

# Enantioselective Michael Addition: An Experimental Introduction to Asymmetric Synthesis

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We adapted a classical asymmetric Michael addition for a 1-day experimental session (6-8 hrs) for third or fourth-year undergraduate students. The experiment follows up three steps : synthesis of a chiral Lewis Acid,  $\text{LiAl}(\text{BINOL})_2$ , then its use as a catalyst in the Michael addition of diethyl malonate on cyclopentenone, followed by purification through column chromatography on silica gel. The desired product can be fully characterized by 1D and 2D NMR experiments and IR spectroscopy. The enantiomeric excess can be determined by polarimetry and  $^1\text{H}$  NMR using chiral lanthanide shift reagent  $\text{Eu}(\text{hfc})_3$ .

## File list (2)

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# Supporting Information

## 1. General

**Nuclear Magnetic Resonance spectra** were acquired on 300 MHz or 400 MHz Bruker Avance III spectrometers fitted with BBFO probeheads (300 or 400 MHz, and 75 or 100 MHz for  $^1\text{H}$  and  $^{13}\text{C}$ , respectively). Chemical shifts were reported in parts per million relative to the solvent residual peak ( $^1\text{H}$ ) or to the central peak of the solvent signal ( $^{13}\text{C}$ ).

The spectra were processed on Bruker Topspin 4.0.7.

**Note about process parameters in  $^1\text{H}$  NMR:**

All  $^1\text{H}$  NMR spectra without  $\text{Eu}(\text{hfc})_3$  were obtained with exponential line broadening of FID signal (command “efp”), with Line Broadening parameter set at 0.3 Hz (command “lb” set to 0.3). It improved signal-to-noise ratio, but to the detriment of the resolution.

To determine enantiomeric ratio of **3** with  $\text{Eu}(\text{hfc})_3$ , it was needed to improve resolution of the spectra: they were obtained with Gaussian broadening of FID signal (command “gfp”) with Line Broadening parameter set to -1 Hz (command “lb” set to -1), and Gaussian maximum position set to 0.3 (command “gb” set to 0.3). It explains distortions in figure S7 and figure S10.

**FTIR spectra (ATR)** were performed on samples using a AGILENT Cary 630 FTIR Spectrometer

**Optical rotation** were performed on POLARTRONIC E polarimeter, using chloroform as solvent and a 10-cm long polarimeter tube.

All reagents were used as received, without further purification. Anhydrous THF and  $\text{LiAlH}_4$  solution 1M in THF were purchased from Sigma-Aldrich and were used as received by students.

Flash column chromatography separations were achieved on silica gel (Merck-Geduran Si 60, 63-200  $\mu\text{m}$ ).

## 2. Experimental procedures

A 50 mL three-neck flask equipped with a magnetic stir bar and a reflux condenser was charged with 300 mg of (S)-BINOL. After purging with  $\text{N}_2$ , 9 mL of anhydrous THF were added with a 10 mL graduated syringe. The medium reaction was cooled at  $0^\circ\text{C}$ , and 0.5 mL of  $\text{LiAlH}_4$  solution (1M in THF) was added dropwise under stirring. The mixture was stirred and allowed to warm to room temperature during 30 min.

Then 0.6 mL of diethylmalonate was added dropwise, followed by 0.5 mL of cyclopentenone. The medium was then heated to reflux during 2 hours.

20 mL of distilled water was added to the mixture, and aqueous layer was extracted two times with ethylacetate. Combined organic layers were washed with brine, then were dried with anhydrous magnesium sulfate, and solvents were removed by evaporation.

Purification by flash chromatography on silica gel ( $\text{EtOAc/cyclohexane}$  8:2) gave the desired product as a colorless oil.

### 3. Characterization

IR (liquid film, ATR) :  $\nu = 2982, 2928, 1726, 1154, 1031 \text{ cm}^{-1}$

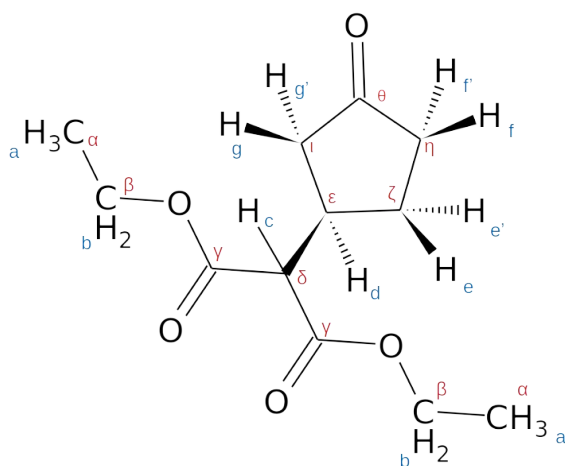
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz) :  $\delta = 4.24\text{-}4.18$  (m, 4H), 3.34 (d,  $J=9.4$  Hz, 1H), 2.89-2.84 (m, 1H), 2.52 (dd,  $J=18.4, 7.8$  Hz, 1H), 2.38-2.18 (m, 3H), 2.02 (dd,  $J=18.4, 10.9$  Hz, 1H), 1.73-1.54 (m, 1H), 1.28 ppm (q,  $J=6.9$  Hz, 6H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz) :  $\delta = 217.1, 168.14, 168.06, 61.61, 61.59, 56.53, 42.90, 38.19, 36.32, 27.49, 14.09, 14.07$  ppm

$[\alpha]_D^{22} = -46, 3^\circ$  (c = 0,4 in  $\text{CHCl}_3$ )

Rf (Cyclohexane : EtOAc 8:2)= 0,45

#### Signal attributions



#### $^1\text{H}$ NMR Assignments (3 in $\text{CDCl}_3$ , 400 MHz)

$\delta$ (ppm)	Assignment	Notes
4.24-4.18	b	4H, multiplet. The two $\text{CH}_2$ groups of ethyl chain are not totally equivalent
3.34	c	1H, doublet, $J = 9.4$ Hz
2.89-2.84	d	1H, multiplet
2.52	$g'$	1H, Doublet of doublet, $J = 18.4, 7.6$ Hz
2.38-2.18	$e', f, f' *$	3H, multiplet
2.02	g	1H, Doublet of doublet, $J = 18.4, 10.9$ Hz
1.73-1.54	e	1H, multiplet
1.28	a	6H, appeared as a quadruplet : two triplets are superposed, with the same coupling constant : $J = 6.9$ Hz

\* e' signals are in the center of the multiplet, f at the left, f' at the right (but they can not be totally distinguish)

### <sup>13</sup>C NMR Assignment (100 MHz, CDCl<sub>3</sub>)

δ (ppm)	Assignment	Notes
217.1	θθ	
168.14	γγ	
168.06	γ'	Very hard to distinguish of γ
61.61	ββ	
61.59	β'	Very hard to distinguish of β
56.53	δ	
42.90	ι	
38.19	ηη	
36.32	εε	
27.49	ζζ	
14.09	αα	
14.07	α'	Very hard to distinguish of α

### NMR correlations for COSY, NOESY, HSQC, and HMBC signals

Signals	COSY	HSQC	HMBC	NOESY
a	b	α	β	b
b	a	β	α	a
c	d	δ	β, ι, ε, ζ	d, e, g
d	c, g, g', e, e'*	ε	ζ, ι, δ, γ	c, e', g'
e	d, e', f, f'	ζ	ι, η, ε, δ, θ	e', c, f
e'	e, d, f, f'***	ζ	η, ε, θ	e, d ***
f, f'	f', f, e, e',	η	ζ, ε, θ	f', f, e ****
g	g', d	ι	ζ, ε, δ, θ	g', c
g'	g, d	ι	ζ, ε, θ, η	g, d

\*\* hard to distinguish

\*\*\* NOESY resolution avoid distinguishable correlation between e' and f and/or f'

