Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2263-2276, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00281-9

Chiral Lewis Acids Supported on Silica Gel and Alumina, and their Use as Catalysts in Diels–Alder Reactions of Methacrolein and Bromoacrolein

José M. Fraile, José I. García, José A. Mayoral*, Ana J. Royo

Instituto de Ciencia de Materiales de Aragón. Departamento de Química Orgánica. Universidad de Zaragoza–C.S.I.C.
E-50009 Zaragoza. España. E-mail: jose.mayoral@msf.unizar.es.

Abstract: Several derivatives of (*S*)-tyrosine are supported on silica gel through the phenolic oxygen atom. The Lewis acids obtained by treatment of these solids with BH_3 are able to promote the reactions of methacrolein and bromoacrolein with cyclopentadiene, but they do not provide asymmetric induction. (*S*)-Prolinol is supported on silica gel and alumina through the nitrogen atom, and the solids obtained by treatment with $AlEtCl_2$ catalyse the reaction between methacrolein and cyclopentadiene, leading to 8% enantiomeric excess (ee). The best results in these reactions (until 31% ee) are obtained by using (–)-menthol–aluminium Lewis acids supported on silica gel and alumina through the aluminium atom. The supported catalysts are compared with the analogous homogeneous Lewis acids. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Chiral catalysis is one of the major goals in the preparation of optically active compounds. This is undoubtedly due to the fact that, if high enantiomeric excess (ee) is obtained, it is possible to reach a high efficiency in the transfer of chirality, *i.e.*, a high number of new chiral molecules can be obtained starting from a small number of molecules of chiral auxiliary. Another advantage, with regard to the use of chiral reagents, is that the catalyst can be easily separated from the reaction medium without using a chemical reaction. However, the separation of the catalyst is often not an easy task, especially when large scale applications are envisaged. For this reason the development of chiral heterogeneous catalysts is a field of great interest, and one of the major strategies followed in order to reach this aim is to support homogeneous catalysts onto organic or inorganic supports. However, frequently, the catalytic properties of the immobilised systems change dramatically with regard to their homogeneous counterparts, which justifies the need for systematic studies on this topic.

Just recently, Blaser and Pugin published[1] an interesting review about the application of heteogeneous enantioselective catalysts. This review shows that more than 50% these catalysts are devoted to hydrogenation reactions, but there are a few examples concerning the oxidation of double bonds, and the C–C bond forming reactions. With regard to cycloadditions there are only two precedents dealing with reactions of cyclopropanation,[2] and recently the use of chiral oxazoborolidinones, supported on organic polymers, to promote enantioselective Diels–Alder reactions has been described.[3]

In this paper we present the results obtained in Diels–Alder reactions catalysed by chiral Lewis acids immobilised on silica gel and alumina, and compare them with those obtained using their homogeneous counterparts. Using two different approaches the chiral complex was immobilised either through the organic part or through the metal.

RESULTS AND DISCUSSION

Chiral oxazoborolidinones, obtained by treatment of *N*-sulphonyl-α-amino acids with BH_3, catalyse the Diels–Alder reactions of α,β-unsaturated aldehydes with high enantioselectivity.[4–6] In particular, excellent results are

obtained in the reaction of 2-bromoacrolein with cyclopentadiene when the amino acid bears an electron-rich aromatic ring, as is the case of (*S*)-tryptophan[5] and (*S*)-tyrosine.[6] The π-stacking interaction between the electron-rich aromatic ring and the electron-deficient dienophile is proposed to account for these high enantioslectivities (Figure 1).

