

ENANTIOSELECTIVE MICHAEL ADDITION OF DIETHYL MALONATE  
TO NITROOLEFINS WITH BIFUNCTIONAL 2-AMINODMAP/UREA  
ORGANOCATALYST

A THESIS SUBMITTED TO  
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES  
OF  
MIDDLE EAST TECHNICAL UNIVERSITY

BY

İREM BAKIRCI ÇETİNKAYA

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
FOR  
THE DEGREE OF MASTER OF SCIENCE  
IN  
CHEMISTRY

MAY 2016



Approval of the thesis:

**ENANTIOSELECTIVE MICHAEL ADDITION OF DIETHYL  
MALONATE TO NITROOLEFINS WITH BIFUNCTIONAL 2-  
AMINODMAP/UREA ORGANOCATALYST**

submitted by **İREM BAKIRCI ÇETİNKAYA** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver  
Dean, Graduate School of **Natural and Applied Sciences** \_\_\_\_\_

Prof. Dr. Cihangir Tanyeli  
Head of Department, **Chemistry** \_\_\_\_\_

Prof. Dr. Cihangir Tanyeli  
Supervisor, **Chemistry Dept., METU** \_\_\_\_\_

**Examining Committee Members:**

Prof. Dr. Özdemir Doğan  
Chemistry Dept., METU \_\_\_\_\_

Prof. Dr. Cihangir Tanyeli  
Chemistry Dept., METU \_\_\_\_\_

Prof. Dr. Adnan Bulut  
Chemistry Dept., Kırıkkale University \_\_\_\_\_

Assoc. Prof. Dr. Akın Akdağ  
Chemistry Dept., METU \_\_\_\_\_

Assist. Prof. Dr. Salih Özçubukçu  
Chemistry Dept., METU \_\_\_\_\_

**Date:** 04.05.2016

**I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.**

Name, Last name: İrem Bakırcı Çetinkaya

Signature:

## ABSTRACT

### ENANTIOSELECTIVE MICHAEL ADDITION OF DIETHYL MALONATE TO NITROOLEFINS WITH BIFUNCTIONAL 2-AMINODMAP/UREA ORGANOCATALYST

Bakırcı Çetinkaya, İrem

M.S., Department of Chemistry

Supervisor: Prof. Dr. Cihangir Tanyeli

May 2016, 117 pages

The enantioselective organocatalytic Michael addition reaction has gained increased attention as an asymmetric synthesis strategy for C-C bond formation. In this regard, (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine derived C<sub>1</sub> symmetrical 2-aminoDMAP has been synthesized in our group. The remaining primary amine was modified with 1-isothiocyanato-(3,5)-bis(trifluoromethyl) benzene 3,5-Bis(trifluoromethyl) phenyl isothiocyanate and 3,5-bis(trifluoromethyl) phenyl isocyanate to afford bifunctional 2-aminoDMAP/thiourea and 2-aminoDMAP/urea organocatalysts. The efficiency of organocatalyst has been tested in Michael addition of diethyl malonate to *trans*-β-nitrostyrene by screening the parameters such as catalyst loading amount, concentration, solvent and temperature. The best condition was found as 5 mol% catalyst loading at room temperature in toluene and the target GABA precursor was synthesized for 4 h in 94% ee. With the optimized reaction condition in hand, the scope of enantioselective organocatalytic conjugate addition was examined further by varying *trans*-β-nitroolefins. Most of the conjugate addition products were obtained in high to excellent yields (65-95%) and selectivities (80-99% ee).

**Keywords:** asymmetric organocatalysis, Michael addition reaction, nitroolefins, bifunctional organocatalyst, 2-AminoDMAP/urea

## ÖZ

### BİFONKSİYONEL 2-AMİNODMAP/ÜRE ORGANOKATALİZÖRÜ İLE DİETİL MALONATIN NİTROOLEFİNLERE ENANTİYOSEÇİCİ MICHAEL KATILMASI

Bakırcı Çetinkaya, İrem  
Yüksek Lisans, Kimya Bölümü  
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Mayıs 2016, 117 sayfa

Enantioseçici organokatalitik Michael katılma reaksiyonu C-C bağ oluşumu ile asimetrik sentez konusunda dikkatleri üzerine çekmiştir. Bu bağlamda, (1*R*,2*R*)-*trans*-1,2-sikloheksandiaminden türetilen C<sub>1</sub>-simetrik 2-aminoDMAP grubumuzda sentezlenmiştir. Birincil amin, bifonksiyonel 2- aminoDMAP/ tiyoüre ve 2-aminoDMAP/üre organokatalizörlerini elde etmek için 3,5-(bistrifluoromethyl) phenyl tiyoizosyanat ve 3,5-(bistrifluoromethyl) phenyl izosyanat ile modifiye edilmiştir. Organokatalizörün etkenliği dietilmalonatın *trans*- $\beta$ -nitrostirene Michael katılmasına katalizör yükleme miktarı, konsantrasyon, çözücü ve sıcaklık gibi parametrelerin taranmasıyla test edilmiştir. En uygun koşul oda sıcaklığında % 5 mol katalizör yükleme ile toluen çözücüsü kullanılarak bulunmuştur ve hedef GABA öncüsü 4 saatte % 94 ee ile sentezlenmiştir. Eldeki optimize reaksiyon koşulları ile daha sonrasında enantiyoseçici organokatalitik konjuge ilavesinin kapsamı *trans*- $\beta$ -nitroolefinler çeşitlendirilerek incelenmiştir. Konjuge ekleme ürünlerinin çoğu mükemmel bir verimle (% 65-95) ve seçicilikle (% 80-99 ee) yüksek sonuçlarla elde edilmiştir.

**Anahtar Kelimeler:** asimetrik organokataliz, Michael katılma reaksiyonu, nitroolefinler, bifonksiyonel organokatalizör, 2-AminoDMAP/üre

*To my dear family...*

## ACKNOWLEDGEMENTS

I would like to thank and express my sincere appreciation to my supervisor Prof. Dr. Cihangir Tanyeli for his endless support, precious guidance and encouragement for this study. It was an honor and good chance for me to work with him.

Also, I would like to thank Murat Işık for his help and guidance in bifunctional organocatalysis concept.

I wish to express my special thanks to Dr. Serdar Sezer for his help and friendship, from whom I have learned many things about experiments and Doc. Dr. Devrim Özdemirhan for their valuable advices, help and support.

I would like to express thanks to Prof. Dr. Özdemir Doğan, Prof. Dr. Adnan Bulut, Assoc. Prof. Dr. Akın Akdağ and Assist. Prof. Dr. Salih Özçubukçu for being committee member and their advices to my thesis.

I would like to extend my gratitude to TÜBİTAK and METU-BAP for the financial support for this study. Also, I would like to thank NMR specialist Betül Eymur for the NMR experiments. Besides, I would like to thank Zeynep Erdoğan at Bilkent University for HRMS analysis.

I would like to express my great thanks to my dear lab mates Duygu İşibol and Deniz Tözendemir for their precious friendship, helping and supporting me whenever I need. I also wish to express my sincere thanks to all Prof. Dr. Cihangir Tanyeli Research group members Nurdan Sargın, Esra Kanberoğlu, Seda Okumuş, Dilşad Susam and Ezgi Bayer for their valuable friendship and help.

I wish to express also my thanks to friends M. Yağız Ünver, Merve Kapucu, Zehra Kabasakal, for their friendship and helping. Moreover, I would like to thank Nursultan Topak and Esen Öztaş for great friendship and understanding.

Finally, I would like to express my deepest gratitude to my dear parents, my sister and my husband for their endless love, encouragement, support and believing in me throughout my whole life. I am the luckiest person to have this family and I love them so much.



## TABLE OF CONTENT

ABSTRACT .....	v
ÖZ.....	vi
ACKNOWLEDGEMENTS.....	viii
LIST OF CONTENT .....	ix
LIST OF TABLES.....	xii
LIST OF FIGURES .....	xiii
LIST OF SCHEMES .....	xvii
LIST OF ABBREVIATIONS .....	xix
CHAPTERS.....	1
1. INTRODUCTION.....	1
1.1 Chirality and Asymmetric Synthesis .....	1
1.1.1 Asymmetric Catalysis.....	2
1.2 Organocatalysis.....	3
1.2.1 History .....	4
1.2.2 Classification .....	10
1.2.3 Bifunctional Organocatalysis.....	14
1.2.3.1. Thiourea/Urea as Bifunctional Organocatalysis.....	14
1.3 Enantioselective Michael Addition Reaction .....	20
1.3.1 Enantioselective Michael Addition of Malonates to Nitroolefins .....	21
1.4 Aim of the Work.....	23
2. RESULTS AND DISCUSSION.....	25
2.1 Synthesis of 2-aminoDMAP.....	25
2.2 Synthesis of 2-aminoDMAP Based Bifunctional Organocatalysts .....	26
2.3 Evaluation of Bifunctional Organocatalysts in Enantioselective Michael Addition of Diethyl Malonates to <i>trans</i> - $\beta$ -Nitrostyrene.....	26
2.3.1 Evaluation of 2-aminoDMAP/urea in Enantioselective Michael Addition of Diethyl Malonate to Various Nitroolefins .....	32

3. EXPERIMENTAL .....	39
3.1 Materials and Methods .....	39
3.2 Synthesis of 2-aminoDMAP 56.....	40
3.3 Synthesis of 2-aminoDMAP/Thiourea Bifunctional Organocatalyst 52 ...	41
3.4 Synthesis of 2-aminoDMAP/Urea Bifunctional Organocatalyst 53.....	43
3.5 General Procedure for Asymmetric Michael Additions of Diethyl Malonate to Nitroolefins .....	44
3.5.1 Synthesis of ( <i>R</i> )-diethyl 2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl) malonate (46a).....	44
3.5.2 Synthesis of ( <i>R</i> )-diethyl 2-(2-nitro-1-phenylethyl)malonate (46b) .....	46
3.5.3 Synthesis of ( <i>R</i> )-diethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl) malonate (46c) .....	47
3.5.4 Synthesis of ( <i>S</i> )-diethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)malonate (46d) .....	48
3.5.5 Synthesis of ( <i>R</i> )-diethyl 2-(1-(2-fluorophenyl)-2-nitroethyl)malonate (46e) .....	49
3.5.6 Synthesis of ( <i>R</i> )-diethyl 2-(1-(2,4-dichlorophenyl)-2-nitroethyl) malonate (46f) .....	50
3.5.7 Synthesis of ( <i>R</i> )-diethyl 2-(1-(2-methoxyphenyl)-2-nitroethyl)malonate (46g) .....	51
3.5.8 Synthesis of ( <i>R</i> )-diethyl 2-(1-(4-bromophenyl)-2-nitroethyl)malonate (46h) .....	52
3.5.9 Synthesis of ( <i>R</i> )-diethyl 2-(2-nitro-1-( <i>p</i> -tolyl)ethyl)malonate (46i)....	53
3.5.10 Synthesis of ( <i>S</i> )-diethyl 2-(1-(furan-2-yl)-2-nitroethyl)malonate (46j) .....	54
3.5.11 Synthesis of ( <i>R</i> )-diethyl 2-(1-(2-chlorophenyl)-2-nitroethyl)malonate (46k) .....	55
3.5.12 Synthesis of ( <i>R</i> )-diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (46l) .....	56
3.5.13 Synthesis of ( <i>R</i> )-diethyl 2-(1-(3-chlorophenyl)-2-nitroethyl)malonate (46m) .....	57

3.5.14 Synthesis of ( <i>R</i> )-diethyl 2-(1-(3-methoxyphenyl)-2-nitroethyl)malonate (46n).....	58
3.5.15 Synthesis of ( <i>S</i> )-diethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (46o) .....	59
3.5.16 Synthesis of ( <i>R</i> )-diethyl 2-(1-(3-bromophenyl)-2-nitroethyl)malonate (46p) .....	60
3.5.17 Synthesis of ( <i>R</i> )-diethyl 2-(2-nitro-1-(2-nitrophenyl)ethyl)malonate (46r).....	61
3.6 General Procedure for Asymmetric Michael Additions of Malonates to <i>trans</i> - $\beta$ -nitrostyrene .....	62
3.6.1 Synthesis of ( <i>R</i> )-dimethyl 2-(2-nitro-1-phenylethyl)malonate (60a) ..	62
3.6.2 Synthesis of ( <i>R</i> )-diisopropyl 2-(2-nitro-1-phenylethyl)malonate (60b)	63
3.6.3 Synthesis of ( <i>R</i> )-diethyl 2-acetamido-2-(2-nitro-1-phenylethyl)malonate (60c).....	64
4. CONCLUSION .....	67
REFERENCES .....	69
APPENDICES .....	73
A. SUPPORTING INFORMATION (NMR).....	73
B. SUPPORTING INFORMATION (HPLC).....	97

## LIST OF TABLES

### TABLES

<b>Table 1.</b> Catalyst loading screening results of 2-aminoDMAP/thiourea 52 .....	27
<b>Table 2.</b> Catalyst loading screening results of 2-aminoDMAP/urea 53 .....	28
<b>Table 3.</b> Reaction concentration screening results.....	29
<b>Table 4.</b> Solvent screening results .....	31
<b>Table 5.</b> Derivatization of nitroolefins with 2-aminoDMAP/urea.....	33
<b>Table 6.</b> Derivatization of malonates with 2-aminoDMAP/urea.....	36

## LIST OF FIGURES

### FIGURES

<b>Figure 1.</b> A number of examples of differences in the behavior of enantiomers ..	1
<b>Figure 2.</b> Publications and number of citations about the term of organocatalysis	3
<b>Figure 3.</b> General classification of organocatalysis according to Berkessel .....	11
<b>Figure 4.</b> General classification of organocatalysis according to List.....	12
<b>Figure 5.</b> General classification of commonly used organocatalysis according to MacMillan .....	13
<b>Figure 6.</b> Bifunctionality of organocatalysis .....	14
<b>Figure 7.</b> General mechanism for the asymmetric hydrogen bonding catalysis.	15
<b>Figure 8.</b> Possible transition state of thiourea based organocatalyst by Takemoto .....	18
<b>Figure 9.</b> Examples of bifunctional thioureas.....	20
<b>Figure 10.</b> The structure of ( <i>R</i> )-(-)-baclofen.....	22
<b>Figure 11.</b> Proposed transition state model.....	38
<b>Figure A.1.</b> <sup>1</sup> H NMR spectrum of 2-aminoDMAP (compound 56) .....	74
<b>Figure A.2.</b> <sup>13</sup> C NMR spectrum of 2-aminoDMAP (compound 56) .....	74
<b>Figure A.3.</b> <sup>1</sup> H NMR spectrum of 2-aminoDMAP/thiourea (compound 52) .....	75
<b>Figure A.4.</b> <sup>13</sup> C NMR spectrum of 2-aminoDMAP/thiourea (compound 52).....	75
<b>Figure A.5.</b> <sup>1</sup> H NMR spectrum of 2-aminoDMAP/urea (compound 53) .....	76
<b>Figure A.6.</b> <sup>13</sup> C NMR spectrum of 2-aminoDMAP/urea (compound 53) .....	76
<b>Figure A.7.</b> <sup>1</sup> H NMR spectrum of Michael product 46a.....	77
<b>Figure A.8.</b> <sup>13</sup> C NMR spectrum of Michael product 46a .....	77
<b>Figure A.9.</b> <sup>1</sup> H NMR spectrum of Michael product 46b .....	78
<b>Figure A.9.</b> <sup>13</sup> C NMR spectrum of Michael product 46b .....	78
<b>Figure A.10.</b> <sup>1</sup> H NMR spectrum of Michael product 46c.....	79
<b>Figure A.11.</b> <sup>13</sup> C NMR spectrum of Michael product 46c .....	79
<b>Figure A.12.</b> <sup>1</sup> H NMR spectrum of Michael product 46d .....	80

<b>Figure A.13.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46d .....	80
<b>Figure A.14.</b> $^1\text{H}$ NMR spectrum of Michael product 46e .....	81
<b>Figure A.15.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46e .....	81
<b>Figure A.16.</b> $^1\text{H}$ NMR spectrum of Michael product 46f .....	82
<b>Figure A.17.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46f .....	82
<b>Figure A.18.</b> $^1\text{H}$ NMR spectrum of Michael product 46g .....	83
<b>Figure A.19.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46g .....	83
<b>Figure A.20.</b> $^1\text{H}$ NMR spectrum of Michael product 46h .....	84
<b>Figure A.21.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46h .....	84
<b>Figure A.22.</b> $^1\text{H}$ NMR spectrum of Michael product 46i .....	85
<b>Figure A.23.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46i .....	85
<b>Figure A.24.</b> $^1\text{H}$ NMR spectrum of Michael product 46j .....	86
<b>Figure A.25.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46j .....	86
<b>Figure A.26.</b> $^1\text{H}$ NMR spectrum of Michael product 46k .....	87
<b>Figure A.27.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46k .....	87
<b>Figure A.28.</b> $^1\text{H}$ NMR spectrum of Michael product 46l .....	88
<b>Figure A.29.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46l .....	88
<b>Figure A.30.</b> $^1\text{H}$ NMR spectrum of Michael product 46m .....	89
<b>Figure A.31.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46m .....	89
<b>Figure A.32.</b> $^1\text{H}$ NMR spectrum of Michael product 46n .....	90
<b>Figure A.33.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46n .....	90
<b>Figure A.34.</b> $^1\text{H}$ NMR spectrum of Michael product 46o .....	91
<b>Figure A.35.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46o .....	91
<b>Figure A.36.</b> $^1\text{H}$ NMR spectrum of Michael product 46p .....	92
<b>Figure A.37.</b> $^{13}\text{C}$ NMR spectrum of Michael product 46p .....	92
<b>Figure A.38.</b> $^1\text{H}$ NMR spectrum of Michael product 46r .....	93
<b>Figure A.39.</b> $^1\text{H}$ NMR spectrum of Michael product 46r .....	93
<b>Figure A.40.</b> $^1\text{H}$ NMR spectrum of Michael product 60a .....	94
<b>Figure A.41.</b> $^{13}\text{C}$ NMR spectrum of Michael product 60a .....	94
<b>Figure A.42.</b> $^1\text{H}$ NMR spectrum of Michael product 60b .....	95
<b>Figure A.43.</b> $^{13}\text{C}$ NMR spectrum of Michael product 60b .....	95

<b>Figure A.44.</b> $^1\text{H}$ NMR spectrum of Michael product 60c.....	96
<b>Figure A.45.</b> $^{13}\text{C}$ NMR spectrum of Michael product 60c .....	96
<b>Figure B.1.</b> HPLC chromatogram of <i>rac</i> -46a .....	98
<b>Figure B.2.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46a....	98
<b>Figure B.3.</b> HPLC chromatogram of <i>rac</i> -46b .....	99
<b>Figure B.4.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46b ...	99
<b>Figure B.5.</b> HPLC chromatogram of <i>rac</i> -46c .....	100
<b>Figure B.6.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46c..	100
<b>Figure B.7.</b> HPLC chromatogram of <i>rac</i> -46d .....	101
<b>Figure B.8.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46d .	101
<b>Figure B.9.</b> HPLC chromatogram of <i>rac</i> -46e .....	102
<b>Figure B.10.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46e	102
<b>Figure B.11.</b> HPLC chromatogram of <i>rac</i> -46f.....	103
<b>Figure B.12.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46f	103
<b>Figure B.13.</b> HPLC chromatogram of <i>rac</i> -46g .....	104
<b>Figure B.14.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46g	104
<b>Figure B.15.</b> HPLC chromatogram of <i>rac</i> -46h .....	105
<b>Figure B.16.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46h	105
<b>Figure B.17.</b> HPLC chromatogram of <i>rac</i> -46i .....	106
<b>Figure B.18.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46i	106
<b>Figure B.19.</b> HPLC chromatogram of <i>rac</i> -46j .....	107
<b>Figure B.20.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46j	107
<b>Figure B.21.</b> HPLC chromatogram of <i>rac</i> -46k .....	108
<b>Figure B.22.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46k	108
<b>Figure B.23.</b> HPLC chromatogram of <i>rac</i> -46l .....	109
<b>Figure B.24.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46l	109
<b>Figure B.25.</b> HPLC chromatogram of <i>rac</i> -46m .....	110
<b>Figure B.26.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46m	110
<b>Figure B.27.</b> HPLC chromatogram of <i>rac</i> -46n .....	111
<b>Figure B.28.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46n	111
<b>Figure B.29.</b> HPLC chromatogram of <i>rac</i> -46o .....	112

<b>Figure B.30.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46o	112
<b>Figure B.31.</b> HPLC chromatogram of <i>rac</i> -46p	113
<b>Figure B.32.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46p	113
<b>Figure B.33.</b> HPLC chromatogram of <i>rac</i> -46r	114
<b>Figure B.34.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 46r	114
<b>Figure B.35.</b> HPLC chromatogram of <i>rac</i> -60a	115
<b>Figure B.36.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 60a	115
<b>Figure B.37.</b> HPLC chromatogram of <i>rac</i> -60b	116
<b>Figure B.38.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 60b	116
<b>Figure B.39.</b> HPLC chromatogram of <i>rac</i> -60c	117
<b>Figure B.40.</b> HPLC chromatogram of <i>enantiomerically enriched</i> product 60c	117



## LIST OF SCHEMES

### SCHEMES

<b>Scheme 1.</b> Oxamide synthesis.....	4
<b>Scheme 2.</b> Hydrocyanation of benzaldehyde catalyzed by quinine or quinidine .	5
<b>Scheme 3.</b> Addition of methanol to ketenes catalyzed by <i>o</i> -acetylquinine.....	5
<b>Scheme 4.</b> Intramolecular asymmetric aldol cyclodehydration .....	5
<b>Scheme 5.</b> Asymmetric epoxidation of enones catalyzed by poly-L-leucine .....	6
<b>Scheme 6.</b> Michael addition reaction catalyzed by quinine .....	6
<b>Scheme 7.</b> Hydrocyanation of benzaldehyde catalyzed by poly-L-leucine .....	7
<b>Scheme 8.</b> Asymmetric alkylation of indanone catalyzed by phase-transfer catalyst.....	7
<b>Scheme 9.</b> Asymmetric epoxidation of olefins catalyzed by Shi's catalyst.....	8
<b>Scheme 10.</b> Strecker reaction .....	8
<b>Scheme 11.</b> Diels-Alder reaction catalyzed by imidazolidone .....	9
<b>Scheme 12.</b> Aldol reaction catalyzed by <i>L</i> -Proline .....	9
<b>Scheme 13.</b> Allylation reaction catalyzed by diarylurea.....	15
<b>Scheme 14.</b> Diaryl(thio)urea catalysis of the Claisen rearrangement .....	16
<b>Scheme 15.</b> Schreiner's thiourea catalyzed Diels Alder reaction 1 .....	17
<b>Scheme 16.</b> Schreiner's thiourea catalyzed Diels Alder reaction 2.....	17
<b>Scheme 17.</b> Takemoto's thiourea catalyzed asymmetric Michael addition reaction .....	18
<b>Scheme 18.</b> Takemoto's bifunctional tert-amine/thiourea catalyzed asymmetric Michael addition reaction .....	19
<b>Scheme 19.</b> The addition of the anion of diethyl malonate to ethylidene malonate .....	20
<b>Scheme 20.</b> The addition of the anion of diethyl malonate to ethylidene malonate .....	21
<b>Scheme 21.</b> Representative aim of the study .....	23

<b>Scheme 22.</b> Synthesis pathway of Baclofen .....	24
<b>Scheme 23.</b> Synthesis of 2-aminoDMAP .....	25
<b>Scheme 24.</b> Synthesis of 2-aminoDMAP based urea and thiourea organocatalysts .....	26
<b>Scheme 25.</b> Michael addition of diethyl malonate to <i>trans</i> - $\beta$ -nitrostyrene .....	29

## LIST OF ABBREVIATIONS

**SOMO** Singly occupied molecular orbital

**LUMO** Lowest unoccupied molecular orbital

**HOMO** Highest occupied molecular orbital

***t*-Bu** *tert*-Butyl

**DMAP** 4-Dimethylamino pyridine

**DCM** Dichloromethane

**THF** Tetrahydrofuran

**HPLC** High performance liquid chromatography

**HRMS** High resolution mass spectrometry

**IR** Infrared radiation

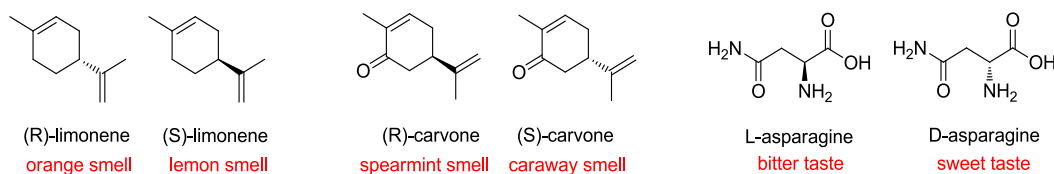


## CHAPTER 1

### INTRODUCTION

#### 1.1 Chirality and Asymmetric Synthesis

In 1874, Pasteur would say “*The universe is dissymmetrical; for if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality. . . . Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, in their structure, in their external forms, functions of cosmic dissymmetry.*” In modern terminology, the description of dissymmetry is chirality. That is why asymmetric synthesis involves the formation of chiral molecules, which are all important in life sciences.<sup>1</sup> Due to being chiral, enantiomers of organic compounds like food additives, flavors, vitamins, insecticides, drugs<sup>2</sup> and also living organisms like DNA, hormones and enzymes<sup>3</sup> have different smell or taste, more importantly, they can reveal diversified pharmacological and biological specifications. Some examples of enantiomers’ different behaviors can be seen in the Figure 1. For instance, (*R*)-limonene has orange odour, while (*S*)-limonene has lemon odour, or while (*R*)-carvone has mint odour, (*S*)-carvone has cumin odour and L-asparagine has a bitter taste whereas D-asparagine has a sweet taste.<sup>1</sup>



**Figure 1.** A number of examples of differences in the behavior of enantiomers

### 1.1.1 Asymmetric Catalysis

Asymmetric catalysis, which is an important constituent of asymmetric synthesis, is defined as the transformation of prochiral or racemic substances into enantioenriched compounds by virtue of chiral catalysis.<sup>4</sup>

There are three pillars of asymmetric catalysis that are biocatalysis, metal catalysis and, organocatalysis.<sup>5</sup>

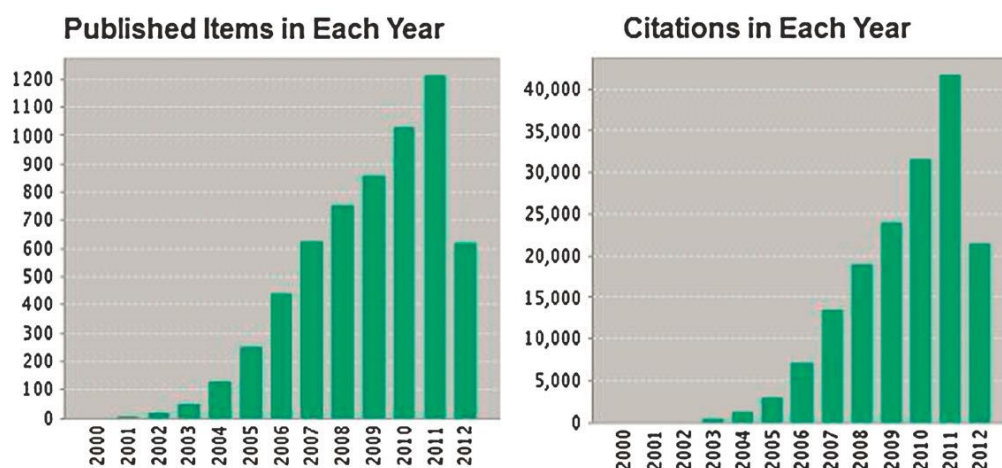
In nonnatural starting materials' synthetic conversions, natural or altered enzymes are used and this process is defined as biocatalysis. Natural compounds like enzymes used in these synthetic conversions, are called as biocatalysts and these processes are called biocatalytic conversions.<sup>6</sup>

Transition- metal catalysts, particularly organometallic catalysts can trigger substrates and accelerate reactions in order to have separation or formation of H-H, C-H and C-C bonds, by virtue of coordination, ligand swap, insertion and elimination, by making use of metal d orbitals. These catalysts are mostly studied uniform catalysts due to their benefits. A lot of transition-metal catalysts have been developed and used in lots of different areas, because their activeness and selectiveness can be altered by changing their ligands<sup>7</sup> and these catalysts are especially advantageous for asymmetric hydrogenations, however in final product, they may leave residual of heavy metal.<sup>8</sup>

Enantioselective organocatalysis can be accepted as one of the major elements of asymmetric synthesis with enzyme-mediated catalysis and metal complexes.<sup>9</sup> Organocatalysis is getting more important as a result of that, small organic molecules, in addition to biocatalysts and metal complexes, are remarkably selective and effective catalysts as almost half of the known enzymes, which are highly enantioselective and effective, do not have metals in their active site.<sup>10</sup>

## 1.2 Organocatalysis

Organocatalysis means the acceleration of chemical reactions with a substoichiometric quantity of an organic compound without metal atom<sup>11</sup> and as a consequence organocatalysis is accepted an equal methodology to enzymatic and organometallic catalysis.<sup>12</sup> Because the effectiveness and selectivity of numerous organocatalytic reactions reach the standards of established organic reactions, the concern for this field stunningly increased due to the originality of the idea and also the effectiveness and selectivity of them. In twelve years since 2000, the number of publications about the organocatalysis field have reached over 6000, more than 1200 only in 2011, and also citations reached over 150000, more than 40000 only in 2011 (Figure 2).<sup>13</sup>



**Figure 2.** Publications and number of citations about the term of organocatalysis

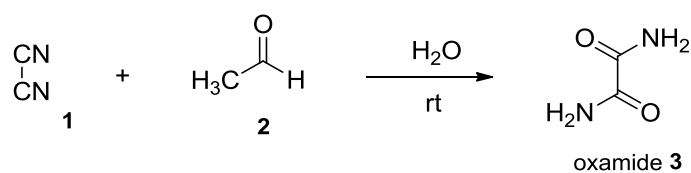
Organocatalysts have many advantages with their ordinarily robust, cheap, accessible and non-toxic features. Besides, many reaction circumstances related to atmosphere, temperature, solvents etc. are not necessary due to their inertness with moisture and oxygen. Moreover, because there is no transition metal in organocatalytic techniques, they are more useful and effective for the compounds that have no tolerance for metal pollution such as pharmaceutical products.

Chiral organocatalysts like proline, cinchona alkaloids such as quinine and several amino acid-, sugar- and peptide-derived compounds are involved in asymmetric synthesis.<sup>11</sup>

In comparison to transition-metal complexes and biocatalysis, organocatalysis has various advantages such as being more stable, cheaper and easily accessible with undemanding reaction circumstances. Because of being eco-friendly, these type of catalysts can facilitate their own recovery and recycling when integrated onto a support, additionally due to lack of heavy-metal residual this type of reaction is attractive for the synthesis of pharmaceutical and agrochemical products. Therefore, the industry will be more concerned with this method because of its skillfulness and favorable effect on environment.<sup>11</sup>

### 1.2.1 History

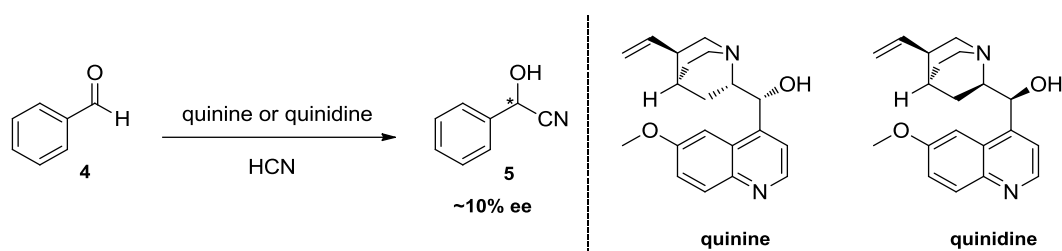
For many years, small-scale pure organic molecules have been using in reaction as a catalyst. In 1860, German chemist Justus von Leibig performed the first organocatalytic reaction without metals in order to synthesize oxamide (**3**) from cyanogen (**1**) and acetaldehyde (**2**) in water (Scheme 1).<sup>14</sup>



**Scheme 1.** Oxamide synthesis

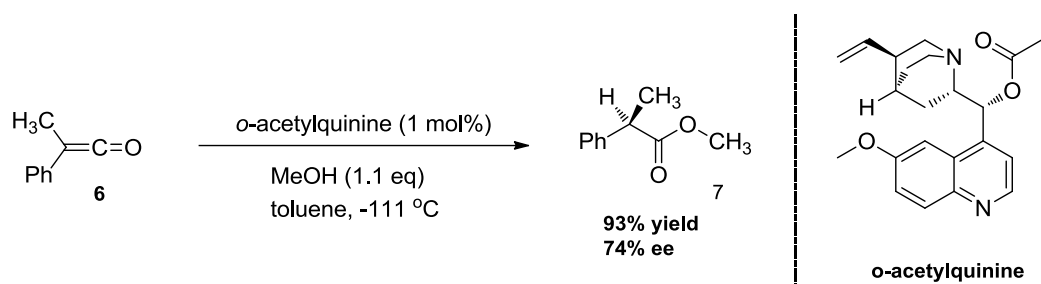
In 1912, Bredig and Fiske explained the addition of HCN to benzaldehyde (**4**) by using cinchona alkaloids (quinine or quinidine) with low enantiomeric excess results (Scheme 2).<sup>15</sup>





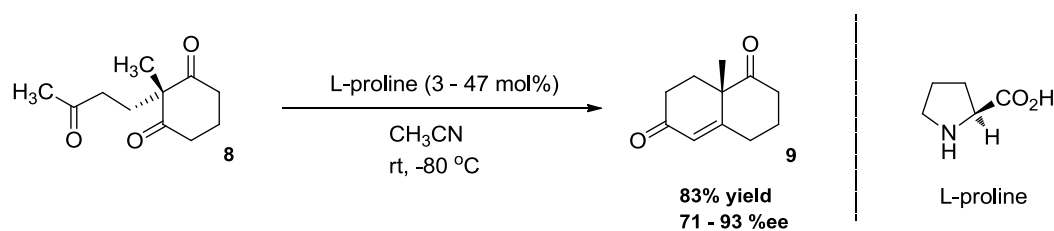
**Scheme 2.** Hydrocyanation of benzaldehyde catalyzed by quinine or quinidine

In 1960, Pracejus described the reaction, which is the first example of high levels of enantioselectivity, by adding methanol to methyl phenyl ketene (**6**) with *o*-acetylquinine used as catalyst (Scheme 3).<sup>16</sup>



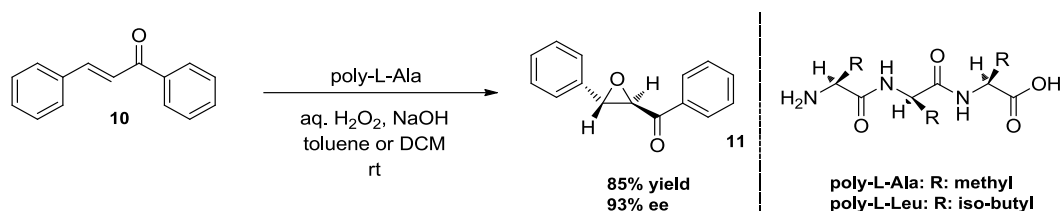
**Scheme 3.** Addition of methanol to ketenes catalyzed by *o*-acetylquinine

In 1971, further leap in this area was achieved by Hajos - Parrish - Eder - Sauer - Wiechert reaction which is the intramolecular asymmetric aldol cyclodehydration of the achiral trione **8** with the product of unsaturated Wieland - Miescher ketone **9** catalyzed by proline (Scheme 4).<sup>17, 18</sup>



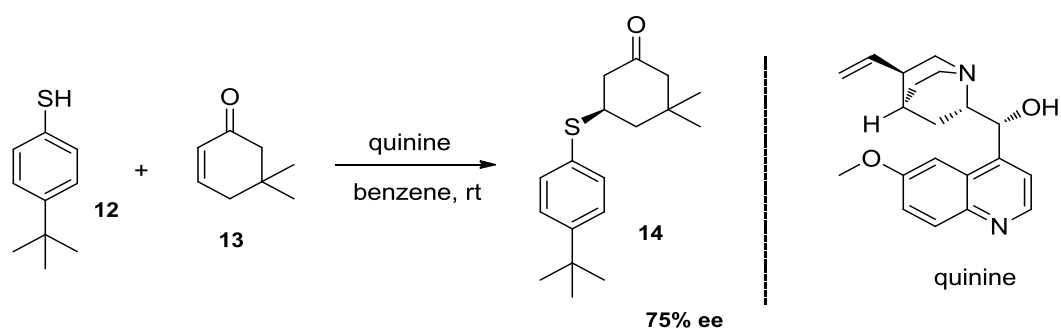
**Scheme 4.** Intramolecular asymmetric aldol cyclodehydration

In 1980, an important development in organocatalysis is the first use of hydrogen-bonding catalysis in asymmetric synthesis that was the epoxidation of chalcone (**10**) by H<sub>2</sub>O<sub>2</sub> with the poly-L-leucine catalyst introduced by Julia and Colonna (Scheme 5).<sup>19</sup>



**Scheme 5.** Asymmetric epoxidation of enones catalyzed by poly-L-leucine

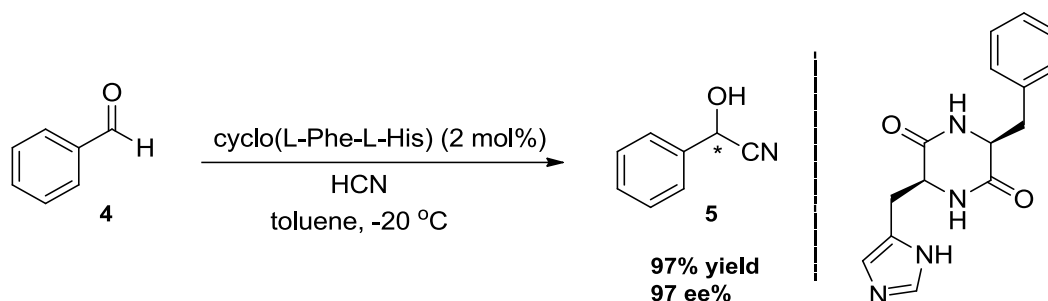
In 1981, Wynberg performed the Michael reaction between the aromatic thiols **12** and conjugated cycloalkenones **13** by using cinchona alkaloid derivatives as chiral catalysts. Furthermore, the cinchona and ephedra alkaloids which contain  $\beta$ -hydroxy amine moiety are classified as bifunctional catalysts. Namely, Wynberg introduced various organocatalytic reactions by using cinchona alkaloids as chiral Lewis base/nucleophilic catalysts (Scheme 6).<sup>20</sup>



**Scheme 6.** Michael addition reaction catalyzed by quinine

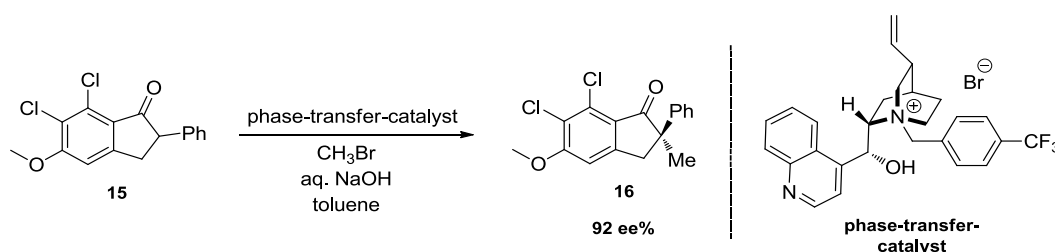
In 1981, Inoue studied the addition of HCN to benzaldehyde (**4**) affording the product **5** with up to 90% ee catalyzed by the cyclic peptide which is obtained

readily from l-histidine and l-phenylalanine. This reaction had a new research area with the addition of nucleophiles to aldehydes and imines by using variety of peptide catalysts (Scheme 7).<sup>21</sup>



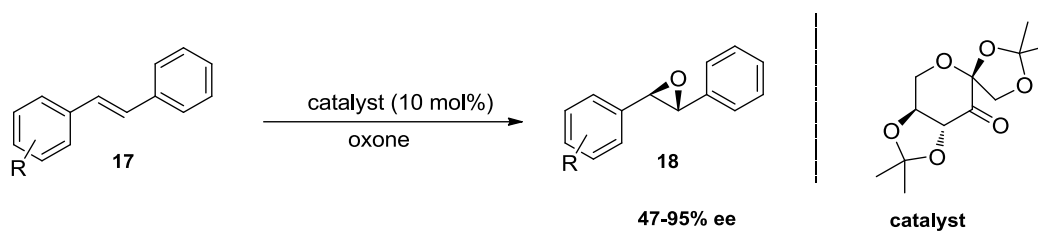
**Scheme 7.** Hydrocyanation of benzaldehyde catalyzed by poly-L-leucine

In 1984, N-benzylcinchoninium bromide derivative, which enables 2-substituted-2-phenyl indanone **16** to be alkylated with high ee, was effectively used in asymmetric phase-transfer reactions by Merck researchers (Scheme 8).<sup>22</sup>



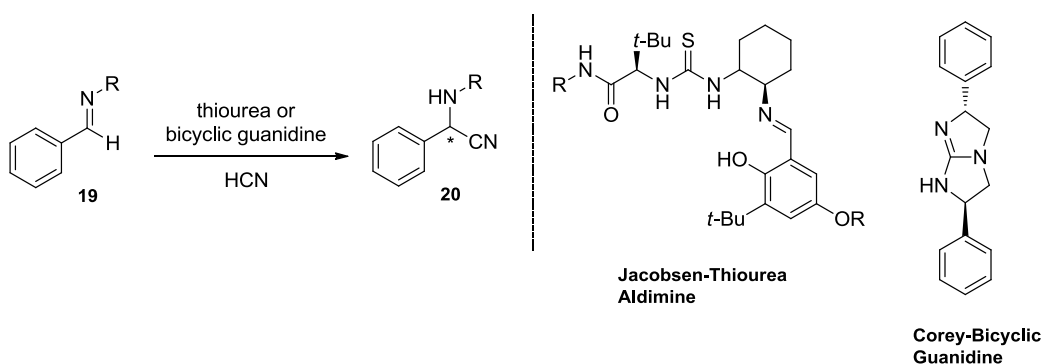
**Scheme 8.** Asymmetric alkylation of indanone catalyzed by phase transfer catalyst

In 1996, another important progress, which is the asymmetric epoxidation of alkenes by using chiral dioxiranes created in situ, was introduced by Shi. The process, by use of fructose derived ketone as the catalyst and oxone as the oxidant, is efficient for disubstituted trans-olefins, and trisubstituted olefins (Scheme 9).<sup>23</sup>



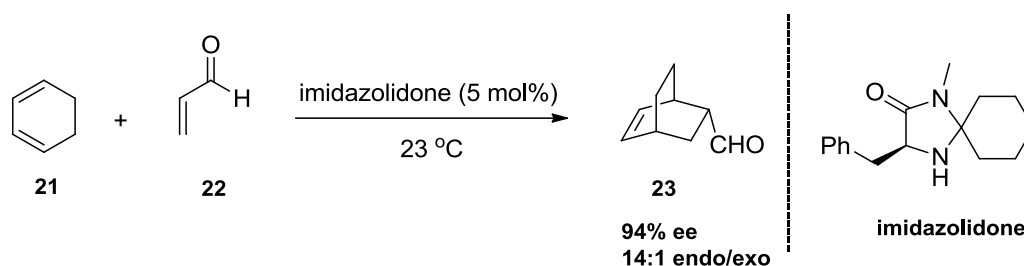
**Scheme 9.** Asymmetric epoxidation of olefins catalyzed by Shi's catalyst

In 1998, Jacobsen studied on Strecker reaction by using chiral Schiff bases as effective catalysts. Moreover, the systems of these reactions could be prepared by using inexpensive materials and in consequence of reactions, enantioselectivity results are highly proper both in solid state and solution.<sup>24</sup> After this experiment, Corey obtained the cyanation product **20** by applying the same reaction which is the addition of hydrogen cyanide to imine **19** catalyzed by bicyclic guanidine (Scheme 10).<sup>25</sup>



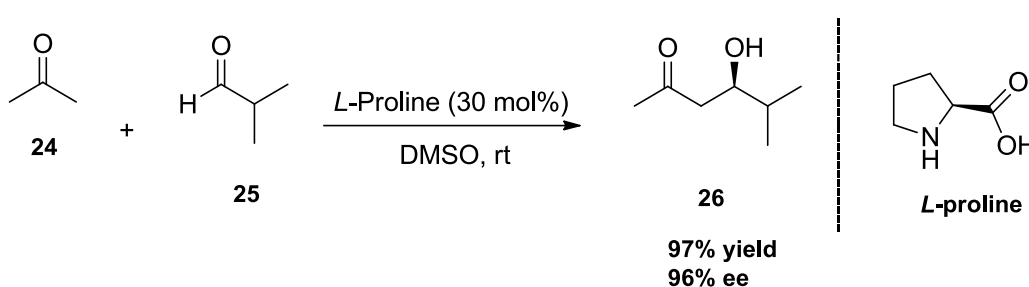
**Scheme 10.** Strecker reaction

In 2010, MacMillan performed the first excessively enantioselective Diels-Alder reaction, which was initiated from cyclohexa-1,3-diene (**21**) and acrolein (**22**) catalyzed by imidazolidone as an organocatalyst. The reaction formed the bicyclic product **23** with 94% ee and 14 to 1 *endo/exo* isomeric ratio (Scheme 11).<sup>26</sup>



**Scheme 11.** Diels-Alder reaction catalyzed by imidazolidone

In the same year, List and Barbas achieved the reaction of acetone (**24**) and isobutyraldehyde (**25**) which is the direct aldol reaction in the presence of L-Proline as a catalyst. At the end of the reaction, aldol product **26** was produced with the perfect enantioselectives and chemical yield (Scheme 12).<sup>27</sup>



**Scheme 12.** Aldol reaction catalyzed by L-Proline

The other important developments in the organocatalysis area are indicated that some of them are chronologically below:<sup>28</sup>

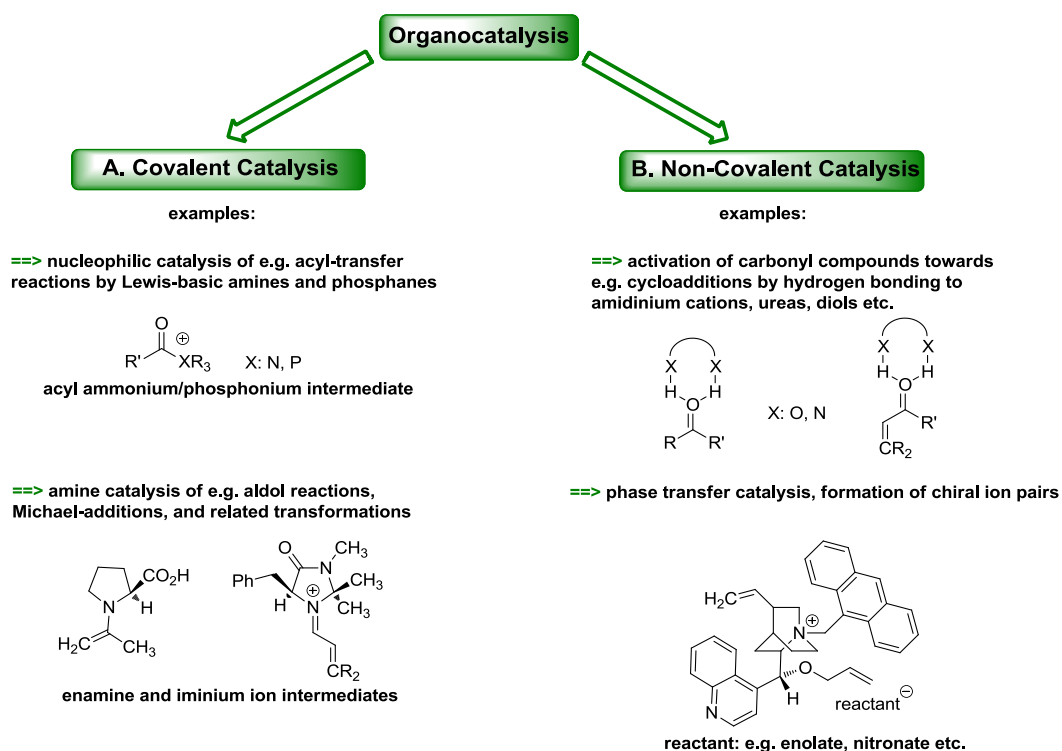
- 2001: MacMillan, development of Friedel-Crafts reaction
- 2003: Takemoto, development of bifunctional base-thiourea catalysts
- 2004: Akyama and Terada, development of new phosphoric acid derivatives as chiral Brønsted acids
- 2005: MacMillan, the first organocascade reaction
- 2005: List and MacMillan, independent development of reduction of enals
- 2005: Rueping, List and MacMillan, almost simultaneous development of enantioselective reductive amination

- 2005: Jorgensen, epoxidation of enals
- 2005: Hayashi, development of the first aldehyde addition of nitroalkenes
- 2006: Enders, development of the multicomponent organocatalytic cascade
- 2006: List, development of asymmetric counteranion-directed catalysis
- 2006: MacMillan, development of the first amine conjugate addition to enals
- 2007: Cordova, development of the first organocatalytic aziridination of enals
- 2007: MacMillan, development of SOMO catalysis
- 2009: MacMillan, development of photoredox catalysis

### **1.2.2 Classification**

Organocatalysis is highly attractive to organic chemists around the world due to being a rapidly growing area. Also, organocatalysis can be categorized with different points of view because there is no significant categorization.