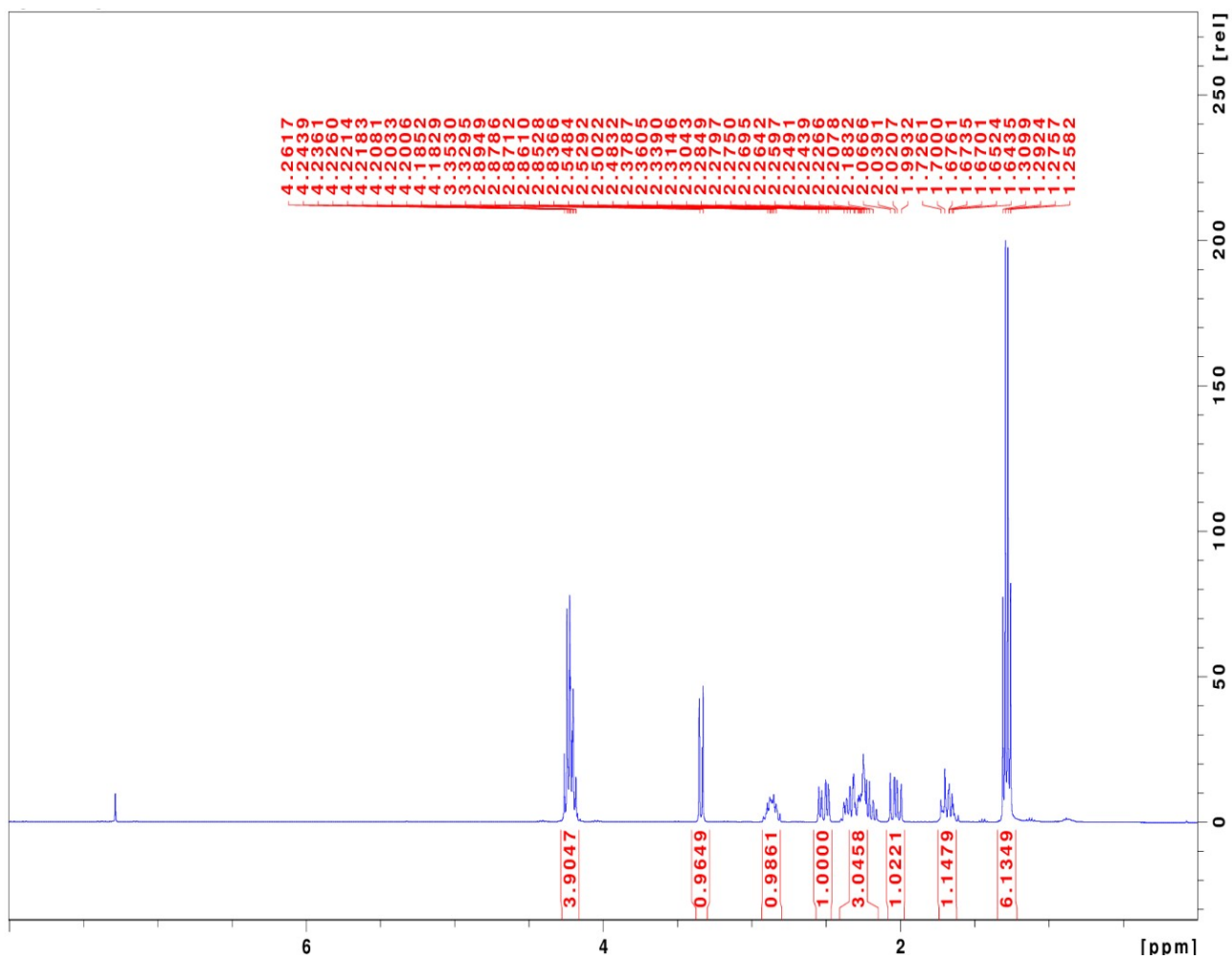


Figure S1 : <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) product 3

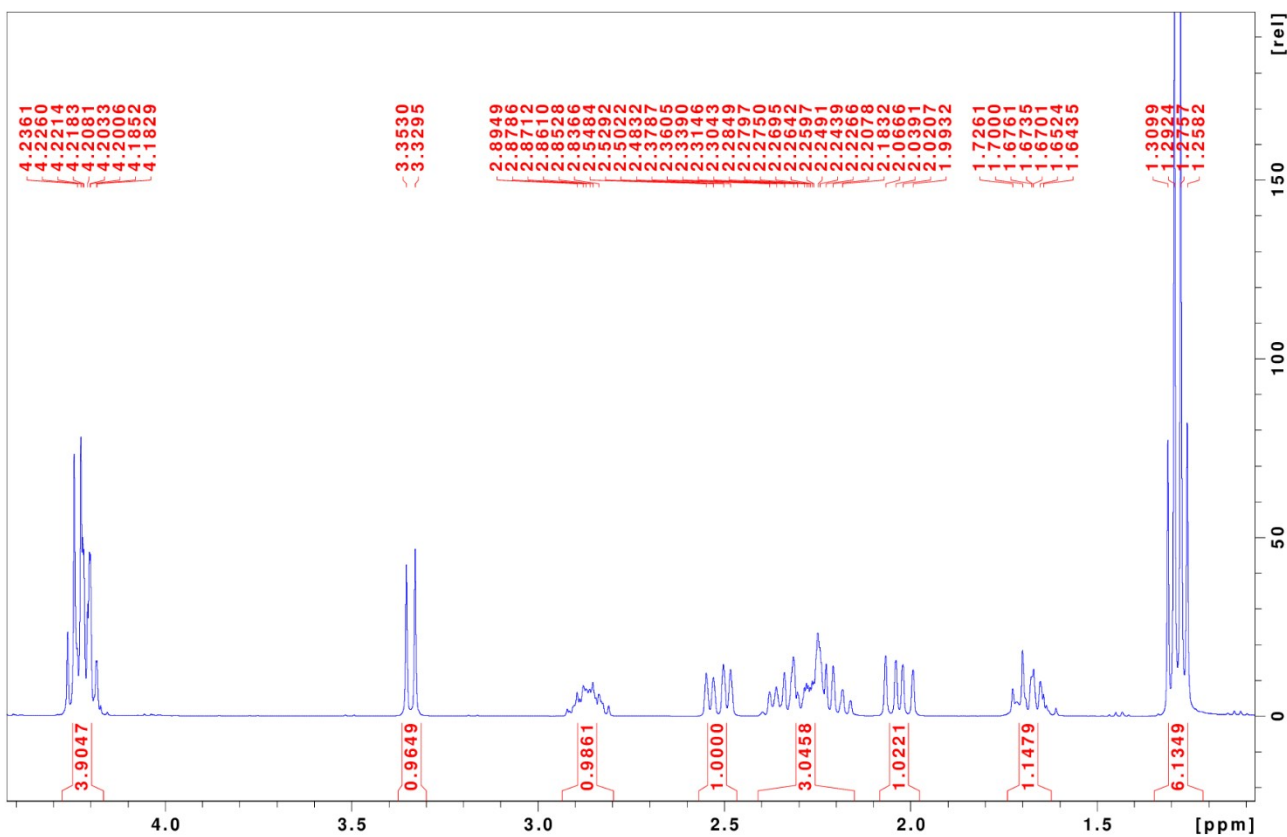


Figure S1 bis : <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) product 3 (details)

