

Polymerisation vs. Grafting in the Preparation of Polymer-Supported Aluminium Catalysts for the Diels-Alder Reaction: The Role of the Polymeric Backbone.

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Abstract: Several polymers containing Al Lewis acids anchored to chiral prolinol moieties have been prepared and studied as catalysts for the Diels-Alder reaction of cyclopentadiene and methacrolein. The chiral fragment has been introduced by grafting and by polymerisation procedures using different crosslinking agents and ratios. All supported catalysts prepared show a good activity, but the polymeric network seems to play a very important role in the determining the selectivity observed. Best results, in terms of enantioselectivity, are obtained when the chiral fragment is introduced through polymerisation of the appropriate chiral monomer, but only when a high crosslinking degree (90% DVB) is used. It is shown that the presence of coordinating atoms in the polymeric backbone is clearly detrimental for the selectivity observed. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric induction, Catalysis, Diels-Alder reactions, Polymeric support.

INTRODUCTION

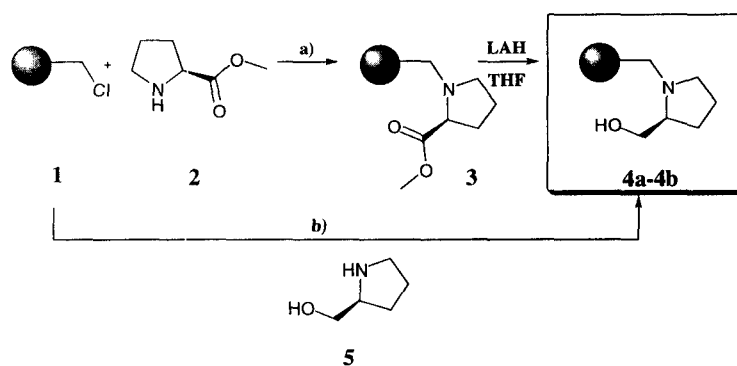
Preparation of novel heterogeneous catalysts is a continuously growing field. This is based on the fact that heterogeneous catalysts are, in principle, best suited for industrial applications as, ideally, they can be recycled and reused through simple filtering and washing procedures. This is especially important when the preparation of chiral enantioselective catalysts is considered. Different supports have been used for this purpose, but polystyrene-divinylbenzene (PS-DVB) and related resins continue being one of the most popular supporting materials.¹⁻⁴ Their use has even increased in recent years because of the important advances made in the preparation and modification of materials of this class for their use in solid-phase combinatorial chemistry.⁴⁻⁵ Several strategies can be employed for the preparation of the appropriate functionalised polymers, mainly depending on the accessibility of the starting materials (functional resins or modified monomers).

The role of the polymeric backbone in these materials is often underestimated, being described as an inert matrix to which the important reactive group is anchored. This is not true, however and very different activities and selectivities can be found when the nature and morphological characteristics (porosity, crosslinking, linker...) of the resin are changed.⁶⁻⁸ Thus, for instance, important differences have been reported for similar polymeric catalysts prepared either by polymerisation or grafting.^{8b} Recently we have studied Ti and Al supported species as Lewis acid catalysts for the Diels-Alder reaction.⁹⁻¹¹ These catalysts can be easily synthesised from PS-DVB resins containing hydroxyl functionalities. In the development of routes for the preparation of chiral catalysts, grafting of aminoalcohols and tartaric acid derivatives was initially considered. The use of the polymer-supported aminoalcohols is attractive because of the easy accessibility of the starting

materials.¹² When supported aminoalcohols derived from different aminoacids were assayed, the best results were obtained, in particular in terms of the enantioselectivity, when the Al-catalyst derived from prolinol was used.¹⁰ The e.e. value obtained was very high, but the result was interesting because such a catalytic activity could not be observed for the homogeneous analogue. Furthermore, the presence of bulky aryl substituents at the α position did not increase the selectivity but, on the contrary, afforded less efficient catalysts. This seems to indicate that the support and/or the heterogenisation procedure can play an important role in the determining the catalytic activity of the supported species. According to this observation and in the search for general protocols for the optimisation of these solid-phase catalysts, we have undertaken a study of the role played by different structural factors associated with the polymeric backbone. Here, we report on the results obtained when different polymeric-supported prolinols were used as the starting materials for the preparation of the corresponding Al catalysts.