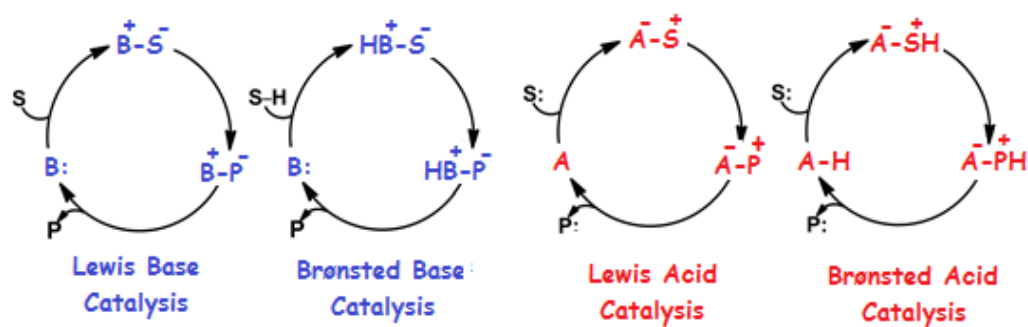
Berkessel<sup>29</sup> classified the organocatalysis in respect of the interactivity with substrate or 'mode of action' as covalent or non-covalent catalysts. The examples of Berkessel about the classification of organocatalysis are shown as Figure 3.<sup>29</sup>



**Figure 3.** General classification of organocatalysis according to Berkessel

In covalent catalysis, a covalent bond is formed between organocatalyst and substrate due to catalytic cycle. Also, the interaction between the substrate and the compound (e.g., aminocatalysts and carbenes) is increased during reaction. Conversely, in case of non-covalent interactions between the substrate and the catalyst, the activation of substrate takes place by hydrogen bonds (e.g., thioureas, squaramides and phosphoric acids) or ionic interactions (e.g., chiral bases like cinchona alkaloids and phase-transfer catalysts).<sup>13</sup>

On the other hand, List categorized the organocatalysts as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids.<sup>8</sup> Examples of catalytic cycles shown below (Figure 4):

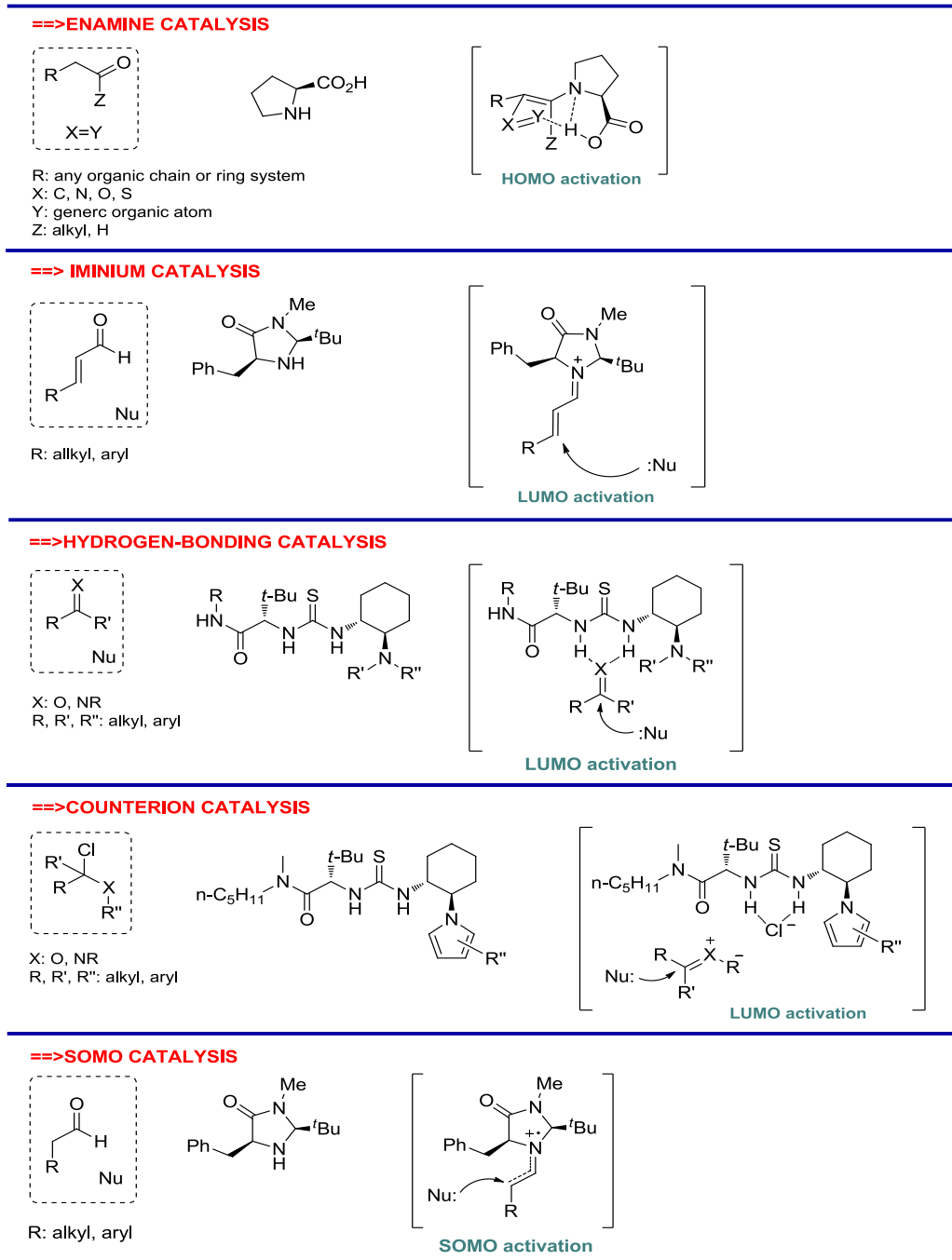


**Figure 4.** General classification of organocatalysis according to List

According to definition of List, catalytic cycle is started with Lewis base catalysts (B:) through nucleophilic addition to substrate (S). The obtained complex is exposed to another reaction by releasing the product (P) and the catalyst for further turnover. Nucleophilic substrates (S:) are activated by the Lewis acid catalysts (A) in a similar way. Brønsted base and acid catalytic cycles starts with a (partial) deprotonation or protonation, respectively.<sup>8</sup>

Moreover, MacMillan classified the organocatalysis with regard to generic activation modes which hold the vital information for improvement of organocatalysts. According to this classification, almost 130 organocatalytic reactions took place during 1998 and 2008. However, they were based on only a limited number of activation modes which are the modes of catalysis: enamine catalysis, iminium catalysis, hydrogen bonding catalysis, counterion catalysis and SOMO catalysis.<sup>30</sup> These modes are classified below (Figure 5):

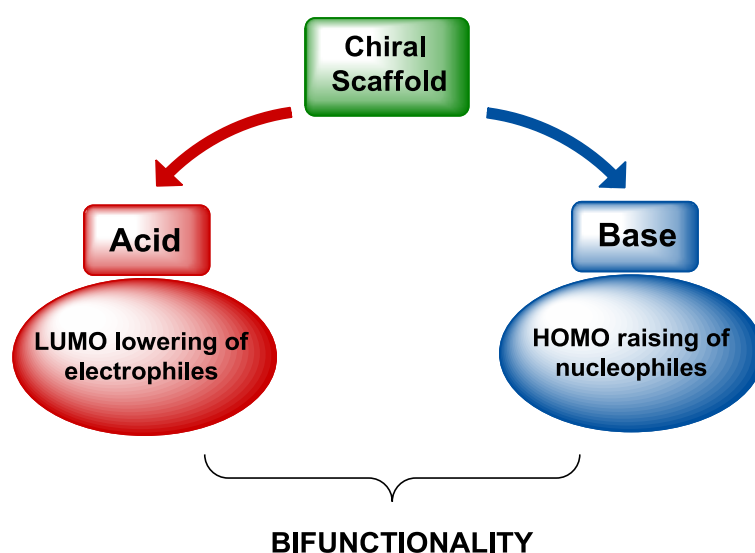




**Figure 5.** General classification of commonly used organocatalysis according to MacMillan

### 1.2.3 Bifunctional Organocatalysis

Bifunctional organocatalysis can be defined as a kind of catalytic process in which an acid-base catalysis has worked cooperatively to activate electrophiles and nucleophiles simultaneously, in a diversity of asymmetric organocatalysis. A bifunctional organocatalyst contains acidic and basic units. While the basic unit raises the highest occupied molecular orbital (HOMO) of nucleophiles, the acidic unit lowers the lowest unoccupied molecular orbital (LUMO) of the electrophile at the same time. In this way, the gap between HOMO and LUMO levels is decreased in order that the reaction can be possible (Figure 6).<sup>31</sup>

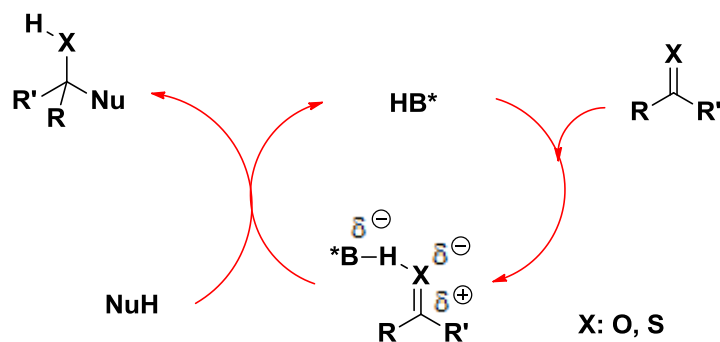


**Figure 6.** Bifunctionality of organocatalysis

#### 1.2.3.1. Thiourea/Urea as Bifunctional Organocatalysis

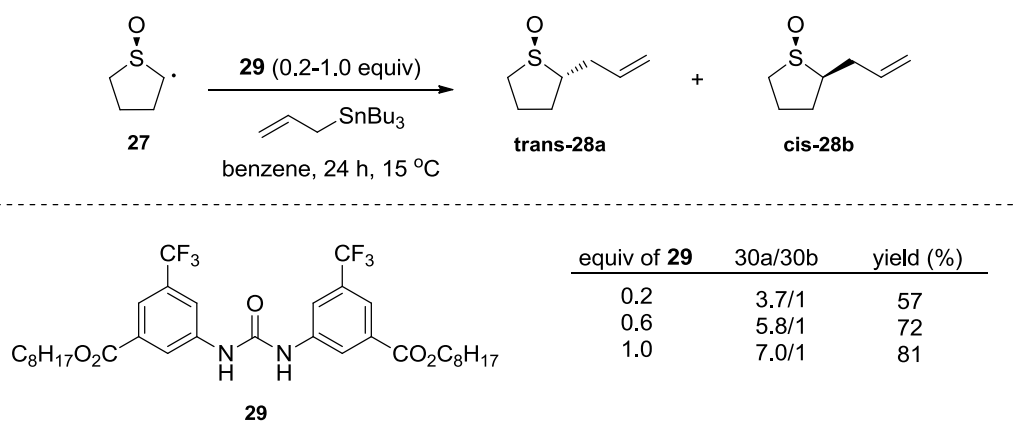
(Thio)urea derivatives used to detect the carboxylic acid, sulfonic acid, nitrate, etc., *via* multiple hydrogen bonds, have been widely studied in the field of molecular recognition due to their high hydrogen bonding activity.<sup>32</sup> During

hydrogen bonding catalysis (hydrogen catalyst bond), in general, the catalyst (donor) and the electrophile substrate (acceptor) interaction reveals reduced electron density for the acceptor that leads easier the nucleophilic attack (Figure 7).<sup>33</sup>



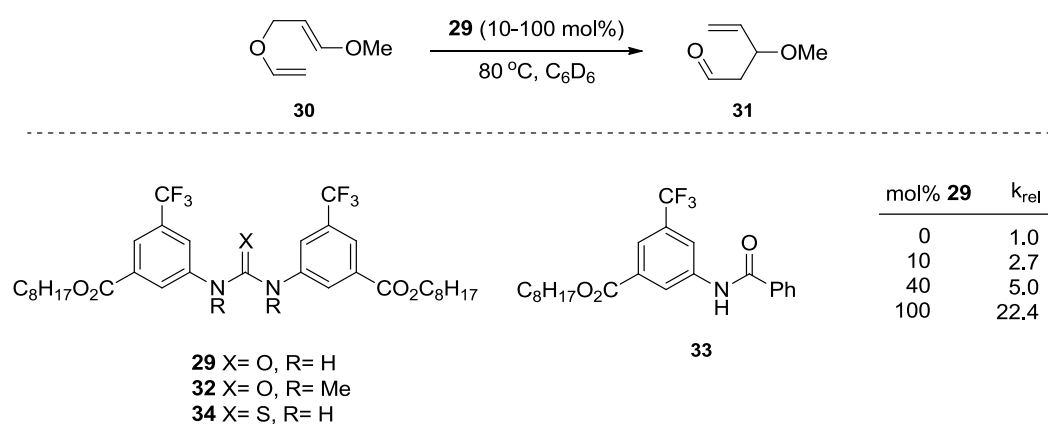
**Figure 7.** General mechanism for the asymmetric hydrogen bonding catalysis

(Thio)urea derivatives are generally used in important reactions like Henry or aza-Henry, Mannich, Strecker, and Friedel–Crafts reactions or Michael and nitro-Michael additions.<sup>34</sup> In 1994, the first example from Curran who reported that addition of a urea derivative improved diastereoselectivity of allylation of cyclic  $\alpha$ -sulfinyl radicals **27** with allyltributylstannane (Scheme 13).<sup>35a</sup>



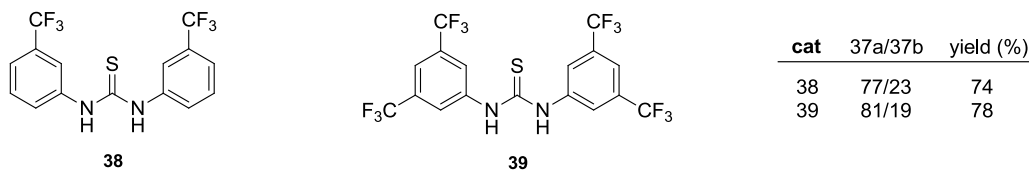
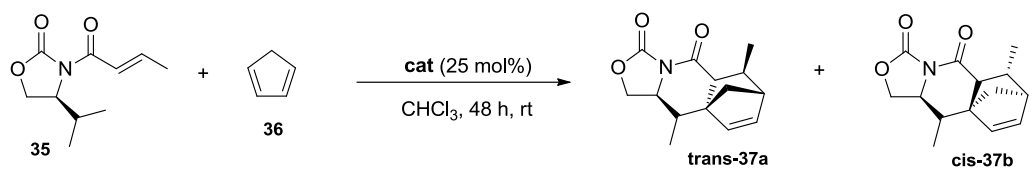
**Scheme 13.** Allylation reaction catalyzed by diarylurea

After the diarylurea catalyzed allylation reaction in 1994, Curran performed the Claisen rearrangement of **30** catalyzed by catalyst **29** with various catalytic quantities (10-100 mol%) (Scheme 14) in 1995. Useful rate acceleration was possible with medium to high catalyst loading. The failure of either dialkylurea **32** or benzanilide **33** in order to have an effective reaction suggested the using both urea protons during catalysis. Furthermore, thiourea derivatives (e.g.; **34**) were found to be promising as hydrogen-bonding catalysts.<sup>35b</sup>



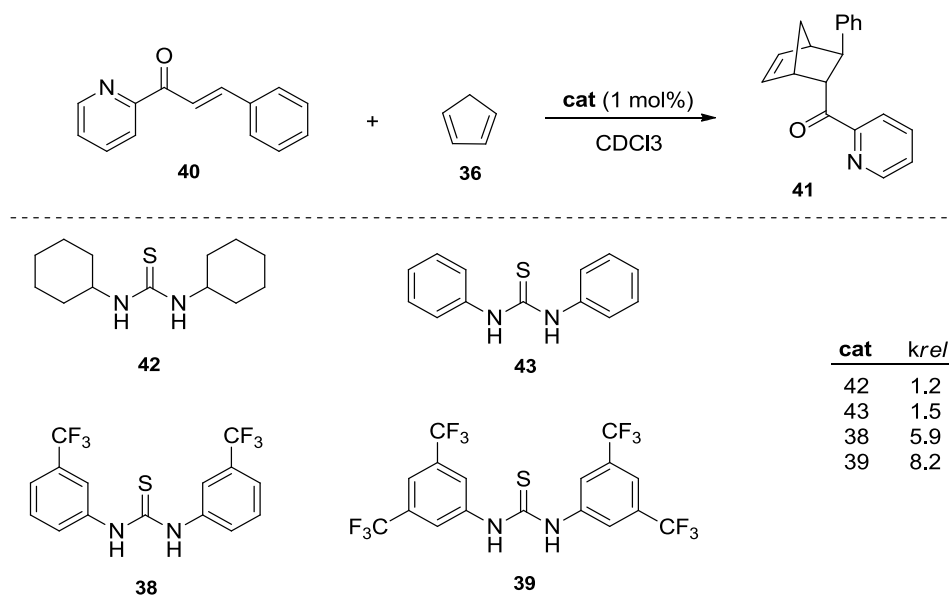
**Scheme 14.** Diaryl(thio)urea catalysis of the Claisen rearrangement

In 2002, Schreiner studied on the reactivity and selectivity of Diels-Alder product formed from enone derivative **35** with cyclopentadiene (**36**) catalyzed by (thio)urea derivatives (Scheme 15). Schreiner showed how catalyst activity's compatibility can be assured by altering N-aryl substituent and introduced that the uniform N-trifluoromethylphenyl substituent increases the solubility and N-H acidity of these materials.<sup>36a</sup>



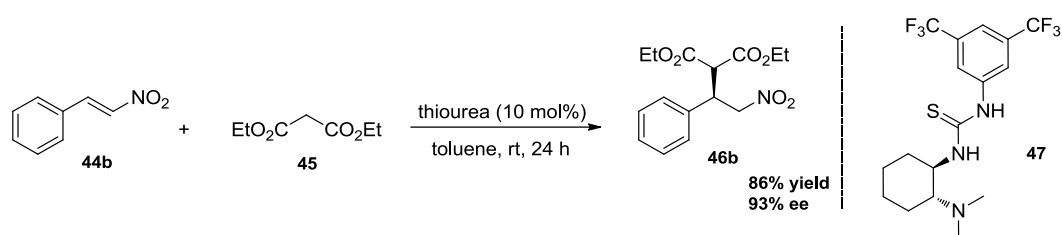
### Scheme 15. Schreiner's thiourea catalyzed Diels Alder reaction 1

Moreover, Schreiner obtained the Diels-Alder product **41** from the reaction of dienophile **40** and cyclopentadiene (**36**) by using various thiourea catalysts **38**, **39**, **42** and **43**. When 1 mol% catalyst **39** was added to the reaction, the reaction rate increased by the factor of  $\sim 6$  (catalyst **41**,  $k_{rel} = 8.2$ ). It was seen that increasing of the acidity of thiourea resulted increasing of the reaction rate accelerations (Scheme 16).<sup>36b</sup>



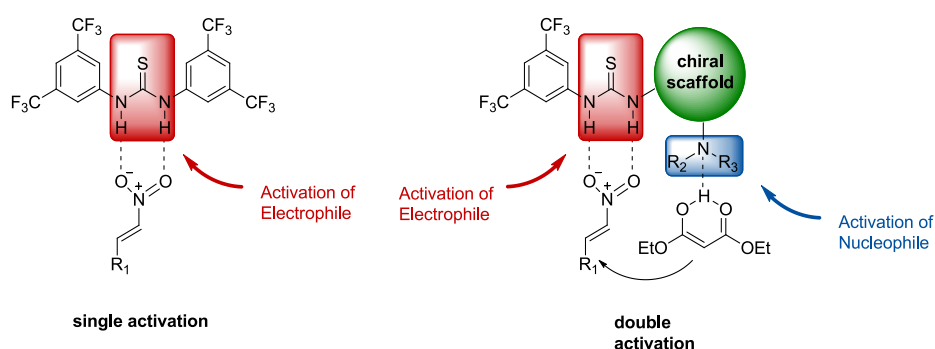
### Scheme 16. Schreiner's thiourea catalyzed Diels Alder reaction 2

The first stereoselective bifunctional organocatalyst was developed by Takemoto in 2003 who inspired from Schreiner's (thio)urea organocatalyst design. Takemoto performed the enantioselective Michael addition of diethyl malonate (**45**) to *trans*-( $\beta$ )-nitrostyrene (**44b**) catalyzed by his (thio)urea bifunctional organocatalyst with high yield and enantiomeric excess value. The Michael product **46b** was known as the first enantioselective acid/base bifunctional organocatalysis product (Scheme 17).<sup>37</sup>



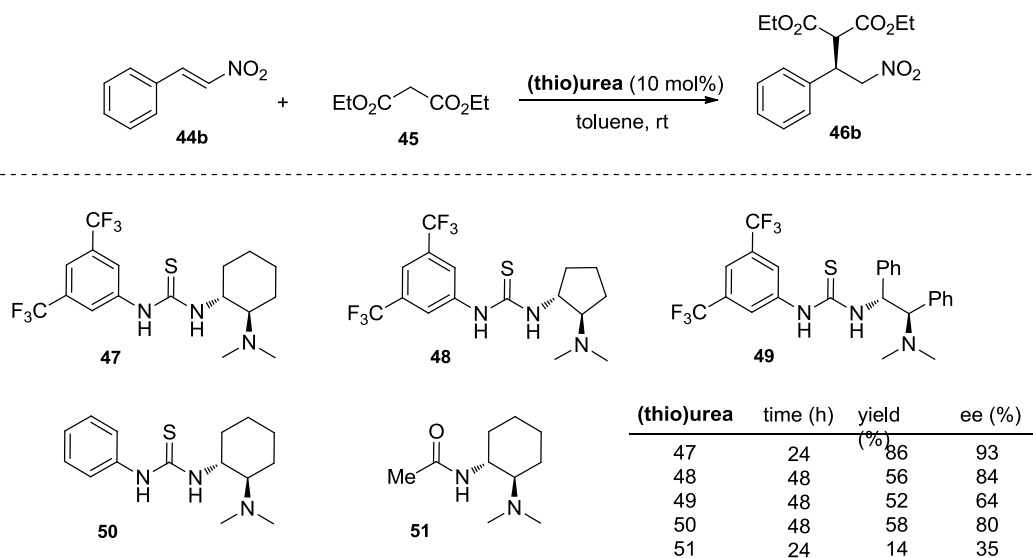
**Scheme 17.** Takemoto's thiourea catalyzed asymmetric Michael addition reaction

The stereoselective bifunctional acid - base thiourea organocatalyst of Takemoto includes chiral (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine as a chiral scaffold, thiourea moiety as Bronsted acidic part and tertiary amine as Lewis basic unit. While acidic part lowers the LUMO level of electrophiles, basic part raises the HOMO level of nucleophiles at the same time. The proposed transition state model was shown in Figure 8.<sup>32</sup>



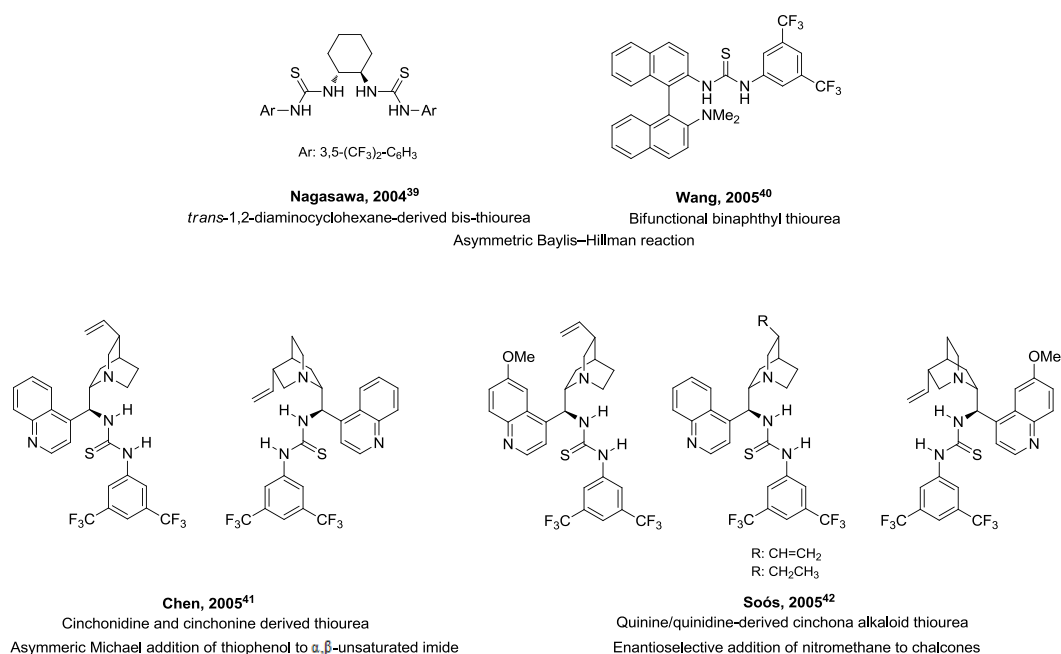
**Figure 8.** Possible transition state of thiourea based organocatalyst by Takemoto

In 2008, Takemoto designed various bifunctional (thio)urea derivatives **47-51** and applied them on the Michael addition of diethylmalonate (**45**) to *trans*-( $\beta$ )-nitrostyrene (**44b**) (Scheme 18).<sup>38</sup>



**Scheme 18.** Takemoto's bifunctional tert-amine/thiourea catalyzed asymmetric Michael addition reaction

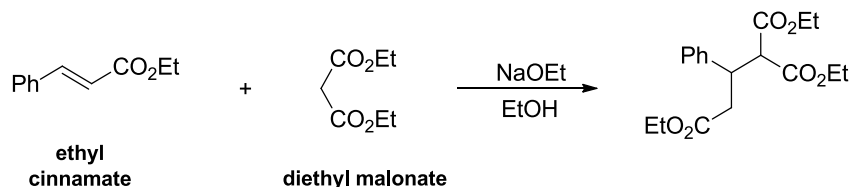
Moreover, Jacobsen designed his (thio)urea derivatives and applied them on the Strecker reaction, Mannich reaction, hydrophosphonylation of imines, and Pictet-Spengler reaction with high enantiomeric excess value between the years of 1998-2004.<sup>32</sup> Moreover, some important reactions catalyzed by (thio)urea organocatalysts are shown in Figure 9.<sup>39-42</sup>



**Figure 9.** Examples of bifunctional thioureas

### 1.3 Enantioselective Michael Addition Reaction

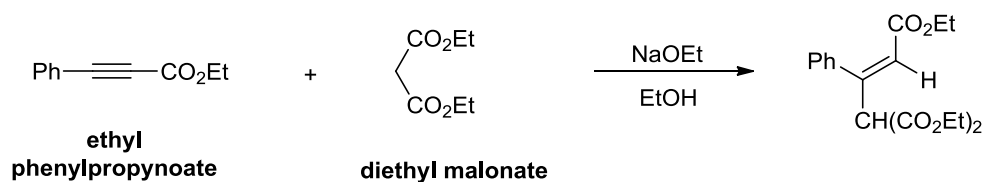
The first example about this topic was published by T. Komnenos in 1883 which was the addition of a carbon nucleophile to an electron deficient double bond, whose study was the addition of the anion of diethyl malonate to ethylidene malonate. In 1887, Arthur Michael performed the addition of diethyl malonate to double bond of ethyl cinnamate by using sodium ethoxide (Scheme 19).<sup>43</sup>



**Scheme 19.** The addition of the anion of diethyl malonate to ethylidene malonate



In 1894, Arthur Michael reported that both electron deficient double bonds and triple bonds are useful to form new carbon-carbon bonds (Scheme 20).<sup>43</sup>



**Scheme 20.** The addition of the anion of diethyl malonate to ethylidene malonate

Today, with the method of Arthur Michael, the stabilized carbon nucleophile addition (Michael donor) to the activated  $\pi$ -systems (Michael acceptor) is defined as Michael addition (or Michael reaction). Besides, Michael addition can be referred to define as the conjugate addition (1,4-addition) of any nucleophile to activated  $\pi$ -systems.<sup>43</sup>

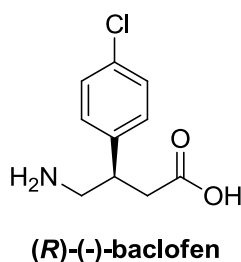
### 1.3.1 Enantioselective Michael Addition of Malonates to Nitroolefins

The major need of the both chemical industry and the synthetic chemistry is a simple synthesis of enantiopure compounds and environmentally friendly treatment. Organocatalysis has been one of the most useful and important choice for the efficient asymmetric reactions. In this field, it is understood that one of the important Michael additions in organic chemistry is the asymmetric Michael addition of carbon-centred nucleophiles to electron deficient nitroolefins because of their multiple reactivity and created the versatile synthetic building blocks.<sup>37</sup>

Nitroolefins have great importance in order to synthesize many natural products with biologically active features.<sup>44</sup> The reactive nitro functional group of the nitroolefins can be converted to a variety of functional groups<sup>45</sup> which include silyl nitronates, nitrile oxides, and hydroximoyl chlorides.<sup>44</sup> Nitroolefins have been one of the most preferable molecules as Michael acceptors due to their nitro

group with a strong e-withdrawing property for many nucleophiles as Michael donors like anilines, indoles, thiols, phenols, malonates, diketones and  $\beta$ -keto esters.<sup>44</sup>

Many scientists have been reported various enantioselective Michael addition of diethyl malonate to nitroolefins by employing stoichiometric amounts of enantiopure additives. The first important example belongs to Takemoto who reported asymmetric Michael addition of malonates to nitroolefins catalyzed by bifunctional catalysts with a thiourea moiety and an amino group on a chiral scaffold in 2003 (Scheme 17).<sup>37</sup> Moreover, the enantioselective Michael product of this reaction was applied to the total synthesis of (*R*)-(-)-baclofen which is an antispastic agent.<sup>32</sup>

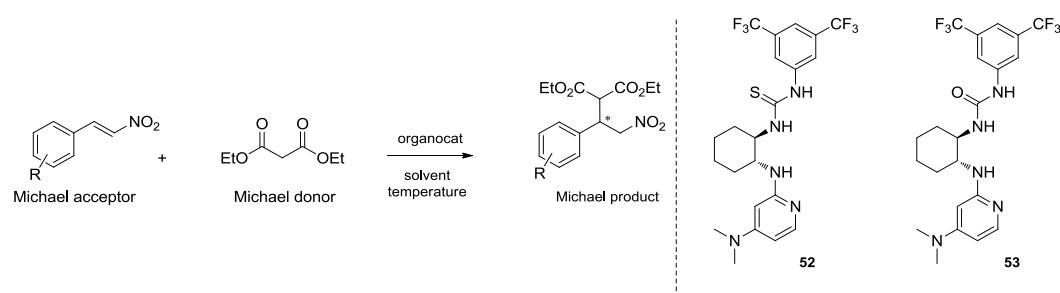


**Figure 10.** The structure of (*R*)-(-)-baclofen

## 1.4 Aim of the Work

Organocatalyst has become an important field of asymmetric synthesis in recent years. At the last few years, the cause of so much increased interest in this area is not just a matter of authenticity, even more importantly, organocatalytic reactions are the method which is compatible with the environment. The enantioselective organocatalytic Michael addition reaction has recently gained increased attention as an asymmetric synthesis strategy. Therefore, using the bifunctional organocatalyst concept, many bifunctional organocatalysts have been synthesized in Tanyeli's research group and applied in different type of asymmetric synthesis.

In this study, the main aim is to perform Michael addition of diethyl malonate to nitroolefins in the presence of 2-aminoDMAP/thiourea **52** and 2-aminoDMAP/urea **53** bifunctional organocatalysts (Scheme 21).



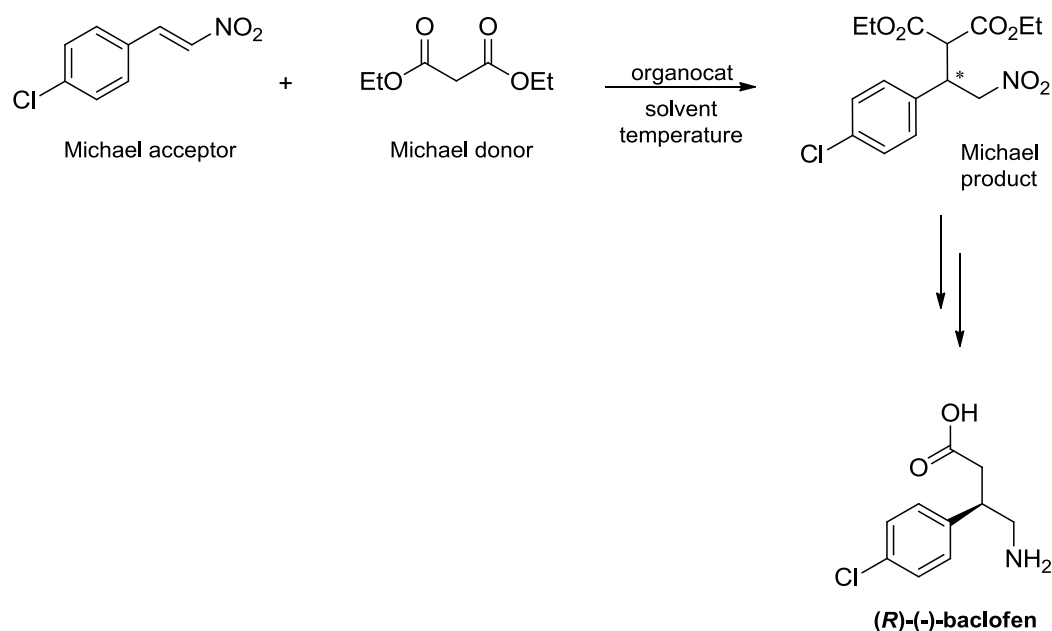
**Scheme 21.** Representative aim of the study

The bifunctional organocatalysts have been synthesized in Tanyeli research group and searched their activity in asymmetric Michael addition reaction in order to obtain Michael product with lower catalyst loading, shorter conversion time, higher reaction yield and higher enantioselectivity.

To achieve the best results in Michael addition reaction, optimum reaction conditions will be found by screening some parameters such as the catalyst

loading, concentration, solvent and temperature. The activity of the bifunctional 2-aminoDMAP/(thio)urea organocatalysts in asymmetric Michael addition of malonates to nitroolefins will be tested to find the optimum conditions.

Consequently, high enantioselectivities and yields are aimed for the formal synthesis of GABA analogue known as (*R*)-(-)-baclofen by performing Michael addition reaction in the presence of developed organocatalyst by using  $\beta$ -nitroalkene (*trans*-4-chloro- $\beta$ -nitrostyrene) (Scheme 22).



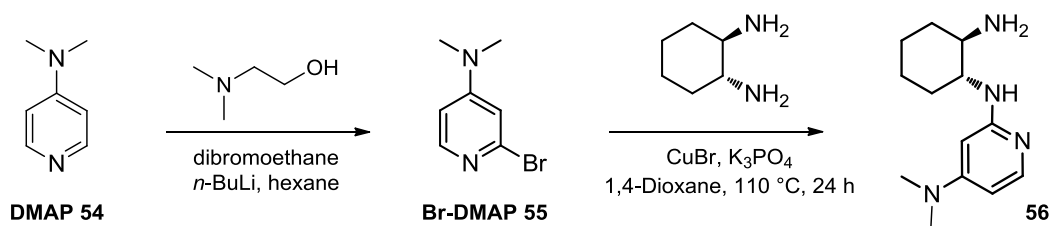
**Scheme 22.** Synthesis pathway of Baclofen

## CHAPTER 2

### RESULTS AND DISCUSSION

#### 2.1 Synthesis of 2-aminoDMAP

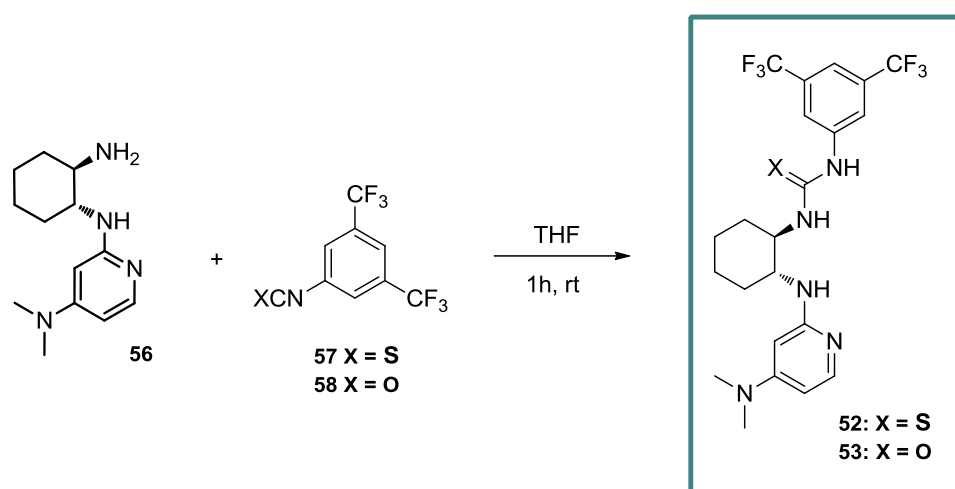
A wide array of acid-base type bifunctional organocatalysts have been synthesized in Tanyeli research group and applied in different type of asymmetric synthesis. The basic catalaphoric side has been derived from (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine via copper catalyzed modified Ullmann coupling method. For this purpose, first 2-bromo-*N,N*-dimethylpyridin-4-amine (2-bromoDMAP) was synthesized from 4-dimethylaminopyridine (DMAP) by using a chelating ligand, *N,N*-dimethyl ethanolamine, a base, *n*-BuLi and an electrophile, dibromoethane.<sup>46</sup> Subsequently, 2-bromoDMAP was reacted with *C*<sub>2</sub>-symmetrical (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine in the presence of 20 mol% CuBr, 200 mol% K<sub>3</sub>PO<sub>4</sub> used as base in 1,4-dioxane at 110 °C for 24 h to afford *C*<sub>1</sub>-symmetrical 2-aminoDMAP in 60% chemical yield (Scheme 23).<sup>47</sup>



**Scheme 23.** Synthesis of 2-aminoDMAP

## 2.2 Synthesis of 2-aminoDMAP Based Bifunctional Organocatalysts

The remaining primary amine of 2-aminoDMAP was anchored with 3,5-(bistrifluoromethyl)phenyl thioisocyanate (**57**) and 3,5-(bistrifluoromethyl)phenyl isocyanate (**58**) to yield corresponding thiourea and urea type acidic motifs, respectively, with high yield (90%) in THF for 1 h (Scheme 24).<sup>37</sup>



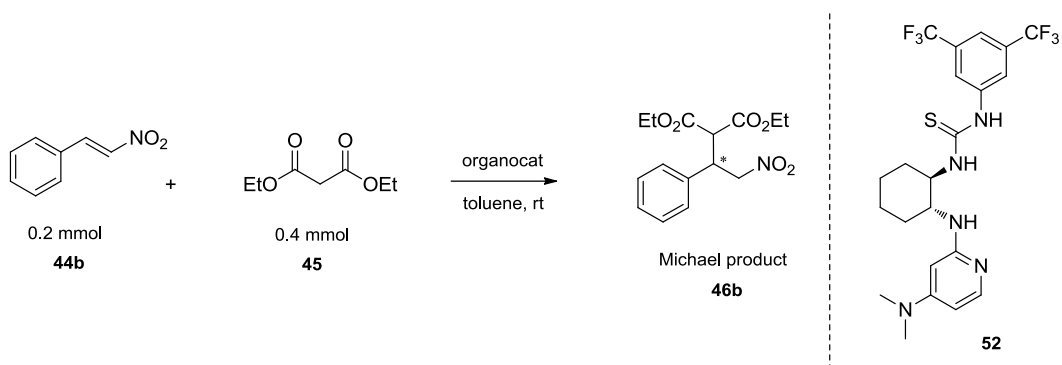
**Scheme 24.** Synthesis of 2-aminoDMAP based urea and thiourea organocatalysts

## 2.3 Evaluation of Bifunctional Organocatalysts in Enantioselective Michael Addition of Diethyl Malonates to *trans*- $\beta$ -Nitrostyrene

The activity of 2-aminoDMAP based thiourea **52** and urea **53** bifunctional organocatalysts was evaluated in asymmetric Michael addition of diethyl malonate (**45**) to *trans*- $\beta$ -nitrostyrene (**44b**). Firstly, the activity of the bifunctional 2-aminoDMAP/thiourea organocatalyst was tested on the Michael addition reaction by screening the catalyst loading. During the process, 1, 2, 5 and 10 mol% catalyst loadings were tested (Table 1). The reaction catalyzed by 10 mol% 2-aminoDMAP/thiourea **52** completed in 12 h with 80% yield and 75% ee (entry

1). When the catalyst loading decreased, lower yield and ee in 5 and 2 mol% catalyst loading were obtained (entries 2 and 3). Further decreasing the catalyst amount (1 mol%) resulted in sharp decrease in chemical yield after 24 h.

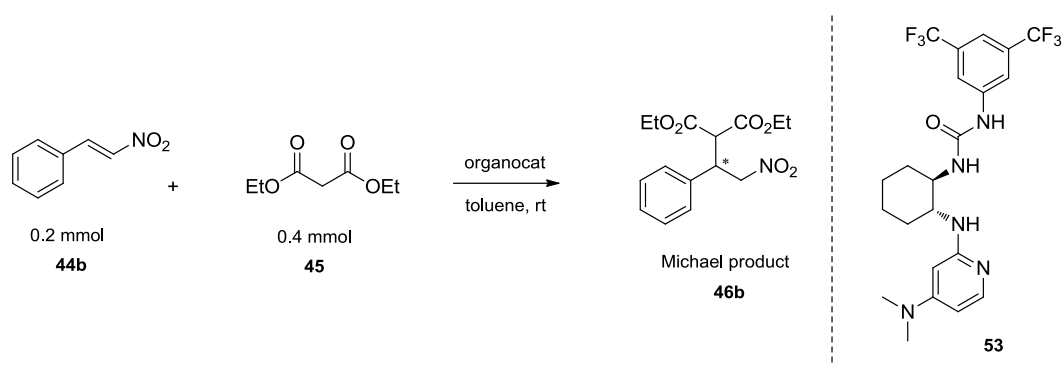
**Table 1.** Catalyst loading screening results of 2-aminoDMAP/thiourea **52**



Entry	Catalyst Loading	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>	<b>10 mol%</b>	<b>12</b>	<b>80</b>	<b>75</b>
<b>2</b>	5 mol%	15	78	<b>69</b>
<b>3</b>	2 mol%	24	65	<b>69</b>
<b>4</b>	1 mol%	24	52	<b>71</b>

*a*: isolated yield *b*: Determined by HPLC

Relatively unsatisfactory results with 2-aminoDMAP/thiourea **52** turned our direction to 2-aminoDMAP/urea **53** organocatalyst. Screening studies started first with catalyst loading parameter as shown in Table 2. To our delight, in the first trial with 10 mol% catalyst we got 91% ee and 89% chemical yield in 3 h (Table 2, entry 1). Further screening with 5 mol% afforded 94% ee in 4 h with 91% yield (entry 2). By decreasing catalyst amount to 2 and 1 mol%, we observed relatively longer reaction durations and low chemical yields, respectively (entry 3 and 4).

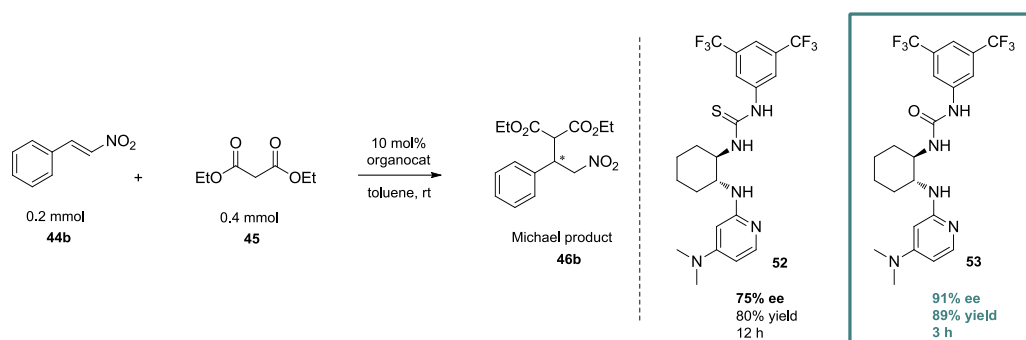
**Table 2.** Catalyst loading screening results of 2-aminoDMAP/urea **53**

Entry	Catalyst Loading	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>	10 mol%	3	89	<b>91</b>
<b>2</b>	<b>5 mol%</b>	<b>4</b>	<b>91</b>	<b>94</b>
<b>3</b>	2 mol%	6	80	<b>91</b>
<b>4</b>	1 mol%	7	75	<b>93</b>

*a*: isolated yield *b*: Determined by HPLC

When the results obtained from bifunctional 2-aminoDMAP/thiourea organocatalyst was compared with 2-aminoDMAP/urea **53** organocatalyst, it was obviously seen that urea containing one gave better results. For example, while 10 mol% thiourea catalyst **52** loading was isolated with 80% yield, 75% ee for 12 h, the same amount urea catalyst **53** loading gave 89% yield and 91% ee in 3 h (Scheme 25). According to these results, we decided to use 2-aminoDMAP/urea with 5 mol% for further screening reactions.

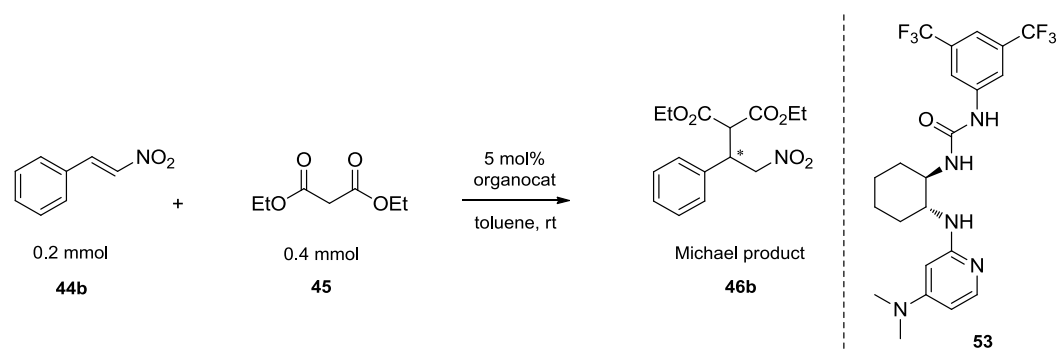




**Scheme 25.** Michael addition of diethyl malonate to *trans*- $\beta$ -nitrostyrene

As a next parameter, we tested the effect of concentration on the efficiency of organocatalyst. The results are summarized in Table 3. With 0.1 M concentration, the reaction completed in 4.5 h with 89% yield and 93% ee (entry 1). In 0.2 M concentration, slight increasing observed in terms of both chemical yield and enantioselectivity (entry 2). Further increase in concentration to 0.3 M, relatively lower values obtained in terms of both chemical yield and enantioselectivity (entry 3). According to these results, 0.2 M concentration was found as the best.

