Comparison of Lewis acids of different hardness supported on silica gel as catalysts of Diels–Alder reactions of (E)-2-cyanocinnamates

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The behaviour of several Lewis acids, derived from zinc, aluminium and titanium, supported on silica gel, as catalysts of the Diels–Alder reactions of cyclopentadiene with methyl, ($1R,2S,5R$)-menthyl, and (R)-pantolactone (E)-2-cyanocinnamates has been compared. The best catalytic activities were observed with the zinc catalysts. The extent and even the direction of the asymmetric induction changes for the same chiral auxiliary depending on the catalyst used. *Ab initio* theoretical calculations, carried out on model dienophile–catalyst intermediates, show that the coordination of the softer zinc derivatives at the nitrogen atom is thermodynamically favoured, whereas coordination to the carbonyl oxygen atom is preferred for the harder aluminium catalysts. However, in both cases the most reactive intermediate comes from the coordination of the Lewis acid to the carbonyl group of the dienophile in the *s-trans* conformation.

Keywords: silica-supported catalysts, hard and soft Lewis acids, asymmetric Diels–Alder reactions, bidentate dienophiles

1. Introduction

Lewis acids supported on silica gel have proven to be useful catalysts to promote Diels–Alder reactions of numerous dienophiles [1,2]. The use of these catalysts has allowed carrying out not previously described reactions [2]. The comparison of different Lewis acids (Et_2AlCl, $TiCl_4$, $ZnCl_2$, ZnI_2) in reactions with different dienophiles has shown that, in general, the Diels–Alder reactions of α,β-unsaturated esters lead to better results in the presence of aluminium and titanium catalysts [1], whereas in the Diels–Alder reactions of α,β-unsaturated nitriles the best results are obtained in the presence of silica-supported zinc catalysts [3]. These differences have been explained on the basis of the hard/soft character of the coordinating group and the catalytic site [3].

These results give rise to an interesting question. What is the behaviour of these solids as catalysts in the Diels–Alder reactions of dienophiles containing both the nitrile and ester groups? In this respect, (E)-2-cyanocinnamates are very interesting dienophiles. The Diels–Alder reactions of several dienes with methyl (E)-2-cyanocinnamate and with (E)-2-cyanocinnamates of enantiomerically pure alcohols have been described [4], and the corresponding cycloadducts have been transformed into the corresponding cycloaliphatic amino acids [5].

The reactions between (E)-2-cyanocinnamates and cyclopentadiene promoted by heterogeneous catalysts have been described [6], but the comparative behaviour of hard and soft Lewis acids supported on silica gel has not yet been studied. Therefore, we considered it interesting to address this question by studying the heterogeneously catalyzed reactions of some achiral and chiral (E)-2-cyanocinnamates with cyclopentadiene (scheme 1).

2. Experimental

$ZnCl_2$ and ZnI_2 were supported on silica gel EP11 (Crossfield) as previously described in [7,8], and activated prior to use by heating at 150 °C for 1 h under a flow of dry air. Et_2AlCl and $TiCl_4$ were supported on Merck silica gel 60 and activated prior to use as previously described [1].

The reactions were carried out following the methods described previously and the results were determined by HPLC and NMR spectroscopy [6].

The *ab initio* theoretical calculations were carried out using the Gaussian 94 program [9]. Full geometric optimizations were performed within the density functional theory (DFT) framework using the hybrid Becke three-parameter correlation functional plus the Lee–Yang–Parr exchange functional (B3LYP) [10], as implemented in Gaussian 94, with an effective core potential (ECP) double-zeta basis set, namely, the LANL2DZ [11].

3. Results and discussion

First, we compared the catalytic activity of Et_2AlCl, $TiCl_4$, and $ZnCl_2$ supported on silica gel in the reaction of methyl (E)-2-cyanocinnamate (**1a**) with cyclopentadiene (**2**). The results obtained are gathered in table 1.

Although all three catalysts promote the reaction, $TiCl_4$ supported on silica gel (hereafter Si(Ti)) is the least active.