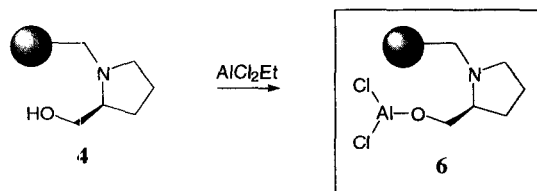
RESULTS AND DISCUSSION

The original procedure for the preparation of a resin-supported prolinol was the initial grafting onto a Merrifield resin (**1**) of the proline methyl ester (**2**) followed by the reduction of the resulting supported aminoester (**3**) with an excess of LAH in THF (*Scheme 1*).¹²



Scheme 1

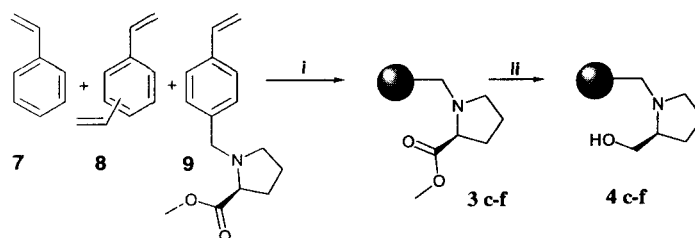
Alternatively, direct attachment of the prolinol can be used, (Method **b**, NaHCO_3 as the base and DMF as solvent) with similar results, but, in general, method **a** proved to be more versatile. Preparation of the corresponding Al catalysts was easily accomplished by the treatment of the resin **4** with AlCl_2Et .



Scheme 2

This affords resins containing Al catalytic sites where the Al is bonded to one oxygen and two chlorine atoms and so having an expectedly good activity as Lewis acids catalysts. Catalysts **6a** and **6b** prepared from both materials (**4a** and **4b**) whose synthesis is shown in *Scheme 1* gave similar results with good catalytic activity and e.e. values around 14%. As stated earlier, no such activities were observed for N-benzylated prolinol derived analogues, and this has been explained through the relative site-isolation afforded by the immobilisation on a polymeric support.¹⁰

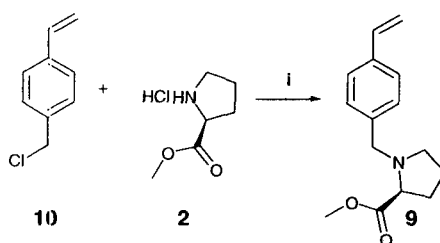
In the search for more efficient catalysts, we prepared different polymers containing the general structure **4**, but having different polymeric backbones.



i: AIBN, Toluene/1-Dodecanol 80°C; ii: LAH, THF

Scheme 3

For that purpose, polymerisation of different mixtures of styrene (**7**), divinylbenzene (**8**) and the prolinol vinyl derivative (**9**) was carried out under radical conditions using AIBN as initiator and toluene/1-Dodecanol as the porogenic mixture (*Scheme 3*).¹³ The final step was the LAH reduction of the ester moiety to give the expected resin-bound prolinols **4c-f**. The prolinol vinyl derivative **9** was obtained in 66% yield by reaction of 4-chloromethylstyrene (**10**) and the proline methyl ester (**2**) (*Scheme 4*).



i: NaHCO₃, THF

Scheme 4

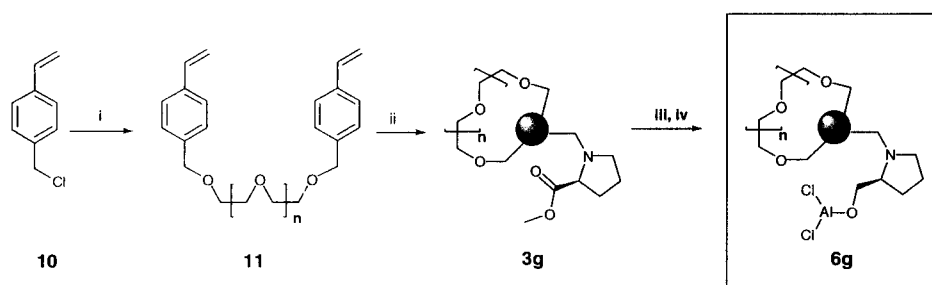
Bulk polymerisations were carried out in general in quantitative yields to obtain resins **4d-f** (see Table 1) having loadings of 0.90, 0.71 and 0.56 mmol/g respectively, as determined by combustion analysis and in good agreement with the loading expected from the monomeric composition. Crosslinking degrees for such polymers range from 20 to 90% (molar percentages of crosslinking agent). For the sake of comparison, a resin having a degree of crosslinking of 20% was also prepared by suspension polymerisation.¹⁴ In this case, however, yields were lower than those obtained for the resin prepared by bulk co-polymerisation (see entry 2, Table 1).