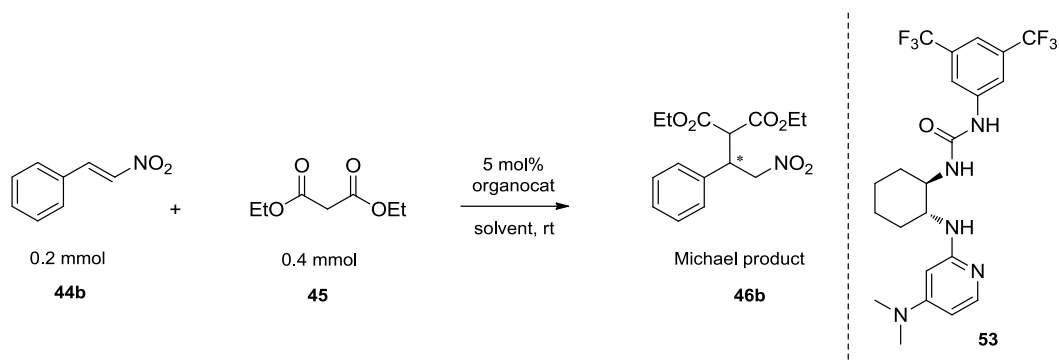
**Table 3.** Reaction concentration screening results



Entry	Solvent	Concentration	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	2 mL	0.1 M	4.5	89	93
2	1 mL	0.2 M	4.0	91	94
3	0.66 mL	0.3 M	3.5	88	90

<sup>a</sup>: isolated yield <sup>b</sup>: Determined by HPLC

Afterward, the effects of solvents were investigated in terms of conversion time, reaction yield and enantioselectivity by trying 10 different solvents except toluene. The reactions with almost all solvents convert to Michael adduct at short notice with quite high yield and high enantiomeric excess value (Table 3). Although the reaction in THF completed more than 24 hours with 55% yield, it gave a moderate enantiomeric excess value as 72%. The reaction in ethanol afforded 78% yield for 6 h but lower enantioselectivity was obtained as 10% ee. This result would be attributed to the interaction of solvent with organocatalyst via hydrogen bond. The experiments with pentane and hexane resulted in Michael product **46b** in shortest reaction duration as 1 h with good yields but not good ee values (Table 4). The most interesting result belongs to heptane with a shorter reaction duration as 1.5 h, 88% reaction yield in 85% ee. Also, toluene gave an excellent enantioselectivity which was 94% in a short time as 4 h with a high chemical yield as 91%. Therefore, we tried to mix toluene and heptane to obtain high enantiomeric excess value with shortest reaction duration. Firstly, we mixed toluene and heptane with 1:1 ratio. The reaction completed in 2 h with 91% ee which is not better than the result obtained in toluene. For this reason, when 2:1 mixture of toluene and heptane was used, enantiomeric excess value was the same as toluene (94% ee) with a shorter reaction duration (3 h). However, chemical yield obtained in toluene was higher than 2:1 mixture of toluene and heptane. It seems that between different solvents, the reaction with toluene gave the best result (Table 4).

**Table 4.** Solvent screening results

Entry	Solvent	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>	<b>toluene</b>	<b>4</b>	<b>91</b>	<b>94</b>
<b>2</b>	xylene	3.5	87	<b>91</b>
<b>3</b>	cyclohexane	3	82	<b>91</b>
<b>4</b>	benzene	4	80	<b>88</b>
<b>5</b>	<b>heptane</b>	<b>1.5</b>	<b>88</b>	<b>85</b>
<b>6</b>	DCM	5.5	85	<b>84</b>
<b>7</b>	CHCl <sub>3</sub>	6	82	<b>81</b>
<b>8</b>	pentane	1	87	<b>76</b>
<b>9</b>	THF	>24	55	<b>72</b>
<b>10</b>	hexane	1	85	<b>65</b>
<b>11</b>	ethanol	6	78	<b>10</b>
<b>12</b>	<b>toluene:heptane (1:1)</b>	<b>2</b>	<b>75</b>	<b>91</b>
<b>13</b>	<b>toluene:heptane (2:1)</b>	<b>3</b>	<b>80</b>	<b>94</b>

*a*: isolated yield *b*: Determined by HPLC

### 2.3.1 Evaluation of 2-aminoDMAP/urea in Enantioselective Michael Addition of Diethyl Malonate to Various Nitroolefins

The scope of the enantioselective organocatalytic conjugate addition was examined further by varying *trans*- $\beta$ -nitroolefins with the optimized reaction condition. All the reactions were conducted in toluene at room temperature with 0.2 M concentration of **44a-r**. The results are summarized in Table 5. Most of conjugate addition product were obtained in high to excellent yields (65-95%) and selectivities (80-99% ee).

It is noteworthy that the reaction worked very well with *p*-benzyloxy substituted *trans*- $\beta$ -nitrostyrene derivative **46a** with 99% ee (entry 1).

Among the electron donor nitroolefins, methoxy substituted derivatives gave almost similar results. *p*-Methoxy **46c** (entry 3) and *o*-methoxy **46g** (entry 7) gave a little bit higher enantiomeric excess values as 94% and 92%, respectively, than the *m*-methoxy substituted derivative **46n** in 88% ee (entry 14).

The halogen substituted nitroolefins, *p*-floro and *o*-floro substituted derivatives **46d** and **46e** (entries 4 and 5), respectively, resulted in higher enantiomeric excess values as 94% and 93%, respectively, when compared with both chloro (entries 6, 11-13) and bromo (entries 8 and 16) substituted derivatives.

Chloro substituted derivatives gave almost similar results. *o*-Chloro-substituted-derivative **46k** (entry 11) and *p*-chloro-substituted-derivative **46l** (entry 12) afforded the same enantiomeric excess values as 90% ee that was slightly higher than *m*-chloro-substituted-derivative **46m** (entry 13, 88% ee). Also, 2,4-dichloro-substituted-derivative **46f** had 92% enantiomeric excess value (entry 6).

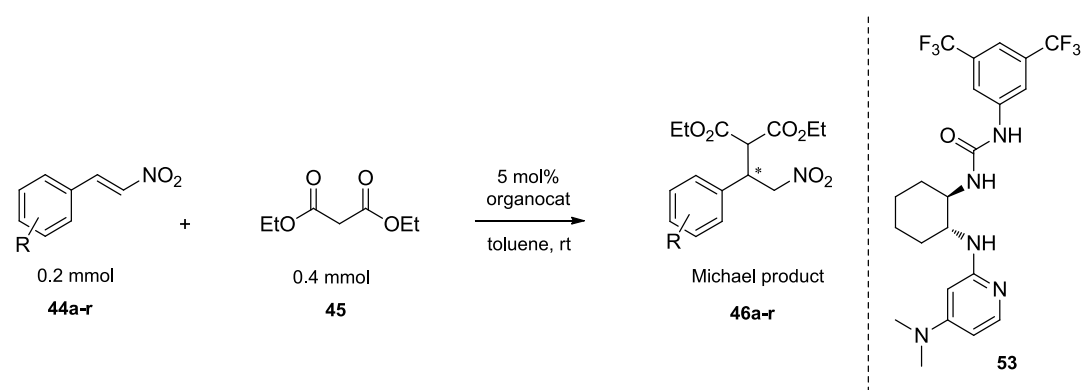
*p*-Bromo substituted derivative **46h** (entry 8) showed higher enantioselectivity as 92% ee than *m*-bromo substituted derivative **46p** (entry 16) in 87% ee.

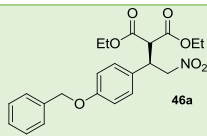
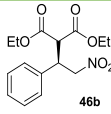
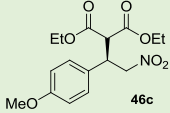
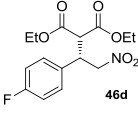
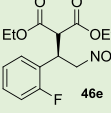
Furyl substituted **46j** (entry 10) and thiophenyl **46o** (entry 15) substituted nitroolefin derivatives resulted in a good enantiomeric excess values as 91% and 88%, respectively.

It appears that the electronic nature of the aromatic rings of nitroolefins has little effect on both reaction kinetics and stereoselection.

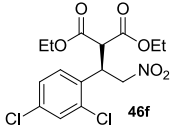
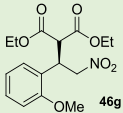
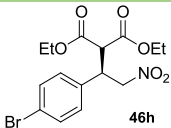
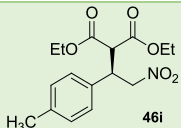
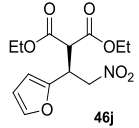
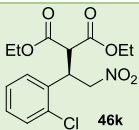
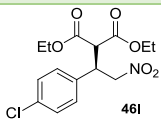
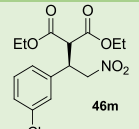
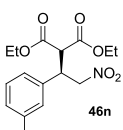
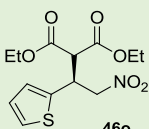
The absolute configurations were determined as (*R*)-*configuration* for all Michael products and (*S*) for the *p*-floro **46d** (entry 4), furyl **46j** (entry 10) and thiophenyl **46o** (entry 15) substituted derivatives according to the specific rotations reported in literature.<sup>32, 48-51</sup>

**Table 5.** Derivatization of nitroolefins with 2-aminoDMAP/Urea

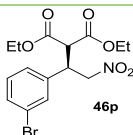
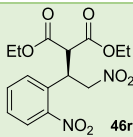


Entry	Compound	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>		10	83	<b>99</b>
<b>2</b>		4	91	<b>94</b>
<b>3</b>		6	88	<b>94</b>
<b>4</b>		3	88	<b>94</b>
<b>5</b>		4	91	<b>93</b>

**Table 5 (continued)**

<b>6</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccc(Cl)c(Cl)c1</chem> <b>46f</b>	<b>3</b>	<b>83</b>	<b>92</b>
<b>7</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1cccc(OC)c1</chem> <b>46g</b>	<b>7</b>	<b>93</b>	<b>92</b>
<b>8</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccc(Br)cc1</chem> <b>46h</b>	<b>4</b>	<b>84</b>	<b>92</b>
<b>9</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccc(C)cc1</chem> <b>46i</b>	<b>9</b>	<b>90</b>	<b>91</b>
<b>10</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccoc1</chem> <b>46j</b>	<b>4</b>	<b>84</b>	<b>91</b>
<b>11</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1cccc(Cl)c1</chem> <b>46k</b>	<b>2</b>	<b>95</b>	<b>90</b>
<b>12</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccc(Cl)cc1</chem> <b>46l</b>	<b>3</b>	<b>81</b>	<b>90</b>
<b>13</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1cccc(Cl)c1</chem> <b>46m</b>	<b>3</b>	<b>82</b>	<b>88</b>
<b>14</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccc(OC)cc1</chem> <b>46n</b>	<b>4</b>	<b>84</b>	<b>88</b>
<b>15</b>	 <chem>CCOC(=O)C(C(=O)OCC)(CCN(=O)=O)c1ccsc1</chem> <b>46o</b>	<b>7</b>	<b>75</b>	<b>88</b>

**Table 5 (continued)**

<b>16</b>	 46p	<b>4</b>	<b>76</b>	<b>87</b>
<b>17</b>	 46r	<b>3</b>	<b>65</b>	<b>80</b>

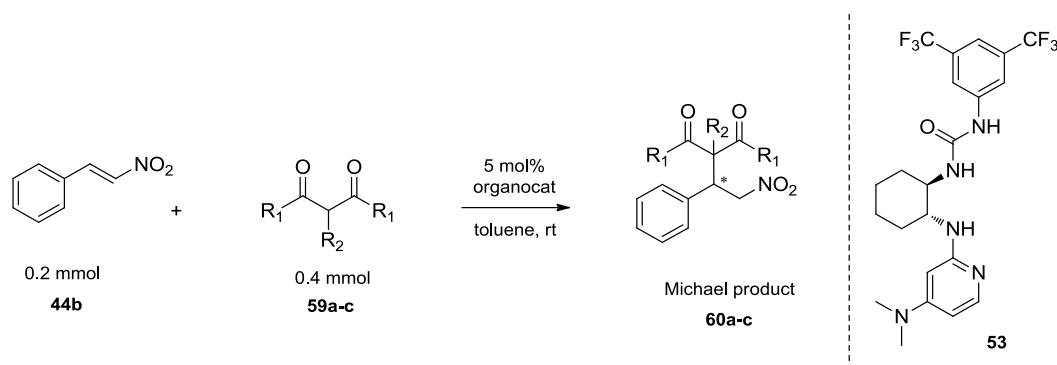
*a*: isolated yield *b*: Determined by HPLC

We tested catalytic activity of 2-aminoDMAP/urea in conjugate addition of several malonates (**59a-c**) to *trans*-( $\beta$ )-nitrostyrene (**44b**). The results are summarized in Table 6.

Dimethyl malonate (**59a**) gave a fast reaction (4h) with 92% ee and 88% chemical yield, whereas 2-acetamido diethyl malonate (**59c**) afforded the lowest enantioselectivity (66% ee) for a long reaction duration as 24 h. Diisopropyl malonate (**59b**) resulted in the Michael adduct with 85% ee and 93% chemical yield in 5 h.

With malonates **59a-b**, we did not observe any noticeable enantioselection over diethyl malonate (**45**).

The absolute configurations were determined as (*R*)-*configuration* for all Michael products according to the specific rotations reported in literature.<sup>48, 49</sup>

**Table 6.** Derivatization of malonates with 2-aminoDMAP/Urea

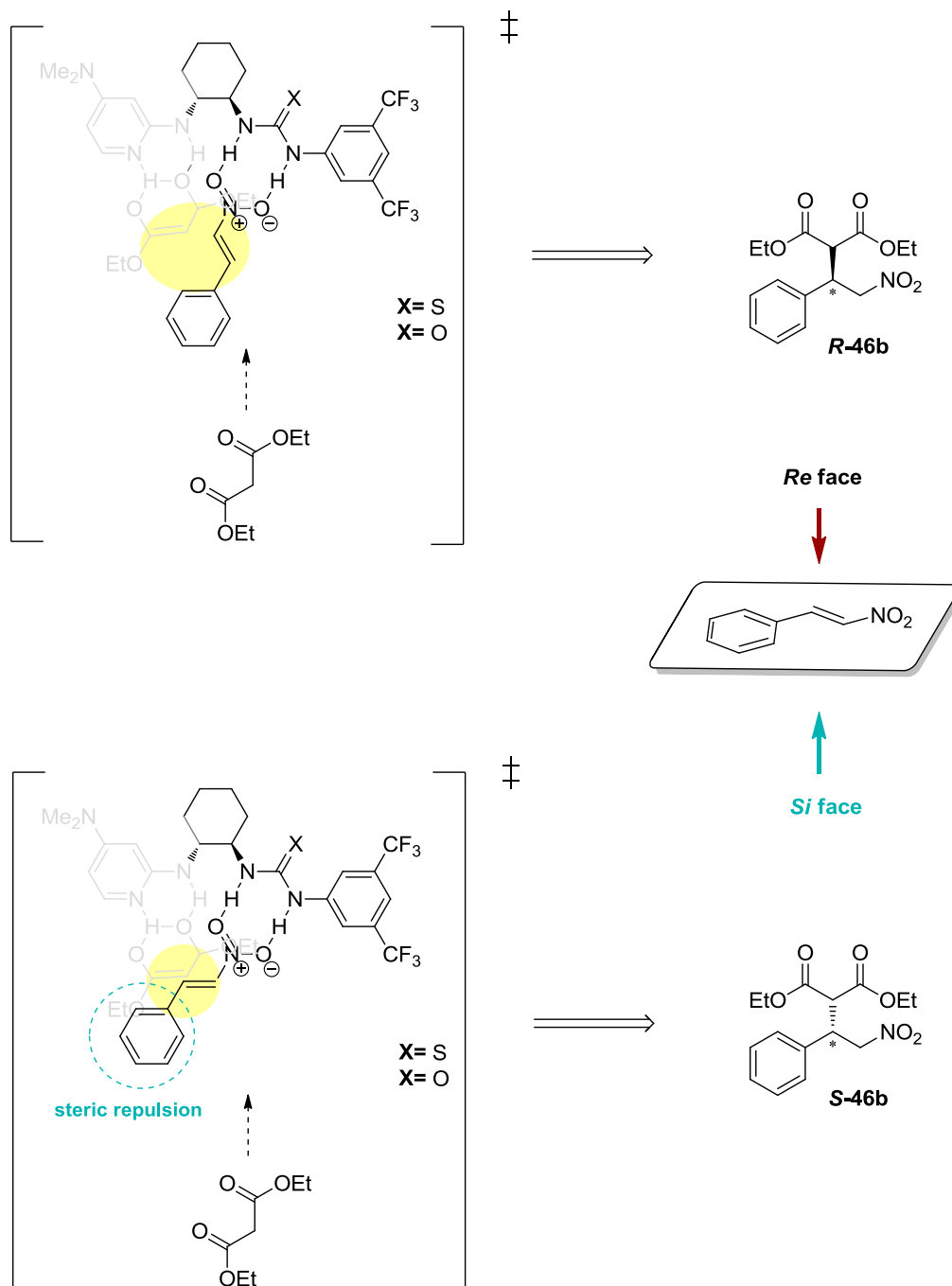
Entry	Compound	Time (h)	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
<b>1</b>	 <b>60a</b>	4	88	<b>92</b>
<b>2</b>	 <b>60b</b>	5	93	<b>85</b>
<b>3</b>	 <b>60c</b>	24	93	<b>66</b>

*a*: isolated yield *b*: Determined by HPLC

In this study, the bifunctional organocatalysts can be able to activate both nitroolefins and nucleophiles simultaneously and can control the approach of nucleophiles to nitroolefins.<sup>37</sup> It can be understood that steric repulsion between benzene ring of *trans*- $\beta$ -nitrostyrene (**44b**) and ethoxy group of diethyl malonate (**45**) causes unpreferable interaction in the second structure of the Figure 11. According to Cahn-Ingold-Prelog nomenclature system, reactive prochiral face of the nitroolefin is the *Si* face with  $sp^2$ -hybridized C center which causes the formation of (*S*)-configured product (*S*)-**46b**.<sup>52</sup> The proposed a favorable transition state model is the first structure of the Figure 11 because the major enantiomer (*R*)-**46b** can be ensured the delivery of the enolate from the *Re* face of



the nitrostyrene. In this transition model, steric repulsion problems are kept away and having the lower energy is expected (Figure 11).<sup>53</sup>



**Figure 11.** Proposed transition state model



## CHAPTER 3

### EXPERIMENTAL

#### 3.1 Materials and Methods

Synthesized chemicals in this study were analyzed by using the following instruments and materials.

Nuclear Magnetic Resonance which contains  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra was recorded on Bruker Spectrospin Avance DPX 400 spectrometer in chloroform-d ( $\text{CDCl}_3$ ). Chemical shifts are expressed in ppm with tetramethylsilane (TMS) as a reference.  $^1\text{H}$  NMR data are ordered as signal value, spin multiplicity and coupling constant. Spin multiplicity data were specified as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet of doublets (td), triplet (t), doublet of triplets (dt), quartet (q), doublet of quartets (dq), heptet (hept), multiplet (m). Also, coupling constants ( $J$ ) were reported in Hertz (Hz).  $^{13}\text{C}$  NMR spectra were measured at 100 MHz.

Enantioselectivity measurements were accomplished with the Daicel Chiralpak AD, AS-H, IA and OJ-H columns on Thermo-Finnigan HPLC instrument by using different isopropyl alcohol and hexane solvent systems at room temperature.

Optical rotation measurements were performed with Rudolph Scientific Autopol III polarimeter instrument by using 1 dm cell and reported as  $[\alpha]_D^T$ .

High Resolution Mass Spectrometry (HRMS) measurements were performed with Agilent 6224 TOF LC/MS instrument at UNAM, Bilkent University.

Infrared radiation (IR) measurements were performed with Bruker Alpha Platinum ATR instrument for the functional groups determination in which the band positions of infrared spectra were reported in  $\text{cm}^{-1}$ .

Melting point measurements were performed with Melt-Temp 1002D instrument.

Thin layer chromatography (TLC) with precoated silica gel plates (Merck Silica Gel 60 F<sub>254</sub>), was used to monitor all reactions (visualized by UV-light).

Flash column chromatography (FC) was performed for the purification process by using thick-walled glass column with silica gel (Merck Silica Gel 60, particle size: 0,063-0.200 mm).

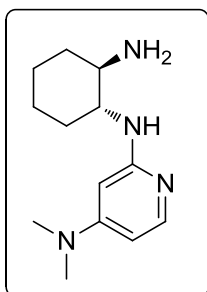
ChemBioDraw Ultra 12.0 program was used in order to analyze the properties of synthesized compounds and to draw schemes on the computer.

NMR spectra was commended with MestReNova 6.0.2 program.

### **3.2 Synthesis of 2-aminoDMAP 56**

In an oven-dried Schlenk tube, CuBr (0.2 mmol, 200 mg) and K<sub>3</sub>PO<sub>4</sub> (2.0 mmol, 2.9 g) were added. After the schlenk tube was evacuated and backfilled with argon thrice, (*R,R*)-cyclohexdiamine (1.2 mmol, 960 mg) and 2-bromoDMAP (1 mmol, 1.4 g) and 1,4-dioxane (7.8 mL) which was dried with Na-benzophenone were added to the schlenk tube under the argon atmosphere. The reaction mixture was stirred at 110 °C for 24 hours with the result of green-blue suspension mixture. After the mixture was allowed to cool until room temperature, water (2 mL) and concentrated ammonia (2 mL) were added. The organic phase, which was obtained by extracting of the resulting dark blue solution with DCM (25 mL) thrice, was dried with brine and MgSO<sub>4</sub>. The purification of the product was applied by using flash column chromatography started with DCM which was saturated with concentrated ammonia and gradually added the methanol, up to

10%. Target product, 2-aminoDMAP **56**, was obtained with 60% yield as light brown solid.<sup>47</sup>



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.69 (d, *J* = 6.1 Hz, 1H, **PyH**), 5.91 (dd, *J* = 6.1, 2.3 Hz, 1H, **PyH**), 5.53 (d, *J* = 2.1 Hz, 1H, **PyH**), 4.19 (d, *J* = 9.4 Hz, 1H, **CHNH<sub>2</sub>**), 3.28 – 3.19 (m, 1H, **CHNH<sub>2</sub>**), 2.87 (s, 6H, **2xCH<sub>3</sub>**), 2.41 (td, *J* = 10.4, 4.0 Hz, 1H, **CHNH**), 2.05 – 1.98 (m, 1H, **CHNH<sub>2</sub>**), 1.93 – 1.87 (m, 1H, **CHNH**), 1.78 (s, 2H, **CH<sub>2</sub>**), 1.68 – 1.62 (m, 2H, **CH<sub>2</sub>**), 1.31 – 1.14 (m, 3H, **CH<sub>2</sub>, CH<sub>2</sub>**), 1.08 – 0.97 (m, 1H, **CH<sub>2</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 160.1 (**PyCNH**), 156.1 [**PyC(NMe<sub>2</sub>)**], 147.9 (**PyCH**), 99.2 (**PyCH**), 87.7 (**PyCH**), 58.4 (**CHNH**), 56.2 (**CHNH<sub>2</sub>**), 39.2 (**2xCH<sub>3</sub>**), 34.8 (**CH<sub>2</sub>**), 32.8 (**CH<sub>2</sub>**), 25.4 (**CH<sub>2</sub>**), 25.0 (**CH<sub>2</sub>**) ppm.

$[\alpha]_{\text{D}}^{25} = -55^{\circ}$  (*c* 0.25, CH<sub>2</sub>Cl<sub>2</sub>)

**HRMS (ESI)** calculated for C<sub>13</sub>H<sub>22</sub>N<sub>4</sub> [M + H]<sup>+</sup> 235.1923, found 235.1918.

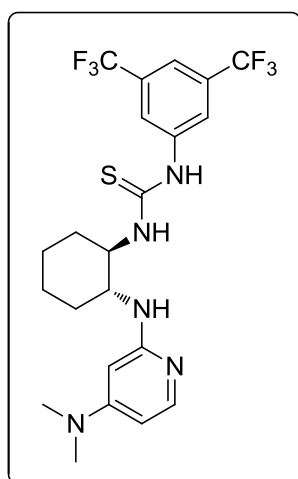
**IR (neat)** 3321, 3254, 2922, 2854, 1599, 1527, 1495, 1444, 1265, 1145, 979, 964, 804.

**Melting point:** 138-140 °C

### 3.3 Synthesis of 2-aminoDMAP/Thiourea Bifunctional Organocatalyst **52**

2-aminoDMAP (47 mg, 0.2 mmol) in THF (1 mL) dried with Na-benzophenone was added to a screw capped vial. Then, 1-isothiocyanato-(3,5)-bis(trifluoromethyl)benzene (54 mg, 37 μL, 0.2 mmol) was added dropwise in 1 minute at 0°C under the argon atmosphere. After the reaction was stirred for

overnight at room temperature, it was purified by using flash column chromatography with DCM which was saturated with ammonia. 2-AminoDMAP/thiourea **52** catalyst was obtained in 90% yield as an off-white amorphous solid.<sup>37</sup>



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 10.11 (bs, 1H, **ArNHC=S**), 8.76 (bs, 1H, **pyNH**), 8.00 (s, 2H, **2xArH**), 7.46 (s, 1H, **ArH**), 7.38 (d, *J* = 7.5 Hz, 1H, **PyH**), 6.77 (bs, 1H, **cyc-hexNHC=S**), 6.03 (dd, *J* = 2.4, 7.5 Hz, 1H, **PyH**), 5.77 (bs, 1H, **pyH**), 4.47 (bs, 1H, **CHNH**), 3.80 (bs, 1H, **CHNH**), 2.99 (s, 6H, **2xCH<sub>3</sub>**), 2.14 – 2.04 (m, 1H, **CH<sub>2</sub>**), 2.04 – 1.94 (m, 1H, **CH<sub>2</sub>**), 1.83 – 1.68 (m, 2H, **CH<sub>2</sub>**), 1.66 – 1.52 (m, 1H, **CH<sub>2</sub>**), 1.52 – 1.29 (m, 3H, **CH<sub>2</sub>, CH<sub>2</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 181.5 (**C=S**), 156.9 (**PyCNH**), 152.1 [**PyC(NMe<sub>2</sub>)**], 141.2 (**PyCH**), 135.0 (**ArCNH**), 131.26 (d, *J* = 99.8 Hz, **ArCCF<sub>3</sub>**), 131.26 (d, *J* = 33.4 Hz, **ArCCF<sub>3</sub>**), 123.26 (d, *J* = 818.2 Hz, **CF<sub>3</sub>**), 123.26 (d, *J* = 272.7 Hz, **CF<sub>3</sub>**), 123.4 (**2xArCH**), 117.4 (d, *J* = 4.0 Hz, **ArCH**), 100.0 (**PyCH**), 87.8 (**PyCH**), 60.4 (**CHNH**), 53.8 (**CHNH**), 39.9 (**2xCH<sub>3</sub>**), 30.9 (**CH<sub>2</sub>**), 29.7 (**CH<sub>2</sub>**), 29.3 (**CH<sub>2</sub>**), 23.7 (**CH<sub>2</sub>**) ppm.

**IR** (neat) 2930, 2857, 1609, 1525, 1471, 1377, 1274, 1168, 1126, 884, 700, 680.

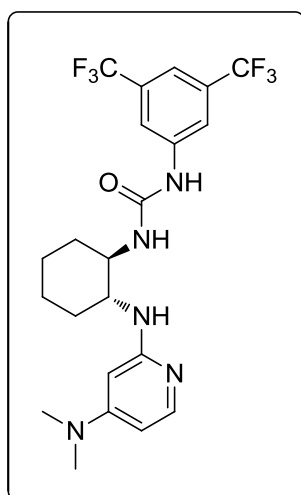
**HRMS** calculated for C<sub>22</sub>H<sub>26</sub>F<sub>6</sub>N<sub>5</sub>S [M + H]<sup>+</sup> 506.1813, found 506.1800.

$[\alpha]_{\text{D}}^{25} = -133.0^{\circ}$  (*c* 1.0, CHCl<sub>3</sub>)

**mp:** 115-121 °C

### 3.4 Synthesis of 2-aminoDMAP/Urea Bifunctional Organocatalyst **53**

2-aminoDMAP (47 mg, 0.2 mmol) in THF (1 mL) dried with Na-benzophenone was added to a screw capped vial. Then, 1-isocyanato-(3,5)-bis(trifluoromethyl)benzene (51 mg, 35  $\mu$ L, 0.2 mmol) was added dropwise in 1 minute at 0°C under the argon atmosphere. After the reaction was stirred for overnight at room temperature, it was purified by using flash column chromatography with DCM which was saturated with concentrated ammonia. 2-aminoDMAP/urea **53** catalyst was obtained with 90% yield as an off-white amorphous solid.<sup>37</sup>



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.03 (bs, 1H, ArNHC=O), 7.71 (s, 2H, 2xArH), 7.55 (d,  $J$  = 6.3 Hz, 1H, PyH), 7.28 (s, 1H, ArH), 6.59 (bs, 1H, cyc-hexNHC=O), 5.90 (d,  $J$  = 4.7 Hz, 1H, PyH), 5.46 (s, 1H, PyH), 4.59 (bs, 1H, cyc-hexNHpy), 3.62 (bs, 1H, CHNH), 3.48 (bs, 1H, CHNH), 2.82 (s, 6H, 2xCH<sub>3</sub>), 2.01 (s, 2H, CH<sub>2</sub>), 1.60 (s, 2H, CH<sub>2</sub>), 1.18 (s, 4H, 2xCH<sub>2</sub>) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  156.9 (PyCNH), 153.9 [PyC(NMe<sub>2</sub>)], 153.6 (C=O), 143.7 (PyCH), 139.3 (ArCNH), 129.5 (d,  $J$  = 99.2 Hz, ArCCF<sub>3</sub>), 129.5 (d,  $J$  = 33.1 Hz, ArCCF<sub>3</sub>), 121.1 (d,  $J$  = 818.1 Hz, CF<sub>3</sub>), 121.1 (d,  $J$  = 272.7 Hz, CF<sub>3</sub>), 115.8 (2xArCH), 112.5 (d,  $J$  = 2.1 Hz, ArCH), 97.8 (PyCH), 86.9 (PyCH), 59.3 (CHNH), 58.8 (CHNH), 36.8 (2xCH<sub>3</sub>), 32.2 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 21.9 (CH<sub>2</sub>) ppm.

**IR (neat):** 2922, 2853, 1610, 1527, 1473, 1389, 1275, 1169, 1125, 878, 702, 681

**HRMS:** calculated for C<sub>22</sub>H<sub>26</sub>F<sub>6</sub>N<sub>5</sub>O [M + H]<sup>+</sup> 490.2042, found 490.2052.

$[\alpha]_{\text{D}}^{25} = -35.3^{\circ}$  ( $c = 1$ , CHCl<sub>3</sub>)

**Melting point:** 180-200 °C

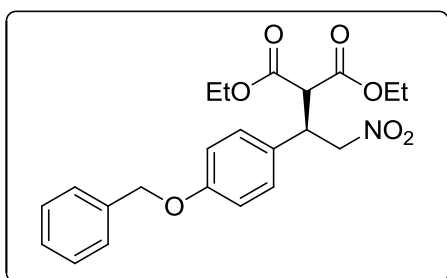
### 3.5 General Procedure for Asymmetric Michael Additions of Diethyl Malonate to Nitroolefins

To a stirred solution of nitroolefins **44a-r** (0.2 mmol) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61 μL, 0.4 mmol) at room temperature under argon. The reaction mixture was stirred until disappearance of the nitroolefin by TLC. The reaction mixture was directly subjected to flash column chromatography over silica gel using EtOAc/n-hexanes (1/8) as the eluant to afford the conjugate addition products.

#### 3.5.1 Synthesis of (*R*)-diethyl 2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl)malonate (**46a**)

To a stirred solution of (*E*)-1-(benzyloxy)-4-(2-nitrovinyl)benzene (**44a**) (0.2 mmol, 51.0 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61 μL, 0.4 mmol) at room temperature for 10 hours to obtain the Michael product **46a** with 83% yield (69 mg) as a colorless oil.





**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 – 7.22 [m, 5H, **5xArH**], 7.11 – 7.05 (m, 2H, **2xArH**), 6.87 – 6.79 [m, 2H, **2xArH**], 4.94 (s, 2H, **OCH<sub>2</sub>**), 4.81 (dd,  $J = 12.9, 4.8$  Hz, 1H, **CHHNO<sub>2</sub>**), 4.73 (dd,  $J = 12.9, 9.3$  Hz, 1H, **CHHNO<sub>2</sub>**), 4.20 – 4.08 (m, 3H, **CHCH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>**), 3.93 (q,  $J = 7.1$  Hz, 2H, **CH<sub>2</sub>CH<sub>3</sub>**), 3.71 [t,  $J = 8.4$  Hz, 1H, **CH(CO<sub>2</sub>Et)<sub>2</sub>**], 1.18 (t,  $J = 7.1$  Hz, 3H, **CH<sub>3</sub>**), 0.98 (t,  $J = 7.1$  Hz, 3H, **CH<sub>3</sub>**).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5, (**C=O**), 165.9 (**C=O**), 157.6 (**ArCO**), 135.7 (**ArCCH, ArCCH<sub>2</sub>O**), 128.2 (**2xArCH**), 127.6 (**2xArCH**), 127.3 (**ArCH**), 127.0 (**ArCH**), 126.5 (**ArCH**), 114.2 (**2xArCH**), 76.9 (**CH<sub>2</sub>NO<sub>2</sub>**), 69.0 (**OCH<sub>2</sub>**), 61.1 (**CH<sub>2</sub>CH<sub>3</sub>**), 60.8 (**CH<sub>2</sub>CH<sub>3</sub>**), 54.1 [**CH(CO<sub>2</sub>Et)<sub>2</sub>**], 41.3 (**CHCH<sub>2</sub>**), 13.0 (**CH<sub>3</sub>**), 12.8 (**CH<sub>3</sub>**) ppm.

**HPLC** (Chiralpak AS-H, 97:3 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{major}} = 38.747$  min,  $t_{\text{minor}} = 43.305$ ; 99% ee.

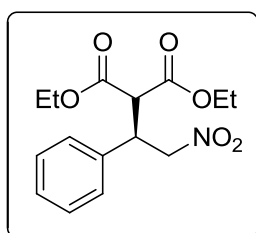
$[\alpha]_{\text{D}}^{25} = +3.50$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**IR** (**neat**) 2985, 2931, 1727, 1611, 1584, 1554, 1511, 1442, 1380, 1290, 1244, 1199, 1177, 1115, 1083, 1060, 1045, 1016, 992, 963, 908, 861, 834, 820, 764, 736, 695, 629, 591, 560  $\text{cm}^{-1}$ .

**HRMS** (**ESI**) calcd for  $\text{C}_{22}\text{H}_{24}\text{NO}_7$  [ $\text{M}+\text{H}$ ] $^-$  414.1553, found 414.1498.

### 3.5.2 Synthesis of (*R*)-diethyl 2-(2-nitro-1-phenylethyl)malonate (**46b**)

To a stirred solution of (*E*)-(2-nitrovinyl)benzene (0.2 mmol, 29.8 mg) (**44b**) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 4 hours to obtain the product **46b** with 91% yield (56 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 – 7.05 (m, 5H, **5xArH**), 4.86 (dd,  $J = 13.1, 4.9$  Hz, 1H, **CHHNO<sub>2</sub>**), 4.79 (dd,  $J = 13.1, 9.1$  Hz, 1H, **CHHNO<sub>2</sub>**), 4.18 – 4.13 (m, 3H **CHCH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>**), 3.93 (q,  $J = 7.1$  Hz, 2H, **CH<sub>2</sub>CH<sub>3</sub>**), 3.75 [d,  $J = 9.4$  Hz, 1H, **CH(CO<sub>2</sub>Et)<sub>2</sub>**], 1.19 (t,  $J = 7.2$  Hz, 3H, **CH<sub>3</sub>**), 0.97 (t,  $J = 7.1$  Hz, 3H, **CH<sub>3</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.4 (**C=O**), 165.8 (**C=O**), 135.2 (**ArCCH**), 127.9 (**2xArCH**), 127.3 (**ArCH**), 127.0 (**2xArCH**), 76.6 (**CH<sub>2</sub>NO<sub>2</sub>**), 61.1 (**CH<sub>2</sub>CH<sub>3</sub>**), 60.9 (**CH<sub>2</sub>CH<sub>3</sub>**), 53.9 [**CH(CO<sub>2</sub>Et)<sub>2</sub>**], 41.9 (**CHCH<sub>2</sub>**), 12.9 (**CH<sub>3</sub>**), 12.7 (**CH<sub>3</sub>**) ppm.

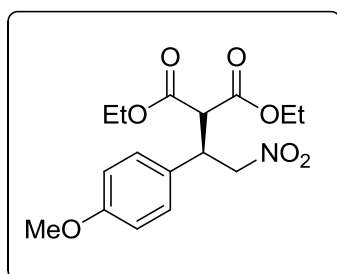
**HPLC** (Chiralpak AS-H, 90:10 n-hexane/isopropyl alcohol, 1 mL/min, 210 nm):  
 $t_{\text{minor}} = 19.172$ ,  $t_{\text{major}} = 23.390$  min; 94% ee.

$[\alpha]_{\text{D}}^{25} = -4.22$  ( $c$  1.0, CHCl<sub>3</sub>).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = +7.3$  ( $c$  1.07, CHCl<sub>3</sub>), [95% ee, (*S*)-enantiomer].

### 3.5.3 Synthesis of (*R*)-diethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate (**46c**)

To a stirred solution of (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (**44c**) (0.2 mmol, 35.8 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 6 hours to obtain the product **46c** with 87% yield (59 mg) as a colorless oil.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 – 7.05 (m, 2H,  $2\times\text{ArH}$ ), 6.81 – 6.72 (m, 2H,  $2\times\text{ArH}$ ), 4.82 (dd,  $J = 12.9, 4.9$  Hz, 1H,  $\text{CHHNO}_2$ ), 4.74 (dd,  $J = 12.9, 9.3$  Hz, 1H,  $\text{CHHNO}_2$ ), 4.20 – 4.08 (m, 3H,  $\text{CHCH}_2$ ,  $\text{CH}_2\text{CH}_3$ ), 3.95 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.72 [d,  $J = 3.8$  Hz, 1H,  $\text{CH}(\text{CO}_2\text{Et})_2$ ], 3.70 (s, 3H,  $\text{OCH}_3$ ), 1.19 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 1.00 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ) ppm.

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5 ( $\text{C}=\text{O}$ ), 165.9 ( $\text{C}=\text{O}$ ), 158.4 ( $\text{ArCO}$ ), 128.1 ( $\text{ArCCH}$ ), 127.0 ( $2\times\text{ArCH}$ ), 113.3 ( $2\times\text{ArCH}$ ), 76.9 ( $\text{CH}_2\text{NO}_2$ ), 61.2 ( $\text{CH}_2\text{CH}_3$ ), 60.8 ( $\text{CH}_2\text{CH}_3$ ), 54.2 ( $\text{CH}_3\text{O}$ ), 54.1 [ $\text{CH}(\text{CO}_2\text{Et})_2$ ], 41.3 ( $\text{CHCH}_2$ ), 13.0 ( $\text{CH}_3$ ), 12.8 ( $\text{CH}_3$ ) ppm.

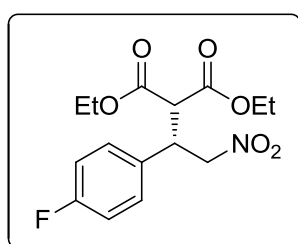
**HPLC** (Chiralpak AD, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{major}} = 12.676$  min,  $t_{\text{minor}} = 39.547$ ; 94% ee.

$[\alpha]_{\text{D}}^{25} = -5.70$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup>  $[\alpha]_{\text{D}}^{25} = -3.0$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ , [88% ee, (*R*)-enantiomer].

### 3.5.4 Synthesis of (*S*)-diethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)malonate (**46d**)

To a stirred solution of (*E*)-1-fluoro-4-(2-nitrovinyl)benzene (**44d**) (0.2 mmol, 33.4 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 3 hours to obtain the product **46d** with 88% yield (57 mg) as a colorless oil.



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.20 – 7.12 (m, 2H,  $2\times\text{ArH}$ ), 7.02 – 6.86 (m, 2H,  $2\times\text{ArH}$ ), 4.84 (dd,  $J = 13.1$ , 4.7 Hz, 1H,  $\text{CHHNO}_2$ ), 4.75 (dd,  $J = 13.1$ , 9.4 Hz, 1H,  $\text{CHHNO}_2$ ), 4.22 – 4.10 (m, 3H,  $\text{CHCH}_2$ ,  $\text{CH}_2\text{CH}_3$ ), 3.95 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.71 [d,  $J = 9.4$  Hz, 1H,  $\text{CH}(\text{CO}_2\text{Et})_2$ ], 1.19 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 1.04 – 0.96 (t, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3 ( $\text{C=O}$ ), 165.7 ( $\text{C=O}$ ), 161.5 (d,  $J = 247.5$  Hz,  $\text{ArCF}$ ), 131.0 (d,  $J = 2.4$  Hz,  $\text{ArCCH}$ ), 128.8 (d,  $J = 8.2$  Hz,  $\text{ArCH}$ ), 114.9 (d,  $J = 21.5$  Hz,  $\text{ArCH}$ ), 76.7 ( $\text{CH}_2\text{NO}_2$ ), 61.2 ( $\text{CH}_2\text{CH}_3$ ), 60.95 ( $\text{CH}_2\text{CH}_3$ ), 53.9 [ $\text{CH}(\text{CO}_2\text{Et})_2$ ], 41.3 ( $\text{CHCH}_2$ ), 12.9 ( $\text{CH}_3$ ), 12.8 ( $\text{CH}_3$ ) ppm.

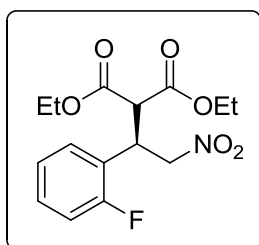
**HPLC** (Chiralpak AS-H, 95:5 n-hexane/isopropyl alcohol, 0.8 mL/min, 215nm):  $t_{\text{minor}} = 18.800$ ,  $t_{\text{major}} = 22.093$  min; 94% ee.

$[\alpha]_{\text{D}}^{25} = -6.0$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*S*) by comparison of the optical rotation with the following literature value: Lit.<sup>32</sup>  $[\alpha]_{\text{D}}^{25} = -7.20$  ( $c$  1.0,  $\text{CHCl}_3$ ), [92% ee, (*S*)-enantiomer].

### 3.5.5 Synthesis of (*R*)-diethyl 2-(1-(2-fluorophenyl)-2-nitroethyl)malonate (**46e**)

To a stirred solution of (*E*)-1-fluoro-2-(2-nitrovinyl)benzene (**44e**) (0.2 mmol, 33.4 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 4 hours to obtain the product **46e** with 91% yield (60 mg) as a colorless oil.



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 – 7.14 (m, 2H,  $2\times\text{ArH}$ ), 7.05 – 6.95 (m, 2H,  $2\times\text{ArH}$ ), 4.94 – 4.79 (m, 2H,  $\text{CHHNO}_2$ ,  $\text{CHHNO}_2$ ), 4.44 – 4.30 (m, 1H,  $\text{CHCH}_2$ ), 4.18 – 4.12 (m, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.91 (dt,  $J = 10.0, 7.7$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CO}_2\text{Et})_2$ ), 1.19 (dd,  $J = 7.1, 5.8$  Hz, 3H,  $\text{CH}_3$ ), 0.96 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3 ( $\text{C=O}$ ), 165.7 ( $\text{C=O}$ ), 160.0 (d,  $J = 247.1$  Hz,  $\text{ArCF}$ ), 129.7 (d,  $J = 4.1$  Hz,  $\text{ArCCH}$ ), 129.2 (d,  $J = 8.6$  Hz,  $\text{ArCH}$ ), 123.5 (d,  $J = 3.3$  Hz,  $\text{ArCH}$ ), 122.1 (d,  $J = 13.0$  Hz, ( $\text{ArCH}$ ), 115.1 (d,  $J = 22.1$  Hz, ( $\text{ArCH}$ ), 75.3 (d,  $J = 2.4$  Hz, ( $\text{CH}_2\text{NO}_2$ ), 61.2 ( $\text{CH}_2\text{CH}_3$ ), 60.9 ( $\text{CH}_2\text{CH}_3$ ), 52.3 [ $\text{CH}(\text{CO}_2\text{Et})_2$ ], 37.6 ( $\text{CHCH}_2$ ), 12.9 ( $\text{CH}_3$ ), 12.7 ( $\text{CH}_3$ ) ppm.

**HPLC** (Chiralpak AD, 90:10 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{major}} = 11.973$  min,  $t_{\text{minor}} = 35.137$ ; 93% ee.

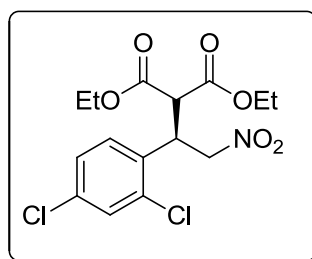
$[\alpha]_{\text{D}}^{25} = -16.0$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**IR** (neat) 2984, 2936, 1730, 1616, 1555, 1492, 1457, 1370, 1297, 1234, 1177, 1152, 1108, 1096, 1025, 943, 859, 838, 759, 687, 610  $\text{cm}^{-1}$ .

HRMS (ESI) calcd for C<sub>15</sub>H<sub>17</sub>FNO<sub>6</sub> [M+H]<sup>-</sup> 326.1040, found 326.0994.

### 3.5.6 Synthesis of (*R*)-diethyl 2-(1-(2,4-dichlorophenyl)-2-nitroethyl)malonate (**46f**)

To a stirred solution of (*E*)-2,4-dichloro-1-(2-nitrovinyl)benzene (**44f**) (0.2 mmol, 43.6 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 3 hours to obtain the product **46f** with 83% yield (63 mg) as a colorless oil.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.36 (s, 1H, *ArH*), 7.18 – 7.10 (m, 2H, *2xArH*), 5.01 (dd, *J* = 13.6, 8.6 Hz, 1H, *CHHNO*<sub>2</sub>), 4.85 (dd, *J* = 13.6, 4.3 Hz, 1H, *CHHNO*<sub>2</sub>), 4.62 (td, *J* = 8.6, 4.3 Hz, 1H, *CHCH*<sub>2</sub>), 4.14 [dd, *J* = 5.0, 2.2 Hz, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>], 4.03 (q, *J* = 7.1 Hz, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 3.96 [d, *J* = 8.7 Hz, 1H, *CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 1.23 – 1.19 (t, 3H, *CH*<sub>3</sub>), 1.07 (t, *J* = 7.1 Hz, 3H, *CH*<sub>3</sub>).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.2 (*C=O*), 165.6 (*C=O*), 133.9 (*ArC*), 133.8 (*ArC*), 131.5 (*ArC*), 129.3 (*ArCH*), 128.8 (*ArCH*), 126.6 (*ArCH*), 74.5 (*CH*<sub>2</sub>*NO*<sub>2</sub>), 61.3 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 61.2 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 52.0 [*CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 40.7 (*CHCH*<sub>2</sub>), 13.0 (*CH*<sub>3</sub>), 12.9 (*CH*<sub>3</sub>).

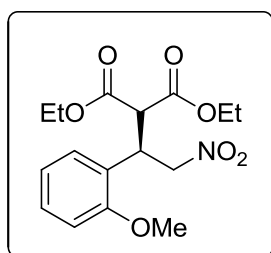
HPLC (Chiralpak AD, 65:35 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  
*t*<sub>major</sub> = 4.922 min, *t*<sub>minor</sub> = 23.089; 92% ee.

$[\alpha]_D^{25} = -11.10$  (*c* 1.0, CHCl<sub>3</sub>).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup> $[\alpha]_{\text{D}}^{25} = -6.3$  (*c* 1.15, CH<sub>2</sub>Cl<sub>2</sub>), [94% ee, (*R*)-enantiomer].

### 3.5.7 Synthesis of (*R*)-diethyl 2-(1-(2-methoxyphenyl)-2-nitroethyl)malonate (**46g**)

To a stirred solution of (*E*)-1-methoxy-2-(2-nitrovinyl)benzene (**44g**) (0.2 mmol, 35.8 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 7 hours to obtain the product **46g** with 93% yield (63 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.21 – 7.15 (m, 1H, *ArH*), 7.07 (dd, *J* = 7.7, 1.6 Hz, 1H, *ArH*), 6.80 (ddd, *J* = 7.4, 4.8, 2.6 Hz, 2H, *2xArH*), 4.95 (dd, *J* = 12.9, 9.1 Hz, 1H, *CHHNO*<sub>2</sub>), 4.80 (dd, *J* = 12.9, 4.5 Hz, 1H, *CHHNO*<sub>2</sub>), 4.31 [td, *J* = 9.6, 4.5 Hz, 1H, *CH(CO*<sub>2</sub>Et)<sub>2</sub>], 4.20 – 4.05 (m, 3H, *CHCH*<sub>2</sub>, *CH*<sub>2</sub>CH<sub>3</sub>), 3.87 (q, *J* = 7.1 Hz, 2H, *CH*<sub>2</sub>CH<sub>3</sub>), 3.80 (s, 3H, *OCH*<sub>3</sub>), 1.19 (t, *J* = 7.1 Hz, 3H, *CH*<sub>3</sub>), 0.93 (t, *J* = 7.1 Hz, 3H, *CH*<sub>3</sub>).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.9 (*C=O*), 166.2 (*C=O*), 156.4 (*ArCO*), 129.9 (*ArCCH*), 128.6 (*ArCH*), 122.8 (*ArCH*), 119.8 (*ArCH*), 110.1 (*ArCH*), 75.2 (*CH*<sub>2</sub>NO<sub>2</sub>), 60.9 (*CH*<sub>2</sub>CH<sub>3</sub>), 60.5 (*CH*<sub>2</sub>CH<sub>3</sub>), 54.4 (*CH*<sub>3</sub>O), 51.7 [*CH(CO*<sub>2</sub>Et)<sub>2</sub>], 39.5 (*CHCH*<sub>2</sub>), 13.0 (*CH*<sub>3</sub>), 12.7 (*CH*<sub>3</sub>).