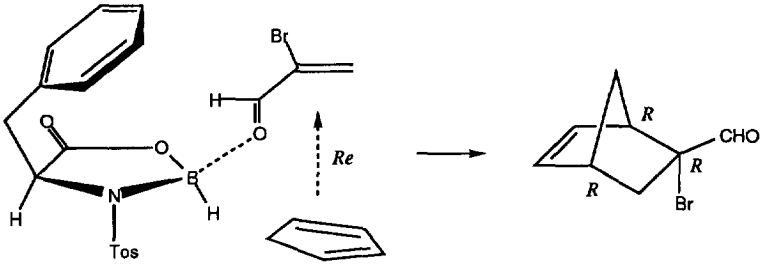


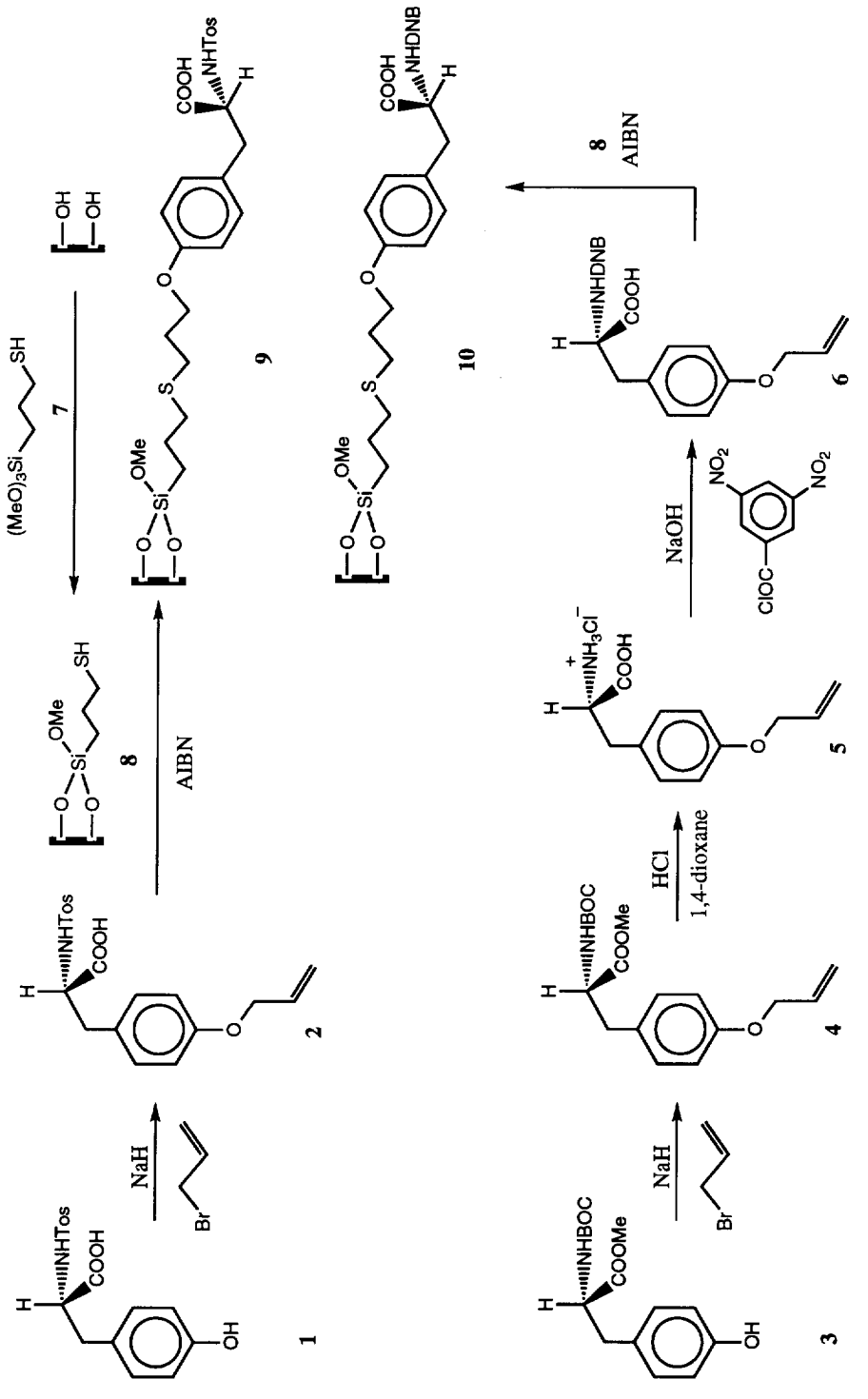
Figure 1

In view of these precedents we tried to support these kind of catalysts on silica gel. In order to keep a similarity between the homogeneous and the heterogeneous systems we decided to graft the tyrosine through the phenolic oxygen atom. *N*-tosyl-(*S*)-tyrosine **1** was supported by a radical-promoted reaction of *N*-tosyl-*O*-allyl-(*S*)-tyrosine **2** with mercaptopropylsilica **8**, in the presence of α,α'-azoisobutylnitrile (AIBN) (Scheme 1). To test a different N-protecting group, *N*-(3,5-dinitrobenzoyl)-*O*-allyl-(*S*)-tyrosine **6** was also supported by the same method.

The results obtained using supported chiral catalysts must be compared with those obtained by using analogous homogeneous catalysts. With this aim, *N*-tosyl-*O*-methyl-(*S*)-tyrosine **11**, *N*-tosyl-*O*-propyl-(*S*)-tyrosine **13**, and *N*-(3,5-dinitrobenzoyl)-*O*-methyl-(*S*)-tyrosine **16**, were transformed into their corresponding oxazoborolidinones (Scheme 2), and used as catalysts in the reactions of methacrolein **17** and 2-bromoacrolein **18** with cyclopentadiene **19** (Scheme 3).

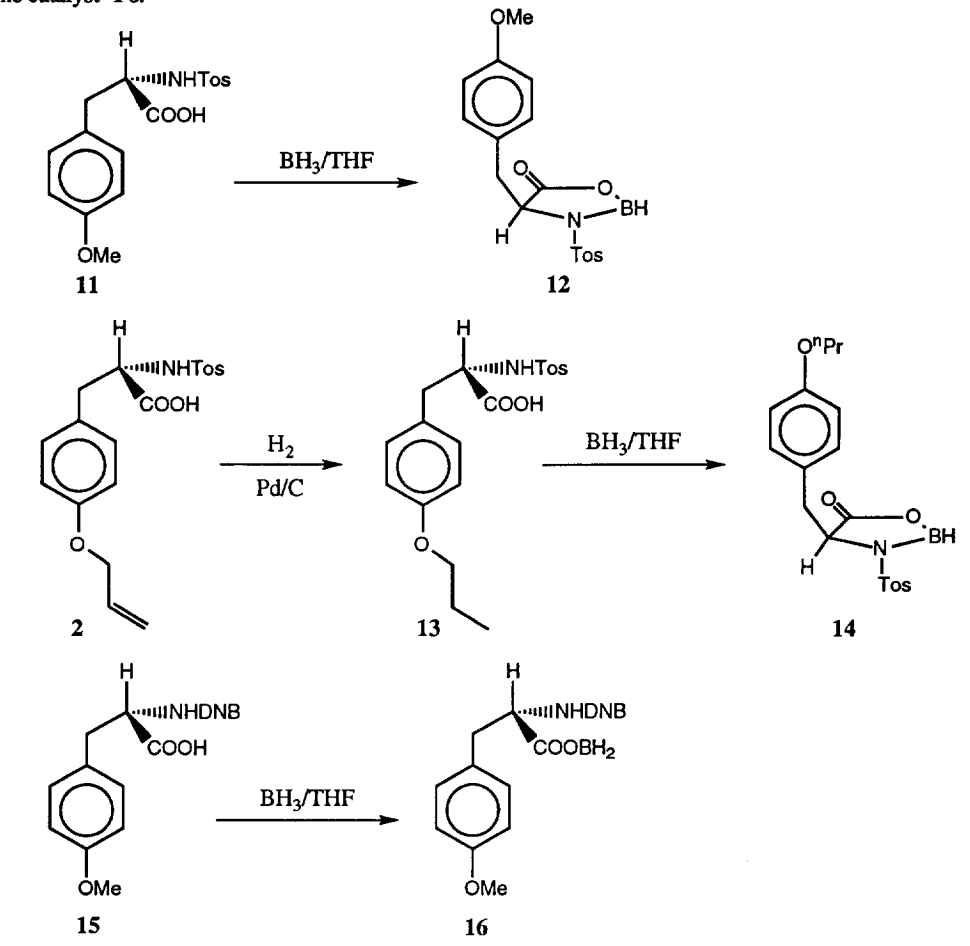
The results obtained (Table 1) show that these homogeneous catalysts efficiently promote the reaction between 2-bromacrolein **18** and cyclopentadiene **19**. The best asymmetric induction is obtained with the *N*-tosyl-*O*-methyl derivative **12**. A comparison with the results obtained using the *N*-tosyl-*O*-propyl derivative **14** indicates that an increase in the size of the *O*-alkyl group slightly reduces the asymmetric induction. In agreement with the previously proposed model (Figure 1), the (1*R*,2*R*,4*R*)-2-bromo-2.formyl-5-norbornene (**21R**) is the major product. However, when the *N*-(3,5-dinitrobenzoyl) derivative **16** is used, the direction of the asymmetric induction is reversed, and the (1*S*,2*S*,4*S*)-2-bromo-2-formyl-5-norbornene **21S** is preferentially obtained. This result may be explained by an open-chain model where the phenolic ring shields the *Re* face of the dienophile (Figure 2). The greater flexibility of this intermediate, with regard to the cyclic oxazoborolidinone, accounts for the lesser asymmetric induction. The NH group of the 3,5-dinitrobenzoyl derivative (**15**) seems not to be acidic enough to react with BH_3.

As previouly reported,[6] the oxazaborolidinone **12** leads to a much worse asymmetric induction when methacrolein **17** is used as a dienophile, and the direction of the asymetric induction is reversed. The lack of strong π-stacking interactions between the phenolic ring and the dienophile accounts for this behaviour, and a different model must be used.[6] Unexpectedly, catalyst **16** is more efficient for this reaction, and a higher conversion is obtained over the same time period. Furthermore, a higher enantiomeric excess of the other enantiomer **20S** is obtained. Again, the lack of strong π-stacking interactions reverses the direction of the



Scheme 1

asymmetric induction with regard to the reaction of 2-bromoacrolein **18** and cyclopentadiene **19** promoted by the same catalyst **16**.



