

## Catalytic enantioselective Michael addition reactions of $\alpha$ -nitroesters to $\alpha,\beta$ -unsaturated ketones

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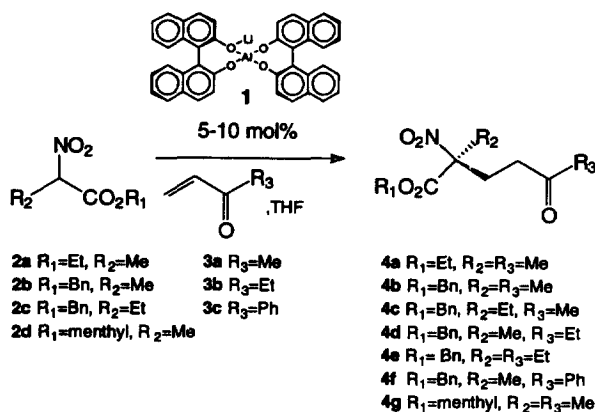
**Abstract:** Enantioselective Michael additions of  $\alpha$ -nitroesters **2a–d** with  $\alpha,\beta$ -unsaturated ketones were carried out in the presence of a catalytic amount of chiral Al-Li-(R,R')-2,2'-dihydroxy-1,1'-binaphthyl ('ALiBINOL') complex prepared *in situ* from LiAlH<sub>4</sub> and 2.45 equiv. of (R,R')-BINOL. The enantioselectivity of the Michael addition proved to be extremely temperature dependent: Michael adduct **4a** showed 7% e.e. when the reaction was performed at RT, whereas 72% e.e. of the opposite enantiomer of **4a** was found when the 1,4-addition was performed at  $-23^{\circ}\text{C}$ . Solvent variation showed that tetrahydrofuran gave the highest selectivity (up to 80% e.e.), whereas the highest enantioselectivity for the opposite enantiomer was found in methylene chloride (up to 25%). X-Ray structure analysis of the AlLi<sub>3</sub>BINOL<sub>3</sub> complex **6** in combination with <sup>27</sup>Al NMR studies showed that 'ALiBINOL' is a mixture of aluminium complexes in solution. © 1997 Elsevier Science Ltd

### Introduction

Conjugate addition reactions of carbon nucleophiles to  $\alpha,\beta$ -unsaturated compounds are among the most widely used methods for carbon–carbon bond formation in organic synthesis.<sup>1</sup> Major efforts have been made to achieve catalytic enantioselective conjugate addition and considerable progress is seen, despite the often complicated nature of many 1,4-addition reactions.<sup>2,3</sup> Although the catalytic enantioselective Michael addition reaction of dialkylmalonates and  $\beta$ -ketoesters has been widely studied,<sup>2,4,5</sup> to the best of our knowledge, only one example of an enantioselective Michael addition of an  $\alpha$ -nitroester has been described in the literature, and the enantiomeric excess (e.e.) of the product was not reported.<sup>6</sup> Furthermore Lewis acid catalysed Michael addition reactions of  $\alpha$ -nitroesters have only occasionally been reported. However rather drastic conditions, *i.e.* refluxing dioxane, were required.<sup>7</sup> As part of our continuing efforts to achieve catalytic (enantioselective) carbon–carbon bond formation, in particular conjugate addition reactions,<sup>8</sup> we reported the highly efficient ytterbium triflate catalysed Michael addition of  $\beta$ -ketoesters<sup>9</sup> and  $\alpha$ -nitroesters<sup>10</sup> in water.

The special features of 'two centre catalysis' currently attracts considerable interest in the field of asymmetric catalysis.<sup>11</sup> Recently Shibasaki and co-workers introduced a new class of lanthanide based BINOL complexes as effective catalysts for carbon–carbon bond formations, such as the Henry reaction of aliphatic nitro compounds<sup>12</sup> and the Michael addition reaction of dialkylmalonates.<sup>4</sup> Stimulated by these elegant reports we examined these chiral Lewis acid complexes in the Michael addition reaction of nitroesters to  $\alpha,\beta$ -unsaturated ketones (Scheme 1). A catalytic enantioselective Michael addition of  $\alpha$ -nitroesters **2** towards  $\alpha,\beta$ -unsaturated ketones **3** using a heterobimetallic (R,R')-dihydroxy-1,1'-binaphthyl derived 'ALiBINOL' catalyst **1** is reported here.

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Scheme 1.