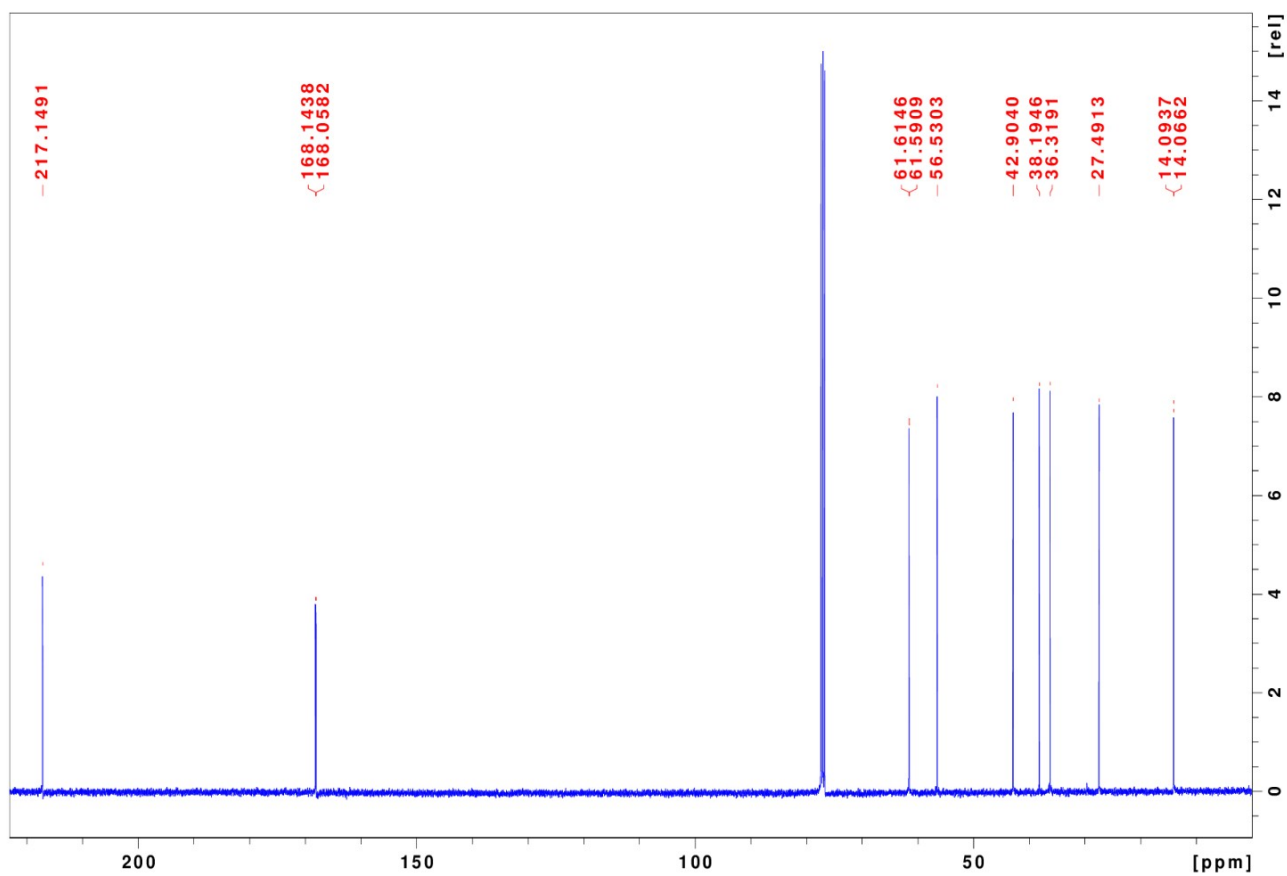


Figure S2 : <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) product 3

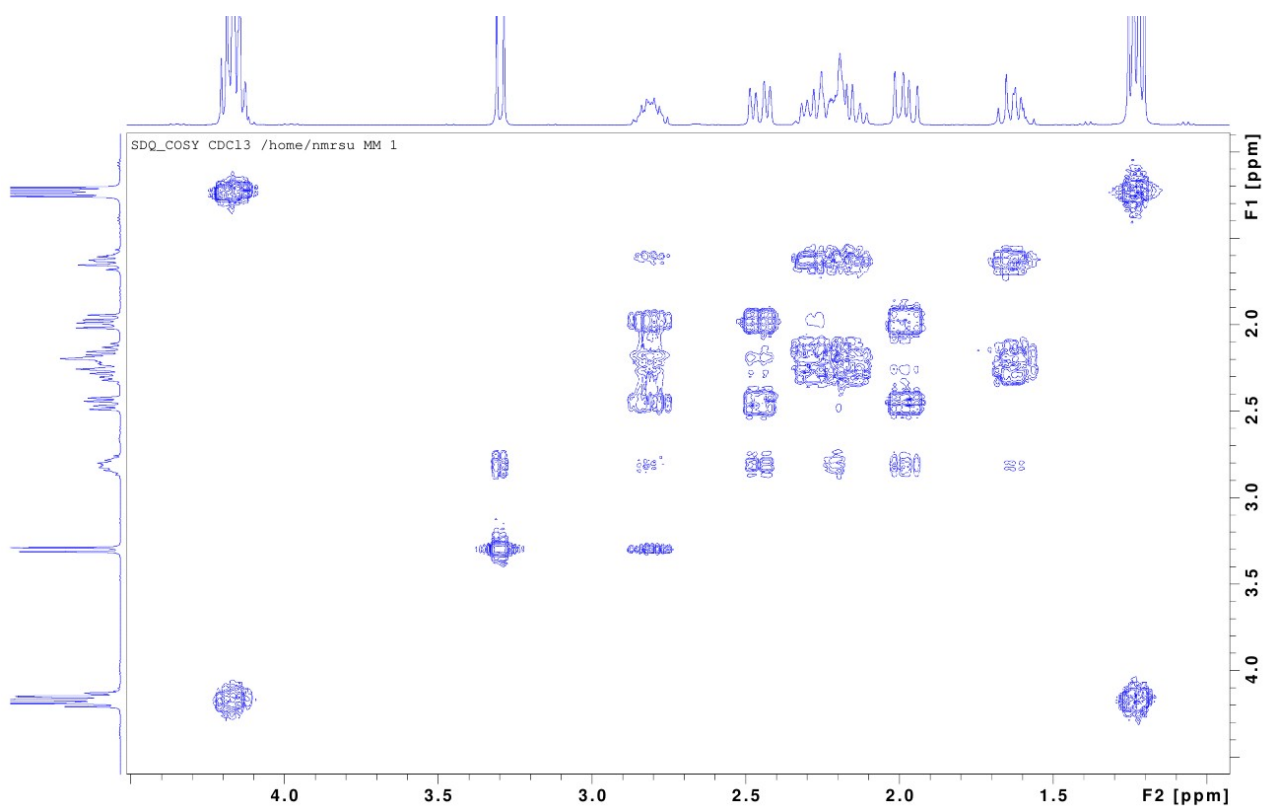


Figure S3 : COSY (400 MHz, CDCl<sub>3</sub>) product 3

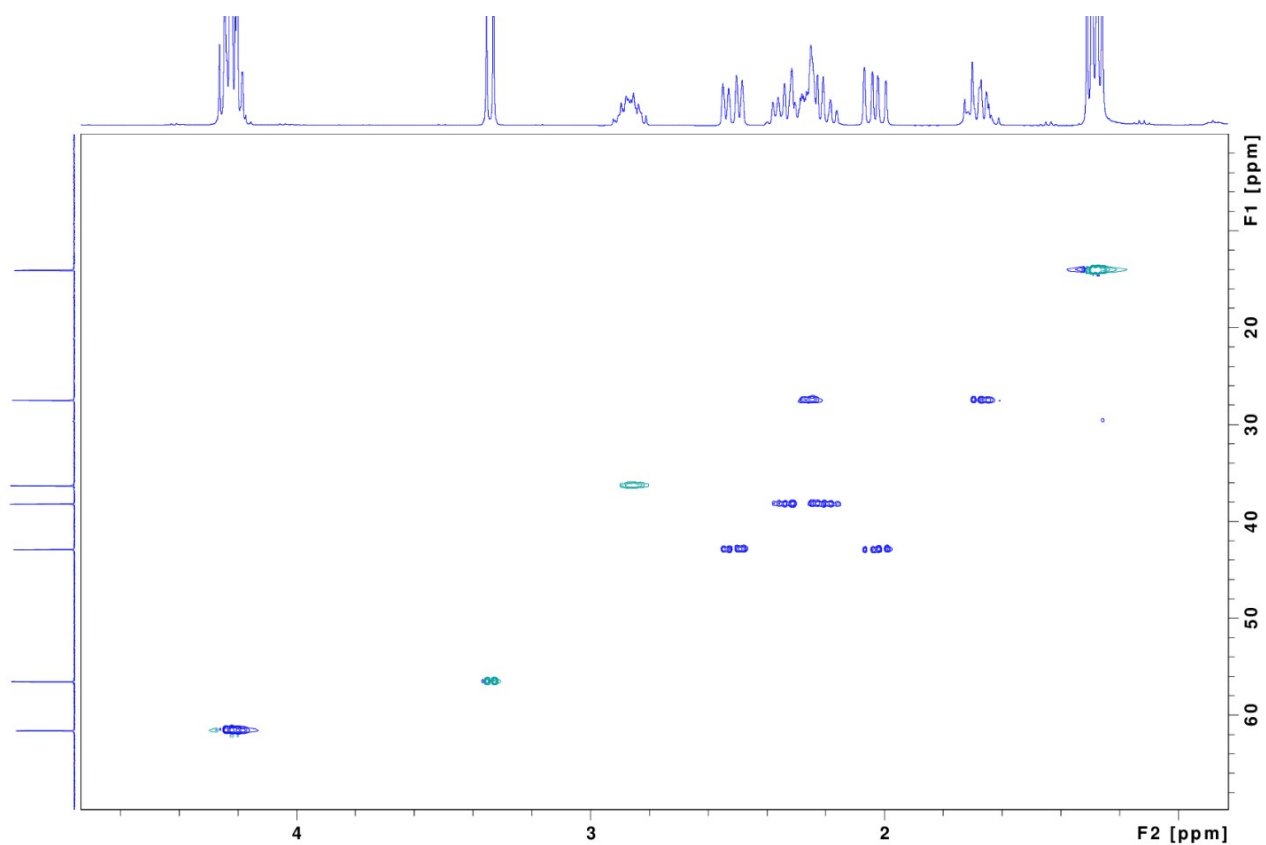


Figure S4 : HSQC (400 MHz, CDCl<sub>3</sub>) product 3

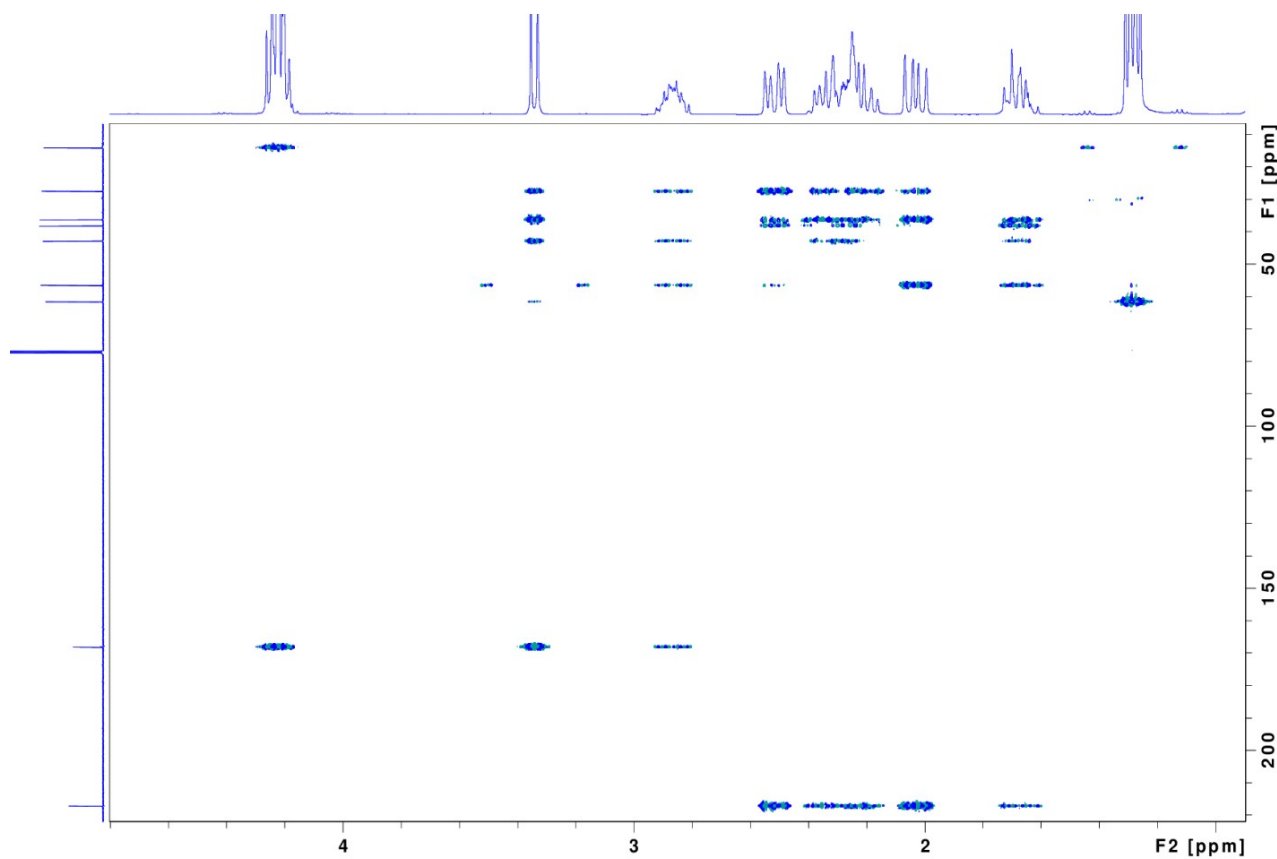


Figure S5 : HMBC (400 MHz, CDCl<sub>3</sub>) product 3

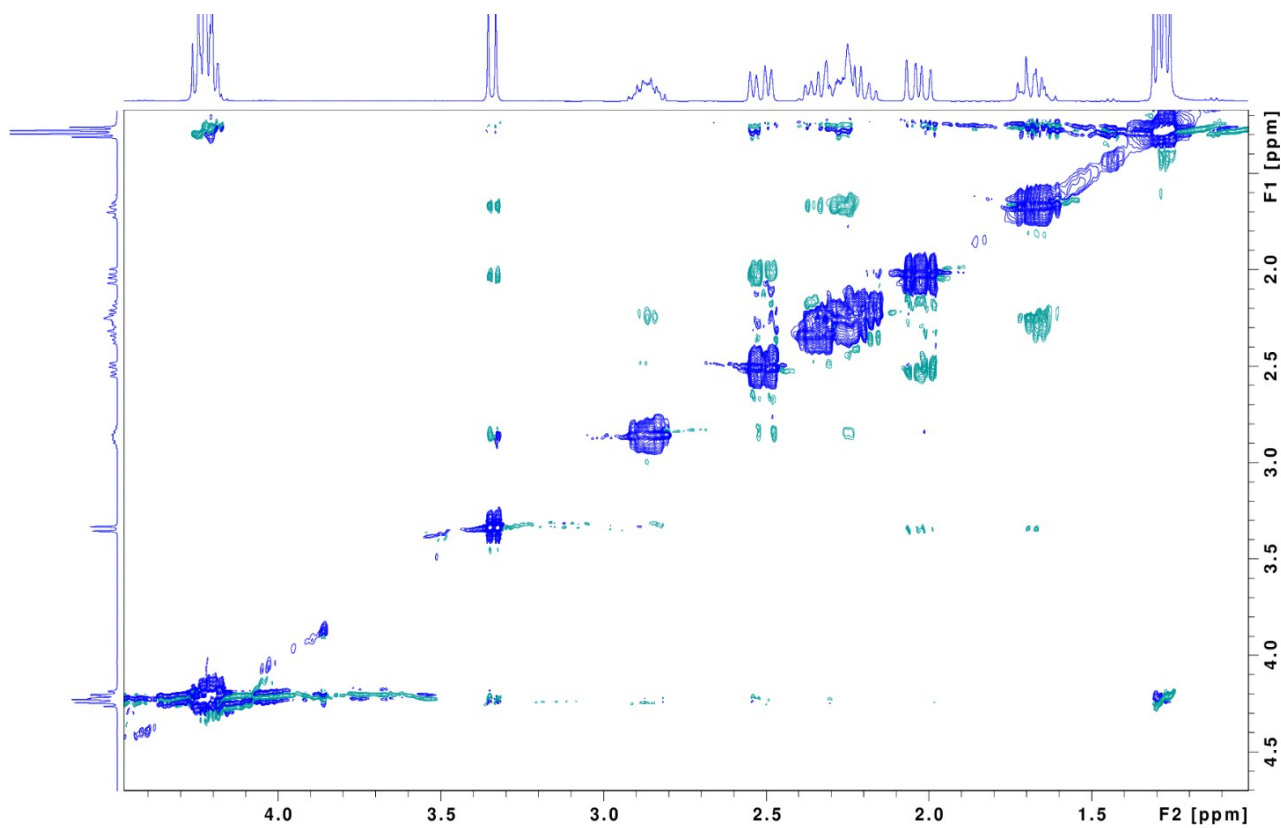


Figure S6 : NOESY (400 MHz,  $\text{CDCl}_3$ ) product **3**

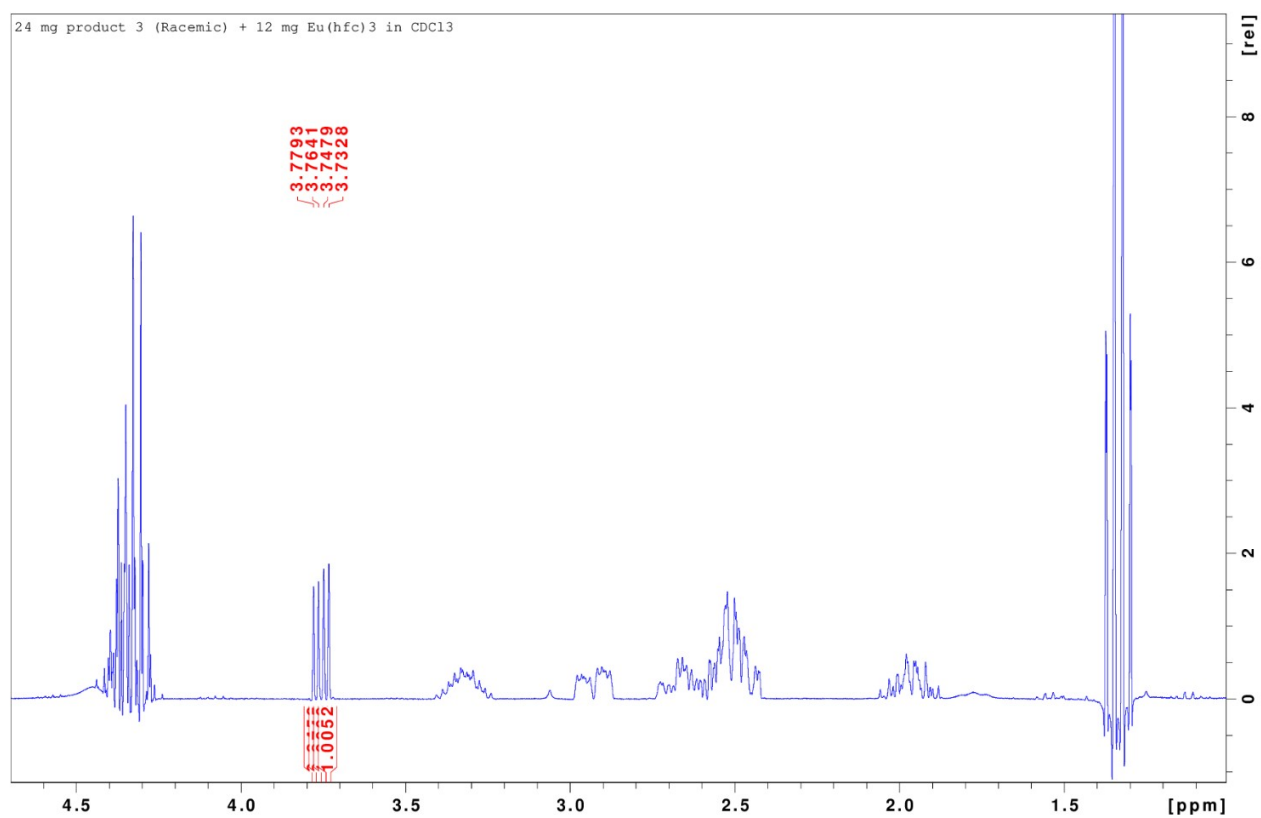


Figure S7 :  $^1\text{H}$  NMR racemic product **3** (24 mg) +  $\text{Eu}(\text{hfc})_3$  (12 mg) ( $\text{CDCl}_3$ , 300 MHz)



