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Asymmetric Michael Addition of Carbonyl Compounds to Nitro-olefins Catalyzed by Simple Organocatalysts

By

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Declaration

I herewith declare that this thesis is my own work and that I have used only the sources listed. No part of this thesis has been accepted or is currently being submitted for the conferral of any degree at this university or elsewhere.

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Dedication

This dissertation is dedicated to my late father, Mian Hazrat Rome, without his moral support and encouragement I could not come so far to do my highest degree in my academics.

Acknowledgement

- I am ever grateful to Allah, the Creator and the Guardian, and to whom I owe my very existence.

- I would like to thank my supervisor, Professor Thomas Christopher Nugent, for his continuous support, guidance and encouragement throughout my research. His passion for research has always been an inspiration to me and this work would not have been possible without his support.

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- Special thanks to Anja Muller for her valuable technical assistance.

- Last but not least: My parents for their everlasting love and encouragement.

List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
aq.	Aqueous
Ar	Aryl
Bs	Broad singlet (^{1}H-NMR)
BOC	*tert*-Butyl carbamates
*i*Bu	*iso*-Butyl
*n*Bu	*n*-Butyl
conv.	Conversion
$CDCl_3$	Deuterated chloroform
d	Doublet (^{1}H-NMR)
DBSAS	Dodecylbenzenesulfonic acid sodium salt
dd	Doublet of doublet (^{1}H-NMR)
DCM	Dichloromethane
de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*'-Dimethylfomamide
DMSO	Dimethylsulfoxide
δ	Chemical shift (^{1}H-NMR)
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization (Mass spectroscopy)
Et	Ethyl

EtOH	Ethanol
EtOAc	Ethylacetate
GC	Gas chromatography
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
J	Coupling constant (^{1}H-NMR)
m	Multiplate (^{1}H-NMR)
M	Molar
Me	Methyl
min.	Minutes
MS	Mass spectroscopy
MTBE	Methyl-*tert*-butyl ether
MW	Molecular weight
m/z	Mass/charge
m	Meta
NMR	Nuclear Magentic Resonance
o	Ortho
p	Para
PMP	Para methoxyphenyl
Pd-C	Palladium on carbon
Ph	Phenyl
*i*Pr	*iso*-Propyl
nPr	*n*-Propyl

Pt-C	Platinum on carbon
pyr	Pyridine
q	Quartet (1H-NMR)
Ref.	Reference
s	Singlet (1H-NMR)
t	Triplet (1H-NMR)
t-Bu	*tert*-Butyl
tert	Tertiary
temp	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
Ts	Tosyl
TsOH	*p*-Toluenesulfonic acid
t-BuLi	*tert*-Butyllithium
$Ti(O\textit{i}Pr)_4$	Titanium(IV) isopropoxide

Abstract:

Asymmetric Michael addition of carbonyl compounds to nitro-olefins is one of the important carbon-carbon bond forming reactions and especially so when quaternary stereogenic carbons are formed. Over the past decade a large number of organocatalysts have been developed for the asymmetric Michael addition of carbonyl compounds to nitro-olefins. Impressive results have been obtained but many parameters require improvement. For example, stereo inductions, catalyst loading, stoichiometry of starting materials, reaction time, limited substrate scope, etc. I focused on improving these parameters by designing new organocatalysts that incorporated old concepts from outside the field and by introducing new templates based on known concepts from within the field. This manifested itself in a two-prong approach: 1) tertiary-primary diamines and 2) assembled catalysts. The assembled catalysts were found to be superior for the intended goal.

Contents

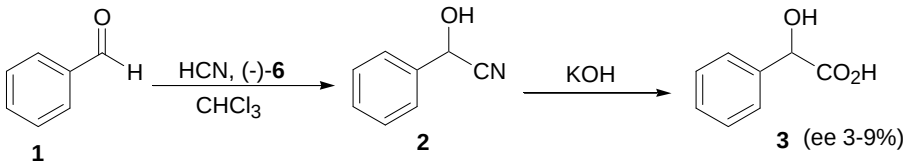
CHAPTER I:

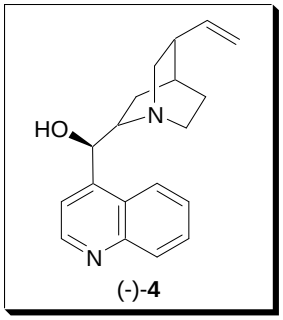
INTRODUCTION

1.1 Organocatalysis

Organocatalysis can be regarded as a chemical reaction which is accelerated by adding substoichiometric amount of an organic molecule in the absence of a metal atom. Recently, this approach has become a popular one for the synthesis of a wide variety of organic molecules.[1-5] The organocatalytic strategy for the synthesis of asymmetric organic molecules was applied for the first time by Bredig and Fiske in 1912.[6] They described the addition of hydrogen cyanide to benzaldeyde catalyzed by natural cinchona alkaloid (-)-Cinchonidine (-)-**4** (Scheme 1). Although the enantioselctivity of the mandelic acid (**3**) that they obtained after hydrolysis of the initially formed benzcyanohydrin (**2**) was very low yet they made it possible to synthesize enantioenriched compounds in the absence of a chiral precursor by using a chiral catalyst (Scheme 1).

Scheme 1. *First asymmetric organocatlytic reaction catalyzed by* **4**.



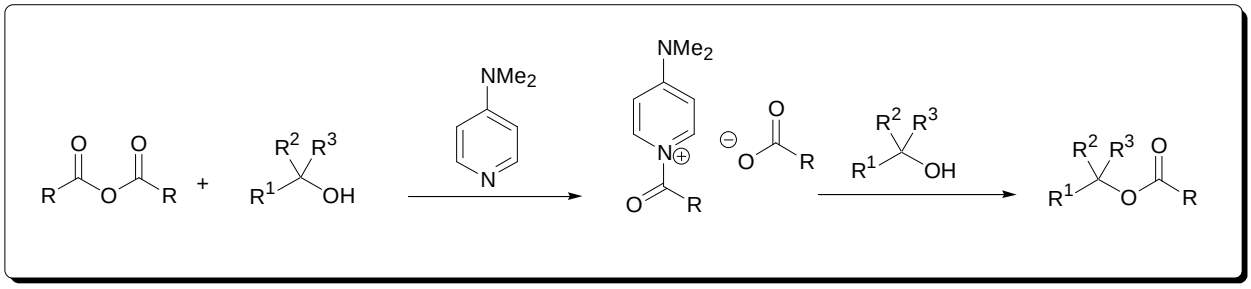


Organocatalysis provides several potential advantages: the catalysts are usually air and room temperature stable, can be inexpensive, are generally considered non toxic in comparison to transition metals, and thus environmentally friendly.[1] Finally if the organocatalyst contains a chiral center, the

catalyzed reaction may become enantioselective. These benefits combined with the possibility of an enantioselective catalytic process, make organocatalysts increasingly attractive in natural product synthesis.

A specific example of organocatalysis is the esterification of alcohol with an anhydride catalyzed by DMAP (4-dimethylaminopyridine) as shown in Figure 1. DMAP is a better nucleophile than alcohol therefore it attacks the acetyl group of anhydride. In the second step the alcohol attacks the DMAP activated acetyl group to form an ester. Behind this simplified explanation is much of the motivation for the current interest in organocatalysis, the possibility of asymmetric organocatalysis. Of the many variations to express this, the following captures the essence: could a chiral DMAP analog allow the kinetic resolution of a racemic alcohol, and if so, could the process compete with or supersede those employing enzymes or metal catalyst.

Figure 1. *Esterification of alcohol catalysed by DMAP.*



1.2 Research goals

- **Amino acid catalyzed asymmetric Michael addition of α-branched aldehyde to nitroalkenes**

  Non covalent interactions may often have a dramatic effect on the transition state of a catalytic system. Amino acids have shown to be poor catalysts for asymmetric Michael addition of aldehydes to nitroolefins. My goal was to evaluate the effect of different hydrogen bonding donors and bases on the amino acid catalyzed Michael addition of aldehydes to nitrostyrenes with the intent to improve a poor catalyst.

- **Pyridyl-primary diamine as an effective catalyst for asymmetric Michael reaction**

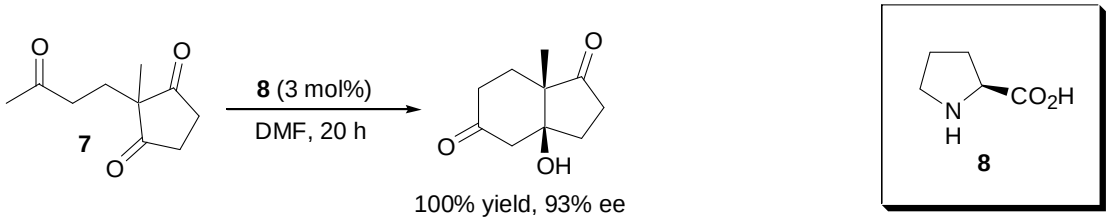
  In the past 10 years, amine based catalysts have been dominated for asymmetric aldol, Michael, Mannich and α-amination reactions. More than 90% of the reported amine-based catalysts are secondary-tertiary diamines, leaving opportunity for the synthesis of perhaps more effective catalysts. My goal was to synthesize organocatalysts based on primary-tertiary diamine template and to find their applications in asymmetric Michael addition of ketones and aldehydes to nitroolefins.

1.3 Enamine Catalysis

Enamine catalysis can be regarded as the electrophilic substitution reaction of α-H atom in carbonyl compounds catalyzed by primary or secondary amines through an enamine intermediate. The enamine intermediate is catalytically generated *via* deprotonation of the iminium ion that is formed initially. The enamine intermediate then acts as a nucleophile attacking the electrophile.

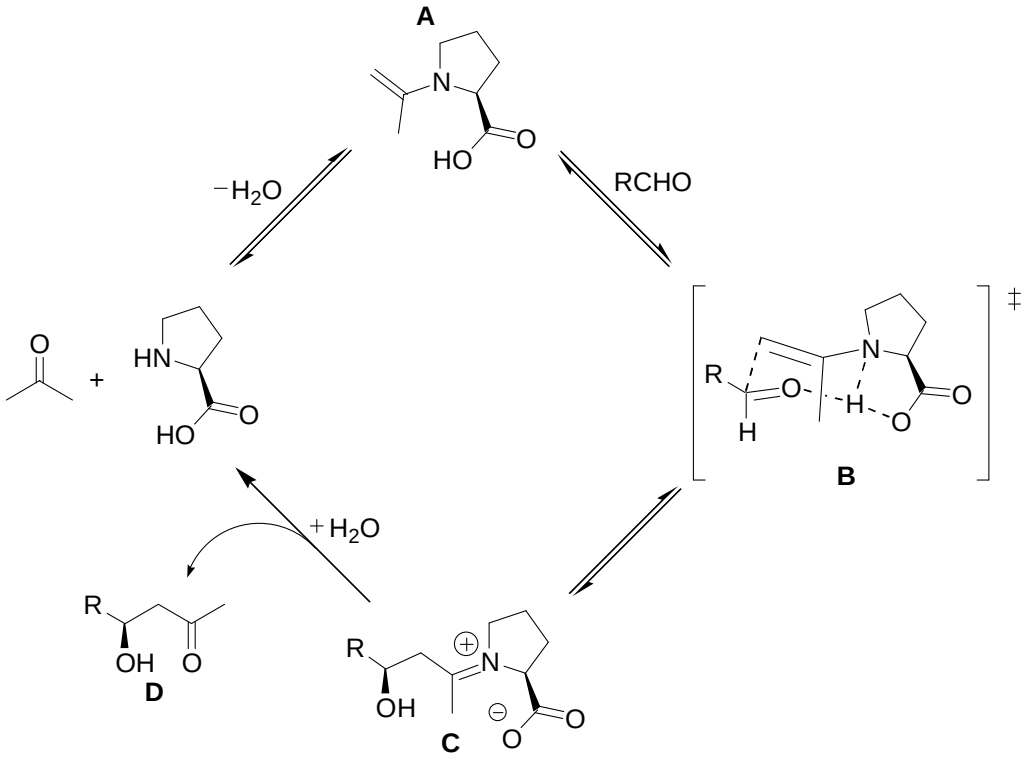
The first useful application of asymmetric enamine catalysis was reported by two industrial groups in the early 1970's.[7] (*S*)-Proline **8** was used to catalyze the enantioselective Robinson annulation of an achiral triketone **7** in quantitative yield (100%) and excellent enantioselectivity (93% *ee*, Scheme 2). This reaction is known as Hajos-Parrish-Eder-Sauer-Wiechert reaction in modern organic chemistry.

Scheme 2. *Proline catalyzed Robinson annulations.*



In 2000, List *et al.* reported the first asymmetric direct intermolecular aldol reaction between acetone and a variety of aldehydes promoted by (*S*)-proline.[8] The author assumed that the reaction occurred via an enamine mechanism as shown in Scheme 3.

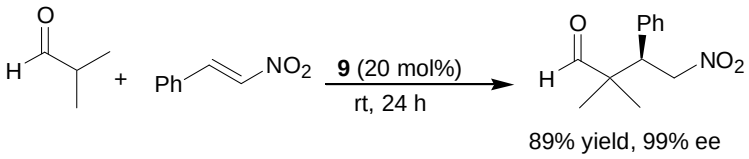
Scheme 3. *Proposed enamine mechanism.*



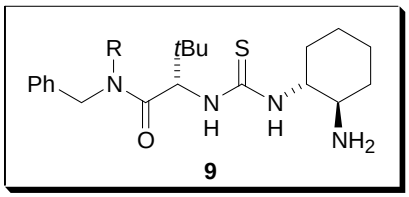
First the secondary amine of (*S*)-proline reacts to form the active enamine intermediate **A**. In the next step, the generated enamine attacks the pre-coordinated aldehyde giving the iminium-aldol intermediate **C**. In the last step intermediate **C** is hydrolysed providing the final product **D**, freeing the catalyst. Transition state **B** in this mechanism resembles the metal-free version of Zimmermann-Traxler-Model.[9]

The reaction mechanism proposed by List *et al.* has been widely accepted. Other examples of organocatalytic reactions proceeding via enamine activation include the Michael reaction,[10-14,33-53] Mannich,[15-23,57-60] α-amination of carbonyl compounds[24-27,] and α-alkylation reactions.[28,29]

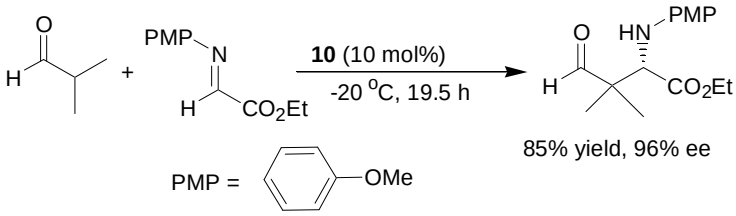
Scheme 5. *Selected example of an* a*symmetric Michael reaction catalyzed via enamine route.*[14]



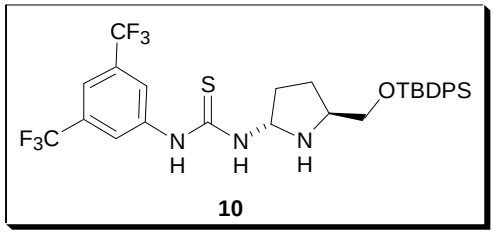
89% yield, 99% ee



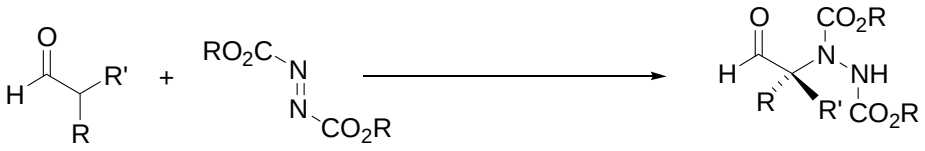
Scheme 6. *Selected example of an* a*symmetric Mannich reaction catalyzed via enamine route.*[23]



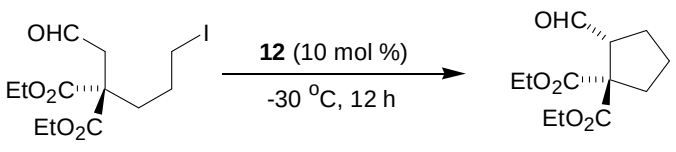
85% yield, 96% ee



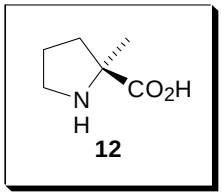
Scheme 7. *Selected example of an* a*symmetric alpha amination catalyzed via enamine route.*[27]



Scheme 8. *Selected example of an* a*symmetric alpha alkylation catalyzed via enamine route.*[29]



92% yield, 95% ee

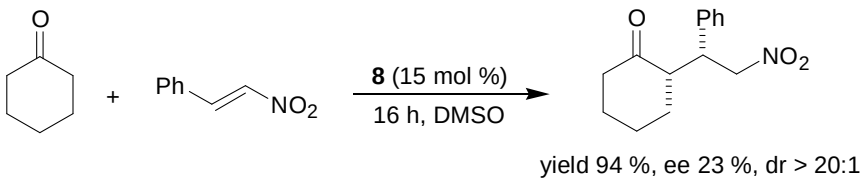


1.4 Enamine catalyzed asymmetric Michael reaction

The Michael addition reaction is regarded as addition of nucleophile to the β position of α, β unsaturated compound. It is one of the important carbon-carbon bond forming reactions and has been widely used in organic synthesis.[30] Over the past decade a large number of chiral organocatalysts have been developed for the enamine catalyzed asymmetric conjugate addition of aldehydes or ketones to different Michael acceptors.

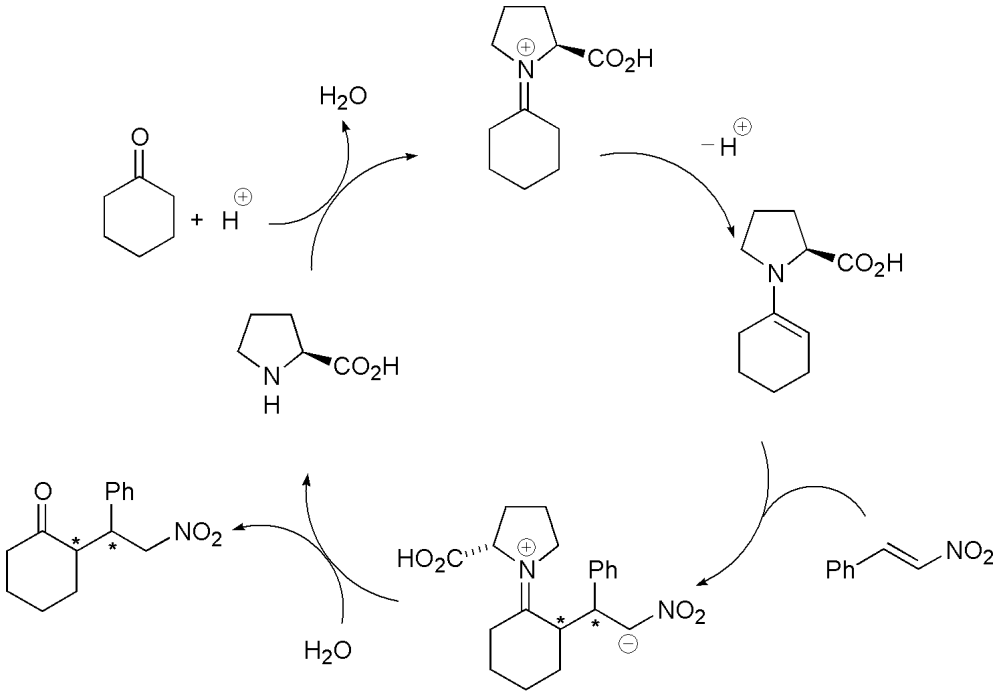
List *et al.* reported the first enantioselective Michael addition of ketones to nitroolefins catalyzed *via* an enamine catalytic route using (*S*)-proline. They got high yield (94%) but the *ee* values were low (Scheme 9)[31]

Scheme 9. *First enantioselective Michael addition of ketones to nitroolefin catalyzed by (S)-proline.*



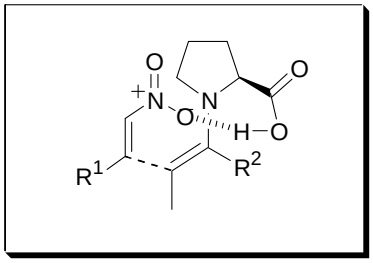
yield 94 %, ee 23 %, dr > 20:1

Figure 2 *Proposed mechanism of Michael reaction.*



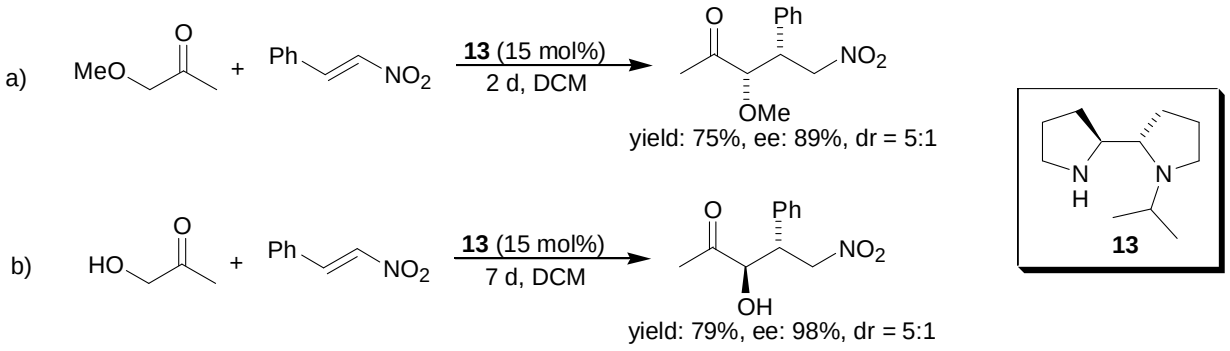
In 2002, Enders *et al.* proposed that the enamine would react with the nitroolefin via a synclinal transition state (Figure 3). This is in consistant with the model proposed by Seebach to explain the *syn* diastereoselectivity and the absolute configuration observed.[32] The partial negative nitro group of the olefin and the partial positive nitrogen of the enamine (developing positive charge) lie in close proximity due to the electrostatic charges. In addition, hydrogen bonding between the carboxylic acid moiety and the nitro group, hold the substrates in such a way that only one diastereorisomer can be formed.

Figure 3. *Proposed transition state of enamine catalyzed conjugate addition of ketones to trans β-nitrostyrene.*



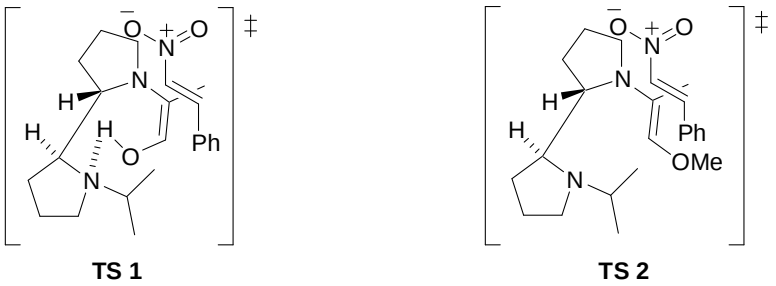
In 2003, Alexakis and co-workers reported the asymmetric Michael addition of α-hydroxy- and α-alkoxycarbonyl compounds to nitroolefins, using a chiral diamine catalyst **13** (Scheme 10a and b).[33] In case of methoxyacetone, the major product obtained was the *syn* isomer whereas in case of hydroxyacetone they unexpectedly observed the *anti* isomer as the major isomer.

Scheme 10: *Inversion of diastereoselctivity with hydroxyacetone.*



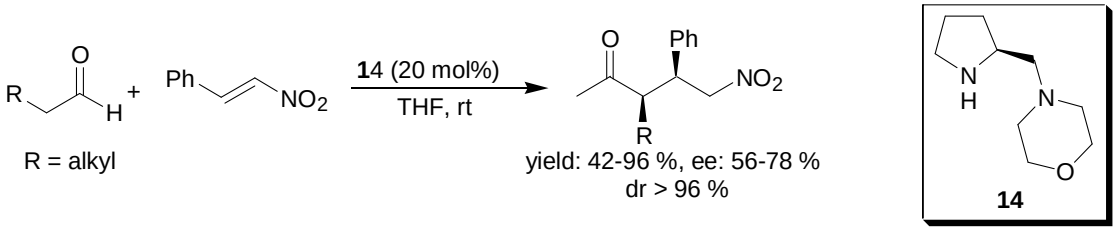
This inversion of diastereoselectivity can be explained by looking at the transition state (Figure 4), where the hydroxyl group of the ketone forms an additional hydrogen bond with the tertiary amine of the catalyst which leads to the *cis* instead of the *trans*-enamine.

Figure 4. *Transition states of the addition of hydroxy and methoxy acetone to trans β-nitrostyrene.*



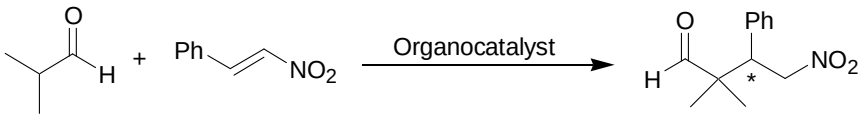
Aldehydes as Michael donors in catalytic asymmetric conjugate reaction with nitroolefin were employed for the first time by Barbas and co-workers (Scheme 11).[34] They got high yield (42-96%), excellent diasteroselectivity (dr > 98:2) and moderate enantioselectivety (56-78%) by using *S*)-2-(morpholinomethyl)-pyrrolidine **39** as catalyst as shown in Scheme 11.

Scheme 11. *Michael addition of aldehydes to nitroolefin.*



α-Branched aldehydes are difficult Michael donors as compared to straight chain aldehydes and have been rarely reported in the literature. Isobutyraldehyde is the most bench mark *α*-branched Michael aldehyde donor examined for the asymmetric Michael addition to nitroolefins (Scheme 12). 24 organocatalysts have been reported by different research groups for the asymmetric Michael addition of isobutyraldehyde to nitroolefins, for example, proline derivatives, thiourea based primary amine, sulfamide based primary amine, lithium salt of amino acids, etc.

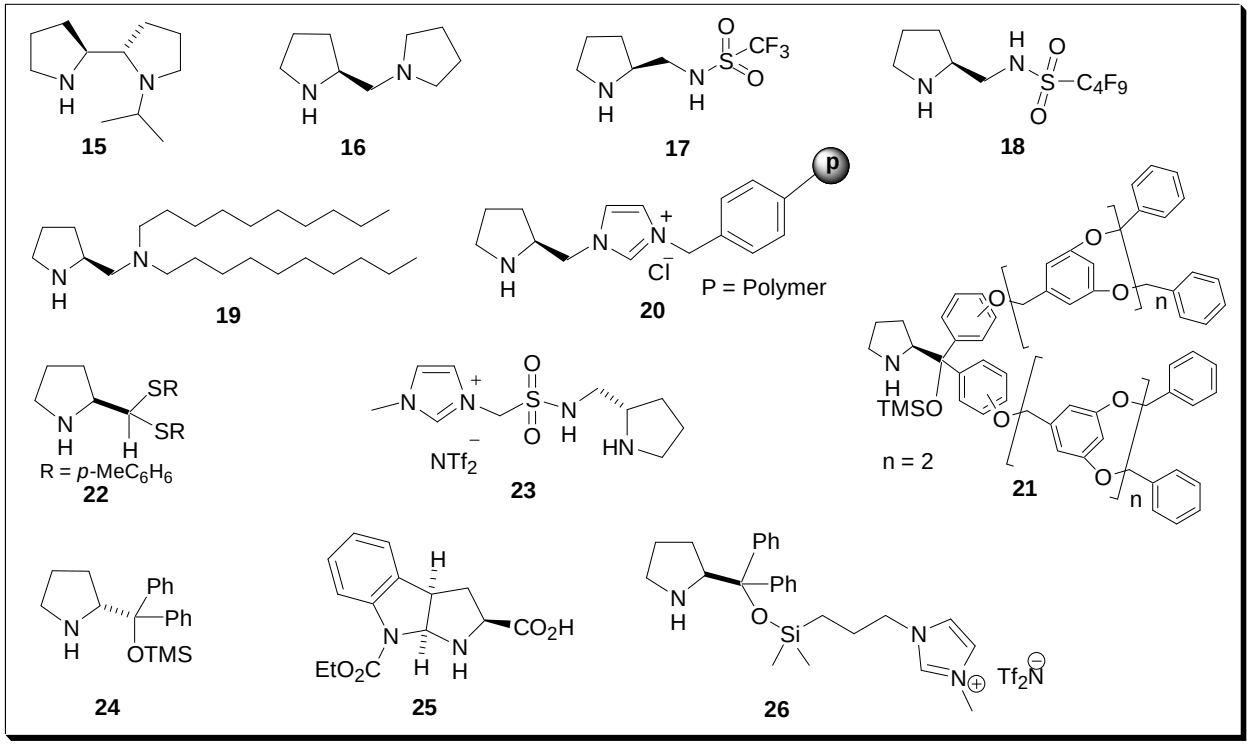
Scheme 12. *Michael addition of isobutyraldehyde to nitrostryrene.*



1.4.1 Organocatalysts based on pyrrolidine ring for asymmetric Michael addition of isobutyraldehyde to nitrostryene

A variety of different organocatalysts, constructed from pyrrolidine ring, has been reported for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene (Figure 5). In 2004, Alexakis and co-workers reported catalyst **15** for the asymmetric Michael addition of various ketones and aldehydes. By using catalyst **15** (15 mol%), the corresponding Michael product of isobutyraldehyde and *trans β- trans β*-nitrostyrene, containing a quaternary center, was obtained after three days in 72% yield and 80% *ee*.[33b]

Figure 5. *Selected organocatalysts based on pyrrolidine ring*.



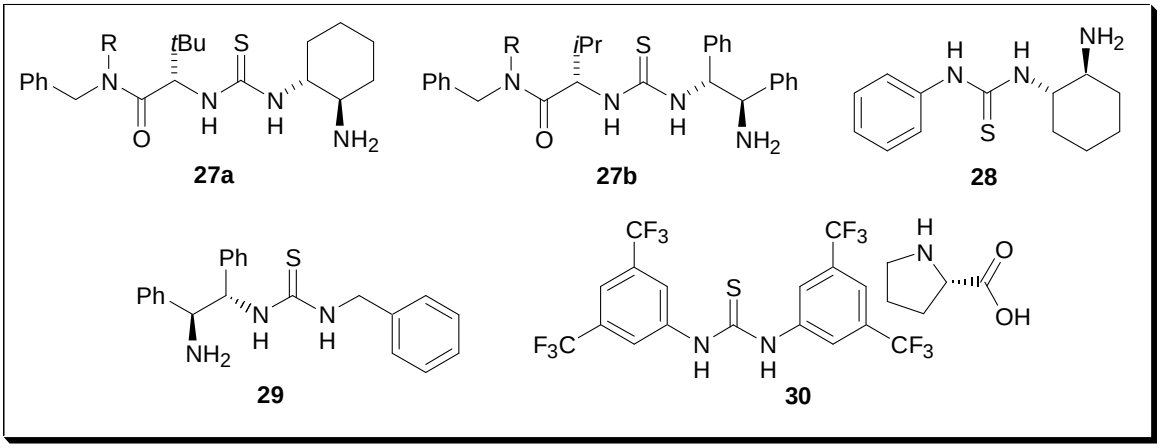
After few months later, Barbas reported catalyst **16** (30 mol%) for the asymmetric Michael addition of various branched aldehydes to *trans* β-nitrostyrene.[35] By using 2 equivalents of isobutyraldehyde, at 4 ^{o}C, the corresponding quaternary Michael product was obtained in 48 hours with 87% yield and 80% *ee*. In 2005, Wang reported pyrrolidine based sulfonamide catalyst **17** for asymmetric Michael addition of different branched and unbranched aldehydes to nitroolefins.[36] They used 20 mol% of the catalyst, 10 equivalents isobutyraldehyde, in 4.5 hours at 0 ^{o}C, they got 85% yield and 90% *ee*. In 2006, they reported a similar catalyst (**18**, Figure 5) and the catalyst loading was improved to 10 mol% for the same reaction.[37] At room temperature, after 18 hours they got 60% yield with 86% *ee*. In 2006, Barbas and co-workers reported pyrrolidine based diamine (**19**, Figure 5), by using 10 mol% of the catalyst, 2 equivalents of isobutyraldehyde, they got 76% yield and 76% *ee* in 30 hours.[38] Pyrrolidine based bulky type catalysts **21** and **22** (Figure 5) have also been reported by Zhao and co-workers in 2006-07 for the asymmetric Michael addition of aldehydes to nitroalkenes.[39,40] Using 10 mol % of **21**, 10 equivalents of isobutyraldehyde, they got 80% yield in 144 hours with 89% *ee*. With 20 mol% of **22**, 3 equivalents of isobutyraldehyde, they got 60% yield in 72 hours with 76% *ee*. Headly in 2008 used 20 mol% of **23,** 6 equivalents of isobutyraldehyde, for Michael addition to *trans* β-nitrostyrene to get 90% the corresponding quaternary product in 72 hours with 84 % *ee*.[41] Ma and co-workers reported 10 mol% of pyrrolidine based bulky type catalyst **24** for the asymmetric Michael addition of isobutyraldehyde (2 equivalents) to *trans* β-nitrostyrene. In 60 hours, they got the resulting Michael product in 97% yield and 92% *ee*.[42]

In conclusion, a range of different organocatalysts based on pyrolidine ring have been reported for the asymmetric Michael reaction. However, drawbacks of low catalytic activity and low substrate scope still remain. Furthermore, the reaction times are long and the reactions typically require a high catalyst loading (10-30 mol%).

1.4.2 Thiourea based organocatalysts for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene

Over the past decade, a variety of thiourea based chiral organocatalysts have been reported by different research groups for the asymmetric Michael addition of aldehydes/ketones to nitroalkenes and mechanistically similar enamine catalyzed asymmetric transformations e.g. Aldol reaction, Mannich reaction etc. Thiourea based organocatalysts that have been reported for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene are shown in Figure 6. In 2006 Jacobsen and co-workers reported thiourea based chiral primary amine **27** (Figure 6) for highly enantioselective Michael addition of alpha branched aldehydes to nitroalkenes.[43] For isobutyraldehyde addition to *trans β*-nitrostyrene, they used 20 mol% of **27a**, 2 equivalent of isobutyraldehyde and after 24 hours the corresponding quaternary Michael product was obtained in 89% yield and 99% *ee*. In 2009, Zhang *et. al* reported a simple thiourea based organocatalyst **28** (20 mol%) to obtain the quaternary product from the Michael addition of isobutyraldehyde (2 equivalents) to *trans β*-nitrostyrene in 92% yield and 98% *ee*.[44] In 2010, He *et. al* applied 30 mol% of **29** to get the Michael product of isobutyraldehyde (3 equivalents) and *trans β*-nitrostyrene in 77% yield and 99% *ee*.[45] Recently, Demir and co-workers reported Schreiner's thiourea/proline self assembly mediated asymmetric Michael addition of ketones/aldehydes to *trans β*-nitrostyrenes in non polar solvents.[46] In 36 hours, 20 mol% each of Schreiner's thiourea and (*S*)-proline (**30,** Fig. 6) gives the resulting Michael product of isobutyraldehyde and *trans β*-nitrostyrene in 66% yield and 73% *ee*.

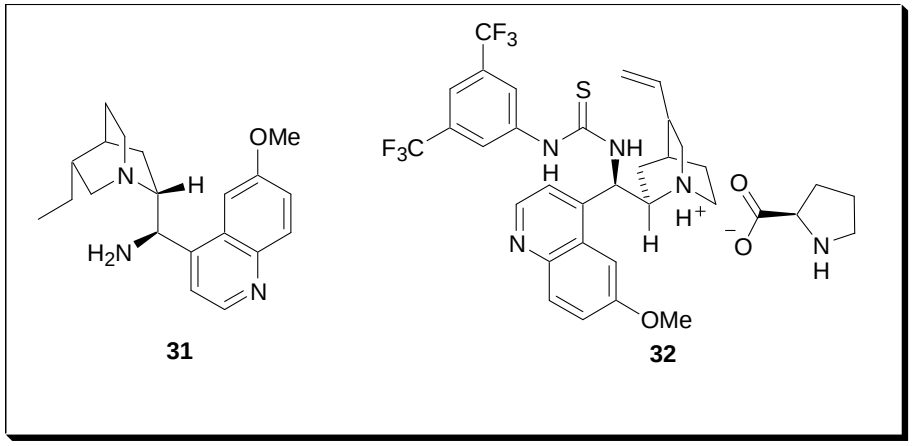
Figure 6. *Selected thiourea based organocatalysts.*



1.4.3 Cinchona alkaloid based organocatalysts for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene

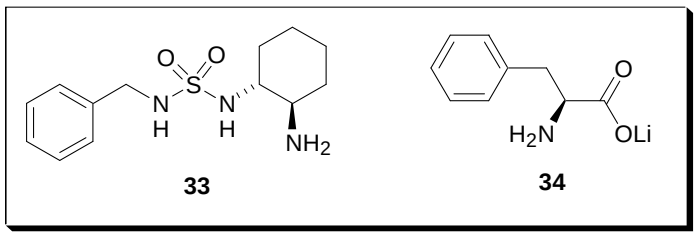
Natural cinchona alkaloids and their derivatives have been successfully applied for effective asymmetric organocatalytic transformations since 1960.[47] In 2007, Connon performed High stereoselective (*ee* 65-99%) Michael-addition of ketones and aldehydes to *α, β* unsaturated nitroolefins catalyzed by cinchona alkaloid derivative **31** in the presence of benzoic acid as cocatalyst.[48] Conjugate addition of isobutyraldehyde (10 equivalents) to trans *trans β*-nitrostyrene was carried out at room temperature, using 10 mol% of **31**, the corresponding quaternary product was obtained after 18 hours in 60% yield and 86% *ee*. In 2008, Zhao and co-workers reported the self assembly mediated organocatalyst for high enantioselective Michael addition of ketones and aldehydes (*ee* 85-99%). He proved via NMR studies that amino acid ligates to the tertiary nitrogen of cinchona alkaloid based thiourea **32** via ionic interaction that acts as bifunctional organocatalyst for the asymmetric Michael reaction. They used 5 mol% each of thiourea and L proline (**32**, Figure 7) for the conjugate addition of isobutyraldehyde (3 equivalents) to trans *trans β*-nitrostyrene to obtain the corresponding Michael product in 71% yield and 85% *ee*.[49]

Figure 7 *Selected cinchona alkaloid based organocatalysts.*



In 2009, Zhang *et. al* reported chiral sulfamide–primary amine bifunctional catalyst **33** (Figure 8) and its application in high enantioselective asymmetric conjugate addition of aldehydes to nitroolefins (*ee* 78-99%).[50] In 3 hours with **33** (20 mol%), 3.67 equivalents of isobutyraldehyde, the corresponding Michael product was obtained in 83% yield and 99% *ee*. Yoshida and co-workers applied lithium salt of phenylalanine **34** (20 mol%, Figure 8) for the asymmetric conjugate addition of aldehydes to nitroalkenes. The corresponding quaternary product from the Michael addition of isobutyraldehyde (2.75 equivalents) to *trans β*-nitrostyrene was obtained in 72% yield and 98% *ee* in 72 hours.[51]

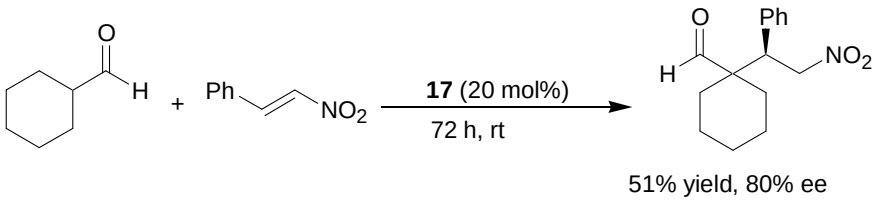
Figure 8. *Miscellaneous organocatalysts for asymmetric Michael addition of aldehydes to nitroolefins.*



1.5 Asymmetric Michael addition of different α-branched aldehydes to *trans β*-nitrostyrene

Despite of the fact that large numbers of chiral organocatalysts have been successfully applied for the asymmetric Michael addition of aldehydes and ketones to nitroolefins, only few research groups have reported cyclohexanecarboxaldehyde as Michael donor. In 2004, Barbas and co-workers performed the asymmetric Michael addition of cyclohexanecarboxaldehyde to *trans β*-nitrostyrene catalyzed by 30 mol% pyrrolidine derivative **16** in the presence of 30 mol% of trifluoroacetic acid. The reaction was carried out at 4 ^{o}C and in 96 hours they got 90% yield and 59% *ee*.[52] In 2006 Wang *et al.* got 64% *ee* and 42% yield in 4 days at 0 ^{o}C, by using 20 mol% of **17** and 10 equivalents of cyclohexanecarboxaldehyde.[37] In 2010, Wang and co-workers reported thiourea based catalyst and the ee was improved to 80% with 51% yield (Scheme 13a).[53]

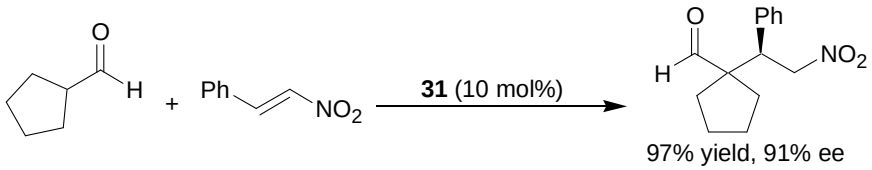
Scheme 13a. *Asymmetric Michael addition of cyclohexanecarboxaldehyde to trans β-nitrostyrene.*



51% yield, 80% ee

Cyclopentanecarboxaldehyde have been reported by few research groups. The best result was achieved by Conon in 2007 (Scheme 13 b).[48]

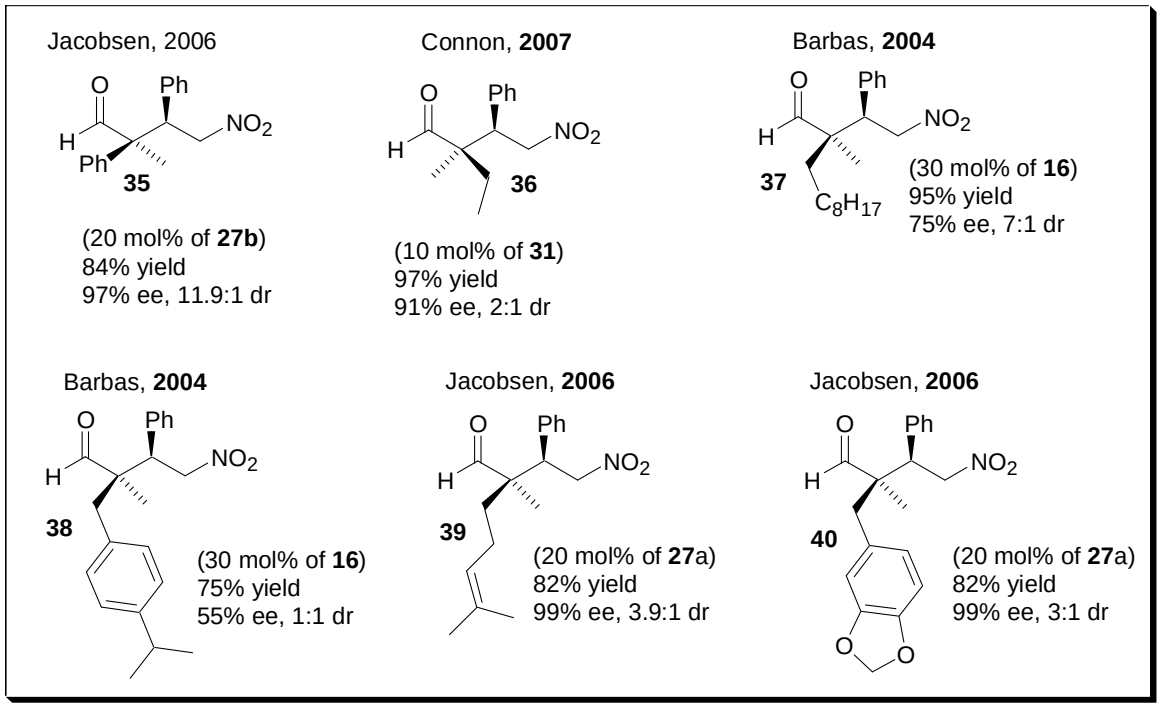
Scheme 13 b. *Asymmetric Michael addition of cyclopentanecarboxaldehyde to trans β-nitrostyrene.*



97% yield, 91% ee

2-Substituted aldehydes that lead to the formation of quaternary stereogenic center have rarely been used as Michael donors in the asymmetric conjugate additions to nitroolifens . The best result with some of these aldehydes has been summarized in Fig. 9.