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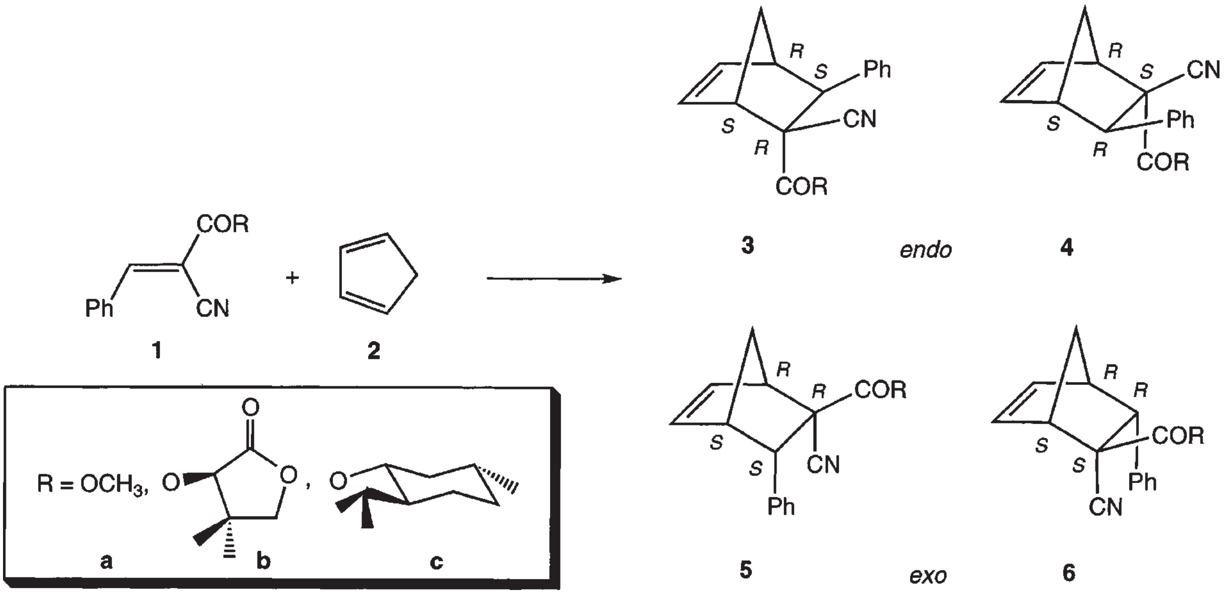


Scheme 1.

Table 1
Results obtained in the reaction of methyl (E)-2-cyanocinnamate (**1a**) with cyclopentadiene (**2**), carried out at $-20\,^{\circ}$C for 24 h.

Catalyst[a]	mmol **1a** g-cat^{-1}	Solvent	Conv.[b] (%)	*Endo*/*exo*[b]
–	–	CH_2Cl_2	5	1.1
Si(Al)	1.5	CH_2Cl_2	90	3.5
Si(Ti)	1.5	CH_2Cl_2	62	2.2
Si($ZnCl_2$)	1.5	CH_2Cl_2	96	2.2
Si(ZnI_2)	0.5	–	74	2.4

[a] Et_2AlCl supported on silica gel = Si(Al), $TiCl_4$ supported on silica gel = Si(Ti), $ZnCl_2$ supported on silica gel = Si($ZnCl_2$), ZnI_2 supported on silica gel = Si(ZnI_2). [b] Determined by HPLC.

In addition, it has been shown that Et_2AlCl supported on silica gel (hereafter Si(Al)) is a better catalyst than $ZnCl_2$ supported on silica gel (hereafter Si($ZnCl_2$)) in the reactions of acrylates, whereas the reverse is true for the reactions of acrylonitrile [3]. When the dienophile bears both functionalities there are no significant differences between Si(Al) and Si($ZnCl_2$).

The same catalysts were used in the reaction of the (E)-2-cyanocinnamate of (R)-pantolactone (**1b**) and cyclopentadiene (**2**), and the corresponding results are gathered in table 2. In this reaction, the supported catalysts derived from $ZnCl_2$ and ZnI_2 are more efficient than those derived from Et_2AlCl and $TiCl_2$. Interestingly, unsupported $ZnCl_2$ does not have any catalytic effect.

With regard to the selectivities, both Si(Al) and Si(Ti) behave in a similar way to homogeneous Et_2AlCl, whereas Si($ZnCl_2$) and Si(ZnI_2) lead to slightly lower *endo*/*exo* selectivities and to a reversed asymmetric induction to give the $(1R,2S,3R,4S)$-cycloadduct (**4**) as the major product. The results obtained with $ZnCl_2$ indicate that this behaviour is typical of zinc catalysts.