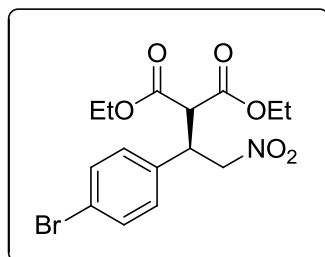
**HPLC** (Chiralpak AD, 90:10 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{major}} = 9.792$  min,  $t_{\text{minor}} = 13.127$ ; 92% ee.

$$[\alpha]_{\text{D}}^{25} = -16.30 \text{ (} c \text{ 1.0, CHCl}_3\text{)}.$$

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>50</sup>  $[\alpha]_{\text{D}}^{25} = -20.3$  (*c* 1.0, CHCl<sub>3</sub>), [96% ee, (*R*)-enantiomer].

### 3.5.8 Synthesis of (*R*)-diethyl 2-(1-(4-bromophenyl)-2-nitroethyl)malonate (**46h**)

To a stirred solution of (*E*)-1-bromo-4-(2-nitrovinyl)benzene (**44h**) (0.2 mmol, 45.6 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 4 hours to obtain the product **46h** with 84% yield (65 mg) as a colorless oil.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 – 7.33 (m, 2H, 2xArH), 7.13 – 7.01 (m, 2H, 2xArH), 4.84 (dd, *J* = 13.2, 4.8 Hz, 1H, CHHNO<sub>2</sub>), 4.76 (dd, *J* = 13.2, 9.3 Hz, 1H, CHHNO<sub>2</sub>), 4.21 – 4.09 (m, 3H, CHCH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 3.96 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.71 [d, *J* = 9.3 Hz, 1H, CH(CO<sub>2</sub>Et)<sub>2</sub>], 1.19 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.02 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.2 (C=O), 166.6 (C=O), 135.3 (ArCCH), 132.1 (2xArCH), 129.8 (2xArCH), 122.5 (ArCBr), 77.3 (CH<sub>2</sub>NO<sub>2</sub>), 62.3 (CH<sub>2</sub>CH<sub>3</sub>), 62.1 (CH<sub>2</sub>CH<sub>3</sub>), 54.7 [CH(CO<sub>2</sub>Et)<sub>2</sub>], 42.4 (CHCH<sub>2</sub>), 14.0 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>) ppm.



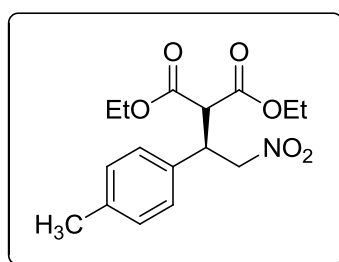
**HPLC** (Chiralpak AD, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  
 $t_{\text{major}} = 14.197 \text{ min}$ ,  $t_{\text{minor}} = 39.377$ , 92% ee.

$$[\alpha]_{\text{D}}^{25} = -4.50 \text{ (} c \text{ 1.0, CHCl}_3\text{)}.$$

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = +8.4$  (*c* 1.04, CHCl<sub>3</sub>), [95% ee, (*S*)-enantiomer].

### 3.5.9 Synthesis of (*R*)-diethyl 2-(2-nitro-1-(*p*-tolyl)ethyl)malonate (**46i**)

To a stirred solution of (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**44i**) (0.2 mmol, 32.6 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 9 hours to obtain the product **46i** with 90% yield (58 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.04 (s, 4H, **4xArH**), 4.83 (dd,  $J = 13.0, 4.9 \text{ Hz}$ , 1H, **CHHNO<sub>2</sub>**), 4.76 (dd,  $J = 13.0, 9.2 \text{ Hz}$ , 1H, **CHHNO<sub>2</sub>**), 4.18 – 4.10 (m, 3H, **CHCH<sub>2</sub>**, **CH<sub>2</sub>CH<sub>3</sub>**), 3.94 (q,  $J = 7.1 \text{ Hz}$ , 2H, **CH<sub>2</sub>CH<sub>3</sub>**), 3.73 (d,  $J = 9.3 \text{ Hz}$ , 1H, **CH(CO<sub>2</sub>Et)<sub>2</sub>**), 2.22 (s, 3H, **CH<sub>3</sub>**), 1.19 (t,  $J = 7.2 \text{ Hz}$ , 3H, **CH<sub>3</sub>**), 0.99 (t,  $J = 7.1 \text{ Hz}$ , 3H, **CH<sub>3</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.5 (**C=O**), 165.9 (**C=O**), 137.1 (**ArCCH**), 132.1 (**ArCCH<sub>3</sub>**), 128.6 (**2xArCH**), 126.8 (**2xArCH**), 76.8 (**CH<sub>2</sub>NO<sub>2</sub>**), 61.1 (**CH<sub>2</sub>CH<sub>3</sub>**), 60.8 (**CH<sub>2</sub>CH<sub>3</sub>**), 54.0 [**CH(CO<sub>2</sub>Et)<sub>2</sub>**], 41.6 (**CHCH<sub>2</sub>**), 20.0 (**CH<sub>3</sub>**), 13.0 (**CH<sub>3</sub>**), 12.7 (**CH<sub>3</sub>**) ppm.

**HPLC** (Chiralpak AD, 85:15 n-hexane/isopropyl alcohol, 1 mL/min, 215 nm):

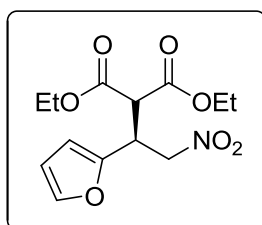
$t_{\text{major}} = 10.902 \text{ min}$ ,  $t_{\text{minor}} = 28.823$ ; 91% ee.

$[\alpha]_{\text{D}}^{25} = -3.20$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = +6.25$  ( $c$  1.36,  $\text{CHCl}_3$ ), [95% ee, (*S*)-enantiomer].

### 3.5.10 Synthesis of (*S*)-diethyl 2-(1-(furan-2-yl)-2-nitroethyl)malonate (**46j**)

To a stirred solution of (*E*)-2-(2-nitrovinyl)furan (**44j**) (0.2 mmol, 27.8 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 4 hours to obtain the product **46j** with 84% yield (50 mg) as a yellow oil.



**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (dd,  $J = 1.8, 0.7 \text{ Hz}$ , 1H, *ArH*), 6.22 (dd,  $J = 3.3, 1.9 \text{ Hz}$ , 1H, *ArH*), 6.15 (d,  $J = 3.3 \text{ Hz}$ , 1H, *ArH*), 4.85 (dd,  $J = 11.5, 6.2 \text{ Hz}$ , 1H, *CHHNO*<sub>2</sub>), 4.81 (dd,  $J = 11.5, 3.3 \text{ Hz}$ , 1H, *CHHNO*<sub>2</sub>), 4.31 (td,  $J = 8.0, 5.2 \text{ Hz}$ , 1H, *CHCH*<sub>2</sub>), 4.18 – 4.12 (m, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 4.07 (q,  $J = 7.1 \text{ Hz}$ , 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 3.87 – 3.79 [m, 1H, *CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 1.19 (t,  $J = 7.1 \text{ Hz}$ , 3H, *CH*<sub>3</sub>), 1.13 (t,  $J = 7.1 \text{ Hz}$ , 3H, *CH*<sub>3</sub>) ppm.

**<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.1 (*C=O*), 165.8 (*C=O*), 148.6 (*ArCCH*), 141.7 (*ArCH*), 109.5 (*ArCH*), 107.4 (*ArCH*), 74.4 (*CH*<sub>2</sub>*NO*<sub>2</sub>), 61.1 (2*xCH*<sub>2</sub>*CH*<sub>3</sub>), 52.0 [*CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 35.8 (*CHCH*<sub>2</sub>), 12.9 (*CH*<sub>3</sub>), 12.9 (*CH*<sub>3</sub>) ppm.

**HPLC** (Chiralpak IA, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):

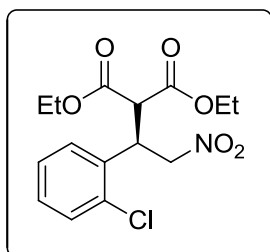
$t_{\text{major}} = 6.238 \text{ min}$ ,  $t_{\text{minor}} = 7.119$ ; 91% ee.

$$[\alpha]_{\text{D}}^{25} = +2.62 \text{ (} c \text{ 1.0, CHCl}_3\text{)}.$$

The absolute configuration was assigned as (*S*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = -2.8$  (*c* 1.22, CHCl<sub>3</sub>), [95% ee, (*R*)-enantiomer].

### 3.5.11 Synthesis of (*R*)-diethyl 2-(1-(2-chlorophenyl)-2-nitroethyl)malonate (**46k**)

To a stirred solution of (*E*)-1-chloro-2-(2-nitrovinyl)benzene (**44k**) (0.2 mmol, 36.7 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethylmalonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 2 hours to obtain the product **46k** with 95% yield (65 mg) as a colorless oil.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 – 7.29 (m, 1H, *ArH*), 7.22 – 7.12 (m, 3H, *3xArH*), 5.03 (dd, *J* = 13.5, 8.5 Hz, 1H, *CHHNO*<sub>2</sub>), 4.88 (dd, *J* = 13.5, 4.4 Hz, 1H, *CHHNO*<sub>2</sub>), 4.67 [td, *J* = 8.6, 4.4 Hz, 1H, *CH(CO*<sub>2</sub>*Et)*<sub>2</sub>], 4.17 – 4.10 (m, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 4.00 (dd, *J* = 14.3, 7.3 Hz, 3H, *CHCH*<sub>2</sub>, *CH*<sub>2</sub>*CH*<sub>3</sub>), 1.17 (t, *J* = 7.1 Hz, 3H, *CH*<sub>3</sub>), 1.03 (t, *J* = 7.1 Hz, 3H, *CH*<sub>3</sub>) ppm.

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  168.4 (*C=O*), 167.8 (*C=O*), 135.2 (*ArCCH*), 134.8 (*ArCCI*), 131.5 (*ArCCH*), 130.5 (*ArCCH*), 129.9 (*ArCCH*), 128.3 (*ArCCH*), 76.7 (*CH*<sub>2</sub>*NO*<sub>2</sub>), 63.1 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 63.0 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 54.2 [*CH(CO*<sub>2</sub>*Et)*<sub>2</sub>], 40.5 (*CHCH*<sub>2</sub>), 14.9 (*CH*<sub>3</sub>), 14.85 (*CH*<sub>3</sub>) ppm.

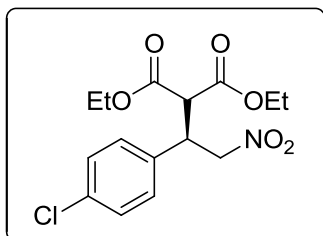
**HPLC** (Chiralpak IA, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215 nm):  $t_{\text{major}} = 6.534$  min,  $t_{\text{minor}} = 28.673$ ; 90% ee.

$$[\alpha]_{\text{D}}^{25} = -5.70 \text{ (} c \text{ 1.0, CHCl}_3\text{)}.$$

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = +11.1$  (*c* 1.13, CHCl<sub>3</sub>), [92% ee, (*S*)-enantiomer].

### 3.5.12 Synthesis of (*R*)-diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (**46l**)

To a stirred solution of (*E*)-1-chloro-4-(2-nitrovinyl)benzene (**44l**) (0.2 mmol, 36.7 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 3 hours to obtain the product **46l** with 81% yield (55 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 – 7.19 (m, 2H, 2xArH), 7.15 – 7.09 (m, 2H, 2xArH), 4.84 (dd, *J* = 13.2, 4.8 Hz, 1H, CHHNO<sub>2</sub>), 4.76 (dd, *J* = 13.2, 9.3 Hz, 1H, CHHNO<sub>2</sub>), 4.21 – 4.10 (m, 3H, CHCH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 3.96 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.71 [d, *J* = 9.3 Hz, 1H, CH(CO<sub>2</sub>Et)<sub>2</sub>], 1.19 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 1.02 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.2 (C=O), 165.6 (C=O), 133.8 (ArCCH), 133.3 (ArCCl), 128.4 (ArCH), 128.2 (ArCH), 76.4 (CH<sub>2</sub>NO<sub>2</sub>), 61.3 (CH<sub>2</sub>CH<sub>3</sub>), 61.0 (CH<sub>2</sub>CH<sub>3</sub>), 53.7 [CH(CO<sub>2</sub>Et)<sub>2</sub>], 41.3 (CHCH<sub>2</sub>), 12.9 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>) ppm.

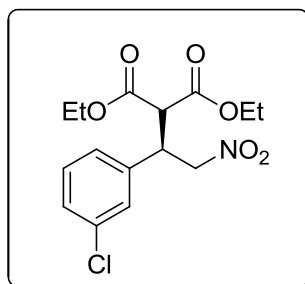
**HPLC** (Chiralpak IA, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 254 nm):  $t_{\text{major}} = 11.175$  min,  $t_{\text{minor}} = 33.172$ ; 90% ee.

$$[\alpha]_{\text{D}}^{25} = -2.40 \text{ (} c \text{ 1.0, CHCl}_3\text{)}.$$

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup>  $[\alpha]_{\text{D}}^{25} = -5.6$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>), [88% ee, (*R*)-enantiomer].

### 3.5.13 Synthesis of (*R*)-diethyl 2-(1-(3-chlorophenyl)-2-nitroethyl)malonate (**46m**)

To a stirred solution of (*E*)-1-chloro-3-(2-nitrovinyl)benzene (**46m**) (0.2 mmol, 36.7 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu$ L, 0.4 mmol) at room temperature for 3 hours to obtain the product **46m** with 82% yield (56 mg) as a colorless oil.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 – 7.14 (m, 3H, 3xArH), 7.12 – 7.03 (m, 1H, ArH), 4.85 (dd, *J* = 13.3, 4.8 Hz, 1H, CHHNO<sub>2</sub>), 4.78 (dd, *J* = 13.3, 9.3 Hz, 1H, CHHNO<sub>2</sub>), 4.23 – 4.08 (m, 3H, CHCH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>), 3.98 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.72 (d, *J* = 9.1 Hz, 1H, CH(CO<sub>2</sub>Et)<sub>2</sub>), 1.19 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>), 1.02 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.2 (C=O), 165.6 (C=O), 137.4 (ArCCH), 133.8 (ArCCl), 129.2 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 125.3 (ArCH), 76.2 (CH<sub>2</sub>NO<sub>2</sub>), 61.3 (CH<sub>2</sub>CH<sub>3</sub>), 61.1 (CH<sub>2</sub>CH<sub>3</sub>), 53.7 [CH(CO<sub>2</sub>Et)<sub>2</sub>], 41.5 (CHCH<sub>2</sub>), 12.9 (CH<sub>3</sub>), 12.7 (CH<sub>3</sub>) ppm.

HPLC (Chiralpak IA, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215 nm):  $t_{\text{major}} = 7.419$  min,  $t_{\text{minor}} = 12.914$ ; 88% ee.

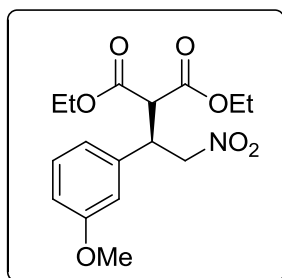
$[\alpha]_{\text{D}}^{25} = -7.20$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**IR** (neat) 2983, 1728, 1554, 1476, 1435, 1369, 1299, 1253, 1231, 1177, 1085, 1024, 860, 789, 695  $\text{cm}^{-1}$ .

**HRMS** (ESI) calcd for  $\text{C}_{15}\text{H}_{17}\text{ClNO}_6$   $[\text{M}+\text{H}]^-$  342.0744, found 342.0724.

### 3.5.14 Synthesis of (*R*)-diethyl 2-(1-(3-methoxyphenyl)-2-nitroethyl)malonate (**46n**)

To a stirred solution of (*E*)-1-methoxy-3-(2-nitrovinyl)benzene (**44n**) (0.2 mmol, 35.8 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 4 hours to obtain the product **46n** with 84% yield (57 mg) as a colorless oil.



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (dd,  $J = 16.6, 8.7$  Hz, 1H, *ArH*), 6.81 – 6.64 (m, 3H, *3xArH*), 4.84 (dd,  $J = 13.1, 5.0$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.78 (dd,  $J = 13.1, 8.9$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.21 – 4.10 (m, 3H, *CHCH*<sub>2</sub>, *CH*<sub>2</sub>*CH*<sub>3</sub>), 3.96 (q,  $J = 7.1$  Hz, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 3.74 [d,  $J = 9.2$  Hz, 1H, *CH(CO*<sub>2</sub>*Et)*<sub>2</sub>], 3.70 (s, 3H, *OCH*<sub>3</sub>), 1.19 (t,  $J = 7.1$  Hz, 3H, *CH*<sub>3</sub>), 1.00 (t,  $J = 7.1$  Hz, 3H, *CH*<sub>3</sub>) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5 (*C=O*), 165.8 (*C=O*), 158.9 (*ArCO*), 136.8 (*ArCCH*), 129.0 (*ArCH*), 119.0 (*ArCH*), 113.1 (*ArCH*), 112.6 (*ArCH*), 76.6 (*CH*<sub>2</sub>*NO*<sub>2</sub>), 61.1 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 60.9 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 54.2 (*CH*<sub>3</sub>*O*), 54.0 [*CH(CO*<sub>2</sub>*Et)*<sub>2</sub>], 41.9 (*CHCH*<sub>2</sub>), 12.9 (*CH*<sub>3</sub>), 12.8 (*CH*<sub>3</sub>) ppm.

**HPLC** (Chiralpak AD, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  
 $t_{\text{major}} = 9.230 \text{ min}$ ,  $t_{\text{minor}} = 12.091$ ; 88% ee.

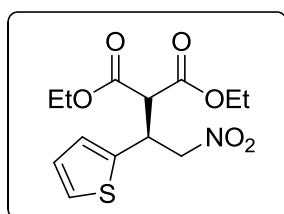
$[\alpha]_{\text{D}}^{25} = -2.76$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**IR** (neat) 2981, 2936, 2906, 1728, 1602, 1586, 1489, 1456, 1438, 1369, 1292, 1259, 1174, 1154, 1095, 1026, 858, 785, 755, 699  $\text{cm}^{-1}$ .

**HRMS** (ESI) calcd for  $\text{C}_{16}\text{H}_{20}\text{NO}_7$   $[\text{M}+\text{H}]^-$  338.1240, found 338.1199.

### 3.5.15 Synthesis of (*S*)-diethyl 2-(2-nitro-1-(thiophen-2-yl)ethyl)malonate (**46o**)

To a stirred solution of (*E*)-2-(2-nitrovinyl)thiophene (**44o**) (0.2 mmol, 31.0 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 7 hours to obtain the product **46o** with 75% yield (47 mg) as a yellow oil.



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.16 (dd,  $J = 5.0, 1.1$  Hz, 1H, *ArH*), 6.89 (d,  $J = 2.5$  Hz, 1H, *ArH*), 6.86 (dd,  $J = 5.0, 3.6$  Hz, 1H, *ArH*), 4.87 (dd,  $J = 12.7, 4.6$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.83 (dd,  $J = 12.7, 7.6$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.48 (td,  $J = 8.1, 5.3$  Hz, 1H, *CHCH*<sub>2</sub>), 4.20 – 4.11 (m, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 4.05 (q,  $J = 7.1$  Hz, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 3.87 – 3.74 [d, 1H, *CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 1.20 (t,  $J = 5.5$  Hz, 3H, *CH*<sub>3</sub>), 1.09 (t,  $J = 7.1$  Hz, 3H, *CH*<sub>3</sub>) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9 (*C=O*), 166.4 (*C=O*), 138.3 (*ArC*), 126.7 (*ArCH*), 126.5 (*ArCH*), 125.3 (*ArCH*), 77.8 (*CH*<sub>2</sub>*NO*<sub>2</sub>), 61.9 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 61.8 (*CH*<sub>2</sub>*CH*<sub>3</sub>), 55.3 [*CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 38.1 (*CHCH*<sub>2</sub>), 13.7 (*CH*<sub>3</sub>), 13.5 (*CH*<sub>3</sub>) ppm.

**HPLC** (Chiralpak AD, 90:10 n-hexane/isopropyl alcohol, 1 mL/min, 215 nm)

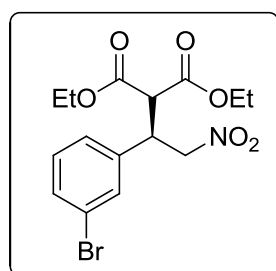
$t_{\text{major}} = 11.318$  min,  $t_{\text{minor}} = 20.136$ ; 88% ee.

$[\alpha]_{\text{D}}^{25} = +3.50$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*S*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup>  $[\alpha]_{\text{D}}^{25} = +8.7$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ), [87% ee, (*S*)-enantiomer].

### 3.5.16 Synthesis of (*R*)-diethyl 2-(1-(3-bromophenyl)-2-nitroethyl)malonate (**46p**)

To a stirred solution of (*E*)-1-bromo-3-(2-nitrovinyl)benzene (**44p**) (0.2 mmol, 45.6 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 4 hours to obtain the product **46p** with 76% yield (59 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.28 (m, 2H,  $2 \times \text{ArH}$ ), 7.18 – 7.07 (m, 2H,  $2 \times \text{ArH}$ ), 4.85 (dd,  $J = 13.4$ , 4.8 Hz, 1H,  $\text{CHHNO}_2$ ), 4.77 (dd,  $J = 13.3$ , 9.3 Hz, 1H,  $\text{CHHNO}_2$ ), 4.20 – 4.10 (m, 3H,  $\text{CHCH}_2$ ,  $\text{CH}_2\text{CH}_3$ ), 3.98 (q,  $J = 7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.71 [d,  $J = 9.1$  Hz, 1H,  $\text{CH}(\text{CO}_2\text{Et})_2$ ], 1.19 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ), 1.02 (t,  $J = 7.1$  Hz, 3H,  $\text{CH}_3$ ) ppm.

**<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2 ( $\text{C}=\text{O}$ ), 165.6 ( $\text{C}=\text{O}$ ), 137.7 ( $\text{ArCCH}$ ), 130.5 ( $\text{ArCH}$ ), 130.2 ( $\text{ArCH}$ ), 129.5 ( $\text{ArCH}$ ), 125.7 ( $\text{ArCH}$ ), 121.9 ( $\text{ArCBr}$ ), 76.2 ( $\text{CH}_2\text{NO}_2$ ), 61.3 ( $\text{CH}_2\text{CH}_3$ ), 61.1 ( $\text{CH}_2\text{CH}_3$ ), 53.7 [ $\text{CH}(\text{CO}_2\text{Et})_2$ ], 41.5 ( $\text{CHCH}_2$ ), 13.0 ( $\text{CH}_3$ ), 12.8 ( $\text{CH}_3$ ) ppm.



**HPLC** (Chiralpak AD, 80:20 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  
 $t_{\text{major}} = 8.934 \text{ min}$ ,  $t_{\text{minor}} = 15.886$ ; 87% ee.

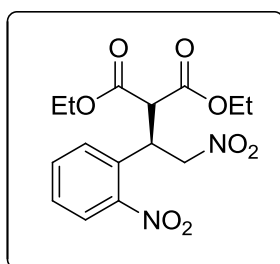
$[\alpha]_{\text{D}}^{25} = -3.70$  ( $c$  1.0,  $\text{CHCl}_3$ ).

**IR** (neat) 2982, 2936, 1727, 1596, 1552, 1474, 1431, 1369, 1299, 1252, 1228, 1177, 1153, 1095, 1075, 1025, 998, 859, 788, 694, 665  $\text{cm}^{-1}$ .

**HRMS** (ESI) calcd for  $\text{C}_{15}\text{H}_{17}\text{BrNO}_6$   $[\text{M}+\text{H}]^-$  386.0239, found 386.0192.

### 3.5.17 Synthesis of (*R*)-diethyl 2-(2-nitro-1-(2-nitrophenyl)ethyl)malonate (**46r**)

To a stirred solution of (*E*)-1-nitro-2-(2-nitrovinyl)benzene (**44r**) (0.2 mmol, 38.8 mg) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl malonate (**45**) (64 mg, 61  $\mu\text{L}$ , 0.4 mmol) at room temperature for 3 hours to obtain the product **46r** with 65% yield (46 mg) as a colorless oil.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (dd,  $J = 8.1, 1.3$  Hz, 1H, *ArH*), 7.52 (td,  $J = 7.6, 1.3$  Hz, 1H, *ArH*), 7.44 – 7.32 (m, 2H,  $2\times\text{ArH}$ ), 5.09 (dd,  $J = 13.8, 7.9$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.98 (dd,  $J = 13.8, 4.3$  Hz, 1H, *CHHNO*<sub>2</sub>), 4.67 (td,  $J = 8.1, 4.3$  Hz, 1H, *CHCH*<sub>2</sub>), 4.21 – 4.09 [m, 3H, *CH*<sub>2</sub>*CH*<sub>3</sub>, *CH*(*CO*<sub>2</sub>*Et*)<sub>2</sub>], 4.05 – 3.94 (m, 2H, *CH*<sub>2</sub>*CH*<sub>3</sub>), 1.19 (dd,  $J = 9.0, 5.2$  Hz, 3H, *CH*<sub>3</sub>), 1.03 (t,  $J = 7.1$  Hz, 3H, *CH*<sub>3</sub>) ppm.

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.3 (*C=O*), 165.6 (*C=O*), 149.0 (*ArCNO*<sub>2</sub>), 132.3 (*ArCCH*), 130.3 (*ArCH*), 128.3 (*ArCH*), 124.4 ( $2\times\text{ArCH}$ ), 75.2 (*CH*<sub>2</sub>*NO*<sub>2</sub>),

61.3 ( $\text{CH}_2\text{CH}_3$ ), 61.2 ( $\text{CH}_2\text{CH}_3$ ), 52.6 [ $\text{CH}(\text{CO}_2\text{Et})_2$ ], 36.7 ( $\text{CHCH}_2$ ), 12.9 ( $\text{CH}_3$ ), 12.7 ( $\text{CH}_3$ ) ppm.

**HPLC** (Chiralpak AS-H, 98:2 n-hexane/isopropyl alcohol, 1 mL/min, 215 nm):  
 $t_{\text{major}} = 47.570$  min,  $t_{\text{minor}} = 64.163$ ; 80% ee.

$[\alpha]_{\text{D}}^{25} = -3.48$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>51</sup>  $[\alpha]_{\text{D}}^{25} = +1.6$  ( $c$  0.8,  $\text{CHCl}_3$ ), [87% ee, (*S*)-enantiomer].

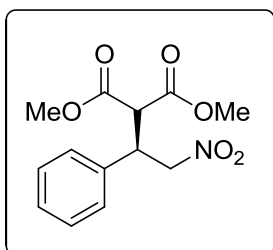
### 3.6 General Procedure for Asymmetric Michael Additions of Malonates to *trans*- $\beta$ -nitrostyrene

To a stirred solution of *trans*- $\beta$ -nitrostyrene (29.8 mg, 0.2 mmol) and 2-aminoDMAP/urea (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added malonate derivatives (0.4 mmol) at room temperature under argon. The reaction mixture was stirred until disappearance of the nitroolefin by TLC. The reaction mixture was directly subjected to flash column chromatography over silica gel using EtOAc/n-hexanes as the eluant to afford the conjugate addition products.

#### 3.6.1 Synthesis of (*R*)-dimethyl 2-(2-nitro-1-phenylethyl)malonate (**60a**)

To a stirred solution of *trans*- $\beta$ -nitrostyrene (**44b**) (29.8 mg, 0.2 mmol) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added dimethyl malonate (**59a**) (52.8 mg, 45.8  $\mu\text{L}$ , 0.4 mmol) at room

temperature for 4 hours to obtain the product **60a** with 88% yield (49 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.29 – 7.12 (m, 5H, **5xArH**), 4.89 – 4.77 (m, 2H **CHHNO<sub>2</sub>**, **CHHNO<sub>2</sub>**), 4.18 (td, *J* = 8.9, 5.3 Hz, 1H, **CHCH<sub>2</sub>**), 3.80 [d, *J* = 9.1 Hz, 1H, **CH(CO<sub>2</sub>Me)<sub>2</sub>**], 3.69 (s, 3H, **CH<sub>3</sub>**), 3.49 (s, 3H, **CH<sub>3</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.8 (**C=O**), 166.2 (**C=O**), 135.1 (**ArC**), 128.0, 127.4, 126.84 (**5xArCH**), 76.4 (**CHCH<sub>2</sub>**), 53.8 [**CH(CO<sub>2</sub>Me)<sub>2</sub>**], 52.0 (**CH<sub>3</sub>**), 51.8 (**CH<sub>3</sub>**), 41.9 (**CHCH<sub>2</sub>**) ppm.

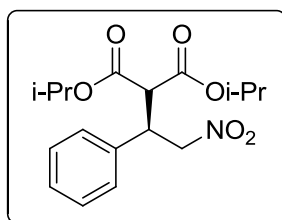
**HPLC** (Chiralpak AD, 90:10 n-hexane/isopropyl alcohol, 1 mL/min, 220 nm) *t*<sub>major</sub> = 17.757 min, *t*<sub>minor</sub> = 24.360; 92% ee.

$[\alpha]_{\text{D}}^{25} = -0.74$  (*c* 1.0, CHCl<sub>3</sub>).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup>  $[\alpha]_{\text{D}}^{25} = -2.5$  (*c* 1.04, CH<sub>2</sub>Cl<sub>2</sub>), [89% ee, (*R*)-enantiomer].

### 3.6.2 Synthesis of (*R*)-diisopropyl 2-(2-nitro-1-phenylethyl)malonate (**60b**)

To a stirred solution of *trans*-β-nitrostyrene (**44b**) (29.8 mg, 0.2 mmol) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diisopropyl malonate (**59b**) (75.3 mg, 76 μL, 0.4 mmol) at room temperature for 5 hours to obtain the product **60b** with 93% yield (63 mg) as a colorless oil.



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 – 7.14 (m, 5H,  $5\times\text{ArH}$ ), 5.01 [hept,  $J = 6.3$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ], 4.86 (dd,  $J = 12.9, 4.6$  Hz, 1H,  $\text{CHHNO}_2$ ), 4.82 – 4.71 (m, 2H,  $\text{CH}(\text{CH}_3)_2$ ,  $\text{CHHNO}_2$ ), 4.14 (td,  $J = 9.5, 4.6$  Hz, 1H,  $\text{CHCH}_2$ ), 3.69 [d,  $J = 9.6$  Hz, 1H,  $\text{CH}(\text{CO}_2i\text{-Pr})_2$ ], 1.18 (d,  $J = 6.3$  Hz, 6H,  $2\times\text{CH}_3$ ), 1.00 (d,  $J = 6.3$  Hz, 3H,  $\text{CH}_3$ ), 0.95 (t,  $J = 6.5$  Hz, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  166.1 ( $\text{C=O}$ ), 165.3 ( $\text{C=O}$ ), 135.3 ( $\text{ArC}$ ), 129.5, 127.9, 127.3, 127.1 ( $5\times\text{ArCH}$ ), 76.9 ( $\text{CHCH}_2$ ), 68.9 [ $\text{CH}(\text{CH}_3)_2$ ], 68.5 [ $\text{CH}(\text{CH}_3)_2$ ], 54.2 [ $\text{CH}(\text{CO}_2i\text{-Pr})_2$ ], 41.9 ( $\text{CHCH}_2$ ), 29.9 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ), 20.4 ( $\text{CH}_3$ ), 20.3 ( $\text{CH}_3$ ) ppm.

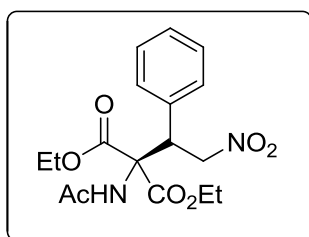
**HPLC** (Chiralpak AD, 95:5 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{major}} = 19.500$  min,  $t_{\text{minor}} = 42.532$ ; 85% ee.

$[\alpha]_{\text{D}}^{25} = -6.60$  ( $c$  1.0,  $\text{CHCl}_3$ ).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>49</sup>  $[\alpha]_{\text{D}}^{25} = -6.5$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ), [89% ee, (*R*)-enantiomer].

### 3.6.3 Synthesis of (*R*)-diethyl 2-acetamido-2-(2-nitro-1-phenylethyl)malonate (**60c**)

To a stirred solution of trans- $\beta$ -nitrostyrene (**44b**) (29.8 mg, 0.2 mmol) and 2-aminoDMAP/urea **53** (4.89 mg, 5% mol, 0.01 mmol) in toluene (1 mL) was added diethyl 2-acetamido malonate (**59c**) (86.9 mg, 0.4 mmol) at room temperature for 24 hours to obtain the product **60c** with 93% yield (68 mg) as a colorless oil.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.22 (dd,  $J = 6.7, 3.6$  Hz, 3H, **3xArH**), 7.13 (ddd,  $J = 5.6, 4.7, 3.5$  Hz, 2H, **2xArH**), 6.64 (s, 1H, **NH**), 5.52 – 5.36 (m, 1H, **CHCH<sub>2</sub>**), 4.72 – 4.54 (m, 2H, **CH<sub>2</sub>CH<sub>3</sub>**), 4.28 – 4.16 (m, 2H, **CH<sub>2</sub>CH<sub>3</sub>**), 4.14 – 4.05 (m, 1H, **CHHNO<sub>2</sub>**), 3.98 (dq,  $J = 10.7, 7.2$  Hz, 1H, **CHHNO<sub>2</sub>**), 2.05 (s, 3H, **NHOCH<sub>3</sub>**), 1.20 (dd,  $J = 7.1, 2.6$  Hz, 3H, **CH<sub>3</sub>**), 1.17 (t,  $J = 7.2$  Hz, 3H, **CH<sub>3</sub>**) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 169.1 (**NHCOCH<sub>3</sub>**), 165.5 (**C=O**), 164.8 (**C=O**), 132.9 (**ArC**), 127.8, 127.8, 127.7 (**5xArCH**), 75.9, **CNH(CO<sub>2</sub>Et)<sub>2</sub>**, 66.3 (**CH<sub>2</sub>NO<sub>2</sub>**), 62.6 (**CH<sub>2</sub>CH<sub>3</sub>**), 61.8 (**CH<sub>2</sub>CH<sub>3</sub>**), 47.4 (**CHCH<sub>2</sub>**), 22.1 (**NHCOCH<sub>3</sub>**), 12.9 (**CH<sub>3</sub>**), 12.8 (**CH<sub>3</sub>**) ppm.

**HPLC** (Chiralpak OJ-H, 85:15 n-hexane/isopropyl alcohol, 1 mL/min, 215nm):  $t_{\text{minor}} = 19.695$ ,  $t_{\text{major}} = 27.980$  min; 66% ee.

$[\alpha]_{\text{D}}^{25} = +21.26$  ( $c$  1.0, CHCl<sub>3</sub>).

The absolute configuration was assigned as (*R*) by comparison of the optical rotation with the following literature value: Lit.<sup>48</sup>  $[\alpha]_{\text{D}}^{25} = -42.5$  ( $c$  1.04, CHCl<sub>3</sub>), [94% ee, (*S*)-enantiomer].



## CHAPTER 4

### CONCLUSION

In this study, the enantioselective Michael addition of diethyl malonate as Michael donor to nitroolefins as Michael acceptor catalyzed by bifunctional 2-aminoDMAP/Urea organocatalyst has been succeeded with excellent results in terms of chemical yield and enantioselectivity.

In the first step of this study, 2-aminoDMAP based thiourea and urea bifunctional organocatalysts were synthesized and tested for the enantioselective Michael addition of diethyl malonate to trans- $\beta$ -nitrostyrene. Bifunctional 2-aminoDMAP/Urea organocatalyst gave good results with faster conversion to Michael product, high yield and high enantiomeric excess value. After scanning some parameters such as catalyst loading, reaction media concentration, solvent and temperature, the optimum conditions was found for the enantioselective Michael addition of diethyl malone to trans- $\beta$ -nitrostyrene by using bifunctional 2-aminoDMAP/Urea organocatalyst. In the second step of this study, the activity of the novel 2-aminoDMAP/Urea organocatalyst in derivatization studies was tested at the optimum conditions in which the best results were obtained.

As a result, intended Michael addition adducts were obtained with high yield up to 95% and high enantioselectivity up to 99% in a short reaction duration with 5 mol% 2-aminoDMAP/Urea in toluene at room temperature.





## REFERENCES

- 1 Lin, G. Q.; Li, Y. M.; Chan, A. S. *Principles and applications of asymmetric synthesis*. John Wiley & Sons, **2003**.
- 2 Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*. 2nd ed.; Elsevier, The Netherlands, **2012**.
- 3 Retrieved from  
[http://www.nobelprize.org/nobel\\_prizes/chemistry/laureates/2001/advanced-chemistryprize2001.pdf](http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/advanced-chemistryprize2001.pdf) (Last accessed on 01.01.2016)
- 4 Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*. University Science Books, **2009**, 2.
- 5 Zhou, J. *Multicatalyst system in asymmetric catalysis*. John Wiley & Sons, **2014**.
- 6 Goswami, A.; Stewart, J. D. *Organic Synthesis Using Biocatalysis*. Elsevier Inc., **2015**.
- 7 Zhou, Q. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 2–4.
- 8 Seayad, J.; List, B. Asymmetric organocatalysis. *Organic & biomolecular chemistry*. **2005**, *3*(5), 719-724.
- 9 Giacalone, F., Gruttadauria, M., Agrigento, P., Noto, R. *Chem. Soc. Rev.* **2012**, *41*(6), 2406-2447.
- 10 Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724.
- 11 Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.
- 12 Pellissier, H. *Tetrahedron*. **2007**, *63*, 9267–9331.
- 13 Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774-793.
- 14 von Liebig, J. *Ann.* **1860**, *113*, 246-247.
- 15 Bredig, G.; Fiske, W. S. *Biochem. Z.* **1912**, *46*, 7-23.
- 16 Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22.
- 17 Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.
- 18 Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.
- 19 Juliá, S.; Masana, J. C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929-931.
- 20 Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417-430.

- 21 Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Com.* **1981**, 183, 229-230.
- 22 Dolling, U.-H.; Davis, P.; Grabowski E. J. *J. Am. Chem. Soc.* **1984**, 106, 446.
- 23 Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, 119(46), 11224-11235.
- 24 Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, 120, 4901-4902.
- 25 Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, 1, 157-160.
- 26 Ahrendt, K. A.; Borths C.J.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2000**, 122, 4243-4244.
- 27 List, B.; Lerner, A. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, 122, 2395-2396.
- 28 Torres, R. R. *Stereoselective organocatalysis: bond formation methodologies and activation modes*. John Wiley & Sons, **2013**.
- 29 Berkessel, A.; Harald, G. *Asymmetric organocatalysis: from biomimetic concepts to applications in asymmetric synthesis*. John Wiley & Sons, **2006**.
- 30 MacMillan, D.W.C. *Nature* **2008**, 455, 304-308.
- 31 Ojima, I. *Catalytic asymmetric synthesis*. 3rd Edition; Wiley VCH: New York, **2010**.
- 32 Okino, T.; Hoashi, Y.; Furukawa, T.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, 127, 119-125.
- 33 Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, 41(6), pp. 2406-2447.
- 34 Andres, J. M.; Manzano, R.; Pedrosa, R. *Chem.–A Eur. J.* **2008**, 14(17), 5116-5119.
- 35 (a) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, 59, 3259; (b) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, 36, 6647.
- 36 a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, 4, 217-220. b) Schreiner, P. R.; Wittkopp, A. *Chem. Eur. J.* **2003**, 9, 407.
- 37 Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, 125, 12672-12673.
- 38 Miyabe, H.; Takemoto, Y. *Bulletin of the Chemical Society of Japan*. **2008**, 81(7), 785-795.

- 39 Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.
- 40 Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.
- 41 Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett.* **2005**, 603.
- 42 Vakulya, B.; Varga, S.; Csa'mpai, A.; Soo' s, T. *Org. Lett.* **2005**, *7*, 1967.
- 43 Kurti, L.; Czako', B. *Strategic applications of named reactions in organic synthesis.* Elsevier, **2005**.
- 44 Agarwal, J.; Naganaboina, R.T.; Peddinti, R.K. *Ind. J. Chem.* **2013**, *52*, 511-518.
- 45 Almaşı, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry.* **2007**, *18*, 299.
- 46 Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 238-241.
- 47 Isık, M.; Tanyeli, C. *J. Org. Chem.* **2013**, *78*, 1604–1611.
- 48 Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*(37), 11583-11592.
- 49 Almasi, D.; Alonso, D. A.; Gomez-Bengoa, E.; Najera, C. *J. Org. Chem.* **2009**, *74*(16), 6163-6168.
- 50 Lee, M.; Zhang, L.; Park, Y.; Park, H. G. *Tetrahedron*, **2012**, *68*(5), 1452-1459.
- 51 Andrés, J. M.; Manzano, R.; Pedrosa, R. *Chem.-A Euro. J.* **2008**, *14*(17), 5116-5119.
- 52 Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567.
- 53 Işıık, M. PhD. Thesis, METU, **2011**.

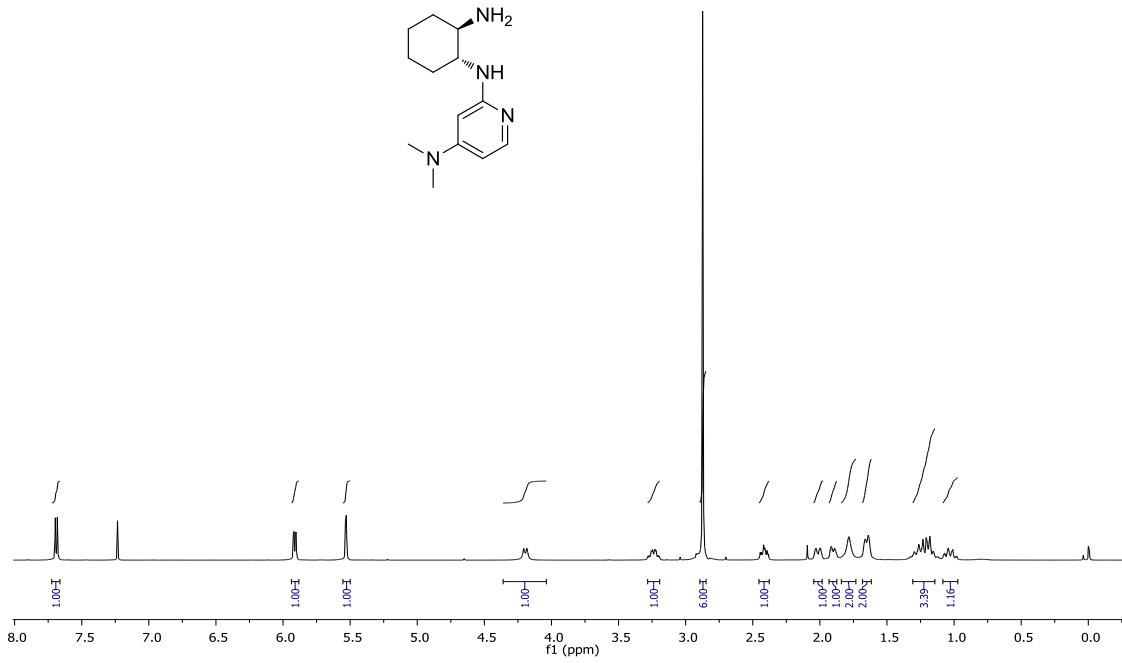


## APPENDICES

### A. SUPPORTING INFORMATION (NMR)

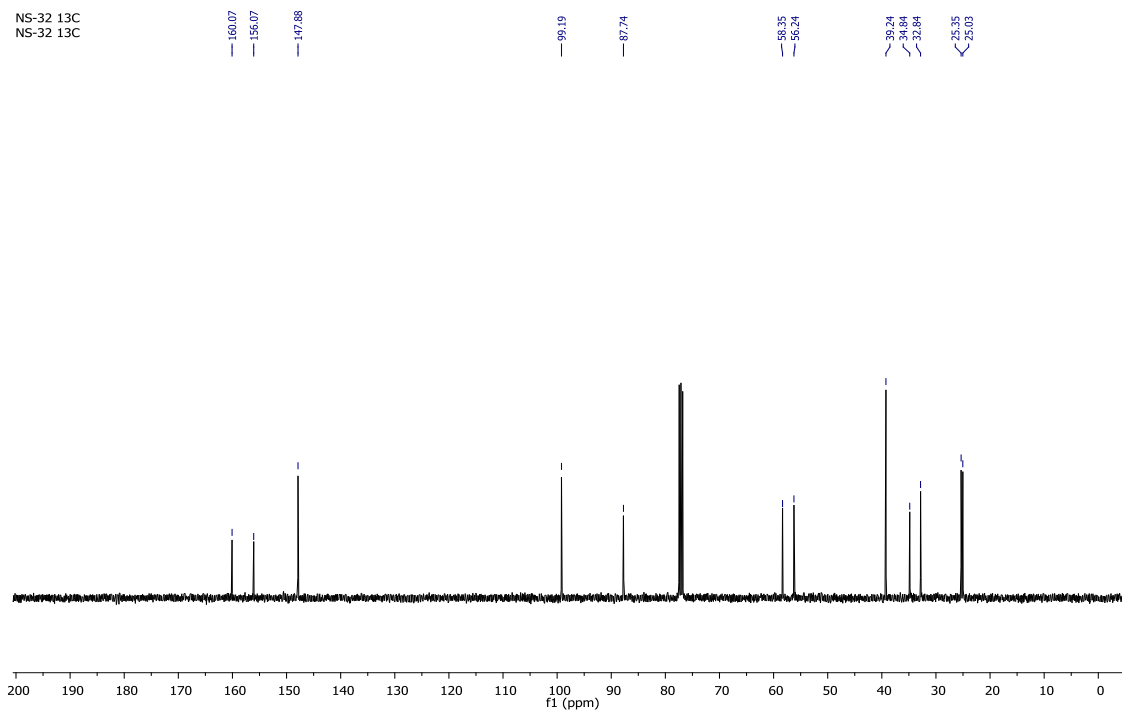
In this part,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR results of synthesized compounds in this study are presented in the following pages.