Scheme 2

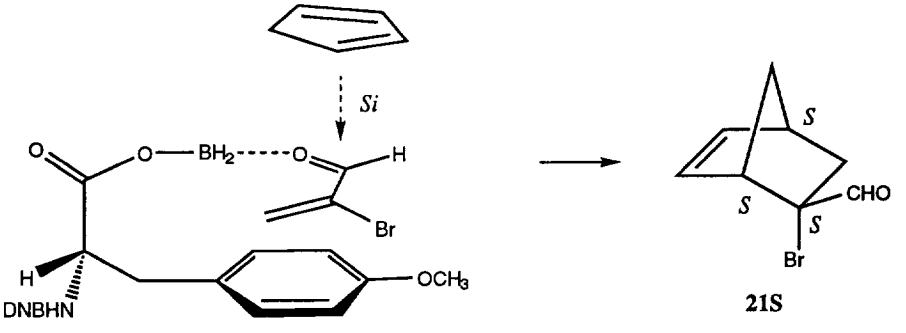
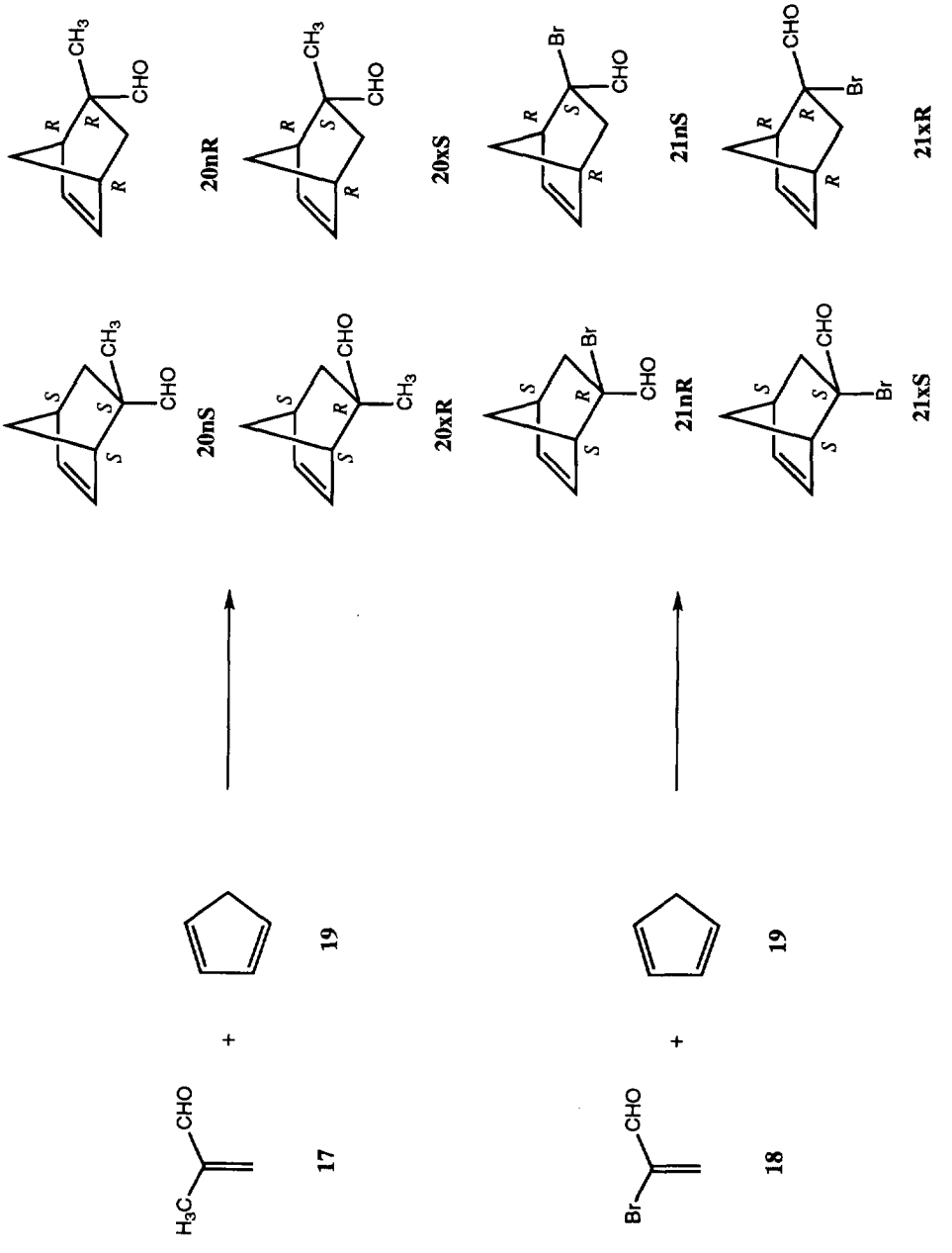


Figure 2


CH3
CHO
R
R
R
20nR
CH3
CHO
R
S
R
20xS
Br
CHO
R
S
R
21nS
CHO
Br
R
R
R
21xR
CH3
CHO
S
S
S
20nS
CHO
CH3
S
R
S
20xR
Br
CHO
S
R
S
21nR
CHO
Br
S
S
S
21xS
19
+
H3C
CHO
17
19
+
Br
CHO
18

Scheme 3

Table 1. Results obtained in the reactions of methacrolein **17** and 2-bromoacrolein **18** with cyclopentadiene **19**, promoted by the boron catalysts **12**, **14**, and **16**.[a]

Dienophile	Catalyst	T (°C)	t (h)	% Conv.	*exo/endo*[b]	%ee[c]	Major Cycloadduct[c]
17	**12**	–78	3	56	94:6	10	**20R**
18	**12**	–78	3	100	96:4	62	**21R**
18	**12**	0	1	100	91:9	30	**21R**
18	**14**	–78	3	100	96:4	50	**21R**
18	**14**	0	1	100	91:9	21	**21R**
17	**16**	–78	3	100	92:8	25	**20S**
17	**16**	0	1	100	82:18	14	**20S**
18	**16**	–78	3	100	88:12	28	**21S**
18	**16**	0	1	100	82:18	15	**21S**

[a] 1 mmol of dienophile, 3 mmol of cyclopentadiene, and 0.2 mmol of catalyst. [b] Determined by gas chromatography. [c] Determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. The absolute configuration was assigned by comparison with the spectrum obtained from reactions carried out in previously described conditions.