Table 1: Properties of the new polymers prepared.

Entry	Monomeric composition ^{a)}		Polymer (Yield, %)	D.C. ^{b)} (%)	Polymer (%) ^{c)}	Loading (mmol/g)
	9 (n ₉ /n _t)	7 (n ₇ /n _t)				
1	0.10	0.70	3c (80%)	20	4c (100%)	1.14
2	0.10	0.70	3d (>99%)	20	4d (100%)	0.90
3	0.10	0.30	3e (>99%)	60	4e (100%)	0.71
4	0.10	0.00	3f (>99%)	90	4f (100%)	0.56
5	0.10	0.00	3g (>99%)	90	4g (100%)	0.16
6	0.10	0.00	3h (>99%)	90	4h (100%)	0.35

a) Molar ratios, $n_t = n_{(9)} + n_{(7)} + n_{\text{crosslinking agent}}$; b) D.C.: Degree of Crosslinking (molar percentage of crosslinking agent); c) yields refers to the conversion from 3 to 4.

For resins **4a-4f**, the crosslinking agent was always divinylbenzene (DVB). The use of an additional agent containing polyoxyethylene bridges was also assayed. It was expected that the resulting polymer should have important physico-chemical differences to resins **4a-4f**, according to the higher flexibility and to the chemical nature of the crosslinker.¹⁵ These changes had been shown to be important to increase the selectivity observed in related processes catalysed by boron derivatives.^{8b}

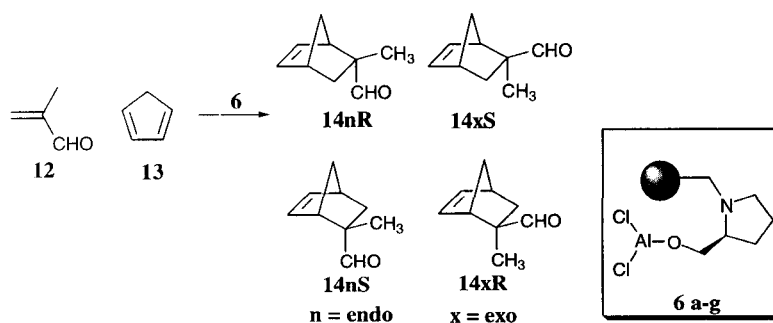


i: NaH, THF, PEG 400; ii: (9), AIBN, Toluene/1-Dodecanol, 80°C; iii: LAH, THF 24h iv: EtAlCl₂, CH₂Cl₂

Scheme 5

The crosslinking agent **11** was prepared in good yields from chloromethylstyrene (**10**) and PEG 400 using the reported methodology.⁸ From this monomer and the proline vinyl derivative (**9**), a highly crosslinked resin **3g** was obtained in quantitative yields by block copolymerisation (*Scheme 5*). The prolinol-supported **4g** was prepared from **3g** by the usual reduction methodology.

The corresponding heterogeneous Al catalysts were obtained from resins **4** by reaction with EtAlCl₂ as shown in *Scheme 2*. Quantitative conversions were always obtained as determined by elemental analyses. The catalytic activity of resins **6** was assayed for the reaction of methacrolein (**12**) with cyclopentadiene (**13**) (*Scheme 6*).^{10a} Results obtained are shown in Table 2. As can be seen, all the supported catalysts showed a high activity (>90% yields after 3 h).



Scheme 6

This is in contrast with the results observed for the homogeneous catalyst derived from *N*-benzylprolinol, for which the conversion was lower than 1% under similar conditions. Only for catalyst **6c**, derived from a polymer prepared by suspension polymerisation was the conversion slightly lower (76%). The exo/endo selectivity is not greatly affected by the nature of the polymeric backbone and remains essentially constant at a value of ca. 90:10. Only for the polymeric catalyst **6g**, whose polymeric structure is considerably different, was a minor decrease in this selectivity detected.