NS-32 1H  
NS-32 1H



**Figure A.1.** <sup>1</sup>H NMR spectrum of 2-aminoDMAP (compound 56)

NS-32 13C  
NS-32 13C



**Figure A.2.** <sup>13</sup>C NMR spectrum of 2-aminoDMAP (compound 56)

MI-402A 1H  
MI-402A 1H

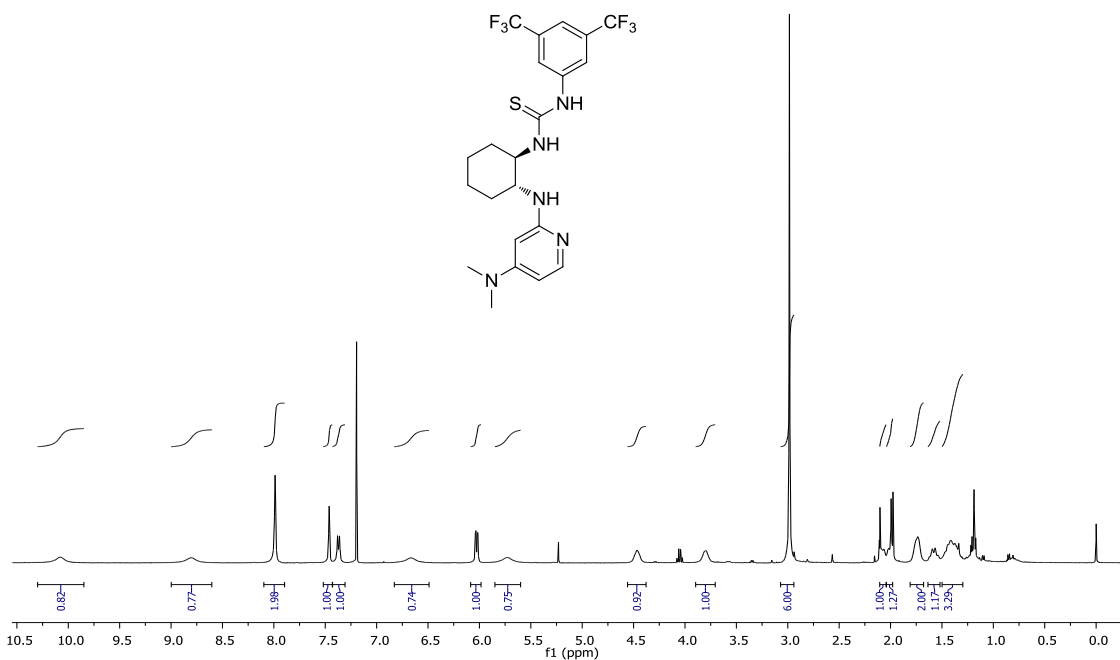


Figure A.3. <sup>1</sup>H NMR spectrum of 2-aminoDMAP/thiourea (compound 52)

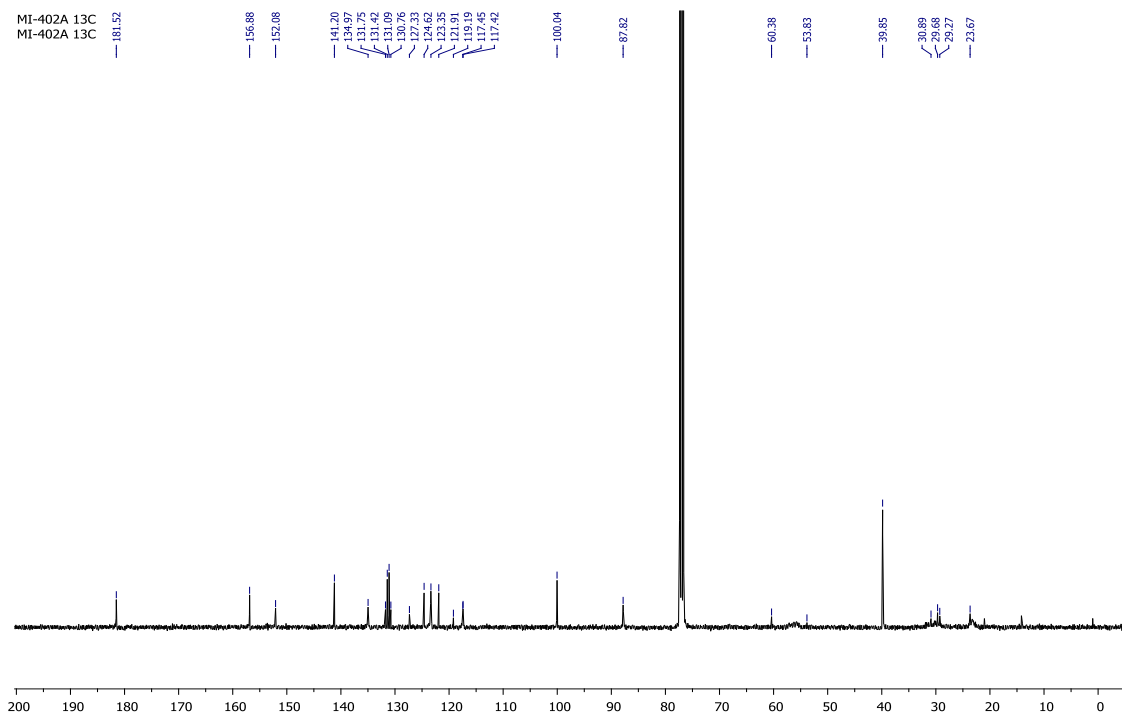
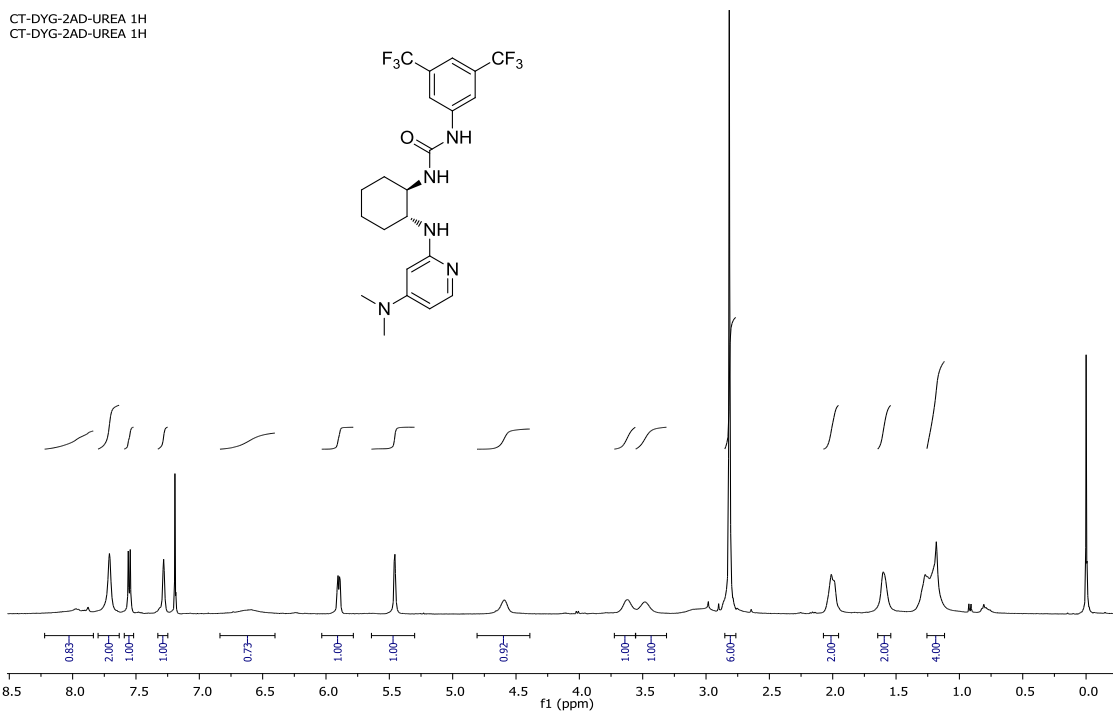
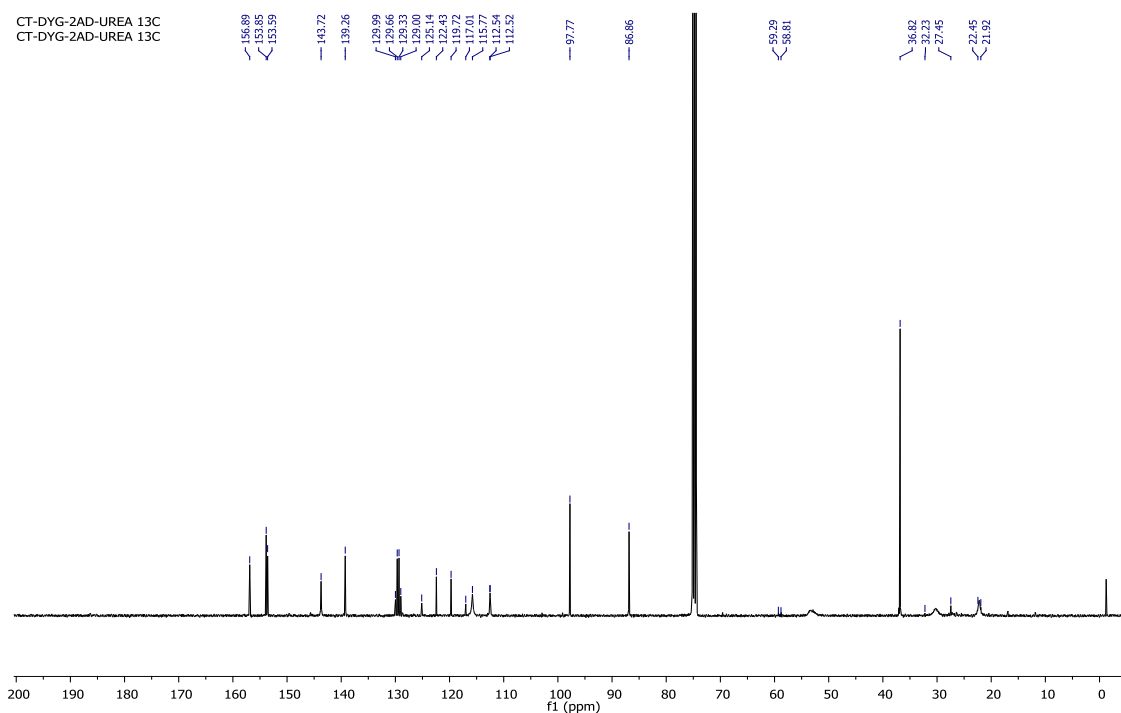


Figure A.4. <sup>13</sup>C NMR spectrum of 2-aminoDMAP/thiourea (compound 52)



**Figure A.5.** <sup>1</sup>H NMR spectrum of 2-aminoDMAP/urea (compound 53)



**Figure A.6.** <sup>13</sup>C NMR spectrum of 2-aminoDMAP/urea (compound 53)



CT-IRM-OBEN 1H  
CT-IRM-OBEN 1H

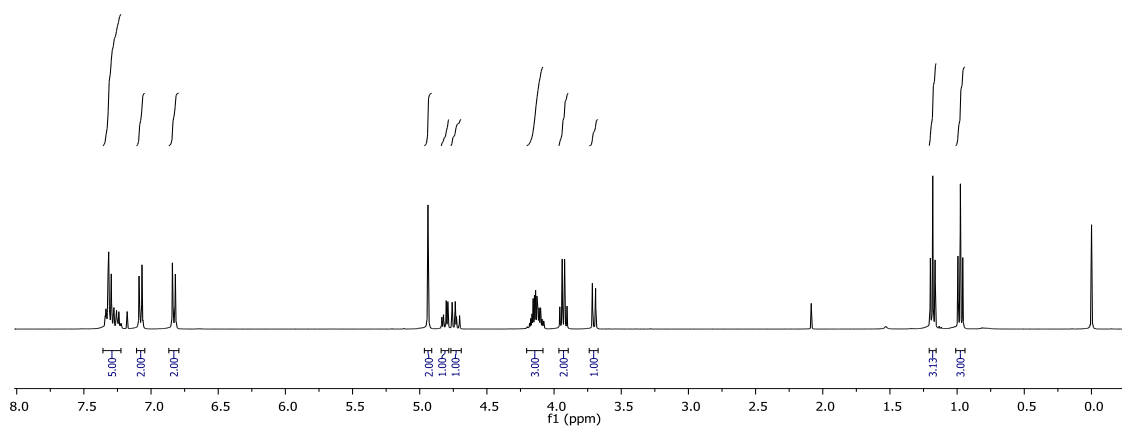
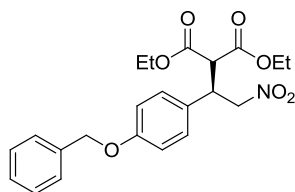


Figure A.7. <sup>1</sup>H NMR spectrum of Michael product 46a

CT-IRM-OBEN 13C  
CT-IRM-OBEN 13C

166.50  
165.86  
157.64  
135.72  
128.18  
127.57  
127.33  
127.01  
126.45  
114.19  
76.85  
68.97  
61.08  
60.82  
54.09  
41.31  
12.95  
12.77

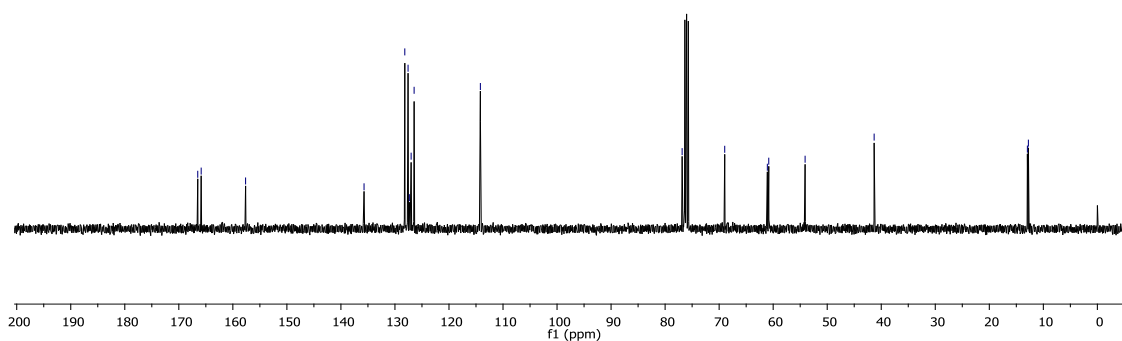


Figure A.8. <sup>13</sup>C NMR spectrum of Michael product 46a

IRMB-17 1H  
IRMB-17 1H

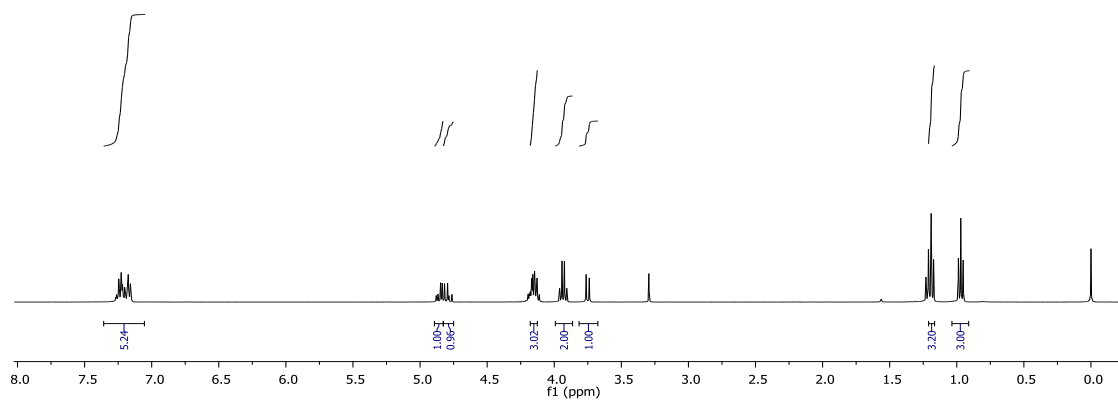
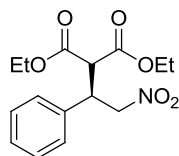


Figure A.9. <sup>1</sup>H NMR spectrum of Michael product 46b

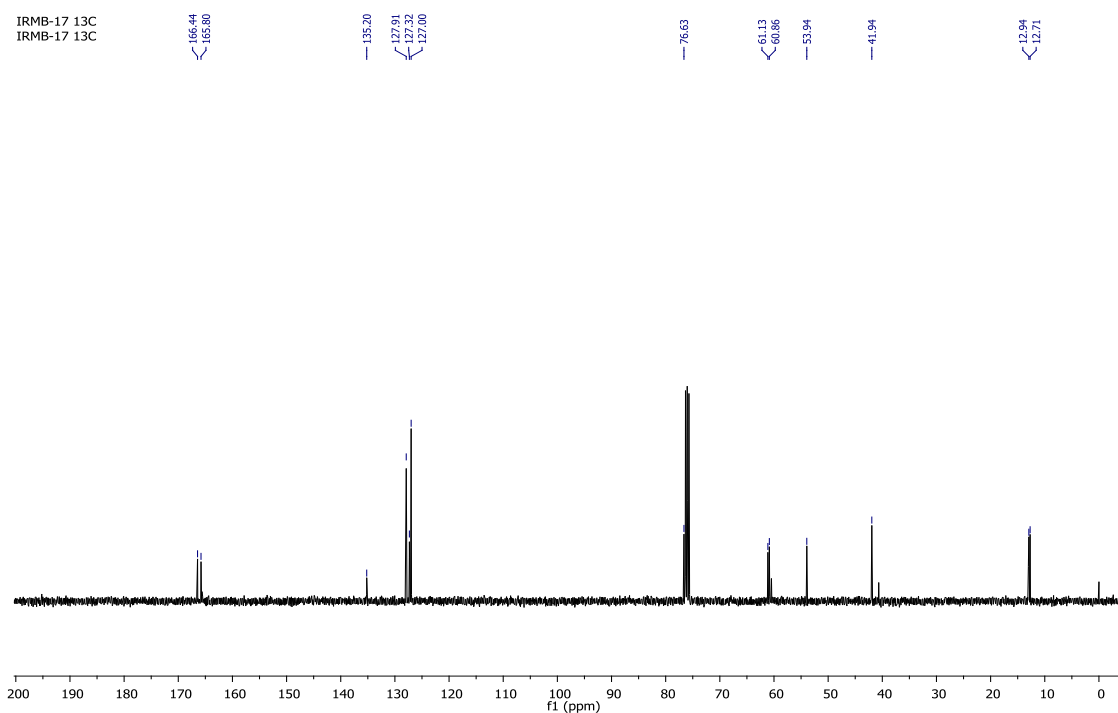


Figure A.9. <sup>13</sup>C NMR spectrum of Michael product 46b

CT-IRM-4MEOX 1H  
CT-IRM-4MEOX 1H

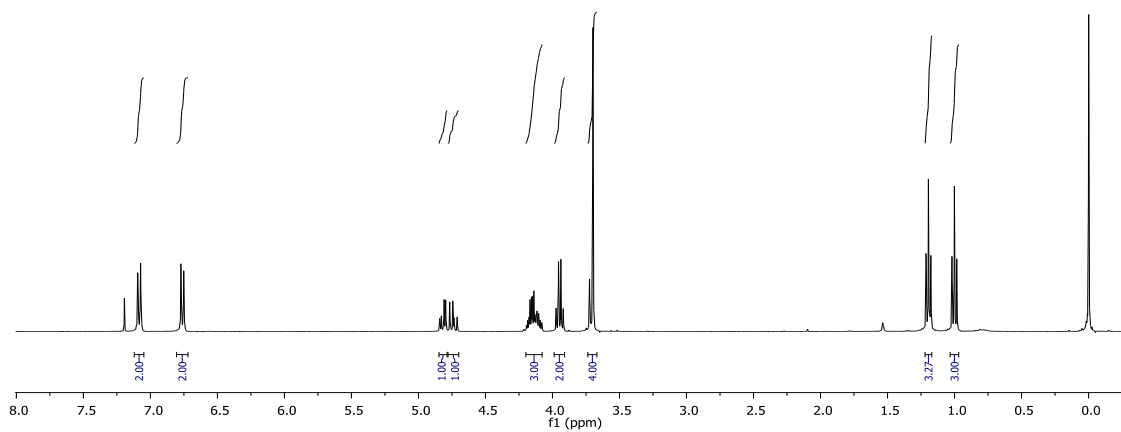
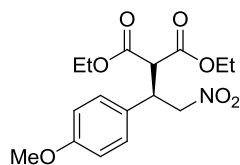


Figure A.10. <sup>1</sup>H NMR spectrum of Michael product 46c

CT-IRM-4MEOX 13C  
CT-IRM-4MEOX 13C

166.51  
165.86  
158.43  
128.14  
127.03  
113.28  
76.90  
61.08  
60.82  
54.20  
54.12  
41.32  
12.95  
12.78

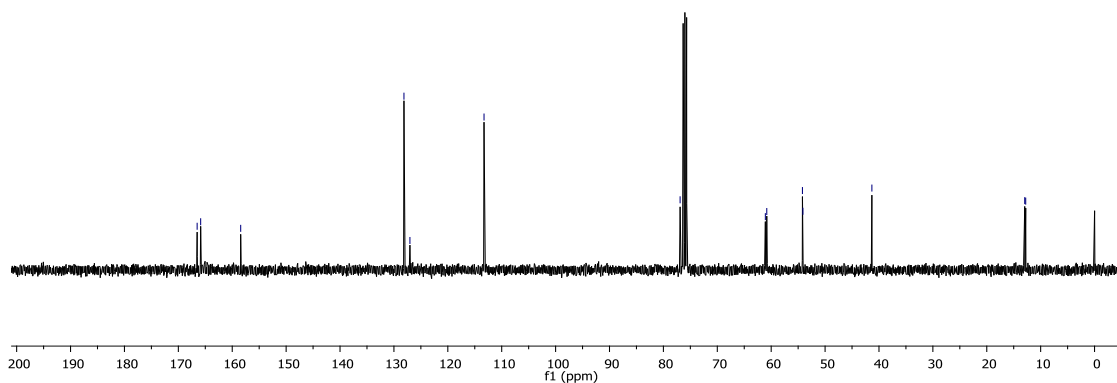


Figure A.11. <sup>13</sup>C NMR spectrum of Michael product 46c

CT-IRM-4F2 1H  
CT-IRM-4F2 1H

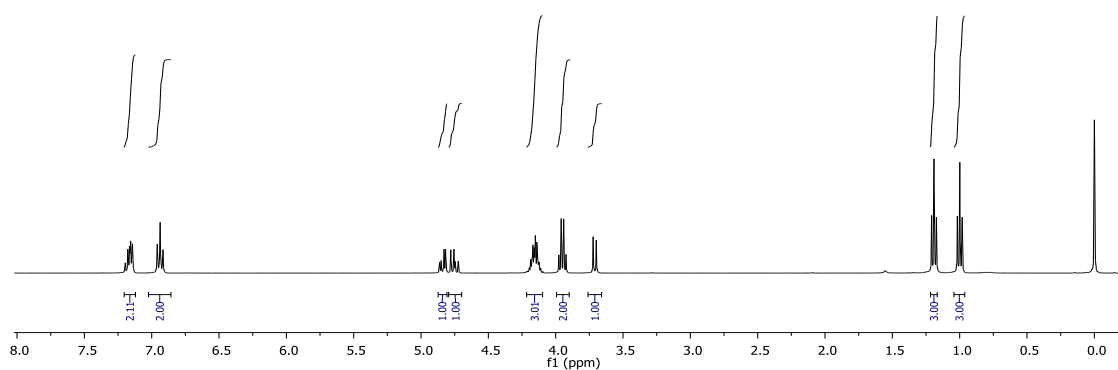
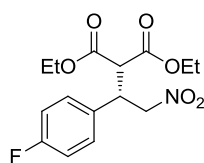


Figure A.12. <sup>1</sup>H NMR spectrum of Michael product 46d

CT-IRM-4F2 1H  
CT-IRM-4F2 13C

166.20  
165.70  
162.73  
160.27

131.03  
131.01  
128.55  
128.78

115.01  
114.80

76.65

61.21  
60.95

53.93

41.29

12.94  
12.75

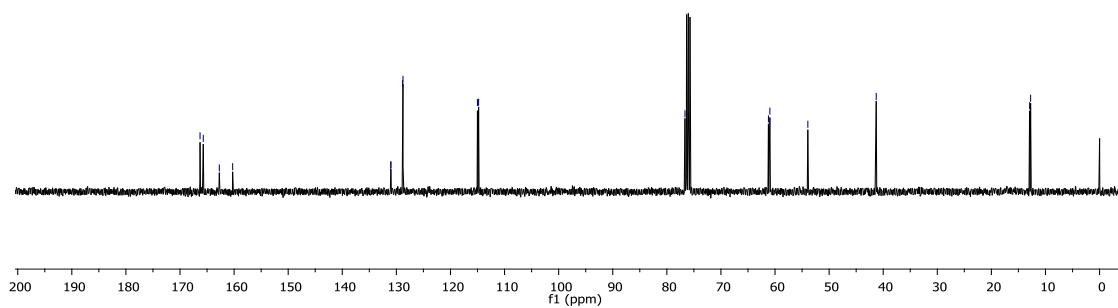


Figure A.13. <sup>13</sup>C NMR spectrum of Michael product 46d

CT-IRM-2F 1H  
CT-IRM-2F 1H

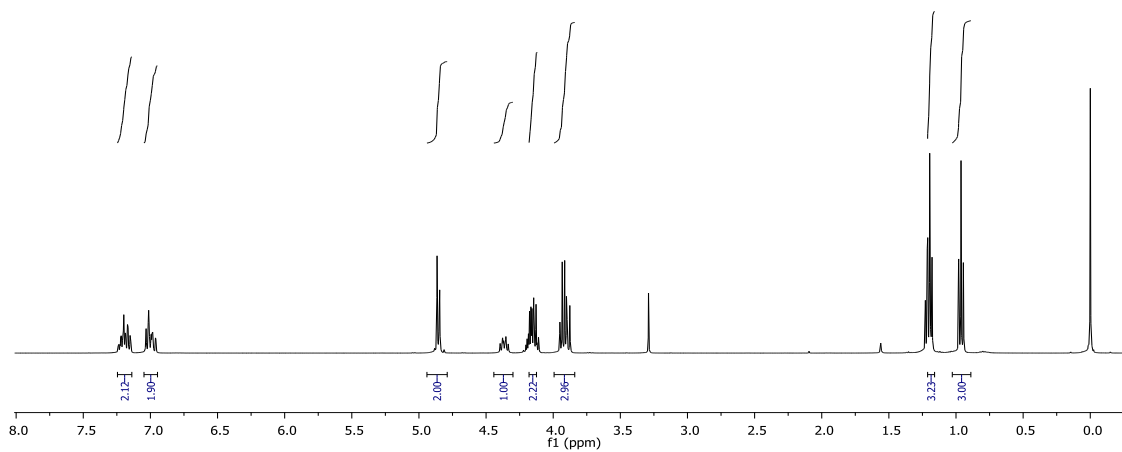
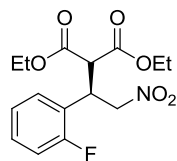


Figure A.14. <sup>1</sup>H NMR spectrum of Michael product 46e

CT-IRM-2F 1H  
CT-IRM-2F 13C

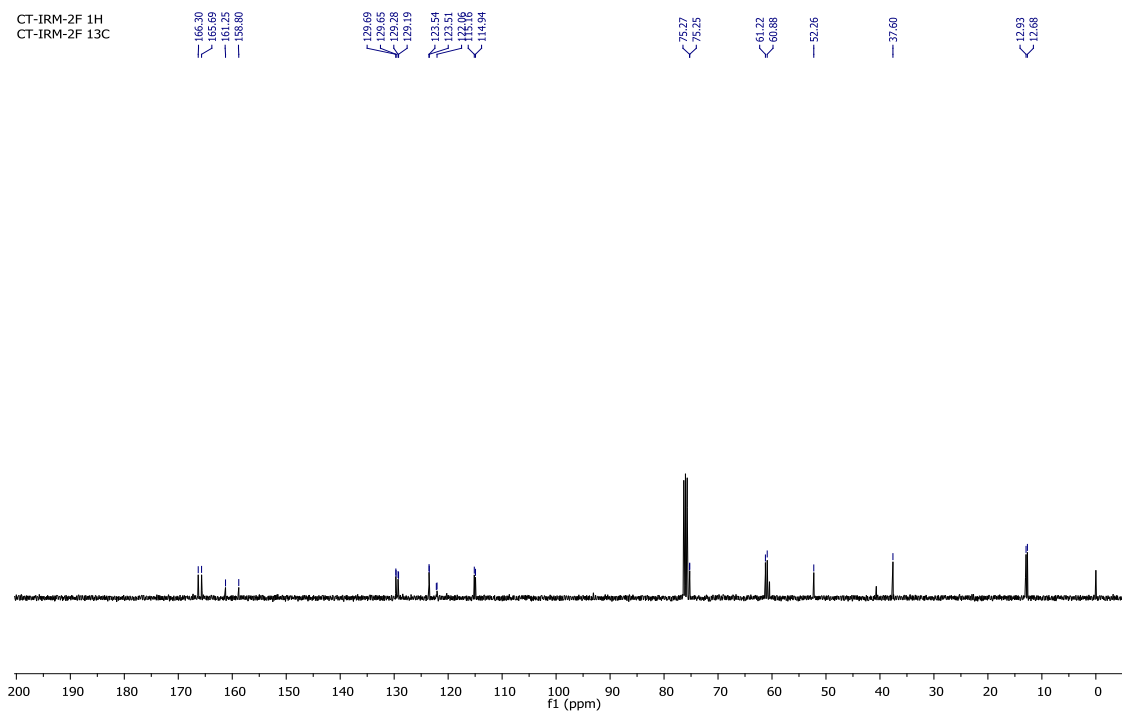


Figure A.15. <sup>13</sup>C NMR spectrum of Michael product 46e

CT-IRM-2-4 1H  
CT-IRM-2-4 1H

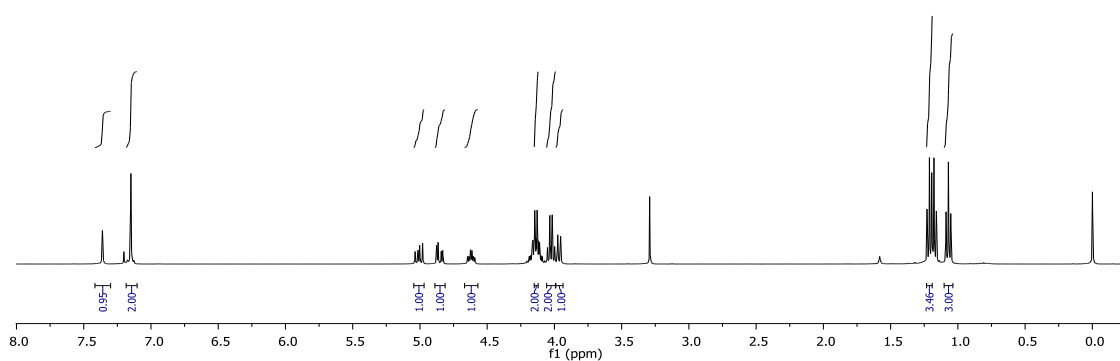
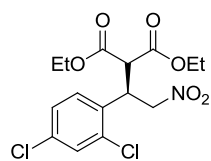


Figure A.16. <sup>1</sup>H NMR spectrum of Michael product 46f

CT-IRM-2-4 13C  
CT-IRM-2-4 13C

166.20  
165.63  
133.91  
133.80  
129.77  
128.76  
126.98  
74.50  
61.26  
61.17  
51.99  
40.67  
13.03  
12.83

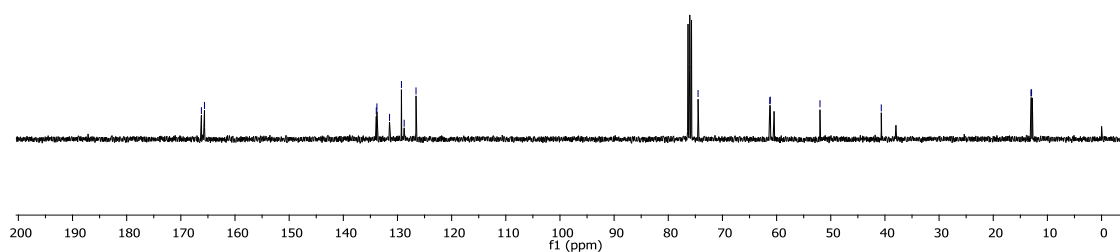


Figure A.17. <sup>13</sup>C NMR spectrum of Michael product 46f

CT-IRM-2MEOX 1H  
CT-IRM-2MEOX 1H

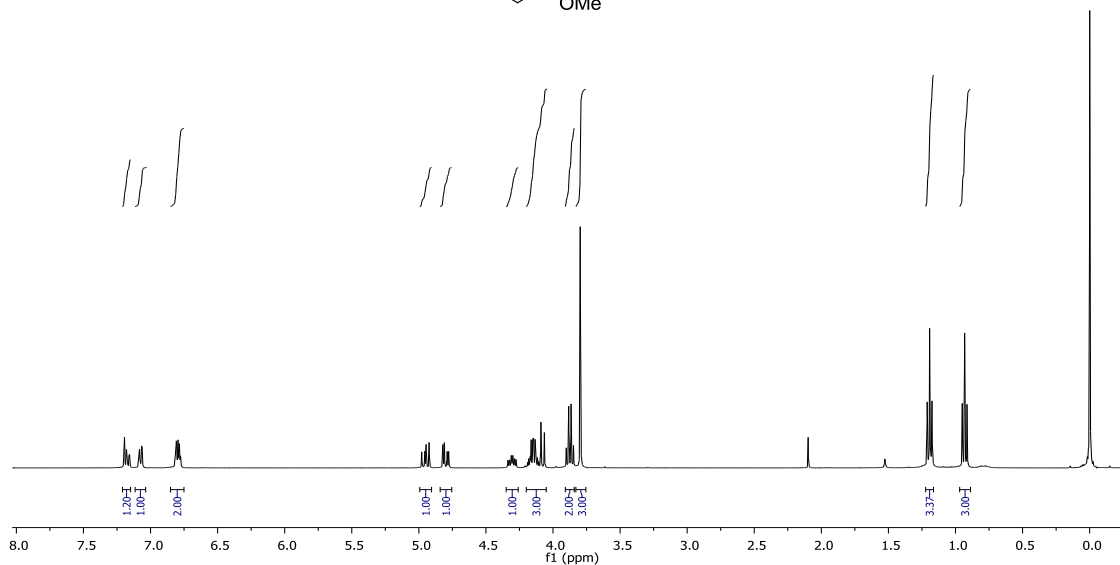
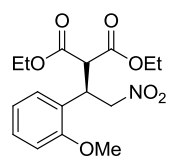


Figure A.18. <sup>1</sup>H NMR spectrum of Michael product 46g

CT-IRM-2MEOX 13C  
CT-IRM-2MEOX 13C

166.91  
166.17  
156.41  
129.85  
128.58  
122.76  
119.76  
110.07  
75.19  
60.93  
60.53  
54.40  
51.74  
39.46  
12.87  
12.71

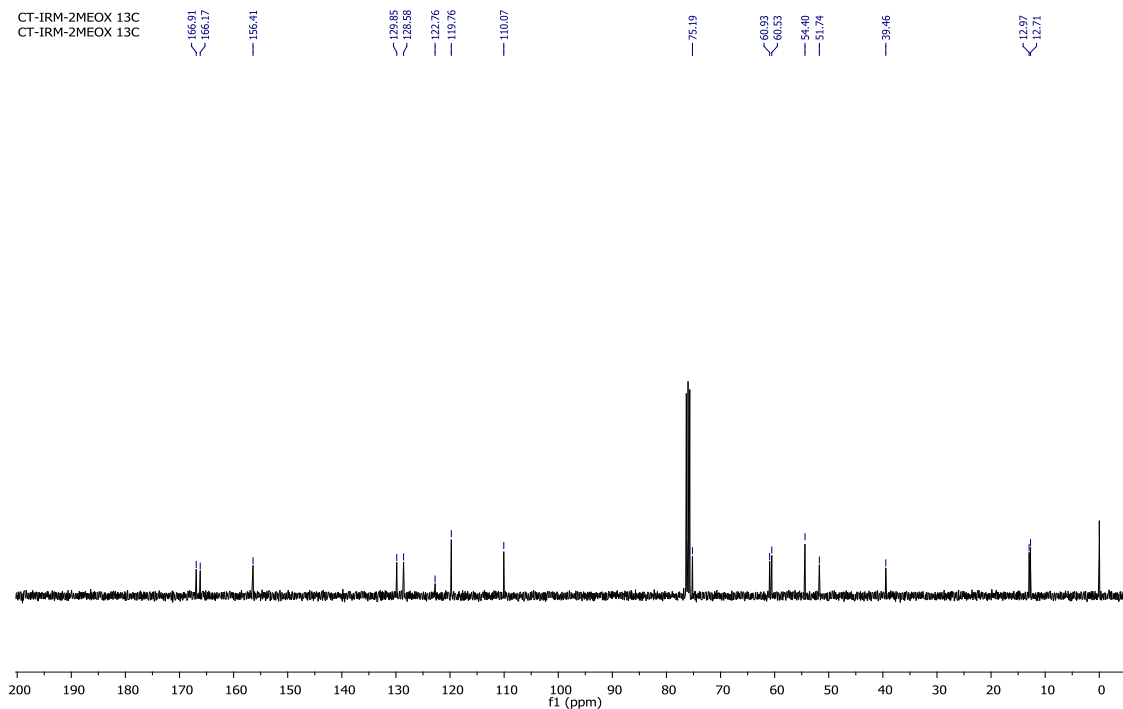


Figure A.19. <sup>13</sup>C NMR spectrum of Michael product 46g

CT-IRM-4BR 1H  
CT-IRM-4BR 1H

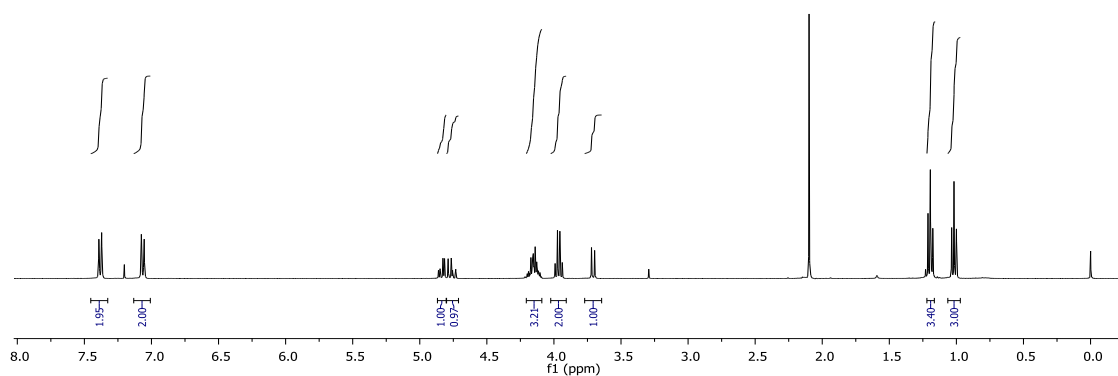
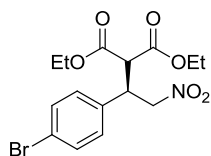


Figure A.20. <sup>1</sup>H NMR spectrum of Michael product 46h

CT-IRM-4BR 1H  
CT-IRM-4BR 13C

167.22  
156.62  
135.32  
132.11  
129.77  
122.45  
77.33  
62.28  
62.05  
54.69  
42.40  
13.95  
13.77

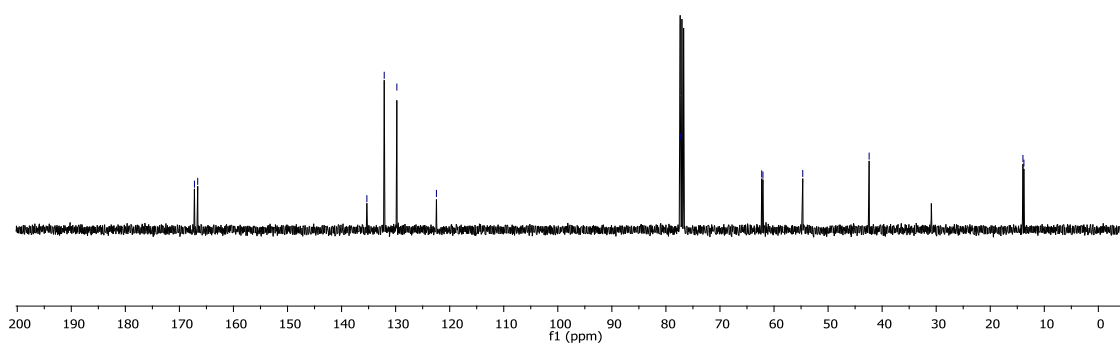


Figure A.21. <sup>13</sup>C NMR spectrum of Michael product 46h



CT-IRM-4ME 1H  
CT-IRM-4ME 1H

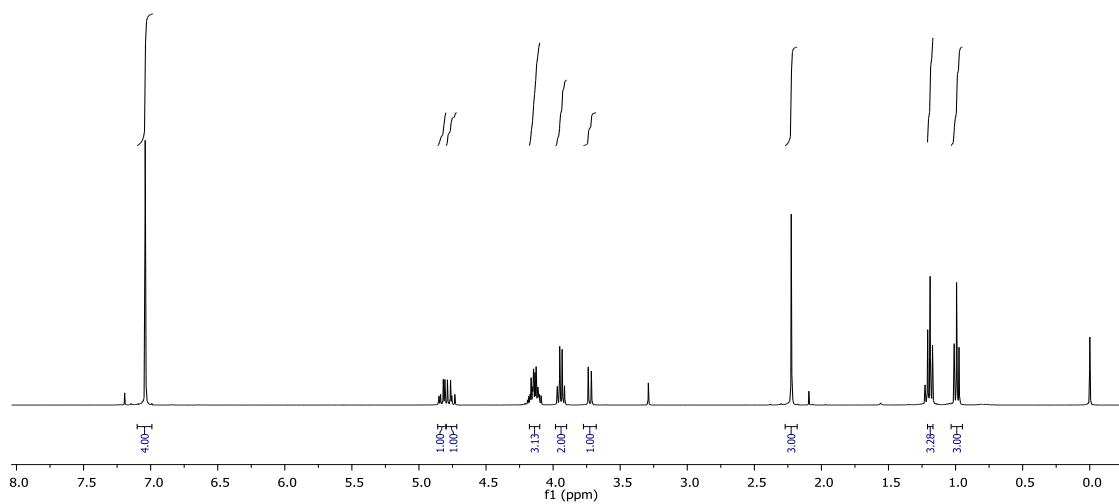
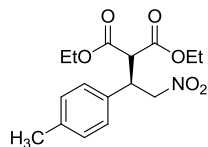


Figure A.22. <sup>1</sup>H NMR spectrum of Michael product 46i

CT-IRM-4ME 1H  
CT-IRM-4ME 13C

166.51  
165.85

137.05  
132.12  
128.98  
126.82

76.77

61.07  
60.82

54.04

41.62

20.03  
12.95  
12.73

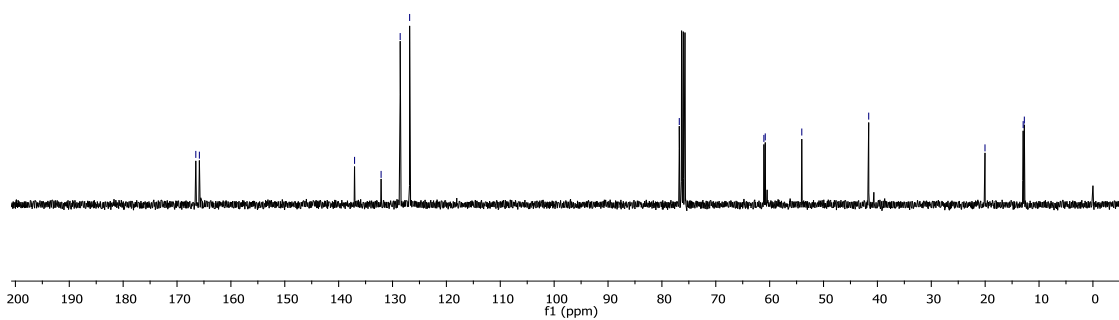


Figure A.23. <sup>13</sup>C NMR spectrum of Michael product 46i

CT-IRM-FUR 1H  
CT-IRM-FUR 1H

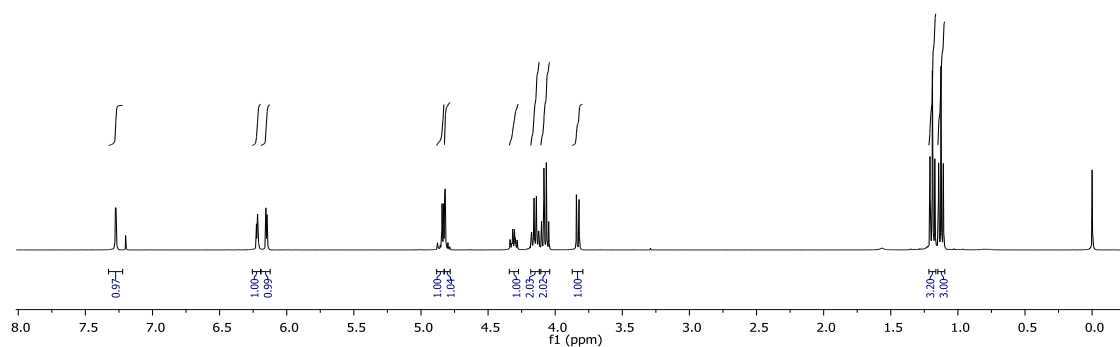
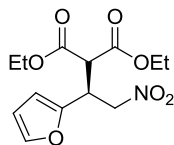


Figure A.24. <sup>1</sup>H NMR spectrum of Michael product 46j

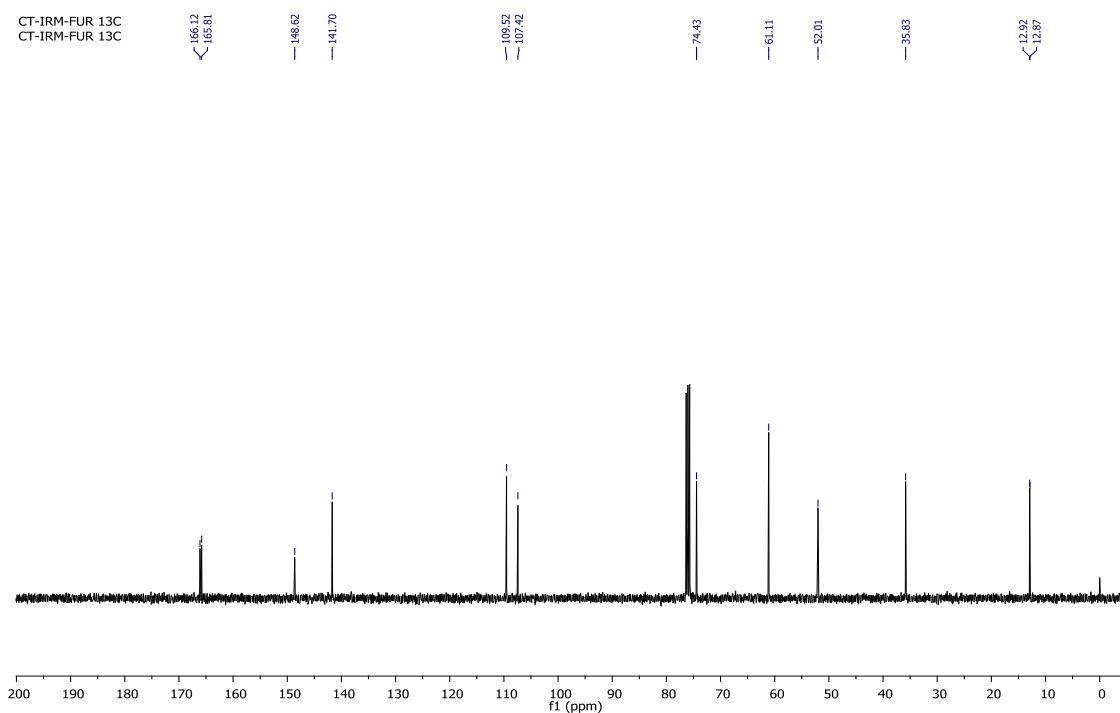


Figure A.25. <sup>13</sup>C NMR spectrum of Michael product 46j

CT-IRM-2CL 1H  
CT-IRM-2CL 1H

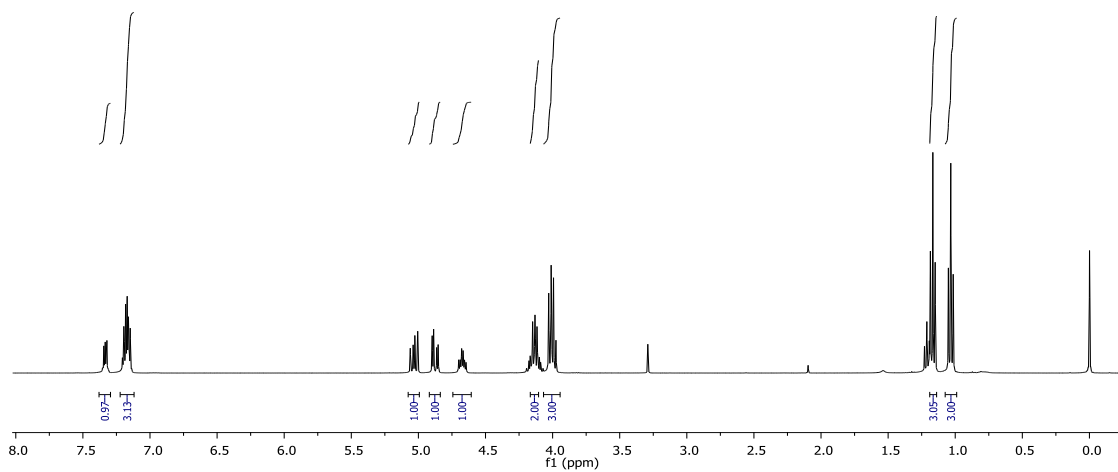
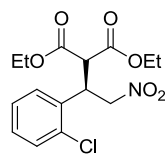


