The first highly diastereo- and enantioselective polymeric catalyst for the 1,3-cycloaddition reaction of nitrones with alkenes

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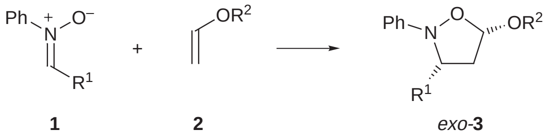
A highly diastereo- and enantioselective 1,3-dipolar cycloaddition reaction of nitrones with alkenes catalyzed by chiral polybinaphthyl Lewis acids has been developed giving isoxazolidines with up to 99% ee; the chiral polymer ligand shows almost identical stereoselectivity to its monomeric version but has the advantage of easy recovery and reuse, and this work further demonstrates that a rigid and sterically regular polymer chain can be used to preserve the catalytic properties of monomeric catalysts.

The potential of polymer-based catalysts, compared to the traditional monomeric catalysts, has stimulated the development of new polymeric chiral Lewis acid catalysts for asymmetric catalysis.[1] Easy recovery of the reusable catalyst/ligand and an often simplified purification procedure are among the obvious advantages of this class of catalysts. Furthermore, these catalysts may lead to the development of enantioselective continuous reactions by means of flow reactors or flow membrane reactors.

Two entries have been used to prepare chiral polymeric catalysts: (i) the traditional approach, where a chiral monomeric ligand is attached to a polymer support, often resulting in a marked decrease in selectivity when compared to the monomeric ligand,[1] and (ii) systems in which the optically active monomer is a part of a polymer backbone. Recently, optically active polymeric ligands of the latter type, based on a binaphthol (BINOL) backbone, have been developed,[1*c*,2] and shown the ability, in combination with a Lewis acid, to catalyse the addition of Et_2Zn to aldehydes[3] and a hetero-Diels–Alder reaction with high enantioselectivity.[4]

The asymmetric 1,3-dipolar cycloaddition (1,3-DC) reaction between nitrones and alkenes has been studied extensively recently because of the importance of the isoxazolidines formed.[5] The development of catalytic enantioselective 1,3-DC reactions has mainly involved electron-deficient alkenes reacting with various types of nitrones,[6] whereas only a few examples of catalytic enantioselective cycloaddition reaction of nitrones, activated by chiral Lewis acid complexes, with electron-rich alkenes are known.[7]

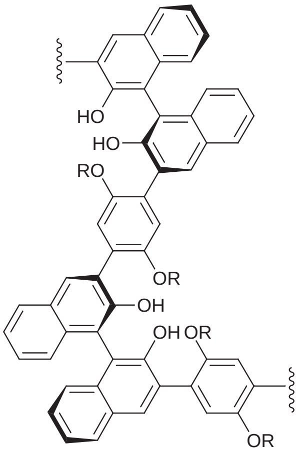
Here we report the first example of a polymer-catalyzed highly diastereo- and enantioselective 1,3-DC reaction. In this study, the reaction of *N*-phenyl nitrones **1** with vinyl ethers **2** gives the *exo*-diastereomer of the isoxazolidines **3** catalyzed by the polymeric ligand (*R*)-**4**, as well as the monomeric counterpart-ligands (*R*)-**6**, in combination with $AlMe_3$ as the Lewis acid [(eqn. (1)]. To the best of our knowledge only one example of a 1,3-DC reaction for nitrones with electron-deficient alkenes catalyzed by a polymeric catalyst, based on solid supported Ti-TADDOLates, has been reported and with varying diastereoselectivity (52–86% de), but with only modest enantioselectivity (< 56% ee).[8]



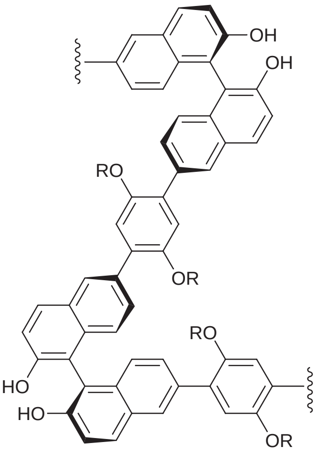
(1)