## Results and discussion

In the initial attempts the Michael addition of **2a** to 3-buten-1-one (**3a**) provided the desired Michael adduct **4a** with high chemoselectivity. However no enantioselectivity was found using either a LaLiBINOL complex or the alkali metal free LaBINOL complex.<sup>13</sup> In contrast an 'ALiBINOL' complex,<sup>14</sup> prepared using a modification of the method reported by Shibasaki for reasons given later, yielded **4a** with 7% e.e.<sup>15</sup> when the reaction was performed at room temperature using 10 mol%<sup>16</sup> of the catalyst. Moreover when the same reaction was performed at  $-23^{\circ}\text{C}$  **4a** was isolated with 72% e.e. Much to our surprise the opposite enantiomer<sup>15</sup> of Michael adduct **4a** was obtained. To the best of our knowledge this is the first example of a metal mediated enantioselective Michael addition of an  $\alpha$ -nitroester. For practical reasons<sup>17</sup> the remarkable temperature dependence of the enantioselectivity was further studied using benzyl ester **2b**. In all cases Michael adduct **4b** was isolated in satisfactory yield (81–86%). The temperature dependence of the enantioselectivity is shown in Figure 1. As can be seen from Figure 1, **4b** could be obtained with an e.e. up to 74% when the reaction was performed at  $-30^{\circ}\text{C}$ . The highest selectivity for the opposite enantiomer is seen at RT albeit with very low e.e. (7%).

This temperature dependent study seems to indicate that competing enantioselective Michael additions take place, most probably due to different chiral 'ALiBINOL' catalysts in solution.

Therefore several reaction parameters were studied in more detail. First the influence of the amount of catalyst on the enantioselectivity of the Michael addition was tested. The reaction of **2b** with MVK under the influence of 10 mol% of 'ALiBINOL' at  $-30^{\circ}\text{C}$  gave **4b** with 74% e.e., whereas when 5 mol% of 'ALiBINOL' was used **4b** was isolated with 80% e.e. These data show that a decrease in the amount of catalyst used, results in an increase in enantioselectivity of the Michael addition, but further decrease of the amount of catalyst leads to excessive long reaction times.

Next the effect of various solvents on the reaction was investigated. The results are shown in Table 1. THF gave the best results providing (–)-**4b** in good yield with an e.e. of 71% at  $-20^{\circ}\text{C}$ . Noteworthy is the result obtained with methylene chloride as the solvent. The Michael addition performed in THF furnished (+)-**4b** with an e.e. of 7% at RT, whereas the same reaction in methylene chloride yielded (+)-**4b** with 20% e.e. The selectivity could even be improved to 25% e.e. by performing the reaction in refluxing methylene chloride (at  $-20^{\circ}\text{C}$  6% e.e. was found in this solvent).

In order to examine the scope of this new enantioselective reaction catalysed by **1** several substrates were tested in the enantioselective Michael addition. The results are listed in Table 2. Again the *in situ* prepared catalyst **1** (5–10 mol%)<sup>16</sup> provided Michael adducts **4c–f** in good yields with enantiomeric excesses ranging from 5% to 55% when  $\beta$ -unsubstituted enones were used (Table 2). However  $\beta$ -substituted enones and cyclic enones were unreactive under the present conditions (entries 9 and 10).<sup>18</sup>

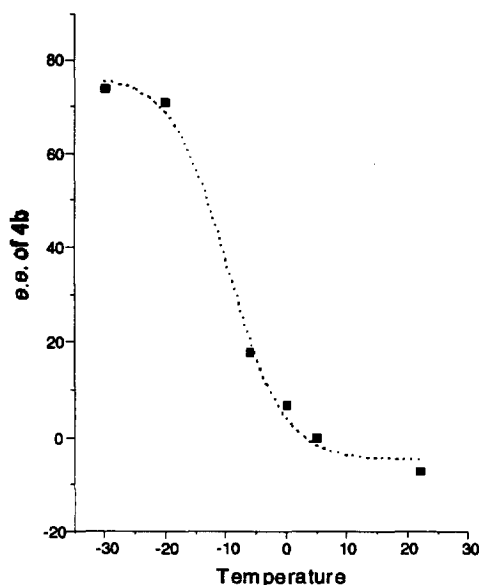
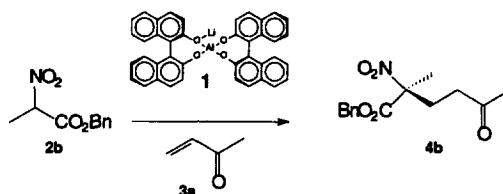


Figure 1. Temperature dependence of the enantioselectivity of the Michael addition of **2b** to **3a**.

Table 1. Solvent effect on the asymmetric Michael addition of **2b** to **3a**



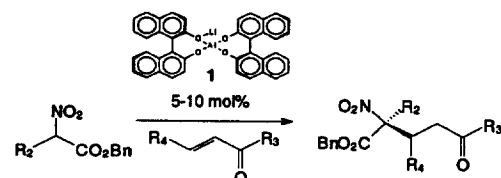
Entry	solvent	catalyst amount (mol%)	time (h)	e.e. (%)	T (°C)
1	tetrahydrofuran	10	72	71(-)	-20
2	toluene	10	72	7(-)	-30
3	diethylether	10	72	19(-)	-30
4	methylene chloride	10	72 <sup>a</sup>	6(+)	-20
5	methylene chloride	10	72	20(+)	RT
6	methylene chloride	10	72	25(+)	40
7	dioxane	10	18	4(+)	RT
8	dichloroethane	10	72 <sup>a</sup>	4(-)	-30

<sup>a</sup> Low conversion even after 72 h (<40%).