Finally, we also tested the reaction of $(1R,2S,5R)$-menthyl (E)-2-cyanocinnamate (**1c**) with cyclopentadiene (**2**), and the corresponding results are gathered in table 2. As in the case of the (E)-2-cyanocinnamate of (R)-pantolactone (**1b**), Et_2AlCl is more efficient than Si(Al), whereas Si($ZnCl_2$) promotes the reaction and $ZnCl_2$ is inactive. All of the catalyzed reactions with this dienophile give the $(1R,2S,3R,4S)$-cycloadduct (**4**) as the major product, although the diastereofacial selectivity is very low in the reaction promoted by Si(Al). The direction of the asymmetric induction is opposite in the non-catalyzed reaction, where the $(1S,2R,3S,4R)$-cycloadduct (**3**) is preferentially obtained with low diastereomeric excess.

Analysis of these results leads to a number of general conclusions. First, the zinc derivatives supported on silica gel are suitable catalysts for these reactions. Si($ZnCl_2$) is far more active than $ZnCl_2$, whereas the opposite is true for Si(Al) when compared to Et_2AlCl. Both the direction and the extent of the asymmetric induction depend on the nature of the chiral auxiliary and the catalyst.

The higher catalytic activity of Si($ZnCl_2$) in comparison to $ZnCl_2$ has also been observed in other reactions [7], and it has been explained on the basis of the differences between active $ZnCl_2$ in the mesopores of the support and crystalline $ZnCl_2$ with low surface area [7,8]. The lower activity of Si(Al) in comparison to Et_2AlCl may be attributed to the different nature of the catalytic sites [1] and to the greater steric crowding around the aluminium atom in the supported catalyst. ZnI_2 and Si(ZnI_2) lead to almost the same results, which may be due to the leaching of ZnI_2 by complexation with the dienophile and products.

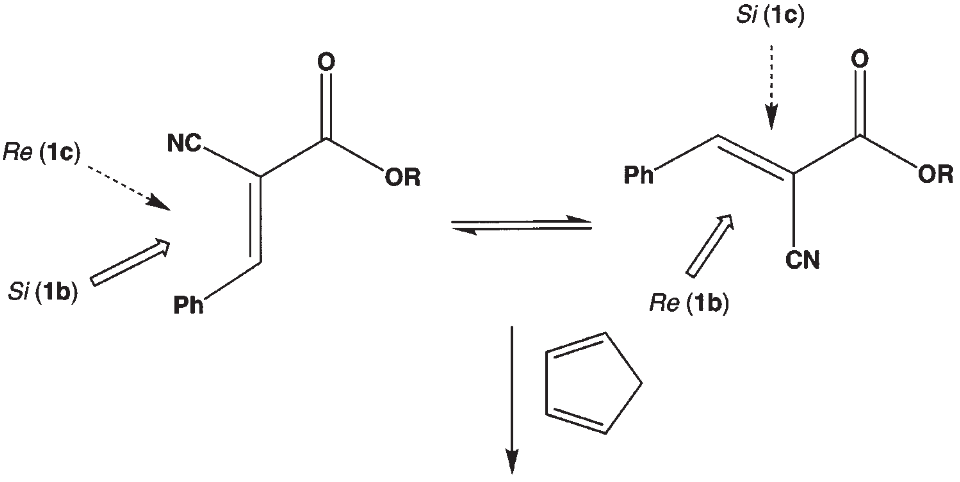
The changes in the direction of the asymmetric induction are not easy to explain. These changes are the result of the preferential attack of the diene on the *Si* or on the *Re* faces of the carbon–carbon double bond of the dienophile, so that attach on the *Si* face leads to the $(1S,2R,3S,4R)$- and $(1R,2R,3S,4S)$-cycloadducts (**3** and **5**), whereas attack on the *Re* face leads to the $(1R,2S,3R,4S)$- and $(1S,2S,3R,4R)$-products (**4** and **6**).

Table 2

Results obtained in the reaction of **1b** and **1c** with cyclopentadiene in CH_2Cl_2.