1 **2** *exo*-**3**

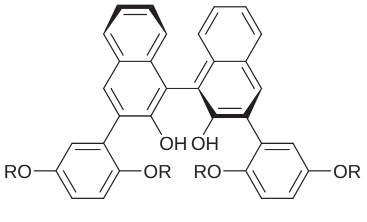
The active polymeric chiral aluminium catalysts were prepared *in situ* by addition of a solution of $AlMe_3$ in hexane to a solution of the polymer (*R*)-**4** (20 mol%) in CH_2Cl_2 (1 mL). The solution was allowed to stand for 1 h before diphenyl nitrone **1a** and ethyl vinyl ether **2a** were added in an 1:2.5 ratio. Complete conversion of **1a** was observed after 2 h whereupon the catalysts were hydrolyzed and precipitated by addition of MeOH (1–2 mL).[9] The polymeric ligand was precipitated and isolated by centrifugation and the clear solution was removed by decantation and evaporated to give isoxazolidine *exo*-**3a** in nearly quantitative isolated yield (97%) as an enantiopure compound (99% ee) and with very high diastereoselectivity (> 96% de). The purity of the reaction without any form of purification is notable as a ^1H NMR spectrum of the crude product after evaporation only gives signals consistant with *exo*-**3a**. When the reaction was tested with 10 mol% catalyst, a slight decrease in enantioselectivity was observed, but due to the fact that the polymeric ligand can be recycled (*vide infra*) with only moderate degeneration the use of 20 mol% is reasonable.



(*R*)-**4** R = C_6H_{13}



(*R*)-**5** R = C_6H_{13}



(*R*)-**6** R = C_6H_{13}

The use of the 6,6′ linked polymeric catalyst (*S*)-**5**–AlMe (20 mol%) on the same substrates resulted in a 75 : 25 *exo* : *endo* ratio of **3a** and a significant decrease in enantioselectivity (23%

Table 1 1,3-Dipolar cycloaddition reaction of nitrones **1a**,**b** with vinyl ethers **2a**–**c** catalyzed by the polymer catalyst (*R*)-**4**-AlMe (20 mol%)

Entry	**1**	R^1	**2**	R^2	**3**	Yield[a] (%)	*Exo* : *endo*[b]	Ee *exo*[c] (%)
1	**1a**	Ph	**2a**	Et	**3a**	97	> 98 : < 2	99
2[d]	**1a**	Ph	**2a**	Et	**3a**	80	> 98 : < 2	94
3	**1a**	Ph	**2b**	Bu^t	**3b**	86	> 98 : < 2	95
4	**1a**	Ph	**2c**	Bn	**3c**	72	> 98 : < 2	93
5	**1b**	*p*-Tolyl	**5b**	Bu^t	**3d**	77	> 98 : < 2	94

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Determined by HPLC using a Daicel Chiralcel OD column. [d] 10 mol%.

ee). Despite this low selectivity, this result is better than the reaction using the (*S*)-1,1′-bi-2-naphthol-derived catalyst which gives the same diastereoselectivity, but less than 5% ee.[7c] The catalytically active species for the (S)-1,1′-bi-2-naphthol-based aluminium catalyst may not be monomeric, but rather may be an aggregate.

The polymeric catalyst (*R*)-**4**–AlMe was applied to the 1,3-DC reaction of different nitrones **1a**,**b** with vinyl ethers **2a**–**c**. Generally, *exo*-**3a**–**d** were isolated in very high yield, diastereoselectivity and ee (Table 1, entries 1–5).

The polymeric ligand (*R*)-**4** has been isolated and reused successfully in at least four consecutive reactions of nitrone **1a** with ethyl vinyl ether **2a**, as shown in Fig. 1. Both the yield and ee of *exo*-**3a** showed only slight decreases after the catalyst had been reused four times. The reason for the slight decrease is probably that the reactions are performed on a small scale and that a small part of the catalyst is lost when recovered. However, after four cycles the catalyst still gives *exo*-**3a** in 88% yield and with 90% ee.