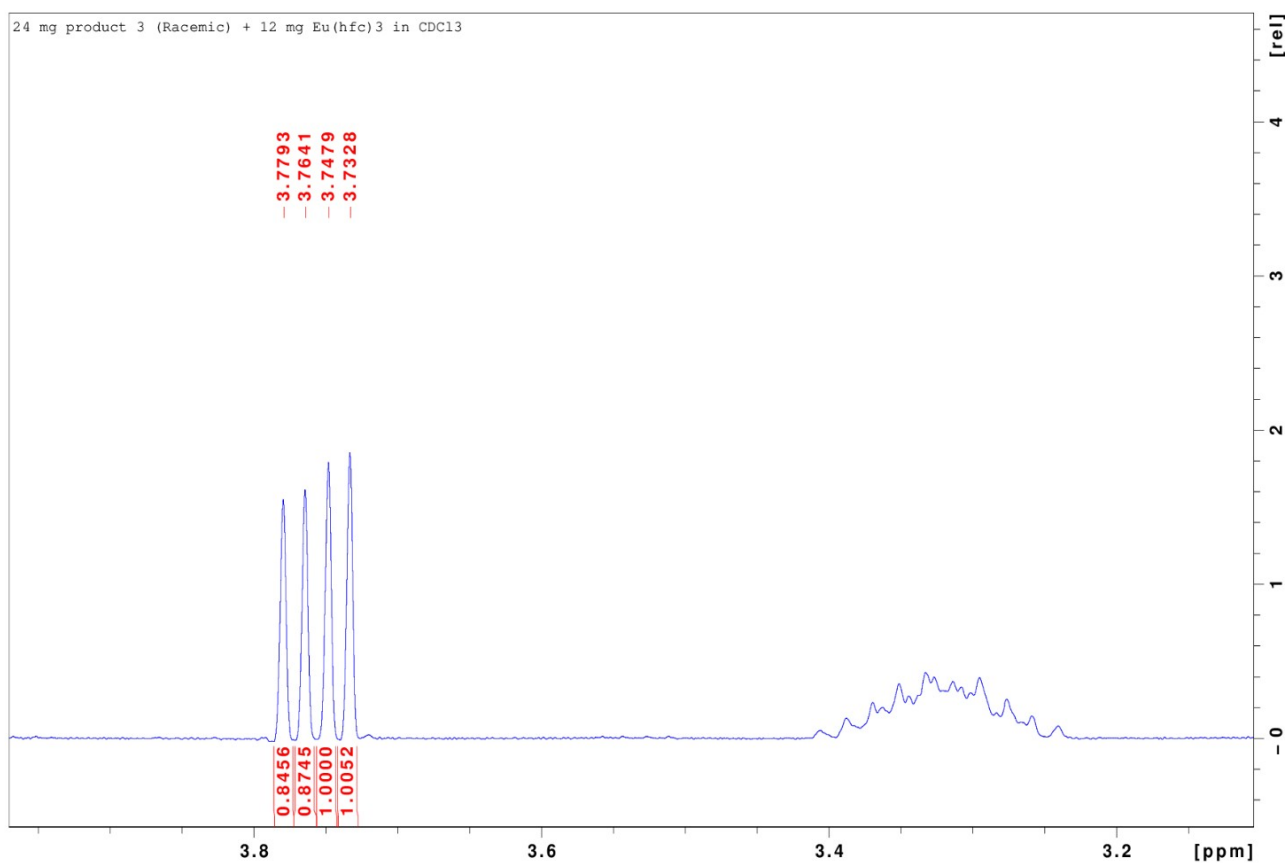


Figure S7 bis : <sup>1</sup>H NMR racemic product **3** (24 mg) + Eu(hfc)<sub>3</sub> (12 mg) - details - (CDCl<sub>3</sub>, 300 MHz)

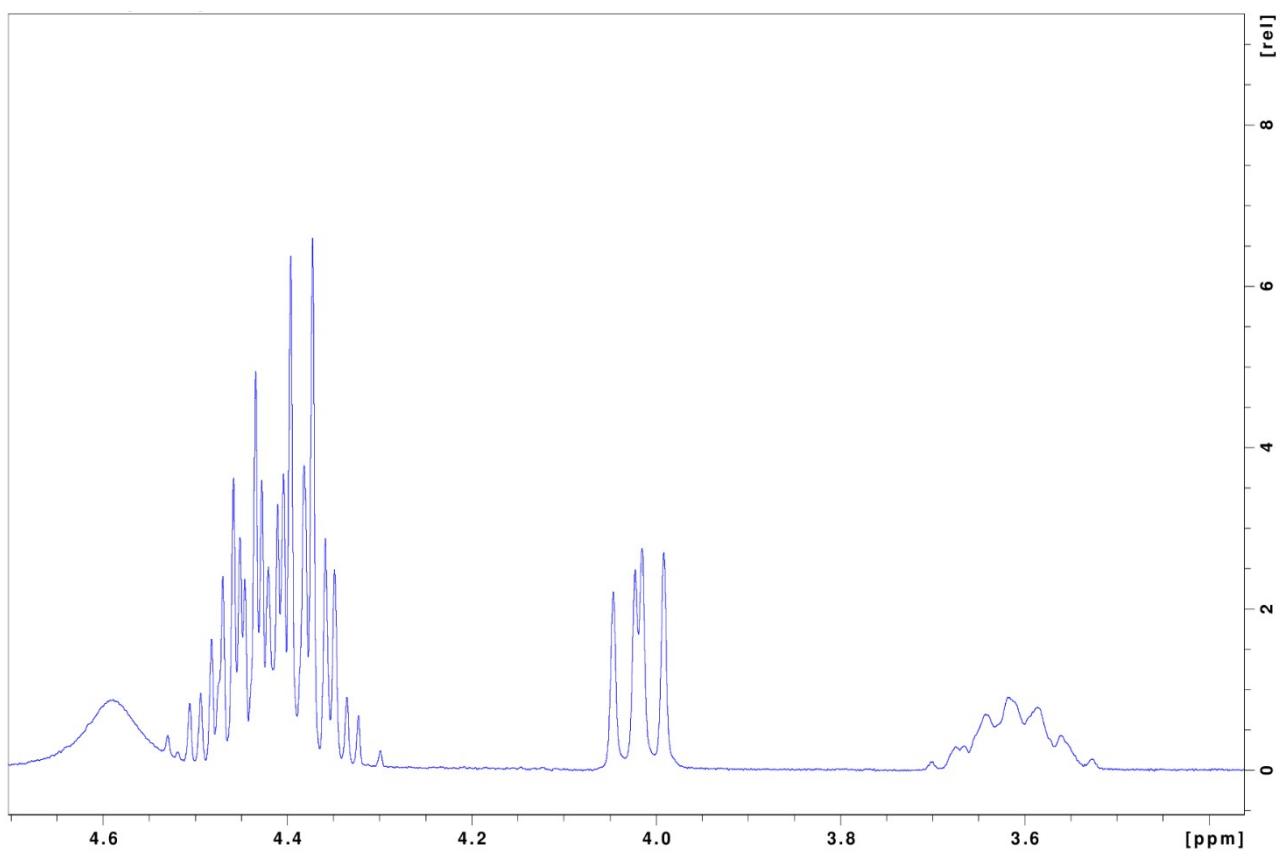


Figure S8 : <sup>1</sup>H NMR racemic product **3** (24 mg) + Eu(hfc)<sub>3</sub> (21 mg) - details - (CDCl<sub>3</sub>, 300 MHz)

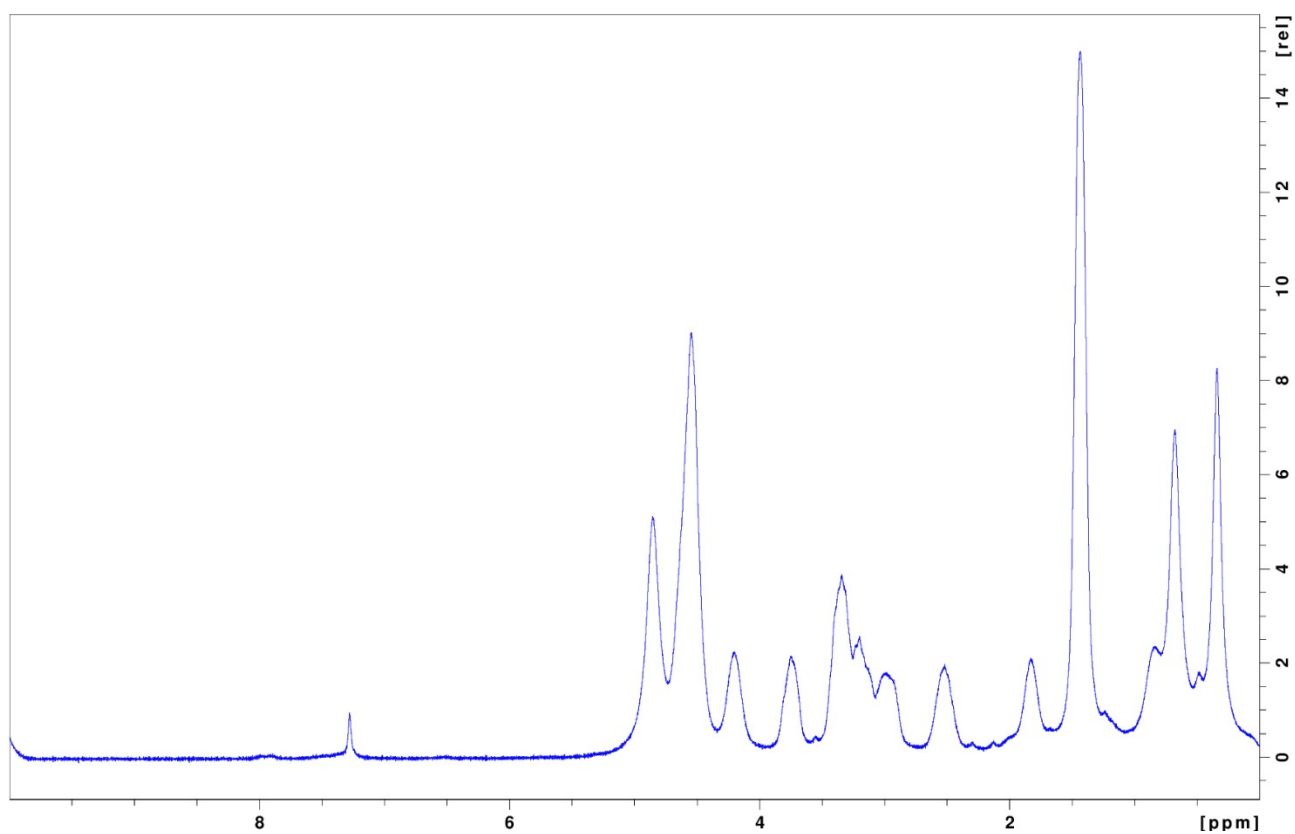


Figure S9 :  $^1\text{H}$  NMR racemic product **3** (24 mg) +  $\text{Eu}(\text{hfc})_3$  (45 mg) ( $\text{CDCl}_3$ , 300 MHz)

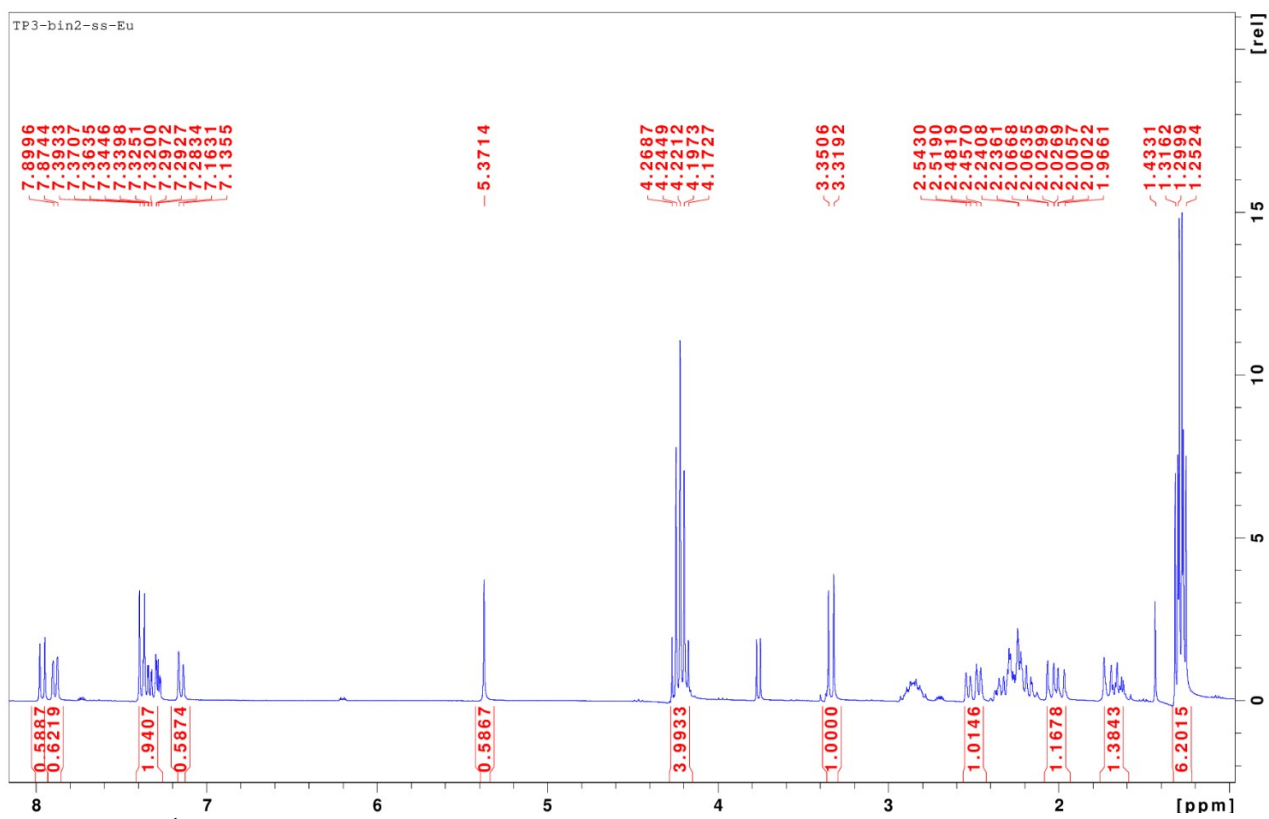


Figure S10 :  $^1\text{H}$  NMR spectrum after purification of **3** (with BINOL) from *student pair 1* ( $\text{CDCl}_3$ , 300 MHz)

