure for the preparation of the catalyst. In fact, the catalyst can be simply prepared starting from BINOL and $ZrCl_4(thf)_2$ in CH_2Cl_2 or in Et_2O. As shown in Table 1 high ees were achieved by employing Et_2O as the reaction solvent. Despite the high ees which we obtained, those reported for the same reactions promoted by $Zr(OiPr)_4$·^{i}PrOH–BINOL Lewis acid[5] were higher. Moreover, at least 10% mol of the zirconium catalyst was necessary to achieve good levels of ees.

Recently Mikami and Matsukawa reported that certain titanium–BINOL Lewis acids, capable of promoting the ene reaction, are activated by the addition of chiral phenols.[6] In particular, they showed that the presence of enantiopure BINOL enhances the reactivity of racemic titanium–BINOL catalysts and increases the ees of ene[6] and Diels–Alder reactions.[7]

We report here a spectacular activation of the zirconium–BINOL catalyst by adding achiral 4-*tert*-butylcalix[4]arene,[8] a phenol derivative, to the reaction mixture (Scheme 2). This new Lewis acid system is generated *in situ* by treating a mixture of BINOL, $ZrCl_4(thf)_2$ and 4-*tert*-butylcalix[4]arene with allyltributyltin.‡ The 4-*tert*-butylcalix[4]arene has low solubility in the reaction solvent (Et_2O) and the addition of allyltributyltin to



Scheme 1



Scheme 2

Table 1 Enantioselective allylation of aldehydes promoted by (*S*)-**1**[a]

Entry	Zr salt	Solvent	BINOL : Zr	RCHO	*T*/°C	Time/h	Yield (%)[d]	ee (%)[e]
1	$ZrCl_4$[b]	CH_2Cl_2	1 : 1	PhCHO	0	3	83	50
2	$ZrCl_4$[b]	CH_2Cl_2	1 : 1	PhCHO	−20	19	52	40
3	$ZrCl_4$[b]	CH_2Cl_2	2 : 1	PhCHO	−20	21	53	54
4	$ZrCl_4$[b]	CH_2Cl_2	2 : 1	PhCHO	−20	72	64	62
5	$ZrCl_4$[b]	Et_2O	2 : 1	PhCHO	−20	36	10	79
6	$ZrCl_4(thf)_2$[c]	CH_2Cl_2	1 : 1	*n*-C_7H_{15}CHO	0	36	70	53
7	$ZrCl_4(thf)_2$[c]	CH_2Cl_2	2 : 1	*n*-C_7H_{15}CHO	−20	24	78	73
8	$ZrCl_4(thf)_2$[c]	Et_2O	2 : 1	*n*-C_7H_{15}CHO	−20	24	65	85
9	$ZrCl_4(thf)_2$[c]	Et_2O	2 : 1	PhCHO	−20	24	40	87

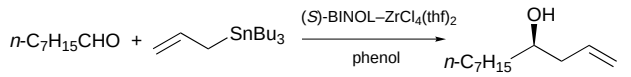
[a] All reactions were run by the employment of 10% catalyst based on Zr. Reactions performed with lower % of the catalyst gave lower yield and enantioselectivity. [b] The catalyst was prepared by dissolving $ZrCl_4$ (0.1 mmol) and BINOL in MeCN followed by the evaporation of the solvent. The solid residue was suspended in CH_2Cl_2 and allyltributyltin (2 mmol) was added. The resulting mixture was stirred for 1 h followed by the addition of the aldehyde (1 mmol). [c] The catalyst was prepared in CH_2Cl_2 or Et_2O by stirring $ZrCl_4(thf)_2$ (0.1 mmol) and BINOL for 1 h followed by the addition of allyltributyltin (1.7 mmol) in the same solvent. The resulting yellow solution was stirred for another hour at room temp., then the mixture was cooled to the temperature reported in the Table and the aldehyde was added (1 mmol). [d] Isolated yield after chromatographic purification. [e] The ees were determined by GC analysis with a chiral Megadex-5 column.