The chiral auxiliaries supported on silica gel were treated with BH_3 and tested in the same Diels–Alder reactions. The results obtained are gathered in Table 2. As can be seen, all the solids promote the reaction, but they do not give rise to asymmetric induction. Two factors can explain the lack of asymmetric induction: a bad reaction with BH_3, and the catalytic role of the non-functionalized silanols. In fact, it has been described that silica gel is able to promote Diels–Alder reactions, even with fairly unreactive dienophiles.[7] In order to study the influence of the first factor, the time period of treatment with BH_3 was noticeably increased. This lead to an increase in the catalytic activity, but did not modify the enantioselectivity.In order to avoid the catalytic role of the support the mercaptopropyl silica was "end-capped" by treatment with hexamethyldisilazane (HMDS) before incorporating the chiral auxiiary. Although this methodology slightly reduces the amount of chiral auxiliary supported as well as the catalytic activity, it does not lead to the appearance of enantioselectivity. The lack of asymmetric induction is in agreement with the results published by Itsuno and co-workers, who used a closely related system grafted onto an organic polymer. The low enantioselectivity obtained with this system contrasts with the good results obtained using the same chiral auxiliary, but when incorporated into the solid by co-polimerisation.[3]

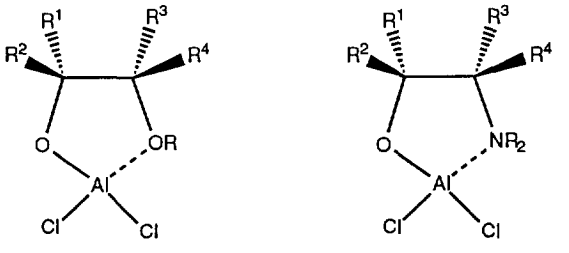


Figure 3

In view of the above results we considered it interesting to test the use of supported amino alcohols as chiral auxiliaries. This is a more simple strategy and it has allowed noticeable asymmetric inductions in several reactions to be obtained.[8] Furthermore, Kagan and co-workers[9] have shown that the presence of a vicinal

oxygen atom in 1,2-diols of α-hydroxy ether allows the formation of chelate complexes with $AlEtCl_2$, which reduces the flexibility of the catalyst and increases the asymmetric induction. In this regard, 1,2-aminoalcohols are related to 1,2-dioxygenated compounds (Figure 3).

Table 2. Results obtained in the reactions of methacrolein **17** and 2-bromoacrolein **18** with cyclopentadiene **19**, promoted by the supported catalysts.[a]

Dienophile	Catalyst	time of treatment with BH_3	T (°C)	t (h)	% Conv.	*exo/endo*[b]	%ee[c]
18	**9**+BH_3[d]	50 min	–45	20	82	91:9	0
18	**9**+BH_3	7.5 h	–45	14	86	90:10	0
18	**9EC**+BH_3[e]	50 min	–45	20	76	91:9	0
18	**9EC**+BH_3	7.5 h	–45	14	88	90:10	0
18	**10**+BH_3[f]	50 min	–45	20	54	92:8	0
18	**10**+BH_3[g]	50 min	–45	20	45	92:8	0
17	**9**+BH_3	50 min	20	20	69	92:8	7[h]
17	**9EC**+BH_3	50 min	20	48	90	88:12	7
17	**10**+BH_3	50 min	20	20	51	87:13	0

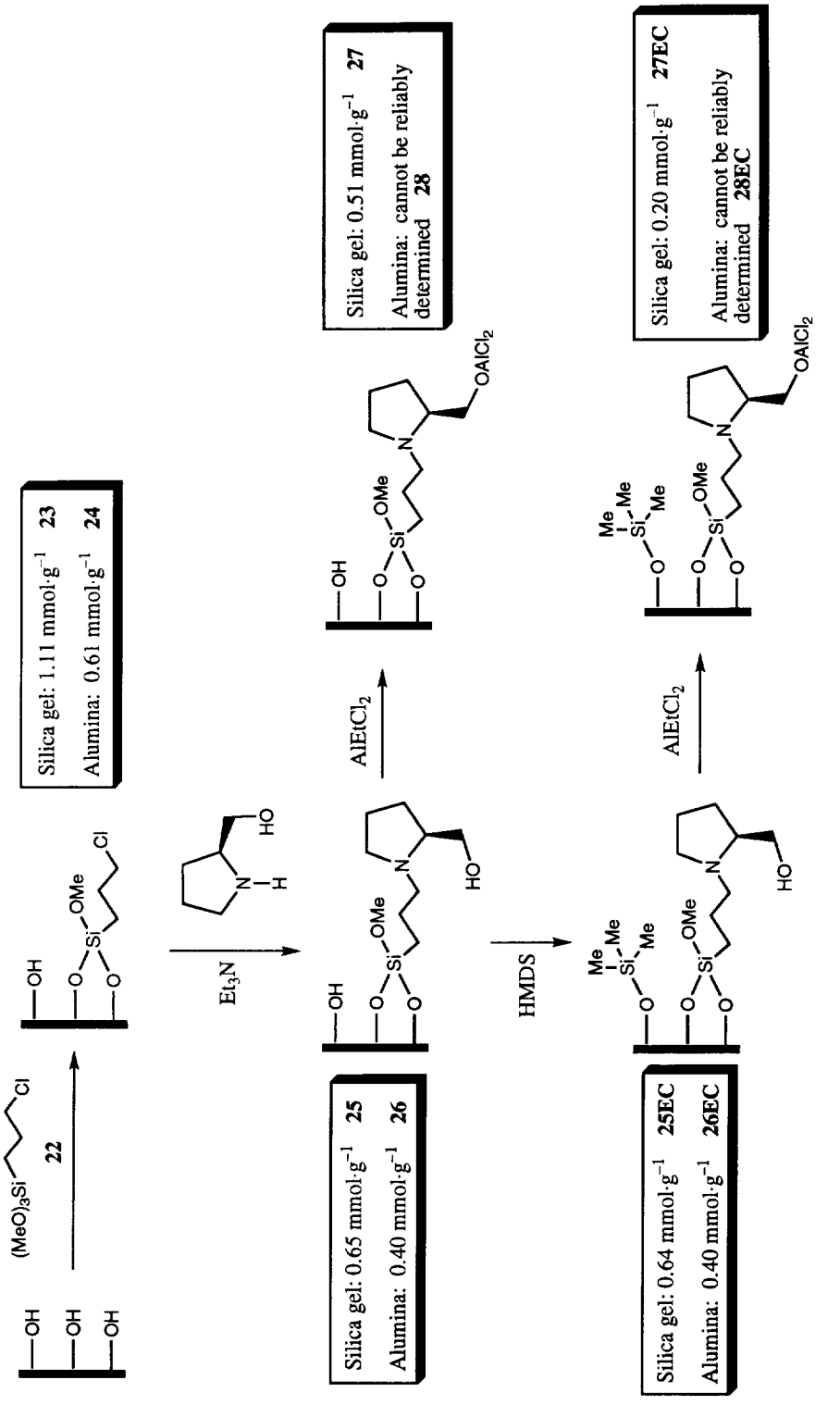
[a] 1 mmol of dienophile, 3 mmol of cyclopentadiene, and 0.2 mmol of catalyst. [b] Determined by gas chromatography. [c] Determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. [d] 0.40 mmol·g^{-1} of chiral auxiliary. [e] 0.32 mmol·g^{-1} of chiral auxiliary. [f] 0.22 mmol·g^{-1} of chiral auxiliary. [g] 0.18 mmol·g^{-1} of chiral auxiliary. [h] **20S** is the major cycloadduct.