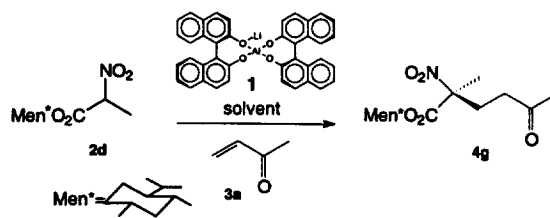
Furthermore ethyl acrylate (entry 11)<sup>18</sup> and acrolein (entry 12)<sup>19</sup> were not converted into the Michael adducts under these conditions. The presence of sterically demanding substituents often results in an increase in the enantioselectivity, however in the reactions tested here this effect was not observed. The introduction of larger substituents either in the Michael donor or the Michael acceptor resulted in a lower enantioselectivity. This is most striking when 1-phenyl-propenone (**3c**) is used in the reaction with **2b**, in which the desired Michael adduct **4f** is isolated with very low e.e. (5–8%, entries 7,8).

The addition of (1R,2S,5R)-menthyl-2-nitropropionate **2d** to **3a** under the influence of *in situ* prepared catalyst **1** furnished **4g** with diastereoselectivities comparable to the values obtained for **4a** and **4b** (RT: d.e.=7%, -25°C: d.e.=70%, Scheme 2).<sup>20</sup> These results show that the asymmetric induction was exclusively accomplished by the chiral catalyst as the chiral auxiliary did not significantly influence the selectivity of the reaction.

Table 2. Substrate variation



Entry	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Temp.(°C)	"ALLiBINOL" (mol%)	Time (h)	Yield (%) <sup>a</sup>	e.e. (%)
1	Me	Me	H	-30	10	72	83	74
2	Me	Me	H	-30	5	96	81	80
3	Me	Et	H	-23	10	72	84	49
4	Me	Et	H	-24	5	72	nd	55
5	Et	Me	H	-21	10	72	86	47
6	Et	Et	H	-23	10	72	84	33
7	Me	Ph	H	RT	10	18	87	8
8	Me	Ph	H	-24	10	72	86	5
9	Me	Me	Me	RT or -20	10	72	0	-
10	Me	(CH <sub>2</sub> ) <sub>3</sub>	H	RT or -20	10	72	0	-
11	Me	OEt	H	RT or -20	10	72	0	-
12	Me	H	H	RT	10	18	0	-

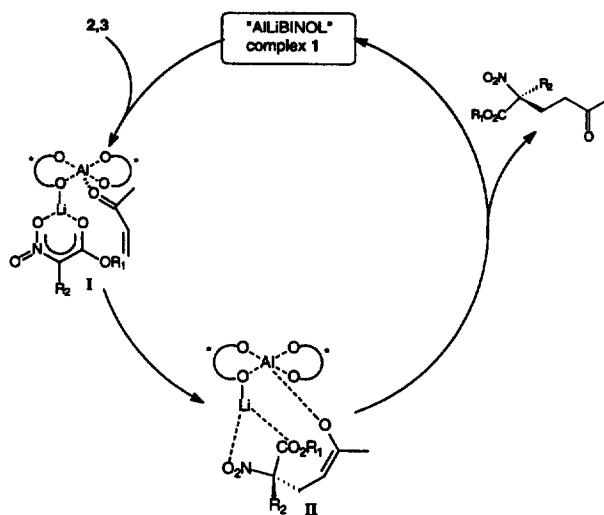
<sup>a</sup>Isolated yield

Scheme 2.

In contrast with the results reported by Shibasaki and co-workers<sup>14</sup> on the Michael addition of dialkylmalonates to cyclic enones, the use of the 'AlNaBINOL' complex (instead of 'AlLiBINOL') in the reaction of **2b** with **3a** resulted in nearly racemic **4b**, however with high chemoselectivity. Furthermore the use of (R,R')-3,3'-dimethyl-2,2'-dihydroxy-1,1'-binaphthyl as chiral ligand resulted in a poorly soluble catalyst complex. When this heterogeneous system was utilised in the reaction of **2b** with enone **3a**, Michael adduct **4b** was isolated in 89% yield but with very low enantioselectivity (e.e. <5%).