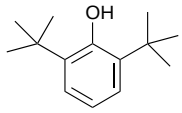
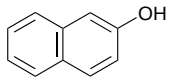
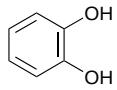
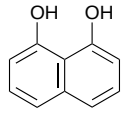
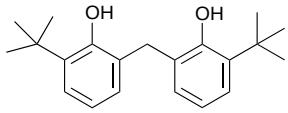
Table 2 Enantioselective allylation with Zr–BINOL complex activated by 4-*tert*-butylcalix[*n*]arenes[a]

Entry	$ZrCl_4(thf)_2$ (%)[b]	Calix[*n*]arene	%	RCHO	Time/h	Yield (%)[c]	ee (%)[d]
1	10	Calix[4]arene	10	*n*-$C_7H_{15}CHO$	60	68	93
2	5	Calix[4]arene	5	*n*-$C_7H_{15}CHO$	60	65	96
3	2	Calix[4]arene	1	*n*-$C_7H_{15}CHO$	60	40	92
4	2	Calix[4]arene	0.5	*n*-$C_7H_{15}CHO$	60	57	95
5	10	Calix[4]arene	10	*c*-$C_6H_{11}CHO$	72	52	90
6[e]	6	Calix[4]arene	6	PhCHO	50	78	78
7	5	Calix[4]arene	5	PhCHO	72	85	85
8	10	Calix[4]arene	10	PhCH=CHCHO	90	38	77
9[f]	4	Calix[6]arene	3	PhCH=CHCHO	50	43	62
10[f]	4	Calix[8]arene	3	PhCH=CHCHO	50	30	70

[a] All reactions were carried out in Et_2O at −20 °C. [b] For all reactions the molar ratio between $ZrCl_4(thf)_2$ and BINOL was 1 : 1. [c] Isolated yield after chromatographic purification. [d] The ees were determined by GC analysis with a chiral Megadex-5 column. [e] The reaction was performed at 0 °C. [f] The reaction was performed in CH_2Cl_2.

Table 3 Enantioselective allylation promoted by BINOL–zirconium–phenol systems[a]



Entry	Phenol	Yield (%)[b]	ee (%)[c]
1		30	66
2		40	71
3		47	19
4		0	—
5		0	—

[a] All reactions were performed employing the following stoichiometric ratio: BINOL : $ZrCl_4(thf)_2$: phenol : allyltributyltin : aldehyde; 0.1 : 0.1 : 0.1 : 1.6 : 1.0 at −20 °C for 48 h. [b] Isolated yield after chromatographic purification. [c] The ees were determined by GC analysis with a chiral Megadex-5 column.

the mixture solubilizes the complex with the appearance of a yellow colour only in the case of low catalyst loading (2–3%). In addition, the experimental procedure is simple, all the reagents are commercially available, and no particular drying procedure is required for the calixarene.

The remarkable aspect of this procedure is that, even without the use of molecular sieves, it is possible to obtain very high ees (up to 96% with linear aldehydes) using only 2% of the chiral promoter. Our results indicate that the amount of calixarene added to the mixture can be reduced (entries 3 and 4, Table 2). As shown in Table 2, the results are generally good with both aliphatic and aromatic aldehydes. Only in the case of cinnamaldehyde the yield and the ees are not satisfactory. Other calixarenes can be used with comparable results (entries 9 and 10, Table 2). It is noteworthy that this dramatic activation is obtained specifically with the calixarenes, whereas other phenols do not show the same activating effect (Table 3). Our system is interesting not only from the point of view of low catalyst loading giving high ees, but from the perspective that new frontiers can be opened in the field of metal–BINOL complexes in asymmetric catalytic applications.

Future work in our laboratory will address the general scope of Lewis acid catalyst activation and the characterization of the species responsible for the performance of the catalyst.

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Footnotes and References

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† Preliminary spectroscopic investigations have shown that the catalyst formation probably occurs through the proton abstraction from an initial adduct between the $ZrCl_4$ and BINOL due to the allylating reagent, as previously described by Carreira and co-workers[3] for the TiF_4–BINOL system. Tributyltin chloride and propene are the products of the reaction.

‡ Typical experimental procedure: a suspension of (*S*)–BINOL (0.05 mmol), 4-*tert*-butylcalix[4]arene (0.05 mmol) and $ZrCl_4(thf)_2$ (0.05 mmol) was stirred for 1 h in Et_2O (1.5 ml), then allyltributyltin (1.7 mmol) was added at room temperature. After stirring for 1 h and cooling to −20 °C, the aldehyde (1 mmol) was added. The mixture was stored in the freezer at −20 °C for 50–90 h, then diluted with Et_2O and quenched with a saturated solution of $NaHCO_3$. The insoluble materials were filtered and the organic phase separated. The aqueous phase was extracted with Et_2O. The organic phases were collected, dried, evaporated under reduced pressure and purified by flash chromatography.

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