Figure 9. *Selected Michael products of the addition of α-branched aldehydes to trans β-nitrostyrene having stereogenic quaternary centers.*



1.6 Asymmetric Mannich reaction of α-branched aldehydes

Mannich reaction is an important C-C bond forming reaction in organic chemistry which represents an addition of nucleophilic molecules to the *C=N* double.[54-56] Over the past decade a large number of chiral organocatalysts have been applied for the asymmetric Mannich reaction of straight chain and branched aldehydes. Only few research groups have reported the asymmetric Mannich reaction of N-p-methoxyphenyl (PMP)-protected *α*-iminoglyoxylate **41** with α-branched aldehydes. The different catalysts reported for the asymmetric Mannich reactions are shown in Fig. 10.

Scheme 14. *Asymmetric Mannich reaction.*

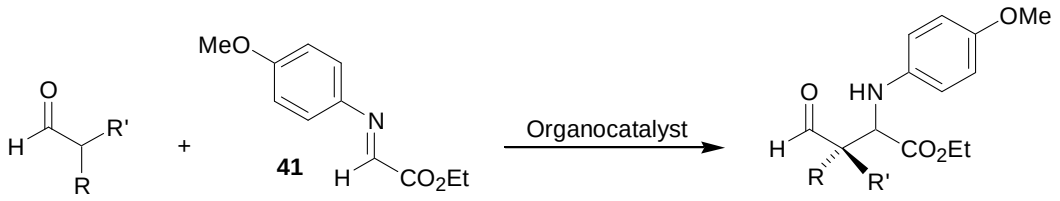
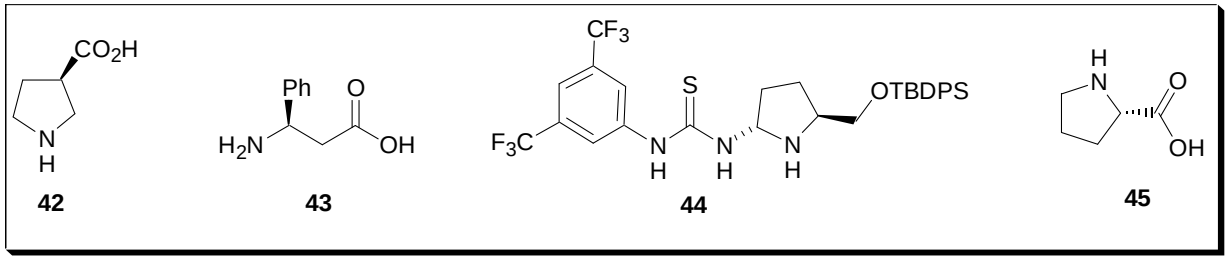


Figure 10. *Catalysts for Mannich-type reaction of N-p-methoxyphenyl (PMP)-protected iminoglyoxylate with isobutyraldehyde.*



Only two reports are available for the asymmetric Mannich reaction of aldimine **41** with isobutyraldehyde **46** till todate.[56,57] Pauliquen *et al.* got 76% yield and 92% *ee* in 8 hours, by using 2 equivalents of isobutyraldehyde in the presence of 5 mol% of amino acid **43**. Zhang *et al.* achieved 85% yield and 96% *ee* in 19.5 hours, using 5 equivalents of isobutyraldehyde, catalyzed by 10 mol% of proline based thiourea **44**.

The Mannich type reaction of aldimine **41** with selected α,α-disubstituted aldehydes e.g. isobutyraldehyde, cyclohexane carboxaldehyde, cyclopentane carboxaldehyde and hydrotopaldehyde have been summarized in the Table 1.

Table 1. *Enantioselective anti-Mannich reaction of aldimine **41** with α,α-disubstituted aldehydes catalysed by various catalysts.*

Entry	Ald. (Equiv)	Cat. (mol%)	Temp. (°C)	Time (h)	Yield %	Dr	*ee* %
1[57]	 (5)	**44** (5-10)	- 20	19.5	85	-	96
2[58]	 (3)	**43** (5)	0	8	76	-	92
3[57]	 (5)	**44** (5-10)	0	48	66	-	96
4[58]	 (3)	**43** (5)	0	8	73	-	60
5[58]	 (3)	**43** (5)	-10	20	79	-	97
6[58]	 (3)	**43** (5)	0	3	92	-	99
7[59]	 (1.5)	**45** (30)	25	48	85	-	55
8[59]	 (1.5)	**45** (30)	25	6	94	-	98
9[59]	 (1.5)	**45** (30)	25	6	66	85:15	86/25
10[60]	 (2)	**42** (10)	25	1	99	36:64	24/37

1.7 α-Amination of α-branched aldehydes

Asymmetric α-amination, introduction of nitrogen electrophiles into the α-position of carbonyl compounds, is important C-N bond forming reaction in organic synthesis. The corresponding optically active nitrogen containing compounds are important building blocks for a variety of valuable synthetic intermediates such as α-amino acids and α-amino alcohols.[61] A large number of organocatalysts have been applied for the asymmetric α-amination of aldehydes[62-72] but only few people have reported the amination of α-branched aldehydes. The organocatalytic asymmetric amination of α-branched aldehydes (Scheme 15) have been summarized in Table 2.

Scheme 15. *α-amination of α,α-disubstituted aldehydes to azodiacarboxylate.*

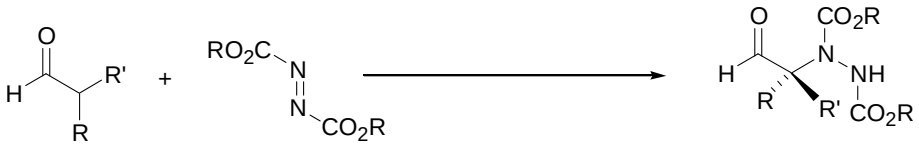


Figure 14. *Catalysts used in the asymmetric α-amination of α,α-disubstituted aldehydes with azodiacarboxylates.*

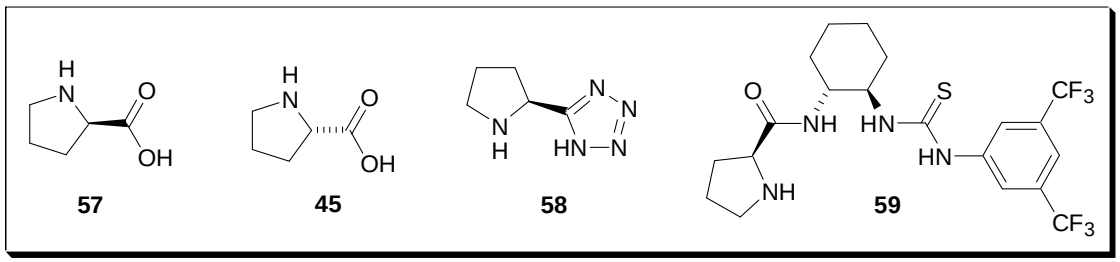
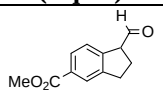
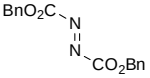
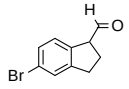
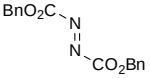
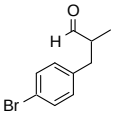
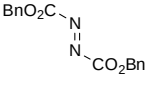
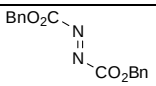
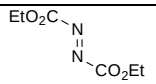
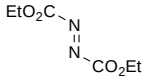
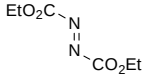
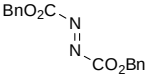
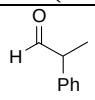
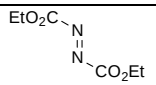
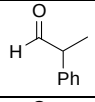
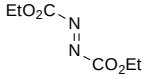
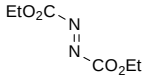
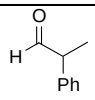
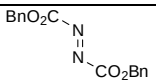


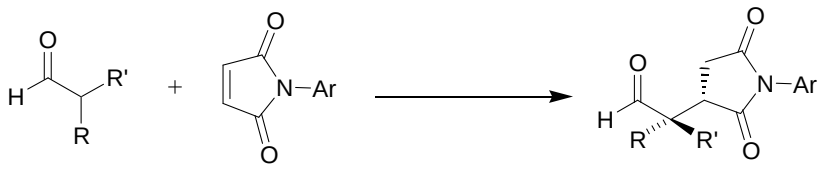
Table 2. *Asymmetric α-amination of α,α-disubstituted aldehydes with azodiacarboxylates.*

Entry	Ref.	Ald. (Equiv)	Azo compd.	Cat. (mol %)	Temp. °C	Time (h/d)	Yield %	*ee* %
1[67]	1	 (1.4)		**57** (20)	25	4h	96	99
2[67]	1	 (1.5)		**57** (20)	25	4h	75	99
3[68]	2	 (1.5)		**58** (15)	25	3h	95	80
4[69]	3	 (1.2)		**45** (50)	25	3d	83	-
5[69]	3	 (1.2)		**45** (50)	25	3d	85	-
6[69]	3,4	 (1.2)		**45** (50)	25	3d	52	28
7[69]	3	 (1.2)		**45** (50)	25	4d	55	-
8[69]	3	 (1.2)		**45** (50)	25	4d	51	-
9[70]	5	 (1.5)		**59** (10)	0	23h	96	96
10[71]	6	 (1.5)		**45** (50)	60 (micro wave 200W)	1 h	99	84
11[72]	4	 (1.5)		**45** (50)	25	3d	62	80
12[72]	4	 (1.5)		**45** (50)	25	3d	83	81

1.7 Asymmetric Michael addition of α-branched aldehydes to maleimides

Maleimide have also been reported as Michael donors in the Asymmetric Michael addition reactions. The Michael addition of α,α-disubstituted aldehydes to maleimides (Scheme 16) can be summarized in Table 3. The different organocatalysts used for Michael addition of α-branched aldehydes to maleimides are shown in Figure 16.

Scheme 16. *Asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides.*



Ar = Ph (**60**)
Ar = Bn (**61**)

Figure 16. *Catalysts used for Asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides.*

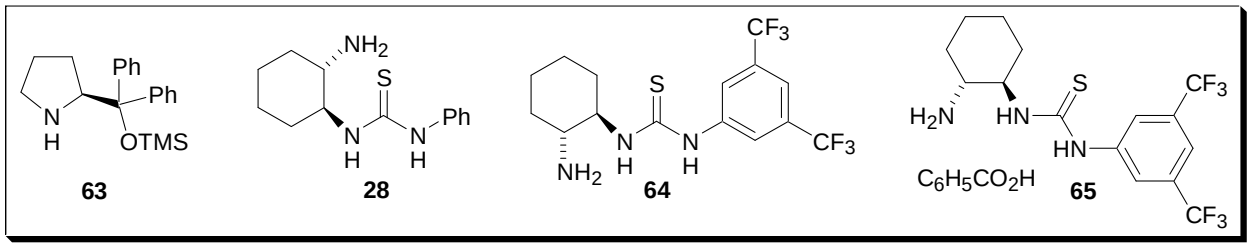
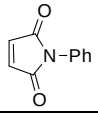
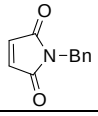
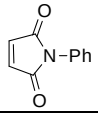
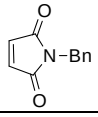
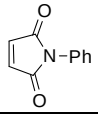
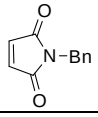
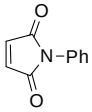
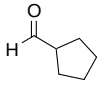
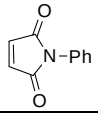
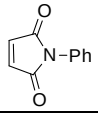
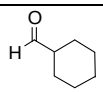
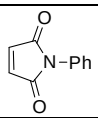
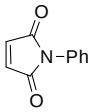
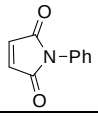
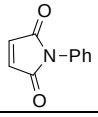
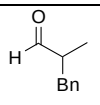
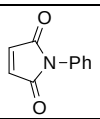
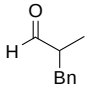
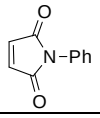


Table 3. *Asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides.*

Entry	Ald. (Equiv)	Maleimide	Cat. (mol%)	Temp. (°C)	Time (h)	Yield %	dr	*ee*%
1[73]	 (2)		**28** (1)	25	22	87	-	97
2[73]	 (2)		**28** (1)	25	18	91	-	99
3[74]	 (2)		**64** (5)	25	6	98	-	99
4[74]	 (2)		**64** (5)	25	6	98	-	99
5[75]	 (2)		**65** (10)	25	1	96	-	99
6[75]	 (2)		**65** (10)	25	1	97	-	99
7[76]	 (2)		**63** (10)	25	24	40	-	51
10[73]	 (10)		**28** (15)	25	6	69	-	96
11[74]	 (2)		**64** (5)	25	6	55	-	98
13[75]	 (2)		**11** (10)	25	5	97	-	98
14[73]	 (8)		**28** (15)	25	12	72	-	95
15[75]	 (2)		**65** (10)	25	3	95	-	98
17[75]	 (2)		**65** (20)	35	36	90	8:1	91

18[73]	 (2)		**28** (5)	25	70	79	2.3:1	98
19[74]	 (2)		**64** (5)	25	6	85	1:1	93/94

1.8 Asymmetric Michael addition of α,α-disubstituted aldehydes to sulphones and phosphonates

Sulphones and phosphonates (Figure) have also been reported as Michael acceptors in asymmetric organocatalytic Michael reaction (Scheme). Different catalysts used in the asymmetric Michael addition of α,α-disubstituted aldehydes to sulphones and sulphonates are shown in Fig. 18.

Scheme 17. *Asymmetric Michael addition of α-branched aldehydes to maleimides.*

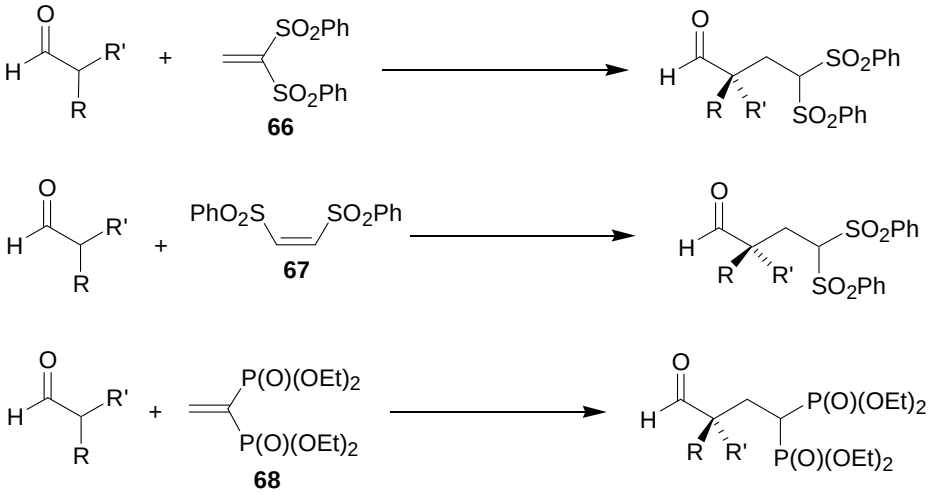


Figure 18. *Catalysts used in the asymmetric Michael addition of α-branched aldehydes to sulphones and sulphonates.*

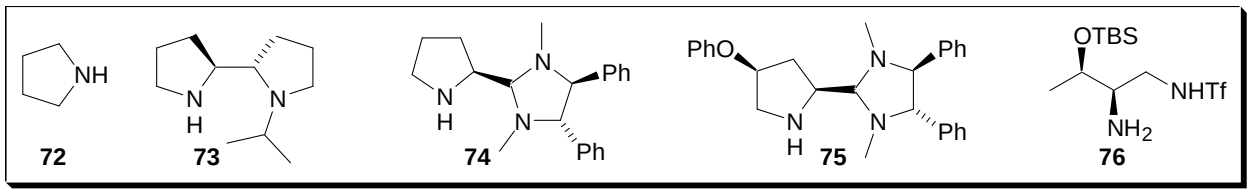
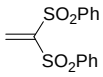
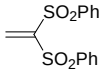
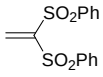
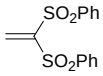
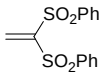
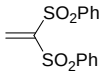
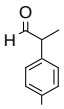
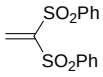
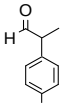
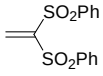
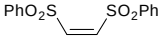
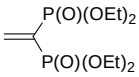


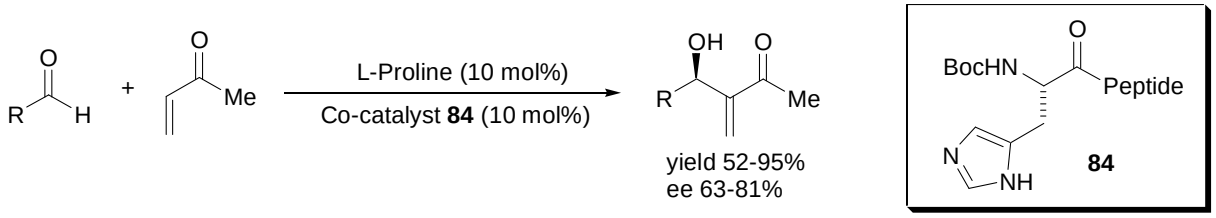
Table 4. *Asymmetric Michael addition of α,α-disubstituted aldehydes to sulphones and sulphonates.*

Entry	Ald. (Equiv)	Unsat. Sulph./Phosph.	Cat. (mol%)	Temp. (°C)	Time (h)	Yield %	*ee*%
1[77]	 (10)		**72** (50)	25	1	73	-
2[77]	 (10)		**73** (25)	25	4	59	12
3[77]	 (10)		**73** (25)	25	7	14	0
4[78]	 (10)		**74** (10)	25	4	84	16
5[79]	 (5)		**75** (5)	25	1.5	81	73
6[79]	 (5)		**75**(5)	25	17	53	83
7[80]	 (2)		**76** (5)	25	12	93	81
8[80]	 (2)		**76** (5)	25	12	90	75
9[81]	 (5)		**74** (20)	25	17	76	30
10[82]	 (10)		**72** (20)	25	24	80	-

1.9 Cooperative organocatalysis

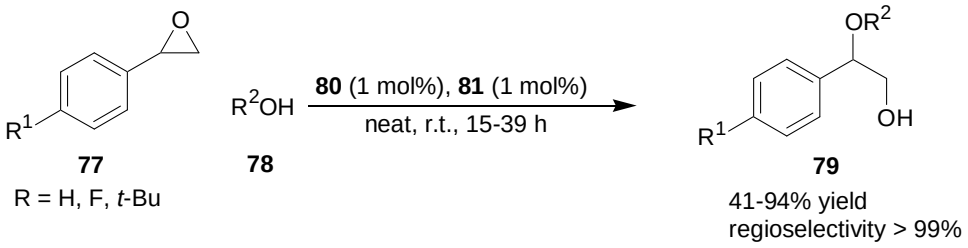
Addition of additive/co-catalyst (small, neutral, organic molecules capable of binding or activating either catalyst or substrates or both via noncovalent interactions particularly H-bonding) can be crucial for enhancing the reactivity and/or stereoselectivity of the catalytic system. For example, it has been shown that the addition of small amount of water often enhances both the reactivity and enantioselectivity of proline catalyzed aldol reaction.[83-90] In 2003, Miller and co-worker reported that nucleophile loaded peptide acts as a co-catalyst for proline catalyzed asymmetric ketone-based Baylis-Hillman reaction Scheme 18.[91] Both of the components were ineffective in term of reactivity and enantioselctivity. Their combination leads to the Baylis-Hillman products in yields 52-95% and *ee* 63-81%.

Scheme 18. *Asymmetric Baylis-Hillman reaction catalyzed by proline/co-catalyst.*

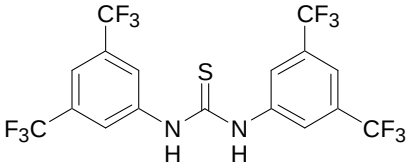


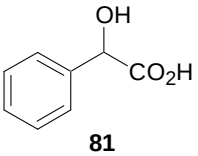
It has been shown by Schriener that the addition of *N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea **38** (1 mol%) allows the mandelic acid (1 mol%) catalyzed non-stereoselective alcoholysis of styrene oxides.[92] Under neat conditions at rt or 50 °C, the corresponding β-alkoxy alcohols were obtained in good yields (41–89%; 15 h–32 h) and in excellent regioselectivity (>99%) at full conversion of the styrene oxides Scheme 19.

Scheme 19. *Cooperative Bronsted acid-type organocatalysis mediated alcoholysis of styrene oxides.*

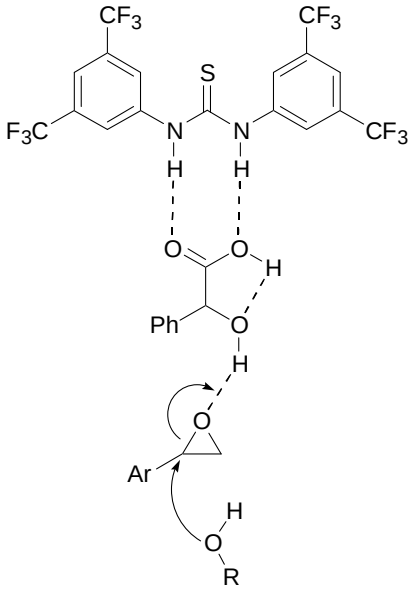


Cooperative Brønsted acid-type organocatalytic system



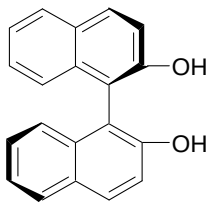


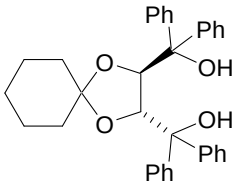
H-bonding mediated
cooperative Brønsted acid catalysis

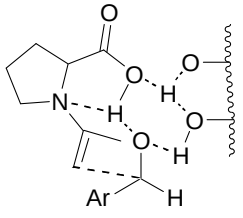


Shan and coworkers have shown that the addition of a chiral diol **82**, **83** (H-bonding source) can improve the enantioselectivity of proline catalyzed aldol reaction Figure 19.[93]

Figure 19. *Shan's hydrogen bond donors acting as co-catalysts.*







CHAPTER 2:

AMINO ACID CATALYZED ASYMMETRIC MICHAEL ADDITION OF ALDEHYDES TO NITROALKENE

2.1 Results and discussion

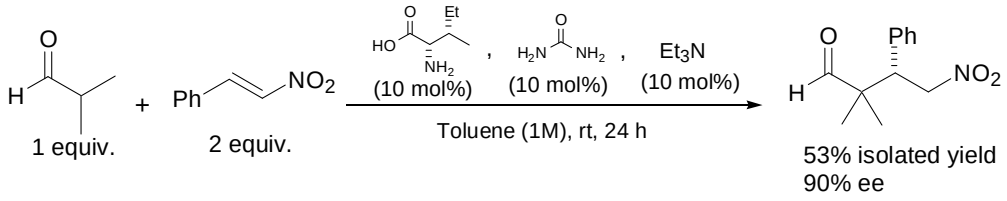
Amino acids, particularly (*S*)-proline, have been successfully applied for a considerable range of asymmetric transformations. However, amino acids show poor catalytic activity towards a considerable range of reactions. Therefore, tremendous research has been carried out to develop amino acid derivatives in order to improve their reactivity and/or stereoselectivity. The carboxylic group of amino acid ((*S*)-proline) has been targeted as a site for modification with intent to enhance its reactivity and selectivity. Therefore, to find an effective organocatalyst, one has to synthesize and screen a library of organocatalysts.

An alternative and simple approach would be the use of additive/co-catalyst in order to enhance the reactivity and or selectivity of the amino acids catalyzed asymmetric transformations. For example, it has been reported that triethylamine enhances the reactivity (92-98%, isolated yield in 3 hours) and selectivity (ee 10-37%) of (*S*)-proline catalyzed Michael addition of aldehydes to *trans β*-nitrostyrenes.[94] DMAP was used as additive for 4,4`-disubstituted (*S*)-proline catalyzed Michael addition of aldehydes to nitrostryrenes with good yield (66-89%), good to high diastereoselectivities (66-96%) and high enantioselectivities (70-95%).[95] Zhao used cinchona alkaloid based bifunctional thiourea for (*S*)-phenylglycine catalyzed Michael addition of ketones and aldehydes to *trans β*-nitrostyrenes.[96] Recently, Demir *et al.* reported hydrogen bonding donor (*N*,*N'*-bis[3,5-(trifluoromethyl)phenyl]thiourea) as co-catalyst for (*S*)-proline catalyzed asymmetric Michael addition of ketones and aldehydes to *trans β*-nitrostyrenes.[97]

Moreover, the self assembly of amino acid with hydrogen bond donors is well known in the presence of base e.g. it has been shown that (*S*)-proline with (thio)urea in the presence of tertiary ammonium hydroxide acts as solvating agent.[98] This prompted me to apply this thiourea-amino carboxylate self-assembly as catalysts for C-C bond formation reaction. In particular, I was interested in the asymmetric Michael reaction, which provides synthetically useful building blocks and has important applications in natural products synthesis. I hypothesized that the base will free the primary amine for enamine catalysis and the carboxylate will ligate to hydrogen bond donor. The resulting self assembly will either allow the *trans* β-nitrostyrene to approach from the less hindered side or to hold the nitro group of the *trans* β-nitrostyrene that will facilitate the cooperative bifunctional catalysis.

To test our hypothesis, I examine 10 mol% each of L-isoleucine (amino acid), triethylamine (base) and simple urea (hydrogen bond donor) for the conjugate addition of isobutyraldehyde (2 equiv) to *trans* β-nitrostyrene (limiting reagent) in toluene (1 M) at room temperature (Scheme 2.1).

Scheme 2.1 *Michael reaction of isobutyraldehyde catalyzed by isoleucine in presence of urea & Et_3N.*



This initial result prompted me to examine different hydrogen bond donors, amino acids and bases for the same reaction. A large number of hydrogen bond donors (Figure 2.1), amino acids (Figure 2.2), bases (Figure 2.3) and different polar and non polar solvents were examined for asymmetric Michael addition of isobutyraldehyde to *trans* β-nitrostyrene.

Figure 2.1 *Hydrogen bond donors screened for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*

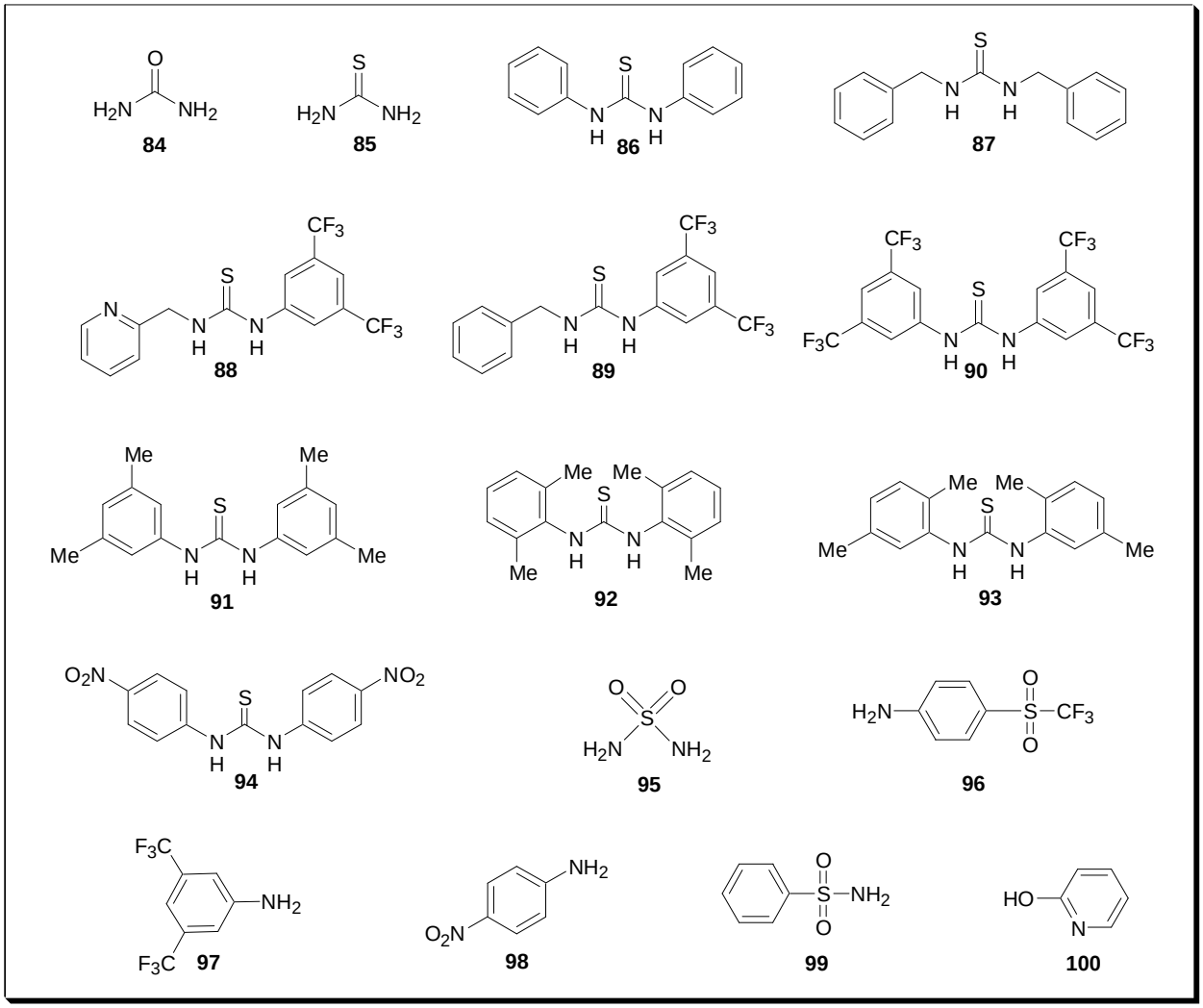


Figure 2.2 *Amino acids and their salts screened for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*

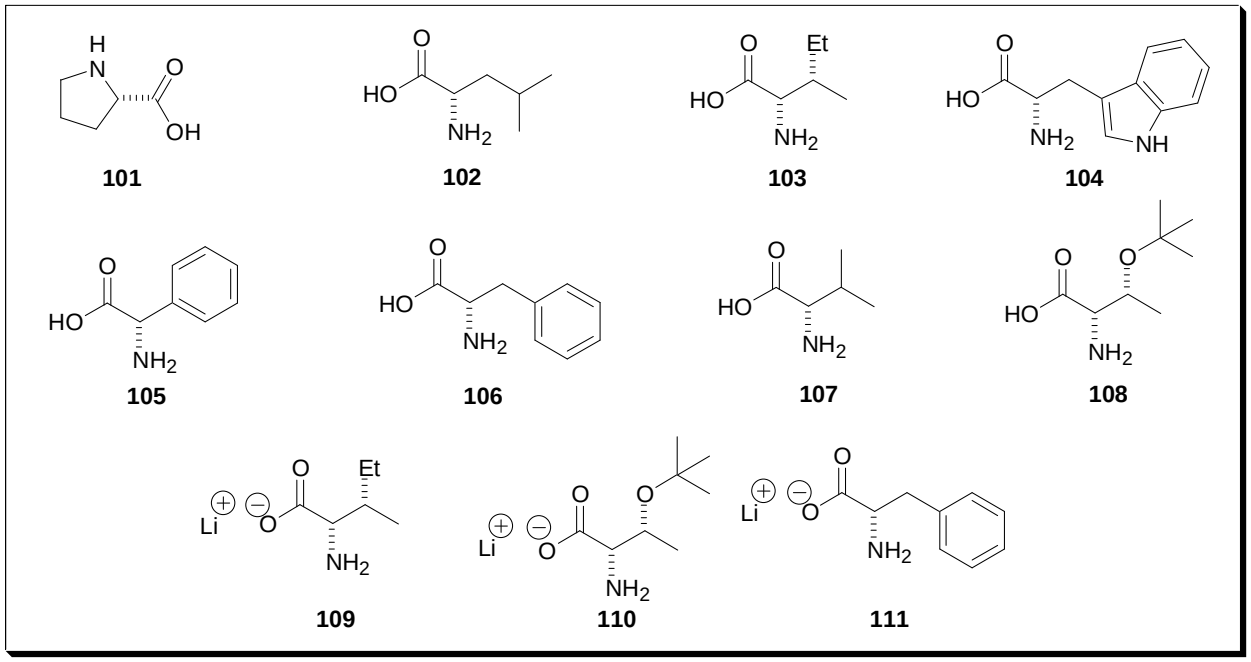
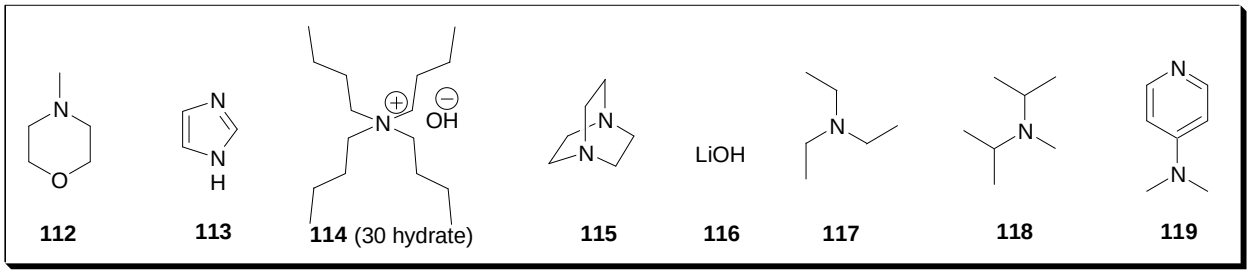


Figure 2.3 *Bases screened for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*

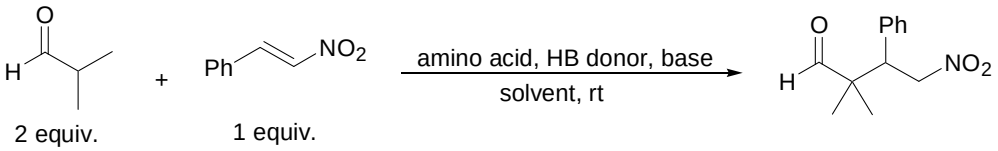


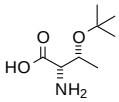
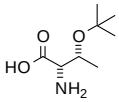
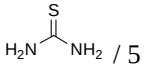
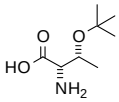
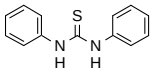
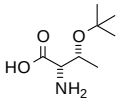
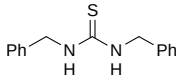
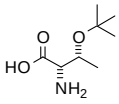
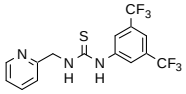
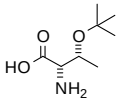
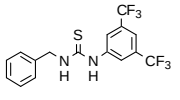
2.1.1 Screening of various thioureas for asymmetric Michael addition of isobutyraldehyde to nitrostyrene.

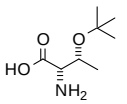
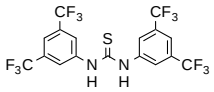
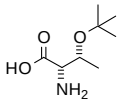
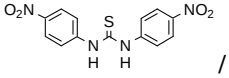
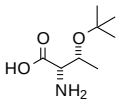
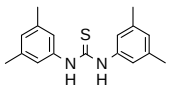
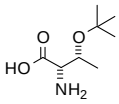
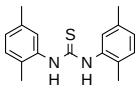
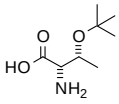
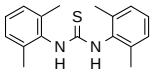
Different thioreas were examined for the asymmetric Michael addition of isobutyraldehyde to *trans* *β*-nitrostyrene catalyzed by L-^{t}butoxy threonine in the presence of DMAP as shown in Table 2.1. In the absence of thiorea only ~5% conversion was observed by HPLC in 7 h (entry 1, Table 2.1). However, in the presence of commercially available simple thioureas (85 & 86, Table 2.1), the

reaction proceeded with excellent rate and moderate enantioselectivity (entries 2 & 3, Table 2.1). Sterically and electronically different thioureas were synthesized and examined for the Michael reaction (entry 3-9, Table 2.1). Schreiner's thiourea was the most effective in terms of both reactivity and selectivity (entry 7, Table 2.1).

Table 2.1 *Screening of thioureas for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*



S No.	Amino Acid / mol%	H. B. donor / mol%	Base / mol%	Solvent (1 M)	Time	Conversion % (hplc)	ee %[a]
1	 / 5	-	DMAP / 5	Toluene	7 h	~8	-
2	 / 5	 / 5	DMAP / 5	Toluene	2 h	95	89
3	 / 5	 / 5	DMAP / 5	Toluene	7 h	90	87
4	 / 5	 / 5	DMAP / 5	Toluene	5 h	20	86
5	 / 5	 / 5	DMAP / 5	Toluene	2 h	75	89
6	 / 5	 / 5	DMAP / 5	Toluene	2 h	75	89

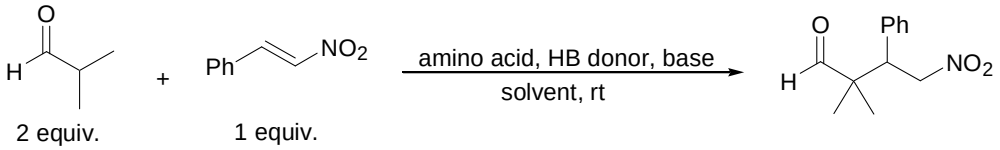
7	 **/ 5**	 **/ 5**	**DMAP / 5**	**Toluene**	**2 h**	**100**	**92**
8	 **/ 5**	 **/ 5**	DMAP / 5	Toluene	5 h	70	82
9	 / 5	 / 5	DMAP / 5	Toluene	5 h	45	83
10	 / 5	 / 5	DMAP / 5	Toluene	5 h	38	82
11	 / 5	 / 5	DMAP / 5	Toluene	5 h	25	82

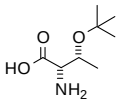
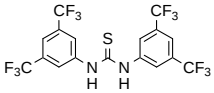
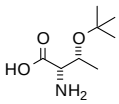
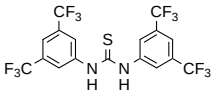
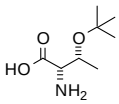
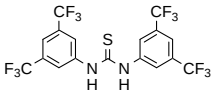
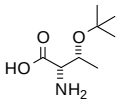
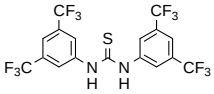
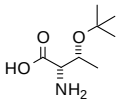
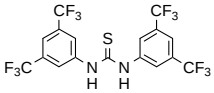
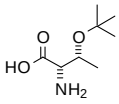
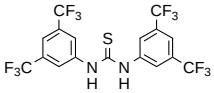
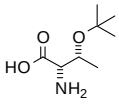
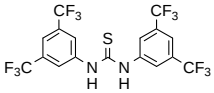
[a] determined by HPCL using chiral cel OD-H column.

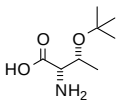
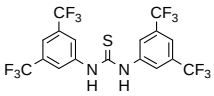
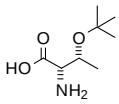
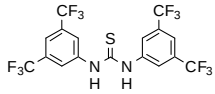
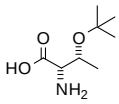
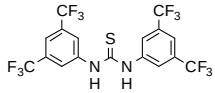
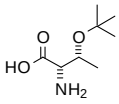
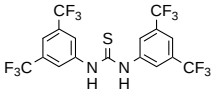
2.1.2 Solvent screening for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene.

A variety of polar and non-polar solvents were examined as shown in Table 2.2. Higher stereoselectivities and reactivitivites were observed with non polar solvents. Cyclohexane and p-xylene were the best in terms of both enantioselectivity and rate of reaction (entries 3 & 8, Table 2.2). To further test the efficiency of our three components catalyst system, 2 mol% each of amino acid **108**, thiourea **90** and DMAP were employed for isobutyraldehyde to *trans β*-nitrostyrene, but the rate of reaction dropped significantly i.e. in 10 hours, 70% conversion by HPLC was observed, however, the stereoinduction was unaffected (entry 9, Table 2.2). However, the reactivity of the reaction was enhanced by the addition of excess DMAP (entry 11, Table 2.2).

Table 2.2 *Solvent screening for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*



S No.	Amino Acid / mol%	H. B. donor / mol%	Base / mol%	Solvent (1 M)	Time	Conversion % (hplc)	ee %[a]
1	 / 5	 / 5	DMAP / 5	Cl-Benzene	2 h	100	90.8
2	 / 5	 / 5	DMAP / 5	n-Hexane	2 h	100	90.8
3	 **/ 5**	 **/ 5**	**DMAP / 5**	**p-Xylene**	**2 h**	**100**	**93**
4	 / 5	 / 5	DMAP / 5	Toluene	2 h	100	92.7
5	 / 5	 / 5	DMAP / 5	Chloroform	2 h	100	86.5
6	 / 5	 / 5	DMAP / 5	Water	5 h	Solid by-product	-
7	 / 5	 / 5	DMAP / 5	Methanol	5 h	Solid by-product	-

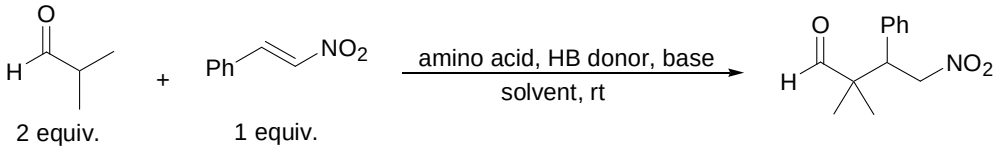
8	 **/ 5**	 **/ 5**	**DMAP / 5**	**Cyclohexane**	**2 h**	**100**	**94**
9	 / 2	 / 2	DMAP / 2	Cyclohexane	10 h	55	94
10	 / 2	 / 2	DMAP / 6	Cyclohexane	3 h	80	94
11	 **/ 2**	 **/ 2**	**DMAP / 8**	**Cyclohexane**	**3 h**	**94**	**94**

[a] determined by HPCL using chiral cel OD-H column.

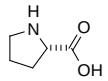
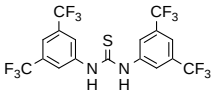
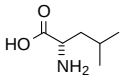
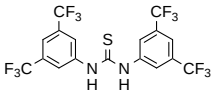
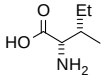
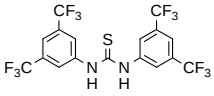
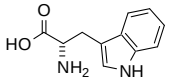
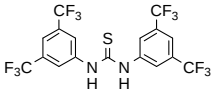
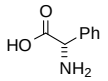
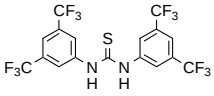
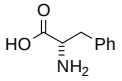
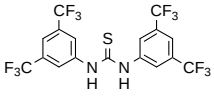
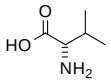
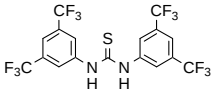
2.1.3 Amino acids screening for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene.

A number of commercially available amino acids were examined for asymmetric Michael reaction of isobutyraldehyde and *trans β*-nitrostyrene as shown in Table 2.3. Highest stereoinduction was observed with isoleucine and phenylalanine (entries 3 & 6, Table 2.3). However, the reaction proceeds at low rate and after 3 h the reaction stops.

Table 2.3 *Amino acids screening for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*



2 equiv. 1 equiv.

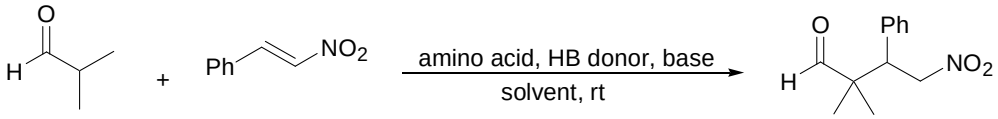
S No.	Amino Acid / mol%	H. B. donor / mol%	Base / mol%	Solvent (1 M)	Time	Conversion % (hplc)	ee %[a]
1	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	52	-43
2	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	16	85
3	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	37	95
4	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	32	85
5	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	10	82
6	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	18	93
7	 / 2	 / 2	DMAP / 8	Cyclohexane	3 h	10	84

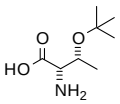
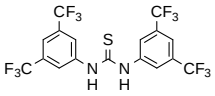
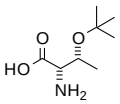
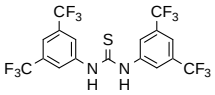
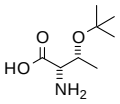
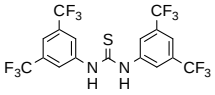
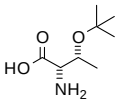
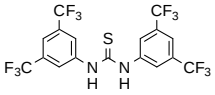
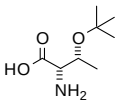
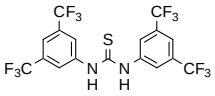
[a] determined by HPCL using chiral cel OD-H column.

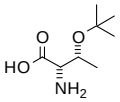
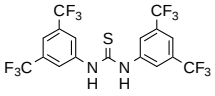
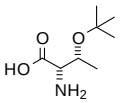
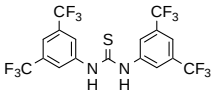
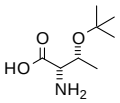
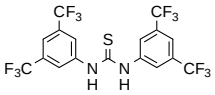
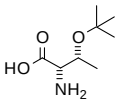
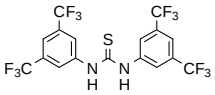
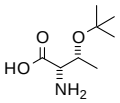
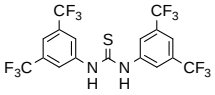
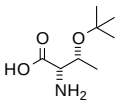
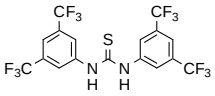
2.1.4 Base screening for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene.