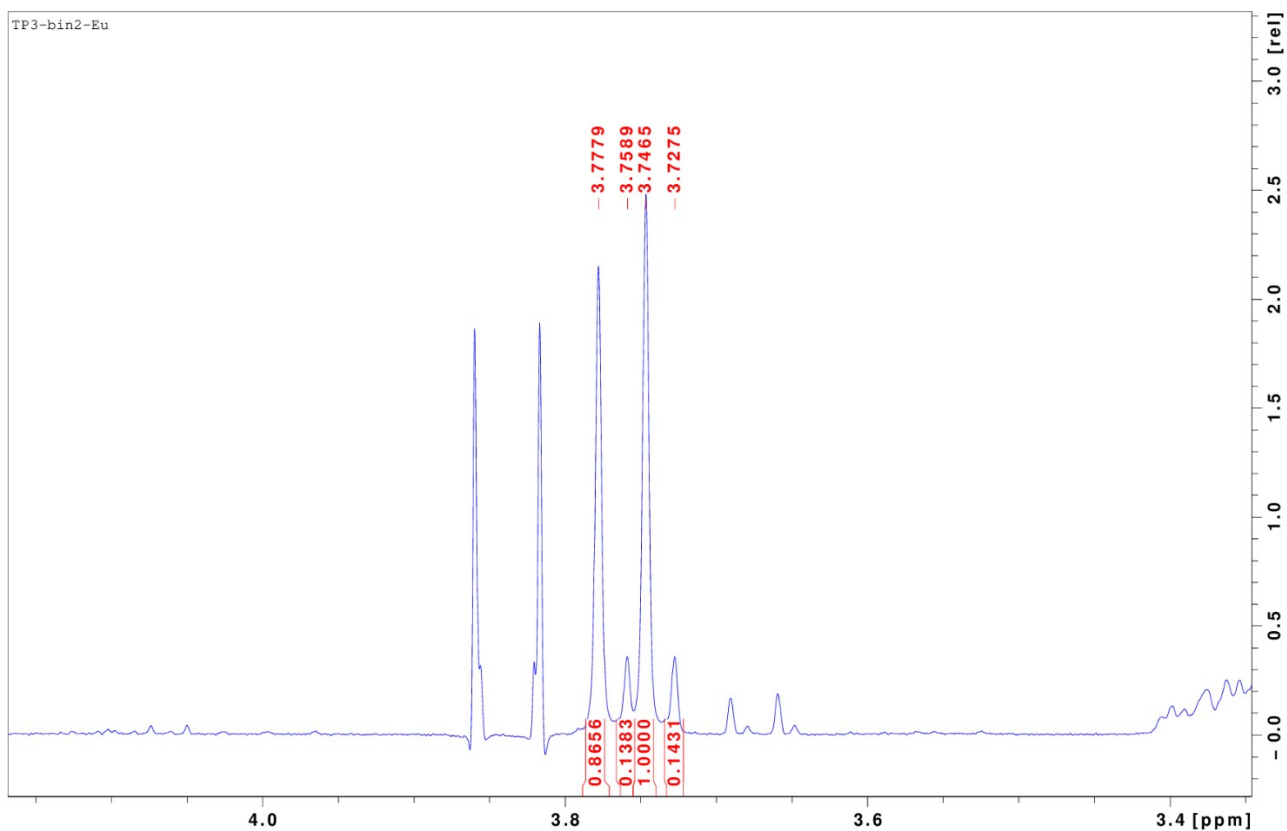


Figure S10 bis :  $^1\text{H}$  NMR spectrum of **3** with  $\text{Eu}(\text{hfc})_3$  from *student pair 1* ( $\text{CDCl}_3$ , 300 MHz)

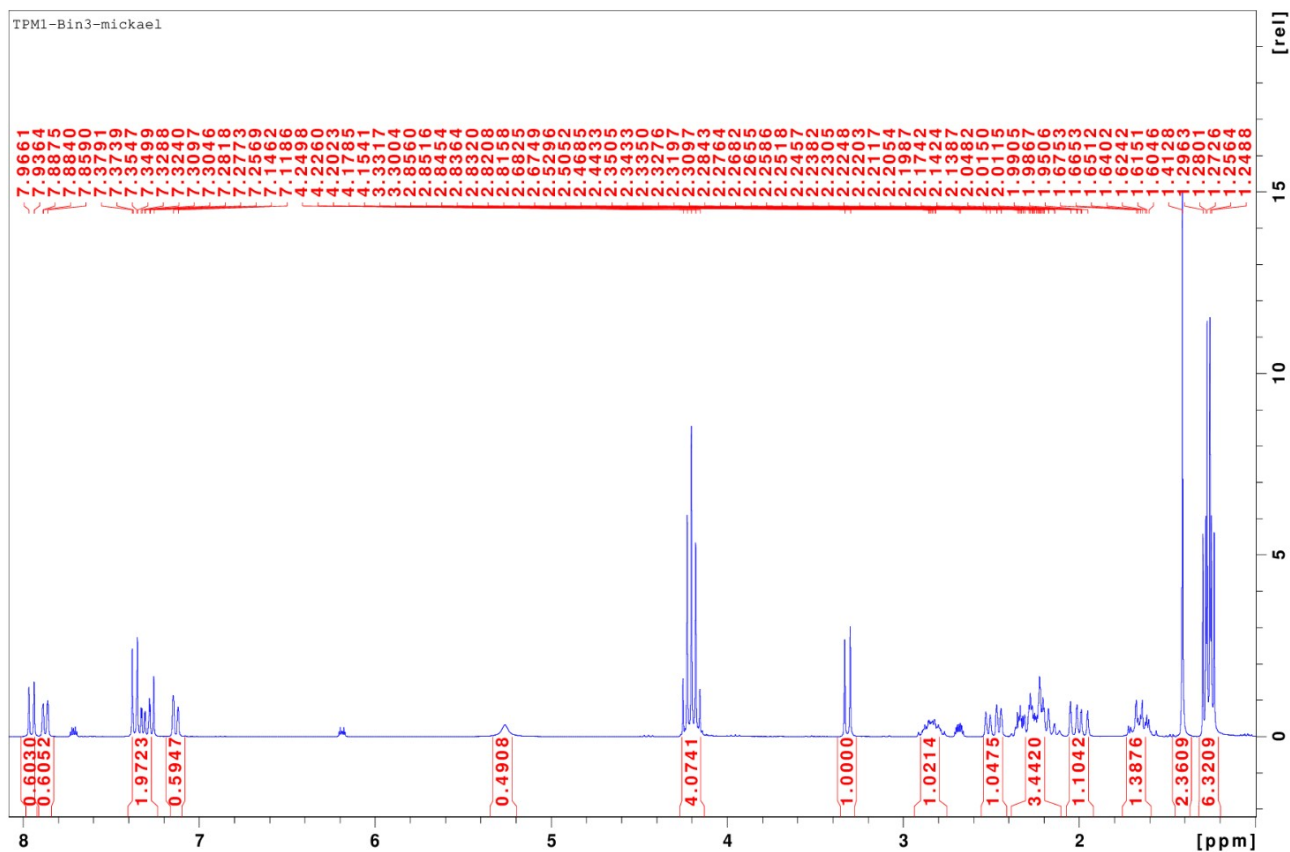


Figure S11 :  $^1\text{H}$  NMR spectrum after purification (**3** + BINOL) from *student pair 2* ( $\text{CDCl}_3$ , 300 MHz)

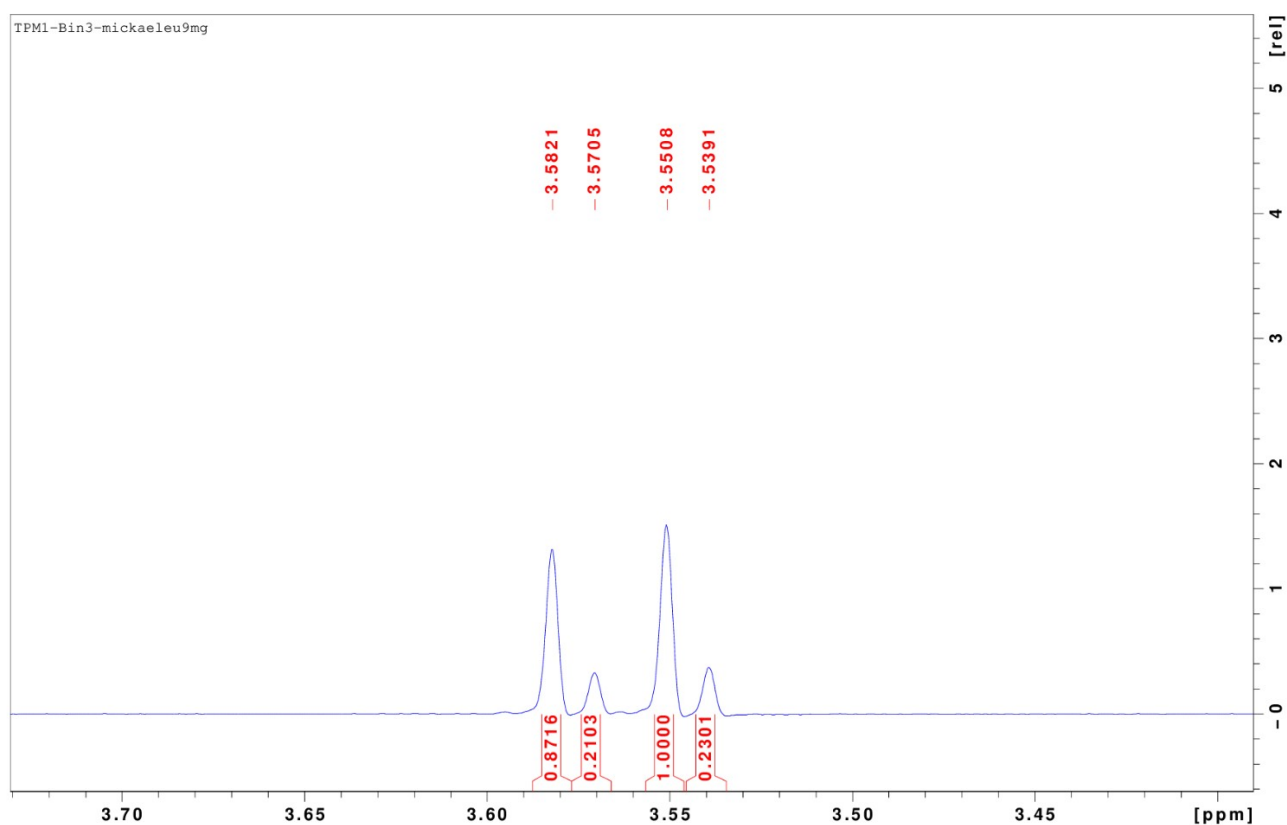


Figure S11 bis :  $^1\text{H}$  NMR spectrum of **3** with  $\text{Eu}(\text{hfc})_3$  from *student pair 2* ( $\text{CDCl}_3$ , 300 MHz)

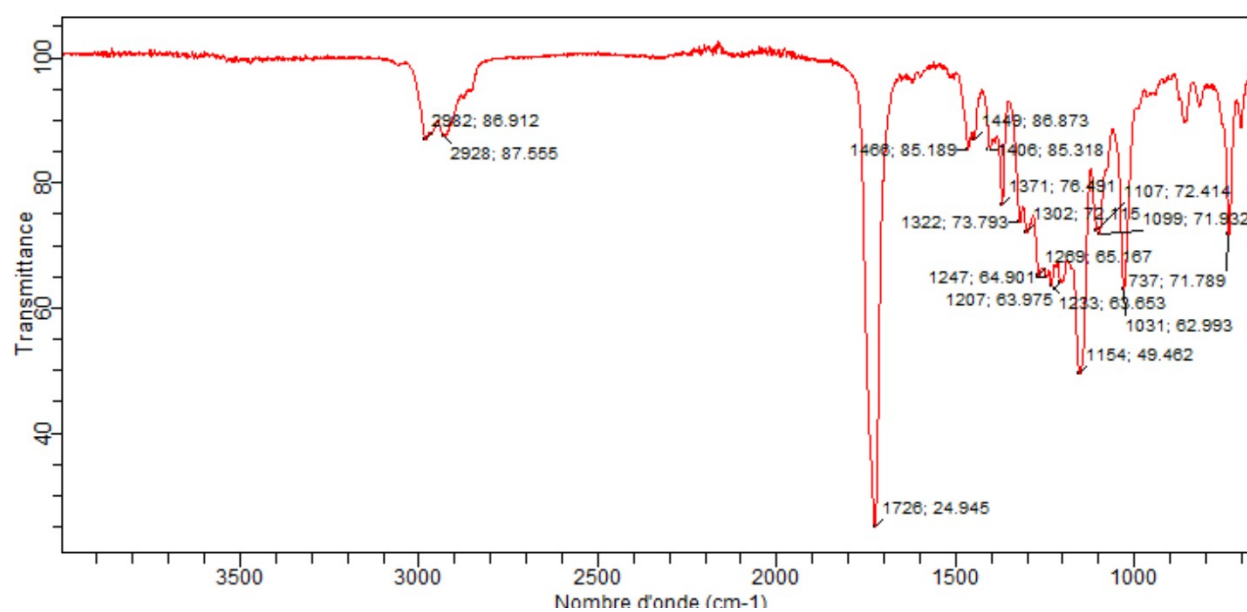


Figure S12 : IR spectrum of pure compound **3** (ATR, liquid film)

## 4 Student's instructions (translated from french)

In the context of the synthesis of biologically active compounds, obtaining enantiopure products is essential. Three strategies are employed:

- Use of a chiral substrate, enantiomerically pure (or enriched), with diastereoselective reactions (eg: reduction of camphor by hydrides)
- resolving of a racemic mixture (ex: resolving of racemic binaphthol mixture)
- Enantioselective reaction using a chiral catalyst (or other chirality inducer)

The purpose of this session is to implement this third strategy by realizing:

1. The synthesis of a chiral catalyst:  $\text{LiAl}[(S)\text{-BINOL}]_2$
2. The Michael addition reaction of diethyl malonate to cyclopentenone.