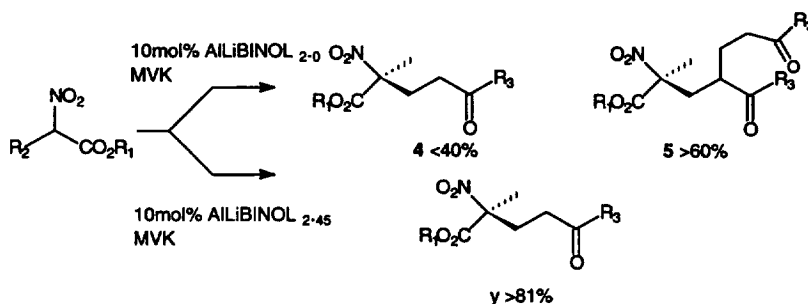
The 1,4-addition reaction is proposed to proceed *via* double coordination of the Michael donor as well as coordination of the Michael acceptor to the heterobimetallic catalyst in accordance with the mechanism proposed by Shibasaki and co-workers. The lithium naphthoxide moiety can function as a Brønsted base and the aluminium alkoxide functions as a Lewis acid. The reaction of the  $\alpha$ -nitroester with the 'AlLiBINOL' complex gives the corresponding lithium enolate (I). This enolate then reacts with the enone, which is pre-coordinated to the aluminium Lewis acid centre to give the aluminium enolate (II) after 1,4-addition. The resulting alkoxide then reacts with an acidic hydrogen of a Michael donor to generate the desired Michael adduct and the 'AlLiBINOL' complex is regenerated to react in the following catalytic cycle (Scheme 3).

When we used the *in situ* prepared catalyst, according to the procedure described by Shibasaki and co-workers (using 2.0 eq. of BINOL),<sup>14</sup> the yields of the Michael adducts **4** were low because the 1,4-addition reaction was accompanied by the formation of tandem Michael adducts **5** (Scheme 4). The yields of the desired mono-Michael adducts could be improved by using more BINOL for the formation of the catalyst. Careful adjustment of the stoichiometry of the reagents showed that the highest yields



Scheme 3. Possible reaction path for the 1,4-addition.

of Michael adducts **4** were obtained when 2.45 equiv. of BINOL and 1.0 equiv. of  $\text{LiAlH}_4$  in THF were used for the catalyst preparation. Using this stoichiometry a homogeneous catalyst solution was obtained which could be directly used for the reaction, whereas larger amounts of BINOL resulted in a white precipitate from the reaction mixture.



Scheme 4.

These results together with the unexpected reversal of enantioselectivity when the reaction was performed at different temperatures (*vide supra*), encouraged us to further investigate the structure of the active species responsible for the enantioselective catalysis.

Shibasaki proposed a structure of the heterobimetallic catalyst **1** with a ratio of  $\text{Li}:\text{Al}:\text{BINOL}=1:1:2$ , based on the amount of reagents used for the preparation of the catalyst and the X-ray structure of a complex of  $\text{AlLi}(\text{BINOL})_2$  and cyclohexenone.<sup>14,21</sup> Furthermore Shibasaki reported an X-ray structure of a complex of indicated ratio.<sup>22</sup>

In our hands a solution of 'AILIBINOL' ( $\text{LiAlH}_4:\text{BINOL}=1:2.45$ ) in THF provided crystals suitable for X-ray analysis. The molecular structure of **6** is shown in Figure 2. The complex consists of one aluminium, three lithium, three BINOL and six THF molecules. The aluminium is surrounded by three BINOL molecules stabilised by three lithium ions. The six THF molecules are present to complete the lithium coordination sites. The complex has a slightly distorted octahedral geometry around the aluminium centre, with an  $\text{Al}-\text{O}$ -distance of 1.891(3) Å and an  $\text{Li}-\text{O}$ -distance of 1.944(11) Å. This structure in fact resembles the structure of the heterobimetallic lanthanide-tris-lithium-tris-BINOL

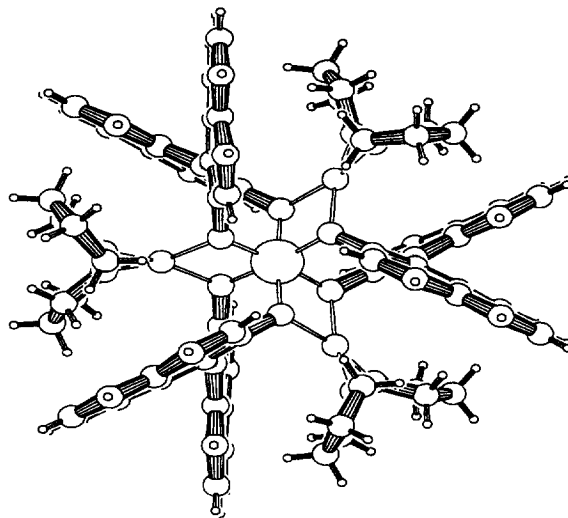


Figure 2. Molecular structure of AlLi<sub>3</sub>BINOL<sub>3</sub>·6THF **6**.

complexes described recently by Shibasaki.<sup>4b</sup> The crystalline complex **6** efficiently promoted the Michael reaction of **2b** with **3a** at 20°C in THF to give **4b** with 65% e.e. This indicates that complex **6** is indeed involved in the enantioselective catalytic process, or can at least function as a precursor for the actual active catalyst.