Defferent bases were evaluated for the asymmetric Michael addition of isobutyraldehyde to *trans β*-nitrostyrene. Highest conversion was observed with DBU, however, the enantioinduction was low (entry 8, Table 2.4). DMAP, Et_3N and Hünig's base gave the highest enantioselectivities (entry 1, 9 & 10, Table 2.4).

Table 2.4 *Base screening for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*



S No.	Amino Acid / mol%	H. B. donor / mol%	Base / mol%	Solvent (1 M)	Time	Conversion % (hplc)	ee %[a]
1	 / 2	 / 2	DMAP / 2	Cyclohexane	10 h	70	95
2	 / 2	 / 2	Imidazol / 2	Cyclohexane	10 h	>3	90.8
3	 / 2	 / 2	DABCO / 2	Cyclohexane	10 h	25	94
4	 / 2	 / 2	LiOH / 2	**Cyclohexane**	10 h	10	90.5
5	 / 2	 / 2	LiOH / 2	Tertbutylmethylether	10 h	7	88.5

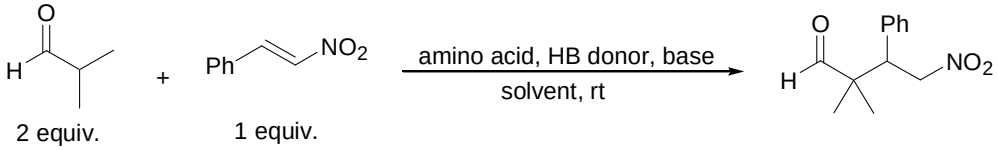
6	 / **2**	 / **2**	LiOH / 2	Tertbutylmethylether + 5 drops of H_2O	10 h	>3	-
7	 / 2	 / 2	Tetrabutylammoniumhydroxide / 2	Cyclohexane	10 h	55	85
8	 / 2	 / 2	DBU / 2	Cyclohexane	10 h	95	80
9	 / 2	 / 2	Triethylamine / 2	Cyclohexane	10 h	50	93
10	 / 2	 / 2	Hünig's base / 2	Cyclohexane	10 h	40	92
11	 / 2	 / 2	N-methyl morpholine / 2	Cyclohexane	10 h	10	96

[a] determined by HPCL using chiral cel OD-H column.

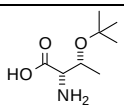
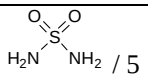
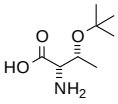
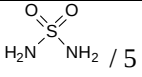
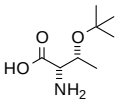
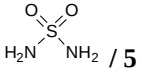
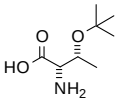
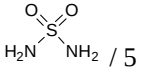
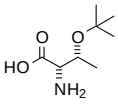
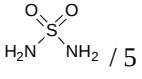
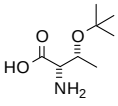
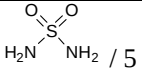
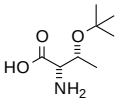
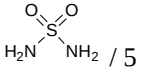
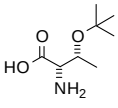
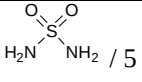
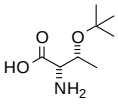
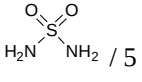
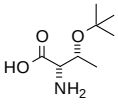
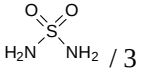
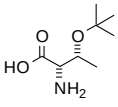
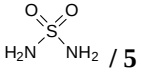
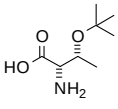
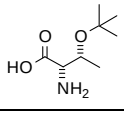
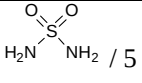
2.1.5 Screening of hydrogen bond donors other than thiourea

A variety of analine derivatives, sulfonamides and sulfamide were examined as hydrogen bond donors for the asymmetric Michael addition of isobutyraldehyde to trans β-nitrostyrene as shown in Table 2.5. It has been observed that commercially available simple (**95**) gave the best stereoinduction, reactivity and excellent conversion (entry 8, Table 2.5). Different solvents were examined with sulfamide and toluene gave the best result in terms of both enantioselectivity and rate of reaction (entry 15, Table 2.5). 1.2 equivalents of isobutyraldehyde was used and the reaction proceeded with excellent rate (7 h, 97% isolated yield) and excellent enantioselectivity (23, Table 2.5)

Table 2.5 *Screening of hydrogen bond donors other than thiourea for Michael addition of isobutyraldehyde to trans β-nitrostyrene.*



S No.	Amino Acid / mol%	H. B. donor / mol%	Base / mol%	Solvent (1 M)	Time	Conversion % (hplc)	ee %[c]
1	/ 5	/ 5	DMAP / 5	Toluene	24 h	95	85
2	/ 5	/ 5	DMAP / 5	Toluene	24 h	100	84
3	/ 5	/ 5	DMAP / 5	Toluene	4 h	23	83
4	/ 5	/ 5	DMAP / 5	Toluene	24 h	60	82
5	/ 5	/ 5	DMAP / 5	Toluene	4 h	36	89
6	/ 5	/ 5	DMAP / 5	Toluene	24 h	78	89
7	/ 5	/ 5	DMAP / 5	Toluene	16 h	No Product	-
8	**/ 5**	**/ 5**	**DMAP / 5**	**Toluene**	**4 h**	**100**	**98**
9	/ 5	/ 5	DMAP / 5	Cyclohexane	8 h	73	98
10	/ 5	/ 5	DMAP / 5	Cyclohexane	20 h	100	98
11	/ 5	/ 5	DMAP / 5	Benzene	6 h	100	98
12	/ 5	/ 5	DMAP / 5	DCM	5 h	100	97

13	 / 5	 / 5	DMAP / 5	Methanol	8 h	Solid by-product	
14	 / 5	 / 5	DMAP / 5	tBut-methylether	8 h	98	97
15	 **/ 5**	 **/ 5**	**DMAP / 5**	**Toluene**	**4 h**	**> 99 [a]**	**98**
16	 / 5	 / 5	DMAP / 5	Chloroform	8 h	98 %	94
17	 / 5	 / 5	DMAP / 5	THF	8 h	80 %	96
18	 / 5	 / 5	DMAP / 5	Water	8 h	Solid by-product	-
19	 / 5	 / 5	DMAP / 5	Acetonitrile	8 h	Solid by-product	-
20	 / 5	 / 5	DMAP / 5	n-Heptane	3.5 h	100	96
21	 / 5	 / 5	DMAP / 5	Toluene	4 h	99 [a]	98
22	 / 3	 / 3	DMAP / 5	Toluene	24 h	86 [a]	97
23 [b]	 **/ 5**	 **/ 5**	**DMAP / 5**	**Toluene**	**7 h**	**97 [a]**	**98**
24 [b]	 / 5	-	DMAP / 5	Toluene	7 h	~5	-
25 [b]	 / 5	 / 5	-	Toluene	7 h	~2	-

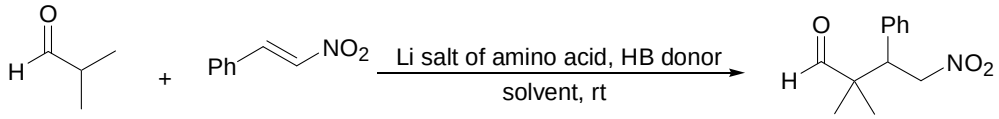
[a] isolated yield, [b] 1.2 equivalents of isobutyraldehyde was used, [c] determined by HPCL using chiral cel OD-H column.

It is important to note that all the three catalyst components i.e. amino acid, hydrogen bond donor and bases are crucial for the reaction to occur and removal of one of the three components results in reaction failure (entry 24 & 25, Table 2.5).

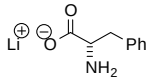
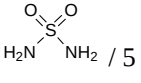
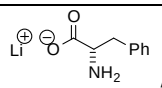
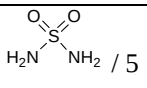
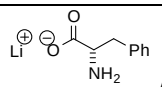
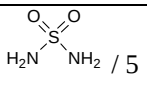
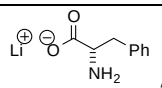
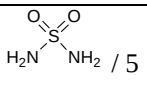
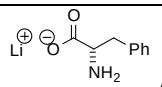
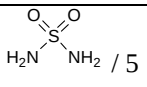
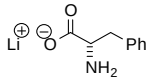
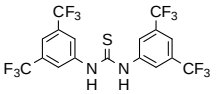
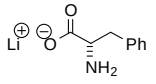
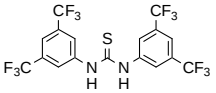
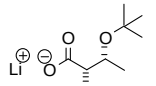
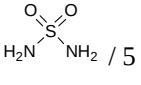
2.1.6 Screening of Li-salt of amino acids for asymmetric Michael reaction of isobutyraldehyde

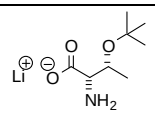
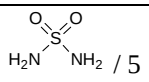
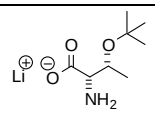
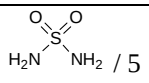
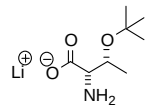
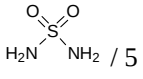
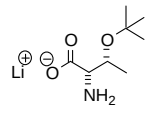
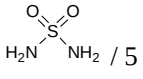
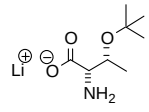
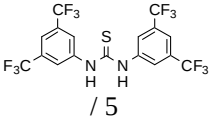
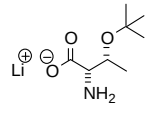
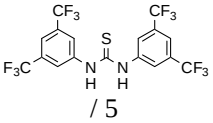
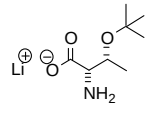
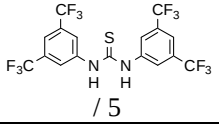
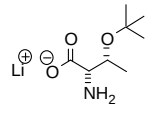
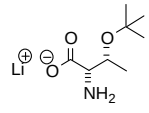
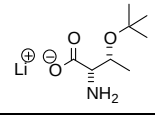
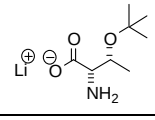
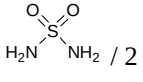
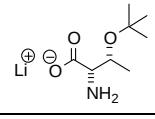
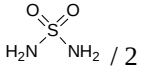
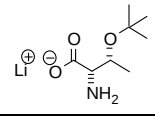
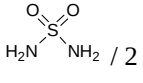
Lithium salts of different amino acids were also examined for the asymmetric Michael addition of isobutyraldehyde to nitrostryrene both in presence and absence of hydrogen bond donors. Interestingly, the lithium salts enable the reaction to occur in the absence of hydrogen bond donors (entry 17 vs 12, Table 2.6), but the reaction was slower (4 h vs. 24 h) and stereoinduction (87% *ee* vs 95% *ee*) was also lower as compared to the one that proceed in the presence of hydrogen bond donor (entry 17 vs 12, Table 2.6).

Table 2.6 *Li-salts of amino acids and hydrogen bond donors screening.*



2 equiv. 1 equiv.

S No.	Li salt of AA/ mol%	HB donor / mol%	Base / mol%	Solvent (1M)	Time	Conversion (HPLC)	ee %[a]
1	 / 5	 / 5	-	Toluene	4 h	50 %	95
2	 / 5	 / 5	-	Toluene	24 h	64	95
3	 / 5	 / 5	-	DCM	4 h	50 %	96
4	 / 5	 / 5	-	DCM	24 h	70 %	96
5	 / 5	 / 5	DMAP / 5	DCM	4 h	50 %	95
6	 / 5	 / 5	-	DCM	4 h	14 %	95
7	 / 5	 / 5	-	Cyclohexane	4 h	33 %	89
8	 / 5	 / 5	-	DCM	2 h	50 %	94

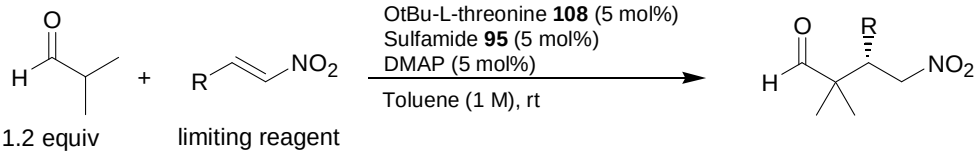
9	 / 5	 / 5	-	DCM	4 h	92 %	95
10	 / 5	 / 5	-	DCM	6 h	100 %	95
11	 / 5	 / 5	-	Toluene	2 h	64 %	95
12	 / 5	 / 5	-	Toluene	4 h	96 %	95
13	 / 5	 / 5	-	Cyclohexane	2 h	20 %	93
14	 / 5	 / 5	-	Cyclohexane	8 h	35 %	93
15	 / 5	 / 5	-	Cyclohexane	24 h	43 %	93
16	 / 5	-	-	Toluene	2 h	30 %	87
17	 / 5	-	-	Toluene	8 h	85 %	87
18	 / 5	-	-	Toluene	24 h	97 %	87
19	 / 2	 / 2	-	Toluene	12 h	50 %	94
20	 / 2	 / 2	DMAP / 6	Toluene	12 h	86 %	94
21	 / 2	 / 2	DMAP / 6	Toluene	20 h	92 %	95

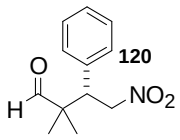
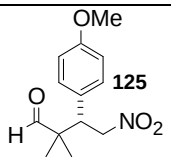
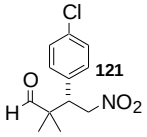
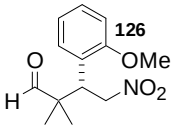
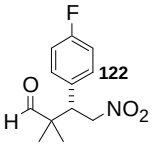
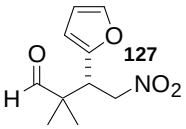
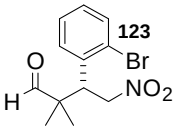
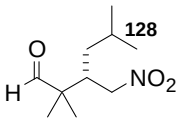
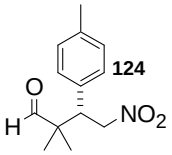
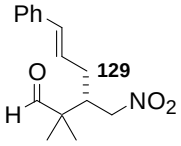
[a] determined by HPCL using chiral cel OD-H column.

2.1.7 Isobutyraldehyde addition to different nitroalkenes

Commercially available, simple sulfamide (**95**) (5 mol%) provided the highest stereoinduction (98% ee) and 99% isolated yield in 4 hours, in the presence of 5 mol% each of amino acid **90** and DMAP (entry 15, Table 2.5). When the aldehyde to *trans* β-nitrostyrene ratio was reduced (1.2:1.0), the reaction takes 7 hours to complete (97% isolated yield) with 98% enantioselectivity (entry 23, Table 2.5). To the best of our knowledge this is the lowest ever aldehyde to *trans* β-nitrostyrene ratio to date. With these optimized conditions in our hand, a large number of electron deficient and electron rich nitroalkenes were examined (Table 2.7) with only 1.2 equivalents of isobutyraldehyde. In all cases, except one (entry 7, Table 2.7), excellent isolated yield (85-98%) and enantioselectivity ($\geq$ 96%) were achieved within 24 hours. Non-aromatic nitroalkene e.g. 2-isobutyl-nitroethene and 2-styryl-nitroethene were also examined, again with only 1.2 equivalent of isobutyraldehyde, the best product profile up to date was observed (entries 9 & 10, Table 2.7).

Table 2.7 *Isobutyraldehyde addition to different nitroalkenes.*



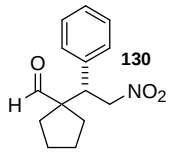
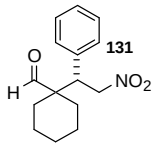
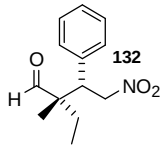
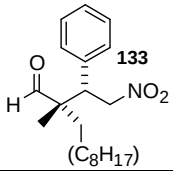
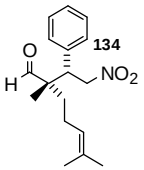
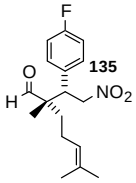
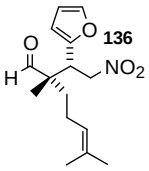
entry	Product	Time (h)	Isolated yield (%)	*ee*[a] (%)	Entry	Product	Time (h)	Isolated yield (%)	*ee*[a] (%)
1	 **120**	7	97	98	6	 **125**	24	90	98
2	 **121**	24	98	96	7	 **126**	36	72	96
3	 **122**	24	93	98	8	 **127**	8	98	98
4	 **123**	24	88	96	9	 **128**	36	70	96
5	 **124**	24	85	99	10	 **129**	6	98	97

[a] Determined by HPLC (using chiral cel OD-H column), See experimental section (page 47-70).

2.1.8 Various aldehyde addition to different nitroalkenes

To further test the performance of our three component catalyst system I examined cyclopentanecarboxaldehyde and cyclohexanecarboxaldehyde as Michael donors in the asymmetric Michael addition to *trans* *β*-nitrostyrene. Only few research groups have reported cyclopentancarbaxaldehyde in asymmetric Michael addition to nitroalkene. The best reported *ee* is 91% by Connon *et. al* (10 mol% catalyst loading, 5 equivalents of cyclopentanecarboxaldehyde, 80 h, 97% yield).[48]

Table 2.8 *Various aldehyde additions to 2-substituted-nitroethenes.*[a]

Entry	Product	Time (h)	Yield (%)	dr[c]	ee (%)[d]
1	 **130**	7	89	-	97
2	 **131**	30	64	-	90
3[b]		48	88	-	91
4	 **132**	12	84	70:30	97
5	 **133**	12	71	78:22	91
6	 **134**	12	70	77:23	98
7	 **135**	36	80	77:23	99
8	 **136**	16	83	76:24	97

[a] Reaction conditions: aldehyde/nitroalkene (2:1), OtBu-L-threonine (**108**) (5 mol%), sulfamide (**95**) (5 mol%), DMAP (15 mol%) in toluene (1.0 M). [b] OtBu-L-threonine (**108**) (10 mol%), sulfamide (**95**) (10 mol%), DMAP (10 mol%) in toluene (1.0 M), [c] determined by HPLC using chiral cel OD-H column (see Experimental Section, page 71-86), [d] determined by HPLC using chiral cel OD-H column (see Experimental Section, page 71-86).

For cyclopentanecarboxaldehyde I achieved the best result concerning starting material ratio (2:1), catalyst loading (5 mol%) and reaction time (7 h), as shown in Table 2.8 (entry 1). Cyclohexanecarboxaldehyde has been rarely used as Michael donor for asymmetric conjugate addition to nirostyrene. The best reported ee is 64% by Wang et. al (20 mol% catalyst loading, 10 equivalents of cyclohexanecarboxaldehyde, 96 h, 42% yield). Using our three component catalyst system, again I achieved the best result to date (5 mol% catalyst loading, 2 equivalents of cyclohexanecarboxaldehyde, 30 h, 64% yield and 90% ee). The yield was improved to 88% by using 10 mol% of the catalyst components (entry 3, Table 2.8).

Our catalyst system was also examined for α-branched aldehydes that lead to the formation of Michael products having stereogenic quaternary carbons. Different α,α-disubstituted aldehydes were used as Michael donor and good yields, excellent enantioselctivities were obtained, but with moderate diastereoselectivities (entries 4-8, Table 2.8).

2.2 NMR Spectroscopy of compounds 120-136

2.2.1 1H-NMR spectroscopy of compounds 120-127

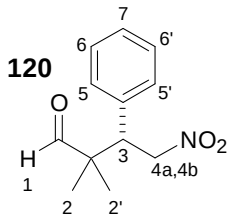


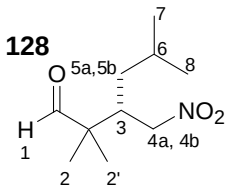
Table 2.9 *^{1}H-NMR data of compound **120***

S.No.	Assignment	δ (ppm)	Multiplicity	J (Hz)	Integration (H)
1	1	9.52	s	-	1
2	2	1.00	s	-	3
3	2`	1.13	s	-	3
4	3	3.78	dd	4.1, 11.4	1
5	4a	4.69	dd	4.1, 12.8	1
6	4b	4.86	dd	11.4, 12.8	1
7	5, 5`	7.19-7.20	m	-	2
8	6, 6`, 7	7.26-7.35	m	-	3

The ^{1}H-NMR spectrum of compound **120** showed a singlet at 9.52 ppm, which confirmed the presence of an aldehydic group in the compound. The protons of the two methyl groups at positions 2, 2` are diastereotopic and therefore give two singlets at 1.00 ppm and 1.13 ppm. The H-3 resonance pattern at 3.78 ppm is slightly downfield as compared to a normal benzylic proton, likely due to the electron withdrawing effect of the carbonyl and nitro groups. This signal is split by two neighboring diastereotopic protons into a doublet of doublets with coupling constants 4.1 Hz and 11.4 Hz. The two protons at position 4a and 4b are diastereotopic, produing separate signals as a doublet of doublets at 4.69 and 4.86 ppm with coupling constants 4.1, 12.8 Hz and 11.4, 12.8Hz. The aromatic protons give two multiplets at 7.19-7.2 ppm and 7.26-7.35ppm.

Compounds **12a** to **127** show similar NMR spectroscopic trend as discussed for the above compound **120** and therefore not discussed further.

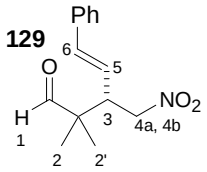
2.2.2 1H-NMR spectroscopy of compounds 128



Compound **128** follows similar general pattern for its ^{1}H-NMR spectrum as compound **120**, except that it has an isobutyl group at position 3 instead of an aromatic group. The resonance pattern for H-3 proton is consequently upfield shift appears as a multiplet at 2.62-2.68 ppm, which is split by two sets of diastereotopic protons at position 4a, 4b and 5a, 5b. The signals from protons of the terminal methyl groups (7, 8) of the isobutyl group are diastereotopic and therefore give two separate doublets at 0.90 and 0.91 ppm with coupling constants 5.8 Hz each. The signal from the proton at position 6 is

split into a multiplet by six vicinal protons of the adjacent methyl groups and the two diastereotopic protons at position 5 and 5a, which appears at 1.61-1.63 ppm.

2.2.3 1H-NMR spectroscopy of compound 129



Compound **129** also follows the same general pattern for its ^{1}H-NMR spectroscopy as compound **120** does, except that it has a styryl group at position 3 instead of an aromatic group. The signal from proton at position 5 is split by vicinal protons at positions 6 and 3. It appears as a doublet of doublets at 6.01 ppm with coupling constants 10.1 and 15.8 Hz. H-6 appears as a doublet at 6.53 ppm with coupling constant 15.8 Hz. The large coupling constant (15.8 Hz) indicates that the protons at positions 5 and 6 are *trans* to each other. The aromatic protons give a multiplet at 7.21-7.35 ppm.

2.2.5 1H-NMR spectroscopy of compound 132

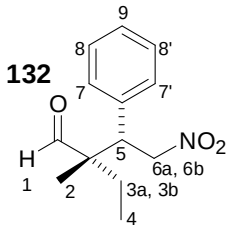


Table 2.10 *^{1}H-NMR data of compound **132***

S.No.	Assignment	δ (ppm)	Multiplicity	J (Hz)	Integration (H)
1	1	9.53	s	-	1
2	2	1.1 (*syn*), 1.13 (*anti*)	s	-	3
3	3a	1.24-1.34	m	-	1
4	3b	1.50-1.77	m	-	1
5	4	0.8 (*syn*), 0.88 (*anti*)	t	7.5, 7.4	3
6	5	3.77 (*anti*), 3.79 (*syn*)	dd	4.4, 11.2 (*anti*), 4.0, 11.5 (*syn*)	1
7	6a	4.61 (*syn*), 4.76 (*anti*)	dd	4.0, 13.0 (*syn*), 4.0, 13.1 (*anti*)	1
8	6b	4.83 (*syn*), 4.85 (*anti*)	dd	11.5, 13.0 (*syn*), 11.2, 13.1 (*anti*)	1
9	7, 7`	7.15-7.21	m	-	2
10	8, 8`, 9	7.27-7.34	m	-	3

Compound **132** has two diastereomers and the sample used for the ^{1}H-NMR spectroscopy was a mixture of both diastereomers. H-2 appears as singlet at 1.1 ppm (*syn*) and 1.13 ppm (*anti*). The protons at position 3a and 3b are diastereotopic. Each of these protons is split by one geminal and three vicinal protons and gives multiplets at 1.24-1.34 and 1.50-1.77 ppm. H-4 appear as triplets at 0.80 ppm for *syn* and at 0.88 ppm for *anti* diastereomer with coupling constant 7.5 and 7.4 Hz. The proton at position 5 gives a doublet of doublets at 3.77 for *anti* diastereomer with coupling constant 4.4 and 11.2 Hz, and at 3.79 ppm for *syn* diastereomer with coupling constant 4.0 and 11.5 Hz. The protons at position 6a and 6b are diastereotopic and give separate signals (a doublet of doublets) at 4.61 ppm (coupling constant 4.0) and 4.83 ppm (coupling constant 11.5). The aromatic protons give two multiplets at 7.15-7.21 ppm and 7.27-7.34 ppm.

Compound **133** is also diastereomeric but it was possible to obtain the *syn* diastereomer in pure form. The ^{1}H-NMR spectrum of the compound shows signals for only the *syn* diastereomer, it shows the same general pattern for its ^{1}H-NMR spectroscopy as compound **132**, except that it has an unbranched nonyl group at alpha position instead of ethyl groups. The methyl group at alpha position gives a singlet at 1.1 ppm. The long alkyl group gives two multiplets at 0.87-0.88 ppm and at 1.14-1.72 ppm.

2.3 Conclusion

I have developed a three component catalytic system, consisting of an amino acid, hydrogen bond donor and base, that offers some advantages: (1) all components of the catalytic system are commercially available and thus no synthesis is required, (2) lowest catalyst loading, (3) lowest aldehyde to nitroalkene ratio, (4) excellent enantioselectivities, (5) good to excellent yield, and (6) short reaction times. The discovery of this catalytic system has opened new door to enantioselective transformations and can be applicable to mechanistically related reactions, for example, Mannich reaction, α-amination, Michael addition to maleimides, sulfones, DEAD etc.

2.3 Experimental

2.3.1 General information

All reactions were performed in 2 mL screw cap vials. Liquid reagents were transferred with glass syringes. Routine monitoring of reactions were performed by thin-layer chromatography (TLC) using precoated plates of silica gel 60 F_{254} and visualized under ultraviolet irradiation (254 nm). Column chromatography separations were performed with silica gel 60 (0.040-0.063 mm). Petroleum ether with a boiling point range of 60-80 °C was used. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent was performed at reduced pressure.

Materials: Commercial reagents were used as received from Sigma-Aldrich.

Nitroalkenes: *trans*-β-Nitrostyrene (Ald. Cat. No. N26806), *trans*-4-methoxy-β-nitrostyrene (Ald. Cat. No. 399299), *trans*-4-methyl-β-nitrostyrene (Ald. Cat. No. 424757), *trans*-4-chloro-β-nitrostyrene (Ald. Cat. No. 642177), *trans*-4-fluoro-β-nitrostyrene (Ald. Cat. No. 09506), *trans*-2-methoxy-β-nitrostyrene (Ald. Cat. No. 639710), *trans*-2-bromo-β-nitrostyrene (Ald. Cat. No.

642215), *trans*-2-(2-nitrovinyl)furan (Ald. Cat. No. 478717). 2-isobutyl-1-nitroethene[99] and 2-styryl-1-nitroethene [(1E,2E)-4-nitrobuta-1,3-dienyl benzene][100] were synthesized according to previously published procedures.

Aldehydes: Isobutyraldehyde (2-methylpropanal, Ald. Cat. No. 240788, 99% pure), 2-methylbutanal (racemic) (Ald. Cat. No. M33476, 95% pure), cyclopentanecarbaldehyde (Ald. Cat. No. 526037, 97% pure), cyclohexanecarbaldehyde (Ald. Cat. No. 108464, 97% pure), 2-methylundecanal (racemic) (Ald. Cat. No. M86758, 95% pure), 2,6-dimethylhept-5-enal (racemic) (Ald. Cat. No. W238902).

Catalyst components: DMAP (Ald. Cat. No. 29224), sulfamide (Ald. Cat. No. 211370), O^{t}Bu-L-threonine (Ald. Cat. No. 20644) were purchased from Sigma-Aldrich. Schreiner's thiourea can be purchased from many smaller sized chemical companies or synthesized.[101]

2.3.2 Instrumentation

NMR spectra were recorded on a JEOL ECX 400 spectrometer, operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (TMS = 0) or relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. Multiplicities are abbreviated as: (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). Coupling constants are expressed in Hz. FT-IR spectra were obtained on Nicolet Avatar 370 thermonicolet spectrometer. MS data was measured on a Bruker Daltonics HCT Ultra. HRMS were recorded on a Bruker micrOTOF instrument with an ionization potential of 70 eV with ESI positive mode. All chiral HPLC analysis were performed on a CHIRALCEL OD-H column with *n*-heptane and *i*-propanol as eluents.

2.3.3 Absolute configuration

Absolute configuration of compounds **120**-**136** was determined by comparison of the HPLC retention time with reported values.[84-89] For compounds **120**-**129** see reference 102-104. For compounds **130**-**34** see reference 105-107.

Absolute configuration of compounds **135** and **136** are based on general trend of our Michael addition products.

2.3.4 Racemate formation

To a screw cap vial was added sulfamide (**95**) (2.4 mg, 0.025 mmol, 5.0 mol%), glycine (1.9 mg, 0.025 mmol, 5.0 mol%) and DMAP (3.1 mg, 0.025 mmol, 5.0 mol%). To this mixture were added toluene (1.0 M, 0.50 mL), and the aldehyde (2.00 equiv, 1.00 mmol). This mixture was then stirred for 2 minutes at room temperature. The nitroalkene (1.00 equiv, 0.50 mmol) was then added and the reaction stirred at room temperature. TLC was used to monitor the reaction. After completion the reaction was quenched by adding water (15 mL) and the resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic extracts were dried over sodium sulfate, and evaporated under reduced pressure. The crude racemate was purified by column chromatography using EtOAc/pet ether.

2.3.5 General procedure for the enantioselective Michael addition of α-branched aldehydes to nitroalkenes

Three general reaction conditions were found to be optimal depending on the aldehyde examined. The limiting reagent was the nitroalkene, which was always used at the 0.50 mmol scale:

Method A (Schreiner's thiourea 108)

To a screw cap vial was added O^{t}Bu-L-threonine **108** (1.8 mg, 0.01 mmol, 2.0 mol%), Schreiner's thiourea **90** (1,3-bis-[3,5-bis(trifluoromethyl)phenyl] thiourea) (5.0 mg, 0.01 mmol, 2.0 mol%), and DMAP (4.9 mg, 0.04 mmol, 8.0 mol%). To this mixture was added cyclohexane (1.0 M, 0.50 mL), and the aldehyde (1.2 equiv (0.6 mmol) or 2.00 equiv (1.0 mmol)). This mixture was then stirred for 2 minutes at room temperature. The nitroalkene (1.00 equiv, 0.50 mmol) was then added and the reaction mixture was stirred for the indicated time at room temperature. TLC was used to monitor the reaction. After completion, the reaction was quenched by adding water (15 mL) and the resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic extracts were dried over sodium sulfate, filtered, rototary evaporated, and finally dried under high vacuum. The crude product was purified by column chromatography using EtOAc/pet ether.

Method B (Sulfamide 95, Table 2.4 reactions)

To a screw cap vial was added O^{t}Bu-L-threonine **108** (4.4 mg, 0.025 mmol, 5.0 mol%), sulfamide **95** (2.40 mg, 0.025 mmol, 5.0 mol%), and DMAP (3.05 mg, 0.025 mmol, 5.0 mol%). To this mixture was added toluene (1.0 M, 0.50 mL), and the aldehyde (1.2 equiv, 0.6 mmol). This mixture was then stirred for 2 minutes at room temperature. The nitroalkene (1.00 equiv, 0.50 mmol) was then added and the reaction became homogenous within 10 minutes of stirring. The reaction time is indicated in the individual descriptions on the pages that follow. TLC was used to monitor the reaction. Work-up as in Method A. Note: Schreiner's thiourea **90** is organic soluble, while sulfamide **95** is water soluble.

Method C (Sulfamide 95, Table 2.5 reactions)

Same as method B, except 15 mol% of the DMAP and 2.00 equivalents (1.0 mmol) of the aldehyde were used.

On the following pages all synthesized products, **120**-**136**, are detailed. Note, compounds **135** and **136** are described here for the first time in the literature.

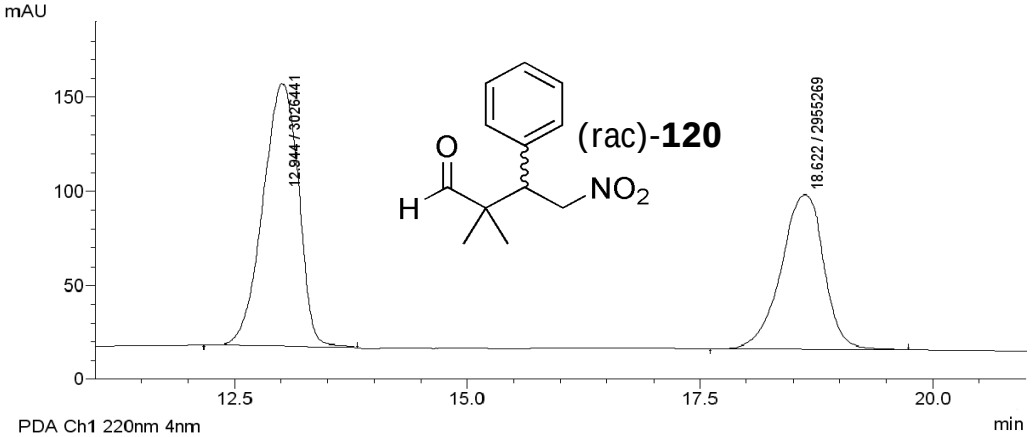
(*S*)-2,2-dimethyl-4-nitro-3-phenylbutanal (120)

The title compound was prepared from *trans*-*β*-nitrostyrene and isobutyraldehyde using methods A and B.

Compound obtained using method A (2 equiv. of isobutyraldehyde): Reaction time: 5 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 82%; ee = 93% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 13.8 min, t_{major}= 18.9 min.

Compound obtained using method B: Reaction time: 7 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-5) and HPLC (chromatogram on p. S-4) of the crude product showed it to be of very high chemical purity; yield = 97%; ee = 98% as determined by HPLC (conditions and retention times as above). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.00 (s, 3H), 1.13 (s, 3H), 3.78 (dd, 1H, *J* = 4.1, 11.4 Hz), 4.69 (dd, 1H, *J* = 4.1, 12.8 Hz), 4.86 (dd, 1H, *J* = 11.4, 12.8 Hz), 7.19-7.20 (m, 2H), 7.26-7.35 (m, 3H), 9.52 (s, 1H).

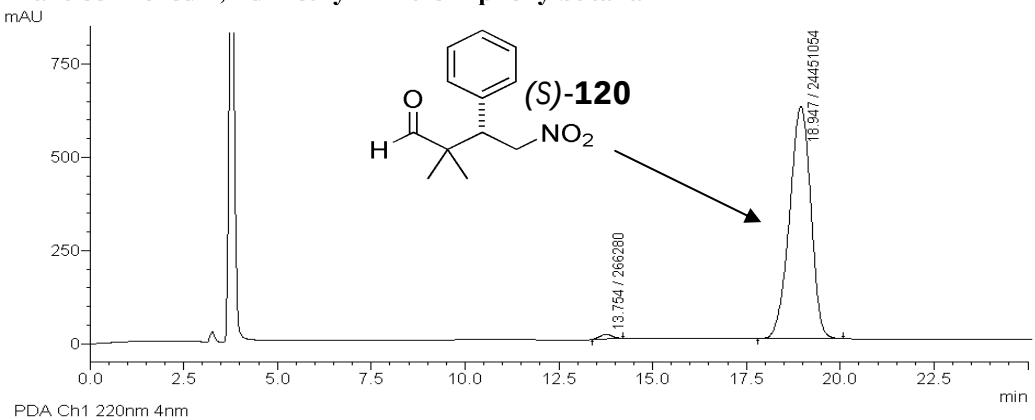
Racemic 2,2-dimethyl-4-nitro-3-phenylbutanal



PDA Ch1 220nm 4nm

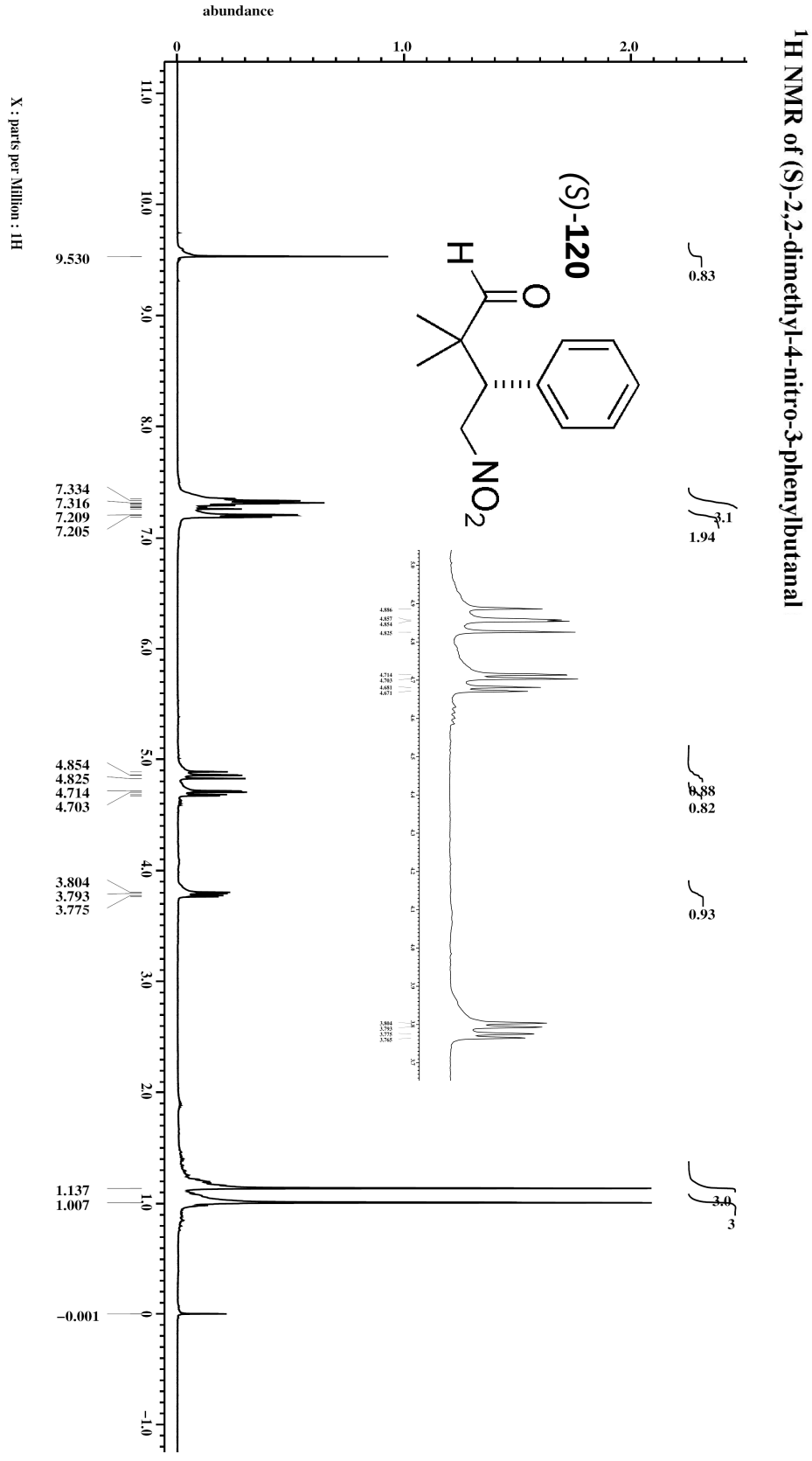
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	12.944	3026441	120607	50.595	60.265	0.728	
2	18.622	2955269	79521	49.405	39.735	1.080	
Total		5981710	200128	100.000	100.000		

Enantioenriched 2,2-dimethyl-4-nitro-3-phenylbutanal



PDA Ch1 220nm 4nm

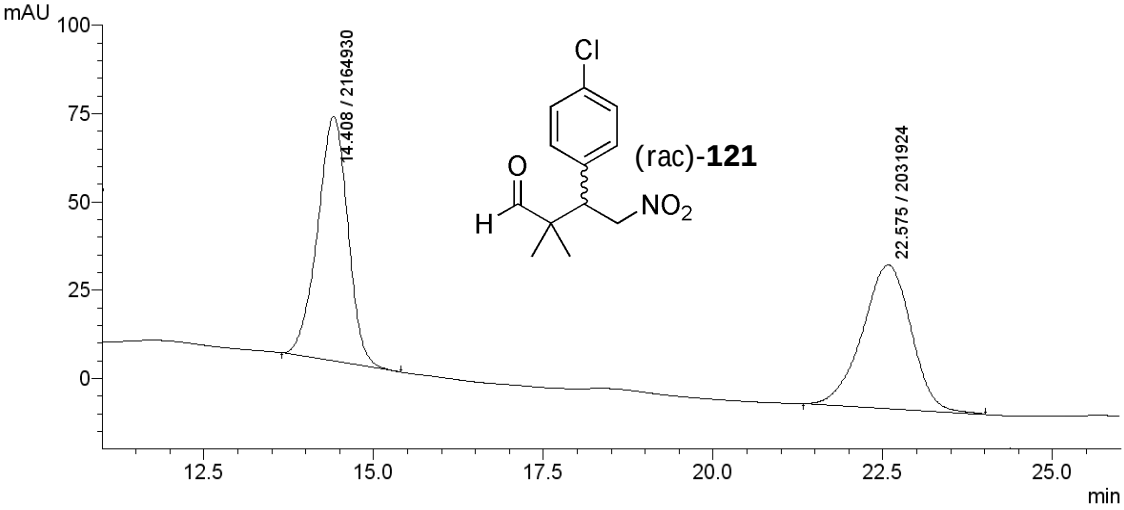
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.754	266280	11675	1.077	1.844	0.632	
2	18.947	24451054	621426	98.923	98.156	1.125	
Total		24717335	633101	100.000	100.000		


^{1}H NMR of (S)-2,2-dimethyl-4-nitro-3-phenylbutanal
(S)-120
abundance
X : parts per Million : 1H
9.530
7.334
7.316
7.209
7.205
4.854
4.825
4.714
4.703
3.804
3.793
3.775
1.137
1.007
−0.001
0.83
3.1
1.94
0.88
0.82
0.93
3.0
3

(*S*)-3-(4-chlorophenyl)-2,2-dimethyl-4-nitrobutanal (121)

The title compound was prepared from *trans*-4-chloro-*β*-nitrostyrene and isobutyraldehyde using method B. Reaction time: 24 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-7) and HPLC (chromatogram on p. S-6) of the crude product showed it to be of very high chemical purity; yield = 98%; ee = 96% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 0.8 mL/min, λ = 220 nm); t_{minor}= 14.1 min, t_{major}= 22.3 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.01 (s, 3H), 1.11 (s, 3H), 3.77 (dd, 1H, *J* = 4.2, 11.4 Hz), 4.69 (dd, 1H, *J* = 4.2, 13.2 Hz), 4.82 (dd, 1H, *J* = 11.4, 13.2 Hz), 7.15 (d, 2H, *J* = 8.2 Hz), 7.31 (d, 2H, *J* = 8.2 Hz), 9.49 (s, 1H).