Table 2: Results Obtained in the Reaction of Methacrolein (**12**) with Cyclopentadiene (**13**) Catalysed by Polymer-supported Prolinol-Aluminium Lewis Acid, in Methylene Chloride at -30°C (Molar ratio Al:12:13=1:4:6).

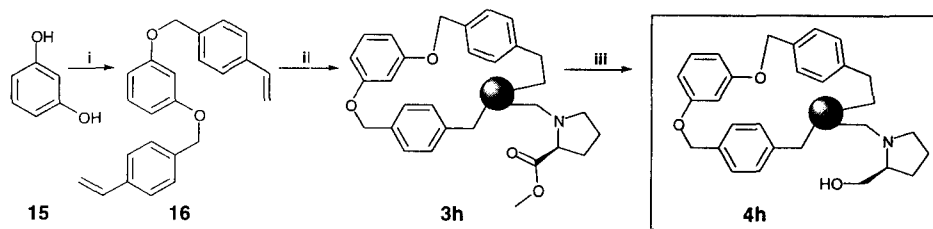
Entry	Starting resin	Catalysts	Loading ^{a)} (mmol/g)	% Conversion	exo/endo	% e.e. ^{b)}
1	4a	6a	0.74	98	92:8	14
2	4c	6c	1.14	76	90:10	10
3	4d	6d	0.90	95	88:12	12
4	4e	6e	0.71	93	89:11	15
5	4f	6f	0.56	97	90:10	25
7	4g	6g	0.16	93	85:15	2
8	4h	6h	0.35	98	85:15	11

a) catalyst content of the resins. b) **14xR** is the major adduct.

When the enantioselectivities are considered, it is observed that the e.e. values are similar for the polymers prepared with lower degrees of crosslinking (catalysts **6c-6e**) and for the polymers prepared through grafting (**4a**). A significant increase in the e.e. (up to 25%) is observed for the catalysts **6f** obtained from the polymer having a crosslinking degree of 90%. This can be related with the creation of more appropriate chiral cavities when the polymerisation takes place in the presence of the corresponding chiral monomers. Because of the high mobility of the PS chains, this is only useful when very high degrees of crosslinking are employed. Similar phenomena have been observed for imprinted polymers.¹⁶

One remarkable result is the almost complete absence of enantioselectivity obtained when the catalyst **6g** containing polyoxyethylene subunits in the crosslinking moiety is used. The major differences between this kind of resins and the standard PS-DVB ones are associated with the high mobility of the polymeric chains and with the presence of the oxygen donor atoms. The increased mobility of the polymeric chain could allow the association of the reactive catalytic sites to produce a situation similar to that described in solution.¹⁰ However, this can be rejected because of the high activity observed for this catalyst (**6g**) (entry 7, Table 2). The same result also rules out that the oxygen donor atoms of the crosslinking chains could efficiently compete with the dienophile in the coordination of the catalytic sites. Most likely, the polyoxyethylene bridges play an important role in the second coordination sphere of the catalytic sites. The high steric demand of those non-chiral moieties surely reduces the importance of the steric factors associated with the presence of the stereogenic centre. Alternatively, a strong interaction of the polyoxyethylene moiety with the Al could preclude their incorporation into the chiral fragment through the O-Al bond formation. This should produce a system which is not truly heterogeneous and whose activity should be intermediate between homogeneous and heterogeneous systems.¹⁷ This is in clear contrast with the results reported for boron catalysts for which the use of those crosslinking agents produced the best results.⁸

In order to clarify this result we prepared an additional polymer (**3h**) derived from the crosslinking agent **16**. The crosslinking agent was prepared from resorcinol and (**10**) in acetone using K_2CO_3 as the base and 18C6 as a catalyst. Related crosslinking agents have been used in imprinting techniques.¹⁸



i: K_2CO_3 , Acetone, 18C6, **10**; ii: **9**, AIBN, Toluene:1-Dodecanol; iii: LAH, THF.