These synthesis steps will be completed by the study of the enantioselectivity of the Michael reaction by a new enantiomeric excess determination technique: the resolution of  $^1\text{H}$  NMR signals by the use of chiral lanthanide complexes (see T. Wiswannatan *et al.*, *J. Chem. Edu.* **1995**, vol 72, 10, pp 945 -946)

- the prediction of regioselectivity and enantioselectivity by molecular modeling using Avogadro and Gaussian tools. (Relevant data from this article will be used: T. Arai *et al.*, *Angew Chem Int* 1996, 35, 104-106)

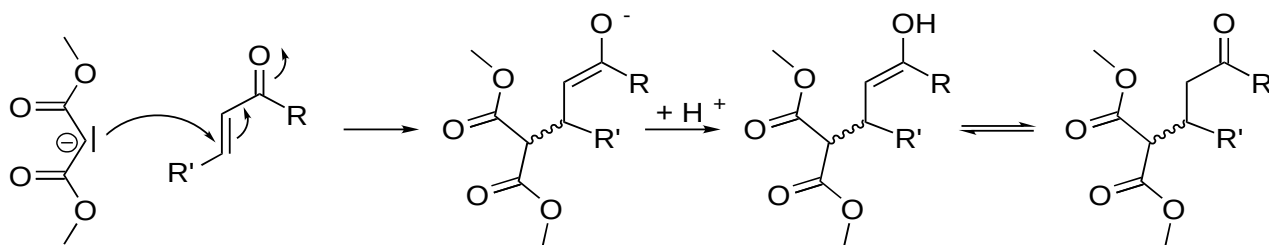
## 1. Products

Name	Formula	Molar weight	Density	Tf / Teb	Hazards
Lithium tetrahydroaluminate solution (1M in THF)	$\text{LiAlH}_4$	---	---	---	<b>H335 H315 H225 H260 EUH019 H351 H302 H336</b>
(S)-binaphthol	$\text{C}_{20}\text{H}_{14}\text{O}_2$	286,3	---	$T_f=205\text{-}11\text{ }^\circ\text{C}$	<b>H301, H319</b>
Diethyl malonate	$\text{C}_7\text{H}_{12}\text{O}_4$	160,2	1,055	$T_{eb}=199\text{ }^\circ\text{C}$	<b>H319</b>
cyclopent-2-en-one	$\text{C}_5\text{H}_6\text{O}$	82,1	0,98	$T_{eb}=150\text{ }^\circ\text{C}$	<b>H302 H315 H319 H335 H226</b>

## 2. Theoretical background

### 2.a. Asymmetric Michael reaction

Michael reactions are classics of organic synthesis, and consist in the creation of a C-C bond by addition of a nucleophilic carbon on a multiple bond conjugated with an electron withdrawing group (EWG)). The addition of an enolate or a carbanion of the malonic diester to an unsaturated  $\alpha$ - $\beta$  carbonyl compound is a typical example thereof (FIG. 1).



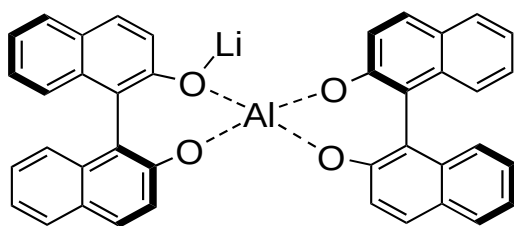
**Figure 1:** Michael addition of a carbanion of dimethyl malonate.

The control of the stereochemistry of the created asymmetric center can be achieved in several ways:<sup>1</sup>

- Use of enolate chiral auxiliaries developed by Evans, Enders, etc.
- Use of chiral nucleophiles
- Use of a chiral catalyst (quaternary ammonium for phase transfer, or Lewis acid, etc.).

## 2.b. Use of Hetero-bimetallic Asymmetric Catalyst

M. Shibasaki and his colleagues developed in the late 1990s bimetallic catalysts of the type :  $M_1-M_2(\text{BINOL})_2$ , where  $M_1$  is an alkali metal (Na or Li), and  $M_2$  a metal of group 13 (Al or Ga ). These complexes are particularly interesting because  $M_1$  gives them basic Brönsted properties, and  $M_2$  gives them Lewis acid properties, and are therefore quite suitable for the catalysis of a Michael reaction, both to generate the carbanion, and to withdraw electrons from the substrate, by interaction with oxygen of enone function (or enal).<sup>2</sup>



**Figure 2 :**  $\text{LiAl}[(\text{S})\text{-BINOL}]_2$

This complex is easily synthesized by adding lithium tetrahydroaluminate (1.0 M in THF) to (S)-BINOL solution in THF.

M.J. Shibasaki *et al.* showed that during Michael addition, the enone oxygen strongly interacts with the aluminum center, thus favoring the malonate ion approach on only one side of the substrate. The enantiomeric excesses obtained are close to 100%, at room temperature in THF.<sup>2</sup>

1 For examples : <https://www.princeton.edu/chemistry/macmillan/group-meetings/JPark-AM.pdf>

2 Shibasaki, M., Sasai, H., Arai, Y. *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1236.

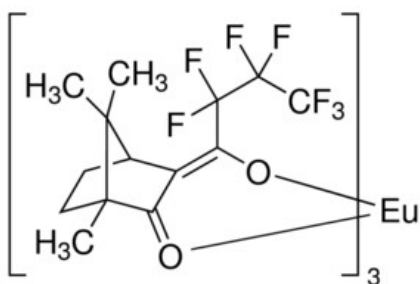
## 2.c Determination of enantiomeric excess by NMR using Chiral Lanthanide Shift Reagents

Polarimetry is not the only method for the determination of enantiomeric excess in research laboratories. This is obviously the case when synthesizing new chiral compounds whose specific rotatory powers are not known ! Three methods are then possible:

- The chemical conversion, using a chiral auxiliary, of the mixture of enantiomers into a mixture of diastereoisomers, followed by the determination of the ratio between the two products obtained by conventional methods (NMR, GC, HPLC, etc.). This method suffers from two disadvantages: the realization of a chemical reaction risks causing an epimerization of the asymmetric center, artificially modifying the enantiomeric excess. Moreover, it adds handling time!
- The direct determination of enantiomeric excess by using chiral column for GC or LC or HPLC.

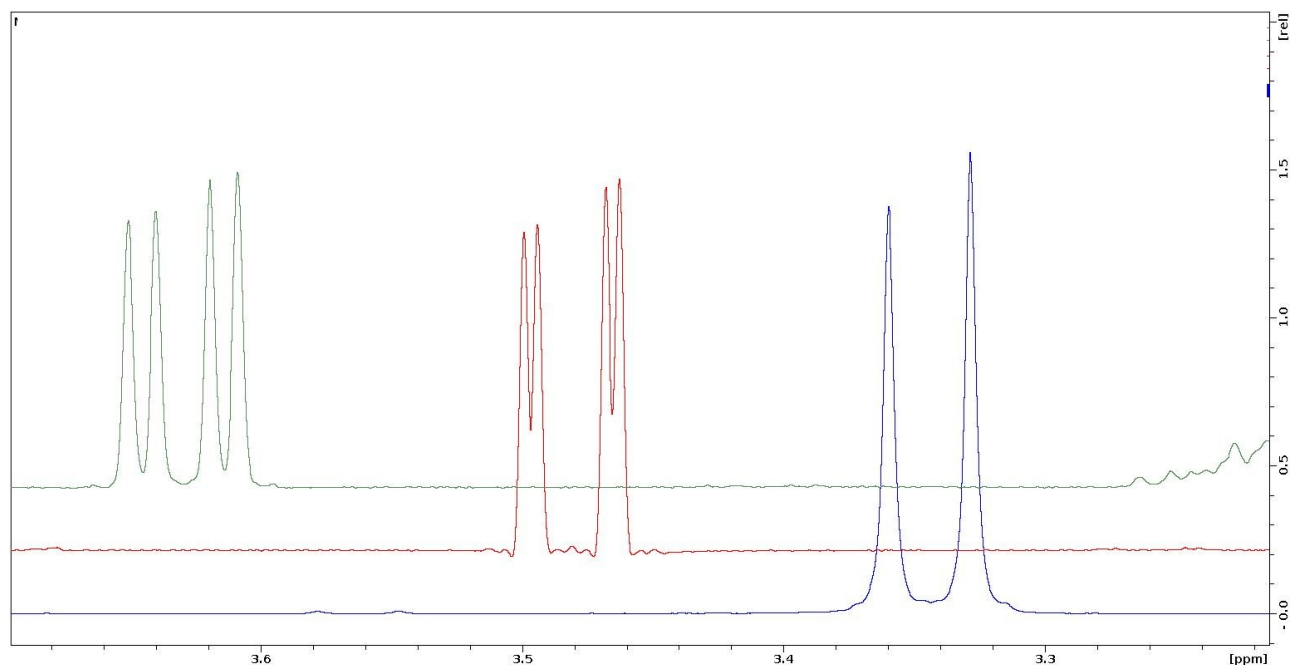
This method is currently the most widespread. Nevertheless it requires the use of expensive specific equipments (HPLC, GC apparatus and their chiral columns). In addition, the development of the separation conditions can be tricky.

- The determination of the ratio between the two enantiomers by means of a chiral agent ("Chiral Lanthanide Shift Reagent") by NMR. This method, implemented in this session, requires the use of a chiral lanthanide complex (here the complex  $\text{Eu}(\text{hfc})_3$  (**Figure 3**) derived from camphor). This one will form with two enantiomers of the compound studied two new diastereoisomeric complexes, whose signals are, *a priori*, discernible in NMR. Due to the paramagnetic nature of the lanthanides used, the amount to be introduced must be as small as possible in order to avoid the widening of the peaks.  $\text{Eu}(\text{hfc})_3$  is therefore added in sub-stoichiometric amount: the complexation equilibrium is very fast, well below the characteristic relaxation times of the NMR signal; the chemical shifts obtained are therefore averages between the chemical displacement of the protons of the uncomplexed substrate and of the complexed substrate, and depend on the concentrations, the complexation equilibrium constants (which may depend on each enantiomer !), and the geometry of the complex obtained (**Figure 4**)



**Figure 3 :** Europium tris[3-(heptafluoropropyl)hydroxymethyl]-(+)-camphorate]

This last method is limited to chiral substrates likely to complex with lanthanide (alcohols, amines, carbonyls, ...). Differences in chemical shift are sometimes low, and require the use of high performance spectrometers, and / or fine signal processing to allow reliable determination of ratios.



**Figure 4 :** signal evolution (doublet) of a proton of a racemic substrate in the presence of Eu (hfc) 3 (blue: without complex, red: Eu(hfc)<sub>3</sub> 2.3% mol, green: Eu(hfc)<sub>3</sub> 5.3% mol).