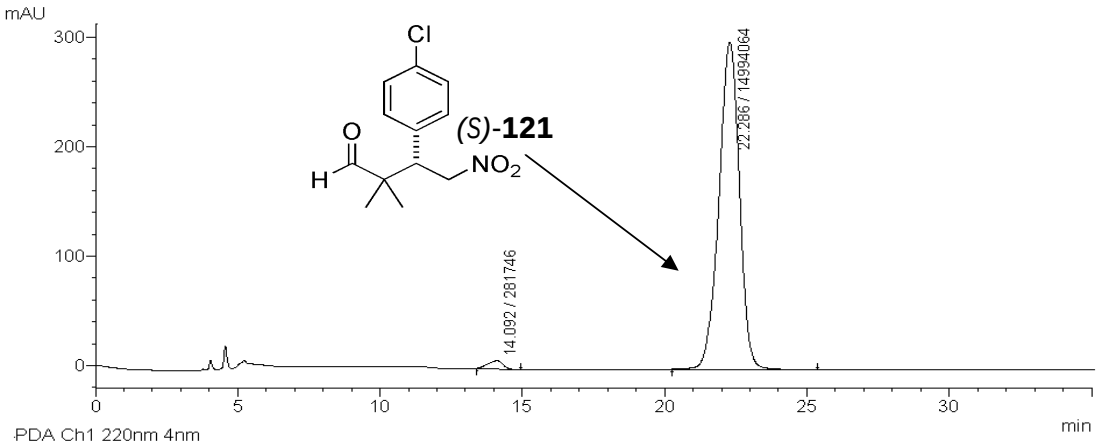
Racemic 3-(4-chlorophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.408	2164930	69382	51.585	63.01	0.914	
2	22.575	2031924	40718	48.415	36.983	1.447	
Total		4196854	110100	100.000	100.000		

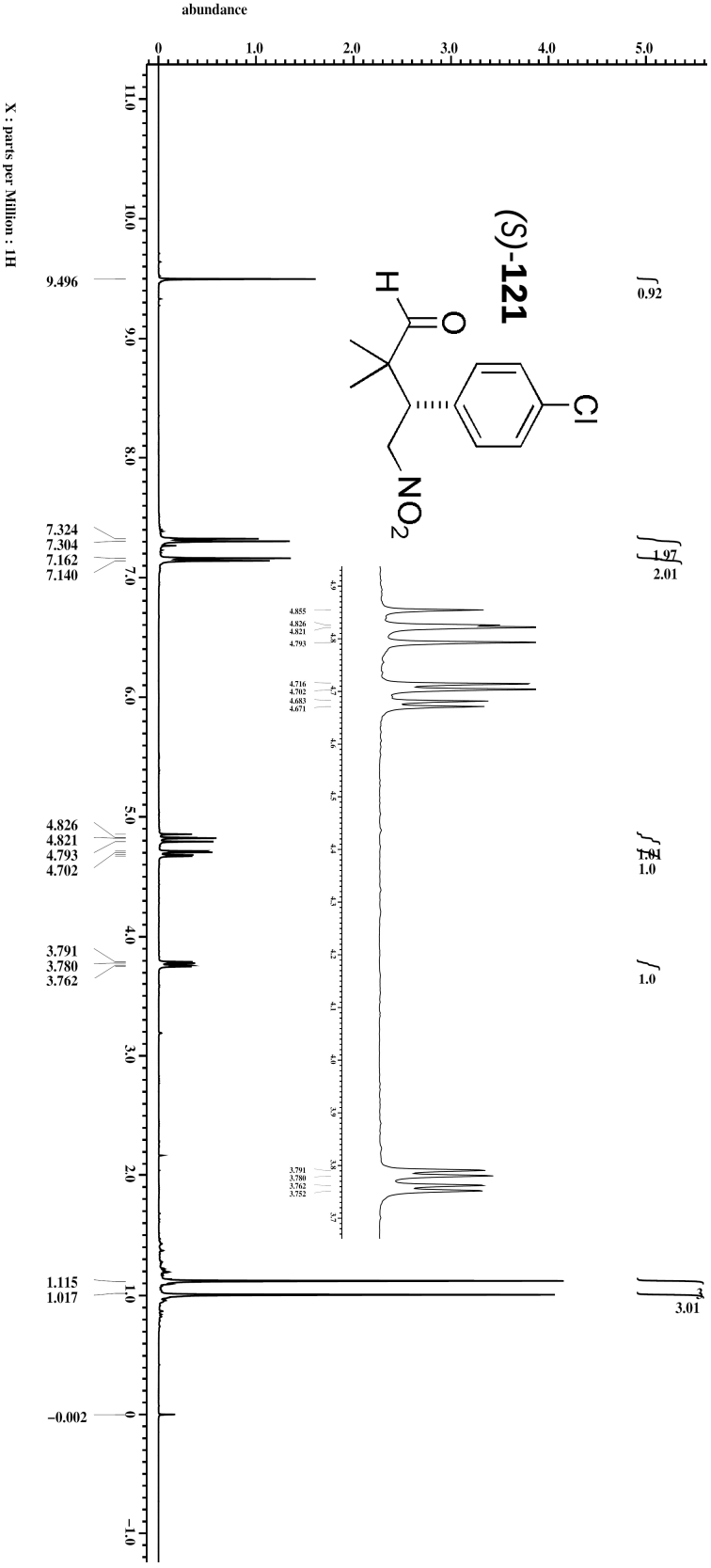
Enantioenriched 3-(4-chlorophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.092	281746	7618	1.844	2.487	1.038	
2	22.286	14994064	298639	98.156	97.513	1.454	
Total		15275810	306257	100.000	100.000		

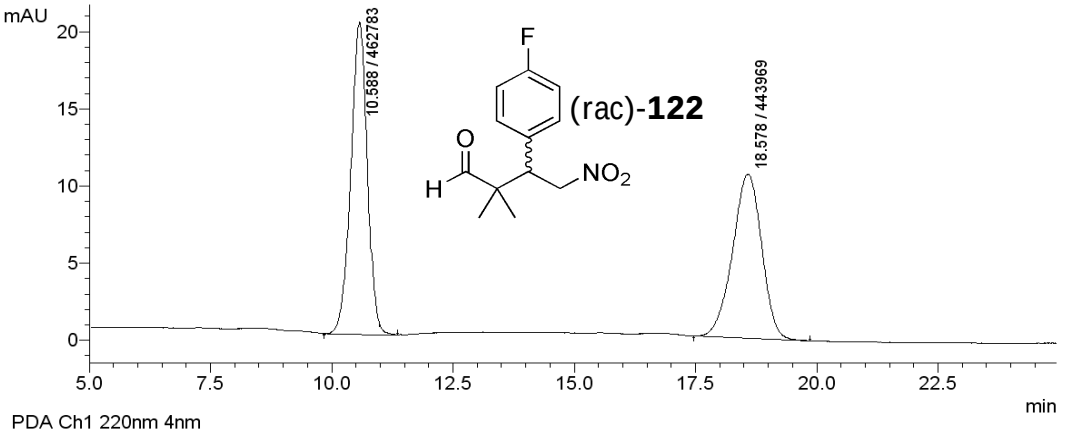
^{1}H NMR of (S)-3-(4-chlorophenyl)-2,2-dimethyl-4-nitrobutanal



(*S*)-3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal (122):

The title compound was prepared from *trans*-4-fluoro-*β*-nitrostyrene and isobutyraldehyde using method B. Reaction time: 24 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-9) and HPLC (chromatogram on p. S-8) of the crude product showed it to be of very high chemical purity; yield = 93%; ee = 98% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 10.3 min, t_{major}= 17.5 min. The compound was tentatively assigned the S configuration according to the general trend of our Michael addition products. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.00 (s, 3H), 1.12 (s, 3H), 3.78 (dd, 1H, *J* = 4.1, 11.4 Hz), 4.69 (dd, 1H, *J* = 4.1, 12.8 Hz), 4.82 (dd, 1H, *J* = 11.4, 12.8 Hz), 6.99-7.01 (m, 2H), 7.16-7.20 (m, 2H), 9.5 (s, 1H).

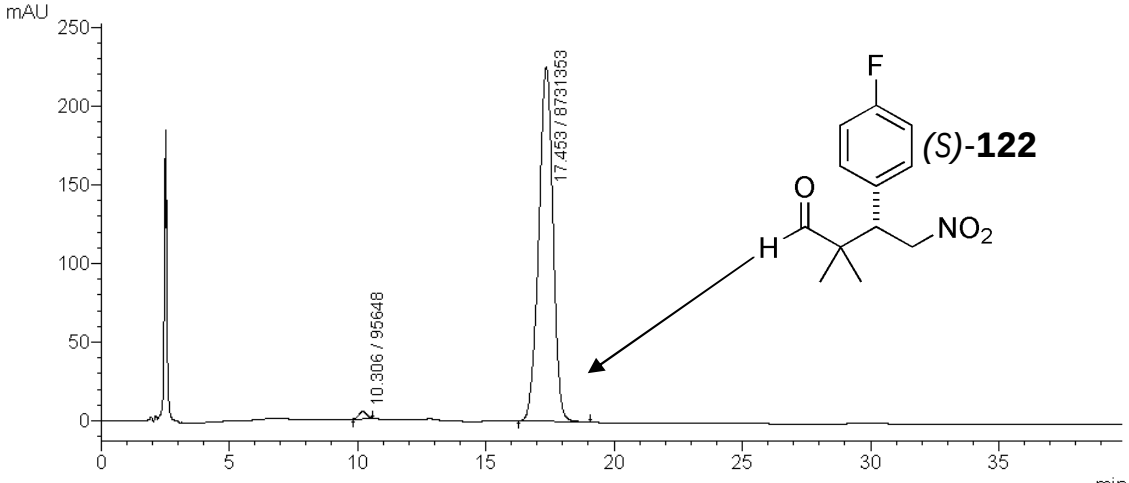
Racemic 3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

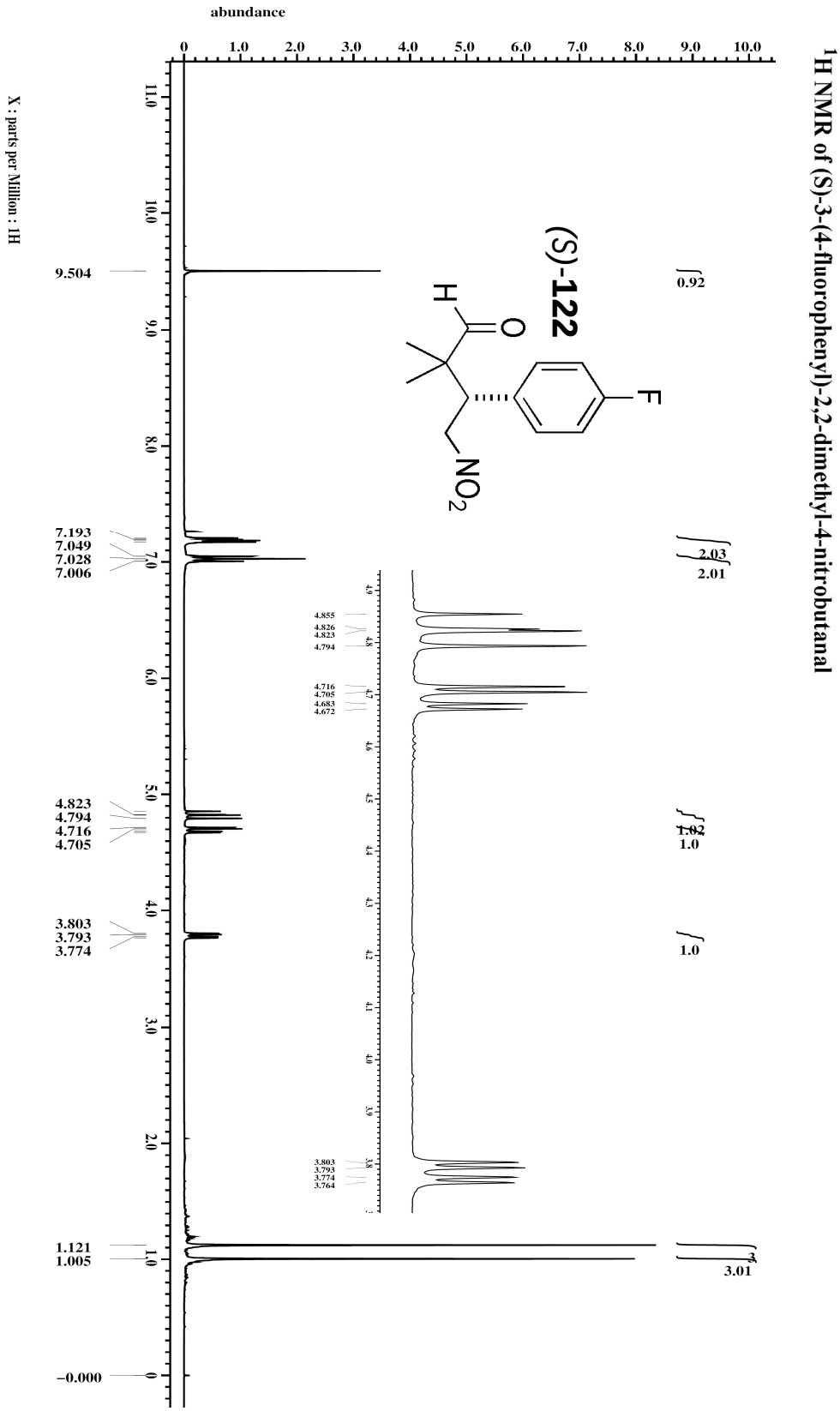
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	10.588	462783	20204	51.037	65.503	0.671	
2	18.578	443969	10641	48.963	34.497	1.213	
Total		906752	30845	100.000	100.000		

Enantioenriched 3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	10.306	95648	4685	1.084	2.036	0.602	
2	17.453	8731353	225368	98.916	97.964	1.127	
Total		8827001	230053	100.000	100.000		

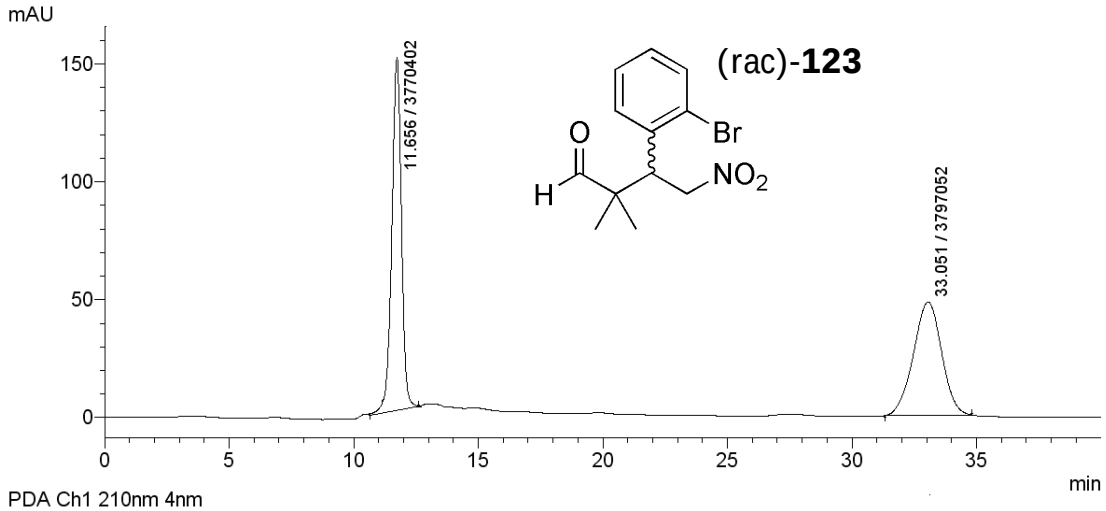


^{1}H NMR of (S)-3-(4-fluorophenyl)-2,2-dimethyl-4-nitrobutanal

(*R*)-3-(2-bromophenyl)-2,2-dimethyl-4-nitrobutanal (123)

The title compound was prepared from *trans*-2-bromo-*β*-nitrostyrene and isobutyraldehyde using method B. Reaction time: 24 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-11) and HPLC (chromatogram on p. S-10) of the crude product showed it to be of very high chemical purity; yield = 88%; ee = 96% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 200 nm); t_{minor}= 11.4 min, t_{major}= 30.7 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.09 (s, 3H), 1.17 (s, 3H), 4.62 (dd, 1H, *J* = 4.1, 11.4 Hz), 4.71 (dd, 1H, *J* = 4.1, 13.3 Hz), 4.83 (dd, 1H, *J* = 11.4, 13.3 Hz), 7.13-7.17 (m, 1H), 7.26-7.34 (m, 2H), 7.61 (d, 1H, *J* = 7.3Hz) 9.56 (s, 1H).

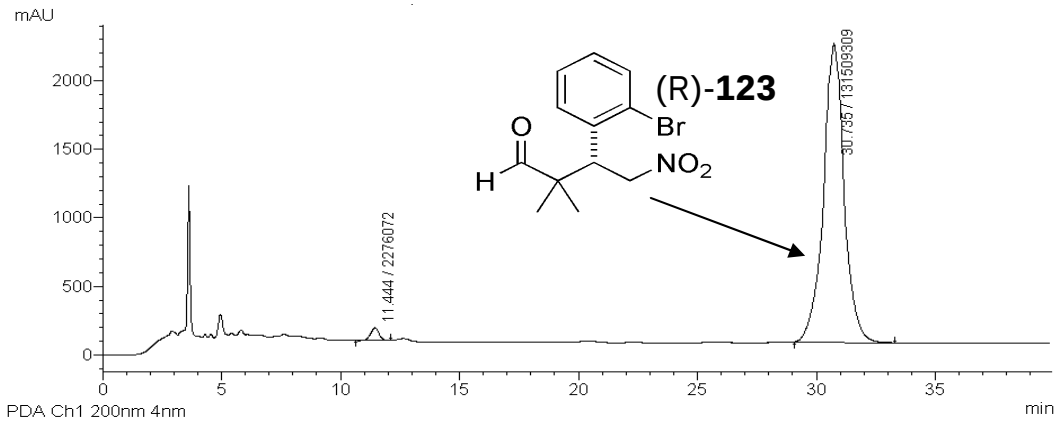
Racemic 3-(2-bromophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	11.656	3770402	146605	49.824	75.333	0.746	
2	33.051	3797052	48004	50.176	24.667	2.307	
Total		7567455	194609	100.000	100.000		

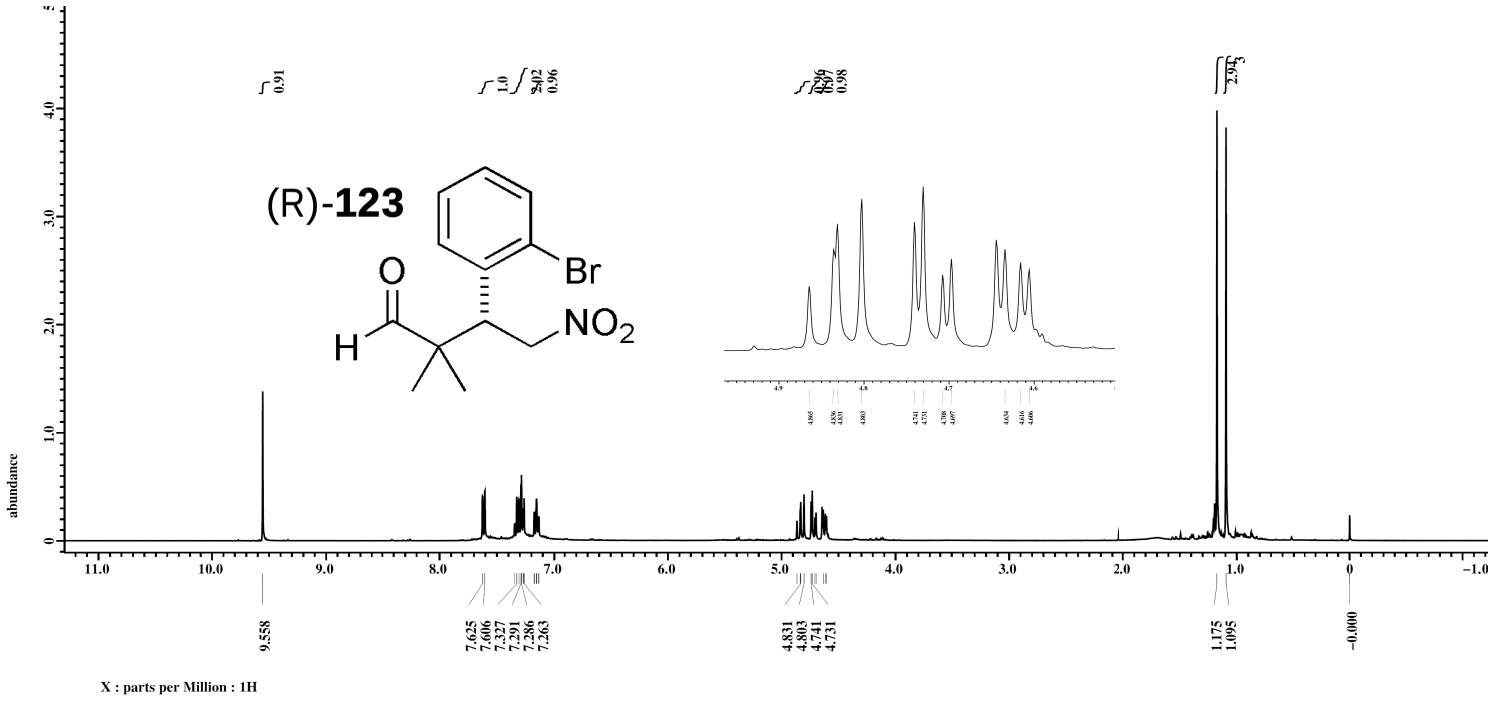
Enantioenriched 3-(2-bromophenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 200nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	11.444	2276072	93958	1.701	4.130	0.710	
2	30.735	131509309	2180908	98.299	95.870	1.900	
Total		133785381	2274866	100.000	100.000		

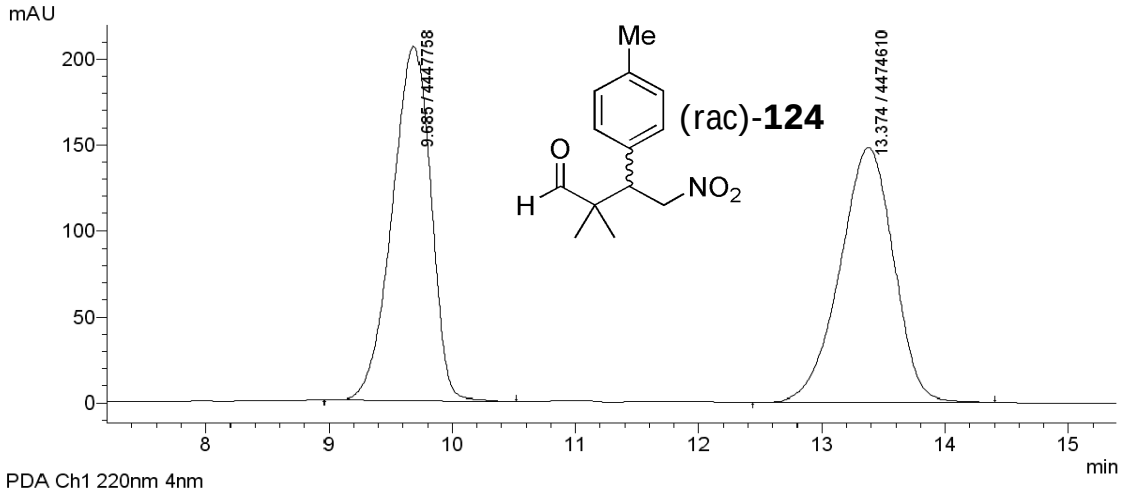
^{1}H NMR of (R)-3-(2-bromophenyl)-2,2-dimethyl-4-nitrobutanal



(*S*)-2,2-dimethyl-4-nitro-3-p-tolylbutanal (124)

The title compound was prepared from *trans*-4-methyl- *β*-nitrostyrene and isobutyraldehyde using method B. Reaction time: 24 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 85%; ee = 99% as /min, λ = 220 nm); determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mLt_{minor}= 10.2 min, t_{major}= 13.9 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 0.98 (s, 3H), 1.12 (s, 3H), 2.31 (s, 3H), 3.74 (dd, 1H, *J* = 4.1, 11.4 Hz), 4.66 (dd, 1H, *J* = 4.1, 12.8 Hz), 4.82 (dd, 1H, *J* = 11.4, 12.8 Hz), 7.07 (d, 2H, *J* = 8.2 Hz), 7.12 (d, 2H, *J* = 8.2 Hz), 9.51 (s, 1H).

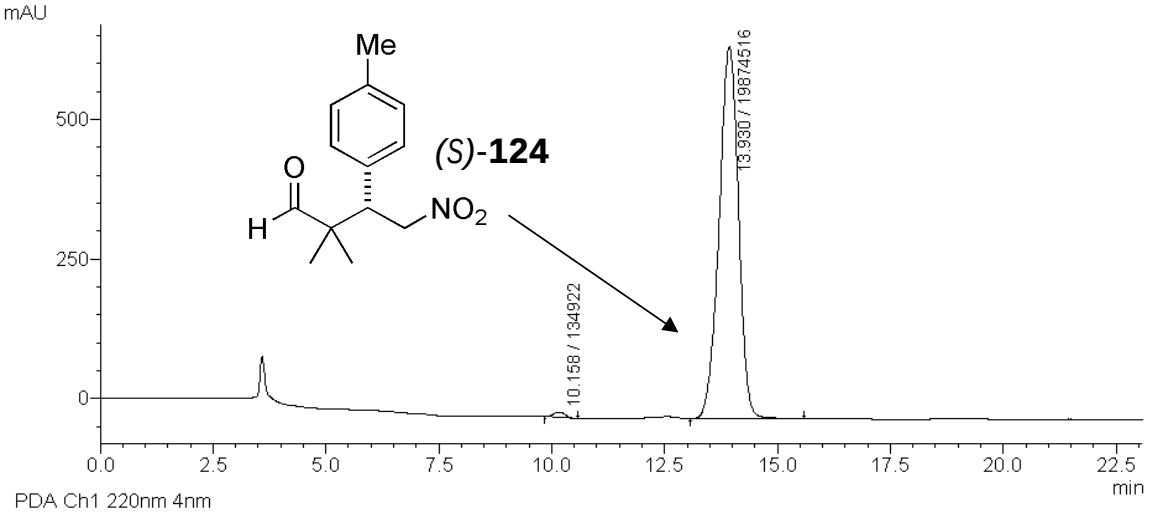
Racemic 2,2-dimethyl-4-nitro-3-p-tolylbutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.685	4447758	206001	49.850	58.167	0.612	
2	13.374	4474610	148151	50.150	41.833	0.870	
Total		8922368	354152	100.000	100.000		

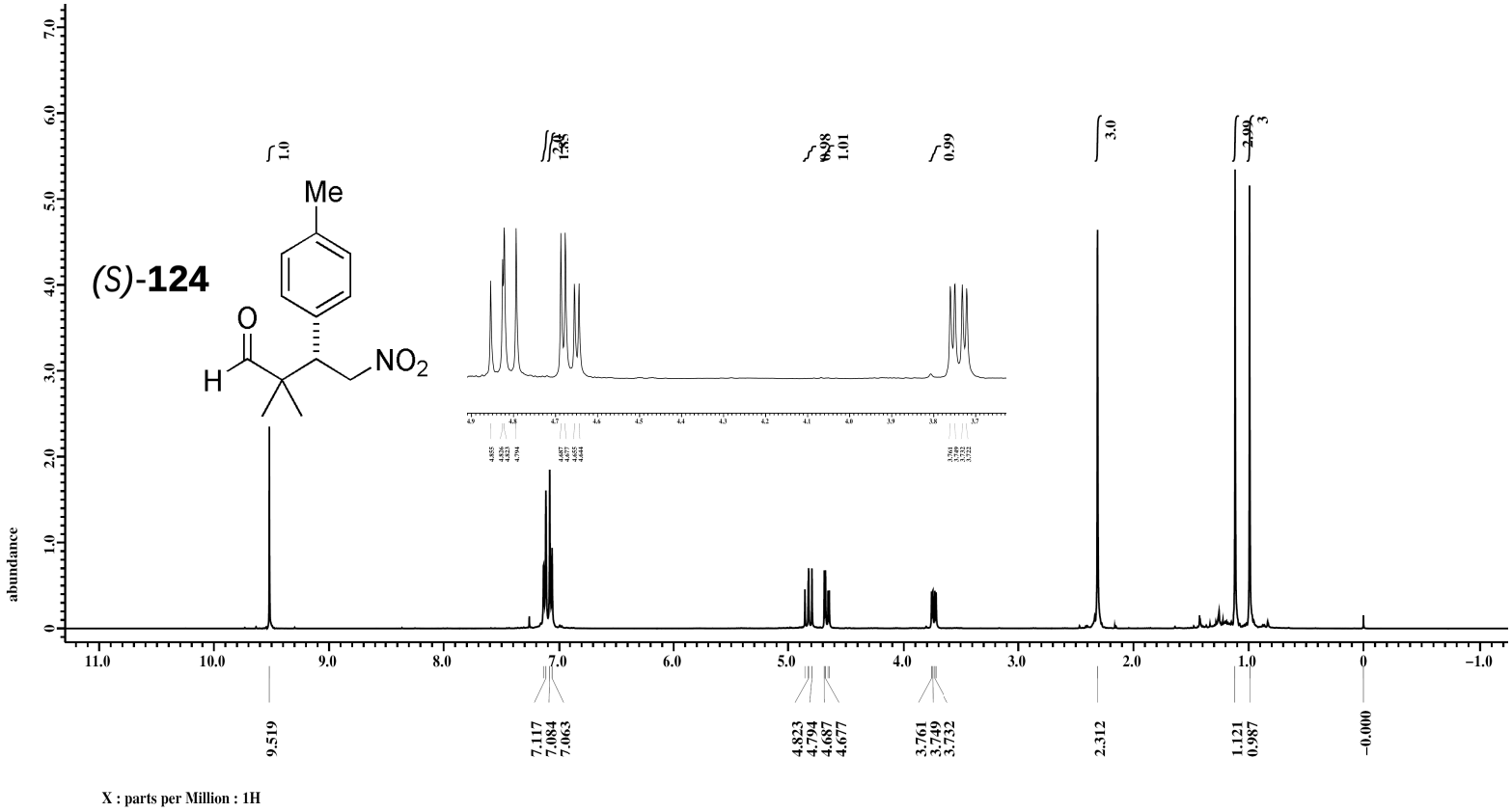
Enantioenriched 2,2-dimethyl-4-nitro-3-p-tolylbutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	10.158	134922	8658	0.674	1.284	0.434	
2	13.930	19874516	665829	99.326	98.716	0.858	
Total		20009438	674487	100.000	100.000		

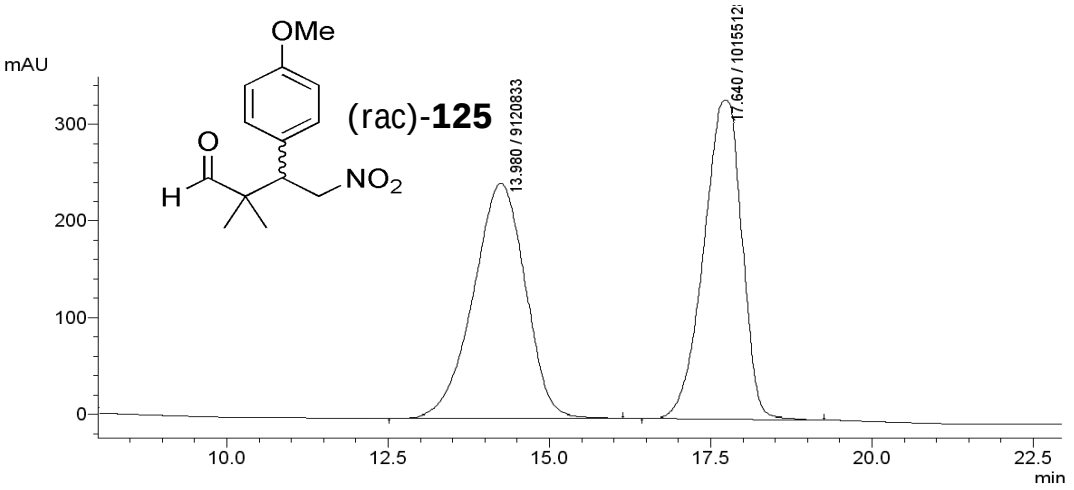
^{1}H NMR of (S)- 2,2-dimethyl-4-nitro-3-p-tolylbutanal



(*S*)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (125)

The title compound was prepared from *trans*-2-methoxy *β*-nitrostyrene and isobutyraldehyde using method B. Reaction time: 24 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 90%; ee = 98% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 10/90, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 11.9 min, t_{major}= 17.3 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 0.99 (s, 3H), 1.11 (s, 3H), 3.72 (dd, 1H, *J* = 4.1, 11.5 Hz), 3.78 (s, 3H), 4.66 (dd, 1H, *J* = 4.1, 12.8 Hz), 4.80 (dd, 1H, *J* = 11.5, 12.8 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 7.11 (d, 2H, *J* = 8.7 Hz), 9.51 (s, 1H).

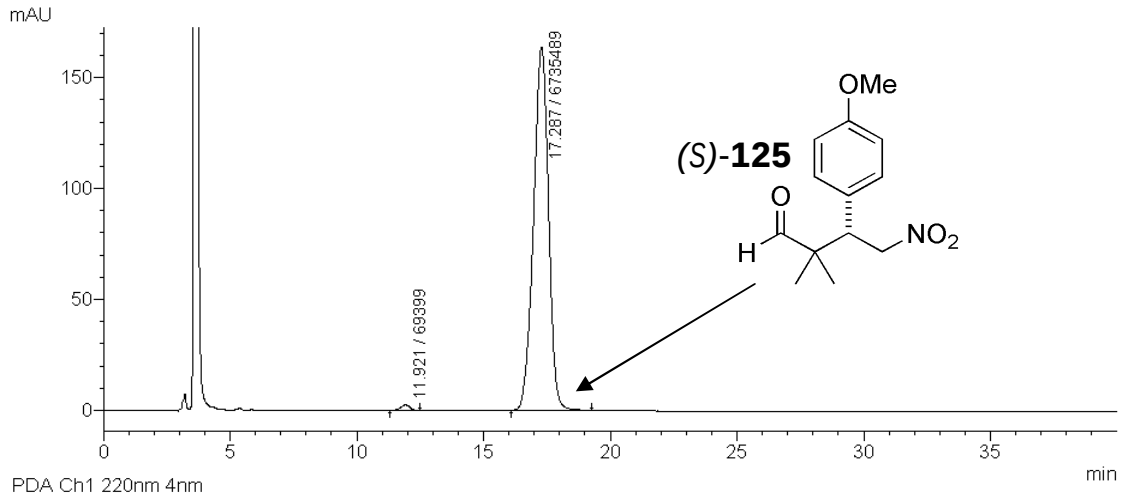
Racemic 3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.980	9120833	195940	47.317	44.914	1.359	
2	17.640	10155128	240320	52.683	55.086	1.229	
Total		19275961	436261	100.000	100.000		

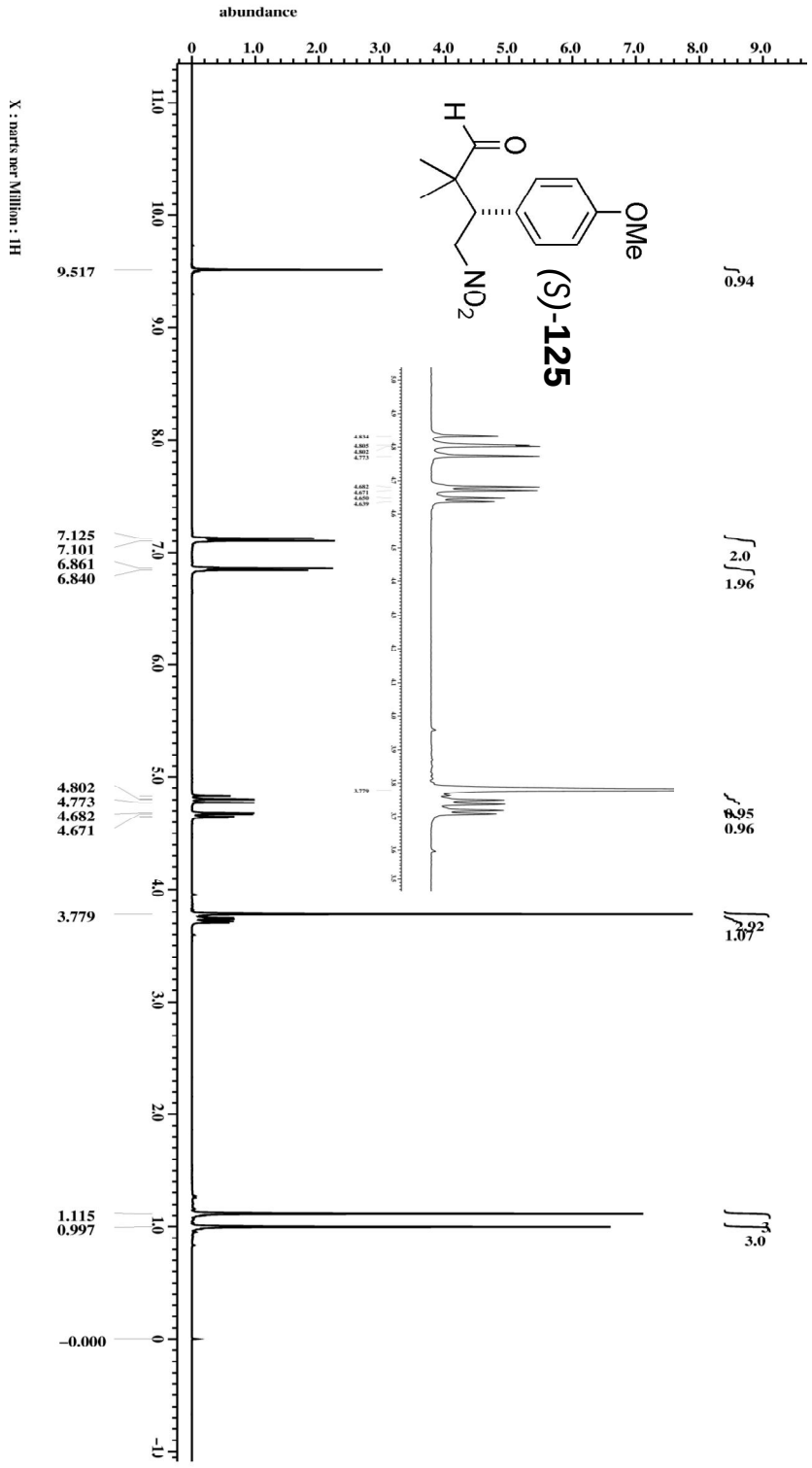
Enantioenriched 3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	11.921	69399	2595	1.020	1.561	0.776	
2	17.287	6735489	163659	98.980	98.439	1.195	
Total		6804888	166254	100.000	100.000		

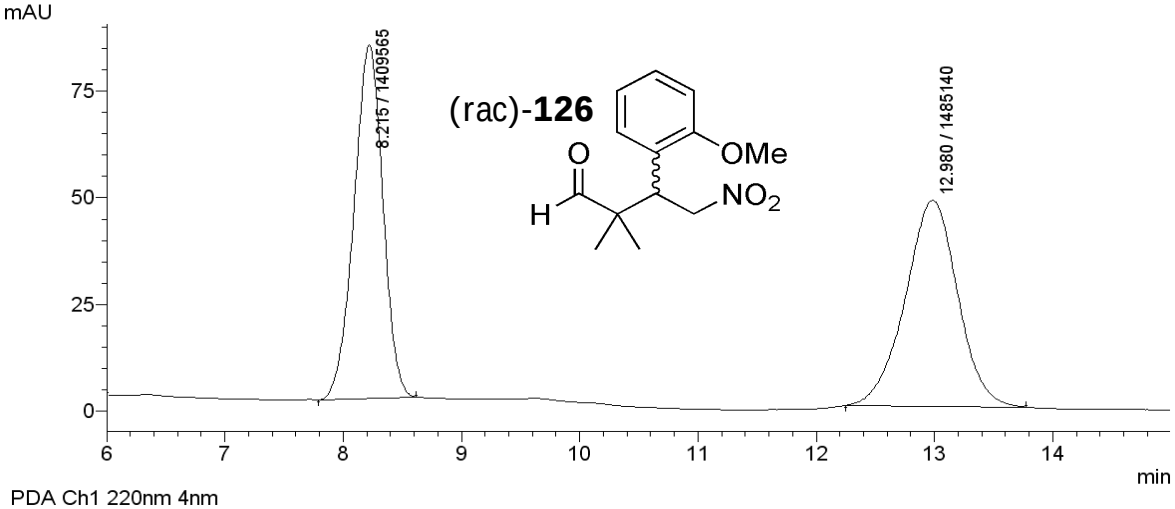
^{1}H NMR of (S)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutan



(*S*)-3-(2-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (126)

The title compound was prepared from *trans*-2-methoxy- *β*-nitrostyrene and isobutyraldehyde accoding to general procedure B. Reaction time: 36 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 72% ; ee = 96% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 8.2 min, t_{major}= 12.9 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.05 (s, 3H), 1.10 (s, 3H), 3.82 (s, 3H), 4.10-4.27 (m, 1H), 4.73 (dd, 1H, *J* = 4.6, 12.8 Hz), 4.90 (dd, 1H, *J* = 11.0, 12.8 Hz), 6.89 (d, 1H, *J* = 7.7 Hz), 6.93 (t, 1H, *J* = 7.5 Hz), 7.13 (dd, 2H, *J* = 1.4, 7.7 Hz), 7.24-7.28 (m, 1H), 9.50 (s, 1H).

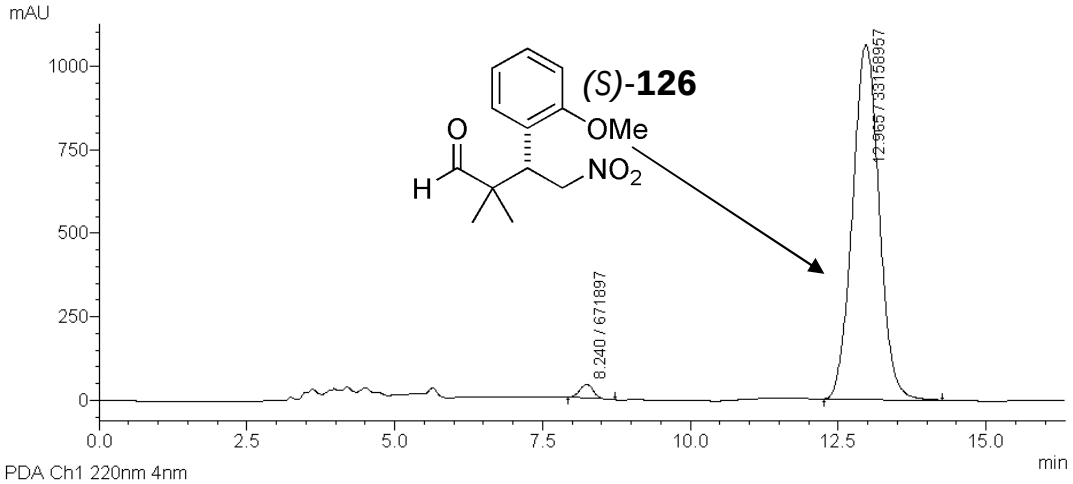
Racemic 3-(2-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	8.215	1409565	82738	48.695	63.172	0.499	
2	12.980	1485140	48234	51.305	36.828	0.914	
Total		2894705	130972	100.000	100.000		

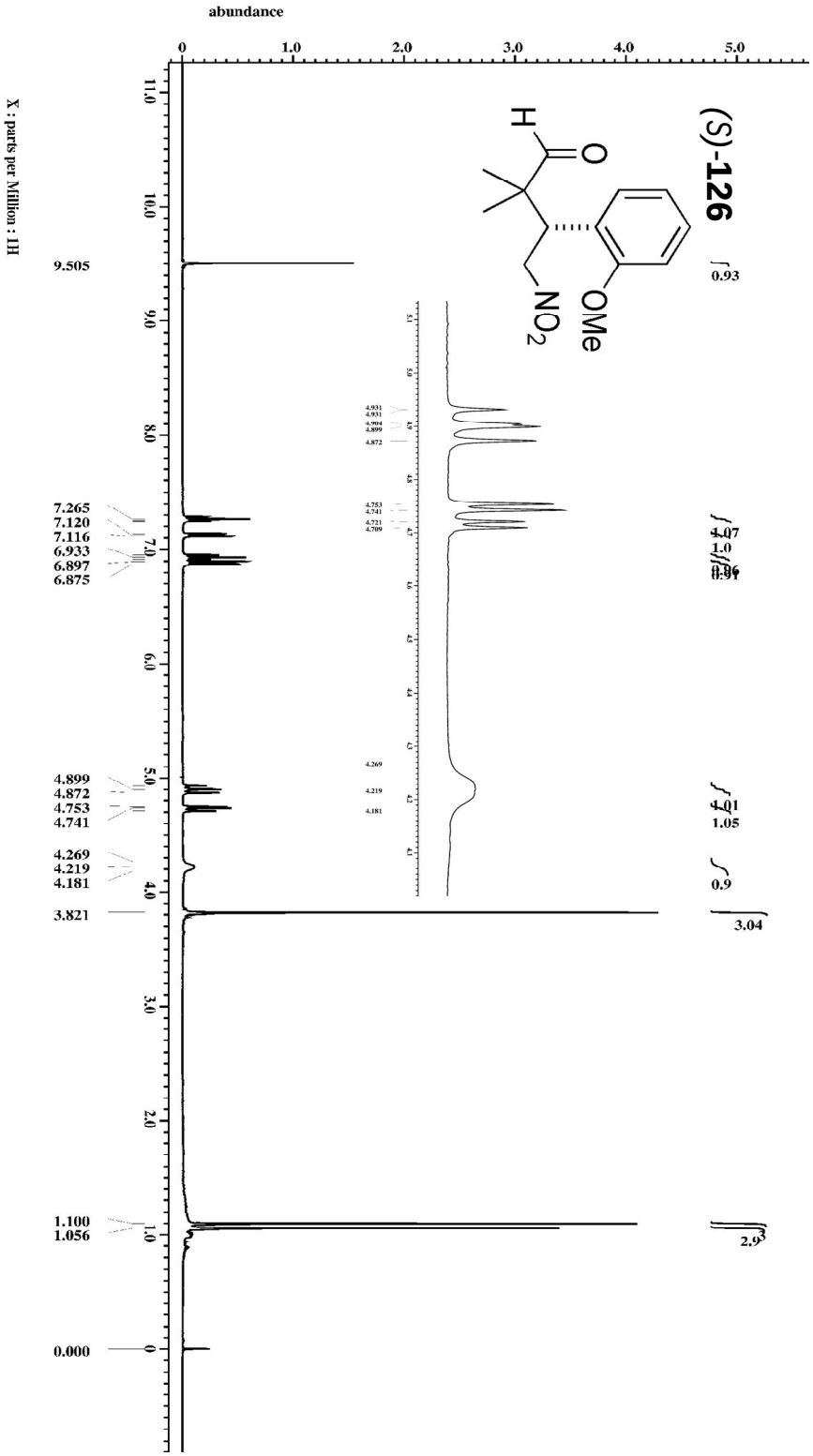
Enantioenriched 3-(2-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	8.240	671897	42117	1.986	3.818	0.458	
2	12.965	33158957	1060869	98.014	96.182	0.906	
Total		33830854	1102986	100.000	100.000		

^{1}H NMR of (S)-3-(2-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal

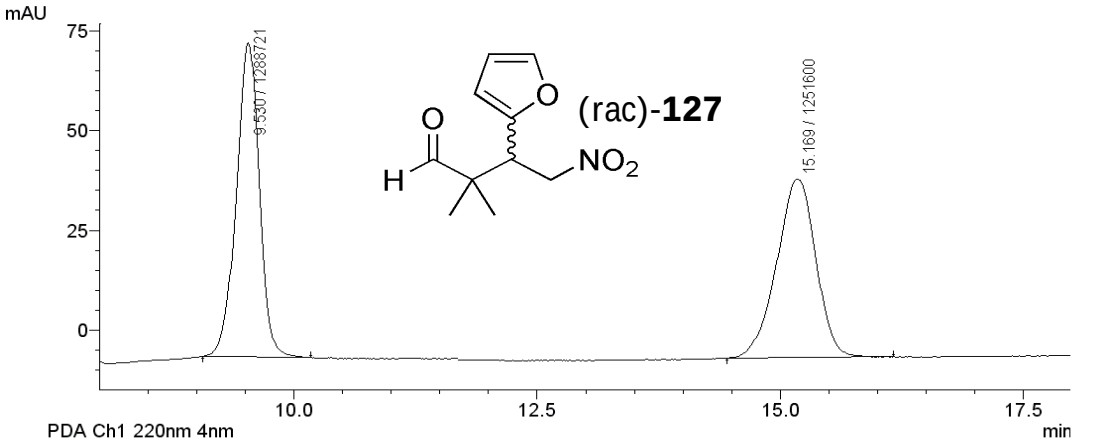


***(S)*-3-(furan)-2-yl)-2,2-dimethyl-4-nitrobutanal (127)**

The title compound was prepared from 2-(2-nitrovinyl)furan and isobutyraldehyde using method B. Reaction time: 10 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-19) and HPLC (chromatogram on p. S-18) of the crude product showed it to be of very high chemical purity; yield = 98%; ee = 98% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 25/75, flow rate = 0.8 mL/min, λ = 220 nm); t_{minor}= 9.4 min, t_{major}= 14.2 min.