In order to further decrease the flexibility of the chiral auxiliary, we used (*S*)-prolinol which was made to react with chloropropyl silica and alumina, and then was treated with $AlEtCl_2$. To avoid the formation of non-chiral catalytic centres by reaction of the $AlEtCl_2$ with the surface hydroxyl groups,[10] the support was previously "end-capped" by treatment with HMDS (Scheme 4). As shown by Kagan and co-workers,[9] the supported Lewis acids were used to promote the reaction between methacrolein **17** and cyclopentadiene **19** (Scheme 3), and the results were compared with those obtained using the homogeneous catalyst coming from the treatment of *N*-benzyl-(*S*)-prolinol with $AlEtCl_2$ **29**. As can be seen in Table 3, the supported catalysts are far more active than the homogeneous system. The slightly higher catalytic activity of the catalysts supported on silica gel may be due to their higher degree of functionalisation. However, the catalysts supported on alumina lead to slightly better *exo/endo* selectivity. With all the catalysts a low 8% ee was observed, and the asymmetric induction was not improved when using the "end-capped" solids.

Table 3. Results obtained in the reactions of methacrolein **17** and cyclopentadiene **19**, promoted by the supported (*S*)-prolinol-aluminium catalysts in toluene at 20°C.[a]

Catalyst	t (h)	%Conversion[b]	*exo/endo*[b]	%ee[c]
27	1	97	85:15	8
27EC	1	93	87:13	8
28	1	92	90:10	8
28EC	1	90	90:10	7
29	4	1	—	—

[a] 1 mmol of dienophile, 1 mmol of diene, and 1 g of catalyst. [b] Determined by gas chromatography. [c] Determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$. **20S** is the major cycloadduct.


(MeO)3Si
Cl
22
Et3N
HMDS
AlEtCl2
AlEtCl2
Silica gel: 1.11 mmol·g−1 23
Alumina: 0.61 mmol·g−1 24
Silica gel: 0.65 mmol·g−1 25
Alumina: 0.40 mmol·g−1 26
Silica gel: 0.51 mmol·g−1 27
Alumina: cannot be reliably determined 28
Silica gel: 0.64 mmol·g−1 25EC
Alumina: 0.40 mmol·g−1 26EC
Silica gel: 0.20 mmol·g−1 27EC
Alumina: cannot be reliably determined 28EC

Scheme 4

These results indicate that the immobilisation of the chiral auxiliary by grafting it on a solid support modifies the structure of the chiral Lewis acid and that of its complex with the dienophile. This modification does not have a bad influence on the catalytic activity, which can even be increased, but leads to a dramatic decrease in the asymmetric induction, with regard to the analogous homogeneous systems.

In view of this, we considered a different strategy in which the metal, and not the chiral auxiliary, is used to graft the chiral Lewis acid to the solid. In order to test this strategy we selected the work carried out by Koga and co-workers,[11] using (*1R,2S,5R*)-menthoxy aluminium derivatives as chiral catalysts in the reaction between methacrolein **17** and cyclopentadiene **19**.

In order to obtain the supported catalysts, (–)-menthol and $AlEt_2Cl$ were made to react in several proportions and then heated in toluene under reflux in the presence of alumina or silica gel. The solid was separated by filtration and washed, and its catalytic activity was tested in the same reaction of methacrolein **17** with cyclopentadiene **19**. Under these conditions a large variety of catalytic centres could be grafted on the solid, and the catalytic activity and enantioselectivity would change from one to another (Figure 4).

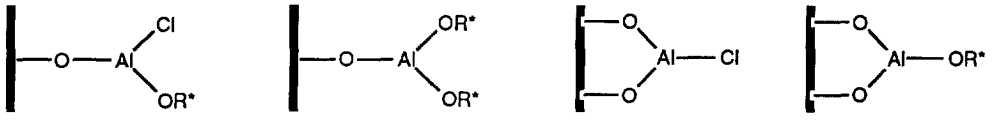


Figure 4

One way to change the proportion of these catalytic sites is to change the (–)-menthol/$AlEt_2Cl$ ratio in the preparation of the catalysts. Thus, using alumina as a support, the catalytic activity decreases when the molar ratio beteween $AlEt_2Cl$ and (–)-menthol decreases, which is in agreement with the reduction in the number of aluminium atoms bearing chlorine atoms. When an excess of $AlEt_2Cl$ is used in the preparation of the catalysts, the enantioselectivity is worse than that obtained with equimolecular amounts of both reagents (Table 4), which can be accounted for by an increase in the number of the very active, but non chiral type C catalytic sites (Figure 4). Unexpectedly, the increase in the proportion of (–)-menthol also gives rise to a decrease in the enantiomeic excess, which suggests that the centres bearing two chiral alcoxy groups (type B sites), are also less discriminating. It is well known[12] that the activation of alumina at high temperatures produces the dehydroxylation of the surface and generates acid sites. The solid obtained from this treatment is a better catalyst than alumina, but its ability to support is reduced. As a consequence, the catalyst obtained using alumina activated at 400°C as a support is more active but not enantioselective. A decrease in the reaction temperature increases the asymmetric induction, but, unfortunately, the most enantioselective catalysts are not very active, so that the reaction cannot be carried out at low temperatures.

The catalyst obtained using silica gel as the support, and equimolecular amounts of $AlEt_2Cl$ and (–)-menthol, leads to a slightly lesser asymmetric induction than that by the same catalyst supported on alumina, but it is more active. As a consequence, the reaction can now be carried out at –50°C to reach 81% conversion with 31% ee. This result is better when compared with the 57% ee described by Koga and co-workers[11] using the homogeneous catalyst at –78°C.

To sum up, supporting the chiral Lewis acid by the metal may have a lesser influence on the conformation of the chiral auxiliary, and hence on the stereochemical reaction course.

Table 4. Results obtained in the reactions of methacrolein **17** and cyclopentadiene **19**, promoted by the supported (*1R,2S,5R*)-menthoxyaluminium catalysts.[a]

Support	AlClEt2/(–)-menthol molar ratio	T (°C)	t (h)	%Conv.[b]	*exo/endo*[b]	%ee[c]
Al_2O_3	2:1	25	1	72	90:10	9
Al_2O_3	2:1	–45	7.5	62	92:8	24
Al_2O_3	1:1	25	24	38	89:11	21
Al_2O_3	1:1	–45	24	3	—	—
Al_2O_3	1:2	25	24	20	88:12	10
Al_2O_3[d]	1:1	25	2	60	89:11	0
SiO_2	1:1	25	1	94	84:16	16
SiO_2	1:1	–50	6	81	90:10	31

[a] 1 mmol of dienophile, 1 mmol of diene, and 1 g of catalyst. [b] Determined by gas chromatography. [c] Determined by ^{1}H-NMR in the presence of Eu(hfc)3. **20S** is the major cycloadduct. [d] Activated at 400°C under vacuum.