Since the ratio of Al and Li found in the structure of **6** did not correspond with the ratio of the reagents used for the formation of the *in situ* prepared catalyst, we set out to further examine the catalyst using <sup>27</sup>Al NMR.<sup>23</sup>

Based on the X-ray structure of the AlLi<sub>3</sub>BINOL<sub>3</sub>·6THF and the stoichiometry of the reagents used we expected at least two signals in the <sup>27</sup>Al NMR spectrum for the different complexes in solution. Both for the solution of 'AlLiBINOL' prepared from 1 equiv. of LiAlH<sub>4</sub> and 2 equiv. of BINOL and for the solution prepared from 1 equiv. of LiAlH<sub>4</sub> and 2.45 equiv. of BINOL we obtained nearly identical spectra (ratios Li:Al:BINOL=1.0:1.0:2.0 and Li:Al:BINOL=1.0:1.0:2.45 respectively, Figure 3a). The spectra consisted of three overlapping signals; one sharp absorption at 18.8 ppm and two broader signals at 35 ppm and 53 ppm. The sharp signal at 18.8 ppm was also found in the <sup>27</sup>Al NMR spectrum of a complex prepared from 1 equiv. of LiAlH<sub>4</sub> and 2 equiv. of BuLi and 3 equiv. of BINOL (ratio Li:Al:BINOL=3:1:3)(Figure 3b). Based on the <sup>27</sup>Al NMR data it appears that AlLi<sub>3</sub>BINOL<sub>3</sub>·6THF is indeed present in the catalyst solution although it cannot be concluded that it is the only complex in solution that is responsible for enantioselective catalysis since at least three aluminium complexes are observed in the catalyst solution by <sup>27</sup>Al NMR.

In conclusion we have developed a new asymmetric Michael addition reaction of  $\alpha$ -nitroesters to  $\alpha,\beta$ -unsaturated ketones using 'AlLiBINOL' as a heterobimetallic chiral catalyst. Enantioselectivities as high as 80% were achieved. Since the nitro group can easily be converted into an amino or an N-hydroxylamino group, the Michael addition products obtained in this reaction are considered to be useful synthetic intermediates for optically active  $\alpha$ -alkylated  $\alpha$ -amino acids. These molecules are frequent in natural products and currently attract great interest e.g. for peptide mimetics and biological investigations.<sup>24</sup>

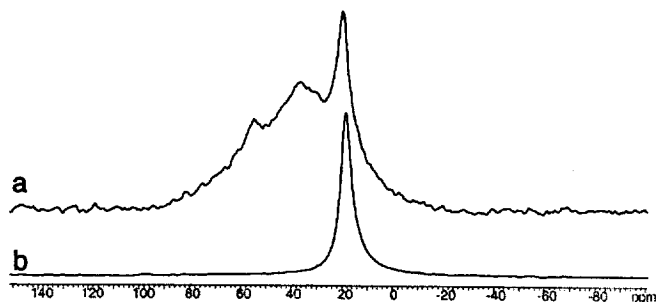


Figure 3.  $^{27}\text{Al}$  NMR spectra of (a) 'ALiBINOL' and (b)  $\text{AlLi}_3\text{BINOL}_3 \cdot 6\text{THF}$ .

## Experimental section

### Instruments and experimental methods

Optical rotations were measured at ambient temperature on a Perkin–Elmer 241 polarimeter.  $^1\text{H}$  NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a Varian-300 (300 MHz) spectrometer. Chemical shifts are denoted in  $\delta$ -units (ppm) relative to residual solvent peaks ( $\text{CHCl}_3$ ,  $\delta=7.26$  ppm).  $^{13}\text{C}$  NMR spectra were recorded on a Varian Gemini-200 (50.32 MHz), a Varian-300 (75.48 MHz) or a Varian-500 (125.80 MHz) spectrometer. Chemical shifts are denoted in  $\delta$ -units (ppm) relative to the solvent and converted to the TMS scale using  $\delta(\text{CHCl}_3)=77.0$  ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet) and br (broad).  $^{27}\text{Al}$  NMR spectra were recorded on a Varian-300 (78.12 MHz) spectrometer. Chemical shifts are denoted in  $\delta$ -units (ppm) relative to  $\text{Al}(\text{OH}_2)_6^{3+}$  as an external standard:  $\delta(\text{Al}(\text{OH}_2)_6^{3+})=0.0$  ppm. Mass spectra were obtained on a JEOL JMS-600H mass spectrometer (CI). Elemental analyses were performed in the Microanalytical Department of this laboratory. HPLC analyses were carried out using a Waters 600E system controller equipped with a Waters 991 photodiode array detector. Chromatographic purification of the Michael adducts **4** was performed by rotating disk chromatography with Chromatotron model 7924T, by Harrison research, equipped with a FMI lab pump RP-G150. All catalytic reactions were performed in oven dried glassware under dry  $\text{N}_2$  atmosphere and solvents were dried using standard procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ethyl-2-nitropropionate **2a** was prepared according to a literature procedure.<sup>25</sup>

### Preparation of 'ALiBINOL' complex **1**

To a stirred solution of (R,R')-BINOL (700 mg, 2.45 mmol) in 9.0 mL dry THF at  $0^\circ\text{C}$ , was slowly added 1.0 mL of  $\text{LiAlH}_4$  (1.0 M) solution in THF, and the mixture was stirred at this temperature for 30 min. This catalyst solution (0.1 M in THF) was used directly.