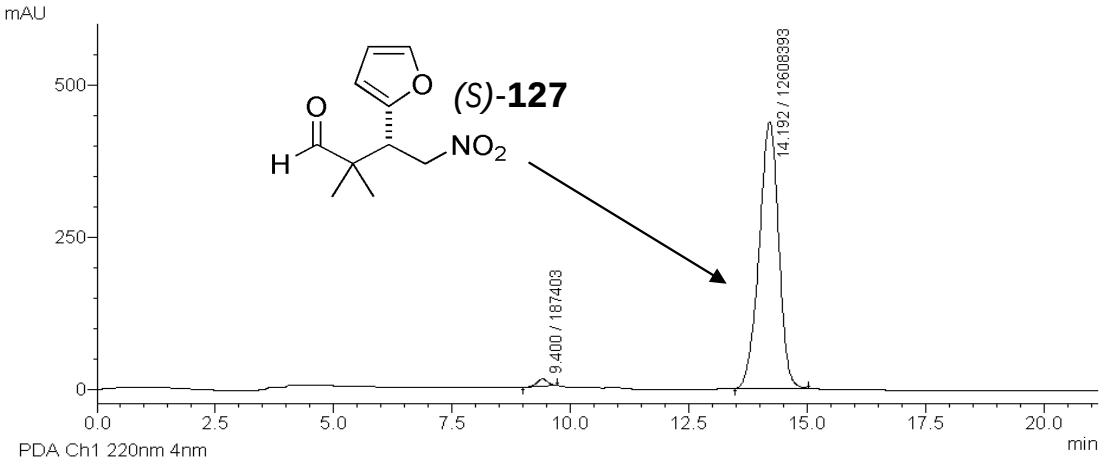
^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.05 (s, 3H), 1.18 (s, 3H), 3.91 (dd, 1H, *J* = 3.7, 11.0 Hz), 4.58 (dd, 1H, *J* = 3.7, 12.8 Hz), 4.75 (dd, 1H, *J* = 11.0, 12.8 Hz), 6.22 (d, 1H, *J* = 3.2), 6.31 (dd, *J* = 1.8, 3.2 Hz), 7.36 (d, 1H, *J* = 1.8 Hz), 9.52 (s, 1H).

Racemic 3-(furan)-2-yl)-2,2-dimethyl-4-nitrobutanal



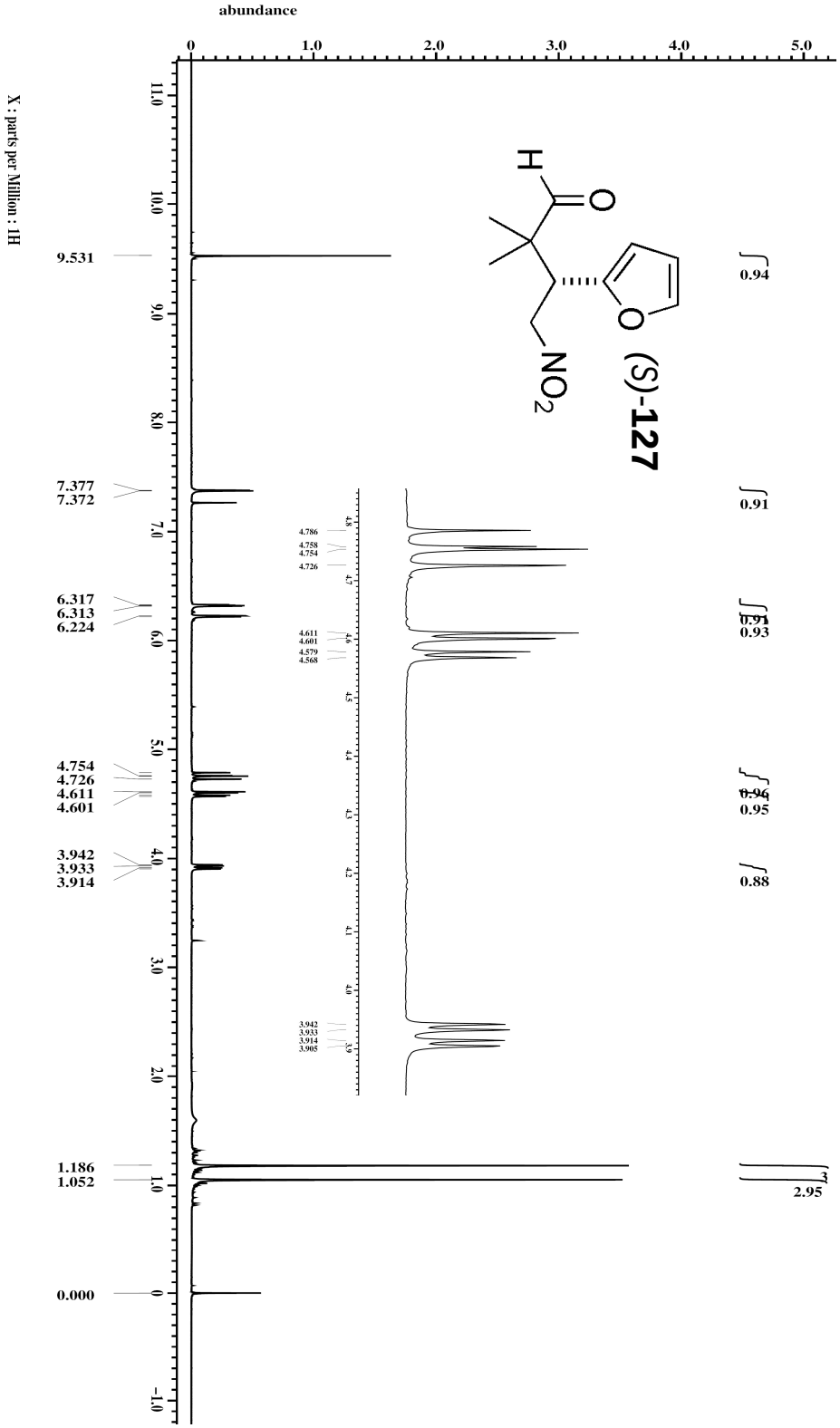
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.530	1288721	78615	50.731	63.722	0.482	
2	15.169	1251600	44757	49.269	36.278	0.813	
Total		2540322	123372	100.000	100.000		

Enantioenriched 3-(furan)-2-yl)-2,2-dimethyl-4-nitrobutanal



Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.400	187403	11880	1.465	2.636	0.466	
2	14.192	12608393	438854	98.535	97.364	0.840	
Total		12795796	450734	100.000	100.000		

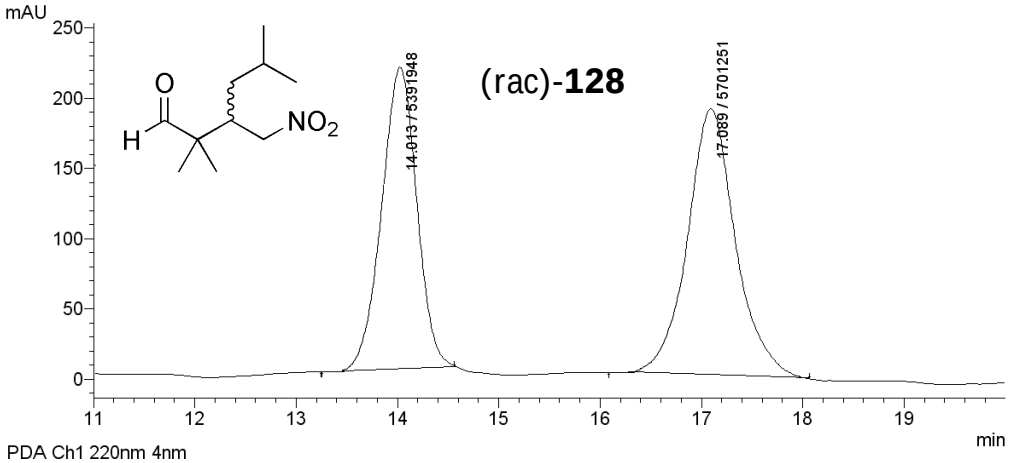
^{1}H NMR of (S)-3-(furan)-2-yl)-2,2-dimethyl-4-nitrobutanal



(2S)-2,2,5-trimethyl-3-nitromethyl-hexanal (128)

The title compound was prepared from 2-isobutyl-1-nitroethene and isobutyraldehyde using method B. Reaction time: 36 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 70%; ee = 96% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 10/90, flow rate = 0.4 mL/min, λ = 220 nm); t_{minor}= 13.9 min, t_{major}= 16.9 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 0.90 (d, 3H, *J* = 5.8 Hz), 0.91 (d, 3H, *J* = 5.8 Hz), 1.06 (s, 3H), 1.07 (s, 3H), 1.09-1.16 (m, 1H), 1.21-1.30 (m, 1H), 2.62-2.68 (m, 1H), 4.23 (dd, 1H, *J* = 5.4, 13.0 Hz), 4.44 (dd, 1H, *J* = 5.4, 13.0 Hz), 9.43 (s, 1H).

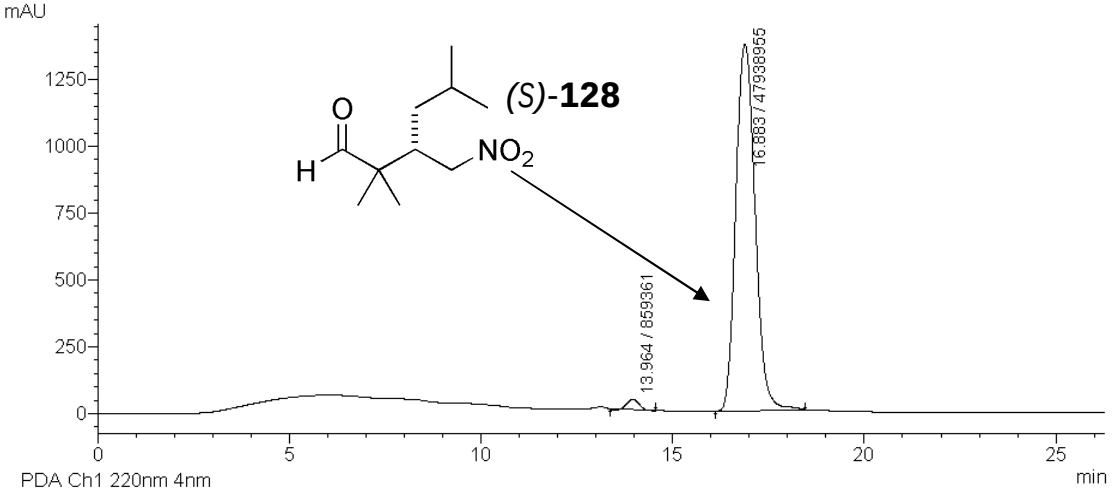
Racemic 2,2,5-trimethyl-3-nitromethyl-hexanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.013	5391948	215623	48.606	54.035	0.000	
2	17.089	5701251	183417	51.394	45.965	0.950	
Total		11093199	399040	100.000	100.000		

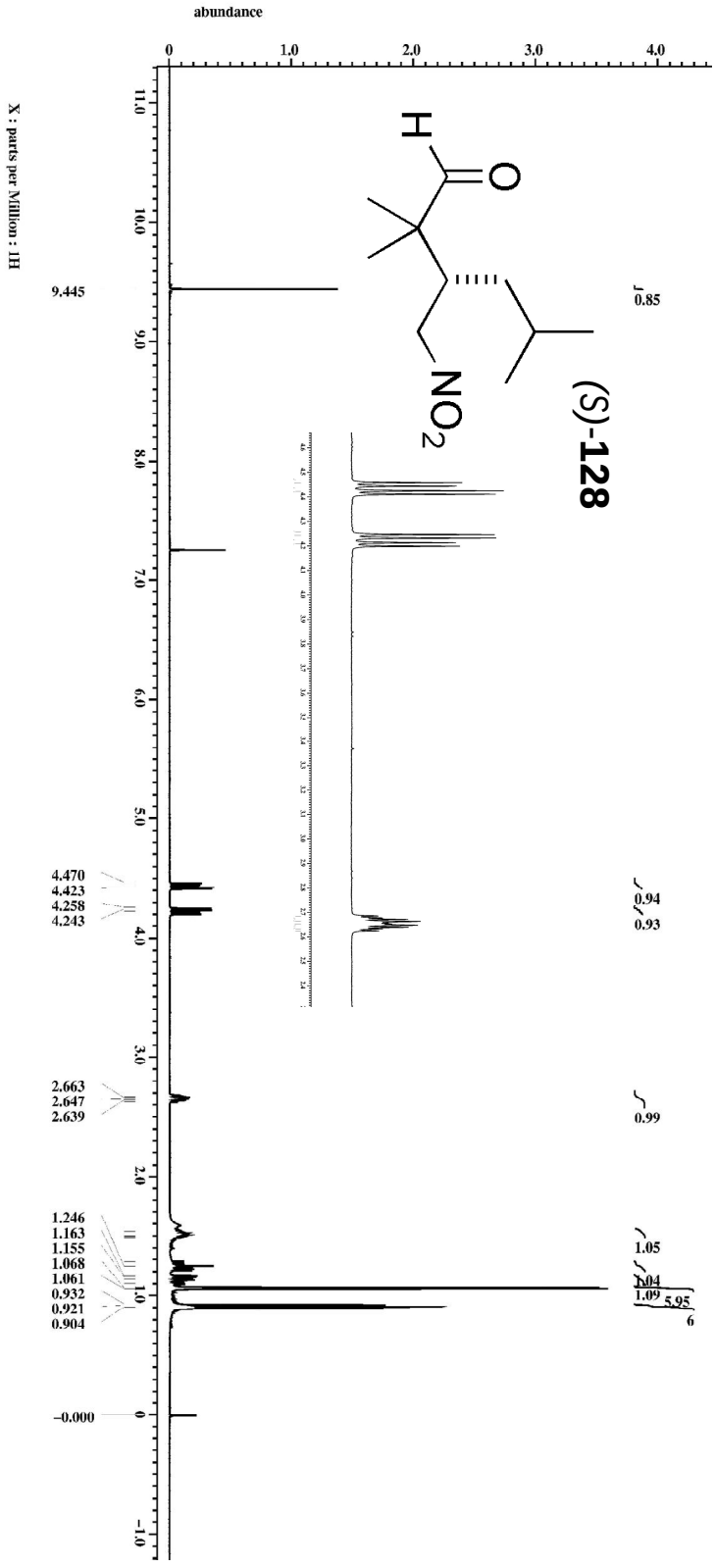
Enantioenriched 2,2,5-trimethyl-3-nitromethyl-hexanal



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.964	859361	40614	1.761	2.876	0.613	
2	16.883	47938955	1371442	98.239	97.124	0.969	
Total		48798316	1412056	100.000	100.000		

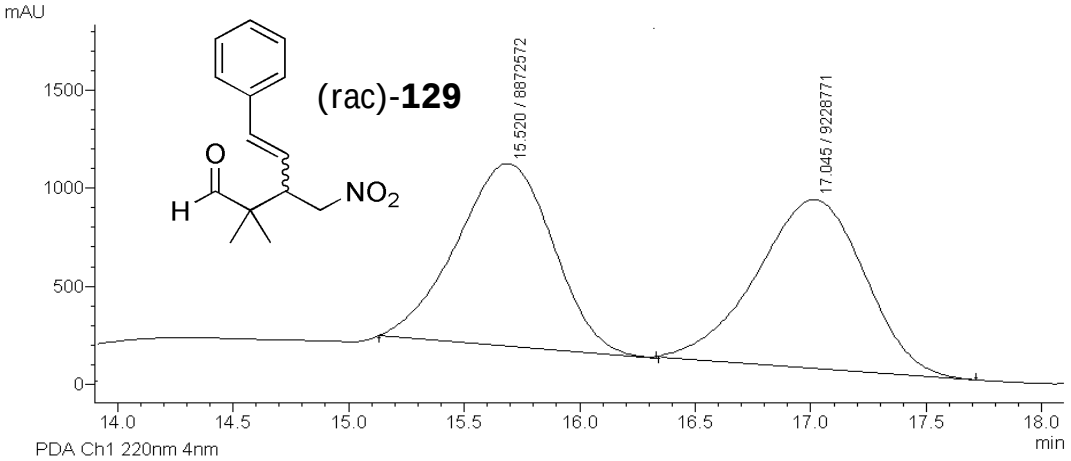
^{1}H NMR of (2S)-2,2,5-trimethyl-3-nitromethyl-hexanal



***(S)*-E-2,2-dimethyl-3-(nitromethyl)-5-phenylpent-4-enal (129)**

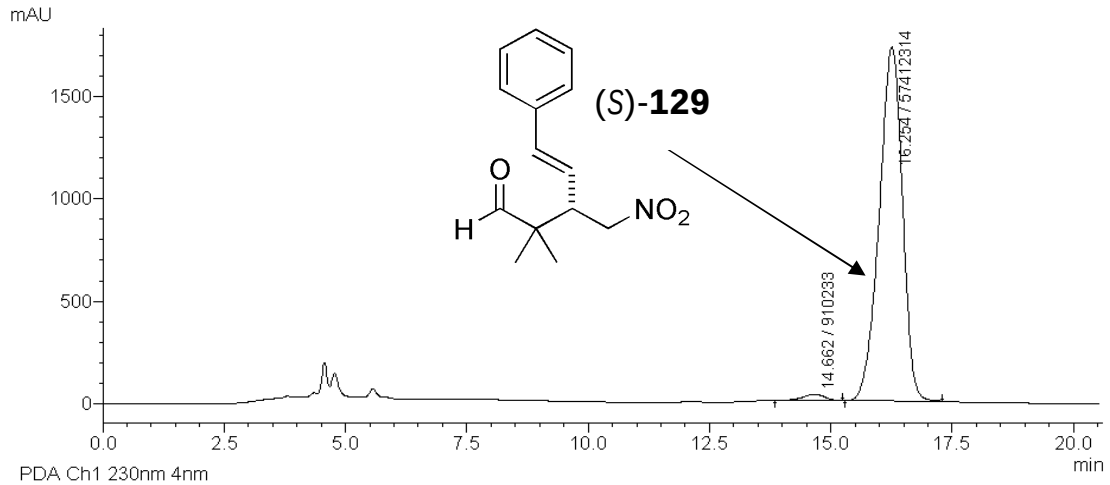
The title compound was prepared from (1E,2E)-4-nitrobuta-1,3-dienylbenzene and isobutyraldehyde using method B. Reaction time: 6 h; No column chromatography was required, ^{1}H NMR (see spectrum on p. S-23) and HPLC (chromatogram on p. S-22) of the crude product showed it to be of very high chemical purity; yield = 98%; ee = 97% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 0.8 mL/min, λ = 220 nm); t_{minor}= 14.7 min, t_{major}= 16.3 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.16 (s, 3H), 1.17 (s, 3H), 3.28 (dt, 1H, *J* = 4.1, 10.5 Hz), 4.45-4.48 (m, 1H), 4.51 (dd, 1H, *J* = 4.1, 12 Hz), 6.01 (dd, 1H, *J* = 10.1, 15.8 Hz), 6.53 (d, 1H, *J* = 15.8 Hz), 7.21-7.35 (m, 5H), 9.51 (s, 1H).

Racemic E-2,2-dimethyl-3-(nitromethyl)-5-phenylpent-4-enal



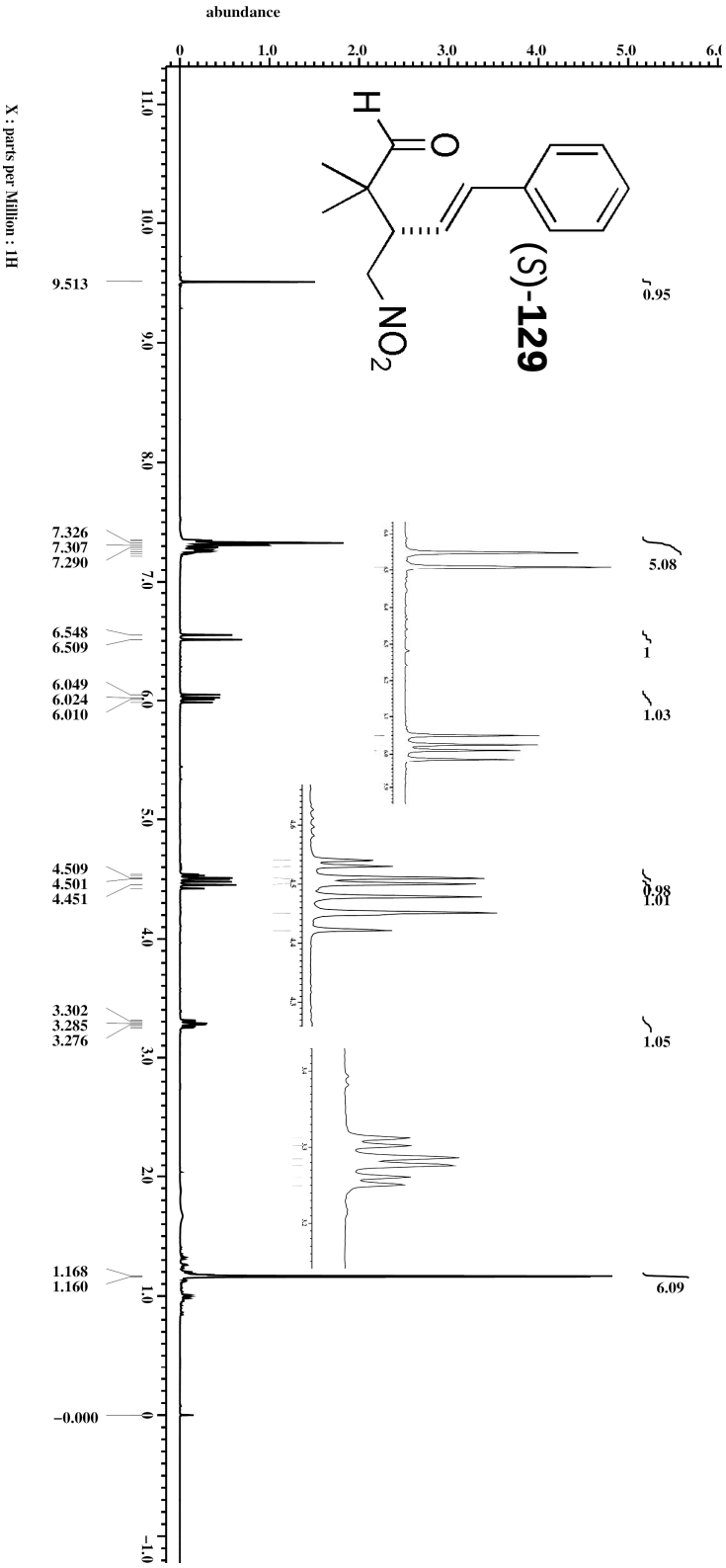
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	15.520	8872572	322497	49.016	51.918	0.792	
2	17.045	9228771	298675	50.984	48.082	0.897	
Total		18101343	621171	100.000	100.000		

Enantioenriched E-2,2-dimethyl-3-(nitromethyl)-5-phenylpent-4-enal



Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.662	910233	30161	1.561	1.714	0.882	
2	16.254	57412314	1729030	98.439	98.286	0.963	
Total		58322546	1759191	100.000	100.000		

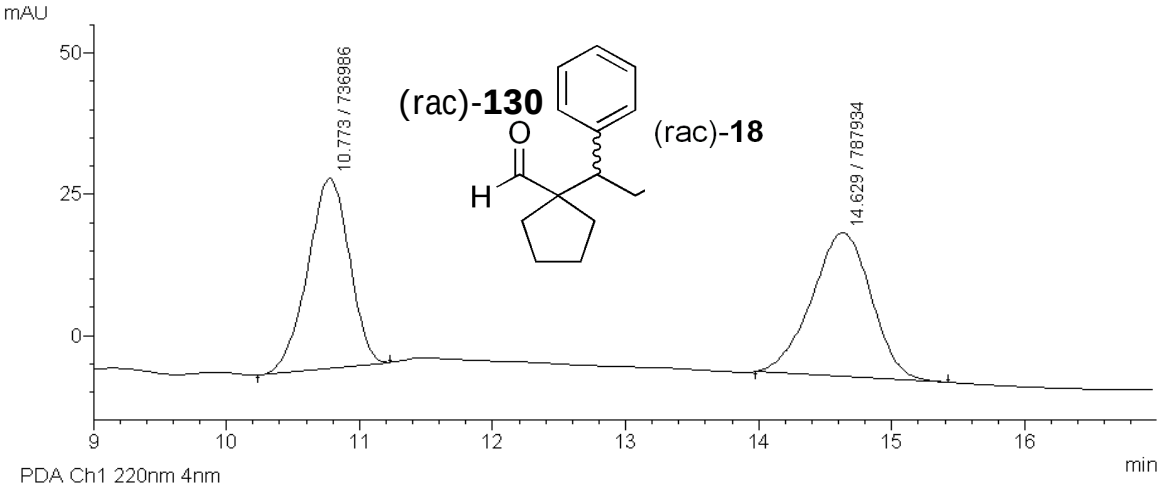
^{1}H NMR of (S)-E-2,2-dimethyl-3-(nitromethyl)-5-phenylpent-4-enal



***(S)*-1-(2-nitro-1-phenyl-ethyl)-cyclopentanecarbaldehyde (130)**

The title compound was prepared from *trans*- *β*-nitrostyrene and cyclopentanecarbaldehyde using method C. Reaction time: 7 h; purified by flash column chromatography; yield = 89%; ee = 97% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 10.6 min, t_{major}= 14.6 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.51-1.67 (m, 6H), 1.86-1.92 (m, 1H), 2.02-2.07 (m, 1H), 3.69 (dd, 1H, *J* = 3.7, 11.5 Hz), 4.7 (dd, 1H, *J* = 3.7, 13.3 Hz), 4.96 (dd, 1H, *J* = 11.5, 13.3 Hz), 7.18-7.20 (m, 2H), 7.26-7.33 (m, 3H), 9.49 (s, 1H).

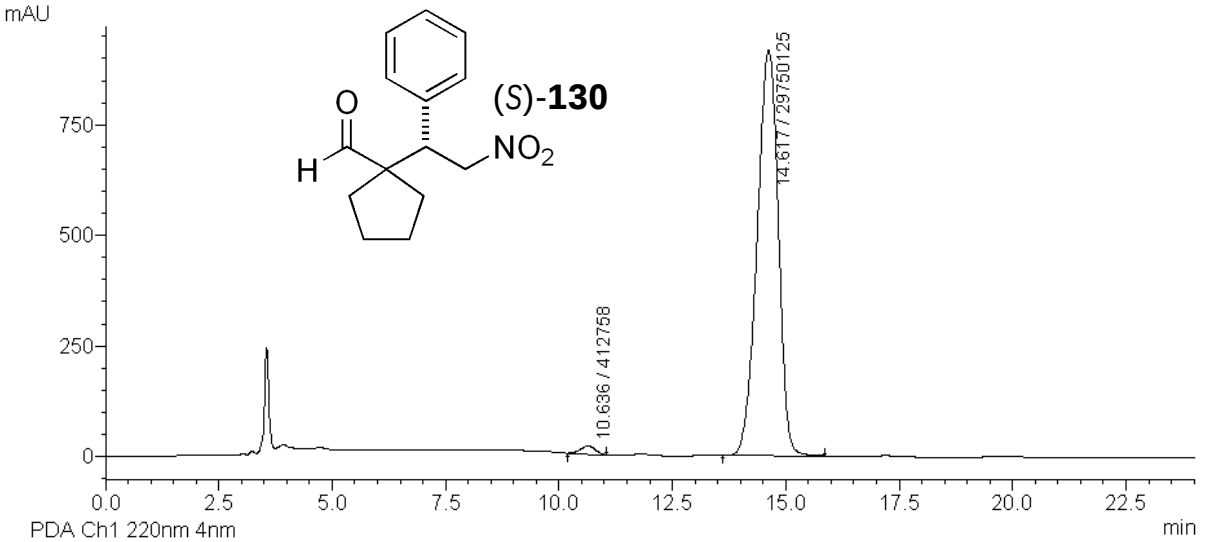
Racemic 1-(2-nitro-1-phenyl-ethyl)-cyclopentanecarbaldehyde



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	10.773	736986	33698	48.330	57.000	0.635	
2	14.629	787934	25421	51.670	43.000	0.900	
Total		1524920	59120	100.000	100.000		

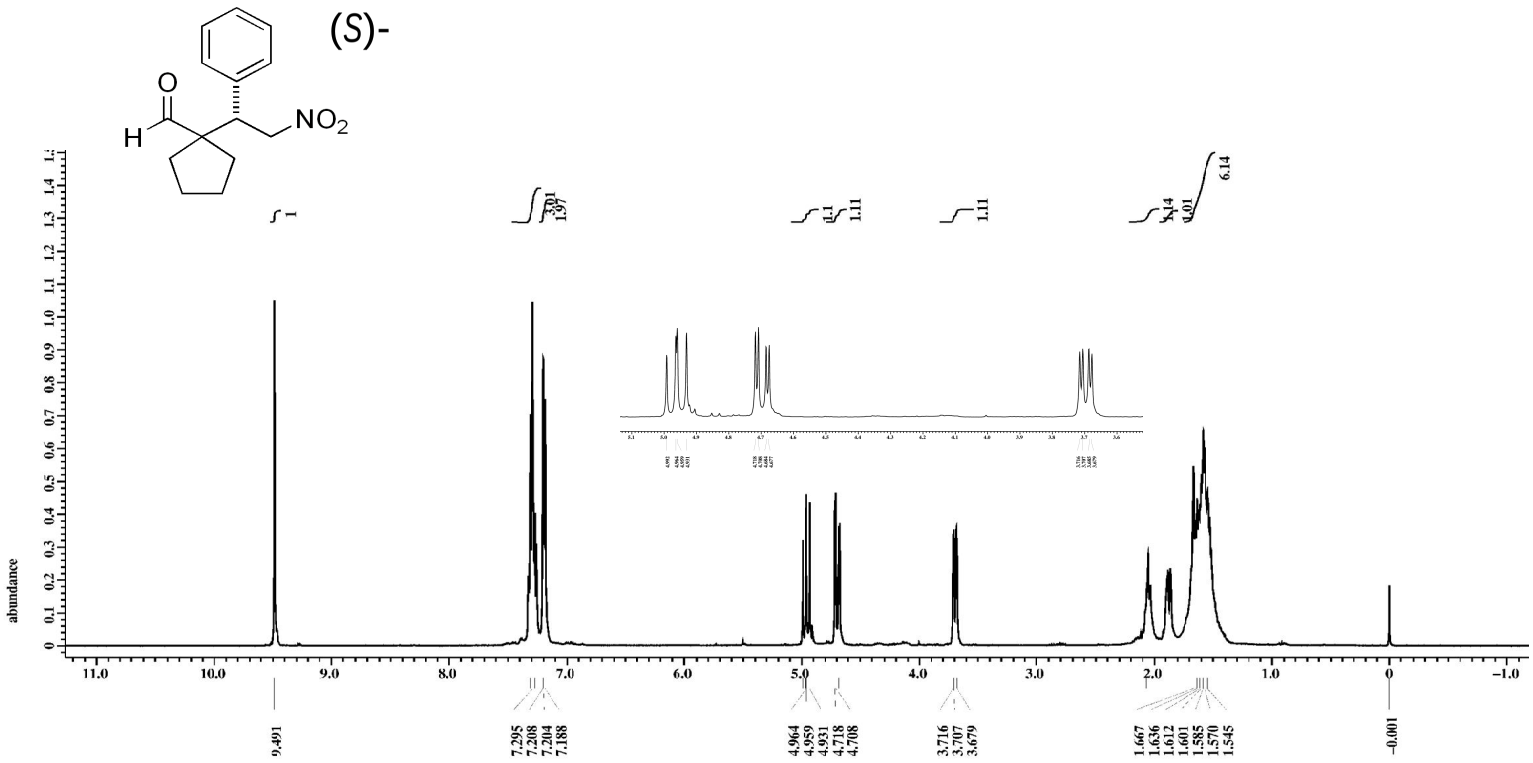
Enantioenriched 1-(2-nitro-1-phenyl-ethyl)-cyclopentanecarbaldehyde



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	10.636	412758	18470	1.368	1.976	0.645	
2	14.617	29750125	916087	98.632	98.024	0.916	
Total		30162883	934557	100.000	100.000		

^{1}H NMR of (S)-1-(2-nitro-1-phenyl-ethyl)-cyclopentanecarbaldehyde (18)



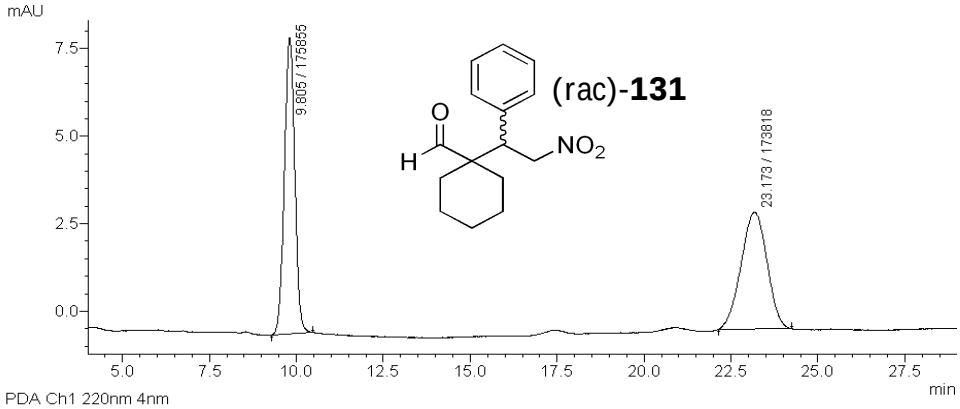
***(S)*-1-(2-nitro-1-phenyl-ethyl)-cyclohexanecarbaldehyde (131)**

The title compound was prepared from *trans*- *β*-nitrostyrene and cyclohexanecarbaldehyde using method C, and using a catalytic system having 10 mol% each of sulfamide, DMAP and O^{t}Bu-L-threonine.

Compound obtained using method C: Reaction time: 30 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 64%; ee = 90% as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 20/80, flow rate = 1.0 mL/min, λ = 220 nm); t_{minor}= 9.4 min, t_{major}= 20.8 min.

Compound obtained using 10 mol% sulfamide, DMAP and O^{t}Bu-L-threonine: Reaction time: 48 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 88%; ee = 91% as determined by HPLC (conditions and retention times as above). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.06-1.27 (m, 4H), 1.36-1.43 (m, 1H), 1.56-1.68 (m, 3H), 1.84-1.88 (m, 1H), 2.06-2.09 (m, 1H), 3.54 (dd, 1H, *J* = 4.6, 11 Hz), 4.73 (dd, 1H, *J* = 4.6, 13.3 Hz), 4.8 (dd, 1H, *J* = 11, 13.3 Hz), 7.10-7.14 (m, 2H), 7.26-7.33 (m, 3H), 9.54 (s, 1H)

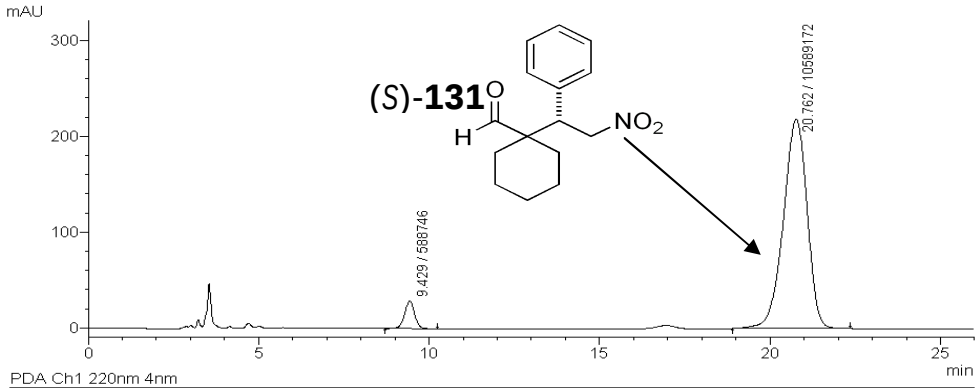
Racemic 1-(2-nitro-1-phenyl-ethyl)-cyclohexanecarbaldehyde



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.805	175855	8453	50.291	71.658	0.595	
2	23.173	173818	3343	49.709	28.342	1.481	
Total		349673	11797	100.000	100.000		

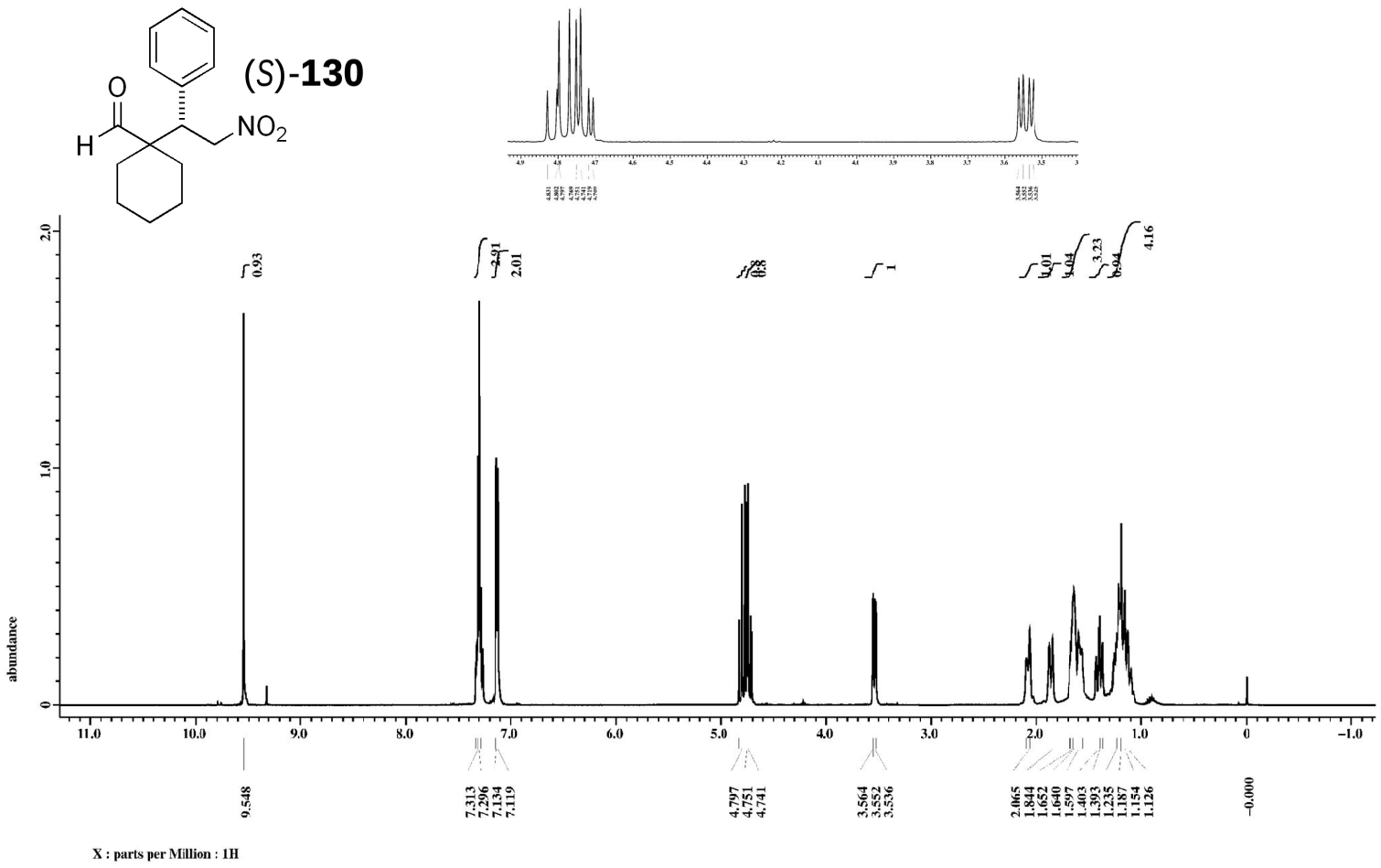
Enantioenriched 1-(2-nitro-1-phenyl-ethyl)-cyclohexanecarbaldehyde



PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.429	588746	28891	5.267	11.673	0.600	
2	20.762	10589172	218616	94.733	88.327	1.389	
Total		11177918	247506	100.000	100.000		

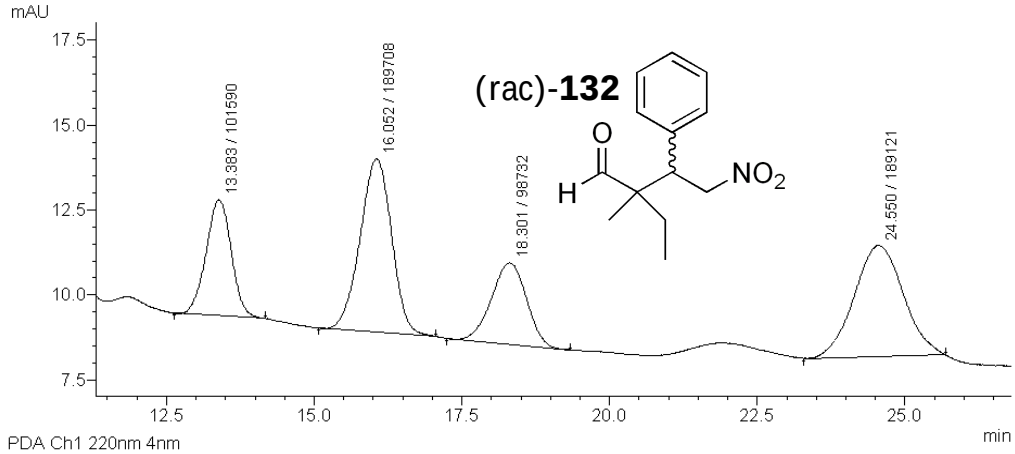
^{1}H NMR of (S)-1-(2-nitro-1-phenyl-ethyl)-cyclohexanecarbaldehyde



(2S,3S)-2-ethyl-2-methyl-4-nitro-3-phenyl-butyraldehyde (132)

The title compound was prepared from *trans-β*-nitrostyrene and 2-methylbutanal using method C. Reaction time: 12 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 84%; ee = 97%, dr = 70:30 (syn/anti) as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 10/90, flow rate = 1.0 mL/min, λ = 220 nm); $t_{(anti,\ minor)}$= 13.4 min, $t_{(syn,\ minor)}$= 15.9 min, $t_{(anti,\ major)}$= 17.8 min, $t_{(syn,\ major)}$= 24.1 min. ^{1}H NMR (400 MHz, $CDCl_3$, diastereomer mixture) (ppm): 0.8 (*syn*) and 0.88 (*anti*) (t, 3H, *J* = 7.5 and 7.4 Hz), 1.1 (*syn*) and 1.13 (*anti*) (s, 3H), 1.24-1.34 (m, 1H), 1.5-1.77 (m, 1H), 3.77 (*anti*) and 3.79 (*syn*) (dd, 1H, *J* = 4.4, 11.2 and 4.0, 11.5 Hz), 4.61 (*syn*) and 4.76 (*anti*) (dd, 1H, *J* = 4.0, 13.0 and 4.4, 13.1 Hz), 4.83 (*syn*) and 4.85 (*anti*) (dd, 1H, *J* = 11.5, 13.0 and 11.2, 13.1 Hz), 7.15-7.21 (m, 2H), 7.27-7.34 (m, 3H), 9.51(*anti*) and 9.53 (*syn*) (s, 1H).