### 3 Experiment protocol

#### 3.a. LiAl(BINOL)<sub>2</sub> synthesis

In a 50 mL three-neck flask equipped with a magnetic stir bar and a reflux condenser, add 300 mg of (S)-BINOL. After purging with N<sub>2</sub>, added with a 10 ml graduated syringe 9 mL of anhydrous THF. Cool the reaction medium to 0°C, and add dropwise 0.5 mL of LiAlH<sub>4</sub> solution (1M in THF) under stirring. The mixture is stirred and allowed to warm to room temperature during 30 min.

#### 3.b. Michael addition

Then add dropwise 0,6 mL of diethylmalonate, followed by 0,5 mL of cyclopentenone. Heat the medium to reflux during 2 hours.

Add 20 mL of distilled water to the mixture, and extract aqueous layer two times with ethyl acetate. Wash combined organic layers with brine, then dry it with anhydrous magnesium sulfate, and remove solvents by rotative evaporation. Proceed o

Proceed to purification by flash chromatography on silica gel (EtOAc/cyclohexane mixture (to be determined) as eluent) gave the desired product as a colorless oil.

*Note : it is difficult to completely separate the BINOL with the product of the addition of Michael.*



### 3.c. Characterization

Determine rotary power (in  $\text{CHCl}_3$ ) with Laurent polarimeter. Realize IR spectrum.

Introduce between 20 mg and 30 mg (accurately weigh) of the product in an NMR tube and add 0.6 ml of deuterated chloroform. Realize the  $^1\text{H}$  NMR spectrum of the product.

Then add 8 to 10 mol% of  $\text{Eu}(\text{hfc})_3$  in the tube, and carry out a new  $^1\text{H}$  NMR spectrum.

Supervisors will give to you  $^{13}\text{C}$  spectrum and 2D spectra (COSY, NOESY, HSQC and HMBC) to achieve a total assignment of NMR signals.

## 5 Questions

1. Explain the interest of obtaining enantioenriched or enantiopure compounds by giving examples in the pharmaceutical and agri-food industry.
2. What type of chirality shows the complex  $\text{LiAl}(\text{BINOL})_2$ ? Give the other types of chirality.
3. Why does the formation of the complex  $\text{LiAl}(\text{BINOL})_2$  require the use of a polar and aprotic solvent? Why should THF be anhydrous and without oxygen?
4. Justify the regioselectivity of Michael's reaction. We will base ourselves in particular on the result of the molecular modelings.
5. Describe the catalytic cycle as completely as possible..
6. Give an other example of an application related to the paramagnetic nature of lanthanide
7. Which symmetry group does  $\text{Eu}(\text{hfc})_3$  complex belong to? ?
8. What parameters are the cause of the shift of the chemical shifts in  $^1\text{H}$  NMR when  $\text{Eu}(\text{hfc})_3$  is present? What is the risk if we add too much europium complex?
9. Determine reaction yield of Michael addition.
10. Assign all signals in  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Assign main absorption bands in IR spectrum.
11. Determine enantiomeric excess by NMR and polarimetry. Compare and comment the results

## 6 List of Chemicals and Equipment (for 1 student pair)

### Chemicals :

- Lithium tetrahydroaluminate solution (1M in THF) : 0.5 mL
- Anhydrous THF : 10 mL
- (S)-Binaphtol : 0.300 g
- Diethyl malonate : 0.5 mL
- Cyclopentenone : 0.6 mL
- Cyclohexane
- Ethyl acetate
- Chloroform
- Deuterated chloroform
- Silica gel : 30 g
- Brine : 20 mL
- Anhydrous magnesium sulfate : to dry 50 mL of ethyl acetate solution
- Distilled water
- $\text{Eu}(\text{hfc})_3$  : 10-15 mg

### Materials :

- 50 mL triple neck round bottom flask
- 1 refrigerant
- 2 septa
- 1 magnetic stirbar
- 1 hot plate stirrer
- 10 mL graduated syringe
- 1 mL graduated syringe
- 100 mL separatory funnel
- 2 x 200 mL Erlenmeyer flask
- 1 spatulas
- Pre-cut silica TLC plates
- TLC developing chamber
- glass column for chromatography
- 1 NMR tube
- Rotary evaporator
- Pasteur pipets
- Pasteur pipet bulb
- Balance
- 1 volumetric flask 20 mL
- 1 polarimeter tube

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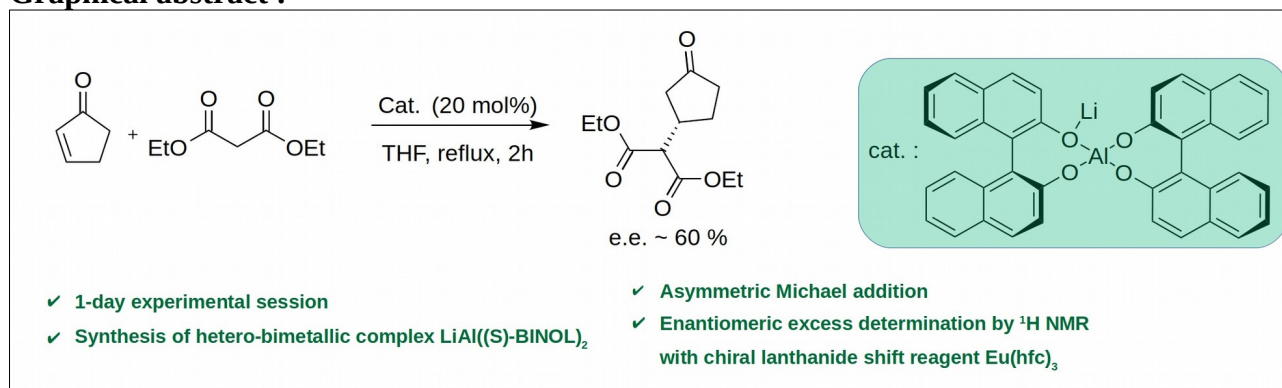
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## Enantioselective Michael addition : an experimental introduction to asymmetric synthesis

Martin Tiano

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### Graphical abstract :



**Abstract :** We adapted a classical asymmetric Michael addition for a 1-day experimental session (6-8 hrs) for third or fourth-year undergraduate students. The experiment follows up three steps : synthesis of a chiral Lewis Acid,  $\text{LiAl}((\text{S})\text{-BINOL})_2$ , then its use as a catalyst in the Michael addition of diethyl malonate on cyclopentenone, followed by purification through column chromatography on silica gel. The desired product can be fully characterized by 1D and 2D NMR experiments and IR spectroscopy. The enantiomeric excess can be determined by polarimetry and  $^1\text{H}$  NMR using the chiral lanthanide shift reagent  $\text{Eu}(\text{hfc})_3$ .

This laboratory experiment bridges the gap between theoretical courses about asymmetric synthesis and practical implementations of enantioselective reactions.

**Key Words :** Chiral Lewis acid, enantioselective reaction, asymmetric synthesis, Michael addition, enantiomeric excess, chiral lanthanide shift reagent, third-year undergraduate, fourth-year undergraduate, organic chemistry.

### Experimental skills :

- Synthesis with reflux under inert conditions
- Follow-up by TLC
- Usual work-up procedures
- Purification by Silica-gel chromatography
- Preparation of samples for NMR analysis, IR spectroscopy, and for polarimetry
- Use of polarimeter

### Knowledge-based skills :

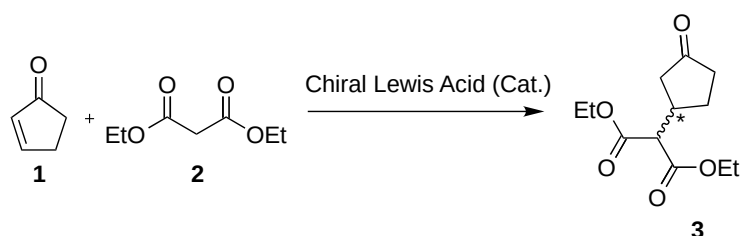
- understanding asymmetric synthesis challenges
- understanding chiral induction in Michael addition
- Interpreting 1D  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and 2D NMR spectra
- Understanding the scopes and limitations of chiral lanthanide shift reagent use
- Understanding measurement of enantiomeric excess by polarimetry and by  $^1\text{H}$  NMR with chiral lanthanide shift reagent

Asymmetric synthesis is a major field of research in organic chemistry, and many theoretical courses focus on it during undergraduate and graduate studies. Students are precociously sensitized to the need of obtaining pure chiral compounds, especially in medicinal chemistry or natural product chemistry. Nonetheless, few experimental sessions of asymmetric synthesis for undergraduate students are reported.<sup>1,2</sup> Thus courses about this domain remain most of time theoretical, and students learned reaction mechanisms and transition state models well before using it in lab experiments.

The main issues of practicing asymmetric syntheses in teaching labs are the cost or the availability of chiral catalysts, reactants and substrates hazards, conditions and durations of enantioselective reactions. For example, use of chiral auxiliaries as Evans oxazolidinones for asymmetric alkylation reactions implies multistep synthesis and harmful alkylating agents.<sup>1</sup> Some enantioselective organocatalyzed experiments for undergraduate are reported but require long reaction time (typically one week between two sessions).<sup>2</sup>

We decided to focus on asymmetric Michael addition for the development of a one-day experiment during which asymmetric catalysis principles are illustrated. Michael addition is a classical reaction, defined by the addition of a nucleophilic carbanion (typically malonate) to an electrophilic multiple bond (typically  $\alpha,\beta$ -unsaturated carbonyl compound). It creates a new C-C bond and, depending on the substrate and the reaction conditions, it can be achieved in a diastereoselective and/or enantioselective manner.

The experimental session described herein involves the preparation of a chiral Lewis acid as catalyst, and its use in enantioselective Michael addition of diethylmalonate **2** on cyclopentenone **1**, purification and complete characterization of the product **3** (Figure 1). All reagents are commercially available, inexpensive, and present reasonable security profile.

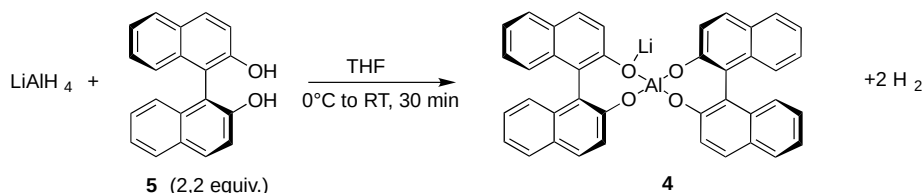


**Figure 1** : Michael addition catalyzed by chiral Lewis acid.

## Experimental Overview

Various Lewis acid ( $\text{SnCl}_4$ ,  $\text{FeCl}_3$ , etc.) efficiently catalyzed Michael addition.<sup>3</sup> We decided to use  $\text{LiAl}((\text{S})\text{-BINOL})_2$  **4** since it is fastly generated *in situ*, by adding (S)-BINOL **5** to a commercially available solution of lithium aluminium hydride 1 M in THF. **4** is a hetero-bimetallic catalyst developed by M. Shibasaki *et al.* It acted as a Brønsted base and Lewis acid simultaneously : As a base it reacts with **2** to generate carbanion, and as a Lewis acid, it activates cyclopentenone **1** toward nucleophilic attack.

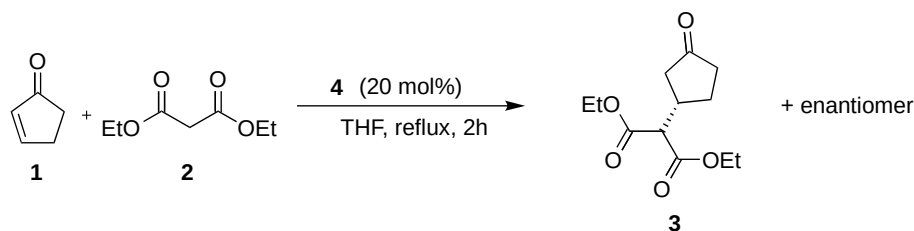
- 1 T. E. Smith, D.P. Richardson, G.A. Truran, K. Belecki, M. Onishi, *J. Chem. Edu.* **2008**, *85*, 695-697.
- 2 For examples : E. Wade, K.E. Walsh *J. Chem. Edu.* **2011**, *88*, 1152-1154, T.C. Wong, C.M. Sultana, D.A. Vosburg, *J. Chem. Edu.* **2010**, *87*, 194-195.
- 3 For examples : L.-W. Xu, L. Li, C.-G. Xia *Helv. Chim. Acta* **2004**, *87*(6), 1522-1526 ; L. Wu, R. Jin, L. Li, X. Hu, T. Cheng, G. Liu, *Org. Lett.*, **2017**, *19*, 3047-3050 ; A. Ueda, T. Umeno, M. Doi, K. Akagawa, K. Kudo, M. Tanaka, *J. Org. Chem.*, **2016**, *81*, 6343-6356 ; M. Shibasaki, H. Sasai, T. Arai *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236-1256.