### Benzyl-2-nitropropionate (**2b**)

Prepared in 65% yield according to the literature procedure<sup>25</sup> for the preparation of a related compound and purified using flash chromatography ( $\text{SiO}_2$ , hexane:ethylacetate=4:1).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta=1.79$  (d,  $J=7.1$  Hz,  $\text{CH}_3$ ), 5.23 (q,  $J=7.1$  Hz, CH), 5.25 (s, 2H,  $\text{CH}_2\text{Ar}$ ), 7.35 (m, 5H, Ar);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 50 MHz)  $\delta=15.45$  (q), 68.28 (t), 82.97 (d), 128.22 (d), 128.62 (d), 128.72 (d), 134.12 (s), 164.87 (s).

### Benzyl-2-nitrobutyrate (**2c**)

Prepared in 62% yield according to the literature procedure<sup>25</sup> for the preparation of a related compound and purified using flash chromatography ( $\text{SiO}_2$ , hexane:ethylacetate=4:1).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz)  $\delta=1.02$  (t,  $J=7.3$  Hz, 3H,  $\text{CH}_3$ ), 2.25 (m, 2H,  $\text{CH}_2$ ), 5.07 (dd,  $J=5.6$  Hz,  $J=9.0$  Hz, 1H,

CH), 5.24 (s, 2H, CH<sub>2</sub>Ar), 7.35 (m, 5H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ=9.86 (q), 23.67 (t), 68.17 (t), 89.16 (d), 128.23 (d), 128.61 (d), 128.71 (d), 134.17 (s), 164.28 (s).

#### *1-(-)-(1R,2S,5R)-Menthyl-2-(R,S)-nitropropionate (2d)*

Prepared in 56% yield, according to the literature procedure<sup>25</sup> for the preparation of a related compound, from 1-(-)-(1R,2S,5R)-menthyl-2-(R,S)-bromopropionate<sup>26</sup> and purified using flash chromatography (SiO<sub>2</sub>, hexane:diethylether=9:1). [α]<sub>D</sub> -62.4 (c=1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ=0.75 (d, *J*=7.1 Hz, 3H, CH<sub>3</sub>), 0.90 (dd, *J*<sub>1</sub>=6.1 Hz, *J*<sub>2</sub>=4.9 Hz, 6H, 2×CH<sub>3</sub>), 0.84–1.73 (m, 8H), 1.78 (d, *J*=7.1 Hz, 3H, CH<sub>3</sub>), 1.99 (m, 1H, CH), 4.77 (dt, *J*<sub>1</sub>=4.4 Hz, *J*<sub>2</sub>=10.7 Hz, OCH), 5.19 (q, *J*=7.1 Hz, 1H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ=15.45 (q), 15.72 (q), 20.41 (q), 21.62 (q), 22.91 (t), 25.88 (d), 25.79 (d), 31.10 (d), 39.87 (t), 40.00 (t), 46.47 (d), 46.53 (d), 77.32 (d), 83.14 (d), 164.45 (s).

#### *General procedure for the synthesis of Michael adducts 4*

To 1.0 mmol of α-nitroester **2** was added 1.0 mL of 'ALiBINOL' solution in THF at ambient temperature. This solution was then brought to the desired temperature and the Michael donor **3** (2.2 mmol) was added in one portion. The reaction mixture was stirred at the indicated temperature and the progress of the reaction was monitored by TLC (SiO<sub>2</sub>, hexane:acetone=9:1) until all of the starting α-nitroester was converted.<sup>27</sup> The reaction mixture was then treated with 1 N HCl (1.0 mL) followed by extraction with methylene chloride (2×10 mL). The combined organic extracts were washed with water (5 mL) and concentrated. Toluene (10 mL) was added and the solution was again concentrated to give a nearly colourless residue. Purification by rotating disk chromatography (SiO<sub>2</sub>, hexane:acetone=9:1) gave the Michael adducts **4** as nearly colourless analytical pure oils. Yields and e.e.s are compiled in Tables 1 and 2.