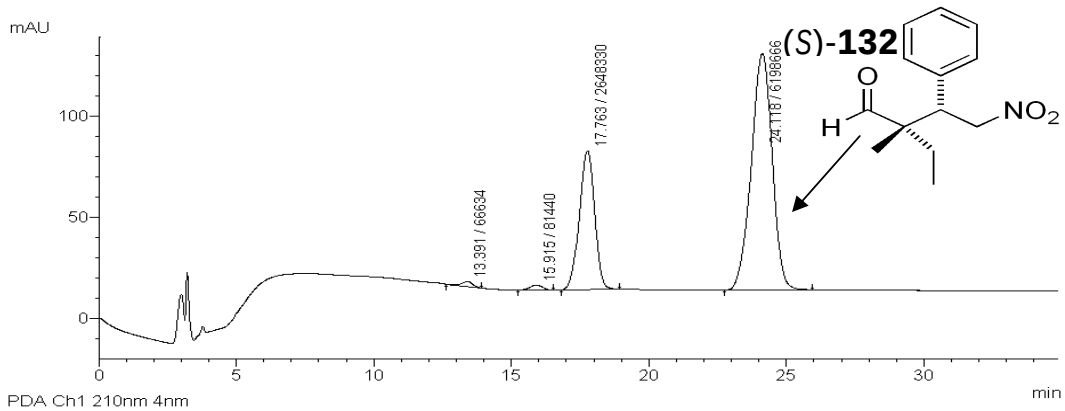
Racemic 2-ethyl-2-methyl-4-nitro-3-phenyl-butyraldehyde



PDA Ch1 220nm 4nm

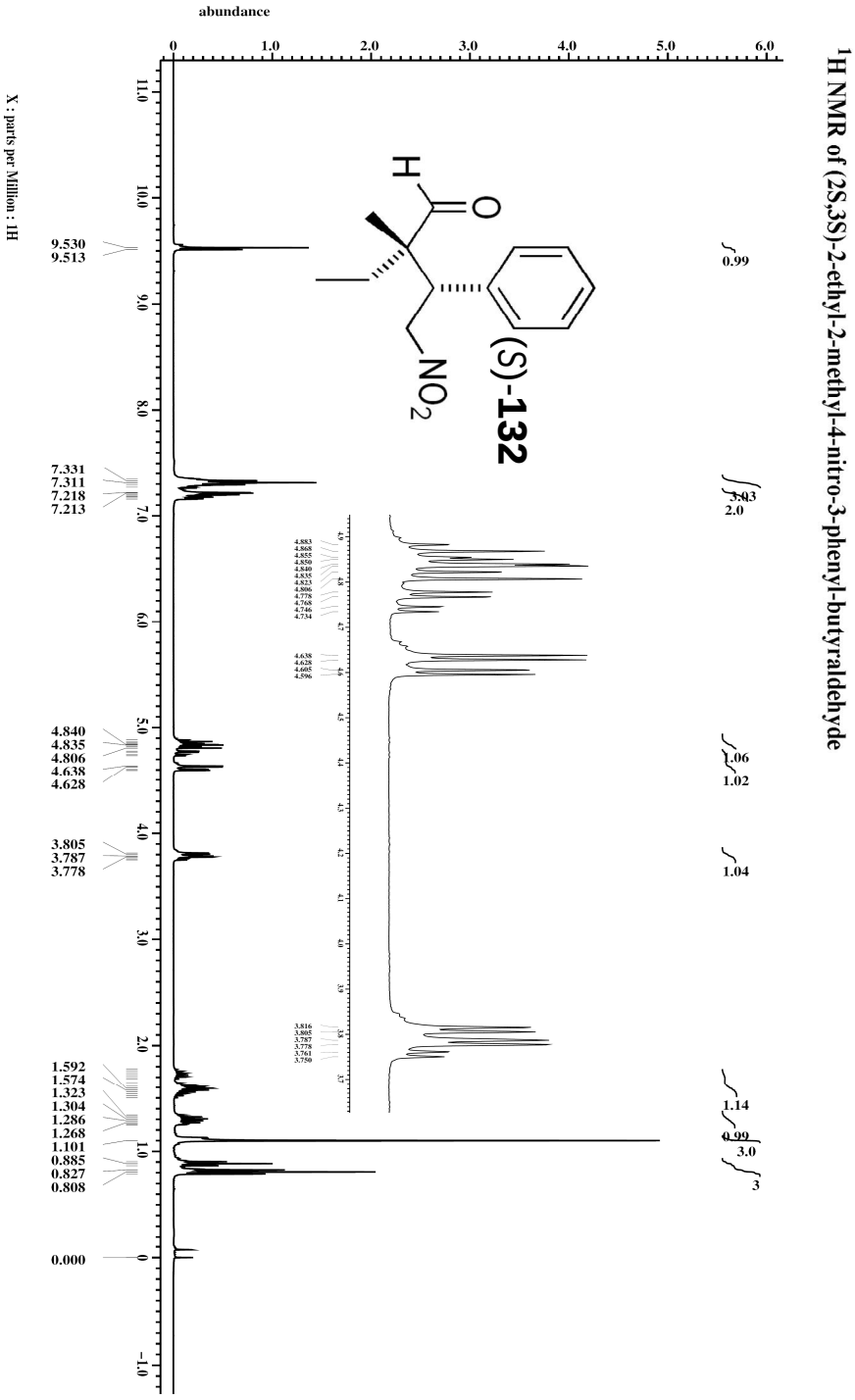
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.383	101590	3416	17.541	24.089	0.858	
2	16.052	189708	5103	32.756	35.984	1.068	
3	18.301	98732	2393	17.048	16.879	1.185	
4	24.550	189121	3268	32.655	23.048	1.703	

Enantioenriched 2-ethyl-2-methyl-4-nitro-3-phenyl-butyraldehyde



PDA Ch1 210nm 4nm

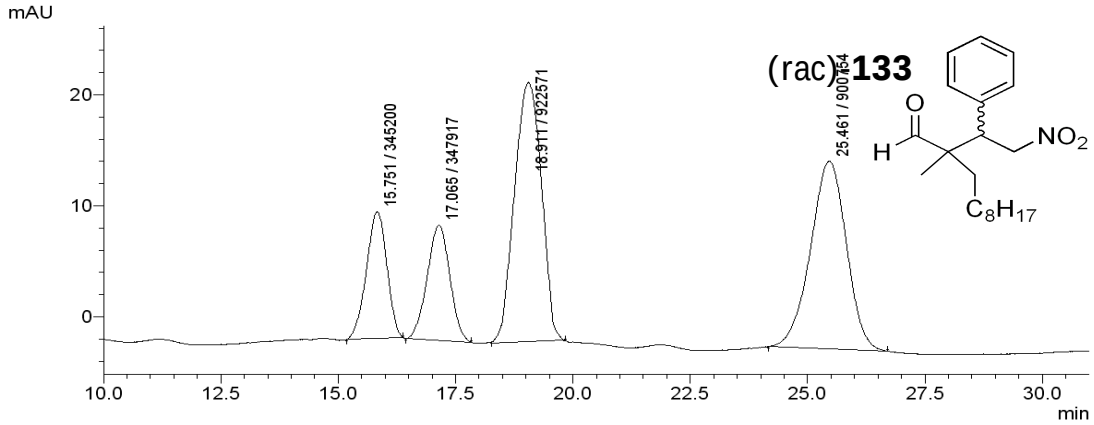
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.391	66634	2411	0.741	1.266	0.805	
2	15.915	81440	2490	0.905	1.308	0.933	
3	17.763	2648330	68580	29.442	36.012	1.118	
4	24.118	6198666	116954	68.912	61.414	1.535	
Total		8995070	190435	100.000	100.000		


^{1}H NMR of (2S,3S)-2-ethyl-2-methyl-4-nitro-3-phenyl-butyraldehyde
(S)-132
abundance
X : parts per Million : 1H
9.530
9.513
7.331
7.311
7.218
7.213
4.840
4.835
4.806
4.638
4.628
3.805
3.787
3.778
1.592
1.574
1.323
1.304
1.286
1.268
1.101
0.885
0.827
0.808
0.000
0.99
3.03
2.0
1.06
1.02
1.04
1.14
0.99
3.0
3

(2S)-2-methyl-2-[(2S)-2-nitro-1-phenylethyl]undecanal (21)

The title compound was prepared from *trans*-*β*-nitrostyrene and 2-methylundecanal using method C. Reaction time: 12 h flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 71%; ee = 91%, dr = 78:22 (syn/anti) as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 5/95, flow rate = 0.7 mL/min, λ = 220 nm); $t_{(anti, minor)}$= 14.9 min, $t_{(anti, major)}$= 16.1 min, $t_{(syn, minor)}$= 17.5 min, $t_{(syn, major)}$= 23.7 min. ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 0.87-0.88 (m, 3H), 1.1 (s, 3H), 1.14-1.72 (m, 16H), 3.79 (dd, 1H, *J* = 4.1, 11.5 Hz), 4.62 (dd, 1H, *J* = 4.1, 12.8 Hz), 4.84 (dd, 1H, *J* = 11.5, 12.8 Hz), 7.15-7.21 (m, 2H), 7.26-7.35 (m, 3H), 9.52 (s, 1H).

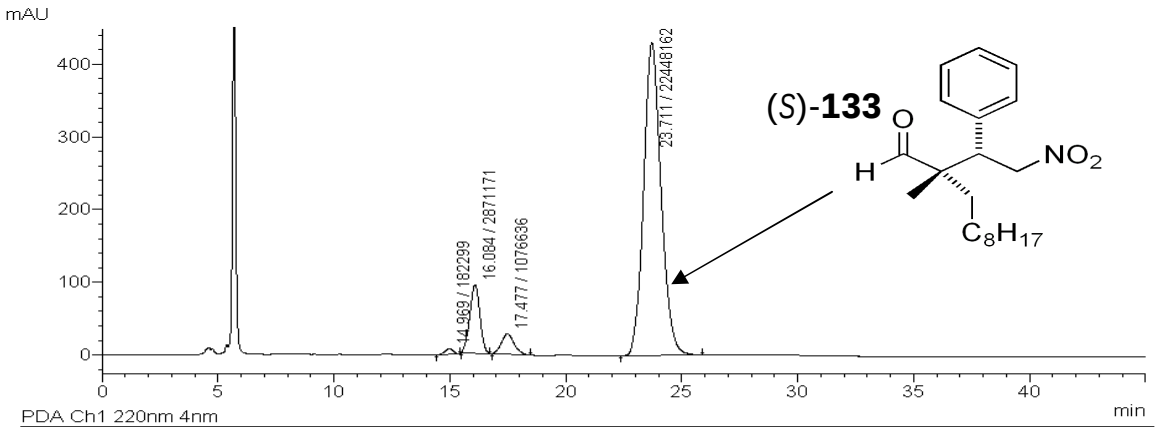
Racemic 2-methyl-2-(2-nitro-1-phenylethyl)undecanal



PDA Ch1 207nm 4nm

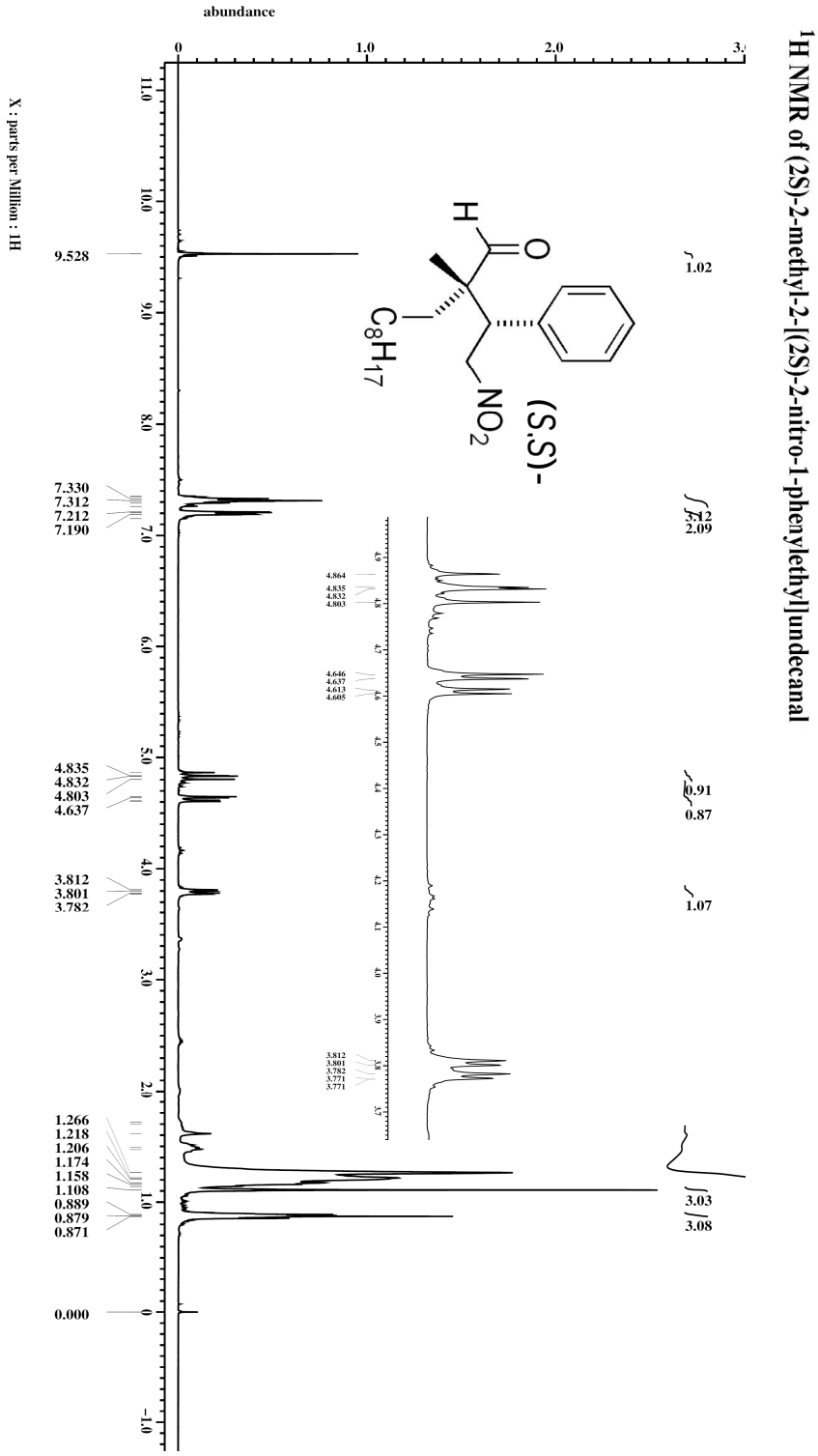
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	15.751	345200	11402	13.718	18.369	0.874	
2	17.065	347917	10373	13.826	16.711	0.972	
3	18.911	922571	23366	36.662	37.645	1.053	
4	25.461	900754	16929	35.795	27.274	1.554	
Total		2516441	62070	100.000	100.000		

Enantioenriched 2-methyl-2-(2-nitro-1-phenylethyl)undecanal



PDA Ch1 220nm 4nm

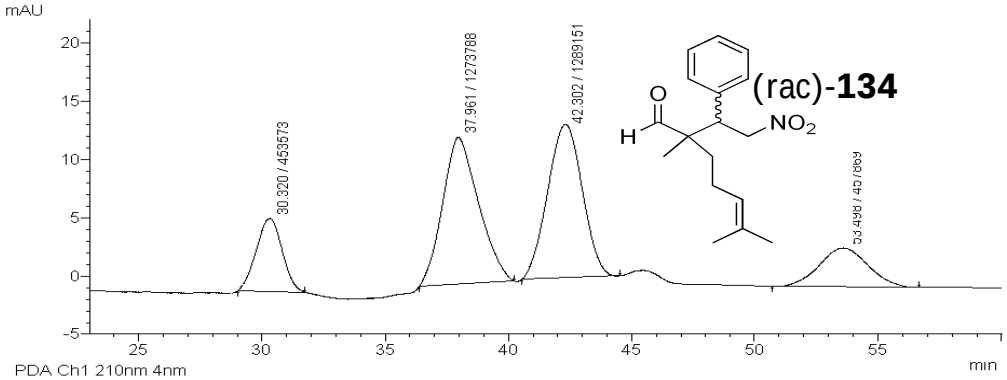
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.969	182299	7444	0.686	1.328	0.696	
2	16.084	2871171	94528	10.803	16.860	0.888	
3	17.477	1076636	28153	4.051	5.021	1.157	
4	23.711	22448162	430549	84.461	76.791	1.569	
Total		26578269	560674	100.000	100.000		


^{1}H NMR of (2S)-2-methyl-2-[(2S)-2-nitro-1-phenylethyl]undecanal
abundance
X : parts per Million : 1H
(S,S)-
C_8H_{17}
NO_2
9.528
7.330
7.312
7.212
7.190
4.835
4.832
4.803
4.637
3.812
3.801
3.782
1.266
1.218
1.206
1.174
1.158
1.108
0.889
0.879
0.871
0.000
1.02
2.12
2.09
0.91
0.87
1.07
3.03
3.08

(2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-phenylethyl]hept-5-enal (134)

The title compound was prepared from *trans-β*-nitrostyrene and 2,6-dimethylhept-5-enal using method C. Reaction time: 12 h; flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 70%; ee = 98%, dr = 77:23 (*syn*/*anti*) as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 1/99, flow rate = 1.5 mL/min, λ = 220 nm); $t_{(anti,\ minor)}$= 28.9 min, $t_{(syn,\ minor)}$= 35.6 min, $t_{(syn,\ major)}$= 38.8 min, $t_{(anti,\ major)}$= 48.3 min. ^{1}H NMR (400 MHz, $CDCl_3$, diastereomer mixture) (ppm): 1.12 (*anti*) and 1.13 (*syn*) (s, 3H), 1.23-1.31 (m, 1H), 1.54-1.72 (m, 1H), 1.52 (*syn*) and 1.55 (*anti*) (s, 3H), 1.63 (*syn*) and 1.65 (*anti*) (s, 3H), 1.83-1.88 (m, 2H), 3.76 (*anti*) and 3.78 (*syn*) (dd, 1H, *J* =4.5, 11 and 4.1, 11.5 Hz), 4.63 (*syn*) and 4.76 (*anti*) (dd, 1H, *J* = 4.1, 12.8 and 4.5, 13.1 Hz), 4.82 (*syn*) and 4.84 (*anti*) (dd, 1H, *J* = 11.5, 12.8 and 11, 13.1Hz), 4.92 (*syn*) and 4.99 (*anti*) (t, 1H, *J* = 7.3 Hz), 7.15-7.21 (m, 2H), 7.27-7.35 (m, 3H), 9.53 (*anti*) and 9.54 (*syn*) (s, 1H).

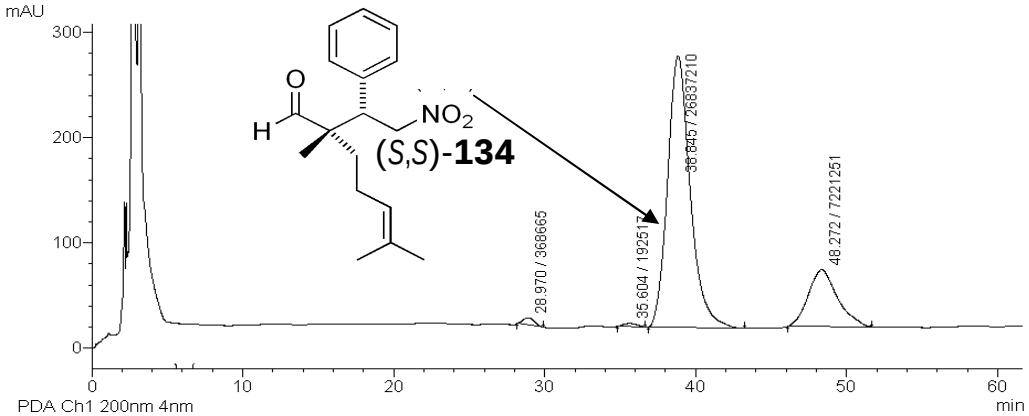
Racemic 2,6-dimethyl-2-(2-nitro-1-phenylethyl)hept-5-enal



PDA Ch1 210nm 4nm

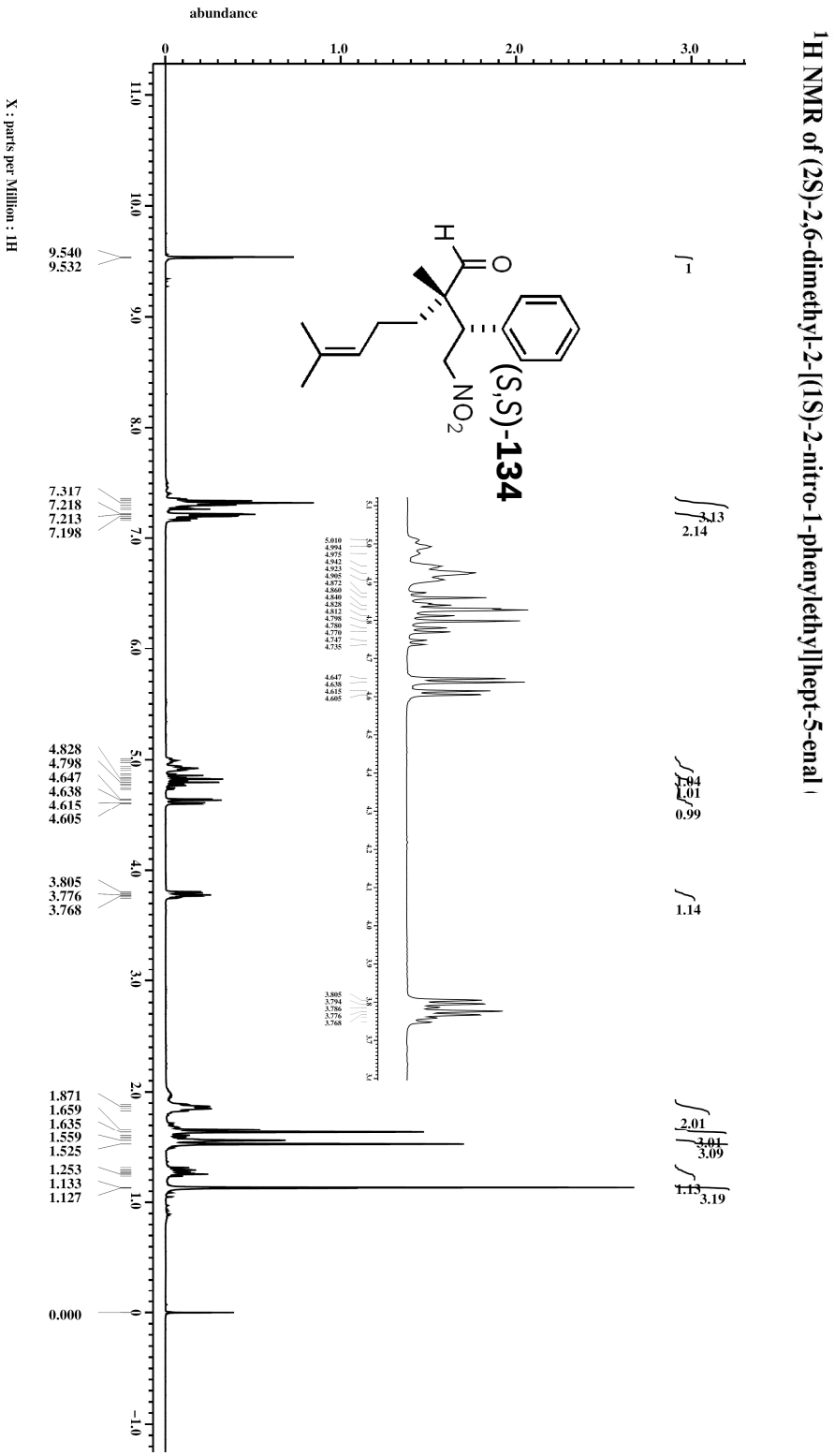
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	30.320	453573	6256	13.055	17.694	2.071	
2	37.961	1273788	12599	36.662	35.632	3.032	
3	42.302	1289151	13168	37.104	37.241	2.768	
4	53.498	457869	3335	13.178	9.433	4.016	
Total		3474381	35358	100.000	100.000		

Enantioenriched 2,6-dimethyl-2-(2-nitro-1-phenylethyl)hept-5-enal



PDA Ch1 200nm 4nm

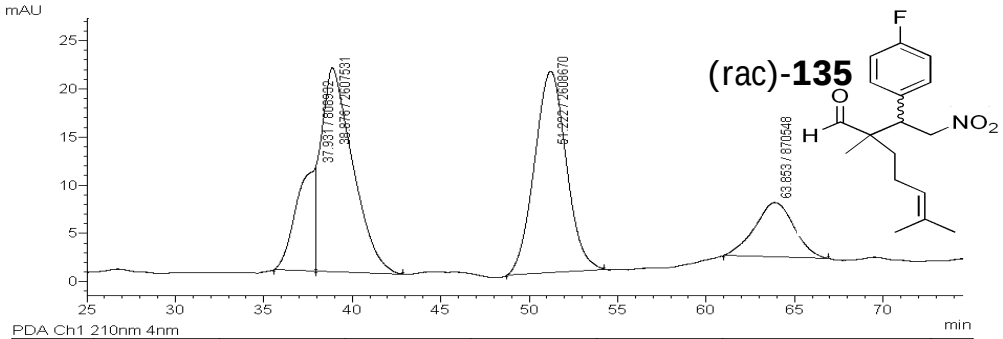
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	28.970	368665	6961	1.065	2.161	1.450	
2	35.604	192517	3187	0.556	0.990	1.646	
3	38.845	26837210	257854	77.520	80.059	3.136	
4	48.272	7221251	54075	20.859	16.789	4.174	
Total		34619643	322078	100.000	100.000		


^{1}H NMR of (2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-phenylethyl]hept-5-enal (
(S,S)-134
abundance
X : parts per Million : 1H
9.540
9.532
7.317
7.218
7.213
7.198
4.828
4.798
4.647
4.638
4.615
4.605
3.805
3.776
3.768
1.871
1.659
1.635
1.559
1.525
1.253
1.133
1.127
0.000
3.13
2.14
1.04
1.01
0.99
1.14
2.01
3.01
3.09
1.13
3.19

(2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(4-fluorophenyl)ethyl]hept-5-enal (135)

The title compound was prepared from *trans*-4-fluoro-*β*-nitrostyrene and 2,6-dimethylhept-5-enal using method C. Reaction time: 36 h; R_f = 0.58 (*syn*) EtOAc/pet ether (2:8); flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 80%; ee 99%, dr = 77:23 (syn/anti) as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/heptane 1/99, flow rate = 1.5 mL/min, λ = 220 nm); $t_{(anti,\ minor)}$= 36.6 min, $t_{(syn,\ minor)}$= 38.9 min, $t_{(syn,\ major)}$= 50.8 min, $t_{(anti,\ major)}$= 63.7 min. The compound was tentatively assigned the S,S (*syn*) configuration according to the ^{1}H NMR chemical shift trend for the *syn* and *anti* products of compound **22**. ^{1}H NMR (400 MHz, $CDCl_3$, diastereomer mixture) (ppm): 1.12 (s, 3H), 1.21-1.30 (m, 1H), 1.48-1.64 (m, 1H), 1.53 (*syn*) and 1.55 (*anti*) (s, 3H), 1.63 (*syn*) and 1.66 (*anti*) (s, 3H), 1.80-1.20 (m, 2H), 3.78 (*syn*) (dd, 1H, *J* =3.7, 11.4 Hz), 4.62 (syn) (dd, 1H, *J* = 4.0, 13.2 Hz), 4.75-4.82 (syn) (m, 1H), 4.90-5.00 (m, 1H), 7.01-7.05 (m, 2H), 7.15-7.26 (m, 2H), 9.50 (*anti*) and 9.52 (*syn*) (s, 1H). ^{13}C NMR (100MHz, $CDCl_3$) (ppm): 15.9, 17.7, 22.6, 25.6, 35.5, 47.0, 51.6, 76.4, 116, 122.8, 130.9, 133.1, 161.1, 163.7, 204.9. FT-IR: (KBr), ν_{max}: 1630, 1556, 1511, 1377, 1105, 741, 470 cm^{-1}; MS: HRMS (ESI-TOF) calculated for $C_{17}H_{22}FNO_3$ $[M+Na]^+$: 330.1461; found: 330.1476.

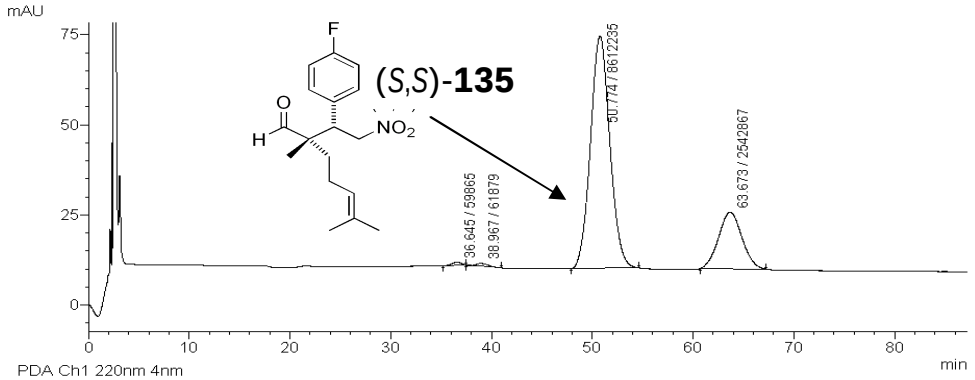
Racemic 2,6-dimethyl-2-[2-nitro-1-(4-fluorophenyl)ethyl]hept-5-enal



PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	37.931	808932	10800	11.731	18.468	0.000	
2	38.876	2607531	21168	37.814	36.198	0.000	V
3	51.222	2608670	20868	37.830	35.685	3.632	
4	63.853	870548	5643	12.625	9.649	4.579	
Total		6895681	58479	100.000	100.000		

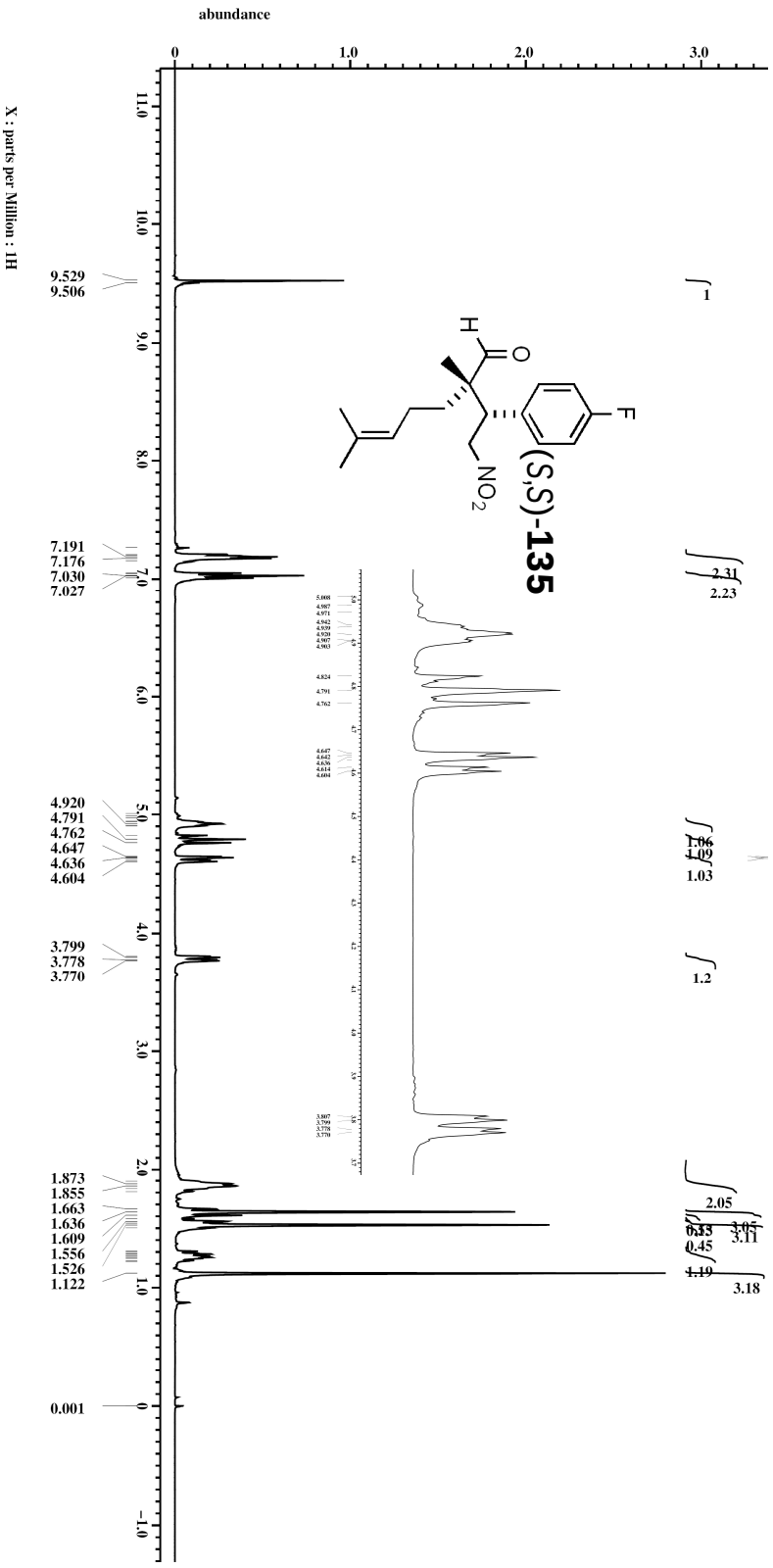
Enantioenriched 2,6-dimethyl-2-[2-nitro-1-(4-fluorophenyl)ethyl]hept-5-enal



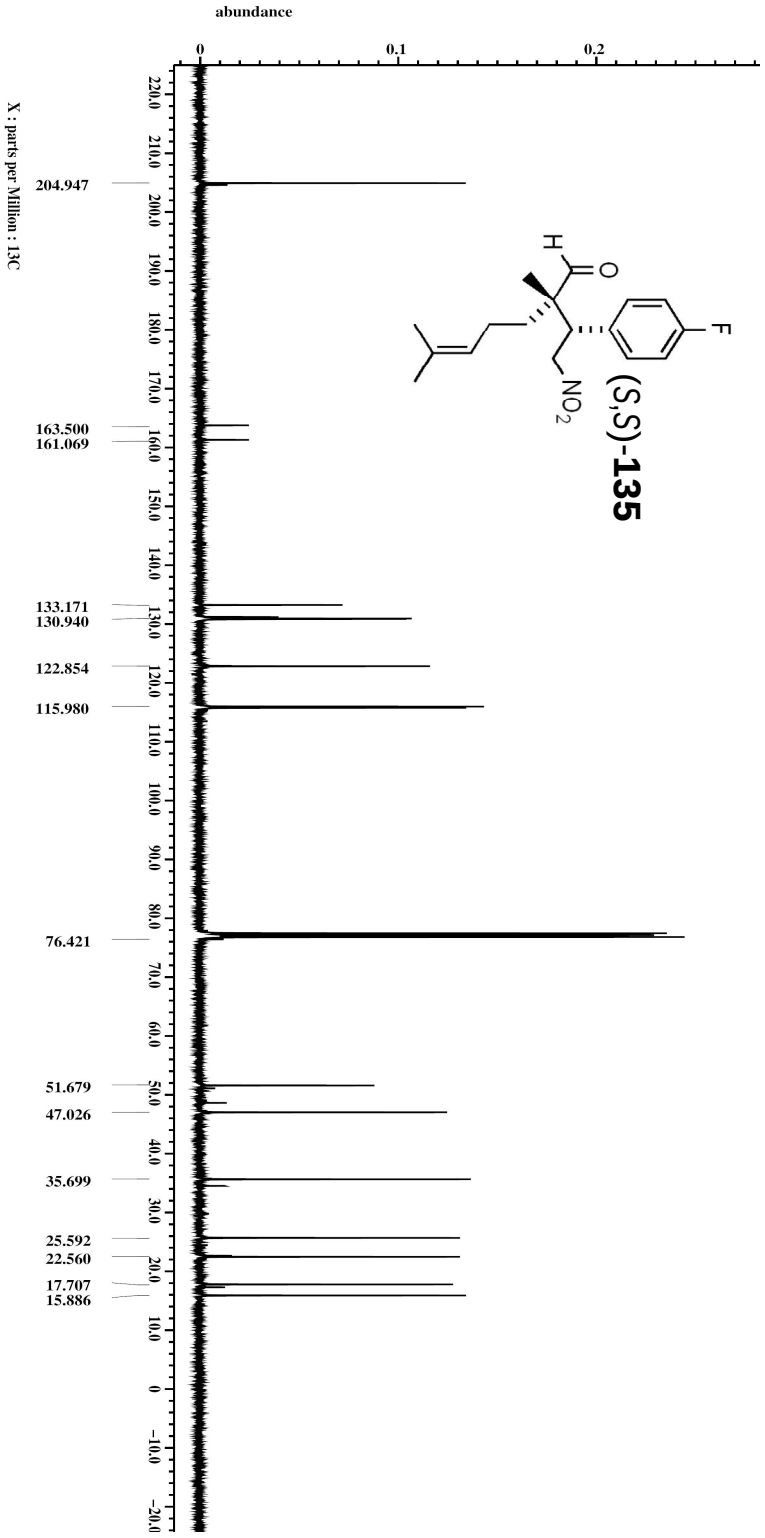
PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	36.645	59865	876	0.531	1.070	1.890	
2	38.967	61879	837	0.549	1.022	2.179	
3	50.774	8612235	64397	76.371	78.645	3.930	
4	63.673	2542867	15773	22.549	19.263	4.714	
Total		11276846	81883	100.000	100.000		

^{1}H NMR of (2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(4-fluorophenyl)ethyl]hept-5-enal



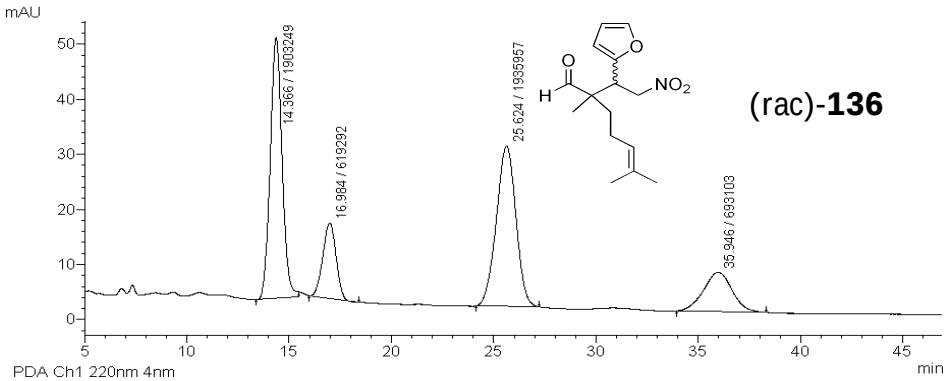
^{13}C NMR of (2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(4-fluorophenyl)ethyl]hept-5-enal



(2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(furan-2-yl)ethyl]hept-5-enal (136)

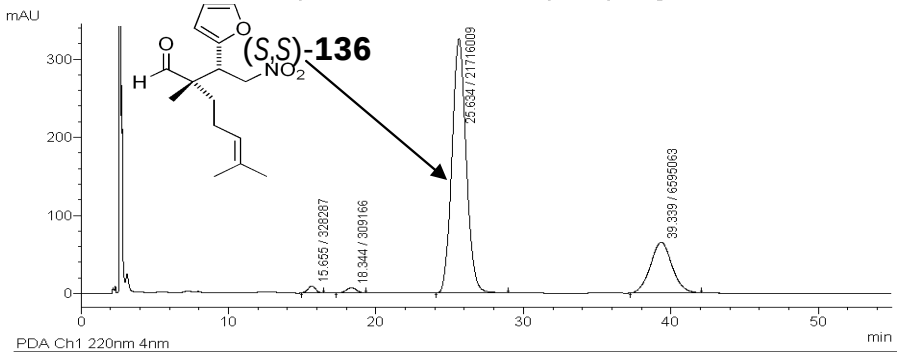
The title compound was prepared from *trans*-2-(2-nitrovinyl)furan and 2,6-dimethylhept-5-enal using method C. Reaction time: 16 h; R_f = 0.63 (*syn*) EtOAc/pet ether (2:8); flash column chromatography: (EtOAc/Pet ether = 7:93); yield = 83% (*syn* and *anti*); ee = 97%, dr = 76:24 (*syn*/*anti*) as determined by HPLC (CHIRALCEL OD-H, *i*-PrOH/n-heptane 1/99, flow rate = 1.5 mL/min, λ = 220 nm); $t_{(syn,\ minor)}$= 15.6 min, $t_{(anti,\ minor)}$= 18.3 min, $t_{(syn,\ major)}$= 25.6 min, $t_{(anti,\ major)}$= 39.3 min. The compound was tentatively assigned the S,S (*syn*) configuration according to the general trend of our Michael addition products. ^{1}H NMR (400 MHz, $CDCl_3$, *syn* product) (ppm): 1.18 (s, 3H), 1.34-1.53 (m, 2H), 1.54 (s, 3H), 1.64 (s, 3H), 1.78-1.88 (m, 1H), 1.89-1.99 (m, 1H), 3.96 (dd, 1H, *J* =3.9, 11.0 Hz), 4.56 (dd, 1H, *J* = 3.9, 12.8 Hz), 4.72 (dd, 1H, *J* = 11.0, 12.8 Hz), 4.92-5.01 (m, 1H), 6.23-6.24 (d, 1H, *J* = 3.2 Hz), 6.31-6.32 (m, 1H), 7.38 (s, 1H), 9.50 (s, 1H). ^{13}C NMR (100MHz, $CDCl_3$, *syn* product) (ppm): 16.5, 17.5, 22.6, 25.8, 35.5, 40.5, 51.7, 75.3, 109.9, 110.5, 122.8, 132.9, 142.8, 149.5, 204.1. FT-IR: (KBr), ν_{max}: 1723, 1630, 1558, 1506, 1435, 1376, 1275, 1261, 1148, 1016, 915, 749 cm^{-1}; MS: HRMS (ESI-TOF) calculated for $C_{15}H_{21}NO_4$ $[M+Na]^+$: 302.1355; found: 302.1363.