**Figure 2 :** Formation of chiral Lewis acid  $\text{LiAl}((S)\text{-BINOL})_2$  (**4**)

This first step of the session allows the student to develop their practice of synthesis under strict inert conditions, and their understanding of complex synthesis reaction. This one is not so common since it implies acid/base reaction between BINOL and aluminium hydride, leading to dihydrogen generation (Figure 2).

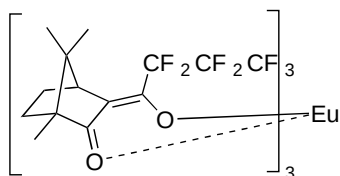
The second step of the session consists in the Michael reaction, in adding directly and slowly cyclopentenone and diethylmalonate in the freshly prepared  $\text{LiAl}((S)\text{-BINOL})_2$  (Figure 3). This reaction was already described at room temperature, during at least 8 hours, with > 98 % enantiomeric excess and excellent yields.<sup>4</sup> We decided to reduce reaction time to 2 hours, in heating the reaction media to THF reflux after addition. This step allows the student to practice a TLC-follow up of the reaction. Since the product **3** doesn't absorb UV, it is necessary to use stains as potassium permanganate solution, or phosphomolybdic acid solution to visualize all compounds.



**Figure 3 :** Michael reaction catalyzed by **4**

The third step of the session consists in the purification of **3**, by silica gel chromatography with a mixture of cyclohexane and ethyl acetate as eluent. This can be quite challenging, since retention factors of BINOL and the desired product are near. Students have to select some pure fractions of the desired product for analysis by NMR, IR, and polarimetry.

We decided though to extend enantiomeric excess measurement with NMR experiments using a chiral lanthanide shift reagent (CLSR), which was a completely new methodology for students. Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] ( $\text{Eu}(\text{hfc})_3$ ) **5** (Figure 4) is one of most used CLSR.  $\text{Eu}(\text{hfc})_3$  is soluble in most polar solvent and deuterated chloroform. It coordinates weakly with esters and ketone. Since  $\text{Eu}^{3+}$  is paramagnetic, it induces large chemical shift changes, even in sub-stoichiometric quantities.<sup>5</sup>



**Figure 4 :**  $\text{Eu}(\text{hfc})_3$  complex **5**

## Hazards

$\text{LiAlH}_4$  1M solution in THF is corrosive and flammable. It must be handled with a lot of care, in inert conditions. BINOL is toxic by ingestion. Diethylmalonate, cyclopentenone, ethyl acetate, cyclohexane are harmful and flammable. Deuterated chloroform is toxic. Students should have

<sup>4</sup> T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 104-106

<sup>5</sup> For a specific experimental course with CLSR, see T. Viswanathan, A. Toland, *J. Chem. Edu.* **1995**, 72, 945-946

adequate eye protection, wear gloves, and work in well-ventilated fume hoods during all the session.

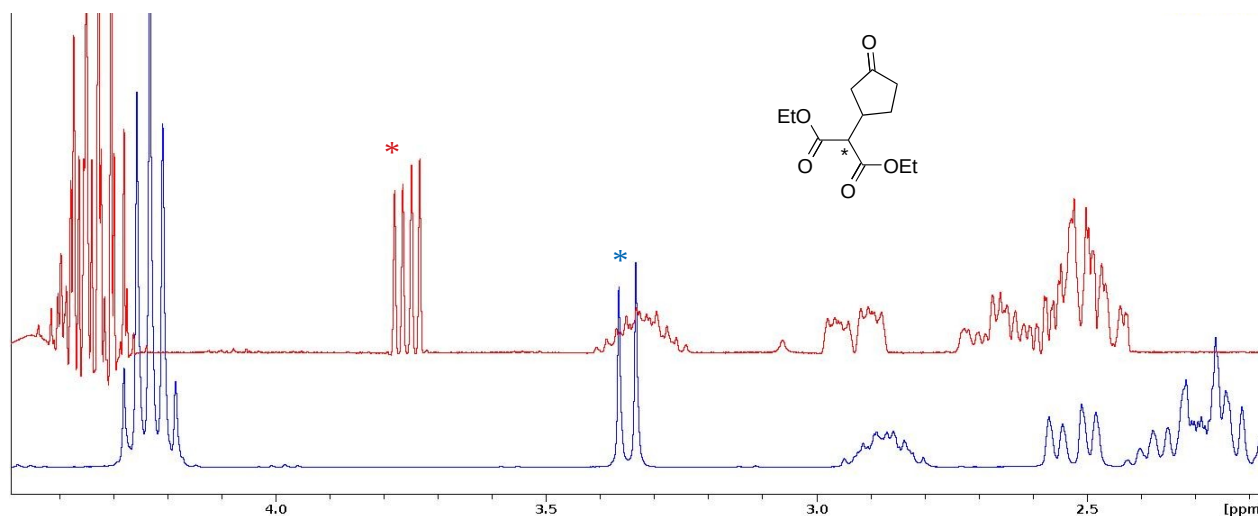
## Results and discussion

The students performed these experiments by pair. Preparation of the catalyst was realized by adding a commercially available solution of  $\text{LiAlH}_4$  (1M in THF) onto a solution of (S)-BINOL (2,2 equiv.) in THF, under  $\text{N}_2$  atmosphere. The addition have to be dropwise at  $0^\circ\text{C}$ , since the reaction led to formation of  $\text{H}_2$ . In order to limit further reduction reaction of cyclopentenone, (S)-BINOL is in slight excess. The medium was allowed to warm to room temperature and stirred for 30 min. During this step, no change in reaction medium was observed. The solution was used as it for Michael addition.

At room temperature, was added dropwise diethyl malonate (5 equiv.) then cyclopentenone (5 equiv.). Reaction medium was then heated to reflux for 2 hours. During heating, the medium turned slowly to orange. After classical work-up procedure, students obtained only two visible products on TLC : BINOL from catalyst degradation and the desired product. Usual work up procedures, followed purification by silica gel chromatography using 80/20 mixture of cyclohexane/ethyl acetate, led to product **3** with often (S)-BINOL traces. The isolated yields were quite low (about 30 %), because of delicate purification.

Fortunately, chemical shifts of hydrogens of **3** (between 1,5 ppm to 4,2 ppm) are very distinct of from those of (S)-BINOL (aromatic regions, between 7,1 ppm to 8 ppm). It allowed students to identify correctly the product by  $^1\text{H}$  NMR even if the purification was not perfect. No other impurities were observed, and the absence of peaks which can be attributed to  $\text{sp}^2$  C-H, confirmed total conversion and perfect regioselectivity of Michael addition.

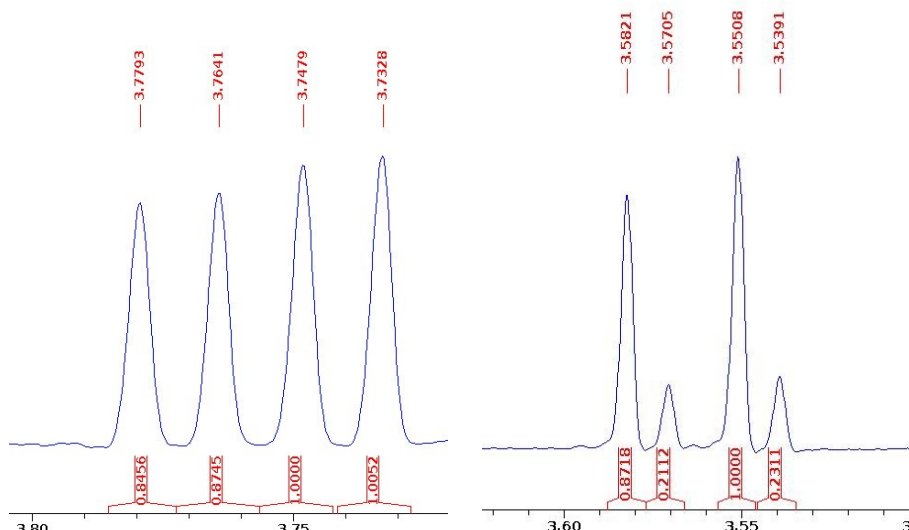
The polarimetric measurements were performed with a Laurent polarimeter, but required solutions of pure product **3**, with no traces of other chiral compounds. Students who didn't obtain pure fraction of **3** weren't able to perform it. In contrast, all students were able to determine the enantiomeric excess of their product with  $^1\text{H}$  NMR with  $\text{Eu}(\text{hfc})_3$ . We observed particularly a big change in chemical shift of the proton of the central carbon of diethylmalonate chain (Figure 5). With racemic compound **3** which was produced by the same protocol with racemic BINOL (not realized by students), the initial doublet without  $\text{Eu}(\text{hfc})_3$  at  $\delta \sim 3,45$  ppm turned in a doublet of doublet at  $\delta \sim 3,75$  ppm.



**Figure 5 :**  $^1\text{H}$  NMR (300 MHz) spectra of racemic product **3**. in blue, 27 mg of **3** without  $\text{Eu}(\text{hfc})_3$  in  $\text{CDCl}_3$  (0,5 mL). In red 24 mg of **3**, 12 mg of  $\text{Eu}(\text{hfc})_3$  in  $\text{CDCl}_3$  (0,5 mL). Stared peaks correspond to hydrogen in stared carbon in **3**.

Enantiomeric ratio was directly determined by peak integration. Because of a roof effect at these signals, we can notice a very little difference even with the racemic product (**Figure 6**). Students

found enantiomeric ratios between 3 : 1 and 5 : 1. From an educational point of view, they are very good ratios, since peaks differences are really noticeable and peaks integrations don't suffer of bad signal-to-noise ratio we would obtain with better enantioselectivity.



**Figure 6 :** Left : integration of dedoubled signals of racemic **3** with  $\text{Eu}(\text{hfc})_3$ . 1:1 ratio is expected. Right : integration of dedoubled signals of **3** with  $\text{Eu}(\text{hfc})_3$  by students. Enantiomeric ratio 1:0.23.

The major problems encountered by students during this session were about the purification steps. Expected good isolated yields were never reached, since the major recovered fraction was composed by (S)-BINOL and product **3** mixture. Although, as noticed before, even a poor purification led to perfectly understandable  $^1\text{H}$  NMR spectra. (see Figure S8 and S9)

The use of  $\text{Eu}(\text{hfc})_3$  required to be cautious. Students first realized  $^1\text{H}$  NMR without CLSR (about 30 mg of **4** by sample in  $\text{CDCl}_3$ ). Then they added very small portion  $\text{Eu}(\text{hfc})_3$  (5-12 mg) to obtain good splits of NMR signals. Some of them added too much CLSR, and their new spectra were illisibles (paramagnetic  $\text{Eu}^{3+}$  caused large broadening of signals) (see Figure S9 and S10).

Students were enthusiastic to determine enantiomeric excess by  $^1\text{H}$  NMR with CLSR. This methodology appeared to them as a better evidence than polarimetric experiments, especially because impurities do not perturb measurement. They noticed that, for synthesis of new chiral products without available datas, rotation power measurement was totally useless to determine enantiomeric excess. Nevertheless, since their final mixture was levorotary, and thanks to specific rotation power of **3** precedently reported,<sup>6</sup> they found that the configuration of the asymmetric carbon of the major enantiomer was (S).

Discussions were about regioselectivity of Michael addition and mechanistic considerations, enantiomeric excess determination by CLSR techniques, and comparison with chiral HPLC analysis. They discussed also about absolute configuration assignment, which requires other experiments, as derivatization procedures, or X-ray diffraction. Improvement of this procedure (lower temperature, lower quantities of catalyst, recovering (S)-BINOL...) and other asymmetric synthesis methodologies were questioned. 2D NMR experiments (COSY, HSQC, HMBC) were very helpful for  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR signals assignment.

## Conclusion

Michael addition is a classical and old reaction, but it is still widely in use, and it remains a very interesting step in multistep organic synthesis thanks to its great regioselectivity, its atom economy,

6 Z. Jiang, W. Ye, Y. Yang, C.-H. Tan *Adv. Synth. Catal.* **2008**, 350, 2345-2351.



and the use of chiral catalysis to transform it in a very good stereoselective reaction. During this session, third-year and fourth-year students had to enforce the addition of a classical nucleophilic reagent, the diethylmalonate, on cyclopentenone with a chiral Lewis acid catalysis. They used classical techniques in organic synthesis and characterization, but it was the first time they enforce enantiomeric excess determination by  $^1\text{H}$  NMR with chiral lanthanide shift reagent. This experiment was the perfect occasion to make connections between theoretical courses about asymmetric synthesis and practical implementation of such a synthesis.

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The author declares no competing financial interest

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