Dienophile	Catalyst	mmol **1** g-cat^{-1}	**2** : **1**	T (°C)	t (h)	Conv.^{a} (%)	*Endo*/*exo*^{a}	**3** : **4**^{a}
1b	–	–	6 : 1	−20	24	31	1.1	24 : 76
1b	$EtAlCl_2$	1.3	5 : 1	−40	6	100	2.2	54 : 46
1b	$TiCl_4$	1.3	5 : 1	−40	5	94	5.7	99 : 1
1b	$ZnCl_2$	1.0	6 : 1	−20	24	14	1.5	24 : 76
1b	ZnI_2	1.0	6 : 1	−20	24	98	1.5	39 : 61
1b	Si(Al)	1.5	6 : 1	−20	24	58	2.1	52 : 48
1b	Si(Ti)	1.5	6 : 1	−20	24	84	2.0	52 : 48
1b	Si($ZnCl_2$)	1.5	6 : 1	−20	24	100	1.6	38 : 62
1b	Si(ZnI_2)^c	1.5	6 : 1	−20	24	100	1.5	38 : 62
1c	–	–	6 : 1	−20	24	25	1.3	53 : 47
1c	$EtAlCl_2$	1.3	6 : 1	−40	68	70	4.2	38 : 62
1c	$ZnCl_2$	1.0	6 : 1	−20	24	0	–	–
1c	Si(Al)	1.5	6 : 1	−20	24	50	1.2	48 : 52
1c	Si($ZnCl_2$)	1.5	6 : 1	−20	24	86	1.9	37 : 63

[a] Determined by HPLC. [b] mmol of dienophile per mmol of catalyst. [c] ZnI_2 supported on silica gel.



3 (*Si* attack)

4 (*Re* attack)

Figure 1. Influence of the conformational equilibrium of the dienophile on the asymmetric induction of the reactions of enantiomerically pure (E)-2-cyanocinnamates with cyclopentadiene.

The high asymmetric induction obtained in the $TiCl_4$-catalysed reactions of (E)-2-cyanocinnamate of (R)-pantolactone (**1b**) and cyclopentadiene (**2**) has been explained by the formation of a dienophile–catalyst chelate complex [5]. The asymmetric inductions obtained (table 2) indicate that this is not the case with the catalysts used in this work. In the absence of chelation, the diastereofacial shielding of both faces of the double bond is caused by the methyl groups of the chiral auxiliary, and the direction of the asymmetric induction strongly depends on the *s-cis*/*s-trans* conformational equilibrium (figure 1). With Et_2AlCl, Si(Ti), and Si(Al) the reaction takes place preferentially through the *s-trans* conformation, leading to **3** through the attack of the diene on the *Si* face, although the low asymmetric induction indicates that the energy differences between both conformations in the transition state are small. The reaction carried out in the absence of a catalyst takes place preferentially through the *s-cis* conformation of the dienophile, and the same situation, but with a lower diastereofacial selectivity, holds for the reactions promoted by zinc catalysts.

For the reaction of ($1R, 2S, 5R$)-menthyl (E)-2-cyanocinnamate, the model proposed by Oppolzer explains the asymmetric induction of the Diels–Alder reaction of ($1R, 2S, 5R$)-menthyl acrylate [12]. In this case, the non-catalyzed reaction takes place preferentially through the *s-cis* conformation, but with a low diastereofacial selectivity. The reverse situation was observed with all the catalysts tested, with the major product coming from the attack of the diene on the less hindered face of the dienophile in its *s-trans* conformation.

In the absence of catalyst, both chiral dienophiles (**1b**, **1c**) react preferentially through the *s-cis* conformation, but the preference for this reaction pathway is greater in the case of the (R)-pantolactone derivative. Both the aluminium and zinc catalysts increase the percentage of reaction through the *s-trans* conformation.