Figure A.26. <sup>1</sup>H NMR spectrum of Michael product 46k

CT-IRM-2CL 13C  
CT-IRM-2CL 13C

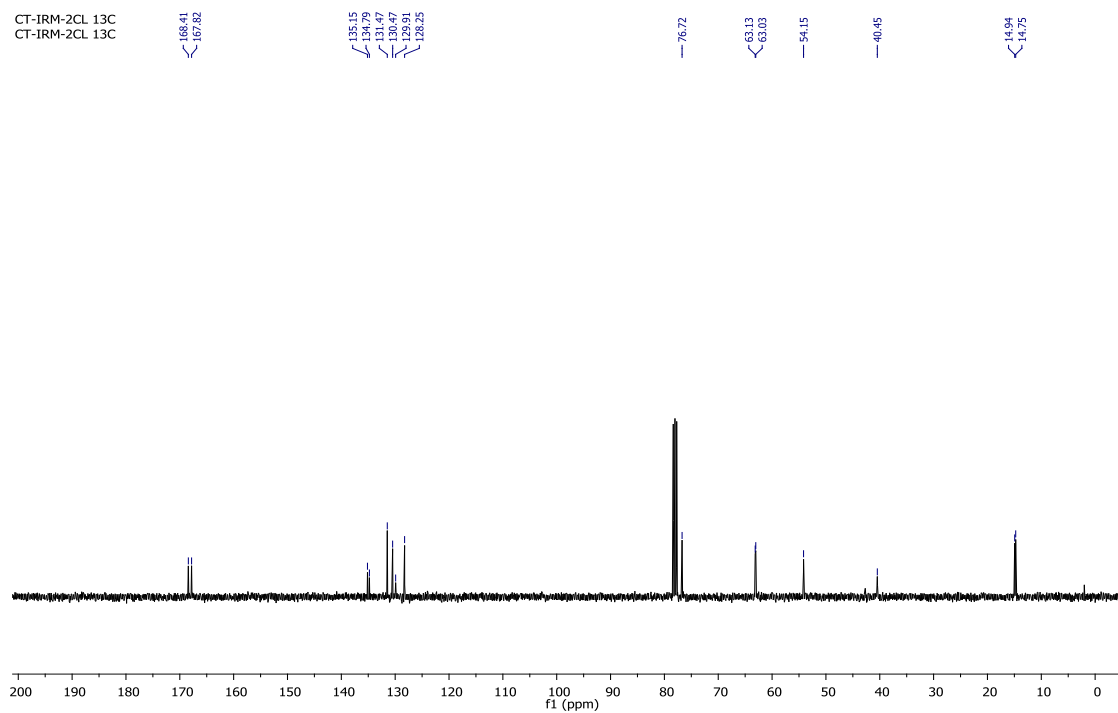


Figure A.27. <sup>13</sup>C NMR spectrum of Michael product 46k

CT-IRM-4Cl 1H  
CT-IRM-4Cl 1H

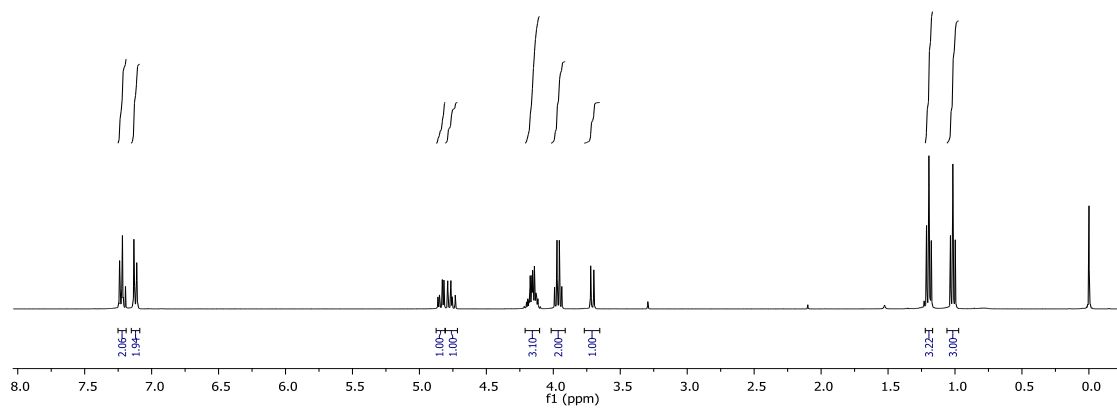
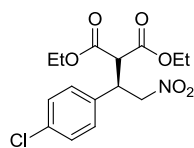


Figure A.28. <sup>1</sup>H NMR spectrum of Michael product 461

CT-IRM-4Cl 13C  
CT-IRM-4Cl 13C

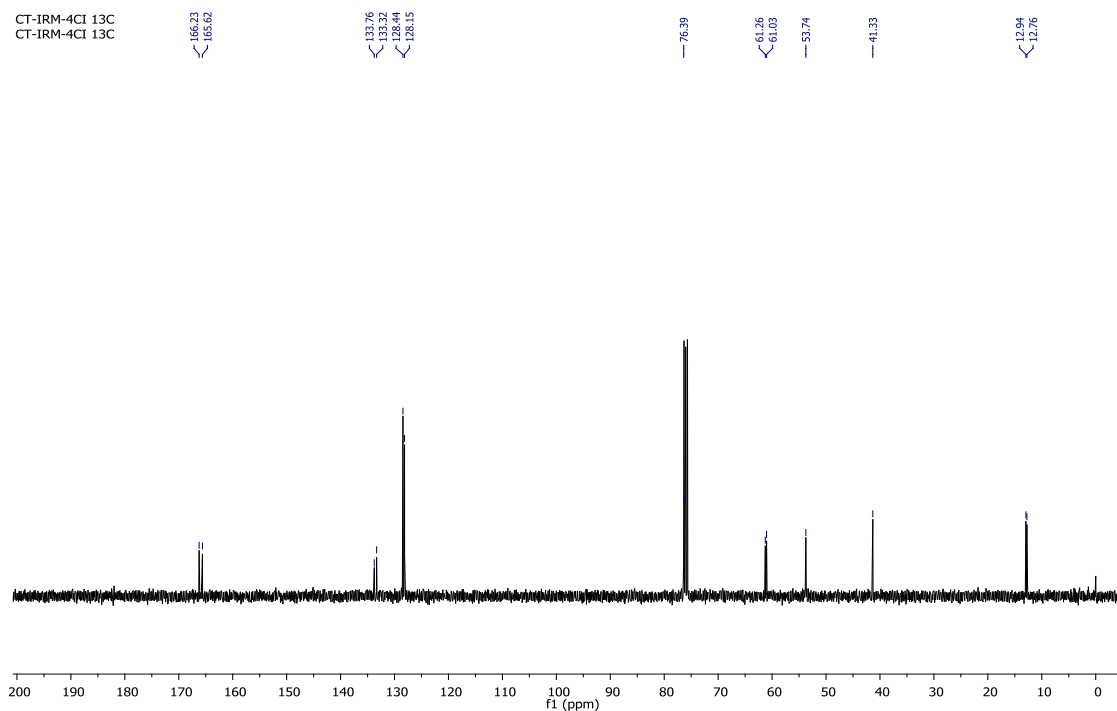


Figure A.29. <sup>13</sup>C NMR spectrum of Michael product 461

CT-IRM-3CL 1H  
CT-IRM-3CL 13C

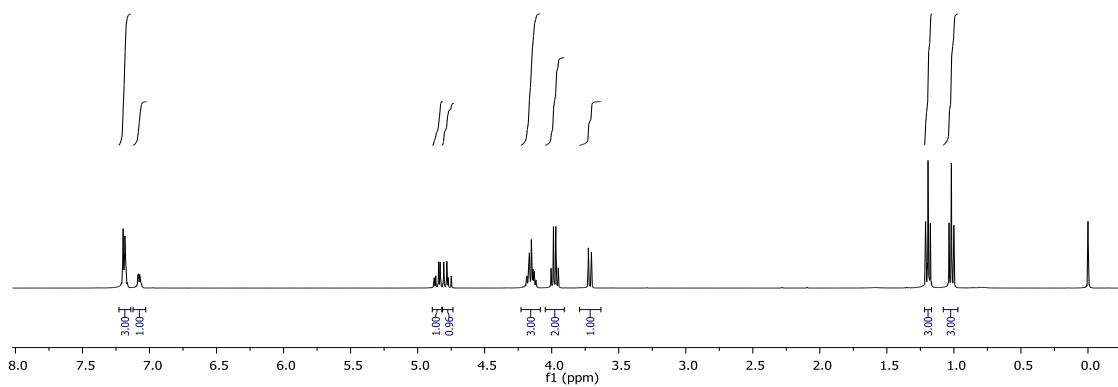
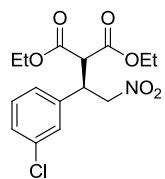


Figure A.30. <sup>1</sup>H NMR spectrum of Michael product 46m

CT-IRM-3CL 13C  
CT-IRM-3CL 1H

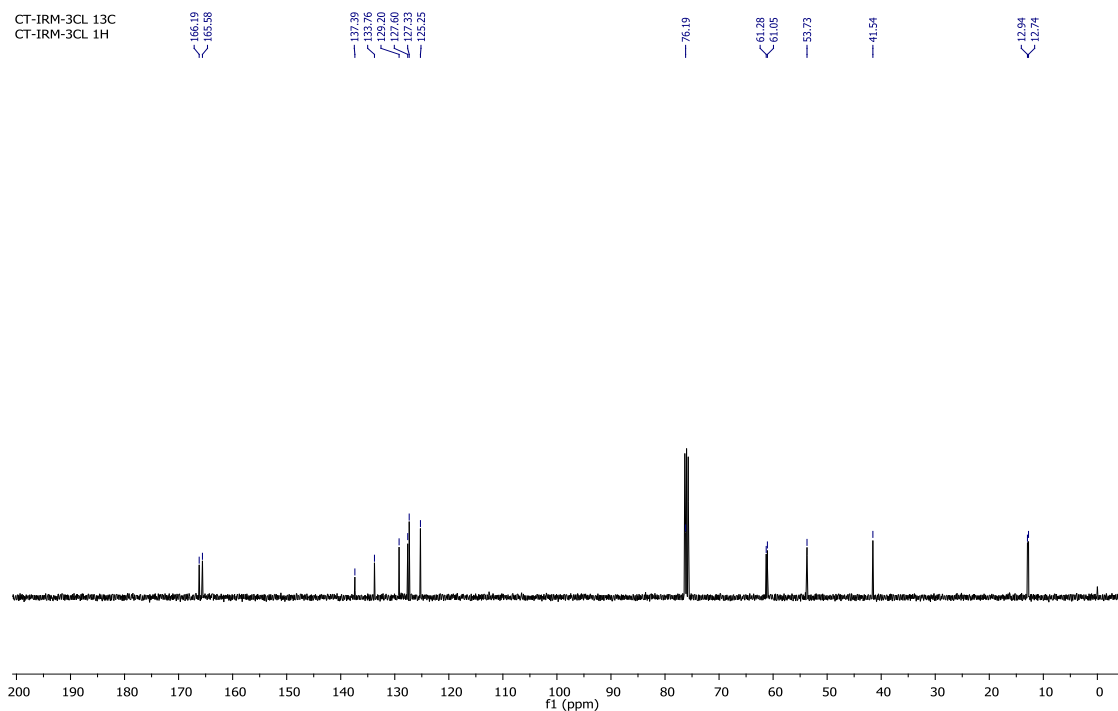


Figure A.31. <sup>13</sup>C NMR spectrum of Michael product 46m

CT-IRM-30ME 1H  
CT-IRM-30ME 1H

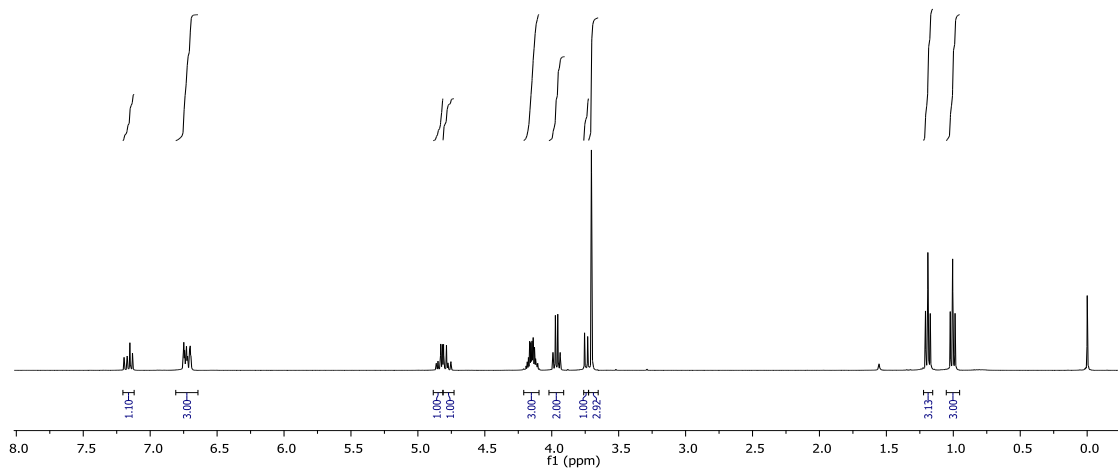
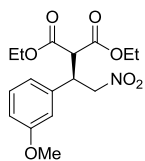


Figure A.32. <sup>1</sup>H NMR spectrum of Michael product **46n**

CT-IRM-30ME 13C  
CT-IRM-30ME 13C

166.46  
165.82  
158.86  
136.84  
128.95  
119.03  
113.05  
112.60  
76.57  
61.12  
60.88  
54.21  
53.96  
41.93  
12.84  
12.75

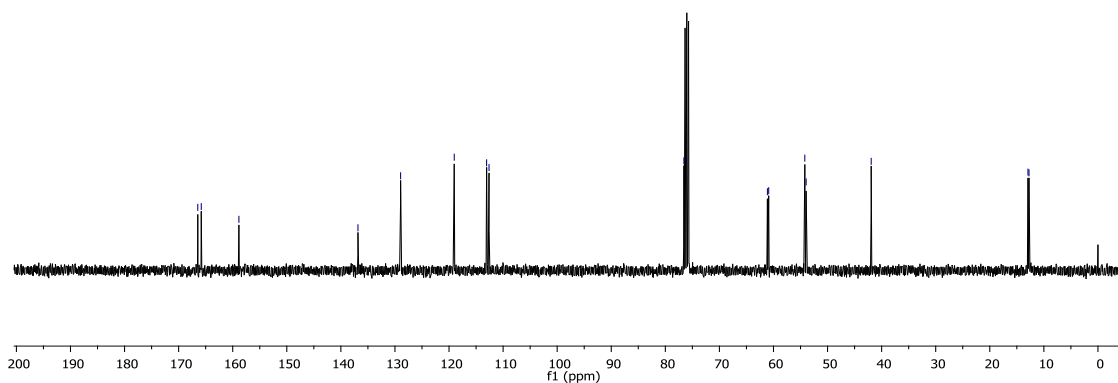


Figure A.33. <sup>13</sup>C NMR spectrum of Michael product **46n**

CT-IRM-THNIT 1H  
CT-IRM-THNIT 1H

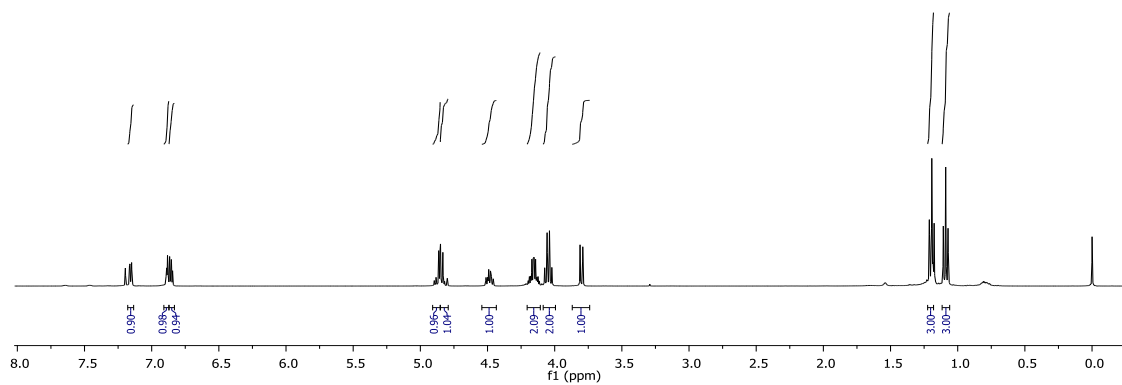
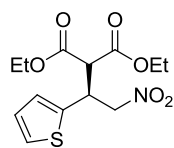


Figure A.34. <sup>1</sup>H NMR spectrum of Michael product 460

CT-IRM-THNIT 13C  
CT-IRM-THNIT 13C

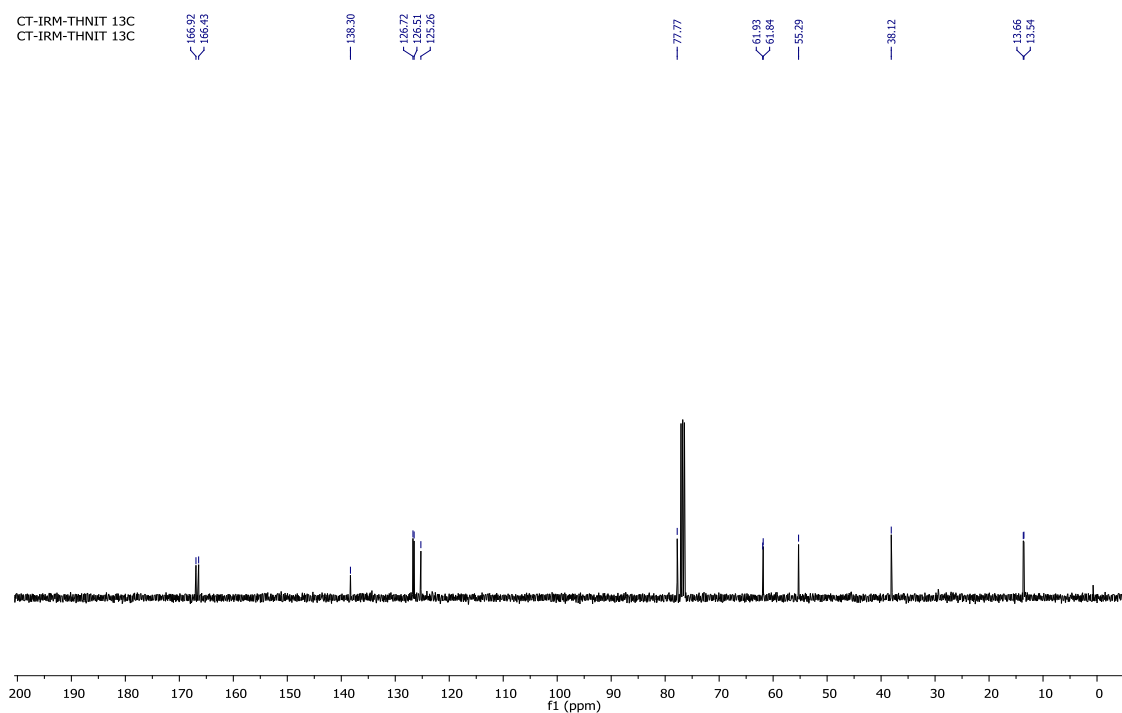


Figure A.35. <sup>13</sup>C NMR spectrum of Michael product 460

CT-IRM-3BR 1H  
CT-IRM-3BR 13C

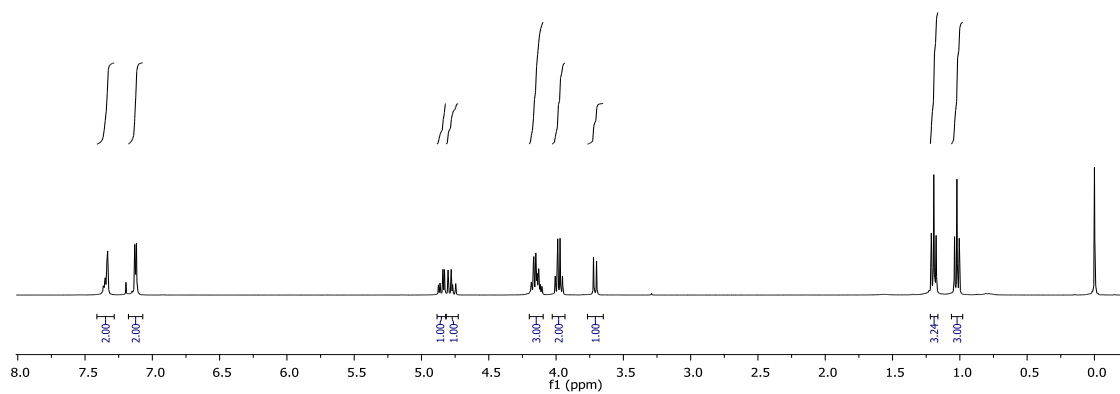
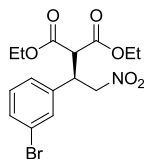


Figure A.36. <sup>1</sup>H NMR spectrum of Michael product 46p

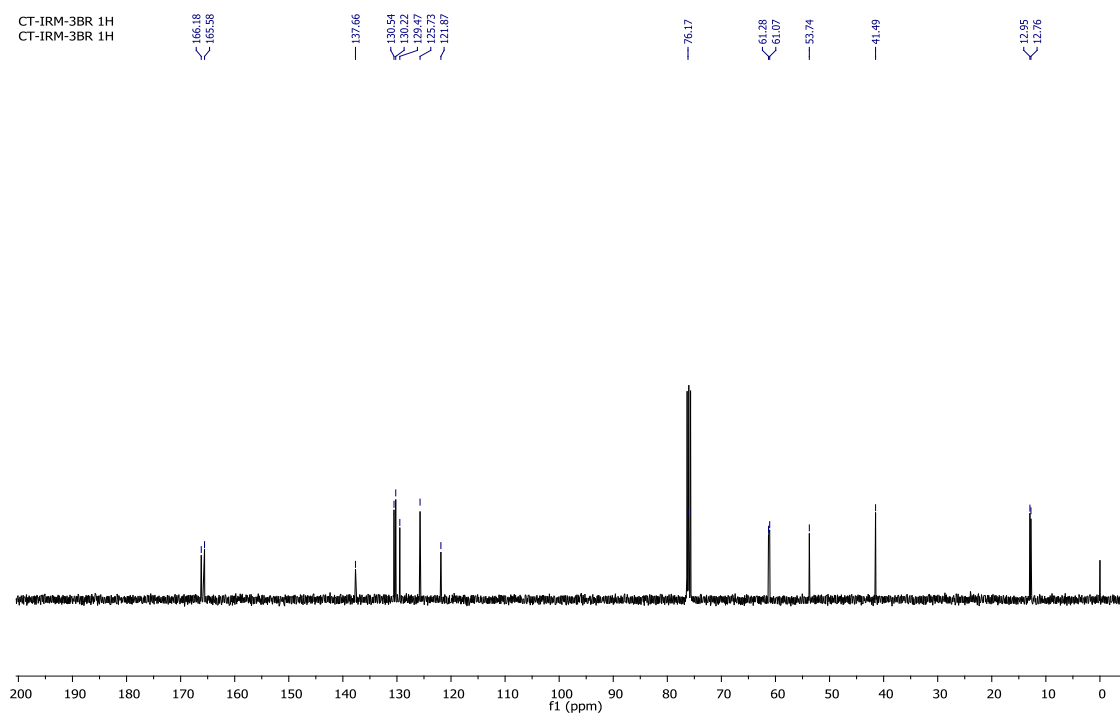
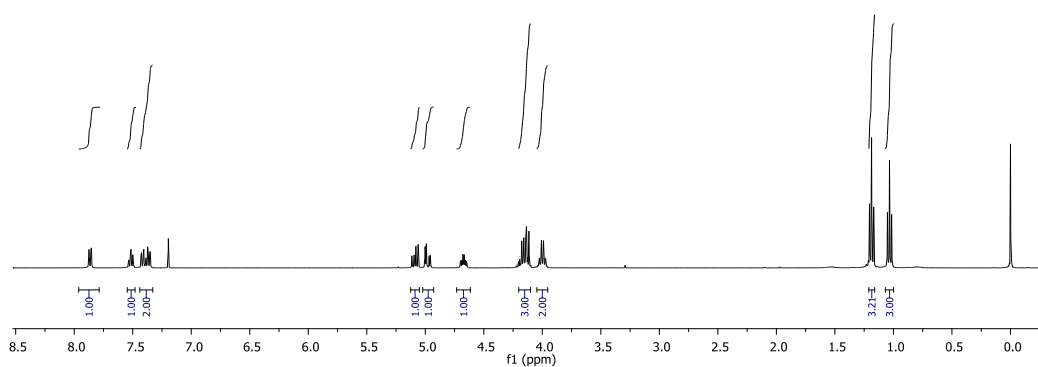
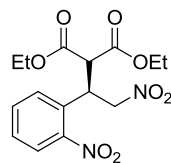


Figure A.37. <sup>13</sup>C NMR spectrum of Michael product 46p



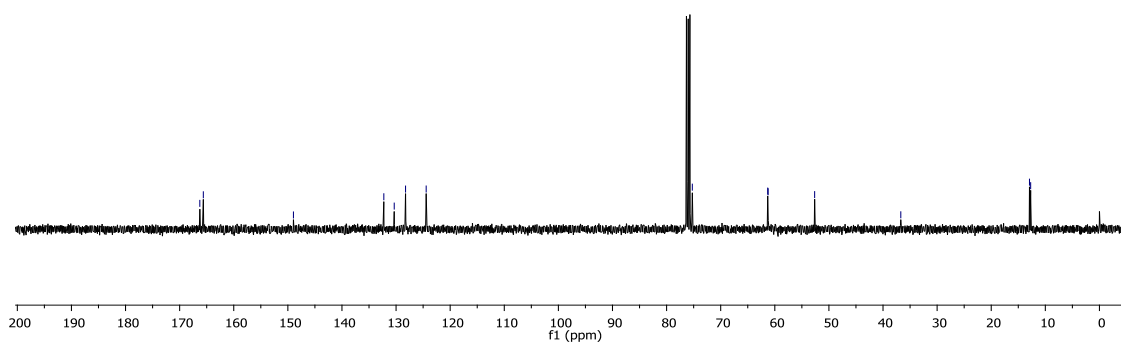
CT-IRM-NO2 1H  
CT-IRM-NO2 1H



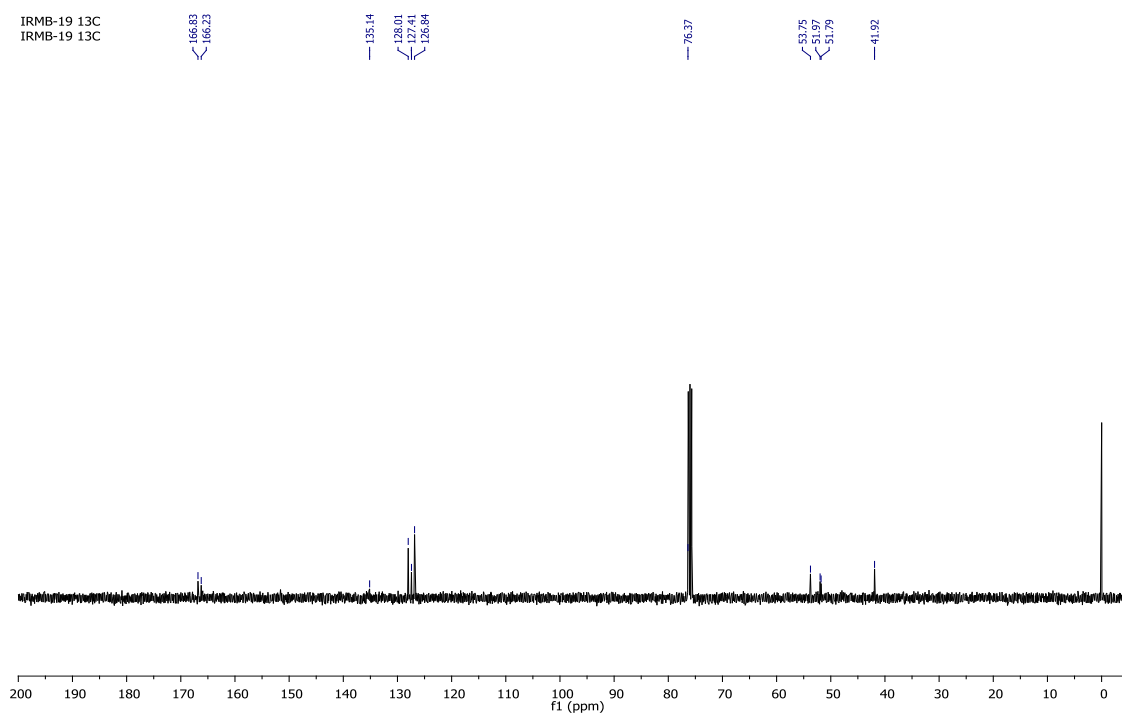
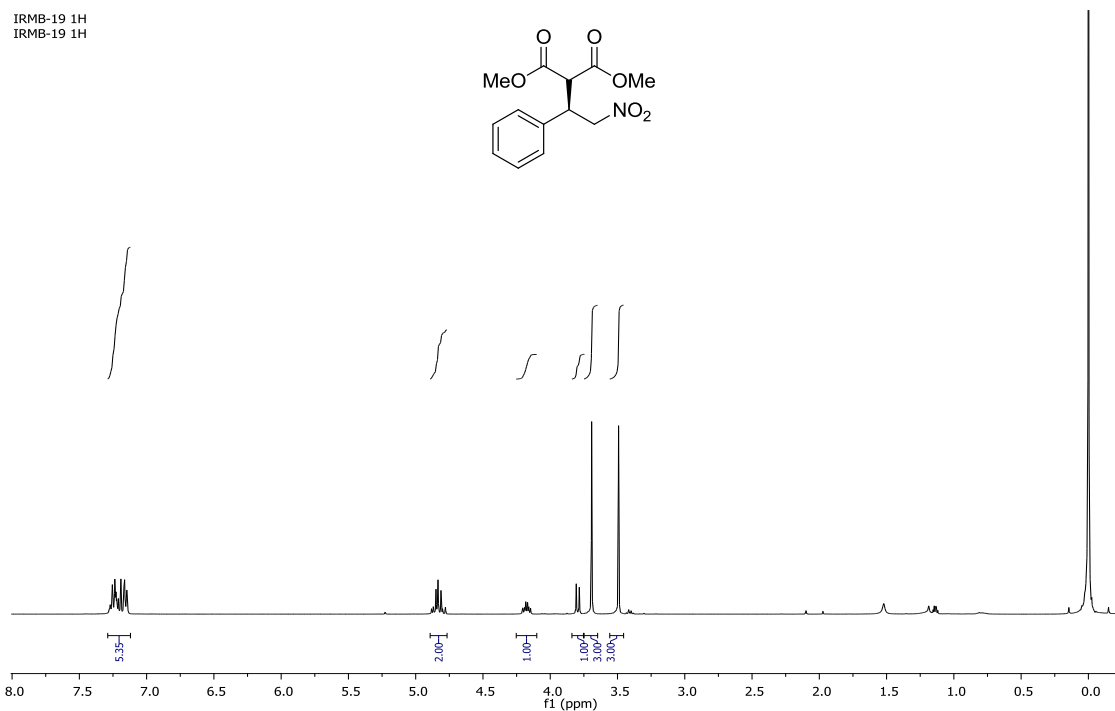
**Figure A.38.**  $^1\text{H}$  NMR spectrum of Michael product **46r**

CT-IRM-NO2 13C  
CT-IRM-NO2 13C

166.27  
165.62  
148.96  
132.26  
130.34  
128.25  
124.43  
75.24  
61.21  
61.23  
52.64  
36.71  
12.93  
12.71



**Figure A.39.**  $^{13}\text{C}$  NMR spectrum of Michael product **46r**



IRM-25 1H  
IRM-25 1H

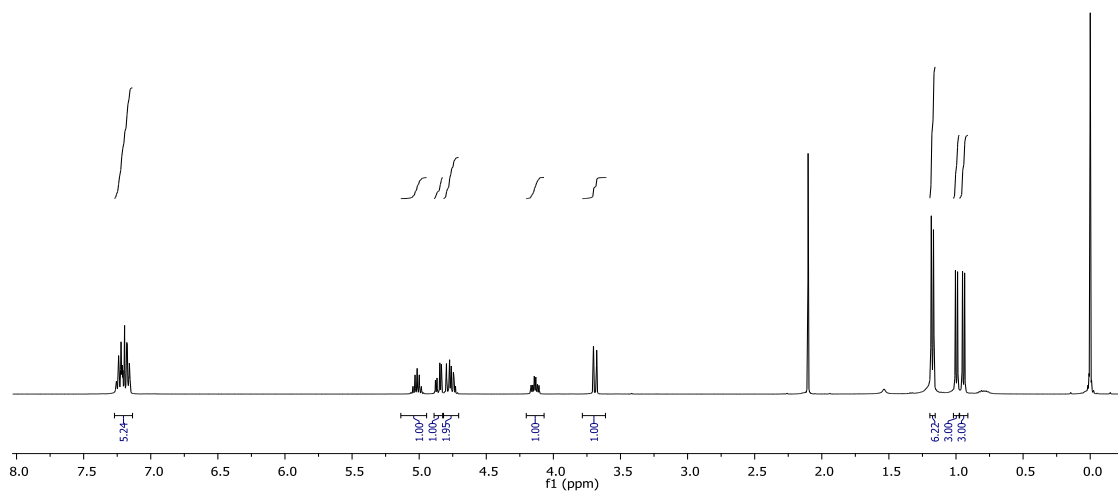
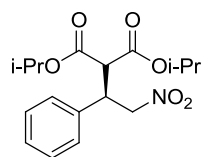


Figure A.42. <sup>1</sup>H NMR spectrum of Michael product **60b**

IRM-25 13C  
IRM-25 13C

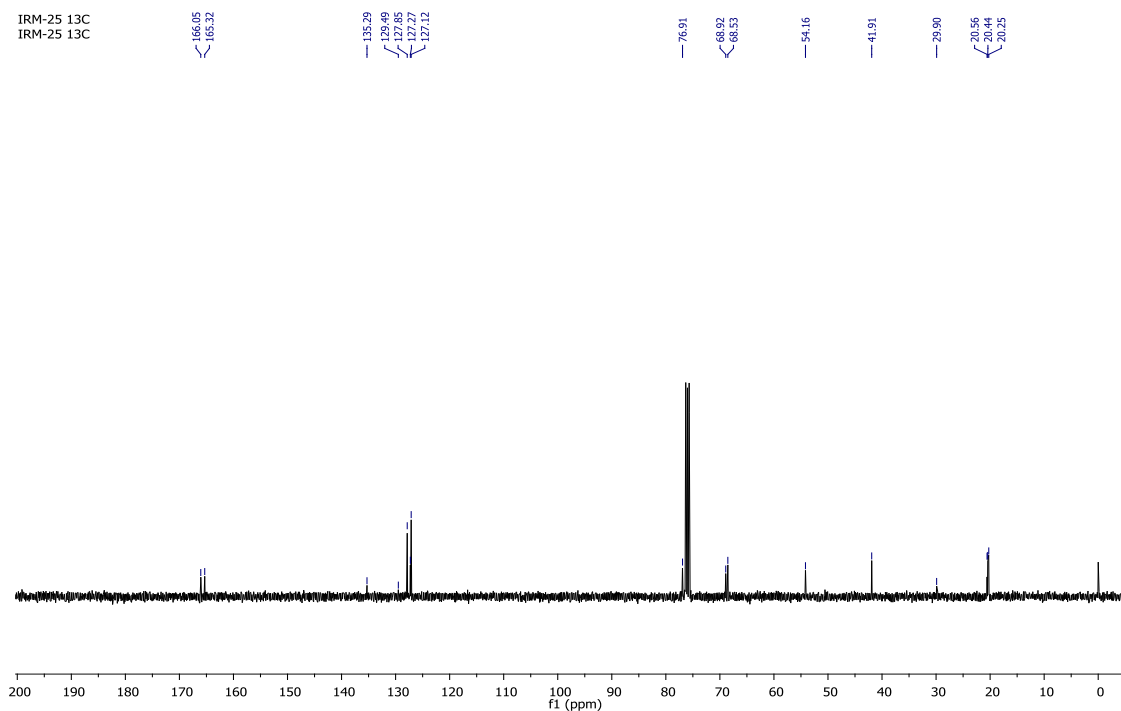


Figure A.43. <sup>13</sup>C NMR spectrum of Michael product **60b**

IRM-24 1H  
IRM-24 1H

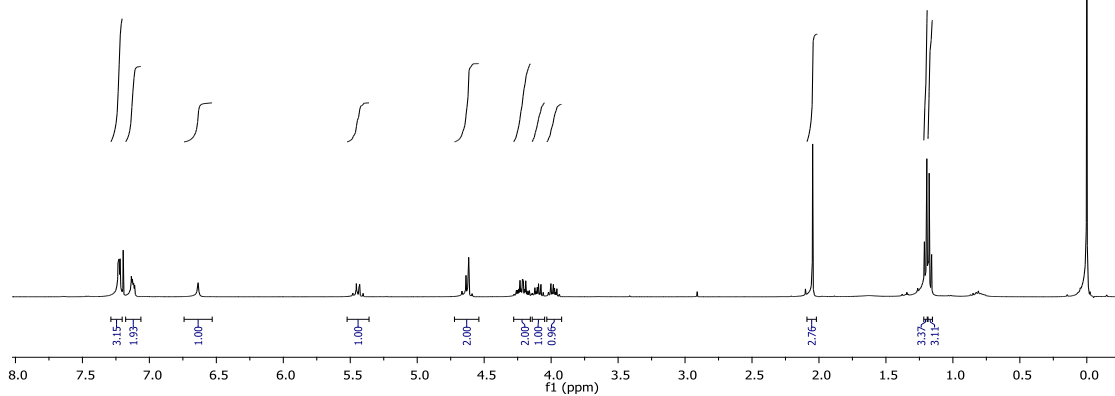
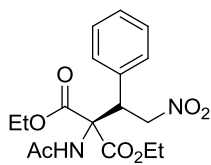


Figure A.44. <sup>1</sup>H NMR spectrum of Michael product **60c**

IRM-24 13C  
IRM-24 13C

169.12  
168.51  
164.76  
133.93  
127.84  
127.80  
127.73  
75.89  
66.28  
62.63  
61.84  
47.37  
22.06  
12.83  
12.81

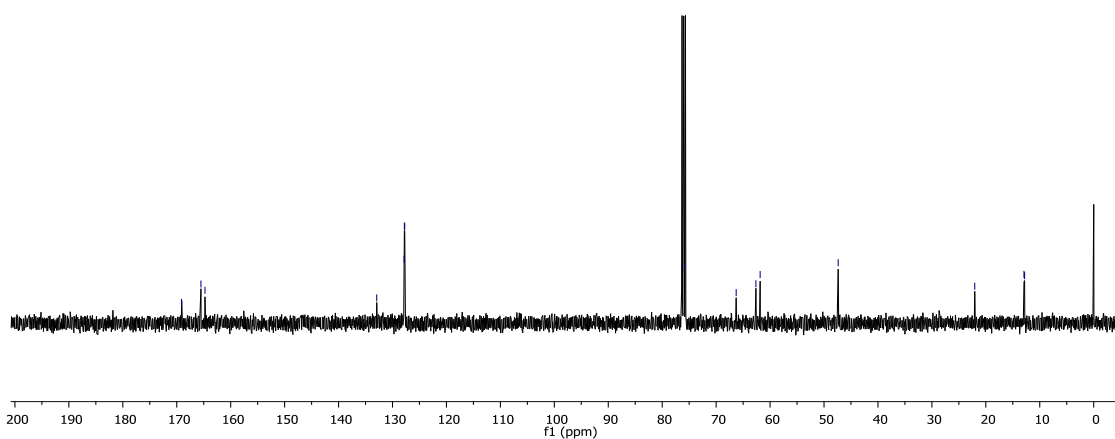
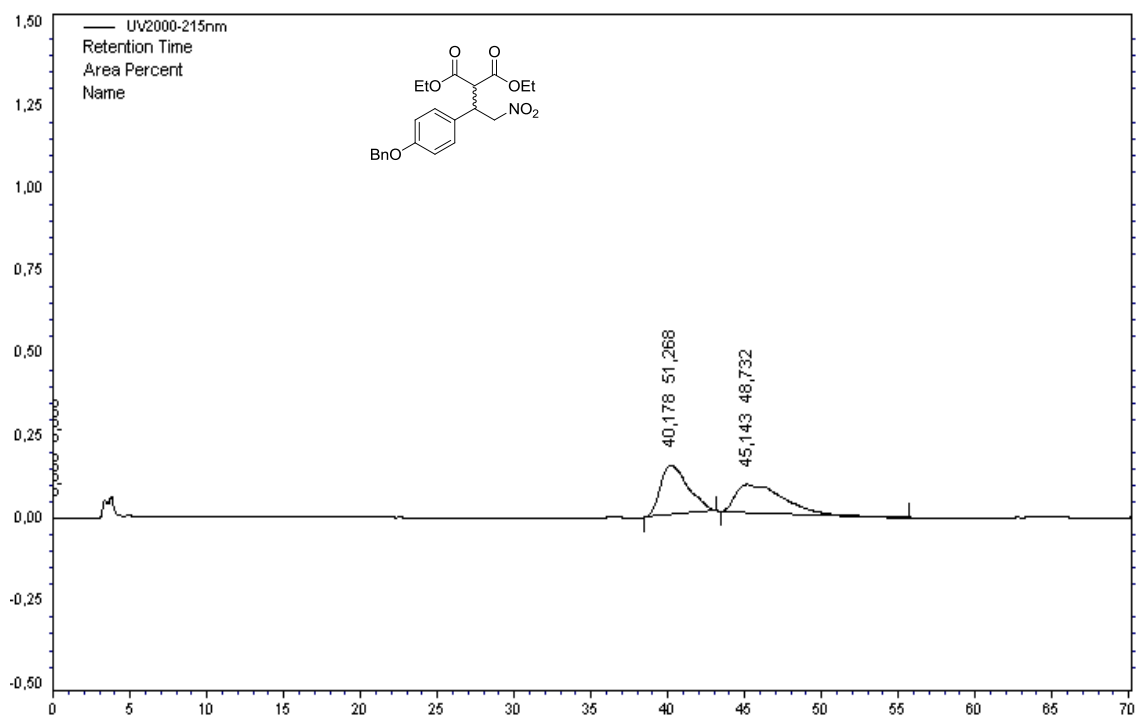


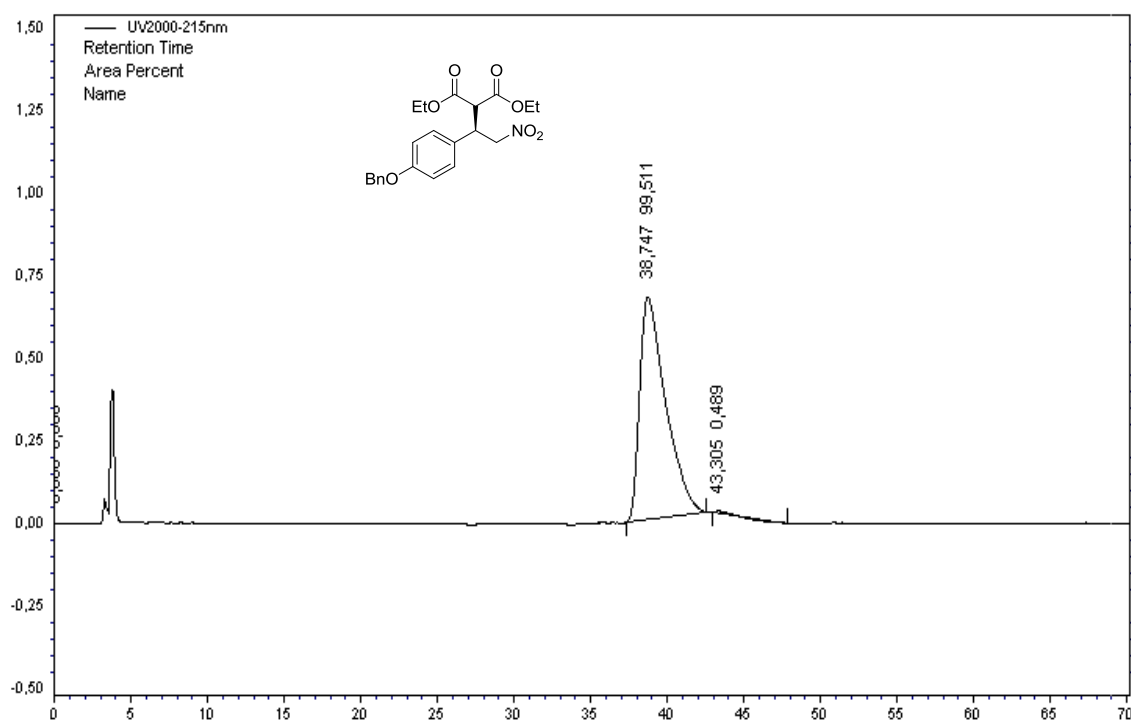
Figure A.45. <sup>13</sup>C NMR spectrum of Michael product **60c**

## **B. SUPPORTING INFORMATION (HPLC)**

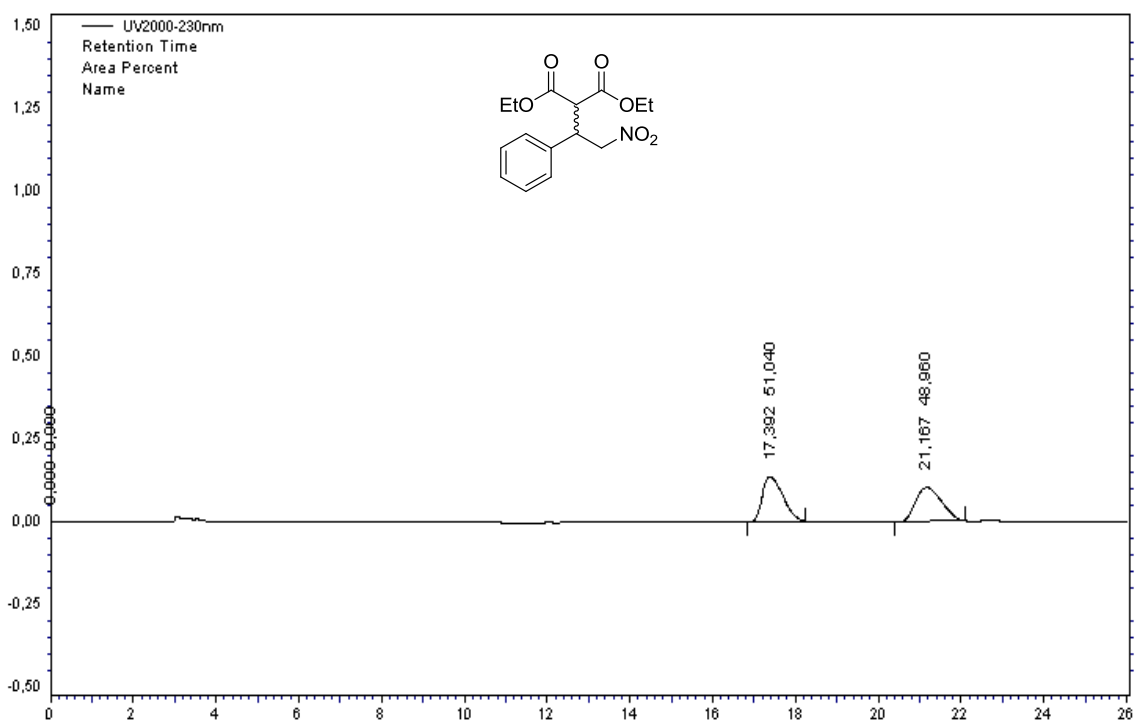
In this part, HPLC chromatogram results of synthesized Michael products in this study are presented in the following pages.