EXPERIMENTAL

1. Supported catalysts derived from (S)-tyrosine

1.1. Synthesis of the homogeneous precursors

• *N*-tosyl-*O*-allyl-(*S*)-tyrosine **2**. Under argon, to a solution of *N*-tosyl-(*S*)-tyrosine **1** (2.345 g, 7 mmol) in dry *N,N*-dimethylformamide (DMF) kept at 5°C, a suspension of NaH (0,504 g, 21 mmol) in dry DMF is added slowly. The mixture is stirred at 10°C for two hours and then allyl bromide (0.93 g, 7.7 mmol) is added dropwise, and the mixture is stirred at room temperature for 48 h. After this time water (250 ml) is added and the stirring is maintained for one hour. The aqueous phase is separated, washed with with benzene, acidified with HCl, and extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulfate, and the solvent eliminated under vacuum to yield a yellow oil, that can be crystallised from ethanol:water (1.30 g, 50%) ^{1}H-NMR ($CDCl_3$, δ ppm): 7.62 (d, 2H, J=8.0 Hz); 7.22 (d, 2H, J=8.0 Hz); 6.99 (d, 2H, J=8.6 Hz); 6.78 (d, 2H, J=8.6 Hz); 6.16 (m, 1H); 5.47 (d, 1H, J=17.2 Hz); 5.31 (d, 1H, J=10.5 Hz); 5.06 (d, 1H, J=8.4 Hz); 4.58 (m, 2H); 4.23 (m, 1H); 3.08 (m, 2H); 2.40 (s, 3H). ^{13}C-NMR ($CDCl_3$, δ ppm): 175.9, 157.5, 143.2, 136.5, 133.2, 130.4, 129.4, 127.9, 126.9, 117.5, 68.6, 57.4, 37.7, 21.4. Elemental analysis ($C_{19}H_{21}NO_5S$): Calcd.: C 60.78%, H 5.64%, N 3.73%, S 8.54%; found: C 60.63%, H 5.73%, N 3.77%, S 8.42%

• *N*-(*tert*-butyloxycarbonyl)-*O*-allyl-(*S*)-tyrosine **4**. Under argon, to a solution of *N*-(*tert*-butyloxycarbonyl)-(*S*)-tyrosine (**3**) (2.21 g, 7.5 mmol) in dry DMF kept at 5°C, NaH (0,46 g, 19.2 mmol) is added slowly. The suspension is stirred at 10°C for two hours and then allyl bromide (0.99 g, 8.3 mmol) is added dropwise, and the mixture is stirred at room temperature for 48 h. After this time water (90 ml) is added and the stirring is maintained for one hour. The aqueous phase is separated, washed with with ethyl acetate, acidified with HCl, and extracted with ethyl acetate. The organic phase is dried over anhydrous sodium sulfate, and the solvent eliminated under vacuum to afford an oil, pure enough to be subsequently used (1.44 g, 60%). The product can be purified by column chromatography on silica gel, using CH_2Cl_2:CH_3OH 9:1 as an eluent. ^{1}H-NMR ($CDCl_3$, δ ppm): 7.06 (d, 2H, J=8.4 Hz); 6.83 (d, 2H, J=8.4 Hz); 6.01 (m, 1H); 5.38 (d, 1H, J=17.2 Hz); 5.25 (d, 1H, J=10.5 Hz); 4.91 (d, 1H, J=7.3 Hz); 4.50 (m, 3H); 3.06 (m, 2H); 1.39 (s, 9H).

• *O*-allyl-(*S*)-tyrosine hydrochloride **5**. *N*-(*tert*-butyloxycarbonyl)-*O*-allyl-(*S*)-tyrosine **4** (2.57 g, 8 mmol) is added over 20 ml of 1,4-dioxane saturated with hydrogen chloride. The solution is stirred at room temperature overnight, the solvent evaporated under reduced pressure and the solid thoroughly washed with diethyl ether to afford **5** (1.40 g, 68%). ^{1}H-NMR (DMSO-d_6, δ ppm): 8.42 (bs, 3H); 7.18 (d, 2H, J=8.1 Hz); 6.90 (d, 2H, 8.1 Hz); 6.02 (m, 1H); 5.37 (d, 1H, J=17.3 Hz); 5.24 (d, 1H, J=10.3 Hz); 4.53 (d, 1H, 4.7 Hz); 4.07 (m, 1H); 3.06 (m, 2H).

• *O*-allyl-(*S*)-tyrosine hydrochloride **6**. 2.57 g (10 mmol) and a solution of NaOH 1M are slowly mixed with magnetic stirring. Then, 3,5-dinitrobenzoyl chloride (2.31g, 10 mmol) is added (the pH of the mixture must be basic, so additional amounts of NaOH can be added). The mixture is stirred overnight at room temperature and then is acidified with HCl 1M. The solid is separated by filtration, washed with water and purified by column chromatography on silica gel, using CH_2Cl_2:CH_3OH 9:1 as an eluent, to afford 2.68 g (65%) of **6**. ^{1}H-NMR (DMSO-d_6, δ ppm): 9.48 (d, 1H, J=8.2 Hz); 9.00 (bs, 1H); 7.21 (d, 2H, J=7.9 Hz); 6.83 (d, 2H, J=8.0 Hz); 6.02 (m, 1H); 5.34 (d, 1H, J=17.7 Hz); 5.05 (d, 1H, J=10.1 Hz); 4.46 (m, 1H); 4.48 (m, 2H); 3.10 (m, 2H). ^{13}C-NMR (DMSO-d_6, δ ppm): 172.7, 162.1, 159.9, 148.1, 136.8, 133.8, 130.3, 127.6, 120.8, 117.2, 114.3, 68.0, 55.5, 35.8. Elemental analysis ($C_{19}H_{17}N_3O_8$): Calcd.: C 54.94%, H 4.13%, N 10.12%; found: C 54.99%, H 4.01%, N 10.21%

1.2. Preparation of the supported chiral auxiliaries

• Synthesis of mercaptopropyl silica **8**. Under argon, to a suspension of 10 g of silica gel (Merck, silica gel 60, 63–200 nm), dried at 140°C under vacuum, in 2.5 ml of dry toluene, 6 ml of dry piridine and γ-mercaptopropyl trimethoxysilane (2.75 g, 14 mmol) are added dropwise. The suspension is heated under reflux for 40 h, the solid is separated by filtration and washed with toluene, THF, and *n*-hexane. The content of sulphur (1.09 mmol·g^{-1}) was determined by elemental analysis.