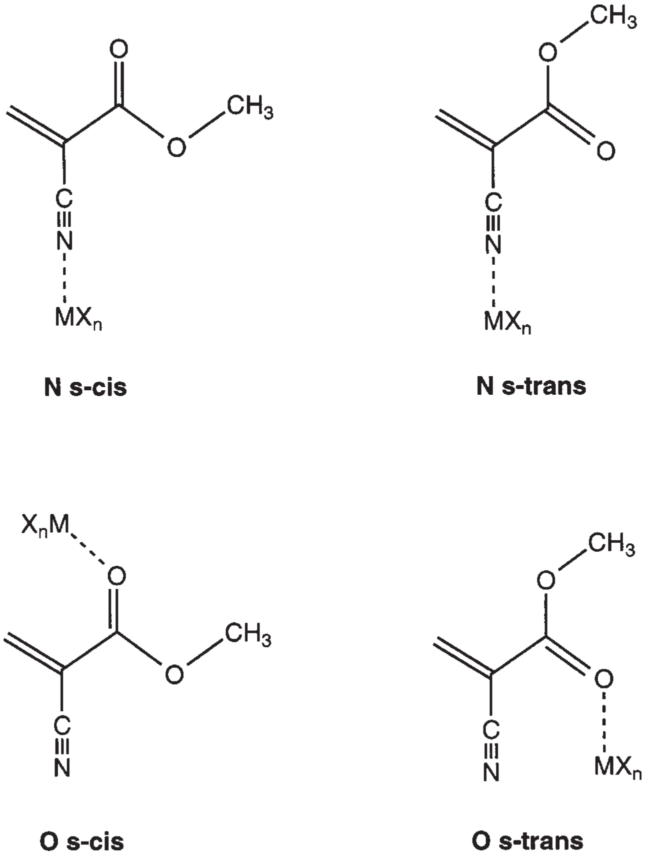


Figure 2. Model dienophile–catalyst complexes considered for the theoretical study.

In order to justify these experimental observations we have carried out theoretical calculations on the complexes of methyl 2-cyanoacrylate with $ZnCl_2$ and $AlCl_3$ as models for the (E)-2-cyanocinnamate reactive intermediates. In both cases, the coordinations of the Lewis acid to the carbonyl oxygen and to the nitrogen atoms have been considered, together with the *s-cis* and *s-trans* conformations of the dienophile (figure 2).

Table 3 shows the calculated relative energies of the different intermediates, together with the relative energies of the LUMO orbitals. There has been some controversy regarding the physical meaning of the Kohn–Sham molecular orbitals, but it has recently been suggested that they have at least as much relevance as the Hartree–Fock molecular orbitals [13]. In the case reported here, some calculations carried out at the Hartree–Fock level using the same basis set have shown that both types of orbitals lead to the same conclusions.

The results obtained show that with the softer $ZnCl_2$ the coordination to the nitrogen atom is thermodynamically favoured. In contrast, with $AlCl_3$ the coordination to the oxygen atom leads to more stable intermediates. The non-coordinated dienophile shows an *s-cis* preference of ca. 1 $\mathrm{kcal\,mol^{-1}}$. This is slightly increased by coordination of the Lewis acid to the nitrile group, and is noticeably increased by coordination of the Lewis acid to the ester group (ca. 5 $\mathrm{kcal\,mol^{-1}}$). This increase may be due to the steric interaction between the nitrile group and the Lewis acid when the latter is coordinated to the oxygen atom in the *s-trans* conformation. In view of these results, the increase in the extent of the reaction occurring through the *s-trans* conformation in the presence of Lewis acids cannot be accounted for by the relative stability of the intermediate complexes, and we must consider their different reactivities. Given that the Diels–Alder reactions studied are of the normal type, they are controlled by the interaction between the HOMO of the diene and the π^* molecular orbital of the dienophile double bond. In all the intermediate complexes this π^* orbital corresponds to the LUMO, as shown in figure 3 for the $ZnCl_2$ complexes. The relative energies of these orbitals are given in table 3.

Table 3
Calculated relative total and LUMO energies (in $\mathrm{kcal\,mol^{-1}}$) for the different dienophile–catalyst intermediates.

Intermediate	$ZnCl_2$		$AlCl_3$	
	ΔE	ΔE_{LUMO}	ΔE	ΔE_{LUMO}
N *s-cis*	0.0	0.0	1.5	4.2
N *s-trans*	1.8	0.2	3.6	4.4
O *s-cis*	0.2	0.5	0.0	0.0
O *s-trans*	5.1	−2.3	5.1	−1.1

The coordination of $AlCl_3$ to the oxygen atom is not only thermodynamically favoured, but also leads to π^* orbitals of lower energy. In order to account for the *s-trans* preference we must consider that most of the reaction takes place through the most unstable intermediate, which has the lowest LUMO energy and hence is the most reactive. This situation is relatively commonplace in catalyzed processes.

The coordination of $ZnCl_2$ to both the oxygen and the nitrogen atoms leads to LUMO orbitals of similar energy. The increasing degree of reaction through the *s-trans* conformation may again be due to the participation of the most unstable, but most reactive intermediate complex, namely that in which the $ZnCl_2$ coordinates to the oxygen atom in the *s-trans* conformation.

The theoretical calculations show that the situation is indeed quite complicated. The differences in stability and reactivity of the different intermediate complexes are small enough to make it reasonable that small changes in the reagents, catalyst or reaction conditions may produce significant changes in the asymmetric induction.