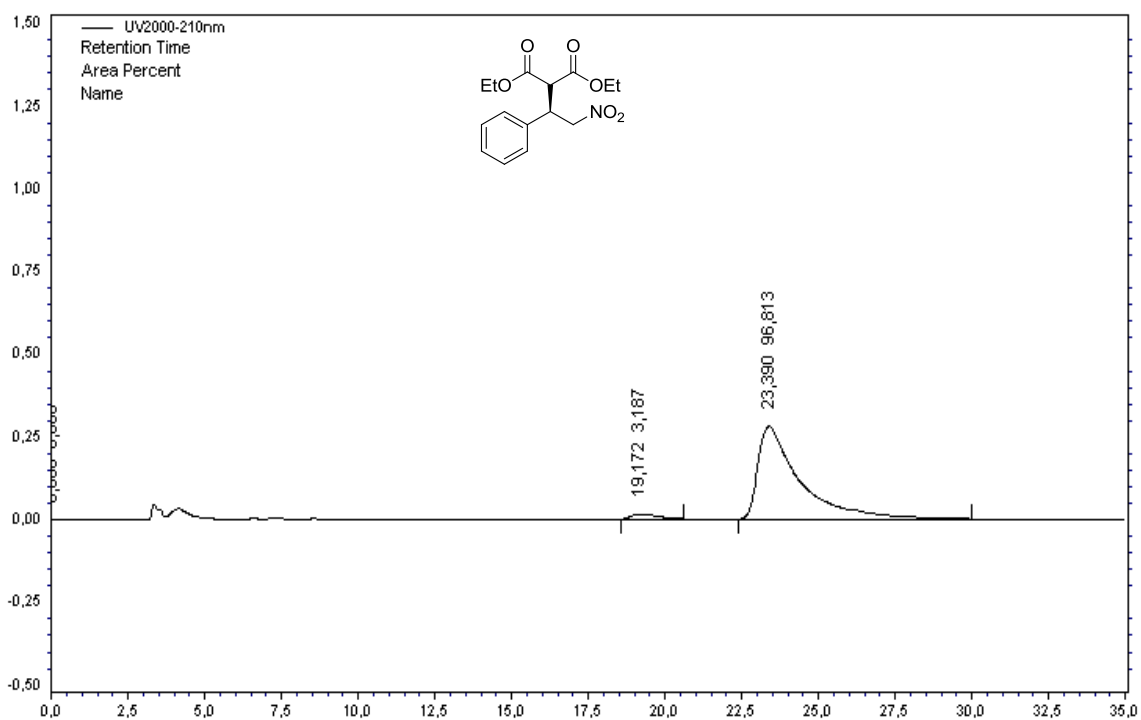
**Figure B.1.** HPLC chromatogram of *rac*-46a



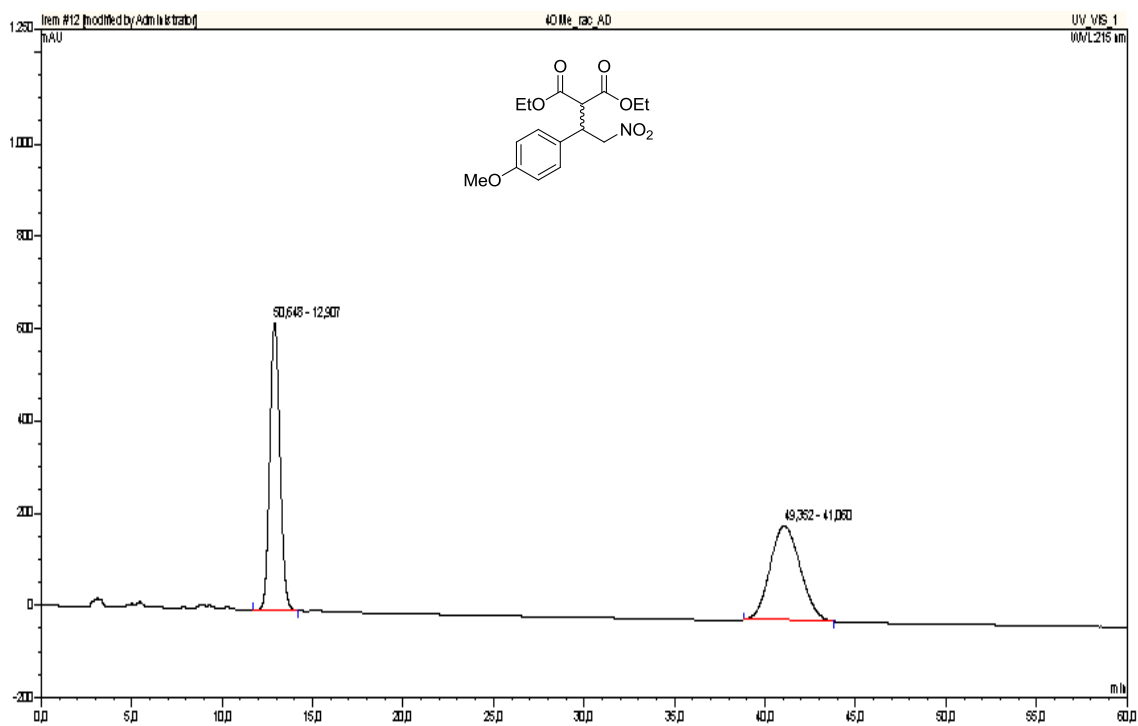
**Figure B.2.** HPLC chromatogram of *enantiomerically enriched* product 46a



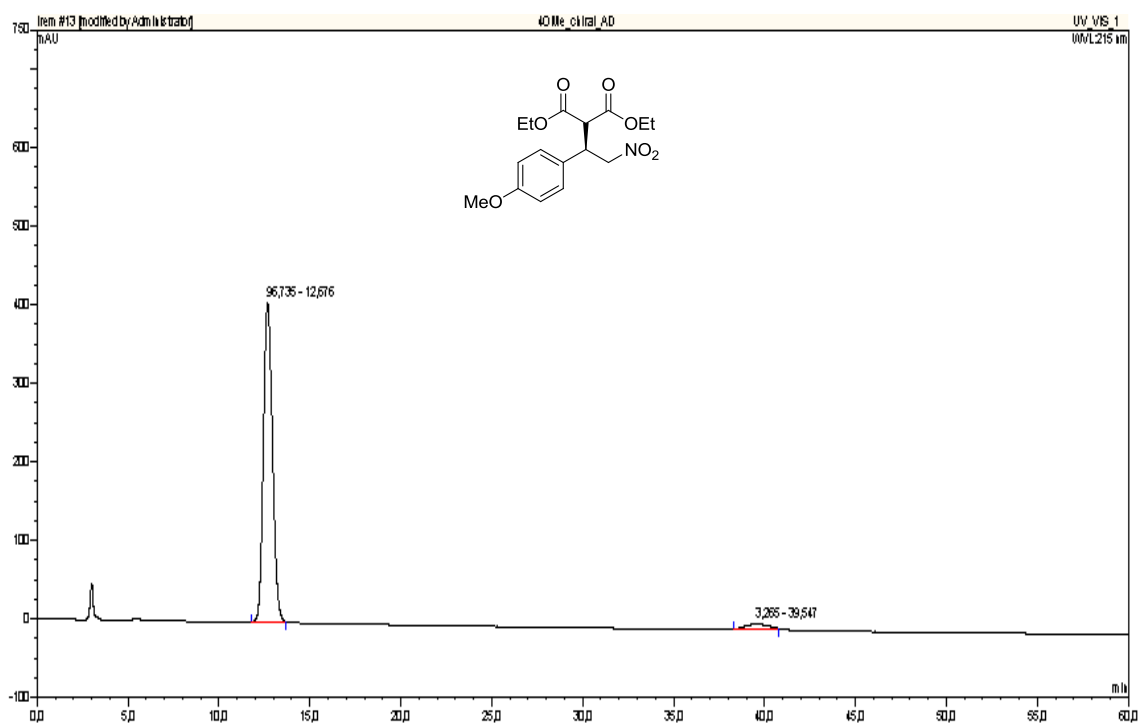
**Figure B.3.** HPLC chromatogram of *rac*-**46b**



**Figure B.4.** HPLC chromatogram of *enantiomerically enriched* product **46b**

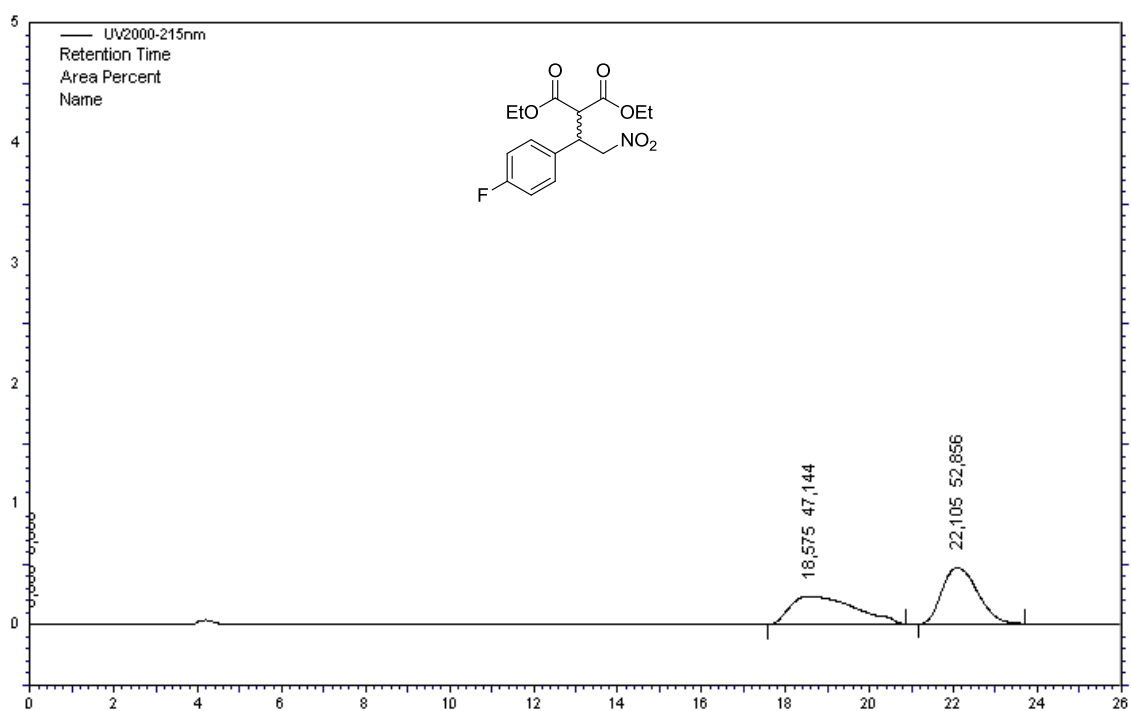


**Figure B.5.** HPLC chromatogram of *rac*-46c

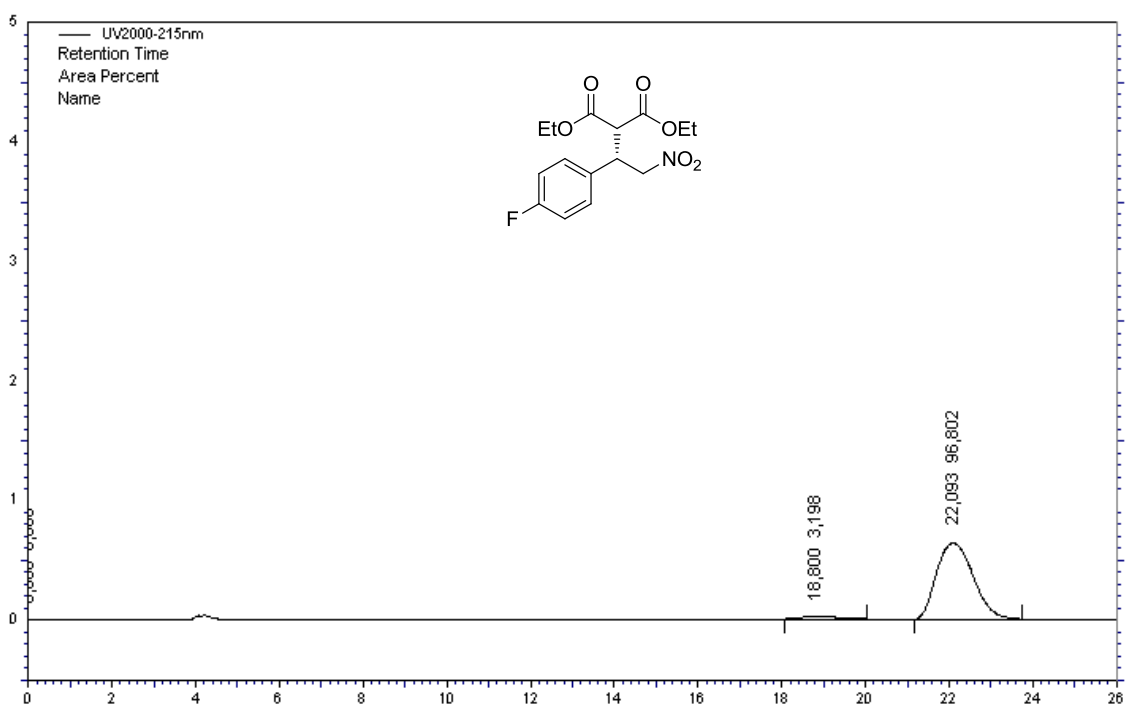


**Figure B.6.** HPLC chromatogram of *enantiomerically enriched* product 46c

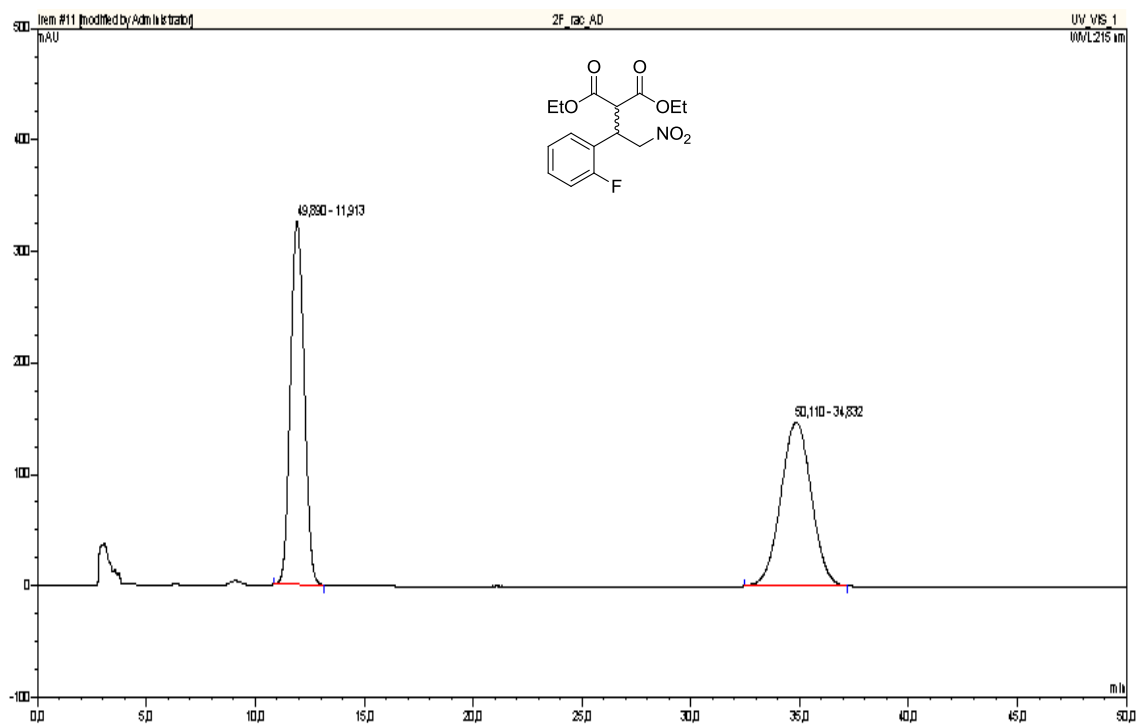




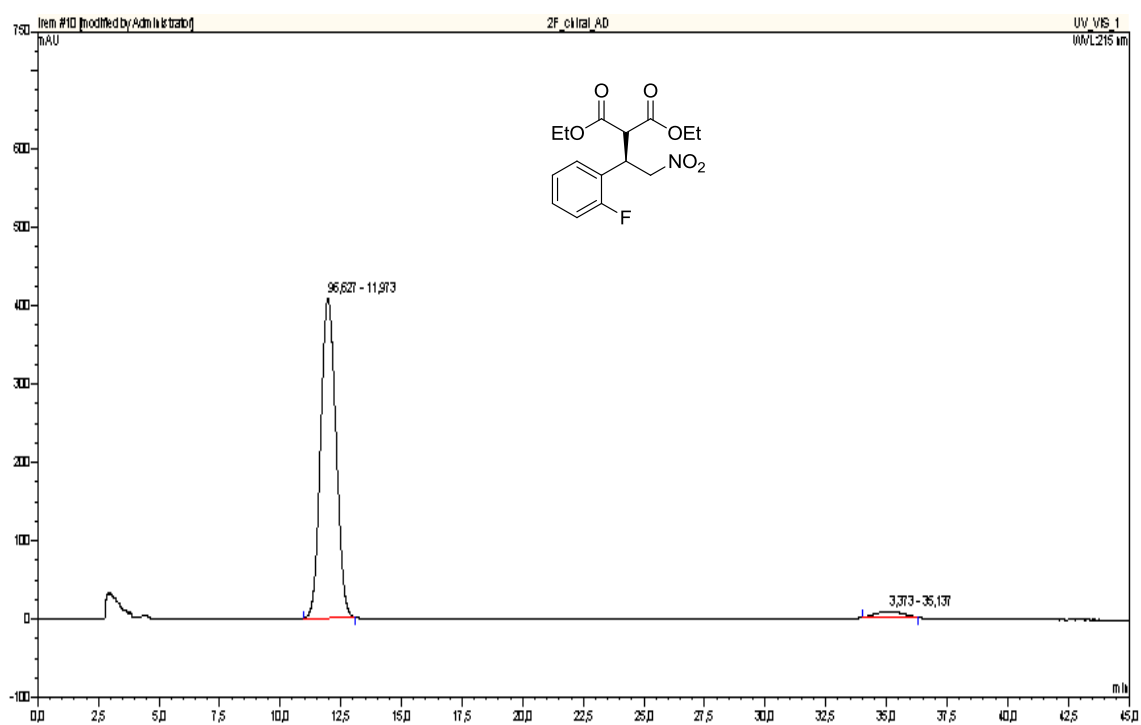
**Figure B.7.** HPLC chromatogram of *rac*-46d



**Figure B.8.** HPLC chromatogram of *enantiomerically enriched* product 46d



**Figure B.9.** HPLC chromatogram of *rac*-46e



**Figure B.10.** HPLC chromatogram of enantiomerically enriched product 46e

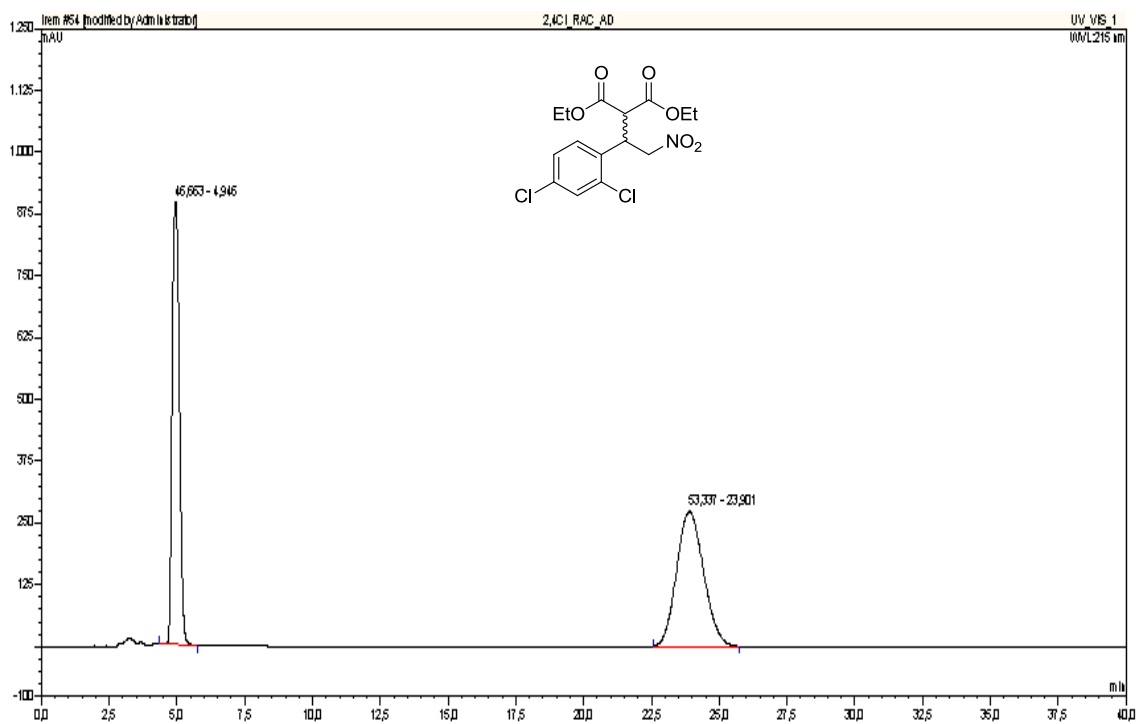


Figure B.11. HPLC chromatogram of *rac*-46f

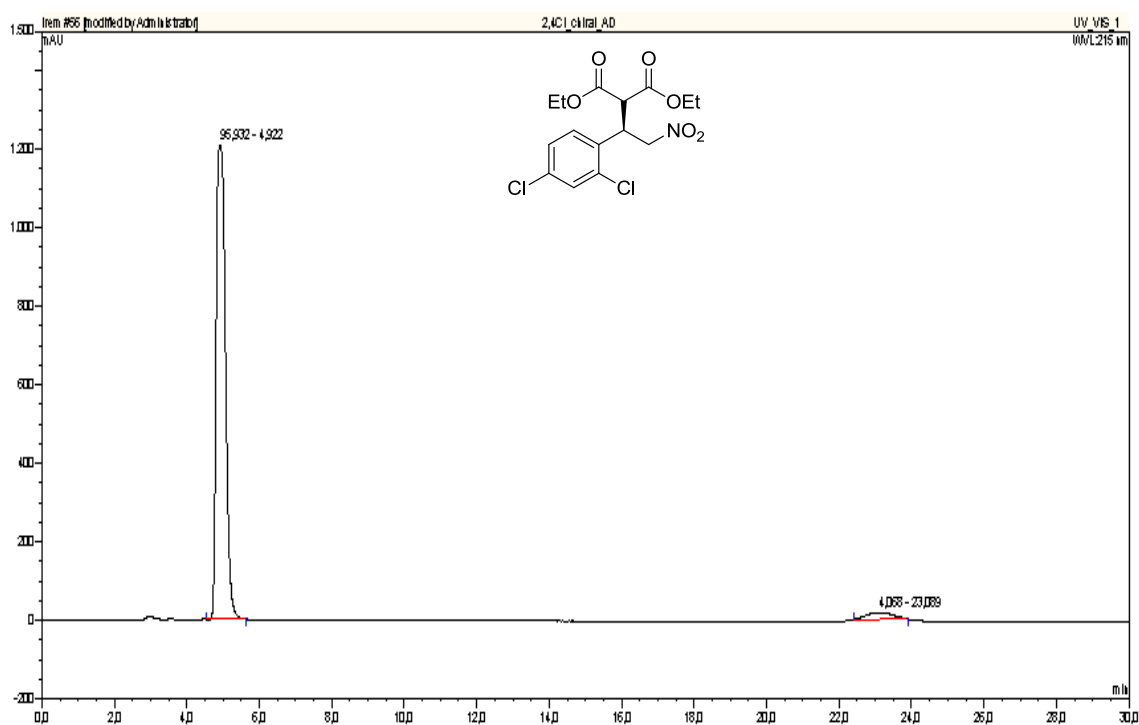


Figure B.12. HPLC chromatogram of enantiomerically enriched product 46f

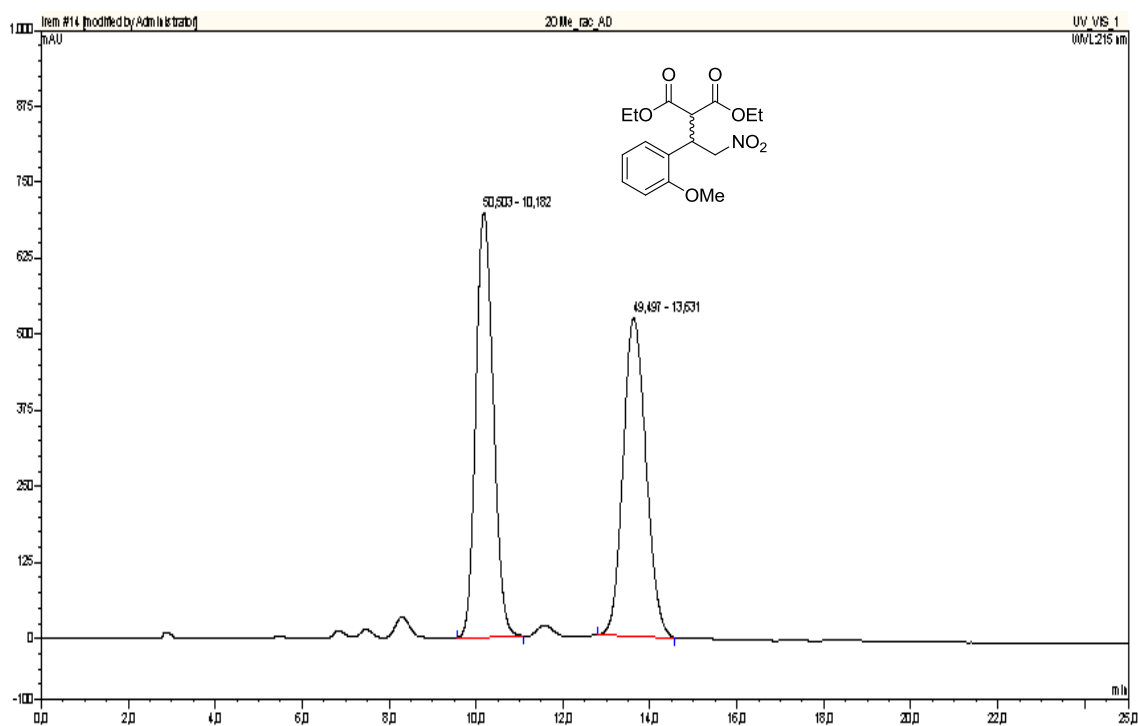


Figure B.13. HPLC chromatogram of *rac*-46g

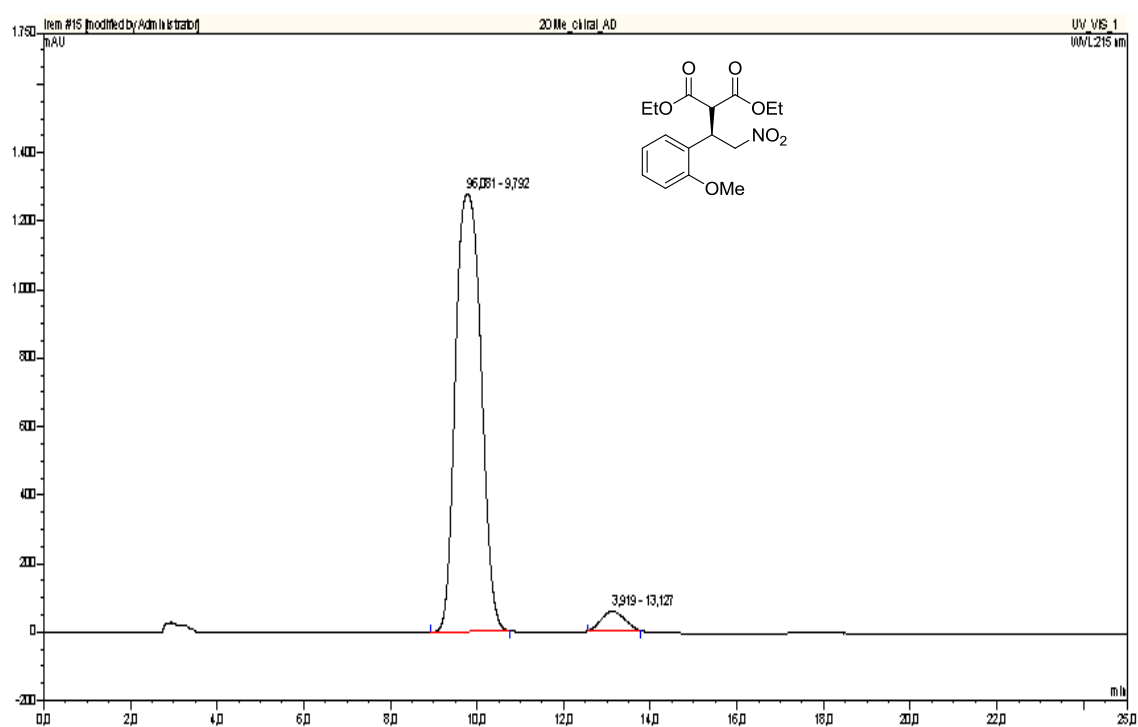
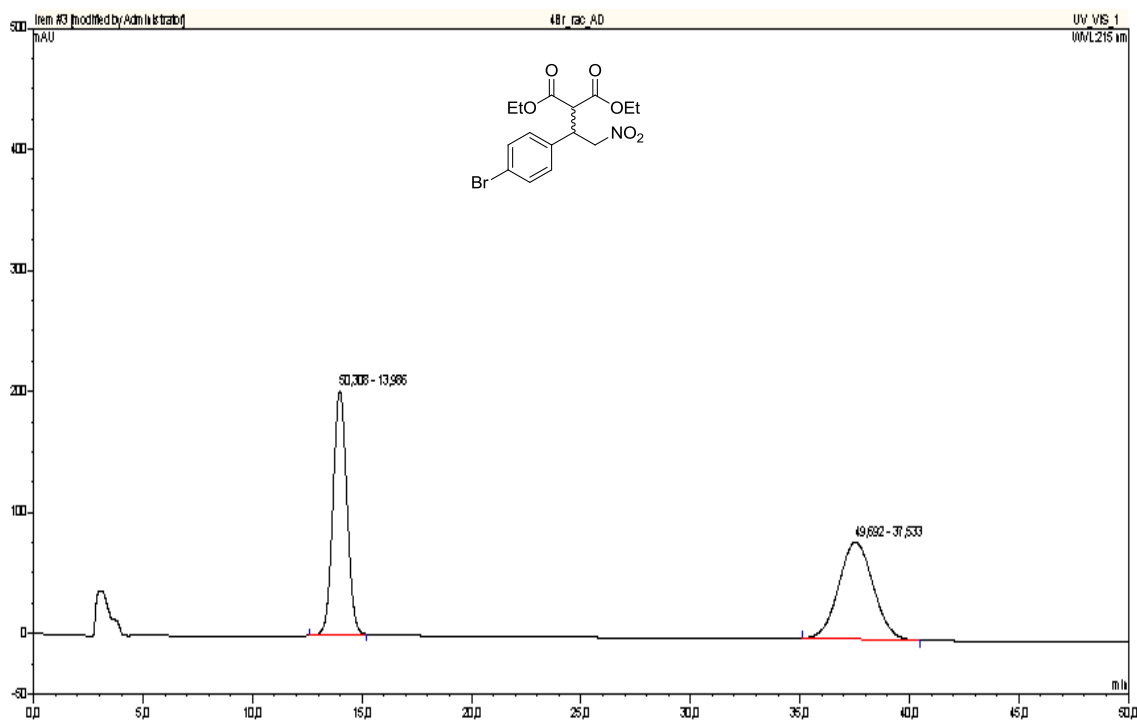
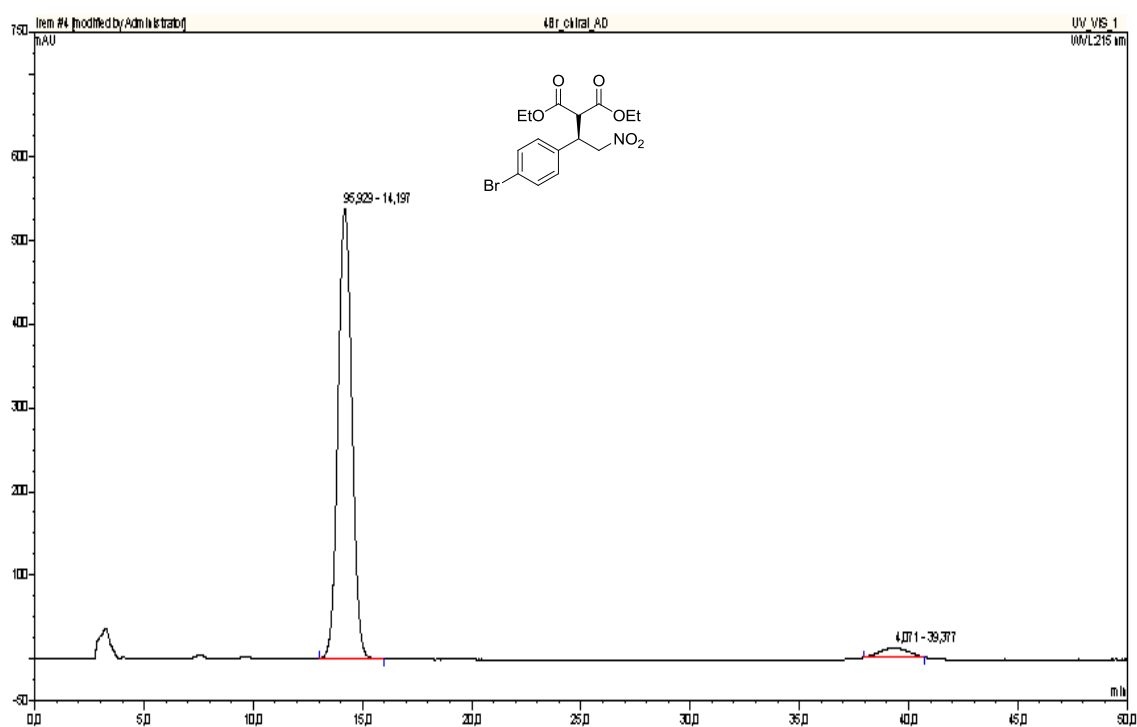


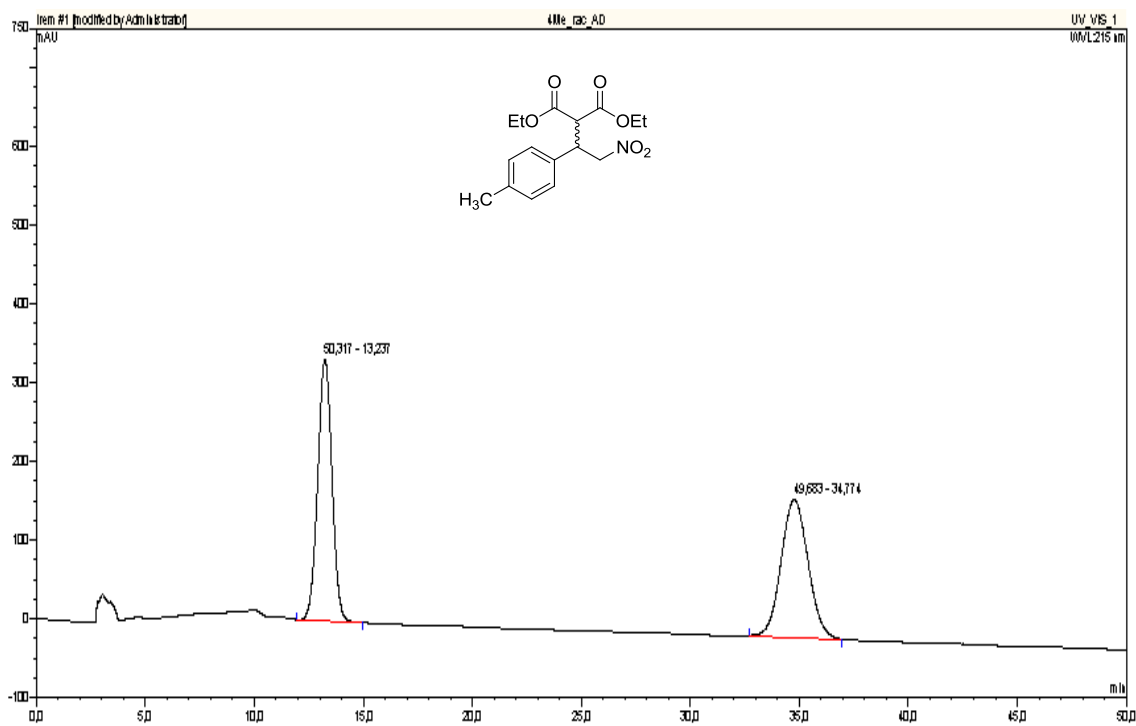
Figure B.14. HPLC chromatogram of enantiomerically enriched product 46g



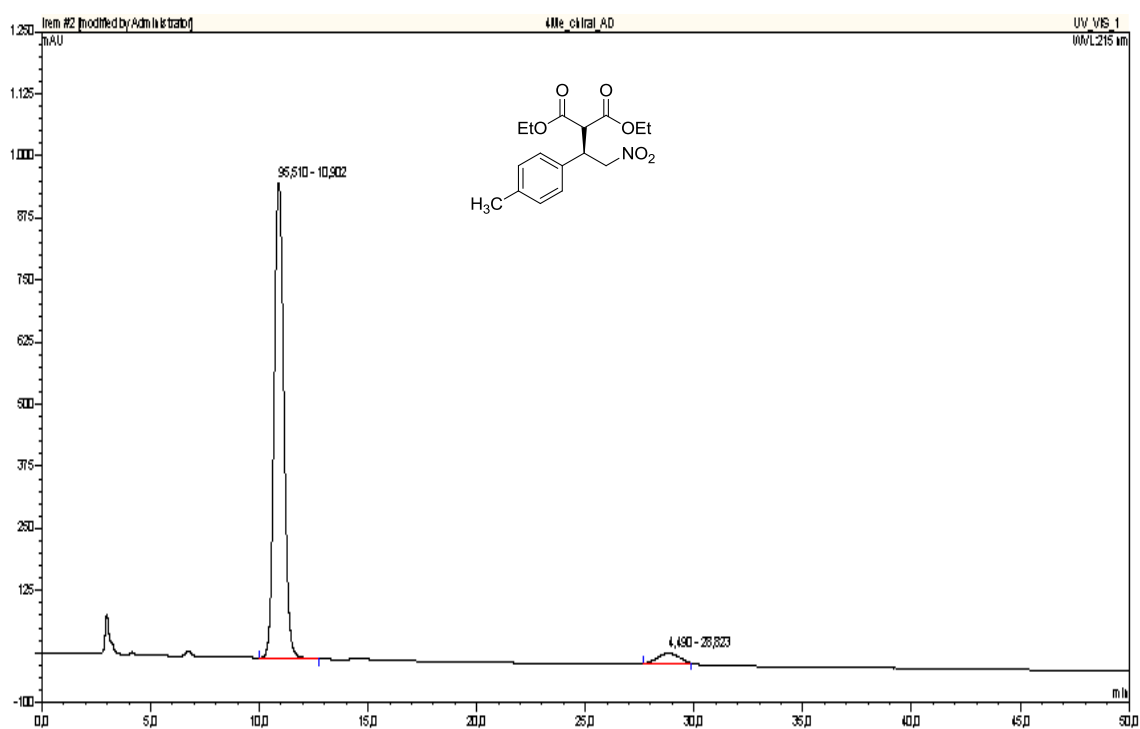
**Figure B.15.** HPLC chromatogram of *rac*-46h