Scheme 7

It was expected that the nature of the crosslinking chain could provide a mobility intermediate between that of the DVB derived chain and that of PEG derived chains. On the other hand, the relative isolation of two oxygen atoms in each chain could reduce their complexing ability. Following the usual protocol, the supported prolinol **4h** and the corresponding Al-catalyst **6h** were prepared. Results obtained for the use of **6h** are shown in entry 8 of Table 2. It can be seen that the exo/endo selectivity is similar to that of catalyst **6g**, which could be related to the presence of the oxygen atoms in the polymeric backbone. However, in contrast with the use of **6g**, some enantioselectivity was observed for **6h**, as it could be expected from a decrease in the participation of the crosslinking chain in the coordination of the active site.

In conclusion, the present studies clearly show how changes just to the nature of the polymeric backbone in resin-supported catalysts dramatically affect the selectivities observed for a given Diels-Alder reaction. The very complex nature of the interactions between the polymeric chains and the catalytic site makes it very difficult to develop models to understand the observed behaviour, and much work is needed in this field. Additionally, a change in the nature of the metal centre acting as the Lewis acid can completely modify the observed pattern for the interaction polymer-catalytic site. For Al (and most likely Ti) supported catalysts the presence of non-chiral functional groups in the polymeric backbone should be avoided as the resulting interactions can produce a dramatic decrease in the stereoselectivity observed.

EXPERIMENTAL

Preparation of monomer 9: N-(4-vinylbenzyl) proline methyl ester.

To the L-proline methyl ester hydrochloride (5.8g, 35 mmol) in THF (30 mL), was added NaHCO₃ (5.9g, 70 mmol) and 4-vinylbenzylchloride (6.45g, 38 mmol). The mixture was stirred for 18 h at 70°C. The NaHCO₃ was filtered, the resulting mixture was concentrated under reduced pressure to remove the THF, and EtOAc was added. The organic layer was then washed with water and dried over MgSO₄. Evaporation of the solvent gave a crude product (**9**), which was purified by flash chromatography (hexane: EtOAc 4:1) to give a yellow oil (66% yield): [α]_D²⁰ -62.1 (c=0.25, CDCl₃). ¹H NMR (300 Hz, CDCl₃) δ 1.5-2 (m, 4H), 2.19 (m, 1H), 2.86 (m, 1H), 3.05 (m, 1H), 3.36 (d, 2H, J=12.7 Hz), 3.45 (s, 3H), 3.68 (d, 2H, J=12.7 Hz), 5.02 (d, 1H, J=11 Hz), 5.54 (d, 1H, J=17.4 Hz), 6.50 (dd, 1H, J=11 Hz, J=17.4 Hz), 7.10 (d, 2H, J=8.2Hz), 7.17 (d, 2H, J=8.2Hz). ¹³C NMR (CDCl₃): 22.7, 29.1, 51.4, 52.9, 58.1, 64.9, 113.0, 125.6, 128.9, 136.0, 137.2, 137.5, 173.9. IR (KBr): 1762 cm⁻¹ Anal. Calcd. for C₁₇H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71; found C, 73.39, H, 7.84; N, 5.72.

Preparation of Crosslinking Agent 16: 1,3 Bis(4-vinylbenzyloxy)benzene.

Resorcinol (1.5g, 13.6 mmol), K₂CO₃ (5.6g, 42 mmol), 18 crown 6 (0.7g, 2.72 mmol) and 4-vinylbenzyl chloride (4.8g, 31.4 mmol) were heated at 60°C and stirred for 12 h. The mixture was poured into water and extracted with ether. The organic extracts were washed with diluted NaOH and water. After drying and evaporation of the solvent, the residue was crystallised to give pure **16** (52% yield): ¹H NMR (300 Hz, CDCl₃): 5.02 (s, 4H), 5.26 (d, 2H, J=11 Hz), 5.76 (d, 2H, J=17.7 Hz), 6.59 (dd, 2H, J=2.4, J=12), 6.6 (t, 1H, J=2.4), 6.72 (dd, 2H, J=11 Hz, J=17.7 Hz), 7.18 (t, 1H, J=8.1), 7.37 (d, 4H, J=8.1), 7.42 (d, 4H, J=8.1). ¹³C NMR (CDCl₃): 69.7, 102.1, 107.3, 113.9, 126.3, 127.6, 129.8, 136.3, 137.1, 159.8. Anal. Calcd. for C₂₄H₂₂O₂: C, 84.18; H, 6.48; O, 9.34; found C, 84.20, H, 6.51; O, 9.29.