It is often observed that the traditional polymeric catalysts give lower ee's than their monomeric counterparts. Therefore, the reaction was carried out with the monomeric 3,3'-bis(2,5-dihexyloxyphenyl)-BINOL (*R*)-**6** as the ligand. When (*R*)-**6**, in combination with $AlMe_3$ (10 mol%) was used as the catalyst, the 1,3-DC reaction between nitrone **1a** and ethyl vinyl ether **2a** showed complete conversion after 1 h with the same high selectivities as found using the polymeric catalyst (Table 2, entry 1). Similar selectivities were also found when the reaction was carried out in the presence of 10 mol% of the catalyst at 0 °C (entry 2) and in toluene (entry 3). This ligand system proved to be quite general. When the same conditions were used for reaction of the nitrones **1a**–**c** with the vinyl ethers **2a**,**b**, the isoxazolidines exo-**3a**–**g** were isolated in good yield (76–93%), very high *endo*:*exo* ratio (96% de) and chiral induction (93% ee) (Table 2, entries 4–8).

The present work on the use of the poly-BINOL–AlMe catalyst represents the first chiral polymer catalyzed highly regio-, diastereo- and enantioselective 1,3-dipolar cycloaddition reaction of nitrones with alkenes. The chiral polymeric ligand can be easily recovered, and after multiple recycling, the polybinaphthyl ligand still maintains most of its original catalytic properties. Unlike many traditional polymer catalysts, the rigid and sterically regular binaphthyl polymer (*R*)-**4** shows almost the same high stereoselectivity as its monomeric version. This demonstrates that a rigid and sterically constrained polymer backbone can be used to preserve the steric and electronic environment of monomeric catalysts, and thus to preserve their catalytic properties.

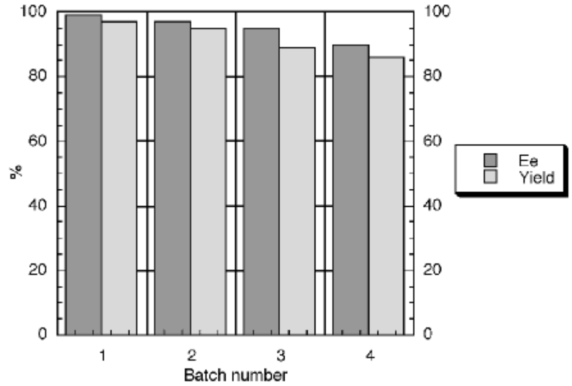


Fig. 1 Isolated yield and ee for formation of *exo*-**3a** using the regenerated polymer (*R*)-**4**-AlMe (20 mol%) in CH_2Cl_2 at room temperature for 12 h. The polymer was precipitated with MeOH and isolated by centrifugation.

Table 2 1,3-Dipolar cycloaddition reactions of aromatic nitrones **1a**–**c** with vinyl ethers **2a**,**b** catalyzed by (*R*)-**6**-AlMe (10 mol%)

Entry	**1**	R^1	**2**	R^2	**3**	Yield[a] (%)	*Exo* : *endo*[b]	Ee *exo*[c] (%)
1	**1a**	Ph	**2a**	Et	**3a**	93	> 98 : < 2	99
2[d]	**1a**	Ph	**2a**	Et	**3a**	83	> 98 : < 2	99
3[d,e]	**1a**	Ph	**2a**	Et	**3a**	76	> 98 : < 2	99
4	**1b**	*p*-Tolyl	**2a**	Et	**3d**	76	> 98 : < 2	94
5	**1c**	*p*-ClC_6H_4	**2a**	Et	**3e**	85	> 98 : < 2	95
6	**1a**	Ph	**2b**	Bu^t	**3b**	89	> 98 : < 2	95
7	**1b**	*p*-Tolyl	**2b**	Bu^t	**3f**	85	98 : 2	93
8	**1c**	*p*-ClC_6H_4	**2b**	Bu^t	**3g**	82	> 98 : < 2	93

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Determined by HPLC using a Daicel Chiralcel OD column. [d] 0 °C. [e] Solvent = toluene.

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9 Experimental procedure. The appropriate ligand (0.02 mmol) was placed in a 5 mL Schlenk flask flushed three times with N_2, and CH_2Cl_2 (1 mL) was added with a syringe. To this solution was added a 2 M solution of $AlMe_3$ in heptane (10 mL, 0.02 mmol). The solution was stirred for 1 h and the nitrone (0.2 mmol) and vinyl ether (0.5 mmol) were added. After the appropriate reaction time, the reaction was quenched with MeOH (1 mL) and the ligand was isolated by centrifugation. The clear solution was evaporated to give the single diasteromer of *exo*-**3** as a pure product (TLC, ^1H and ^{13}C NMR).

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