#### *Ethyl-2-methyl-2-nitro-5-oxohexanoate (4a)*

The e.e. of **4a** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK OJ, *i*PrOH:hexane=1:9) after conversion to the corresponding 1,3-dioxolane. **4a**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ=1.29 (t, *J*=7.2 Hz, 3H, CH<sub>3</sub>), 1.77 (s, 3H, CH<sub>3</sub>), 2.16 (s, 3H, CH<sub>3</sub>), 2.41–2.59 (m, 4H, 2×CH<sub>2</sub>), 4.26 (q, *J*=7.2 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ=13.52 (q), 21.76 (q), 29.69 (q), 29.94 (t), 37.63 (t), 62.74 (t), 91.64 (s), 166.97 (s), 205.73 (s). MS(CI): 235 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>9</sub>H<sub>15</sub>NO<sub>5</sub>: C 49.76, H 6.96, N 6.45; found: C 49.50, H 6.84, N 6.27.

#### *Benzyl-2-methyl-2-nitro-5-oxohexanoate (4b)*

According to the general procedure **4b** was obtained as a nearly colourless oil. [α]<sub>D</sub> -1.87 (c 0.48, CHCl<sub>3</sub>) (75% e.e.); The e.e. of **4b** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane=1:39). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ=1.78 (s, 3H, CH<sub>3</sub>), 2.10 (s, 3H, CH<sub>3</sub>), 2.48 (m, 4H, CH<sub>2</sub>), 5.22 (s, 2H, CH<sub>2</sub>Ar), 7.34 (m, 5H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ=21.91 (q), 19.64 (q), 30.00 (t), 27.55 (t), 68.19 (t), 91.67 (s), 128.20 (d), 128.60 (d), 128.67 (d), 134.25 (s), 166.78 (s), 205.66 (s); MS(CI): 297 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>5</sub>: C 60.21, H 6.14, N 5.01; found: C 60.18, H 6.14, N 4.88.

#### *Benzyl-2-ethyl-2-nitro-5-oxohexanoate (4c)*

According to the general procedure **4c** was obtained as a nearly colourless oil. [α]<sub>D</sub> +2.65 (c 0.64, CHCl<sub>3</sub>) (47% e.e.); The e.e. of **4c** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane=1:39). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ=0.88 (t, *J*=7.4 Hz, 3H, CH<sub>3</sub>), 2.06 (s, 3H, CH<sub>3</sub>), 2.11–2.46 (m, 6H, 3×CH<sub>2</sub>), 5.22 (s, 2H, CH<sub>2</sub>Ar), 7.34 (m, 5H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ=7.67 (q), 27.00 (t), 28.17 (t), 29.62 (q), 37.39 (t), 51.95 (t), 95.55 (s), 128.38 (d), 128.58 (d), 128.69 (d), 134.31 (s), 166.37 (s), 205.72 (s); MS(CI): 311 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>: C 61.42, H 6.53, N 4.78; found: C 61.36, H 6.59, N 4.58.



**Benzyl-2-methyl-2-nitro-5-oxoheptanoate (4d)**

According to the general procedure **4d** was obtained as a nearly colourless oil.  $[\alpha]_D +3.04$ . (c 0.29, CHCl<sub>3</sub>) (49% e.e.); The e.e. of **4d** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane=1:19). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ =1.02 (t, *J*=7.32 Hz, 3H, CH<sub>3</sub>), 1.77 (s, 3H, CH<sub>3</sub>), 2.36 (q, *J*=7.32 Hz, CH<sub>2</sub>), 2.45 (m, 4H, 2×CH<sub>2</sub>), 5.22 (s, 2H, CH<sub>2</sub>Ar), 7.34 (m, 5H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz)  $\delta$ =7.44 (q), 21.86 (t), 30.07 (t), 35.68 (t), 36.19 (t), 68.17 (t), 91.75 (s), 128.17 (d), 128.58 (d), 128.65 (d), 134.27 (s), 167.11 (s), 208.47 (s); MS: 311 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>5</sub>: C 61.42, H 6.53, N 4.78; found: C 61.50, H 6.58, N 4.66.

**Benzyl-2-ethyl-2-nitro-5-oxoheptanoate (4e)**

According to the general procedure **4e** was obtained as a nearly colourless oil.  $[\alpha]_D -1.23$  (c 0.73, CHCl<sub>3</sub>) (33% e.e.); The e.e. of **4e** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane=1:19). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$ =0.87 (t, *J*=7.3 Hz, 3H, CH<sub>3</sub>), 1.01 (t, *J*=7.3 Hz, 3H, CH<sub>3</sub>), 2.00–2.45 (m, 8H, 4×CH<sub>2</sub>), 5.22 (s, 2H, CH<sub>2</sub>Ar), 7.34 (m, 5H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$ =7.67 (q), 7.90 (q), 27.29 (t), 28.30 (t), 35.68 (t), 36.22 (t), 68.18 (t), 95.77 (s), 128.43 (d), 128.64 (d), 128.74 (d), 134.40 (s), 166.43 (s), 208.51 (s); MS(CI): 325 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: C 62.51, H 6.89, N 4.56; found: C 62.71, H 7.12, N 4.78.