General Polymerisation Procedure to Obtain Polymers 3d-h.

Polymerisation Mixture: Azobisisobutyronitrile (1 wt % relative to the monomers) was dissolved in 4 wt parts of a mixture consisting of styrene, crosslinker agent and monomer **9**. The porogenic solvents, mixture of toluene/1-dodecanol (1:5), were admixed slowly to the monomers. The total weight of the porogenic mixture was 6 parts. A glass mold was filled with the polymerisation mixture, purged with nitrogen in order to remove the oxygen and placed in a vertical position into a water bath. The polymerisation was allowed to proceed for 24 h at 80°C. The obtained polymer was washed with THF in a soxhlet to remove the porogenic solvents and any other soluble compounds that remained into the polymer. **3d-h** 100% yield for the different polymeric mixtures IR (KBr): peak at 1737 cm⁻¹.

Polymerisation procedure to obtain polymer 3c.

A solution of monomer **9** (722 mg, 2.39 mmol), styrene (2.05 g, 19.7 mmol), divinylbenzene (80% soln. of DVB in ethylvinylbenzene, 903 mg, 5.56 mmol), and AIBN (208 mg) in benzene (20 mL) and THF (20 mL) was added to a well stirred solution of poly(vinylalcohol) (1 g) in water (100 mL) in a three-necked flask, equipped with a thermometer, condenser and a mechanical stirrer, under an Ar atmosphere. The poly(vinylalcohol) solution was prepared by stirring the initially formed suspension at 50°C and filtering off the insoluble parts. After stirring for 1 h at 0°C (ice-bath) to homogenise the suspension, the apparatus was placed into a heat-bath at 80°C, and the suspension was stirred for 24 h. The obtained polymer beads were washed with THF in a soxhlet and dried (vacuum, 60-70°C) to give the polymer **3c**. 76% yield. IR (KBr): peak at 1737 cm⁻¹. Anal. calcd. for [(C₁₀H₁₀)_{0.20}(C₈H₈)_{0.70}(C₁₅H₁₉O₂N)_{0.10}]: N, 1.2 found N, 1.6; loading: 1.14 mmol/g.

General Procedure for the Preparation of the polymeric prolinols 4b-h by LAH reduction of resins 3b-h.**Synthesis of 4c.**

To a suspension of the polymer **3c** (1.5 g, 1.72 mmol) in dry THF (20 mL) was added a 2.3 M solution of LiAlH₄ in THF (6 mmol LiAlH₄/mmol polymer) and the mixture was stirred at rt for 24 h. The resulting resin was filtered and washed with THF (3x) THF: H₂O (3x), MeOH (3x) and vacuum dried at 70°C to give the polymer **4c** I.R.(KBr): peak absent at 1737 cm⁻¹. Anal. calcd. for [(C₁₀H₁₀)_{0.20}(C₈H₈)_{0.70}(C₁₄H₁₆ON)_{0.10}]: N, 1.16 found: N, 1.25 loading: 0.9 mmol/g.

General Procedure for the Catalytic Diels-Alder Reactions.

Under an argon atmosphere, polymer **4** (1g, for loadings see Tables 1 and 2) was shaken with the Lewis acid (3 mmol AlEtCl₂/mmol of polymer **4**) at -20°C for 30 min and then 1 h at rt in dry methylene chloride. The supported catalyst was then filtered and thoroughly washed with CH₂Cl₂ under an argon atmosphere. Polymer supported catalysts were suspended in dry CH₂Cl₂ in a Schlenk tube under argon atmosphere at the corresponding temperature (-30°C) and freshly distilled methacrolein (**12**) (the amount in relation to the amount

of catalyst are given in Table 2) was added. The suspension was shaken for 30 min and freshly distilled cyclopentadiene (**13**) (a 1.5 fold excess over methacrolein) was added. After 3 hours, the reaction mixture was filtered and washed with dry methylene chloride. The solvent was evaporated under reduced pressure and the cycloadducts were separated and purified by means of column chromatography on silica gel using methylene chloride/n-hexane = 1:1. The enantiomeric composition was analysed in the major EXO cycloadduct using a molar ratio $\text{Eu}(\text{hfc})_3/\mathbf{14} = 0.2$

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