• Synthesis of silanised mercaptopropyl silica **8EC**. Under argon, to a suspension of 4.5 g of mercaptopropyl silica (**8**) in 40 ml of dry toluene, hexamethyldisilazane (2.5 ml) is added and the suspension is heated under reflux for 1 h. The solid is separated by filtration, washed with acetone, water, methanol, and diethyl ether, and dried under vacuum at 50°C over P_2O_5 during 24 h. The solid contains 1.03 mmol of sulphur per gram.

• *N*-tosyl-*O*-allyl-(*S*)-tyrosine supported on silica **9,9EC**. Under argon, 4 g of the corresponding mercaptopropyl silica **8**, **8EC**, *N*-tosyl-*O*-allyl-(*S*)-tyrosine (0.94 g, 2.5 mmol), and α,α'-azoisobutironitrile (53 mg, 0.32 mmol) are heated in dry $CHCl_3$ under reflux (40 ml) for 40 h. The solid is separated by filtration, washed with $CHCl_3$, methanol, acetone, methanol, and diethyl ether, and dried under vacuum over P_2O_5 for 24 h. The content of chiral auxiliary, determined by elemental analysis of nitrogen, is 0.40 mmol·g^{-1} in the case of **9**, and 0.32 mmol·g^{-1} in the case of **9EC**.

• *N*-(3,5-dinitrobenzoyl)-*O*-allyl-(*S*)-tyrosine supported on silica **10,10EC**. These solids are obtained by the same method, but the treatment must be done twice in order to increase the degree of functionalisation, which results, as determined by elemental analysis, 0.22 mmol·g^{-1} in the case of **10**, and 0.18 mmol·g^{-1} in the case of **10EC**.

1.3 Preparation of the catalysts and Diels–Alder reactions

Under argon, to a suspension of the silica modified with the corresponding tyrosine derivative **9,9EC, 10, 10EC**, in the amount corresponding to 1 mmol of chiral auxiliary, in an anhydrous mixture of CH_2Cl_2 (10 ml) and THF (0.65 ml), 1 ml of a 1M solution of BH_3 in THF is added, and the mixture is stirred at 0°C for 50 min. After this time the mixture is left to reach the reaction temperature (Table 2), and methacrolein **17** (0.35g, 5 mmol) or 2-bromoacrolein **18** (0.68 g, 5 mmol) is added. The mixture is shaken for 20 min, and freshly distilled cyclopentadiene **25** (0.99 g 15 mol) is added. The reaction is monitored by gas chromatography (FID form Hewlett–Packard 5890 II, cross-linked methyl silicone column 25 m x 0.2 mm x 0.33 μm), in the following conditions:

• Reaction of methacrolein **17**: helium as carrier gas, 17 p.s.i.; injector temperature 230°C; detector temperature 250°C; oven temperature programme: 40 °C (3 min) – 25°C/min – 100°C (10 min); retention times: methacrolein **17** 2.7 min, *exo* cycloadduct **20x** 10.8 min, *endo* cycloadduct **20n** 11.5 min.

• Reaction of 2-bromoacrolein **18**: helium as carrier gas, 18 p.s.i.; injector temperature 230°C; detector temperature 250°C; oven temperature programme: 50 °C (3 min) – 25°C/min – 100°C (10 min); retention times: 2-bromoacrolein **18** 3.2 min, *exo* cycloadduct **21x** 10.8 min, *endo* cycloadduct **21n** 11.5 min.

After the reactions, the solid is separated by filtration and washed with CH_2Cl_2. The solution is treated with $Na_2CO_3 \cdot 10H_2O$, which is further separated by filtration. The solvent and the remaining dienophile are evaporated under reduced pressure, and the cycloadducts are separated and purified by column chromatography on silica gel, using CH_2Cl_2:*n*-hexane (1:1 for compounds **20** and 7:3 for compounds **21**) as an eluent.

The enantiomeric composition is analysed for the major *exo* cycoadducts by ^{1}H-NMR in $CDCl_3$, in the presence of Eu(hfc)$_3$ (Eu(hfc)$_3$/substrate molar ratio 0.2 for **20x** and 0.3 for **21x**). In both cases the signal at a higher chemical shift corresponds to the (*1R,4R*) cycloadduct **20xS** and **20xR**.

2. Homogeneous catalysts derived from (S)-tyrosine

2.1. Synthesis of the chiral auxiliaries

N-Tosyl-*O*-methyl-(*S*)-tyrosine **11** and *N*-(3,5-dinitrobenzoyl)-*O*-methyl-(*S*)-tyrosine **15** were obtained from *O*-methyl-(*S*)-tyrosine following standard procedures.

• *N*-tosyl-*O*-propyl-(*S*)-tyrosine **13**: *N*-tosyl-*O*-allyl-(*S*)-tyrosine **2** (1.88 g, 5 mmol) is hydrogenated in methanol, at room temperature and atmospheric pressure, in 1h using Pd/C as a catalyst. The catalyst is eliminated by filtration and the solvent evaporated under reduced pressure to afford **13** (1.99 g, 100%).

^{1}H-NMR ($CDCl_3$, δ ppm): 7.57 (d, 2H, J=8.2 Hz); 7.20 (d, 2H, J=8.2 Hz); 6.97 (d, 2H, J=8.6 Hz); 6.73 (d, 2H, J=8.6 Hz); 5.05 (d, 1H); 4.18 (m, 1H); 3.68 (t, 2H, J=6.2 Hz); 2.97 (m, 2H); 2.37 (s, 3H); 1.78 (m, 2H); 1.05 (t, 3H, J=7.1 Hz). ^{13}C-NMR ($CDCl_3$, δ ppm): 175.4, 158.3, 143.6, 136.5, 130.3, 129.5, 127.0, 126.5, 114.6, 69.4, 56.6, 37.9, 22.5, 21.4, 10.4. Elemental analysis ($C_{19}H_{23}NO_5S$): Calcd.: C 60.46%, H 6.14%, N 3.71%, S 8.90%; found: C 60.30%, H 6.16%, N 3.79%, S 8.22%

2.2. Preparation of the catalysts and Diels–Alder reactions

Under argon and at 0°C, 1 ml of a 1M solution of BH_3 in THF is added over a solution of 1 mmol of the chiral auxiliary **11,13,15** and an anydrous mixture of CH_2Cl_2 (10 ml) and THF (0.65 ml), and the mixture is stirred for 50 min. Then, 5 mmol of the corresponding dienophile **17,18** is added, the solution is stirred at the reaction temperature (Table 1) for 20 min, and freshly distilled cyclopentadiene **19** (0.99 g, 15 mmol) is added. The reaction is monitored by gas chromatography, and after the corresponding time (Table 1), a dilute solution of HCl and an additional amount of CH_2Cl_2 are added. The organic phase is separated, dried over anhydrous Na_2SO_4, separated by filtration, and the solvent eliminated under reduced pressure. The cycloadducts are separated and analysed as described above.