An interesting conclusion from this analysis is related to the use of the HSAB theory in catalyzed reactions. It seems clear that this theory is useful to justify the different catalytic activity of harder or softer Lewis acids with harder or softer reagents. Thus, Si($ZnCl_2$) is more efficient than Si(Al) in promoting the Diels–Alder reactions of α,β-unsaturated nitriles, but the opposite is true for the reactions of α,β-unsaturated esters. However, the theory is not so useful when both coordinating groups are present in the same molecule. Of course, coordination of the harder Lewis acid to the harder basic centre and that of the softer Lewis acid to the softer basic centre are favoured, but the

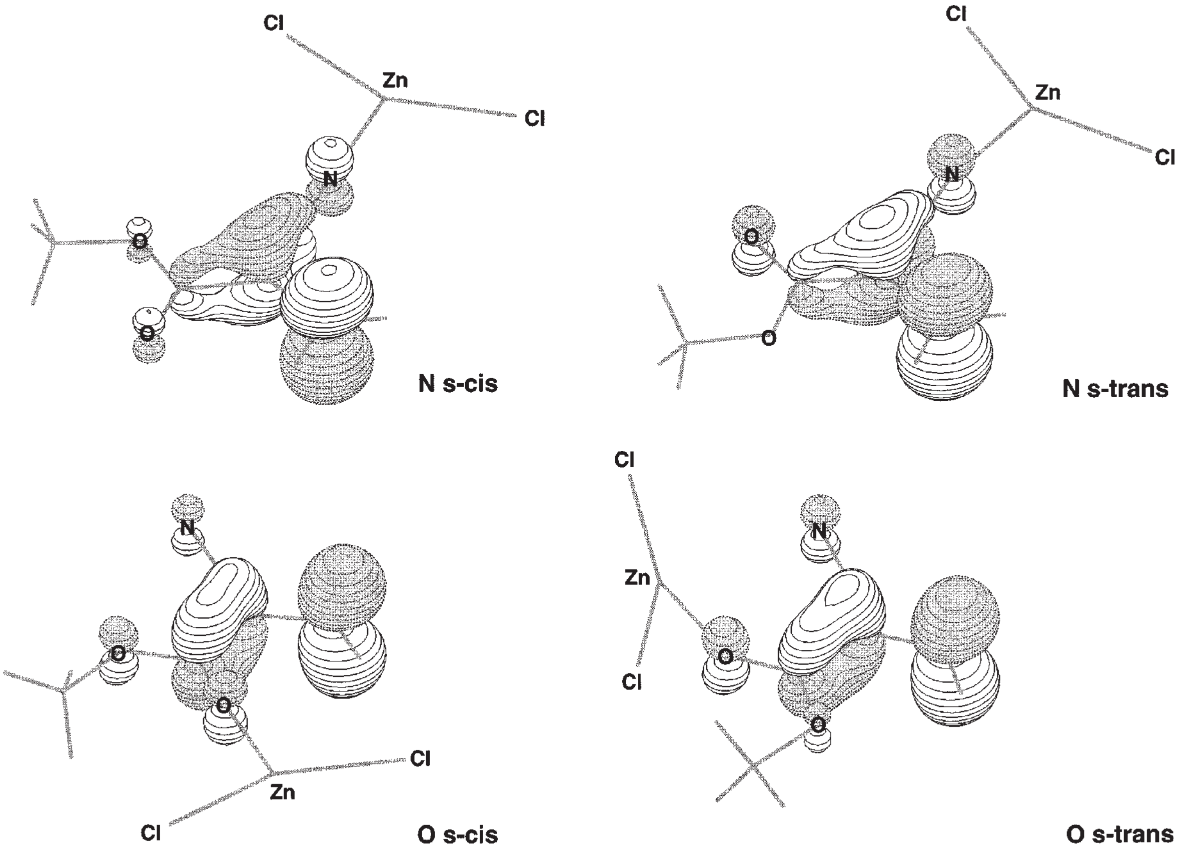


Figure 3. Isodensity (at the 0.075 a.u. level) surfaces of the LUMO, calculated for the different model dienophile–$ZnCl_2$ complexes.

relative reactivity of the resulting intermediates cannot be easily predicted by this theory. In the example studied in this work, the most reactive intermediates always have the Lewis acid coordinated to the ester group, irrespective of the hardness of the Lewis acid used.

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