Racemic 2,6-dimethyl-2-[2-nitro-1-(furan-2-yl)ethyl]hept-5-enal



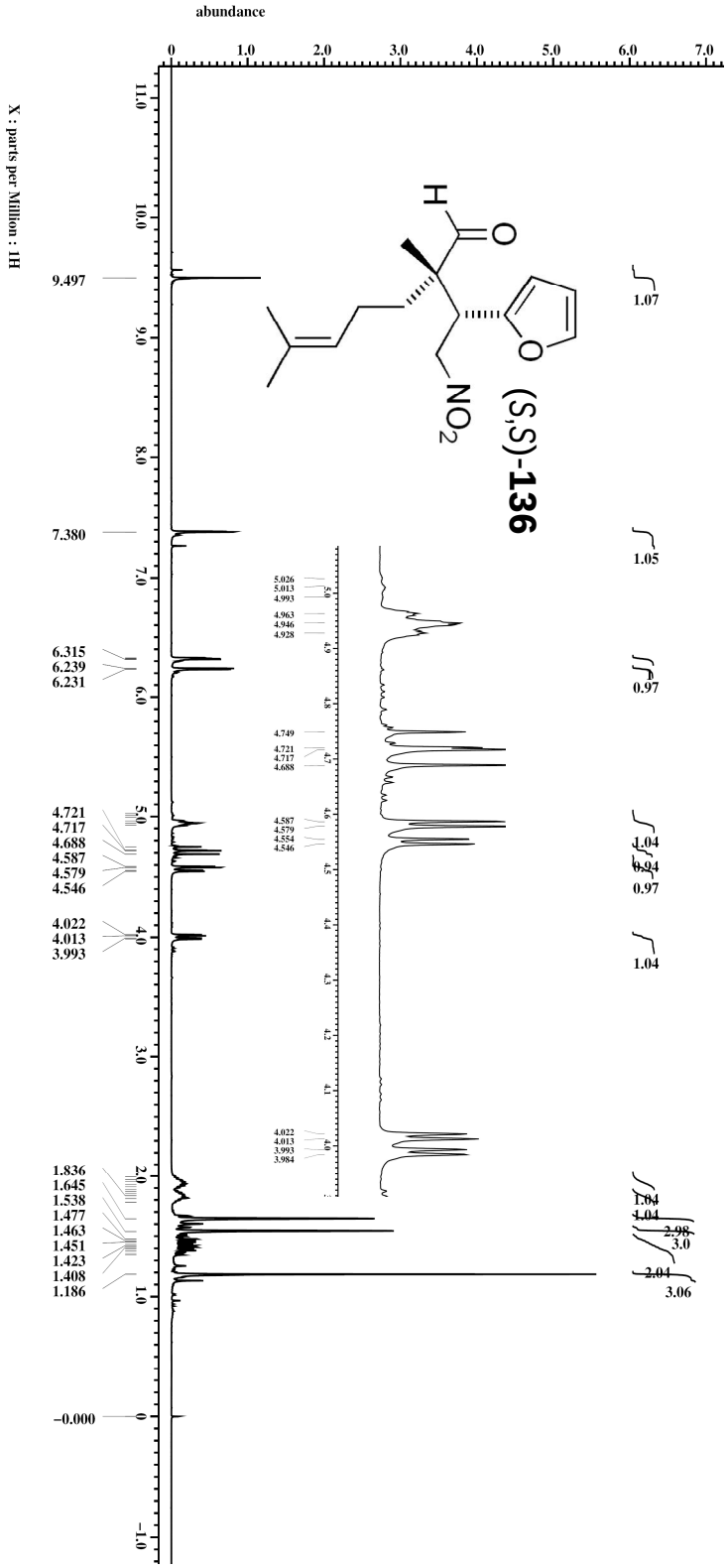
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	14.366	1903249	47338	36.945	48.652	1.181	
2	16.984	619292	13755	12.021	14.137	1.295	
3	25.624	1935957	29080	37.580	29.887	1.925	
4	35.946	693103	7127	13.454	7.325	2.847	
Total		5151601	97300	100.000	100.000		

Enantioenriched 2,6-dimethyl-2-[2-nitro-1-(furan-2-yl)ethyl]hept-5-enal

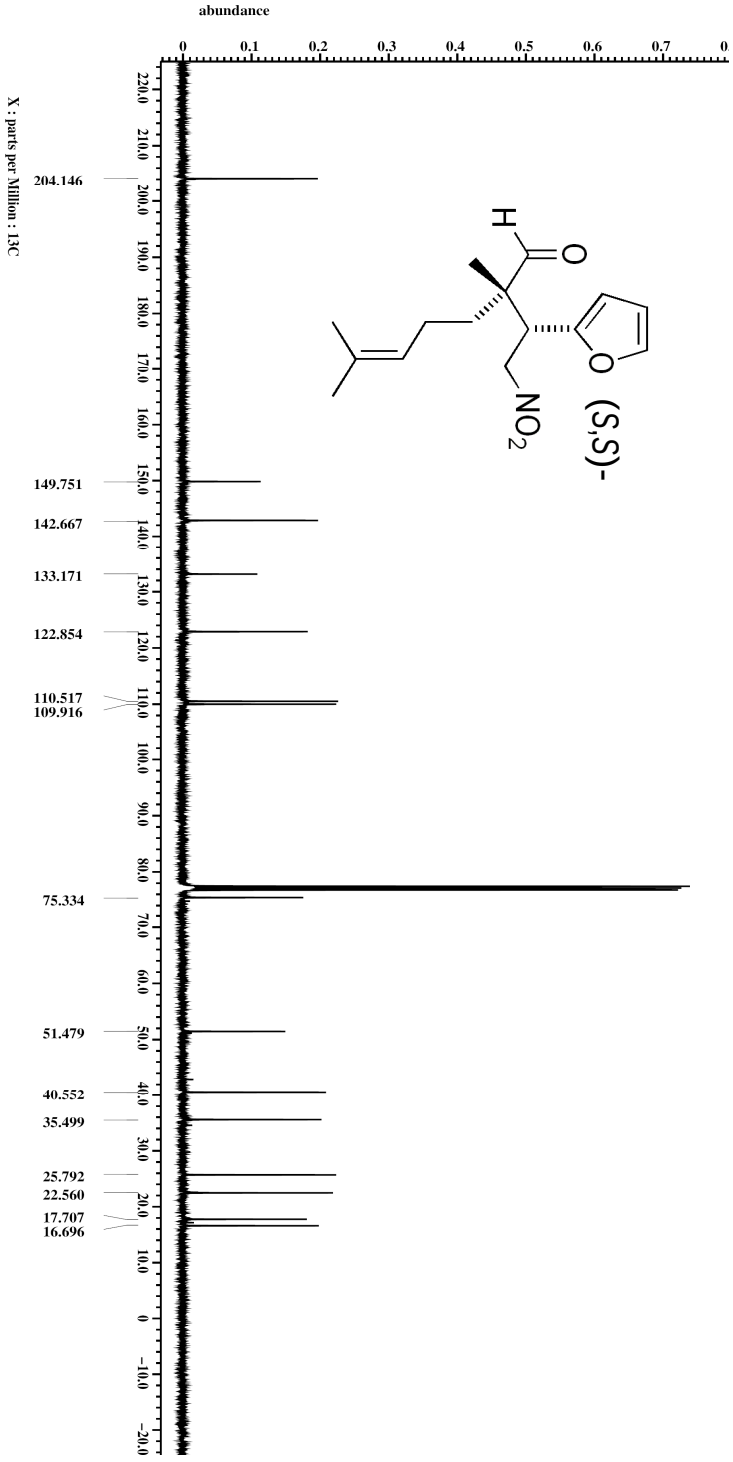


Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	15.655	328287	8930	1.134	2.199	1.060	
2	18.344	309166	6607	1.068	1.627	1.358	
3	25.634	21716009	325649	75.016	80.175	1.968	
4	39.339	6595063	64985	22.782	15.999	3.006	

^{1}H NMR of (2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(furan-2-yl)ethyl]hept-5-enal



^{13}C NMR of (2S)-2,6-dimethyl-2-[(1S)-2-nitro-1-(furan-2-yl)ethyl]hept-5-enal



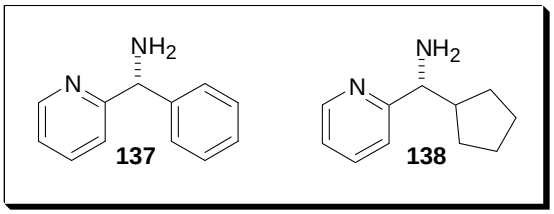
CHAPTER 3:

PYRIDINE BASED PRIMARY AMINE CATALYZED ASYMMETRIC MICHAEL REACTION

3.1 Results and discussions

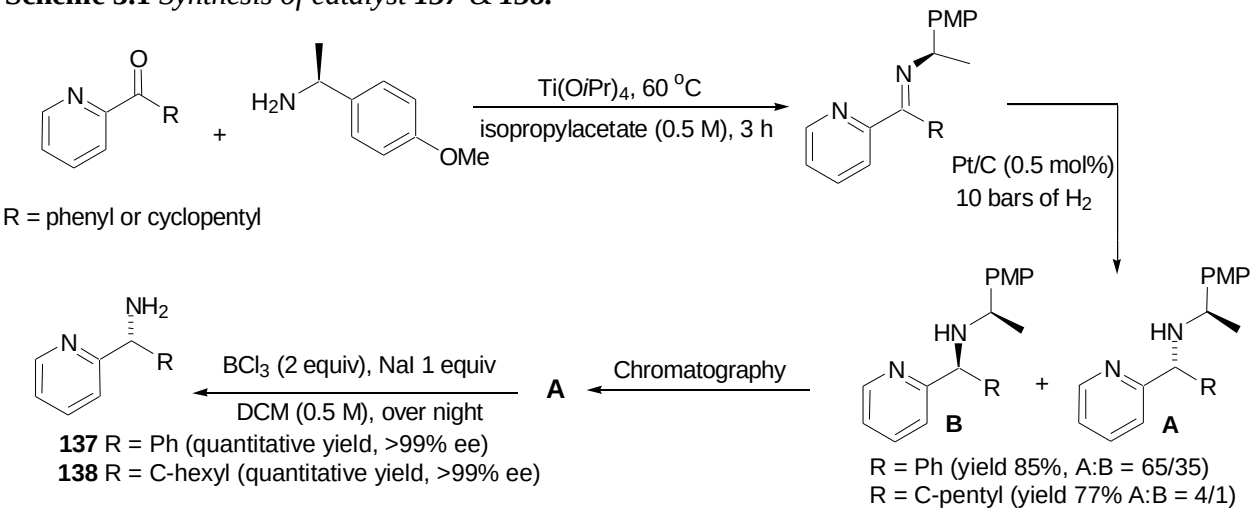
Over the past decade a variety of diamine based bifunctional organocatalysts have been reported for asymmetric transformations. Based on these previous literature reports regarding the usefulness of bifunctional organocatalysts, one of my goal was to synthesize pyridine based chiral 1,2-diamines (Scheme 3.1) with the specific intent of using them as organocatalysts for the asymmetric Michael addition of carbonyl compounds to nitroalkenes and mechanistically related reactions e.g Mannich reaction, Aldol reaction, amination etc. This new class of chiral diamines can be synthesized in a short number of steps and allows a high degree of modularity. Furthermore, these chiral diamines (Figure 3.1) hold several distinguishing features that should allow them to be effective for asymmetric Michael additions of carbonyl compounds to nitroalkenes. For example, the primary nitrogen atom of a diamine should be able to activate electrophiles, e.g. ketones & aldehydes via enamine formation. Meanwhile the tertiary nitrogen of pyridine, once protonated in the presence of an acid, should be able to attract and hold the nitroalkene via hydrogen bonding. In this way, both the nitroalkene and enamine come together in such a close proximity that results in the bond formation.

Figure 3.1 *Proposed pyridine based chiral 1,2-diamines.*



The catalysts **137** & **138** (Figure 3.1) have been synthesized by know procedures as shown in Scheme 3.1. The corresponding ketones were reductively aminated with commercially available (*S*)-*p*-methoxyethylbenzylamine in the presence of Ti(*i*PrO)$_4$ at 60 ^{o}C to afford the imine and then subjected to hydrogenation with Pt/C under 10 bar of hydrogen pressure to get the corresponding secondary amine. The resulting two diasteromers (**A** & **B**) were separated by column chromatography and a single diasteromer was treated with BCl_3 and NaI to afford the enantiopure catalysts (**137** & **138**).[108]

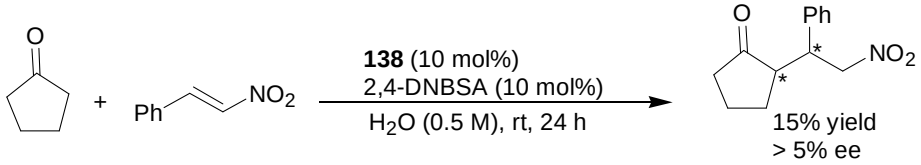
Scheme 3.1 *Synthesis of catalyst **137 & 138.***



Note: the absolute configurations of **137** & **138** are unknown.

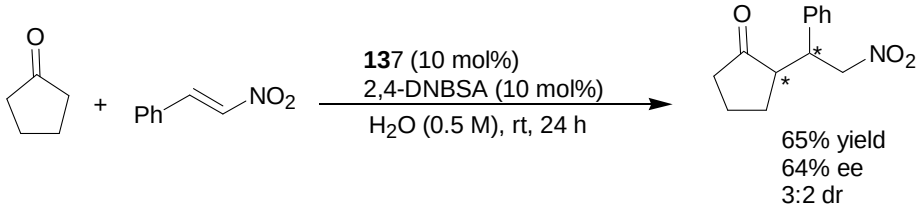
To test the efficiency of our proposed catalysts (**137** & **138**), I selected the Michael addition of cyclopentanone to *trans* β-nitrostyrene as a model reaction. Catalyst **138** showed poor performance both in terms of reactivity and selectivity towards the Michael addition of cyclopentanone to *trans* β-nitrostyrene (Scheme 3.2).

Scheme 3.2 *Michael reaction of cyclopentanone catalyzed by **138**.*



The same reaction was performed in methylene chloride, again the enantioselectivity and conversion was low. On the other hand, catalyst **137** (10 mol%), in the presence of 2,4-dinitrobenzensulfonic acid (10 mol%), gave the Michael product in 65% yield, with poor diastereoselctivity and mediocre enantioselectivity (64% ee) in 24 h (Scheme 3.3).

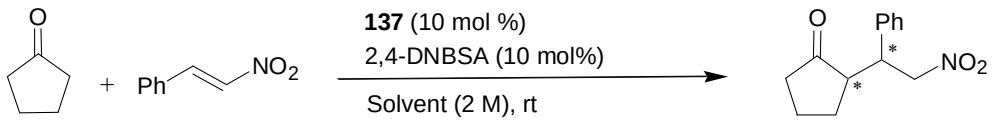
Scheme 3.3 *Michael reaction of cyclopentanone catalyzed by **137**.*



3.1.1 Solvent screening for Michael addition of cyclopentanone to *trans β*-nitrostyrene

Encouraged by this initial result, different solvents were screened with catalyst **137** in the presence of 2,4-dinitrobenzenesulfonic acid (Table 3.1)

Table 3.1 *Solvent screening for the Michael reaciton catalyzed by organocatalyst **137.***



Entry	Solvent	Time (h)	syn/anti[a]	Yield (%)[b]	*ee* (%)[a]
1	H_2O	24	60 : 40	65	64
2.	Brine	24	77 : 23	100	74
3.	**$CHCl_3$**	**24**	**82 : 18**	**65**	**83**
4.	$CHCl_3$+H_2O	14	70 : 30	70	77
5.	THF	24	70 : 30	15	77
6.	MeOH	24	60 : 40	10	80
7.	MeOH+H_2O	14	70 : 30	60	67
8.	$CHCl_3$[c]	24	60 : 40	20	80

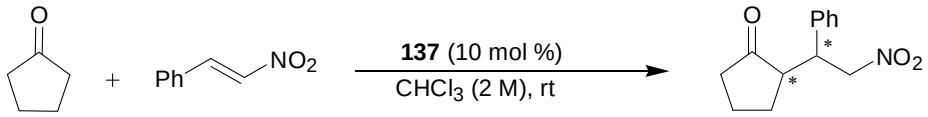
[a] Determined by chiral HPLC analysis. [b] Estimated yield by thin layer chromatography (TLC). [c] The reaction was without any acid.

Chloroform offers the best selectivity with excellent reaction rate (Table 3.1, entry 3), whilst a faster reaction was examined in brine with mediocre selectivity (Table 3.1, entry 2).

3.1.2 Additive screening for Michael addition of cyclopentanone to *trans β*-nitrostyrene

Different chiral and achiral Bronsted acids were examined for the asymmetric Michael addition of cyclopentanone to *trans β*-nitrostyrene catalyzed by **137** (Table 3.2). 2,4-dinitrobenzenesulfonic acid provided good enantioselectivity with excellent reaction rate (Table 3.2, entry 1). The enantioselectivity was further improved by the addition dodecylbenzenesulfonic acid sodium salt (Table 3.2, entry 8).

Table 3.2 *Effect of Acids and salts on Michael reaction catalyzed by **137**.*



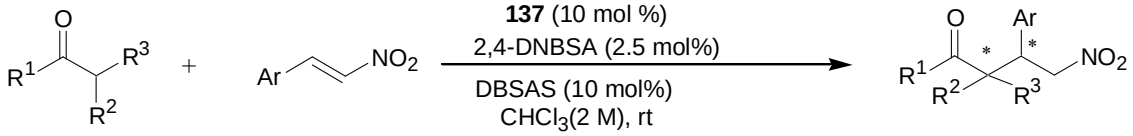
Entry	Acid	Time (h)	syn/anti[a]	Yield (%)[b]	*ee* (%)[a]
1.	2,4-DN BSA	14	82 : 18	60	85
2.	*p*-toluene SA	14	75 : 25	60	80
3.	*p*-nitro BA	14	40 : 60	35	65
4.	Camphor SA	14	75 : 25	35	75
5.	TFA	24	90 : 10	10	80
6.	2,4-DN BSA+DBSAS (1 : 1)	14	81 : 19	60	90
7.	2,4-DN BSA+DBSAS (1 : 2)	14	82 : 18	55	85
8.	**2,4-DN BSA+DBSAS (1 : 4)**	**24**	**90 : 10**	**70**	**90**

[a]Determined by chiral HPLC. [b] Estimated yield by thin layer chromatography (TLC).

3.1.3 Asymmetric Michael addition of cyclopentanone and isobutyraldehyde to different nitroalkenes catalyzed by 137

Next, I examined cyclopentanone & isobutyraldehyde with various electron rich and deficient *trans* *β*-nitrostyrenes catalyzed by organocatalyst **137** under the optimal reaction conditions. The early reported literature shows that both cyclopentanone and isobutyraldehyde are comparatively difficult Michael donors and rarely been used in asymmetric Michael addition to nitro-olefins. The results obtained from the Michael addition of isobutyraldehyde & cyclopentanone to nitro-olefins in the presence of catalyst **137** have been summarized in Table 3.3. In most cases good enantioselectivities, mediocre diastereoselectivities and good to excellent yields were obtained in 21-40 h.

Table 3.3 *Asymmetric Michael addition of various carbonyls to nitro-olefins catalyzed by organocatalyst **137**.*[a]



Entry	Product	R^1	R^2	R^3	Ar	Time (h)	Yield[b] (%)	syn/anti[c]	*ee* (%)[d]
1.	**139**	-$(CH_2)_3$-		H	-Ph	24	76	81/19	87
2.	**139**[f]	-$(CH_2)_3$-		H	-Ph	33	98	77/23	74
3.	**140**	-$(CH_2)_3$-		H	-C_6H_4-4-Me	21	92	76/24	88, > 99[e]
4.	**141**	-$(CH_2)_3$-		H	-C_6H_4-4-OMe	24	85	88/12	77
5.	**142**	-$(CH_2)_3$-		H	-2-furyl	30	89	57/43	81
6.	**143**	H	CH_3	CH_3	-Ph	36	58	-	78
7.	**144**	H	CH_3	CH_3	-C_6H_4-4-Me	40	53	-	80
8.	**145**	H	CH_3	CH_3	-2-furyl	45	70	-	90
9.	**146**	H	CH_3	CH_3	-C_6H_4-4-OMe	52	59	-	90

[a] General reaction conditions: Nitro-olefins (1 equiv), ketone or aldehyde (5 equiv), **137** (10 mol %), DBSAS (10 mol %), 2,4-DNBSA(2.5 mol %), CHCl3 (2 M), room temperature. [b] Isolated yield after column chromatography on silica gel. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Enantioselectivity of the anti product. [f] Reaction condition: *trans* *β*-nitrostyrene (1 equiv), ketone or aldehyde (5 equiv), **137** (4 mol %), DBSAS (4 mol %), 2,4-DNBSA (1.5 mol %), Brine (0.5 M), room temperature.

3.2 Conclusion

Pyridine based chiral diamine **137** was used as an effective organocatalyst for asymmetric Michael addition of isobutyraldehyde & cyclopentanone to various nitro-olefins with good to high enantioselectivities (77-92%), poor to mediocre diastereoselectivities (15 -78%) and mediocre to excellent yield (58-98%).

3.3 Experimental

All reagents and solvents were received from Sigma-Aldrich. Routine monitoring of chemical reactions were performed by High Performance Liquid Chromatography (HPLC) and Thin-Layer Chromatography (TLC) using precoated plates of silica gel 60 F_{254} and visualized under ultraviolet irradiation (254 nm). Column chromatography separations were performed with silica gel 60 (0.040-0.063 mm). Petroleum ether used was of boiling range 60-80 ^{o}C. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents was performed at reduced pressure. Chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (TMS = 0) or relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. Multiplicities are abbreviated as; (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). Coupling constants are expressed in Hz. FT-IR spectra were obtained on Nicolet Avatar 370 thermonicolet spectrometer. MS was measured on Bruker Daltonics HCT Ultra while HRMS were recorded on Bruker microOTOF instrument with an ionization potential of 70 eV with ESI positive mode. The enantiomeric excess and diastereoselectivity ratio were determined by HPLC using a Chiralpak AS-H or OD-H column with *n*-heptane and *i*-propanol as eluents.

3.3.1 General procedure for synthesis of racemic Michael adducts (ketones)

To a mixture of nitro-olefin (1.00 equiv), 2-picolylamine (20 mol%) in the presence of 2,4-dinitrobenzene sulfonic acid hydrate (10 mol%) in chloroform (0.5 M) was added cyclopentanone (20.0 equiv). The reaction was stirred at room temperature and monitored by TLC. At maximum conversion the reaction was quenched with 1N HCl, extracted with dichloromethane, dried on reduced pressure and purified by column chromatography on silica gel.

3.3.2 General procedure for synthesis of racemic Michael adducts (aldehydes)

To a mixture of nitro-olefin (1.00 equiv), aldehyde (20.0 equiv) in chloroform (0.5 M) was added glycine (15 mol%) and dimethyl amino pyridine (15 mol%). The reaction was stirred at room temperature and monitored by TLC. At maximum conversion the reaction mixture was filtered, dried on reduced pressure and purified by column chromatography on silica gel.

3.3.3 General procedure for asymmetric Michael addition of carbonyls to nitro-olefins

To a mixture of nitro-olefin (1.00 equiv) aldehyde or ketone (5.00 equiv) in the presence of dodecylbenzene sulfonic acid sodium salt (0.10 equiv) and 2,4-dinitrobenzene sulfonic acid hydrate (0.025 equiv) in chloroform (2 M) was added **137** (0.10 equiv). The reaction mixture was stirred the reaction at room temperature and monitored by HPLC or TLC. At maximum conversion the reaction mixture was purified by column chromatography on silica gel to afford the Michael adduct.

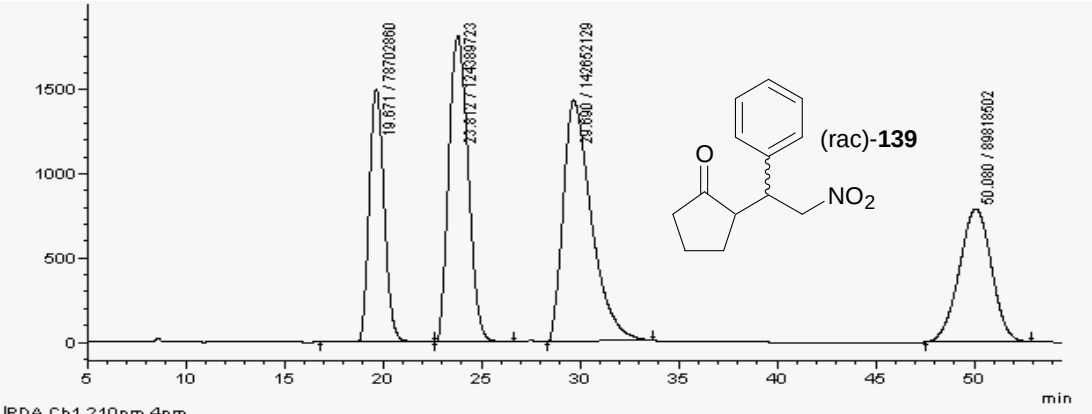
On the following pages all synthesized products, **139**-**146**, are detailed

(S)-2-{(*R*)-2-Nitro-1-phenylethyl}-cyclopentanone (139).[109]

White solid, 76 % yield, *syn/anti* = 81/19, 87 % *ee* (*syn*). The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 5/95, flow rate = 1 mL/min, λ = 210 nm): t_{major} = 24.1 min, t_{minor} = 31.7 min, R_f = 0.37 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (m, 3H), 7.21-7.12 (m, 2H), 5.37-5.29 (dd, *J* = 5.5, 12.8 Hz, 1H), 4.71 (dd, *J* = 10.1, 12.8 Hz, 1H), 3.74-3.66 (m, 1H), 2.40-2.31 (m, 2H), 2.16-2.06 (m, 1H) , 1.96-1.85 (m, 2H), 1.77-1.63 (m, 1H), 1.53-1.42 (m, 1H).

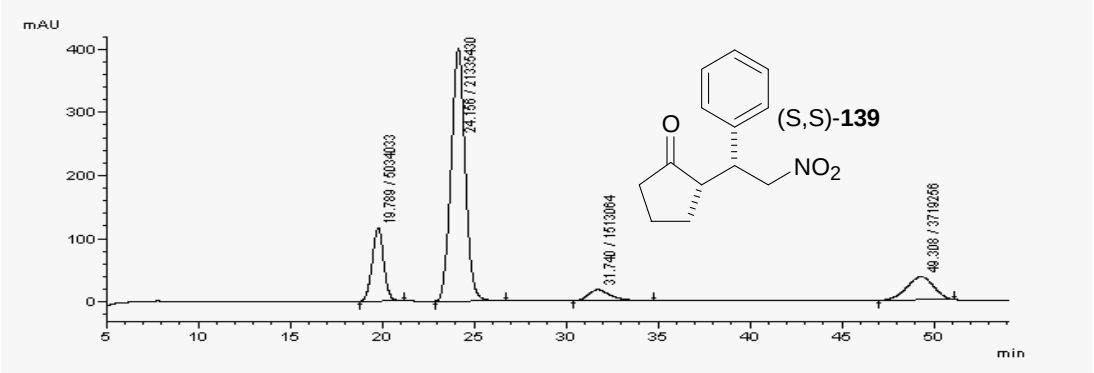
Racemic 139



PDA Ch1 210nm 4nm

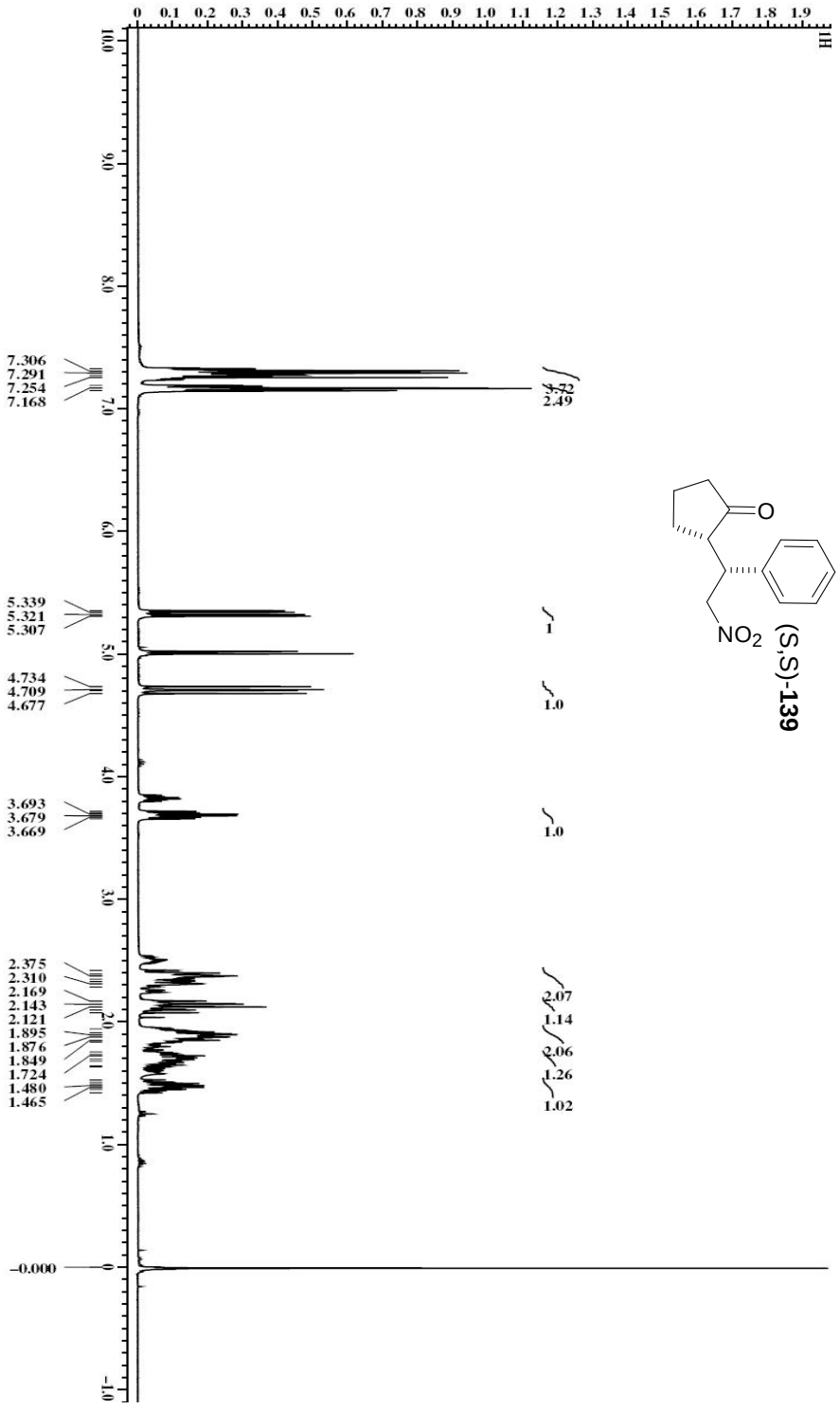
Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	19.671	78702860	1500920	18.069	27.099	1.494	
2	23.812	124389723	1816011	28.558	32.788	1.898	
3	29.690	142652129	1432198	32.751	25.858	3.028	
4	50.080	89818502	789518	20.621	14.255	3.266	
Total		435563213	5538647	100.000	100.000		

(S,S)-**139**



PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	19.789	5034033	116638	15.930	20.427	1.268	
2	24.156	21335430	399881	67.513	70.031	1.567	
3	31.740	1513064	17752	4.788	3.109	2.685	
4	49.308	3719256	36738	11.769	6.434	2.910	
Total		31601783	571010	100.000	100.000		

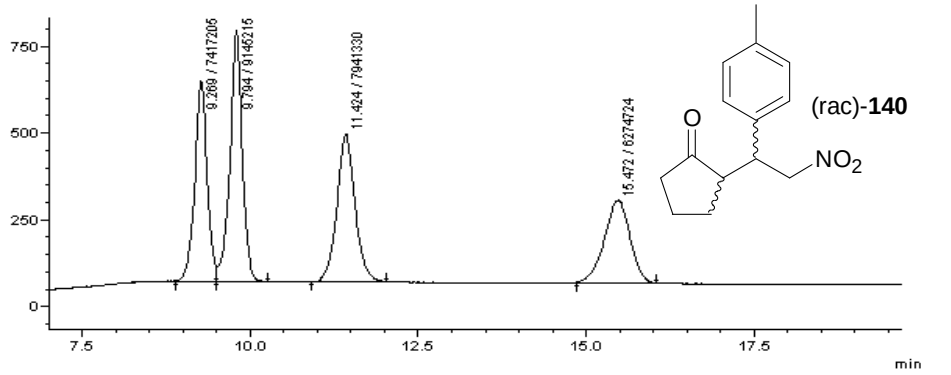

7.306
7.291
7.254
7.168
5.339
5.321
5.307
4.734
4.709
4.677
3.693
3.679
3.669
2.375
2.310
2.169
2.143
2.121
1.895
1.876
1.849
1.724
1.480
1.465
–0.000
2.49
1
1.0
1.0
2.07
1.14
2.06
1.26
1.02
O
NO2
(S,S)-139

(*S*)-2-[{(*R*)-2-Nitro-1-(4-Methylphenylethyl)}]-cyclopentanone (140).[110]

Yellow oil, 92 % yield, *syn/anti* = 76/24, 88 % *ee* (*syn*), >99 % *ee* (*anti*). The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 15/85, flow rate = 1 mL/min, λ = 190 nm): t_{minor} (*anti*) = 9.2 min, t_{major} (*syn*) = 9.7 min, t_{minor} (*syn*) = 11.4 min, t_{major} (*anti*) = 15.4 min, R_f = 0.41 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.01 (m, 4H), 5.34-5.27 (dd, *J* = 5.5, 12.8 Hz, 1H), 4.73-4.62 (dd, *J* = 10.1, 12.8 Hz, 1H), 3.70-3.61 (m, Hz 1H), 2.40-2.30 (m, 1H), 2.29 (s, 3H), 2.18-2.07 (m, 1H), 1.94-1.83 (m, 2H), 1.77-1.58 (m, 2H), 1.53.142 (m, 1H).

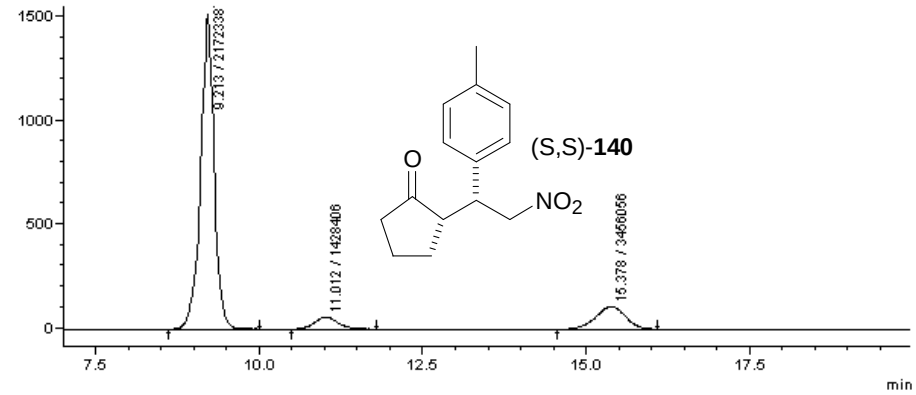
Racemic **140**



PDA Ch1 190nm 4nm

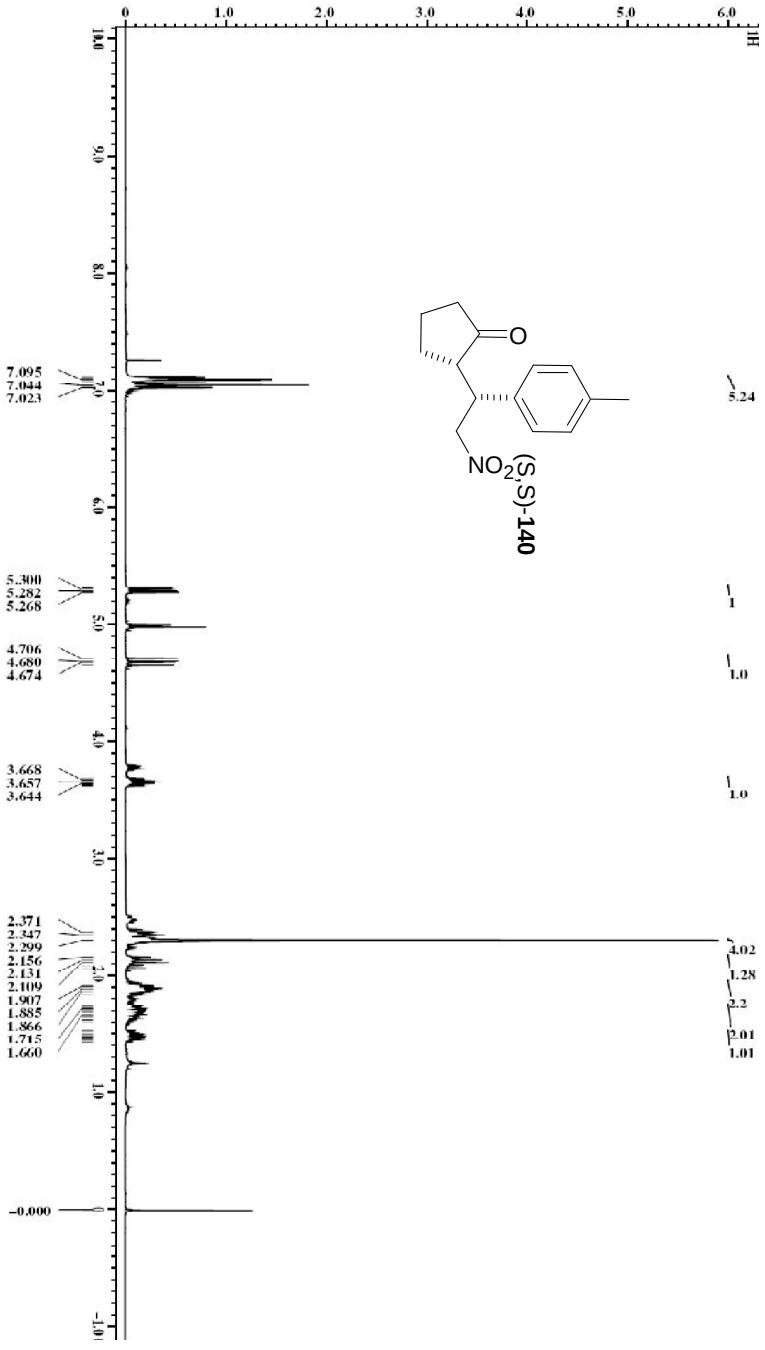
Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.269	7417205	576852	24.099	29.398	0.407	
2	9.794	9145215	723959	29.713	36.895	0.410	
3	11.424	7941330	424339	25.802	21.626	0.577	
4	15.472	6274724	237058	20.387	12.081	0.783	
Total		30778475	1962209	100.000	100.000		

(S,S)-**140**



PDA Ch1 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.213	21723387	1516914	81.643	90.054	0.457	
2	11.012	1428406	57886	5.368	3.437	0.732	
3	15.378	3456056	109642	12.989	6.509	0.918	
Total		26607849	1684443	100.000	100.000		

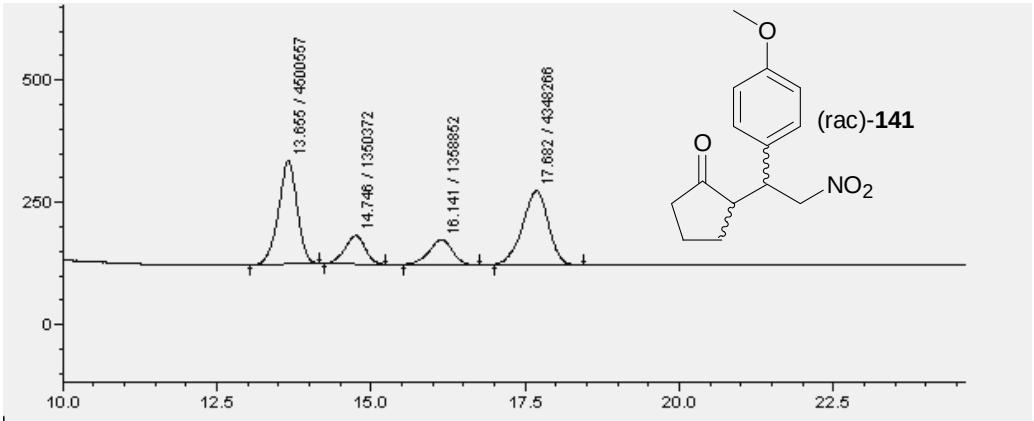

O
NO2
(S,S)-140
7.095
7.044
7.023
5.300
5.282
5.268
4.706
4.680
4.674
3.668
3.657
3.644
2.371
2.347
2.299
2.156
2.131
2.109
1.907
1.885
1.866
1.715
1.660
−0.000
5.24
1
1.0
1.0
4.02
1.28
2.2
2.01
1.01

(S)-2-[{(*R*)-2-Nitro-1-(4-Methoxyphenylethyl)}]-cyclopentanone (141)[111]

Yellowish solid, 85 % yield, *syn/anti* = 88/12, 77 % *ee* (*syn*). The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 190 nm): t_{major} = 15.0 min, t_{minor} = 16.6 min, R_f = 0.29 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$) (ppm):7.08-7.06 (d, 2H), 6.84-6.82 (d, 2H), 5.28-5.24 (dd, *J* = 5.5, 12.4 Hz, 1H), 4.69-4.63 (dd, *J* = 10.07, 12.4 Hz, 1H), 3.77 (s, 3H), 3.66-3.61 (m, 1H), 3.37-3.30 (m, 2H), 2.15-2.05 (m, 1H), 1.95-1.83 (m, 2H), 1.76-1.62 (m, 1H), 1.55-1.42 (m, 1H).