**Figure B.16.** HPLC chromatogram of enantiomerically enriched product 46h



**Figure B.17.** HPLC chromatogram of *rac*-46i



**Figure B.18.** HPLC chromatogram of enantiomerically enriched product 46i

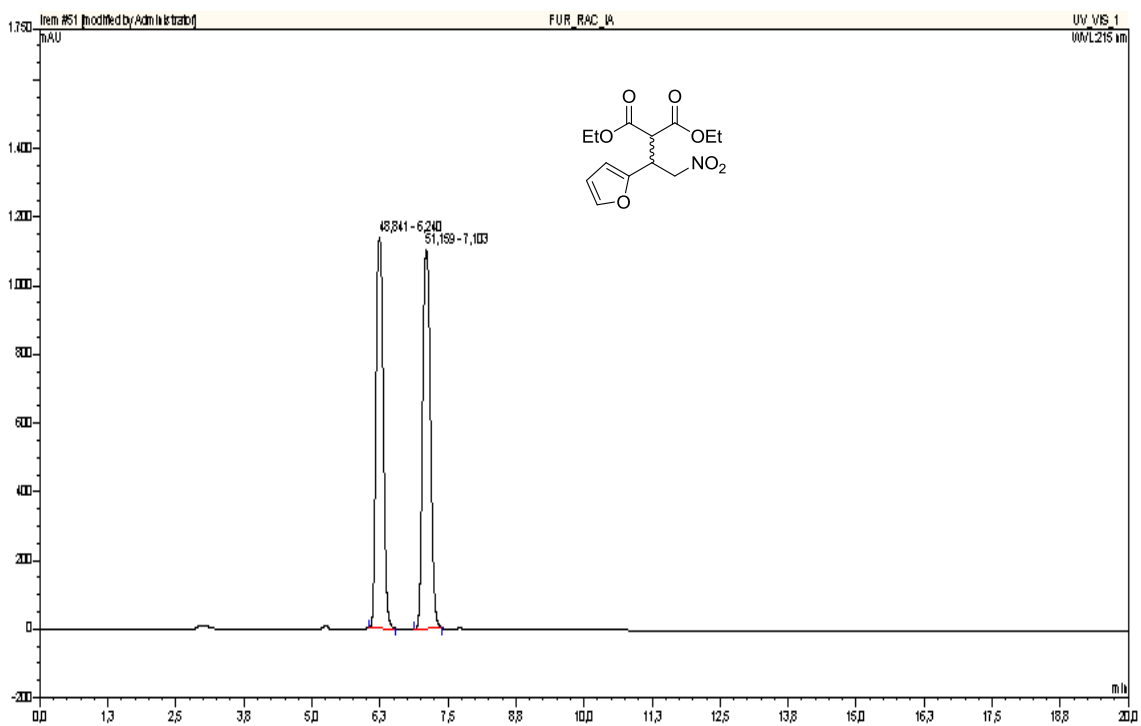


Figure B.19. HPLC chromatogram of *rac*-46j

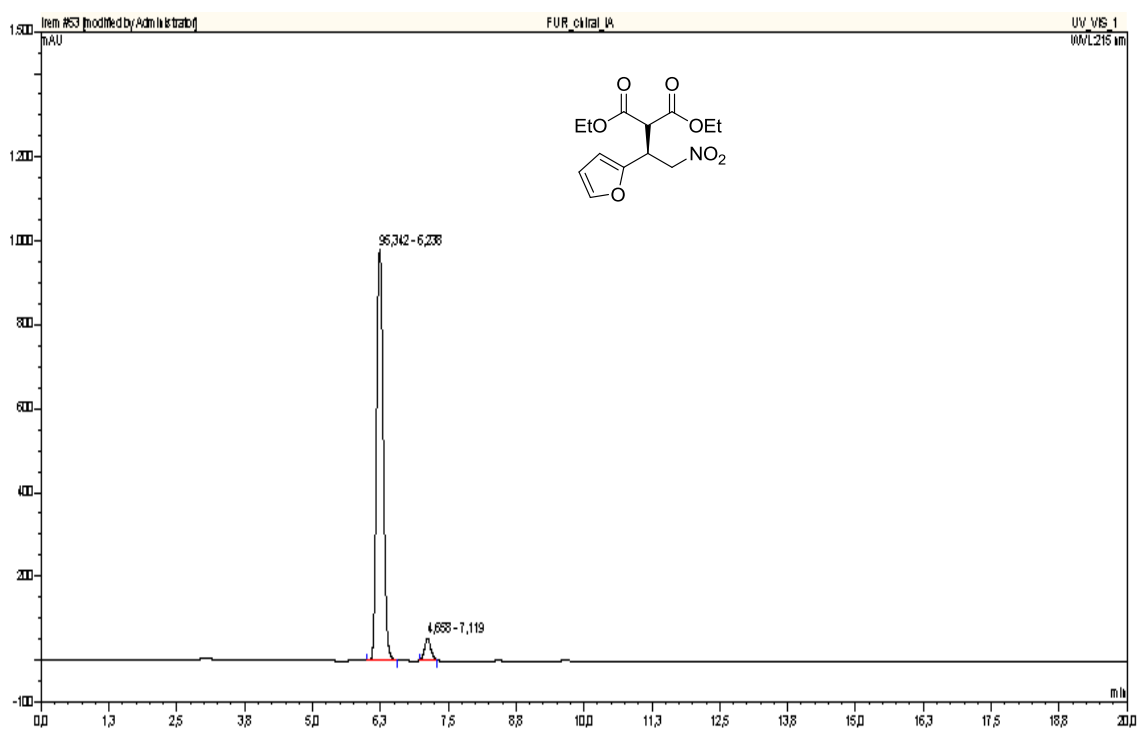


Figure B.20. HPLC chromatogram of enantiomerically enriched product 46j

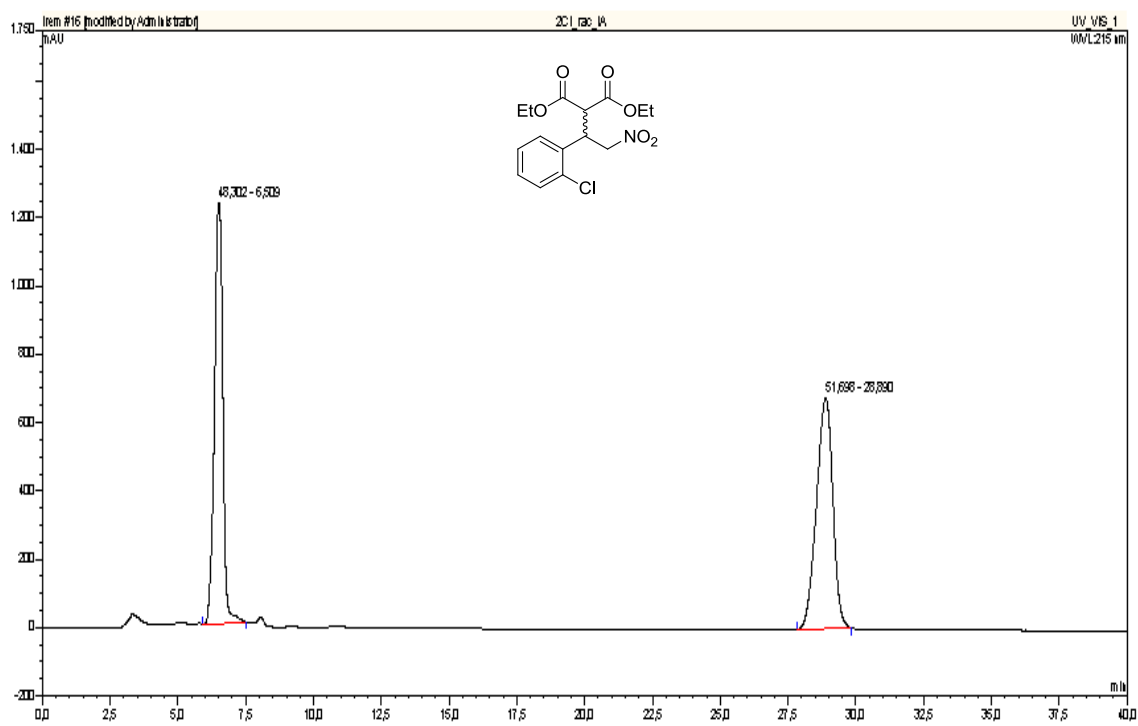


Figure B.21. HPLC chromatogram of *rac*-46k

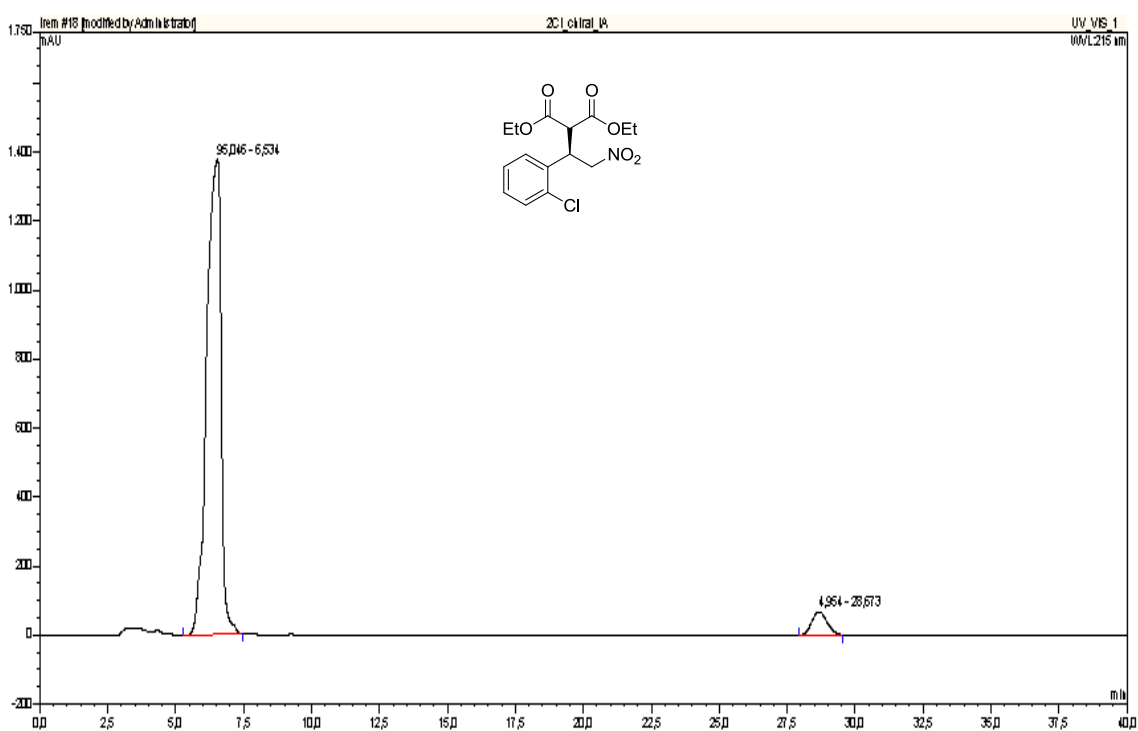


Figure B.22. HPLC chromatogram of enantiomerically enriched product 46k



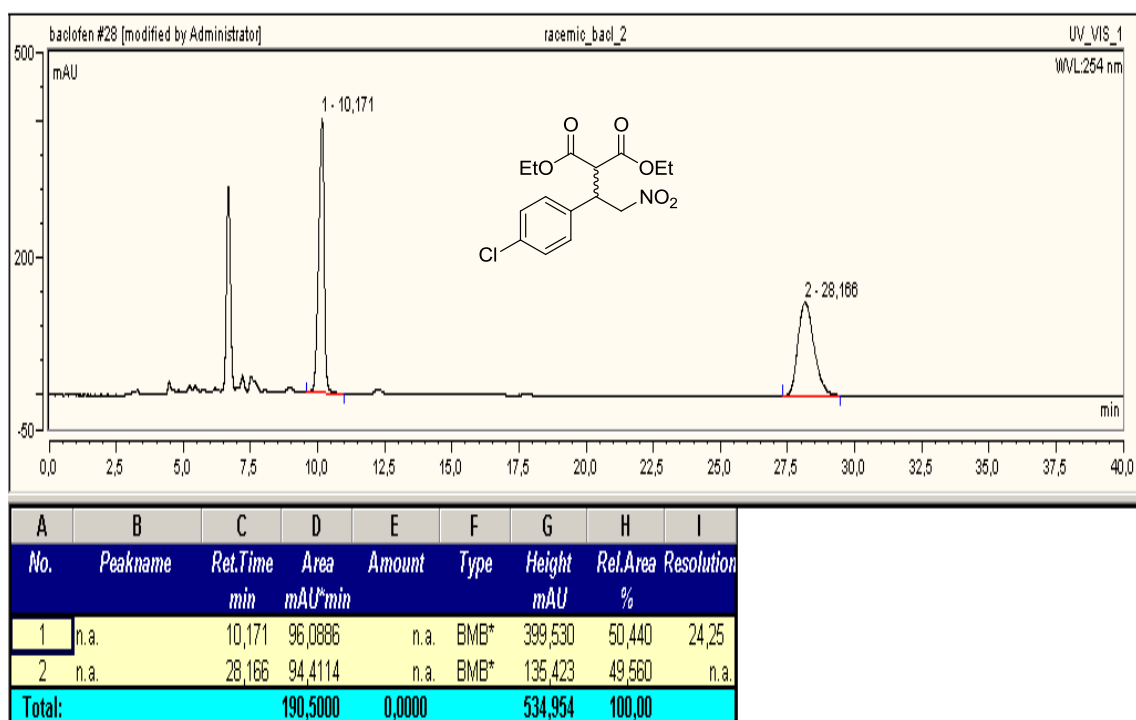


Figure B.23. HPLC chromatogram of *rac*-461

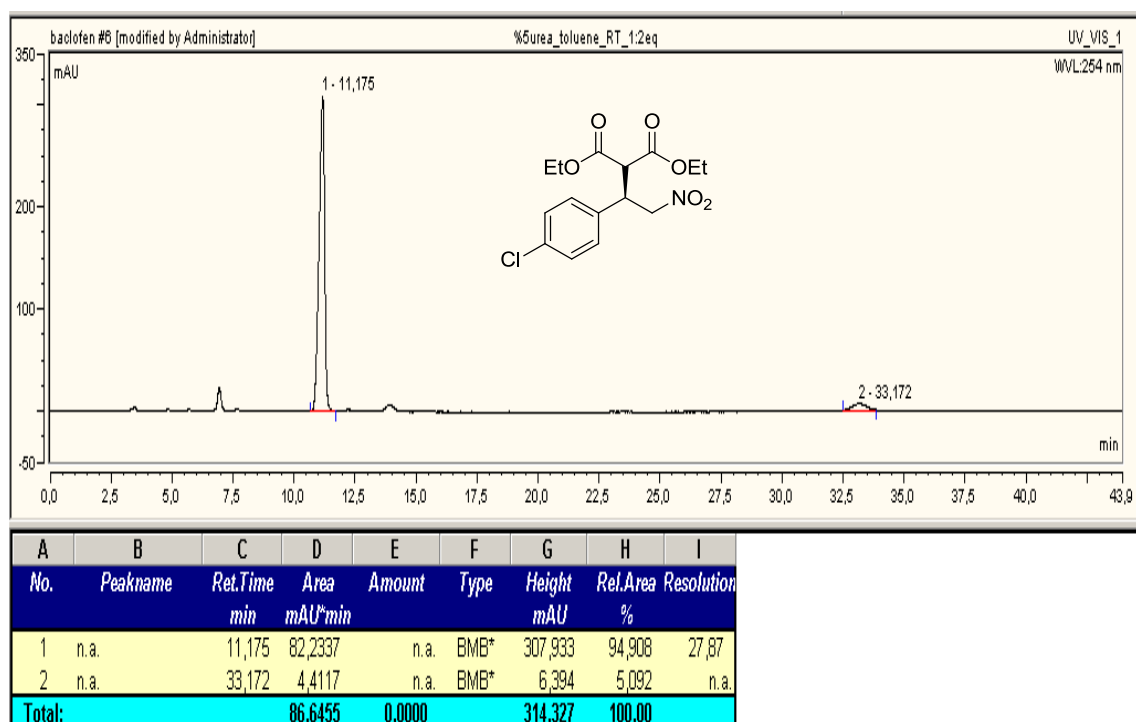
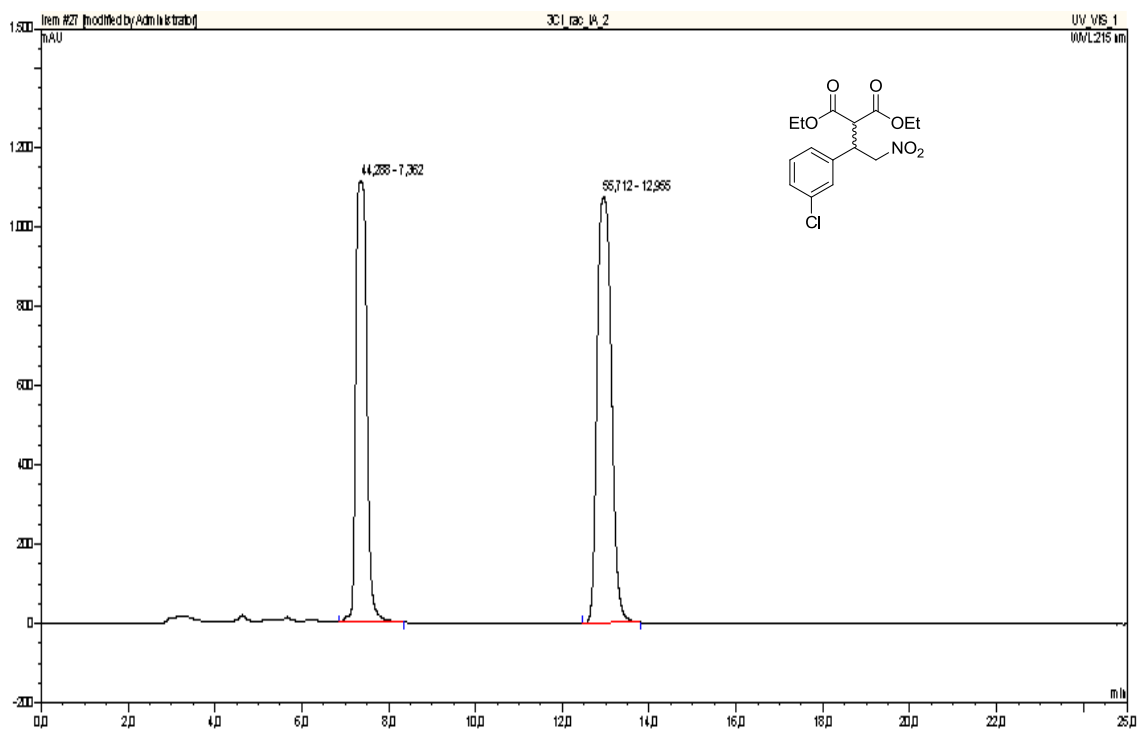
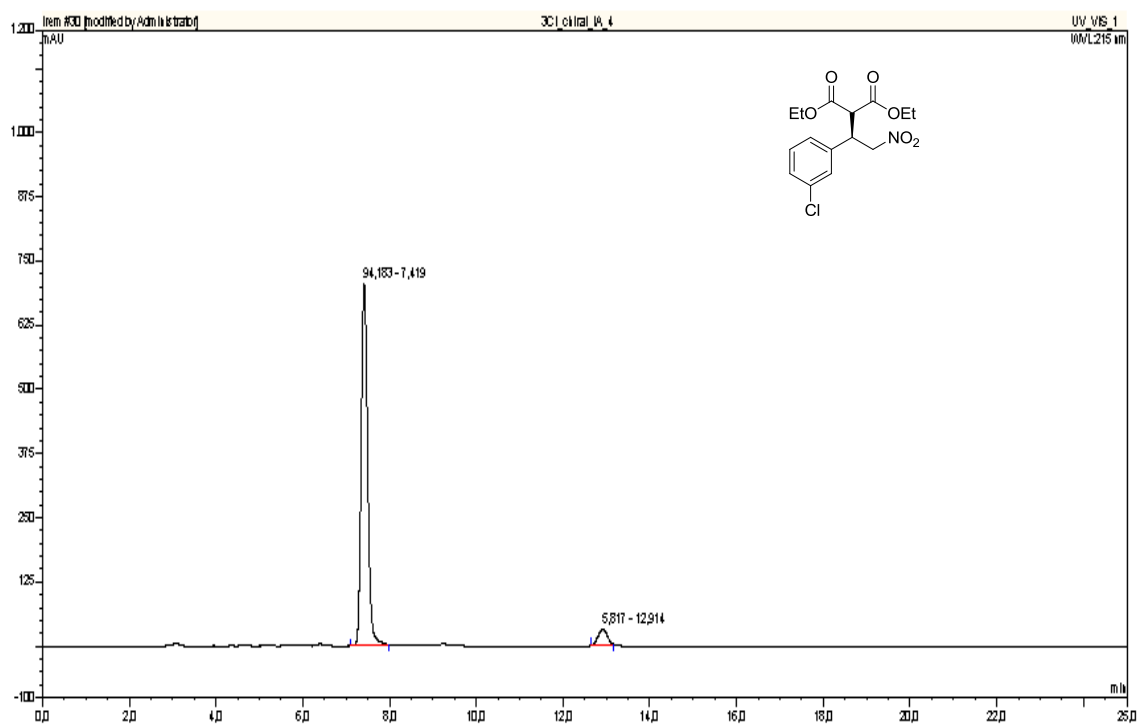


Figure B.24. HPLC chromatogram of enantiomerically enriched product 461



**Figure B.25.** HPLC chromatogram of *rac*-46m



**Figure B.26.** HPLC chromatogram of enantiomerically enriched product 46m

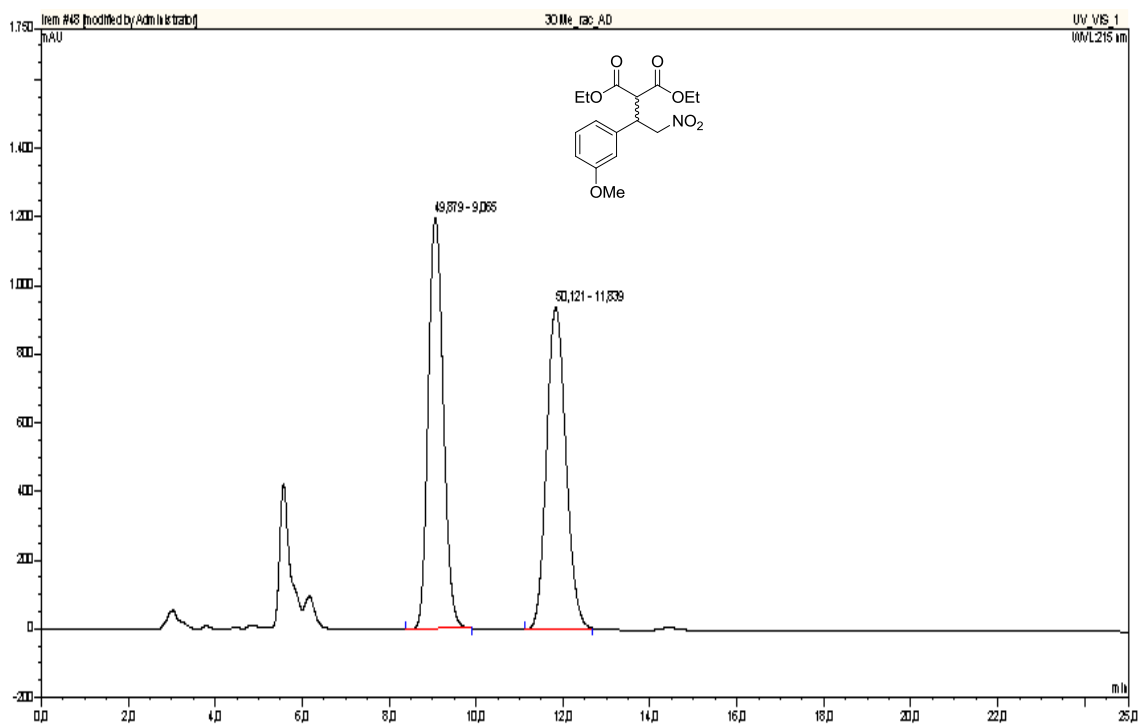


Figure B.27. HPLC chromatogram of *rac*-46n

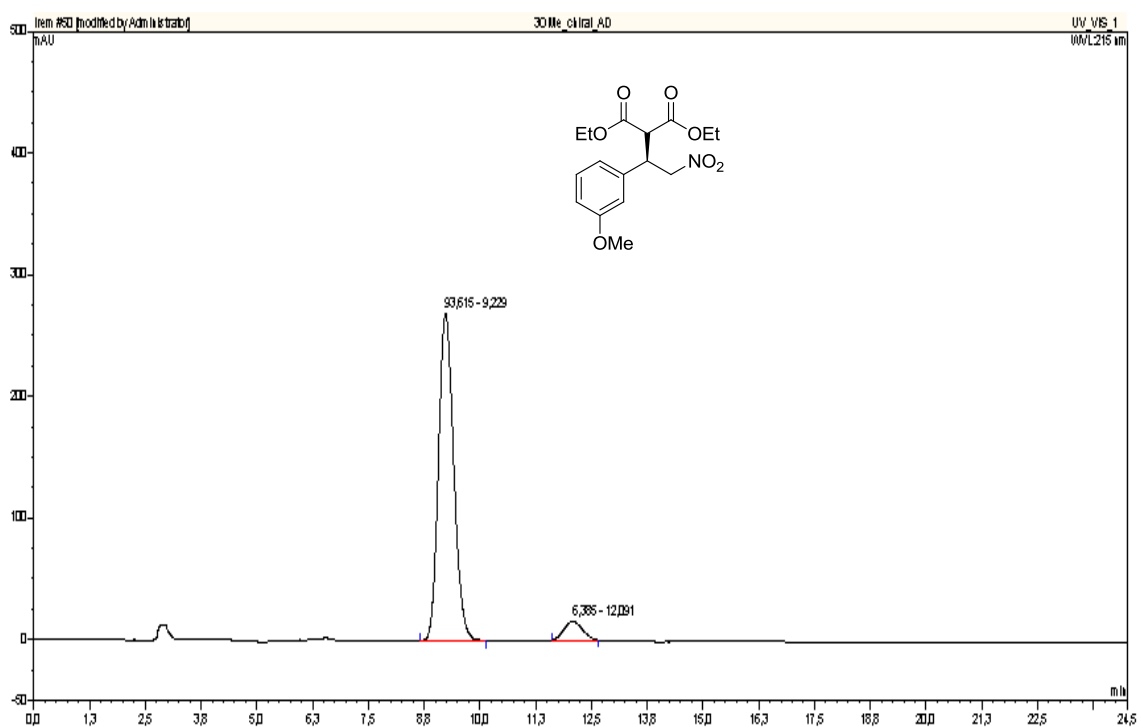


Figure B.28. HPLC chromatogram of enantiomerically enriched product 46n

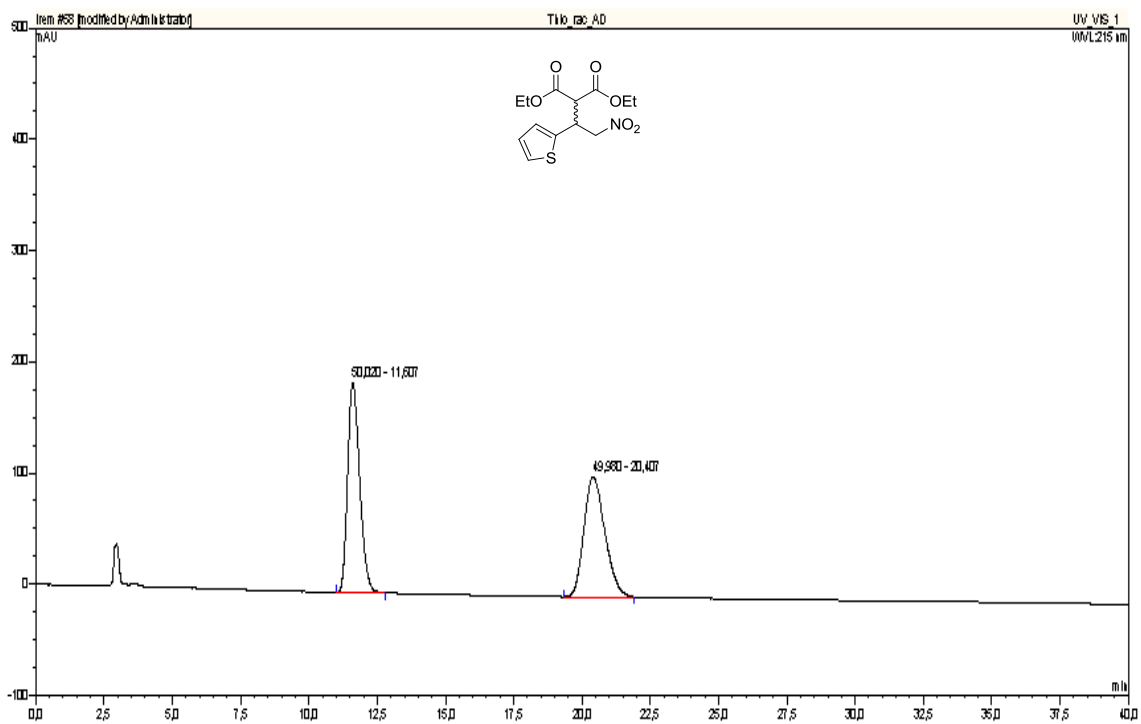


Figure B.29. HPLC chromatogram of *rac*-460

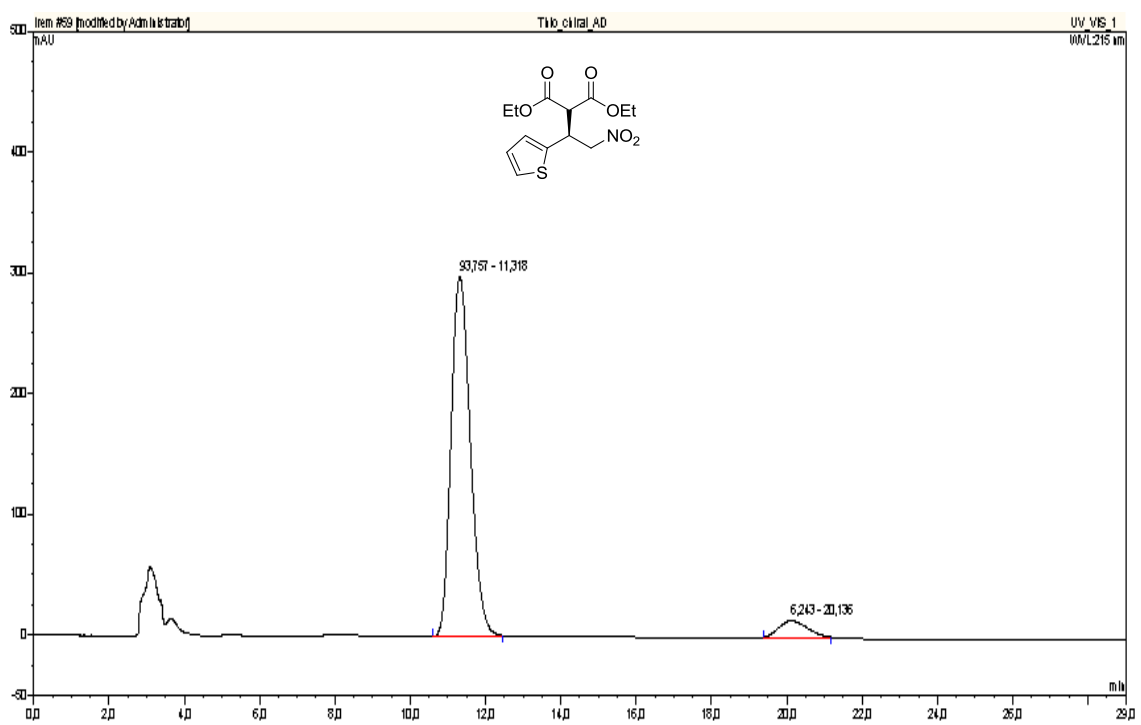


Figure B.30. HPLC chromatogram of enantiomerically enriched product 460

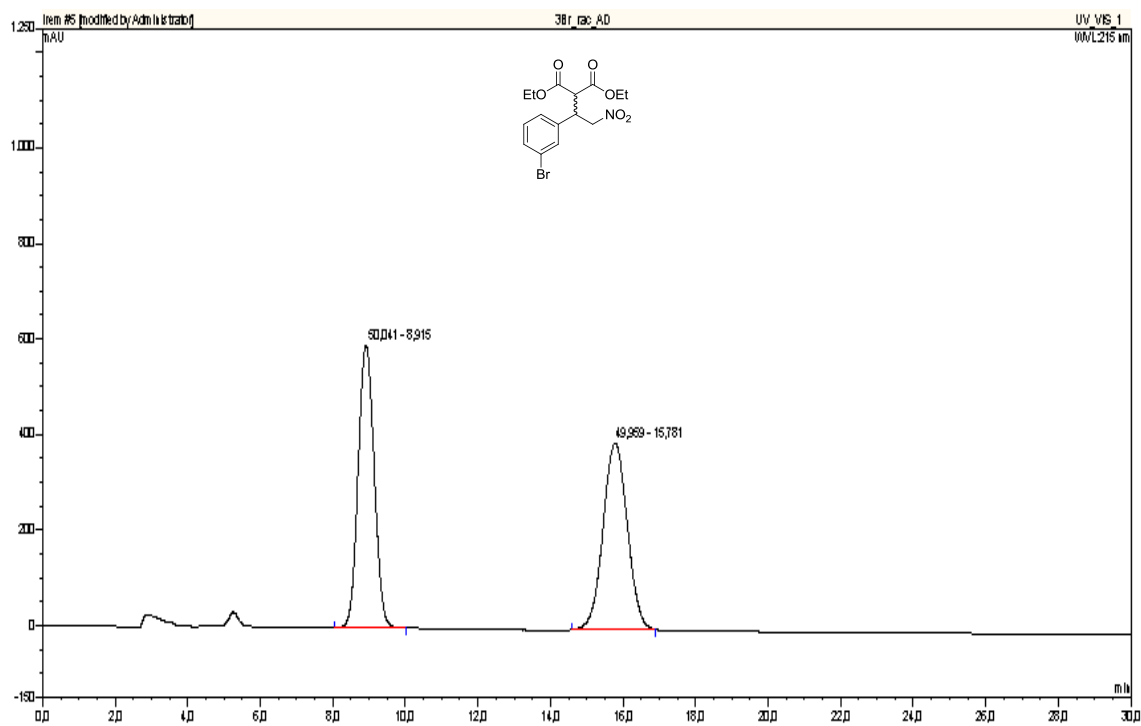


Figure B.31. HPLC chromatogram of *rac*-46p

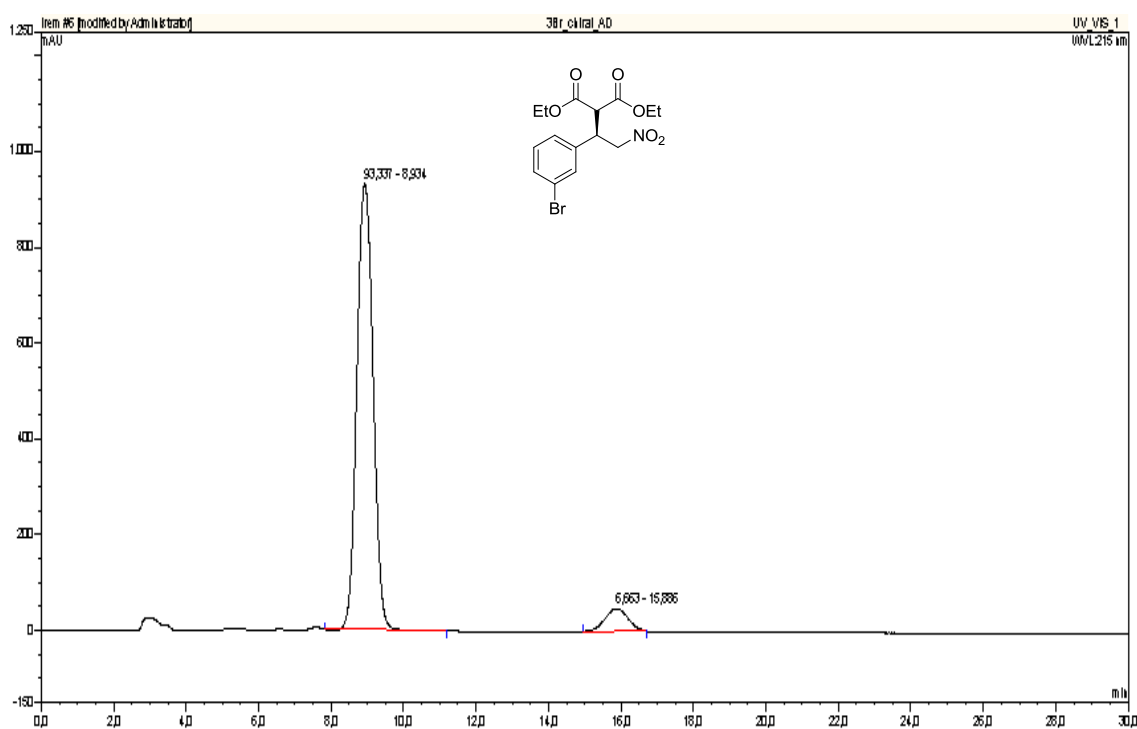
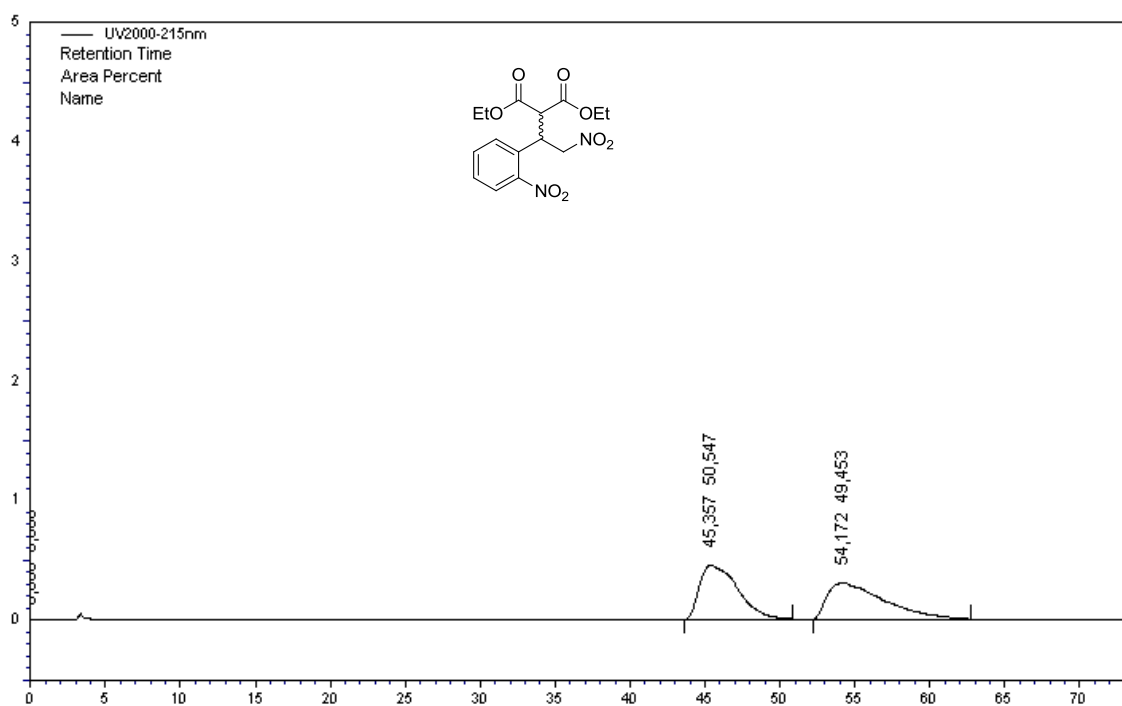
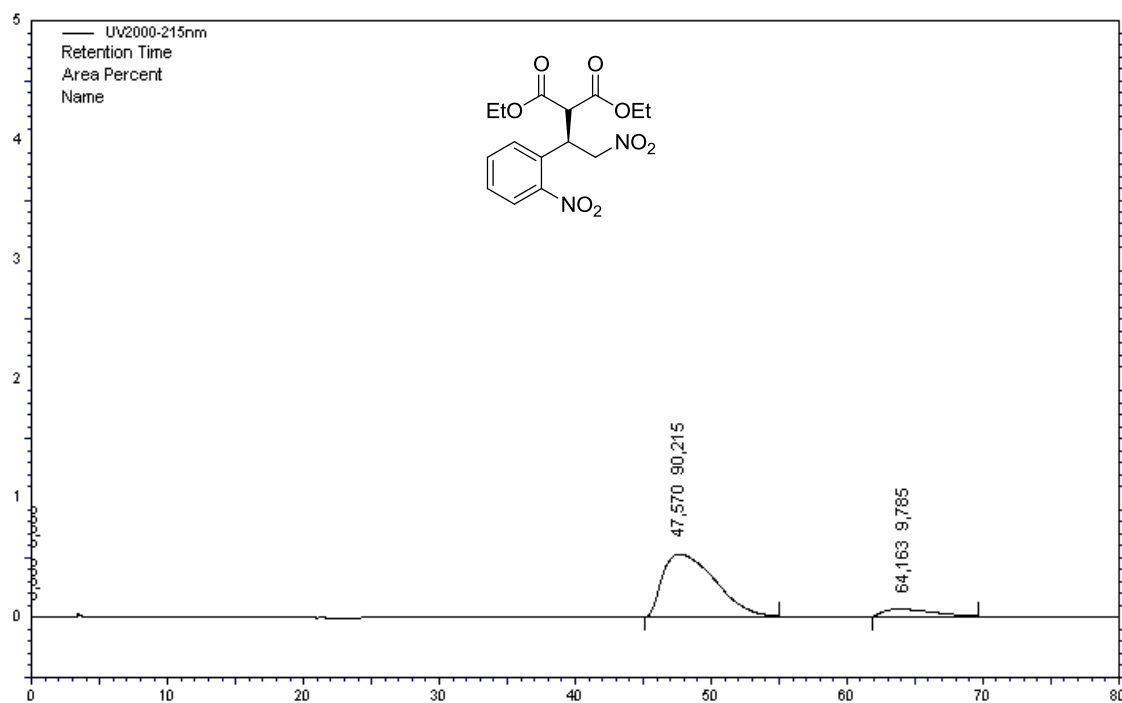


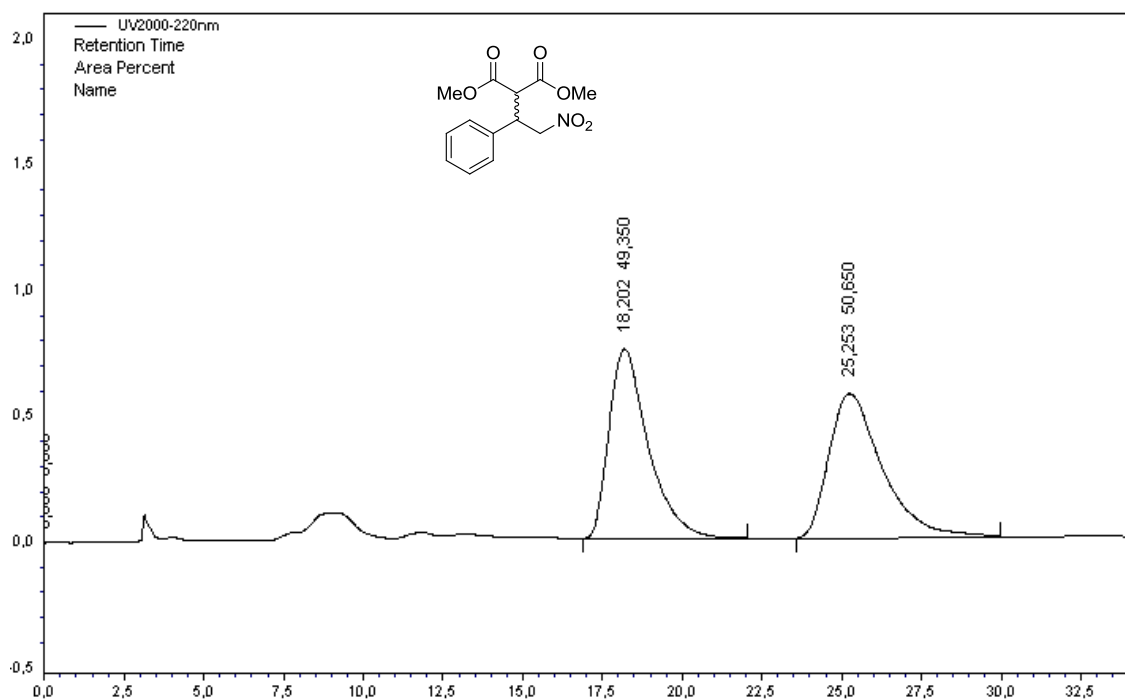
Figure B.32. HPLC chromatogram of enantiomerically enriched product 46p



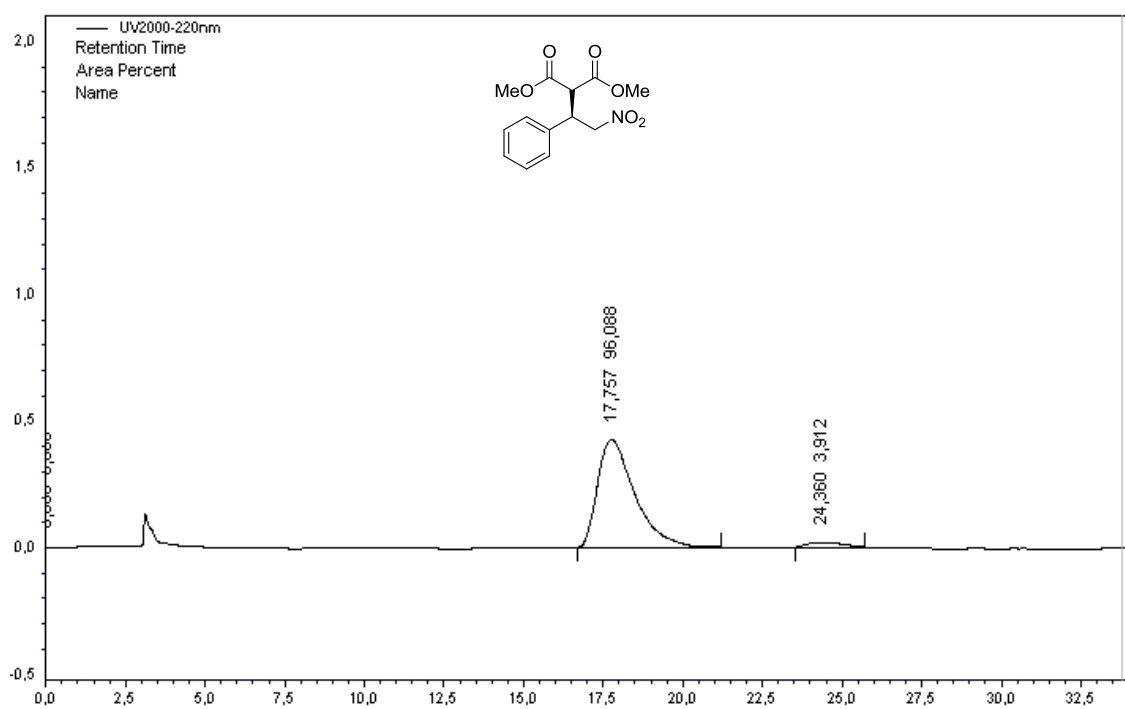
**Figure B.33.** HPLC chromatogram of *rac*-**46r**



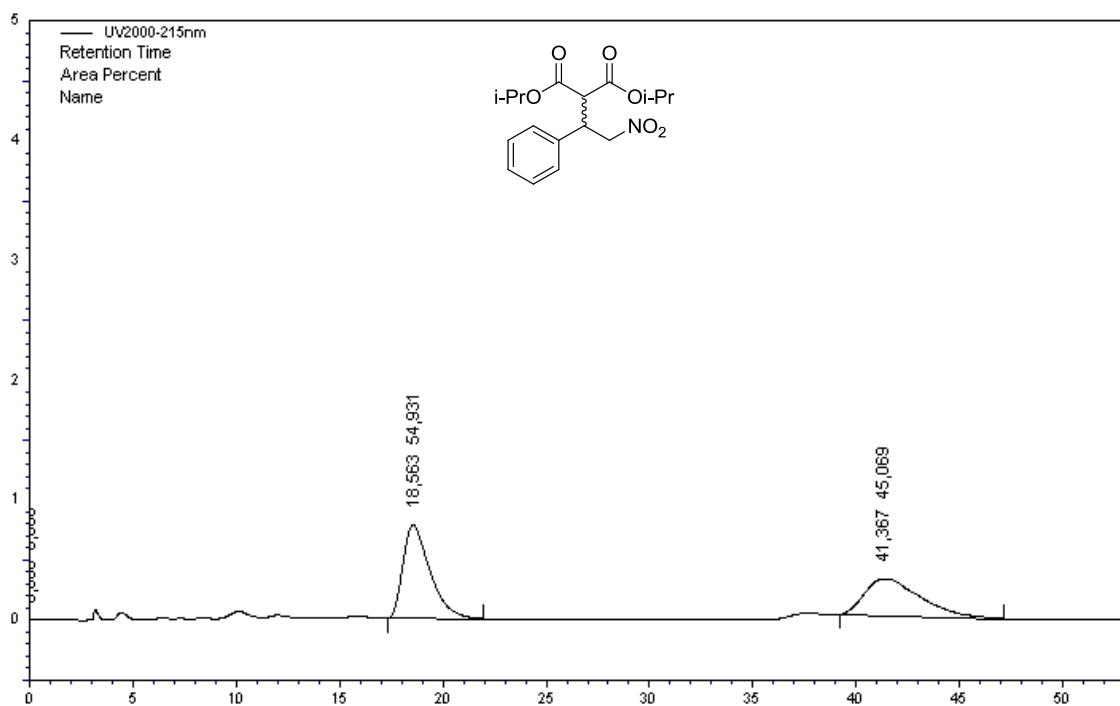
**Figure B.34.** HPLC chromatogram of *enantiomerically enriched* product **46r**



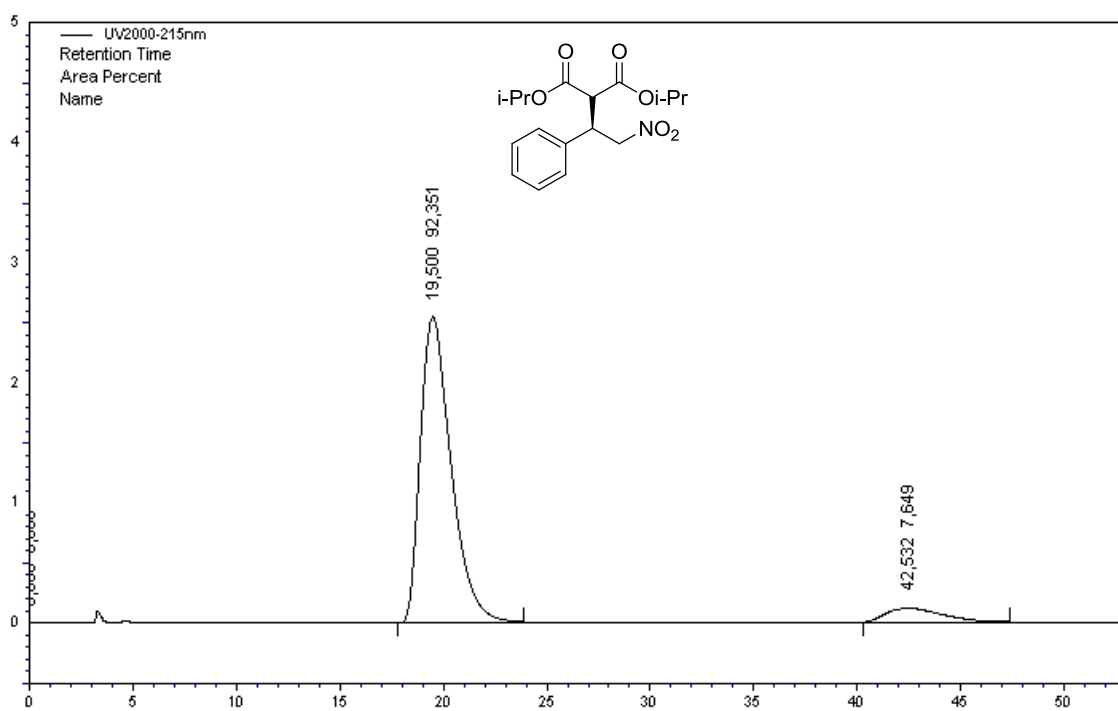
**Figure B.35.** HPLC chromatogram of *rac*-60a



**Figure B.36.** HPLC chromatogram of *enantiomerically enriched* product 60a

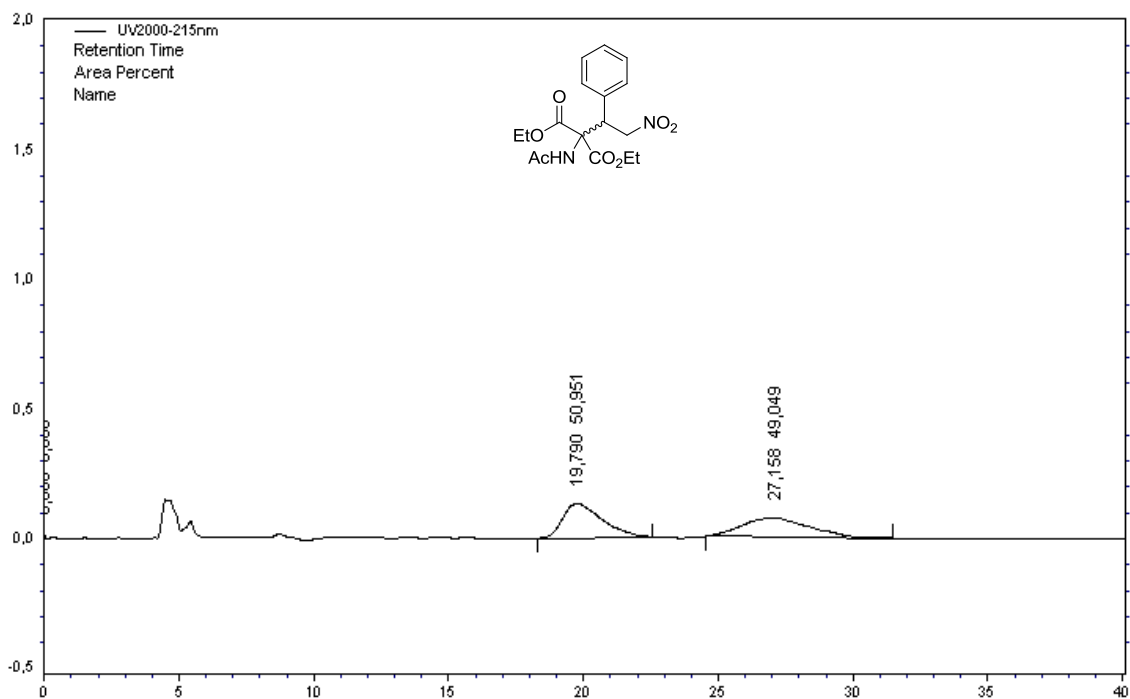


**Figure B.37.** HPLC chromatogram of *rac*-60b

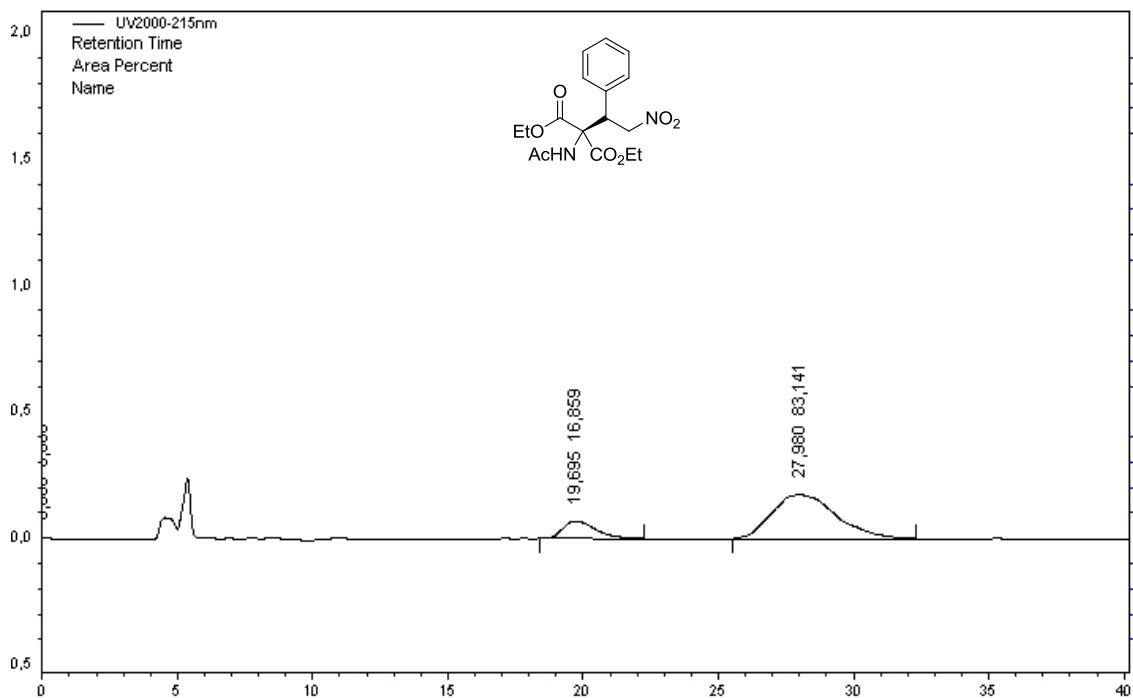


**Figure B.38.** HPLC chromatogram of *enantiomerically enriched* product 60b





**Figure B.39.** HPLC chromatogram of *rac*-**60c**



**Figure B.40.** HPLC chromatogram of *enantiomerically enriched* product **60c**