3. Supported catalysts derived form (S)-proline

3.1. Preparation of the supported chiral auxiliaries

• 3-chloropropyl silica **23** and 3-chloropropyl alumina **24**: Silica gel (Merck silica gel 60, 63–200 nm) or alumina (Merck aluminium oxide 60, 63–200 nm) are activated under vacuum at 140°C. To a suspension of 5 g of solid in dry toluene (25 ml), kept under argon, 3-chloropropyltrimethoxysilane (5.43 mmol) is added dropwise. The mixture is heated under reflux for 1.5 h and 6 ml of solvent are distilled-off. The reflux is continued for a further 1 h and then 6 ml more of solvent distilled-off. After 30 additional minutes of heating under reflux, the solid is separated by filtration and washed with anydrous toluene. The solid is dried under vacuum at 50°C over P_2O_5 overnight. The degree of functionalisation, calculated by elemental analysis, is 1.1 mmol·g^{-1} for silica gel **23** and 0.61·g^{-1} mmol for alumina **24**.

• Immobilisation of (*S*)-prolinol **25,26**: A suspension of the chloropropylated support **23,24** (2 g) and (*S*)-prolinol (0.178 g, 1.76 mmol) is heated under reflux in anhydrous toluene in the presence of triethylamine (0.178 g, 1.76 mmol) for 20 h. The solid is separated by filtration, washed with toluene, diethyl ether, and methanol, and dried over P_2O_5 under vacuum at 50°C overnight. The degree of functionalisation, calculated by elemental analysis of nitrogen, is 0.65 mmol·g^{-1} for silica gel **25** and 0.40 mmol·g^{-1} for alumina **26**.

• Silanisation of the support: A suspension of (*S*)-prolinol supported on silica gel **25** or alumina **26** (2 g) and 1.4 ml of hexamethyldisilazane in anhydrous toluene is heated under reflux for 1 h. The solid is separated by filtration and thoroughly washed with toluene, acetone, water, ethanol, and acetone, and dried under vacuum at 50°C over P_2O_5 overnight. The degree of functionalisation, calculated by elemental analysis of nitrogen, is 0.64 mmol·g^{-1} for silica gel **25EC** and 0.33 mmol·g^{-1} for alumina **26EC**.

3.2. Preparation of the supported catalysts **27,27EC,28,28EC**

Under argon, the activated solid **25,25EC,26,26EC** (1 g) is heated under reflux in anhydrous toluene with 1 ml of a 1 M solution of $AlCl_2Et$ in *n*-hexane. The solid is separated by filtration and washed with toluene. The amount of aluminium, determined by Plasma Emission Spectroscopy, is 0.51 mmol·g^{-1} for **27**, and 0.20 mmol·g^{-1} for **28EC**. The aluminium content could not be reliably determined for aluminas.

3.3. Diels–Alder reactions

Under argon, to 1 g of the corresponding catalyst in dry CH_2Cl_2, freshly distilled methacrolein **17** (70 mg, 1 mmol) is added and the mixture is shaken for 20 min. Then, freshly distilled cyclopentadiene **19** (66 mg, 1 mmol) is added. The reaction is monitored by gas chromatography, the solid is separated by filtration, and the cycloadducts purified and analysed as described above.

4. Supported catalysts derived form (–)-menthol

4.1. Preparation of the catalysts

Under argon, to a solution of (–)-menthol (5, 10, or 20 mmol, Table 4) in dry toluene, 10 ml of a 1 M solution of $AlCl_2Et$ in *n*-hexane are added at –78°C. Then, the solution is stirred at room temperature and 5 g of activated alumina or silica gel are added. The mixture is heated under reflux for 48 h, the solid separated by filtration and thoroughly washed with dry CH_2Cl_2 and toluene.

4.2. Diels–Alder reactions

Under argon, to 1 g of the catalyst in dry CH_2Cl_2, freshly distilled methacrolein **17** (0.511 g, 7.3 mmol) is added. After 20 min at the reaction temperature (Table 4), 0.561 g (8.5 mmol) of freshly distilled cyclopentadiene **19** is added. The reaction is monitored by gas chromatography, the solid is separated by filtration, and the cycloadducts purified and analysed as described above.

Acknowledgements: This work was made possible by the generous financial support of the Comisión Interministerial de Ciencia y Tecnología (Project MAT93-0224) and of the European Union (Contract CHRX CT93-0276).

REFERENCES

1. Blaser, H. U.; Pugin, B. in "Chiral Reactions in Heterogeneous Catalysis", James, G.; Dubois, V. Eds., Plenum Press, New York, 1995.
2. (a) Martlin, S. A; Lough, W. J.; Chan, L.; Abram, D. M. H.; Zhou, Z. *J. Chem. Soc., Chem. Comun.* **1984**, 1039. (b) Doyle, M. P.; Eismont, M. Y.; Bergbreiter, D. E.; Gray, H. N. *J. Org. Chem.* **1994**, *57*, 6103.
3. (a) Itsuno, S.; Kamatori, K.; Watanabe, W.; Koizumi, F.; Ito, K. *Tetrahedron:Asymmetry* **1994**, *5*, 523. (b) Kamatori, K.; Tada, S.; Ito, K.; Itsuno, S. *Tetrahedron;Asymmetry* **1995**, *6*, 2547.
4. (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartos, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (c) Sartos, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron:Asymmetry* **1991**, *2*, 639.
5. (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290.
6. Seerden, J.-P. G.; Scheeren, H. W. *Tetrahedron Lett.* **1993**, *34*, 2669.
7. Cativiela, C.; García, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F. *Tetrahedron* **1995**, *51*, 1295.
8. See for instance: (a) Itsuno, S.; Fréchet, J. M.J. *J. Org. Chem.* **1987**, *52*, 4140. (b) Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. *J. J. Org. Chem.* **1990**, *55*, 304. (c) Soai, H.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *53*, 927. (d) Fréchet, J. M. J.; Bald, E.; Lecavalier, P. *J. Org. Chem.* **1986**, *51*, 3462. (e) Itsuno, S.; Nakano, M.; Hito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615. (f) Itsuno, S., Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (g) Soai, K.; Watanabe, M.; Yamamoto, A. *J. Org. Chem.* **1990**, *55*, 4832.

9. Ribiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron:Asymmetry* **1990**, *3*, 199.
10. (a) Cativiela, C.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F.; de Mènorval, L. C. *Tetrahedron* **1993**, *49*, 4073. (b) Cativiela, C.; García, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F. *Tetrahedron:Asymmetry* **1993**, *4*, 621.
11. (a) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. (b) Takemura, H.; Komeshima, N; Takahashi, I.; Hashimoto, S.; Ikota, N.; Tamioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687.
12. Bains, S.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5663, and references cited therein.

(*Received in UK* 8 *May* 1996; *accepted* 13 *June* 1996)