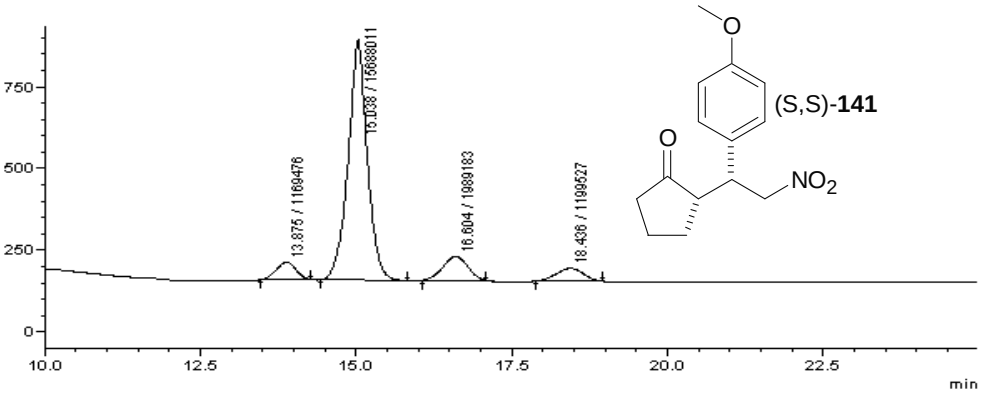
Racemic **141**



PDA Ch1 190nm 4nm

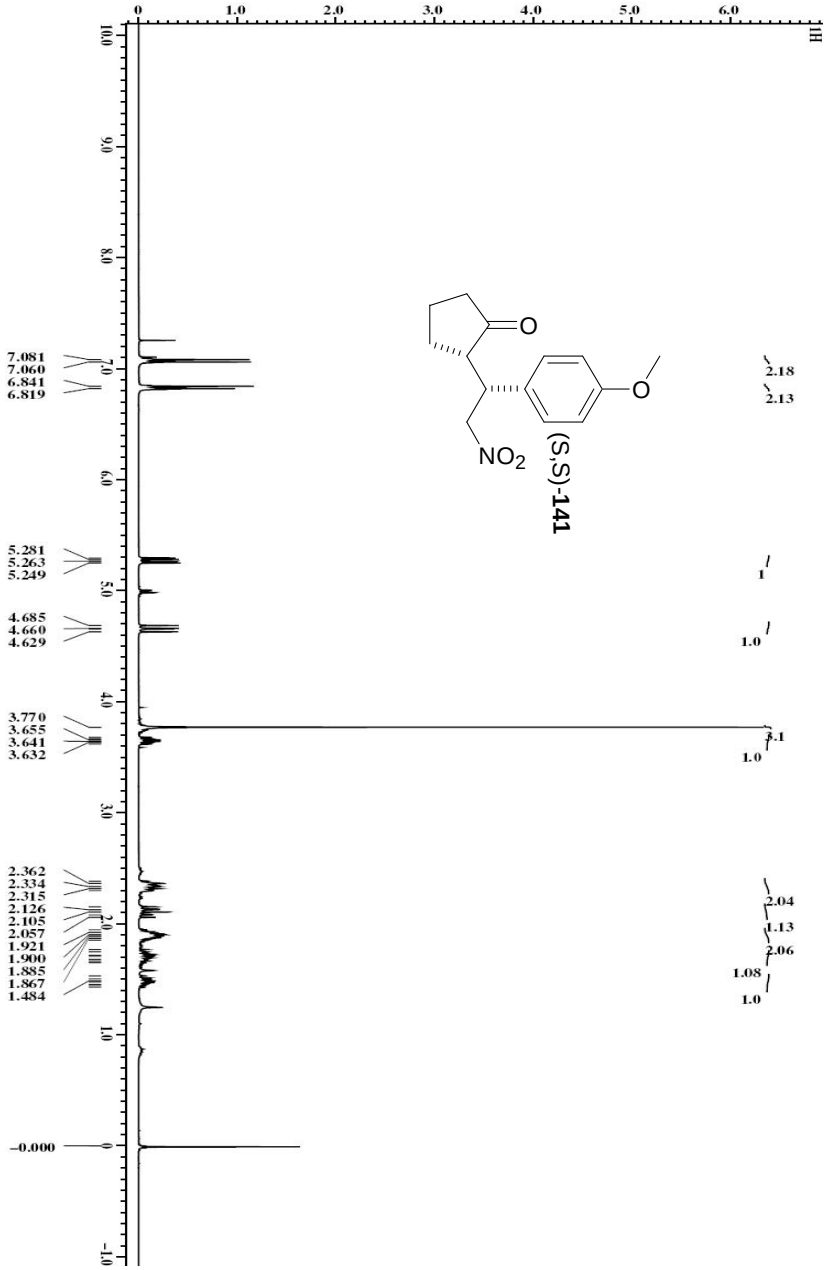
Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.655	4500557	210469	38.939	44.644	0.640	
2	14.746	1350372	58465	11.683	12.401	0.687	
3	16.141	1358852	51553	11.757	10.935	0.787	
4	17.682	4348266	150953	37.621	32.020	0.857	
Total		11558047	471440	100.000	100.000		

(S,S)-**141**



PDA Ch1 190nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.875	1169476	53552	5.834	5.930	0.632	
2	15.038	15688011	736801	78.259	81.583	0.678	
3	16.604	1989183	72924	9.923	8.075	0.779	
4	18.436	1199527	39852	5.984	4.413	0.862	
Total		20046196	903129	100.000	100.000		

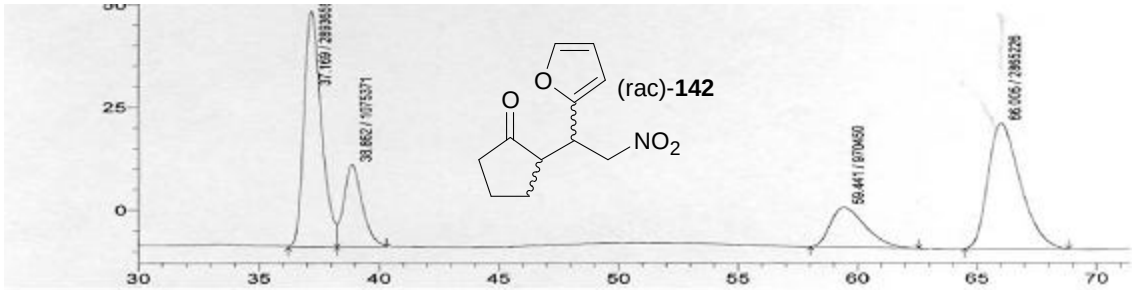

7.081
7.060
6.841
6.819
5.281
5.263
5.249
4.685
4.660
4.629
3.770
3.655
3.641
3.632
2.362
2.334
2.315
2.126
2.105
2.057
1.921
1.900
1.885
1.867
1.484
−0.000
2.18
2.13
1
1.0
3.1
1.0
2.04
1.13
2.06
1.08
1.0
O
O
NO2
(S,S)-141

(*S*)-2-{(*R*)-2-Nitro-1-furylethyl}-cyclopentanone (142)

Dark yellow oil, 89 % yield, *syn/anti* = 57/43, 81 % *ee* (*syn*). The ee was determined by chiral HPLC (Chiral AS-H, *i*-propanol/heptane 10/90, flow rate = 0.5 mL/min, λ = 230 nm): t_{minor} =37.6 min, t_{major} = 67.5 min, R_f = 0.30 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$)(ppm):7.32-7.25 (m, 1H), 6.31-6.22 (m, 1H), 6.13-6.10 (m, 1H), 5.07-5.00 (dd, *J* = 6.4, 13.3, Hz, 1H), 4.96-4.81 (m, 0.75H), 4.78-4.70 (dd, *J* = 9.2, 12.3 Hz, 1H), 4.02-3.92 (m, 1H), 2.41-2.25 (m, 2H), 2.13-1.95 (m, 2H), 1.95-1.63 (m, 2H), 1.60-1.51 (m, 1H); ^{13}C NMR (400MHz. $CDCl_3$) (ppm): 218.4, 217.9, 150.7, 142.7, 110.6, 110.4, 108.4, 76.1, 75.9, 49.6, 38.7, 38.3, 37.9, 37.7, 27.3, 27.0, 20.6, 20.3. FT-IR: (KBr) v_{max}: 3122, 2968, 2882, 1729, 1378, 1150, 1013, 917, 817, 742, 599 cm^{-1}; MS (EI), *m/z* (relative intensity): 246 $[M+Na]^+$; HRMS (ESI-TOF) calculated for $C_{11}H_{13}NO_4$ $[M+Na]^+$ 246.0742; found: 246.0739

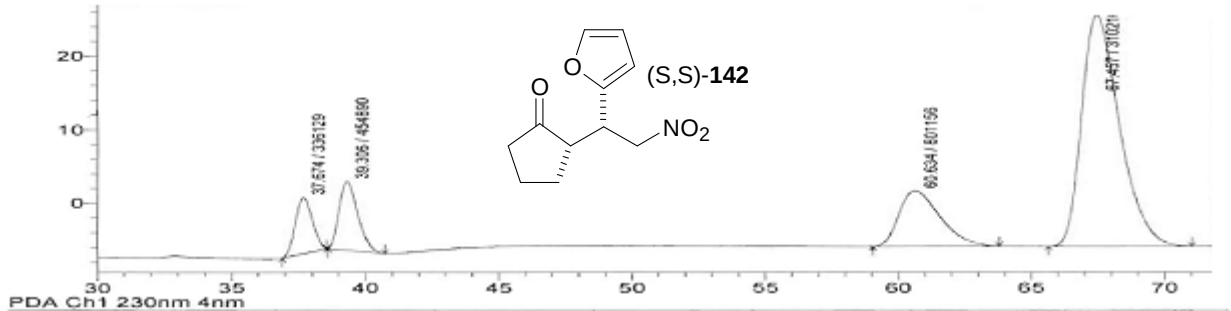
Racemic **142**



PDA Ch1 230nm 4nm

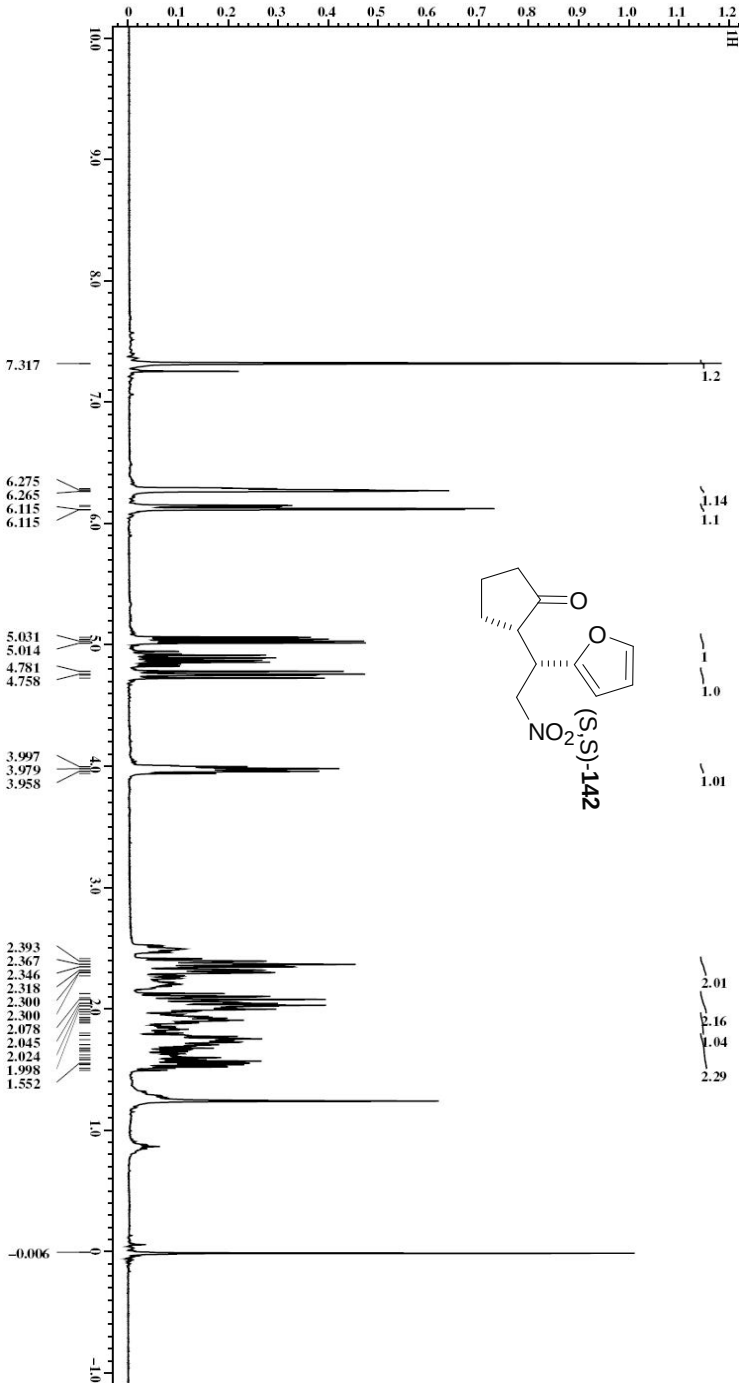
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	37.169	2893659	57310	37.076	48.857	1.581	
2	38.862	1075371	20005	13.778	17.054	0.000	
3	59.441	970450	9538	12.434	8.131	2.949	
4	66.005	2865226	30450	36.712	25.958	2.765	
Total		7804707	117302	100.000	100.000		

(S,S)-**142**



PDA Ch1 230nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	37.674	336129	7587	7.160	13.560	1.253	
2	39.306	454890	9314	9.690	16.647	1.426	
3	60.634	801156	7546	17.066	13.486	3.094	
4	67.457	3102160	31505	66.083	56.307	2.893	
Total		4694335	55951	100.000	100.000		

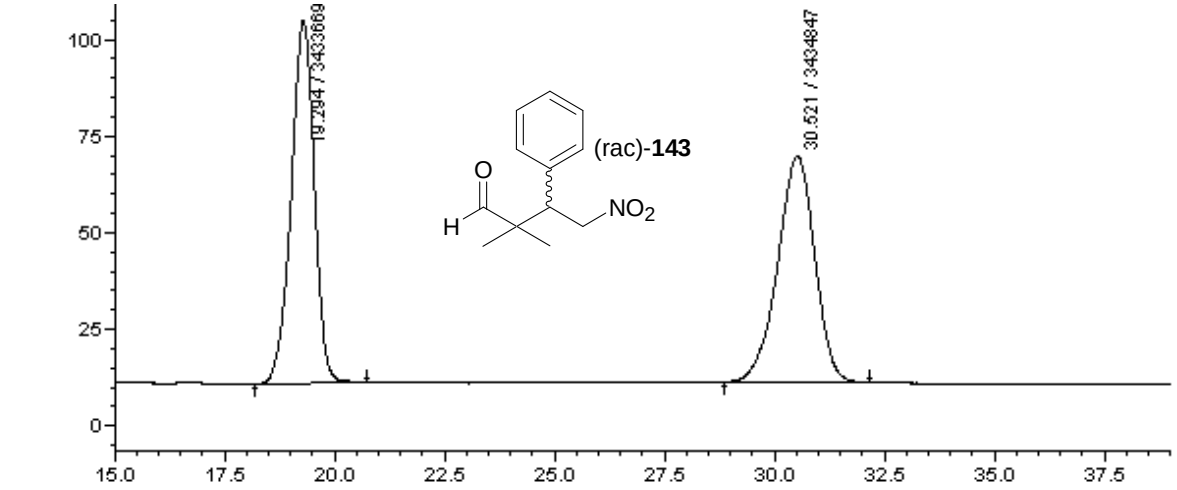

7.317
6.275
6.265
6.115
6.115
5.031
5.014
4.781
4.758
3.997
3.979
3.958
2.393
2.367
2.346
2.318
2.300
2.300
2.078
2.045
2.024
1.998
1.552
−0.006
1.2
1.14
1.1
1
1.0
1.01
2.01
2.16
1.04
2.29
O
O
NO2
(S,S)-142

(S)-2,2-Dimethyl-4-nitro-3-phenyl-butanal (143)[112]

White oil, 58 % yield, 78 % *ee*. The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 8/92, flow rate = 1 mL/min, λ = 210 nm), t_{minor} = 21.1 min, t_{major} = 33.7 min, R_f = 0.38 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$) (ppm):9.52 (s, 1H) 7.39-7.25 (m, 3H), 7.22-7.11 (m, 2H), 4.92-4.83 (dd, *J* = 11.0, 12.3 Hz 1H), 4.71-4.63 (dd, *J* = 4.1, 13.3 Hz, 1H), 3.81-3.72 (dd, *J* = 4.6, 11.4 Hz 1H), 1.13 (s, 3H), 0.9 (s, 3H).

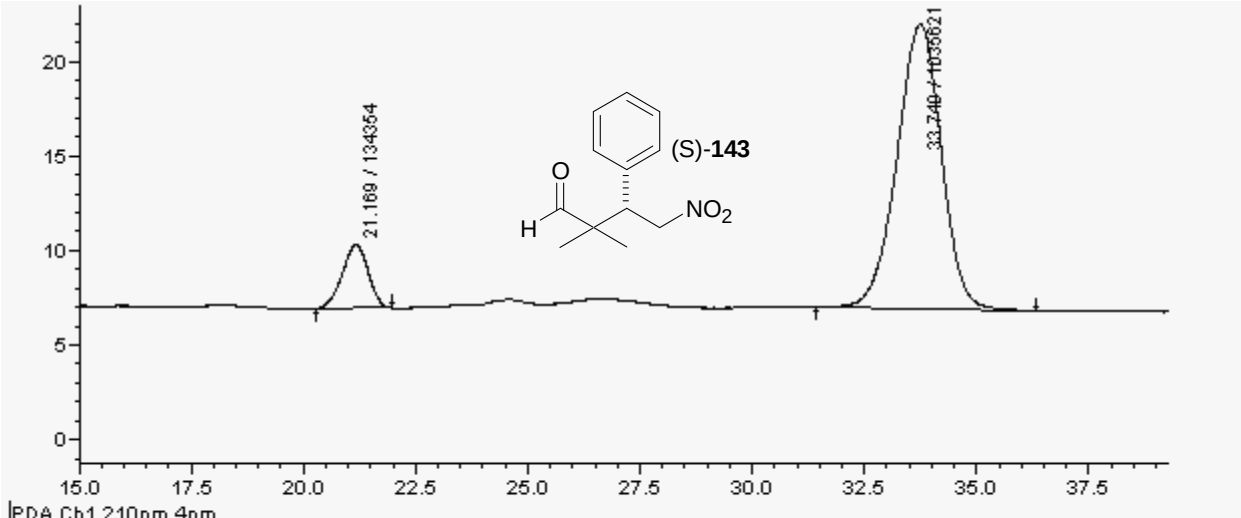
Racemic **143**



PDA Ch1 210nm 4nm

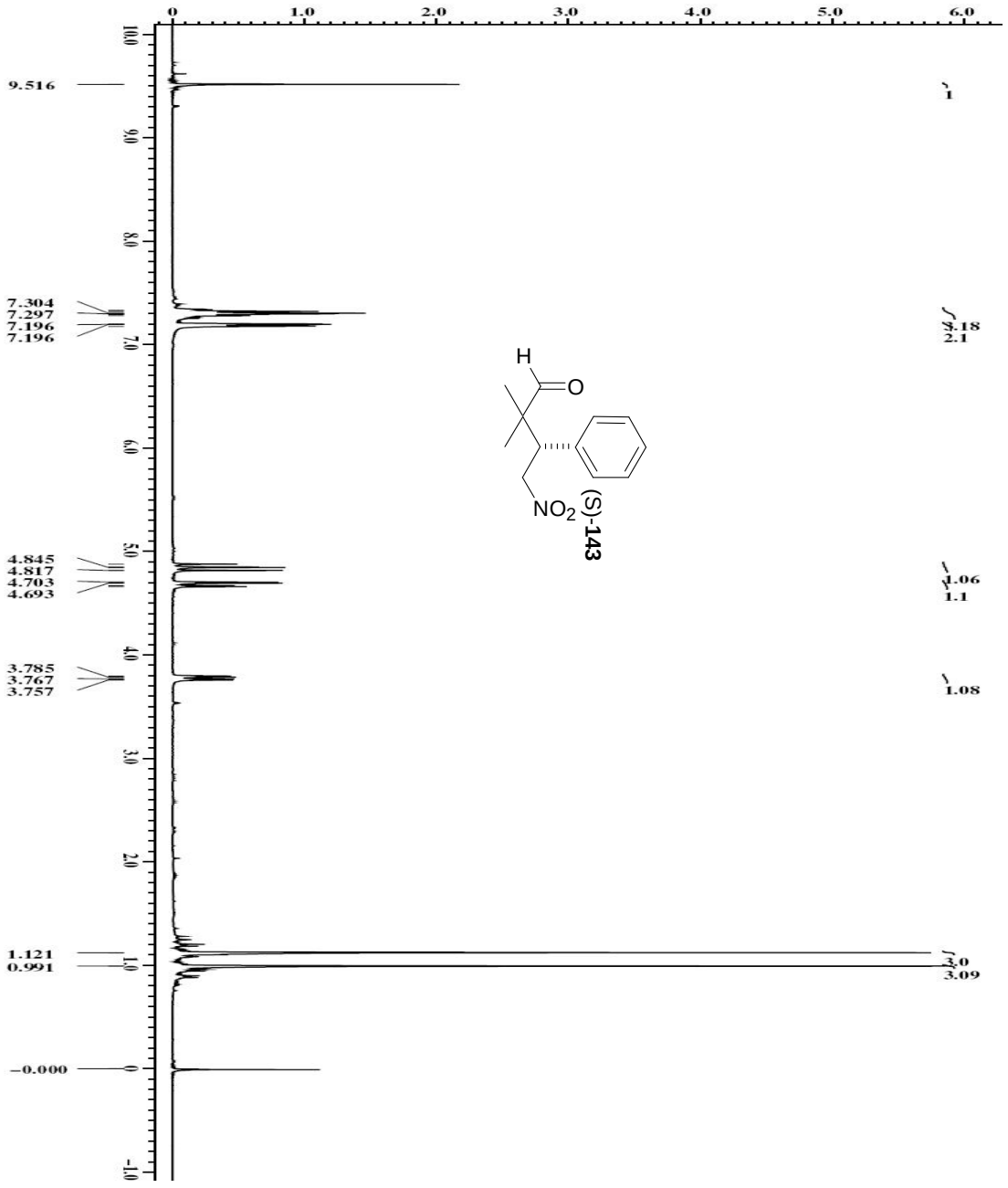
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	19.294	3433669	93860	49.991	61.647	1.071	
2	30.521	3434847	58393	50.009	38.353	1.726	
Total		6868516	152252	100.000	100.000		

(S)-**143**



PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	21.169	134354	3336	11.483	18.146	1.158	
2	33.740	1035621	15047	88.517	81.854	1.985	
Total		1169975	18383	100.000	100.000		

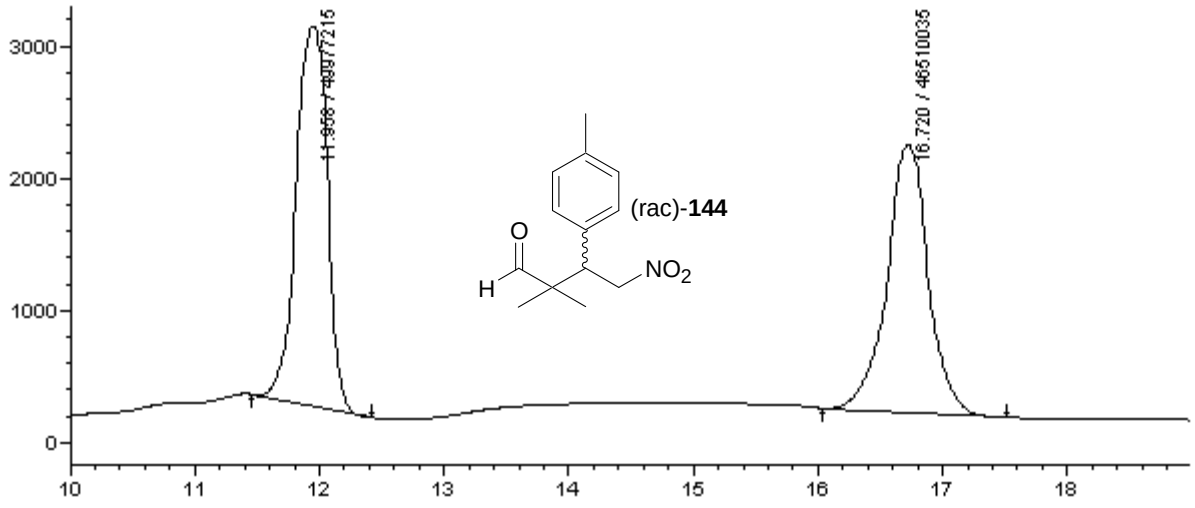

9.516
7.304
7.297
7.196
7.196
4.845
4.817
4.703
4.693
3.785
3.767
3.757
1.121
0.991
−0.000
1
3.18
2.1
1.06
1.1
1.08
3.0
3.09
H
O
NO2
(S)-143

(S)-2,2-Dimethyl-4-nitro-3-p-tolylbutanal (144)[113]

Yellow oil, 53 % yield, 80 % *ee*. The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 215 nm), t_{minor} = 12.0 min, t_{major} = 16.7 min, R_f = 0.39 EtOAc/pet ether (1 : 4).

^{1}H NMR (400 MHz, $CDCl_3$) (ppm):9.52 (s, 1H), 7.13-7.02 (m, 4H), 4.89-4.78 (m, 1H), 4.70-4.59 (dd, *J* = 4.6, 13.3 Hz, 1H), 3.77-3.68 (dd, *J* = 4.1, 11.4 Hz, 1H), 2.31 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H).

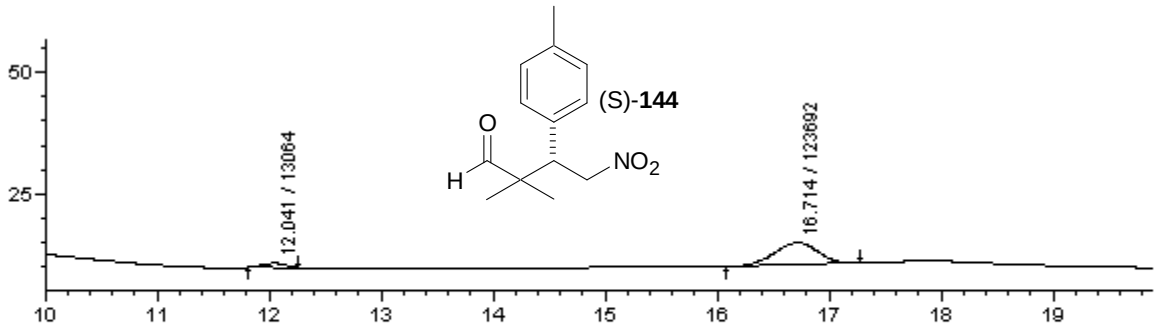
Racemic **144**



PDA Ch1 200nm 4nm

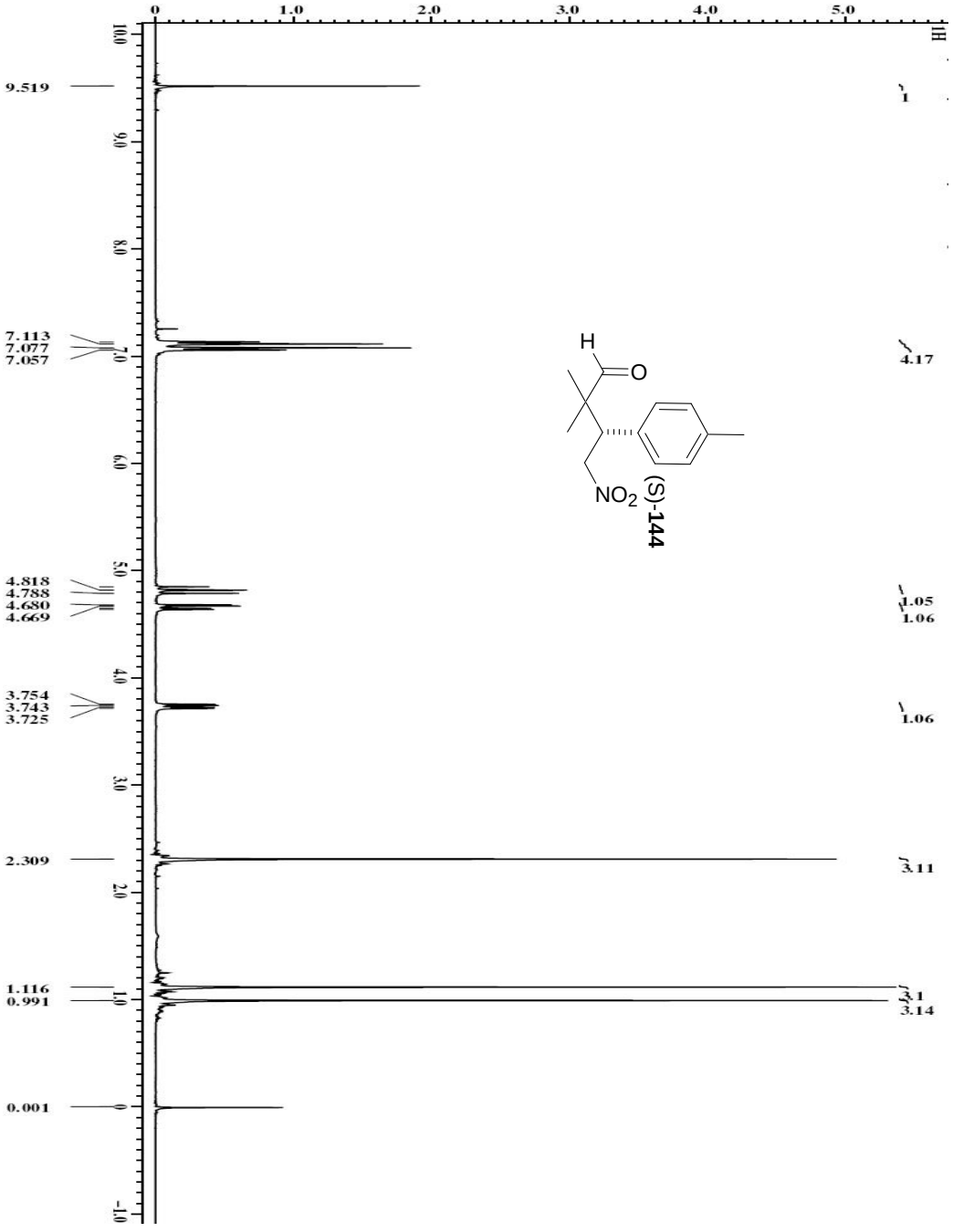
Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	11.958	49977215	2870365	51.797	58.573	0.465	
2	16.720	46510035	2030102	48.203	41.427	0.710	
Total		96487250	4900467	100.000	100.000		

(S)-**144**



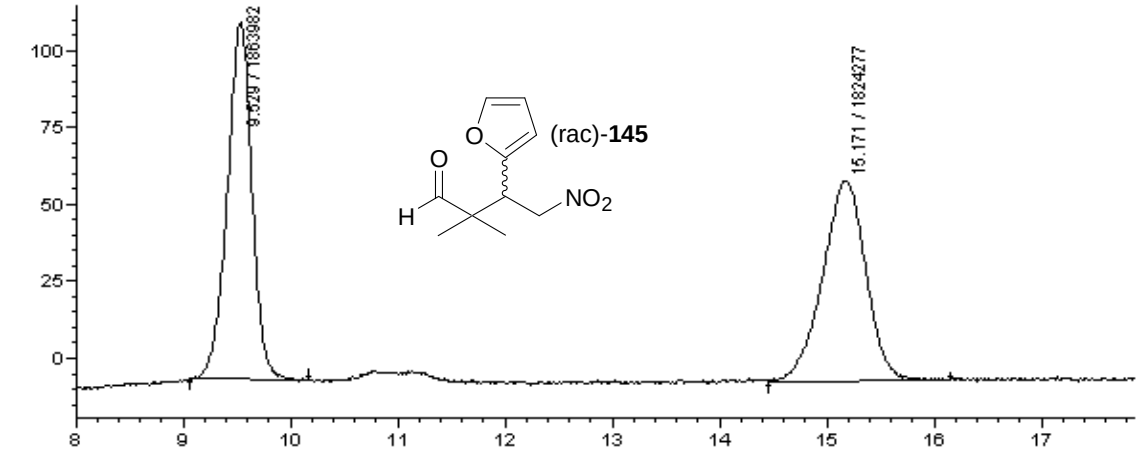
PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	12.041	13064	887	9.552	16.396	0.392	
2	16.714	123692	4524	90.448	83.604	0.777	
Total		136756	5411	100.000	100.000		

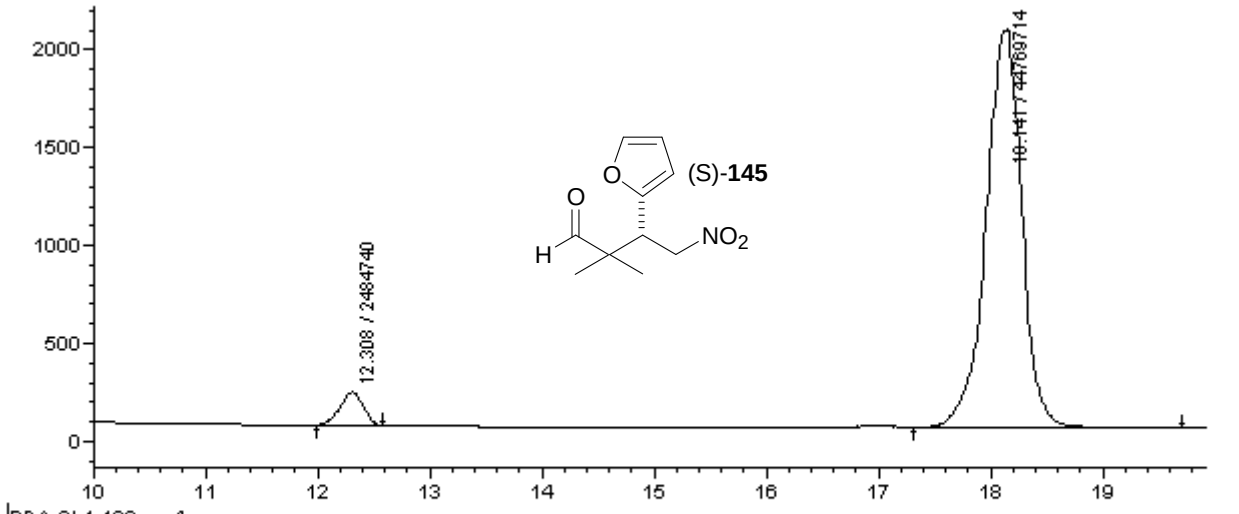

9.519
7.113
7.077
7.057
4.818
4.788
4.680
4.669
3.754
3.743
3.725
2.309
1.116
0.991
0.001
1.00
4.17
1.05
1.06
1.06
3.11
3.1
3.14
H
O
NO2
(S)-144

(S)-2,2-Dimethyl-4-nitro-3-furan-2-yl-butanal (145)[35]

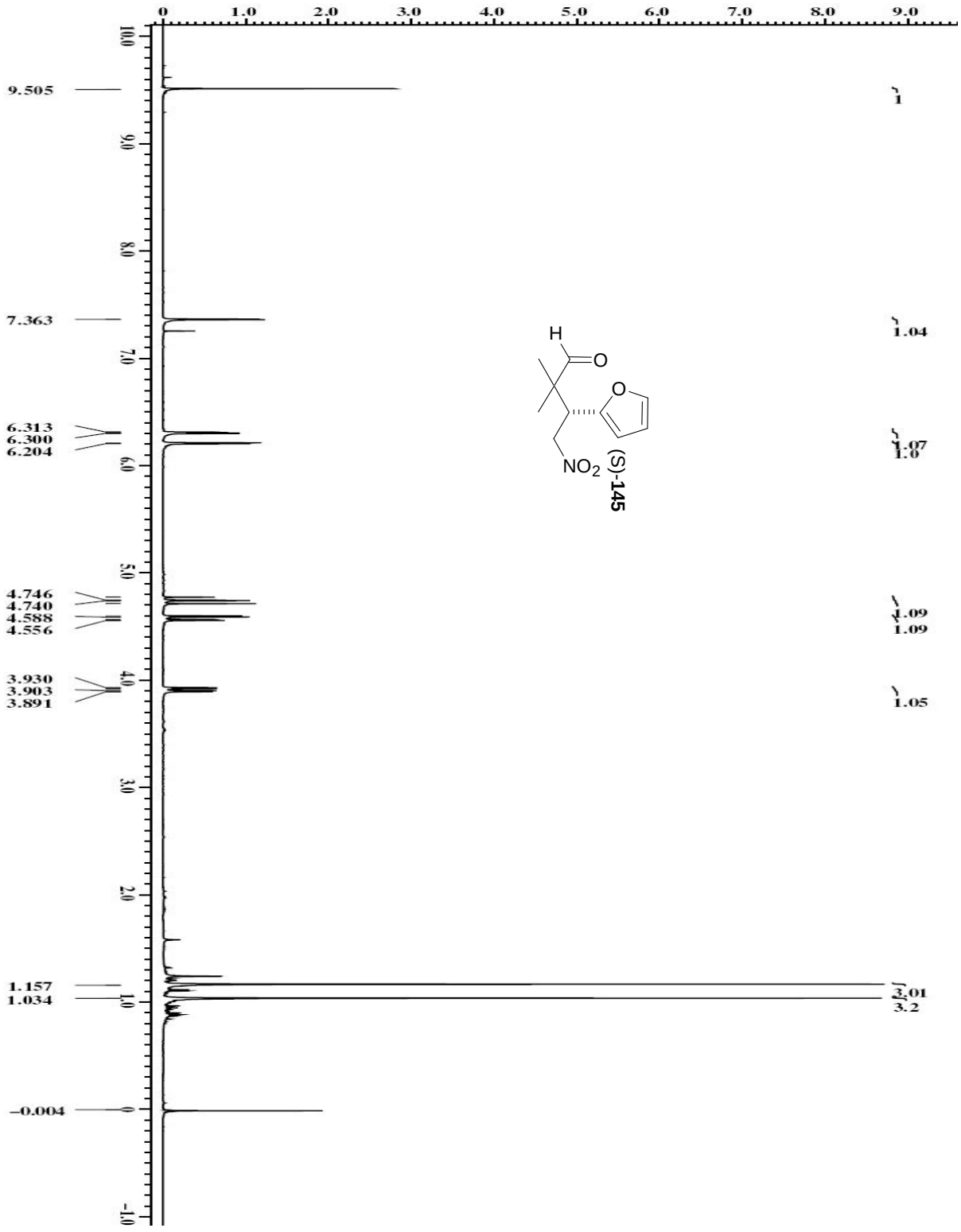
Yellow oil, 70 % yield, 90 % *ee*. The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 25/75, flow rate = 0.8 mL/min, λ = 190 nm), t_{minor} = 12.3 min, t_{major} = 18.1 min, R_f = 0.34 EtOAc/pet ether (1 : 4).
^{1}H NMR (400 MHz, $CDCl_3$) (ppm):9.5 (s, 1H), 7.36 (m, 1H), 6.31 (d, 1H), 6.2 (d, 1H), 4.78-4.69 (dd, *J* = 11.0, 12.3 Hz, 1H), 4.61-4.53 (dd, *J*= 4.1, 13.3 Hz, 1H), 3.93-3.87 (dd, *J* = 3.7, 11.0 Hz, 1H), 1.2 (s, 3H), 1.0 (s, 3H).



Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	9.529	1863982	115908	50.538	64.065	0.475	
2	15.171	1824277	65015	49.462	35.935	0.829	
Total		3688258	180923	100.000	100.000		



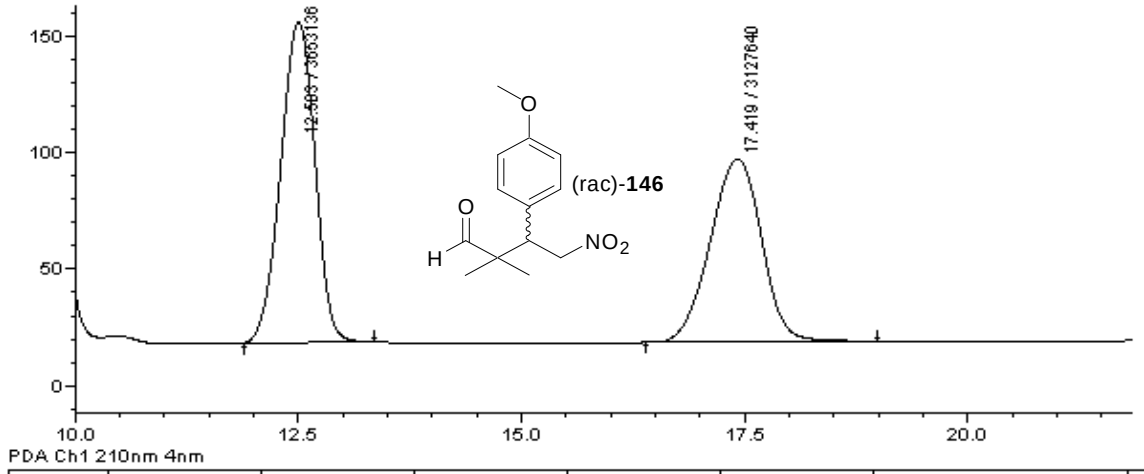
Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	12.308	2484740	169907	5.258	7.708	0.429	
2	18.141	44769714	2034413	94.742	92.292	0.650	
Total		47254454	2204320	100.000	100.000		


9.505
7.363
6.313
6.300
6.204
4.746
4.740
4.588
4.556
3.930
3.903
3.891
1.157
1.034
−0.004
1
1.04
1.07
1.0
1.09
1.09
1.05
3.01
3.2
H
O
O
NO2
(S)-145

(S)-2,2-Dimethyl-4-nitro-3-(4-methoxyphenyl)-butanal (146)

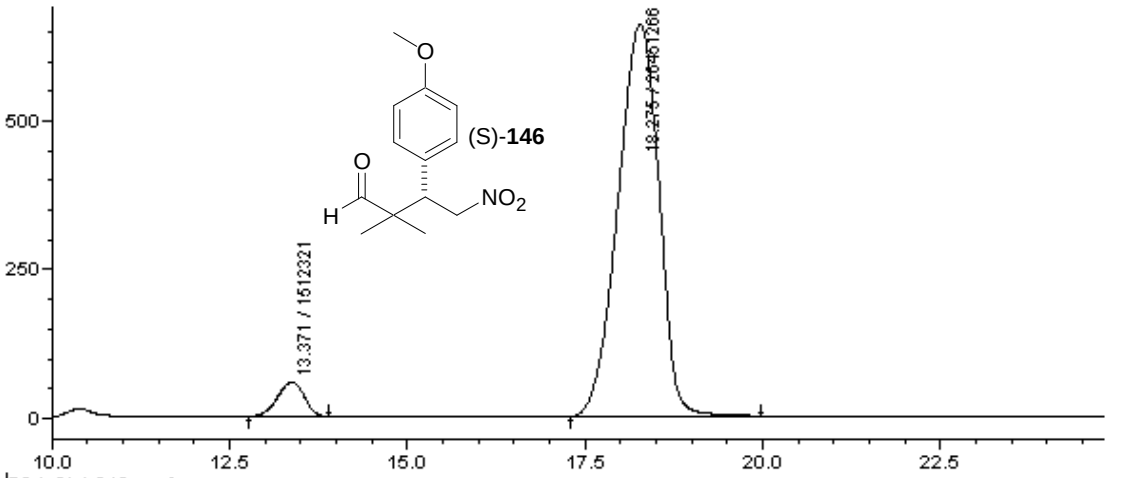
Colourless solid, 59 % yield, 90 % *ee*. The ee was determined by chiral HPLC (Chiral OD-H, *i*-propanol/heptane 10/90, flow rate = 1 mL/min, λ = 210 nm), t_{minor} = 13.3 min, t_{major} = 18.2 min, R_f = 0.33 EtOAc/ pet ether (1 : 4). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm):9.51 (s, 1H), 7.11 (d, 2H), 6.85 (d, 2H), 4.83-4.78 (dd, *J* = 11.4, 12.3 Hz, 1H), 4.61-4.68 (dd, *J* = 4.6, 13.3 Hz, 1H), 3.77 (s, 3H), 3.74-3.68 (m, 1H), 1.1 (s, 3H), 0.99 (s, 3H).

Racemic **146**

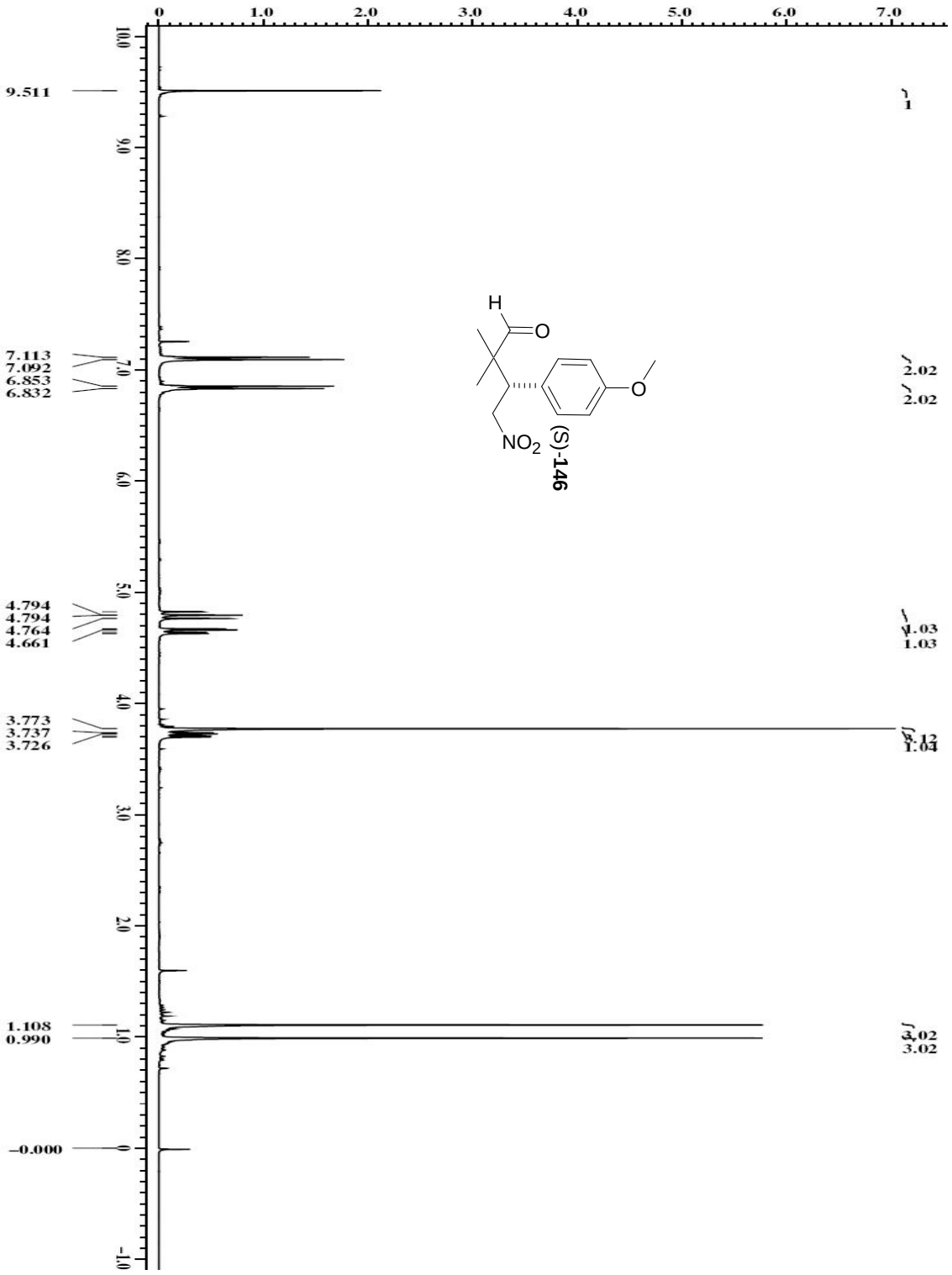


Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	12.503	3653136	137410	53.875	63.640	0.749	
2	17.419	3127640	78507	46.125	36.360	1.120	
Total		6780775	215917	100.000	100.000		

(S)-**146**



Peak#	Ret. Time	Area	Height	Area %	Height %	Width at 10% Height	Mark
1	13.371	1512321	57633	5.408	8.042	0.742	
2	18.275	26451266	658996	94.592	91.958	1.109	
Total		27963587	716629	100.000	100.000		


9.511
7.113
7.092
6.853
6.832
4.794
4.794
4.764
4.661
3.773
3.737
3.726
1.108
0.990
−0.000
H
O
O
NO2
(S)-146

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