**Benzyl-2-methyl-2-nitro-5-oxophenylpentanoate (4f)**

According to the general procedure **4f** was obtained as a nearly colourless oil.  $[\alpha]_D +0.65$  (c 0.62, CHCl<sub>3</sub>) (8% e.e.); The e.e. of **4f** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD, *i*PrOH:hexane=1:39). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ =1.85 (s, 3H, CH<sub>3</sub>), 2.65 (m, 2H, CH<sub>2</sub>), 3.02 (m, 2H, CH<sub>2</sub>), 5.24 (s, 2H, CH<sub>2</sub>Ar), 7.33–7.58 (m, 2H, Ar); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz)  $\delta$ =22.10 (q), 30.56 (d), 32.79 (t), 68.23 (t), 91.91 (s), 127.86 (d), 128.24 (d), 128.54 (d), 128.59 (d), 128.65 (d), 133.30 (d), 134.24 (s), 136.07 (s), 166.86 (s), 197.30 (s); MS(CI): 359 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>5</sub>: C 66.84, H 5.61, N 4.10; found: C 66.84, H 5.73, N 3.92.

**(1*R*,2*S*,5*R*)-Menthyl-2-methyl-2-nitro-5-oxohexanoate (4g)**

According to the general procedure **4g** was obtained as a nearly colourless oil as an inseparable 1:1 mixture of diastereoisomers, see text. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ =0.75 (d, *J*=7.1 Hz, 3H, CH<sub>3</sub>), 0.89 (t, *J*=6.35, 6H, 2×CH<sub>3</sub>), 0.80–1.80 (m, 8H), 1.95–2.02 (m, 1H, CH), 1.74 (s, 3H, CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 2.41–2.55 (m, 4H, 2×CH<sub>2</sub>), 4.30 (dt, *J*<sub>1</sub>=10.74 Hz, *J*<sub>2</sub>=4.39 Hz, 1H, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$ =15.66 (q), 15.72 (q), 20.61 (q), 21.77 (q), 22.84 (q), 28.90 (q), 25.84 (q), 25.91 (q), 31.24 (t), 33.85 (t), 37.75 (t), 39.83 (t), 39.90 (t), 46.58 (q), 77.30 (d), 91.79 (s), 91.84 (s), 166.43 (s), 205.47 (s), 205.51 (s); MS(CI): 345 [M<sup>+</sup>+NH<sub>4</sub><sup>+</sup>]; Anal. calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>5</sub>: C 62.36, H 8.93, N 4.28; found: C 62.40, H 9.05, N 4.14.

**Crystal data for AlLi<sub>3</sub>BINOL<sub>3</sub>·6THF (6)**

C<sub>84</sub>H<sub>84</sub>O<sub>12</sub>AlLi<sub>3</sub>: Space group P6<sub>3</sub>22, Hexagonal, a=b=14.4753(15), c=19.6929(11) Å. V=3573.5(6) Å<sup>3</sup>, d<sub>x</sub>=1.239 g/cm<sup>3</sup>, Z=2, μ(MoKα)=0.9 cm<sup>-1</sup>. X-Ray data were collected on an Enraf–Nonius CAD4T diffractometer on a rotating anode (MOKα, λ=0.71073 Å) at 150 K for a transparent colorless crystal [0.18×0.25×0.50]. The structure solved by direct methods (SHELXS96/TREF) and refined on F<sup>2</sup> using SHELXL96 to a final R=0.0704 (wR<sub>2</sub>=0.158) for 2113 reflections and 152 parameters. Hydrogens were taken into account on calculated positions. A final difference map showed no density excursions outside –0.29 and 0.26 e/Å<sup>3</sup>. Full details may be obtained from one of the authors.

Anal. calcd for AlLi<sub>3</sub>BINOL<sub>3</sub>·6THF (C<sub>84</sub>H<sub>84</sub>O<sub>12</sub>AlLi<sub>3</sub>): Al 1.99, Li 1.54; found: Al 1.95, Li 1.52.

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15. The absolute configuration of the major enantiomer has not been established so far.
16. The amount of catalyst is based upon the assumption of the complete conversion of  $\text{LiAlH}_4$  to **1** (with the stoichiometry  $\text{Li}:\text{Al}:\text{BINOL}=1:1:2$ ), according to Shibasaki *et al.*<sup>14</sup> This is probably not an accurate figure since 'AlLiBINOL' appears to be a mixture of aluminium complexes in solution.
17. The e.e. of Michael adduct **4b** could be determined directly by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK AD).
18. Starting material is recovered, even after prolonged reaction time.
19. Polymerisation of the Michael acceptor is observed.
20. The diastereomeric ratio of **4g** was determined by  $^{13}\text{C}$  NMR (125 MHz).
21. Also three THF molecules were present in the crystal structure.
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27. Mixture for TLC staining: *o*-anisaldehyde dip: (mix at 0°C) anisaldehyde 7.4 mL; ethanol (96%) 383 mL; sulfuric acid 10 mL; acetic acid 3.0 mL.

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